

The utility of neoadjuvant gemcitabine plus carboplatin followed by immediate radical cystectomy in patients with muscle-invasive bladder cancer who are ineligible for cisplatin-based chemotherapy

(シスプラチン不適格筋層浸潤膀胱癌に対するゲムシタビン+カルボプラチンによる術前化学療法の有用性)

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Abstract

There are currently no data supporting carboplatin-based regimens in muscle-invasive bladder cancer patients who are unsuitable for neoadjuvant cisplatin treatment. The aim of this study was to investigate the potential benefit of carboplatin-based regimens in patients with muscle-invasive bladder cancer who were unsuitable for cisplatin. We focused on 171 patients ineligible for cisplatin, including 98 patients who received neoadjuvant gemcitabine and carboplatin (GCarbo) followed by immediate radical cystectomy (GCarbo cohort) and 73 patients who underwent radical cystectomy (RC-alone cohort) at Hiroaki University or Aomori Prefectural Hospital. In the neoadjuvant GCarbo cohort, patients underwent two 21-day cycles of GCarbo. The two courses of neoadjuvant chemotherapy were followed by radical cystectomy at an interval of 1 month. The 5-year overall survival rates for the GCarbo and the RC-alone cohorts were 79.5% and 53.8%, respectively ($P < 0.001$), while the 5-year disease-free survival rates were 75.5% and 55.4%, respectively ($P = 0.013$). Surgical specimens of 16 (16.3%) patients in the GCarbo cohort indicated stage pT0 disease. The rate of positive surgical margins in the RC-alone cohort was significantly higher than that in the GCarbo cohort ($P < 0.001$). In this study, the oncological outcomes were significantly improved in cisplatin-unfit patients with muscle-invasive bladder cancer who received neoadjuvant GCarbo chemotherapy, compared with those in patients who underwent RC alone. The standard of care for muscle-invasive bladder cancer, especially for patients who are unfit for cisplatin, may include neoadjuvant carboplatin chemotherapy followed by radical cystectomy.

Keywords: muscle-invasive bladder cancer, neoadjuvant chemotherapy, cisplatin-unfit, carboplatin

Introduction

Neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is recommended for muscle-invasive bladder cancer (MIBC) patients with muscle-invasive bladder cancer (MIBC) according to the guidelines of the European Association of Urology (EAU) or the National Comprehensive Cancer Network (NCCN) [1,2]. There is increasing evidence supporting the use of NAC in locally advanced bladder cancer (BC). A meta-analysis of randomized trials showed that cisplatin (CDDP)-based NAC, including methotrexate, vinblastine, doxorubicin, and CDDP (MVAC) or CDDP, methotrexate, and vinblastine (CMV), improved overall survival (OS) by 5% in T2-T4a BC patients [3-6]. However, CDDP-based regimens were associated with a high toxicity profile, especially severe renal toxicity [7].

Indeed, CDDP-containing combination chemotherapy has been the standard of care for patients with locally advanced or metastatic urothelial cancer (UC) [8,9]. However, approximately 30-50% of patients with locally advanced or metastatic UC are ineligible (“unfit”) for CDDP owing to poor performance status, impaired renal function, or heavy comorbidities [9]. In addition, the vast majority of MIBC occurs in patients older than 65 years; the median age at onset is 71 years, and this number increases at the time of initial diagnosis [10].

As a treatment option for patients who are ineligible for CDDP, carboplatin (CBDCA)-based regimens, including gemcitabine and CBDCA (GCarbo) are used due to reduced nephrotoxicity and fewer adverse events [11]. There is currently no level I evidence available comparing CDDP-versus CBDCA-based chemotherapy in UC

patients. The clinical outcomes of CBDCA-based regimens are worse than those of CDDP-based regimens for patients with UC [12,13]. Therefore, the NCCN or EAU guidelines recommend CDDP-based chemotherapy as NAC for MIBC patients or as a first-line chemotherapy regimen for patients with locally advanced or metastatic UC [1,2]. In addition, CBDCA should not be replaced by CDDP, especially in the perioperative setting [2]. However, there are currently no data supporting CBDCA-based regimens in MIBC patients who are unfit for CDDP in the neoadjuvant setting. Thus, we investigated the potential benefit of CBDCA-based regimens in patients with MIBC who were unfit for CDDP.

Patients and Methods

Study population

We conducted a retrospective chart review of 513 consecutive patients who underwent RC between April 1997 and October 2015 at Hiroaki University or Aomori Prefectural Hospital. All patients underwent RC and bilateral pelvic lymphadenectomy (PLND). We focused on 171 patients ineligible for CDDP-based chemotherapy, including 98 patients who received neoadjuvant GCarbo followed by immediate RC and PLND (GCarbo cohort) and 73 patients who underwent RC and PLND (RC-alone cohort). A patient was identified as CDDP-ineligible if they met at least one of the following criteria: European Cooperative Oncology Group (ECOG) performance status of 2, creatinine clearance <60 mL/min, hearing loss grade ≥ 2 , neuropathy grade ≥ 2 , and/or New York heart Association (NYHA) Class III heart failure [14].

The study protocol and informed consent documents were reviewed and approved by the Hirosaki University and Aomori Prefectural Hospital institutional review boards.

Treatment schedule

In the neoadjuvant GCarbo cohort, patients received two cycles of GCarbo (800 mg/m² gemcitabine on days 1, 8, and 15, and CBDCA at an area under the curve of 4, according to Calvert' s formula [15], on day 2) (Table 1). Each cycle lasted for 21 days. The two NAC courses were followed by RC and PLND at an interval of 1 month [16]. The choice of urinary diversion was at the surgeon' s and/or patient' s discretion. PLND including the hypogastric, external iliac, obturator, presacral, and common iliac lymph nodes up to the aortic bifurcation was routinely performed.

Patient evaluation

The following baseline information was obtained: complete history and physical examination, ECOG performance status, abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI), and chest radiography or CT.

Tumors were measured at baseline and before RC. Response to treatment was assessed using the Response Evaluation Criteria in Solid Tumors guidelines, version 1.1 [17]. The diagnosis of MIBC was confirmed by a single pathologist at Hirosaki University after reviewing the results of the transurethral resection (TUR) and MRI at baseline. We extensively examined the specimens obtained during cystoprostatectomy to identify the presence of MIBC. Pathological examination of complete transmural sections of the bladder wall was performed to accurately determine the pathological stage. In addition, histological examination of several sections from various sites within the bladder, including the dome,

anterior wall, lateral walls, posterior wall, trigone, and both ureters, was performed to identify superficial disease or a second primary tumor.

All tumors were staged according to the 2002 American Joint Committee on Cancer Staging Manual [18]. All lymph nodes from each designated site were submitted for examination, and representative sections of the surrounding fibroadipose tissue were also examined. Cancer in the bladder and lymph node specimens was classified as pT0 (no evidence).

Follow-up schedule

Each patient was evaluated every 3 months using ultrasonography (to check for hydronephrosis), urine cytology, and renal and liver function tests. CT scans from the chest to the pelvis were performed every 6 months for 5 years, and annually thereafter.

Endpoints and statistical analysis

The primary endpoints were OS and disease-free survival (DFS). According to OS, we also compared the GCarbo cohort with 122 CDDP-fit patients who received NAC followed by RC at Hirosaki University and Aomori Prefectural Hospital between June 1998 and July 2015 (CDDP-fit cohort). Data were analyzed using IBM SPSS statistics 20 (IBM Corp., Armonk, NY, USA). Differences between GCarbo and RC-alone groups were compared using the chi-square test for categorical variables

and Student' s t -test or the Wilcoxon rank sum test for continuous variables. Survival after cystectomy was analyzed using the Kaplan-Meier method. The relationship between survival and subgroup classification was analyzed using the log-rank test. DFS was defined as the time from RC to appearance of local or regional disease/metastasis or death. All P values were two-sided, and a P value <0.05 was considered significant.

Results

Patient characteristics

All patients were CDDP-unfit and diagnosed with muscle-invasive UC on the basis of histological examination for the specimens obtained via TUR. Of these, 165 patients (95.3%) had renal impairment, 7 (4.0%) had NYHA Class III heart failure, and 1 (0.6%) had hearing loss. The patient demographic data, classified into two groups according to treatment, are listed in Table 2.

Surgical outcomes

In the NAC group, all patients underwent RC and PLND within approximately 1 month following neoadjuvant GCarbo therapy. The median interval from the diagnosis of MIBC to RC was 63 days (interquartile range [IQR], 57–69 days). The median surgical time, including urinary diversion, was 279 minutes (IQR, 221–334 minutes) for the GCarbo cohort and 323 minutes (IQR, 246–388 minutes) for the RC-alone cohort ($P = 0.004$). The median estimated blood loss was 1200 mL (IQR, 834–1866 mL) in the GCarbo cohort and 1223 mL (IQR, 880–1875 mL) in the RC-alone cohort ($P = 0.338$).

Oncological outcomes

By the end of the follow-up period, 13 patients (13.3%) in the neoadjuvant GCarbo cohort and 27 patients (37.0%) in the RC-alone cohort had died of BC. Eleven patients (6.4%), including 8 patients in the GCarbo cohort and 3 in the RC-alone cohort, developed clinical recurrence.

The OS curves are shown in Figure 1. The 5-year OS rates were 79.5% for the GCarbo cohort (95% confidence interval [CI], 98.4–116.9) and 53.8% for the RC-alone cohort (95% CI, 83.6–120.5) (Fig. 1; $P < 0.001$). The 5-year DFS rates were 75.5% for the GCarbo cohort (95% CI, 90.8–111.7) and 55.4% for the RC-alone cohort (95% CI, 87.9–126.9) (Fig. 2; $P = 0.013$). According to CDDP eligibility, the 5-year OS rates were 89.2% for the CDDP-fit cohort (95% CI, 110–123.1) and 79.5% for the GCarbo cohort (95% CI, 98.4–116.9) (Fig. 3; $P = 0.07$).

Pathological evaluation

All patients were evaluable for pathological outcomes. Table 3 lists the histopathological details. The surgical specimens of 16 (16.3%) patients in the GCarbo cohort showed stage pT0 disease. The rate of positive surgical margins in the RC-alone cohort was significantly higher than that of the GCarbo cohort. Overall, 10.8% of patients had lymph node involvement that was not evident on preoperative evaluation.

Discussion

MIBC is a systemic disease, and approximately 50% of MIBC patients will develop distant metastasis and eventually die of BC [19, 20]. The most commonly referenced NAC trial is the SWOG 8710 trial, in which neoadjuvant MVAC followed by RC was compared to RC alone [3]. Although the difference between the 5-year OS rates was not statistically significant ($P = 0.06$), the results of this study have been used as evidence of the superiority of NAC over RC alone.

Many investigators have reported that CDDP-based combination chemotherapy is often the standard of care for patients with MIBC [3–6]. However, the use of neoadjuvant CDDP-based chemotherapy may be limited by impaired renal function [10]. Based on the definition of ineligibility for CDDP therapy, at least 40% of patients aged 70 years or over are not eligible for CDDP-based chemotherapy because of impaired renal function [10]. Indeed, BC is an age-related disease and an increase in patients with MIBC seems inevitable because of the aging population in Japan.

The European Organization for Research and Treatment of Cancer–Genitourinary Tract Cancer Cooperative Group conducted a randomized phase II/III trial in UC patients who were ineligible for CDDP [11]. The enrolled patients were randomized to the M-CAVI (methotrexate, CBDCA, and vinblastine) arm or to the GCarbo arm. The overall response rate (RR) was 38% in the GCarbo group and 20% in the M-CAVI group. The rates of severe acute toxicity were 14% and 28% in the GCarbo and M-CAVI groups, respectively. Therefore, the GCarbo regimen may be safe in CDDP-unfit

patients.

To date, there have been no completed randomized phase III trials comparing CDDP- and CBDCA-based regimens in BC. There has been only one randomized trial that directly compared CDDP and CBDCA [13]. Overall RR was 65.9% for patients who received gemcitabine and CDDP (GCis) and 56.4% for those who received GCarbo. Median survival was 12.8 months and 9.8 months for the GCis and GCarbo cohorts, respectively. There were no statistically significant differences between the groups regarding RR or median survival. A meta-analysis of published randomized trials by Galsky *et al.* reported that the pooled risk ratio for achieving an objective response with CDDP-versus CBDCA-based chemotherapy was 1.34 ($P = 0.02$), using the Mantel-Haenszel method for combination trials [21]. However, the pooled risk ratio for overall mortality at 12 months with CDDP- versus CBDCA-based chemotherapy was 0.775 ($P = 0.12$) [21]. In this study, there were significant differences between CDDP-unfit and CDDP-fit patients who received NAC followed by RC (Fig. 3). Mertens *et al.* reported the potential benefit of CBDCA-based chemotherapy for CDDP-unfit patients with non-organ-confined UC compared with CDDP-fit patients who received CDDP-based chemotherapy [7]. Although the cancer-specific survival (CSS) was relatively better with CDDP-based chemotherapy, there were no significant differences in OS, CSS or recurrence-free survival [7].

Based on the EAU or NCCN guidelines, CBDCA combination chemotherapy is less effective than CDDP-based chemotherapy in terms of complete response and survival [1,2]. Therefore, split-dose CDDP-containing regimens have been used in patients with MIBC [22,23]. Kim *et al.* reported the utility and safety of gemcitabine and

split-dose CDDP (GCis-S) chemotherapy for CDDP-unfit patients with UC compared with GCarbo chemotherapy [22]. The RR was 31.6% in the GCarbo group and 68.4% in the GCis-S group ($P = 0.023$). Regarding renal function, there were no significant differences in serum creatinine levels or glomerular filtration ratios between the GCarbo or GCis-S groups ($P = 0.292$ and $P = 0.186$, respectively) [22]. On the other hand, Dash *et al.* reported that for 35.7% of patients who received a split-dose CDDP schedule, the median interval from the diagnosis to RC was 138 days [23]. Several authors have reported that a delay in RC results in a worse pathological stage and diminished survival [24]. In the current study, the interval from diagnosis of MIBC to RC was as short as 63 days. If neoadjuvant GCarbo really does not have an effect on patients with MIBC who are ineligible for CDDP, our regimen may still be advantageous in terms of avoiding a delay in RC. In addition, we believe that the timing of RC may be important in achieving the optimum response to NAC. Therefore, two courses of neoadjuvant GCarbo may be potentially advantageous for obtaining the maximum treatment effect with a combination of NAC followed by immediate RC.

The current study has several limitations. First, it was a retrospective study, with an inherent potential for bias. Second, the use of clinical staging may be associated with understaging or overstaging. Third, a relatively small number of patients were enrolled in this study, and the follow-up period was relatively short. In the near future, other non-nephrotoxic drugs, including antibodies against the PD-1 checkpoint receptor or its ligand, PD-L1, will be applied to CDDP-unfit patients with MIBC or metastatic UC in clinical trials. In

this study, the oncological outcomes, including OS and DFS, were significantly improved in CDDP-unfit patients with MIBC who received neoadjuvant GCarbo chemotherapy, compared with patients who underwent RC alone. Hence, we suggest that the standard care for MIBC patients, especially for MIBC patients who are unfit for CDDP, may include NAC followed by RC.

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Conflict of Interest

None declared.

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Figure legends

Fig. 1 Kaplan-Meier analysis of overall survival in bladder cancer patients who underwent radical cystectomy with or without neoadjuvant therapy. The 5-year overall survival rate was 79.5% for patients who received neoadjuvant gemcitabine and carboplatin followed by immediate cystectomy and 53.8% for patients who underwent cystectomy alone ($P < 0.001$, log-rank test).

Fig. 2 Kaplan-Meier analysis of disease-free survival in bladder cancer patients who underwent radical cystectomy with or without neoadjuvant therapy. The 5-year disease-free survival rate was 75.5% for patients who received neoadjuvant gemcitabine and carboplatin followed by immediate cystectomy and 55.4% for patients who underwent cystectomy alone ($P = 0.013$, log-rank test).

Fig. 3 Kaplan-Meier analysis of overall survival in bladder cancer patients who were eligible or ineligible for cisplatin. The 5-year disease-free survival rate was 89.2% for cisplatin-fit patients and 79.5% for cisplatin-unfit patients ($P = 0.07$, log-rank test)

Table 1. Treatment schedule

		Treatment days			
	Dose	Day 1	Day 2	Day 8	Day 15
Gemcitabine	800mg/m ²	○		○	○
Carboplatin	AUC 4		○		

AUC = area under the curve

Table 2 Patient characteristics

	Neoadjuvant GCarbo (N = 98)	RC alone (N = 73)	<i>P</i>
Age, median, years, (IQR)	70 (63-75)	72 (68-76)	0.020
Sex, number (%)			
Male	75 (76.5)	57 (78.1)	0.812
Female	23 (23.5)	16 (21.9)	
Clinical T stage, number (%)			
T2	34 (34.7)	41 (56.2)	0.299
T3	56 (57.1)	28 (38.4)	
T4	8 (8.2)	4 (5.5)	
Clinical N, number (%)			
Negative	86 (87.8)	72 (98.6)	0.030
Positive	12 (12.2)	1 (1.4)	
Tumor grade, number (%)			
2	27 (27.6)	18 (32)	0.727
3	71 (72.4)	38 (68)	
Tumor size, median, cm (IQR)	4.3 (3-5.1)	4.5 (2.8-5.2)	0.6282
Follow-up period, median, months, (IQR)	63 (26-51)	59 (18-134)	0.055

IQR = interquartile rate; GCarbo = gemcitabine and carboplatin; RC = radical cystectomy

Table 3. Pathological outcomes

	Neoadjuvant GCarbo (N = 98)	RC alone (N = 73)	<i>P</i>
Pathological stage, number (%)			
T0	16 (16.3)	2 (2.7)	
T1	24 (24.5)	18 (24.7)	
T2	31 (31.6)	23 (31.5)	0.011
T3	18 (18.4)	20 (27.4)	
T4	9 (9.2)	10 (13.7)	
Lymph node involvement, number (%)	14 (14.3)	10 (13.7)	0.918
Positive surgical margins	0	9 (12.3)	< 0.001
Lymph node yield, number (IQR)			
Median	18 (12-22)	10 (6-18)	0.065

IQR = interquartile rate

Fig. 1

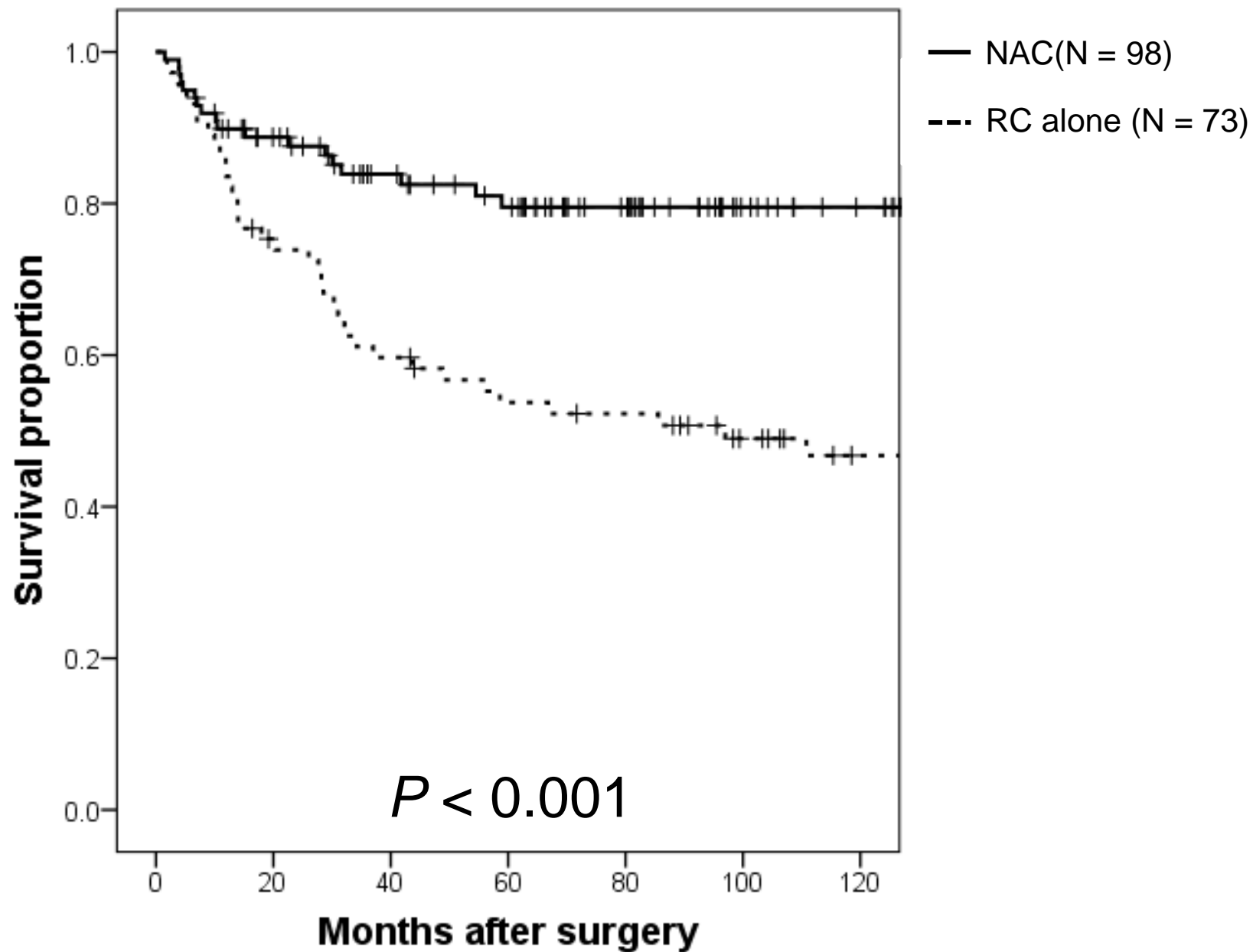


Fig. 2

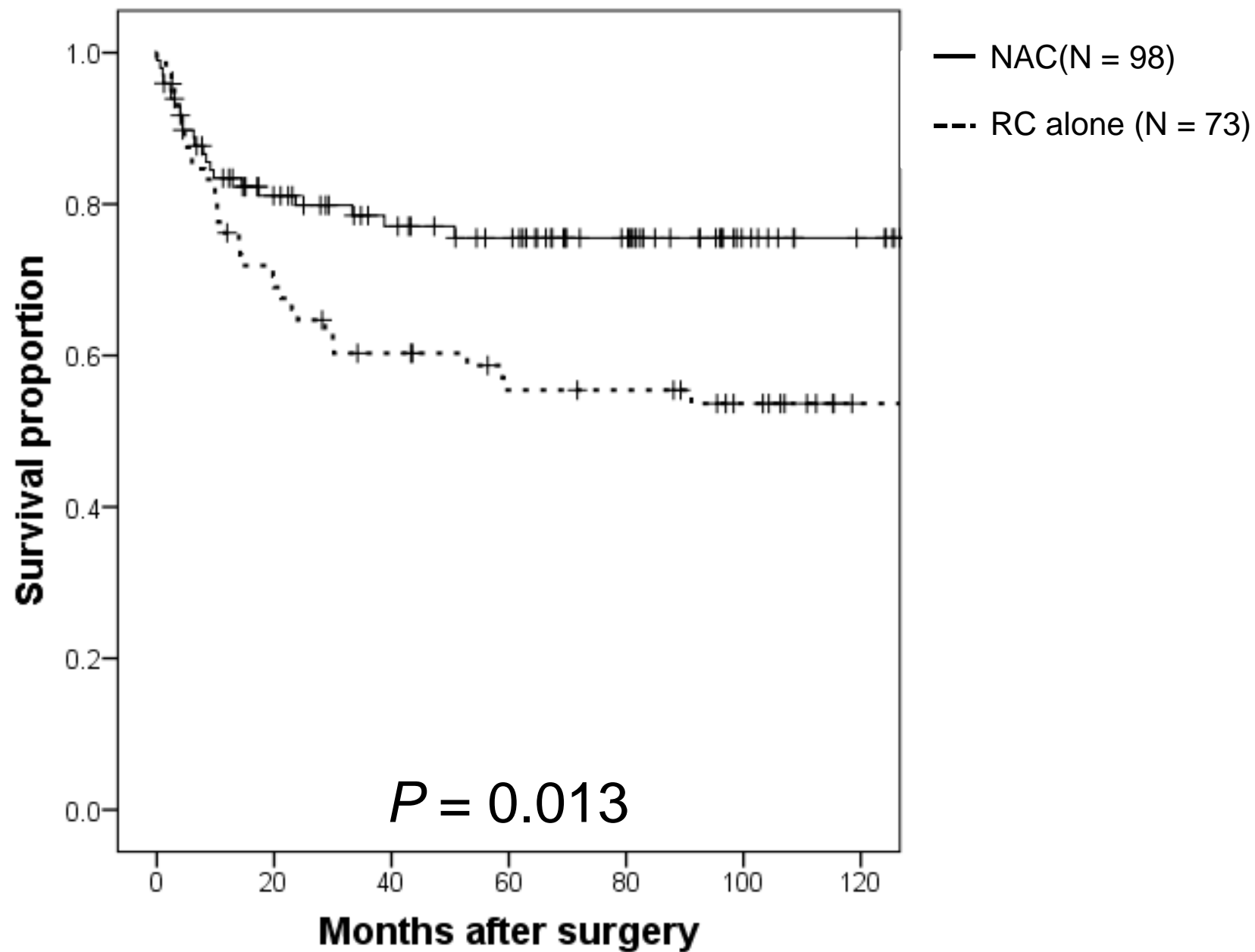


Fig. 3

