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Neoadjuvant chemotherapy followed by surgery has no therapeutic advantages over concurrent chemoradiotherapy in International Federation of Gynecology and Obstetrics stage IB-IIB cervical cancer

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ABSTRACT

Objective: We aimed to assess the efficacy of neoadjuvant chemotherapy followed by surgery (NACT+S), and compared the clinical outcome with that of concurrent chemoradiotherapy (CCRT) in patients with International Federation of Gynecology and Obstetrics (FIGO) IB–IIB cervical cancer.

Methods: We reviewed 85 patients with FIGO IB–IIB cervical cancer who received NACT+S between 1989 and 2012, and compared them to 358 control patients who received CCRT. The clinical application of NACT was classified based on the following possible therapeutic benefits: increasing resectability after NACT by reducing tumor size or negative conversion of node metastasis; downstaging adenocarcinoma regarded as relatively radioresistant; and preservation of fertility through limited surgery after NACT.

Results: Of 85 patients in the NACT+S group, the pathologic downstaging and complete response rates were 68.2% and 22.6%, respectively. Only two young patients underwent limited surgery for preservation of fertility. Patients of the NACT+S group were younger, less likely to have node metastasis, and demonstrated a higher proportion of FIGO IB cases than those of the CCRT group (p≤0.001). The 5-year locoregional control, progression-free survival, and overall survival rates in the NACT+S group were 89.7%, 75.6%, and 92.1%, respectively, which were not significantly different from the rates of 92.5%, 74%, and 84.9% observed in the CCRT group, respectively (p>0.05).

Conclusion: NACT+S has no therapeutic advantages over CCRT, the standard treatment. Therefore, NACT+S should be considered only in selected patients through multidisciplinary discussion or clinical trial setting.

Keywords: Chemoradiotherapy; Hysterectomy; Uterine Cervical Neoplasms

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INTRODUCTION

Although the incidence of cervical cancer has decreased over several decades, it is the 7th most common cancer among Korean women [1]. The current standard treatments for International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIB cervical cancer are recommended according to disease stages. For most patients presenting with FIGO stage IB–IIA disease either confined to the cervix or with limited vaginal extension, no differences were observed between radiotherapy and surgery in terms of 5-year survival rates, which were 85% to 90%. In practice, radical surgery tends to be selected for FIGO stage IB1 and IIA1, while concurrent chemoradiotherapy (CCRT) is offered to patients with FIGO stage IB2–IIA2 who have bulky tumors larger than 4 cm confined to the cervix. Additionally, CCRT is the standard treatment method for patients with FIGO stage IIB, and is the preferred treatment for patients with pelvic and/or para-aortic lymph node metastasis, regardless of disease stage [2,3].

After platinum and anthracycline chemotherapy emerged as effective treatments for solid tumors in recurrent and metastatic settings in the late 1970s, the clinical application of these regimens was extended progressively to both the adjuvant and neoadjuvant settings, particularly in head and neck cancer and uterine cervical cancer [4]. Notably, several questions persist concerning the use of neoadjuvant chemotherapy (NACT), such as whether it is useful, which chemotherapy regimens and intensities are optimal, and precisely which patients benefit [5].

Over the last 30 years, NACT for stage IB–IIB cervical cancer has often been used in practice by gynecologic oncologists to improve resectability, although evidence that such a goal is achievable is scarce [4]. We conducted this retrospective study to explore the clinical efficacy of NACT followed by surgery (NACT+S) compared with that of CCRT as a standard arm in patients with stage IB–IIB cervical cancer.

MATERIALS AND METHODS

1. Patients

We retrospectively retrieved the data of 85 cervical cancer patients who underwent NACT+S at the Yonsei Cancer Center between January 1989 and December 2012. The patients met the inclusion criteria of histopathologically confirmed cervical cancer, including squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma; and stage IB to IIB according to the FIGO. The patients did not have other malignant diseases, and had not received any prior treatment for cervical cancer. At our institution, NACT+S is used for select patients with stage IB–IIB cervical cancer per the physician's discretion as follows: (1) to enhance resectability after NACTs, in case of large tumors, vaginal/parametrial invasion, or clinically positive node; (2) to completely resect adenocarcinomas that are considered to be relatively more radioresistant than squamous cell carcinoma; and (3) for preservation of fertility using limited surgical treatment and omitting radiotherapy.

We also reviewed the data of 358 cervical cancer patients who received CCRT as a standard treatment under the same eligibility criteria, and used them as a control group to compare treatment outcomes between groups.

2. Treatment

Patients who were treated with NACT+S (n=85) received median 3 (range, 1 to 8) cycles of platinum (75 to 100 mg/m^2) based chemotherapy 3 weeks prior to surgery. The regimens combined with platinum were used as follows: platinum alone (n=12), vincristine (n=44), 5-fluorouracil (n=7), etoposide (n=14), and others (n=8). After receiving platinum-based NACT every 3 weeks, radical surgery was performed in 82 patients, while radical trachelectomy with lymphadenectomy was performed in two young patients. According to institutional policy, adjuvant treatments such as postoperative radiotherapy (PORT) and adjuvant chemotherapy were administered to patients with pathologic risk factors including lymphovascular invasion (LVI), perineural invasion (PNI), positive margin, and pathologic pelvic lymph node metastasis. After NACT+S, adjuvant treatments were administered as follows; PORT in 15 patients, adjuvant chemotherapy in 13 patients, and both in seven patients. Thirty-five patients treated with adjuvant treatments had pathological risk factors: 18 had LVI, four had PNI, 13 had positive margin, and 14 had pathologic pelvic lymph node metastasis. PORT with a median 50.4 Gy (range, 30 to 70.8 Gy) was administered to the pelvis with external beam radiation therapy (EBRT) alone (n=13), EBRT followed by intracavitary brachytherapy (ICR; n=6), and ICR alone (n=1). Patients were administered adjuvant chemotherapy with platinum alone (n=5), platinum with paclitaxel (n=8), platinum with vincristine (n=5), or platinum with other agents (n=2).

Patients treated with CCRT (n=358) received a median external beam irradiation of 45 Gy (range, 36 to 50.4 Gy) in 25 fractions (range, 20 to 28) with a midline block at median 36 Gy (range, 21 to 45 Gy) followed by a high dose rate ICR of median 30 Gy (range, 21 to 50 Gy) in 6 to 13 fractions at point A using ^{60}Co or ^{192}Ir as sources. A lymph node boost with a median of 9 Gy (range, 3.6 to 14.4 Gy) was performed in patients with lymph node metastases; these metastases were assessed using magnetic resonance imaging (MRI) to determine lymph node enlargement (diameter ≥1 cm) or fluorine-18–2-fluoro-2-deoxy-d-glucose (FDG) positron emission tomography-computed tomography (PET-CT) that evaluated FDG uptake greater than that of the liver or similar to that of the brain cortex. Concurrent platinum-based chemotherapy with a median of 6 cycles (range, 1 to 9) was administered to patients once a week for 6 to 8 weeks. The regimens combined with platinum were as follows: none (platinum alone; n=214), 5-fluorouracil (n=138), vincristine (n=1), and others (n=5).

3. Treatment outcome assessment

At our institution, pretreatment evaluation of patients with cervical cancer consisted of recording medical history, physical examinations, gynecological pelvic examination with biopsy, complete blood count, routine blood chemistry, urinalysis, chest radiography, intravenous pyelography, cystoscopy, sigmoidoscopy, CT, and pelvic MRI. PET-CT was additionally performed if necessary. After completion of therapy, the patients received follow-up examinations every 3 months for the first 2 years, then at 6-month intervals for 3 years, and once every year thereafter. Recurrences involving the cervix, vagina, or parametrial tissue were classified as local failure, lymph node recurrence within the pelvis as regional failure, and recurrences involving distant organs as distant failure. The primary end point of the study was locoregional control (LRC), progression-free survival (PFS), and overall survival (OS). Patient survival was defined as follows: (1) LRC was defined as the interval period from the end of treatment to the date of locoregional failure; (2) PFS was defined as the interval period from the end of treatment to the date of disease progression or recurrence, last follow-

up, or death; and (3) OS was defined as the interval period from the end of treatment until last follow-up or death from any cause. As a secondary end point in the NACT+S group, we examined both resectability rate and pathologic response after the procedure.

4. Statistical analysis

We performed the analysis of associations between the clinicopathologic variables and treatment groups (NACT+S group vs. CCRT group) by using the chi-square test. LRC, PFS, and OS were calculated by using the Kaplan-Meier method, and the differences between the possible prognostic factors were compared using the log-rank test. Cox regression models, adjusted for possible prognostic factors including age, histopathologic type, tumor size, FIGO stage, clinical metastatic lymph node status, and overall treatment time, were fitted to evaluate the impact of the treatment groups on LRC, PFS, and OS. A $p \leq 0.05$ was considered significant in all statistical tests. Statistical analyses in this study were performed with SPSS ver. 20.0.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline characteristics

In the NACT+S group, the median age was 41 years (range, 27 to 62 years). Twenty-nine patients in this group (34.1%) had adenocarcinoma/adenosquamous carcinoma (Adenoca/AdenoSCa), while 56 (65.9%) had squamous cell carcinoma (SCCa). There were significant differences between the two treatment groups in distribution of tumor characteristics such as age, histopathologic type, FIGO stage, clinical lymph node status, and overall treatment time ($p \leq 0.001$). The NACT+S group represented younger patients (41 years vs. 54 years), a larger proportion of stage FIGO IB patients (58% vs. 15%), and a smaller proportion of stage FIGO IIB patients (26% vs. 81%) than the CCRT group. The latter group had more patients with clinical node metastasis than the former group (55% vs. 33%, respectively). Median overall treatment time was significantly shorter in the CCRT group than in the NACT+S group (61 days vs. 83 days, respectively). The baseline characteristics of patients are shown in **Table 1**.

2. Efficacy of NACT+S

Of 85 patients, 58 (68.2%) experienced pathologic downstaging based on surgical specimens. Pathologic downstaging was observed in 29 of 48 patients with FIGO IB tumors (60.4%), 11 of 15 with FIGO IIA tumors (73.3%), and 18 of 22 with FIGO IIB tumors (81.8%). Nineteen patients (22.6%) showed pathologic complete response (pCR). Seventy-two patients (84.7%) underwent complete resection after NACT, while 13 (15.3%) underwent incomplete resection with microscopic residual tumors, including five patients with FIGO IB, one patient with FIGO IIA, and seven patients with FIGO IIB stage tumors. Additionally, of 25 patients with clinical node metastasis, 18 (72%) showed no tumor cells in lymph node specimens after surgery.

There was no difference observed according to histopathologic subtype, Adenoca/AdenoSCa vs. SCCa, with respect to pathologic downstaging rate (72% vs. 66%, respectively; p=0.552), pCR (21% vs. 23%, respectively; p=0.791), and complete resection rate (90% vs. 82%, respectively; p=1.804). All patients underwent radical hysterectomy and pelvic lymph node dissection, except two young patients aged 27 and 32 years with no parity who responded to NACT with partial response (PR) and underwent radical trachelectomy with lymphadenectomy to preserve fertility.

Table 1. Baseline characteristics of patients

Variable	CCRT (n=358)	NACT+S (n=85)	p-value
Age (yr)			<0.001
Median (range)	54 (25–82)	41 (27–62)	
<50	121 (33.8)	65 (76.5)	
≥50	237 (66.2)	20 (23.5)	
Histopathologic type			<0.001
SCCa	320 (89.4)	56 (65.9)	
Adenoca/AdenoSCa	38 (10.6)	29 (34.1)	
Tumor size (cm)			0.102
Mean±SD	4.1±1.5	3.5±1.4	
<4	138 (38.5)	41 (48.2)	
≥4	220 (61.5)	44 (51.8)	
FIGO stage at diagnosis			<0.001
IB	52 (14.5)	48 (56.5)	
IIA	14 (3.9)	15 (17.6)	
IIB	292 (81.6)	22 (25.9)	
Clinical LN status			<0.001
Negative	162 (45.2)	60 (70.6)	
PLN positive	143 (39.9)	24 (28.2)	
PALN positive[*]	53 (14.8)	1 (1.2)	
OTT (day)			<0.001
Median (range)	61 (11–148)	83 (26–325)	
<65	222 (62.0)	29 (34.1)	
≥65	136 (38.0)	56 (65.9)	

Values are presented as number (%) unless otherwise indicated.

Adenoca, adenocarcinoma; AdenoSCa, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; NACT+S, neoadjuvant chemotherapy followed by surgery; OTT, overall treatment time; PALN, para-aortic lymph node; PLN, pelvic lymph node; SCCa, squamous cell carcinoma.

[*]PALN positive with/without PLN positivity.

3. Patterns of failure of NACT+S

Of the 85 women who underwent NACT+S, 13 (15.3%) developed recurrent tumors. The detection of PNI after surgery appeared to be significantly correlated with recurrence on univariate (p=0.006) and multivariate (p=0.009) analyses among the selected variables (**Supplementary Tables 1, 2**). We observed local failure in five cases, regional failure in three cases, and distant failure in eight cases. In patients who did not receive PORT (n=63), we found that six (9.5%) had locoregional failure. Of these patients, four had pathologic risk factors after NACT+S, such as lymph node metastasis in two cases, no downstaging in two cases, positive surgical margin in one case, and PNI/LVI in two cases. In patients who received PORT (n=22), two (9%) had locoregional failure. The patterns of failure are reported in **Fig. 1**.

4. Treatment outcomes

The median follow-up time was 62 months (range, 2 to 215 months) for all patients. The 5-year LRC rates of patients undergoing NACT+S versus CCRT were similar (89.7% vs. 92.5%, p=0.430) (**Fig. 2A**). Tumor size was an independent prognostic factor for LRC on both univariate (p=0.015) and multivariate (p=0.045) analyses.

At the end of the follow-up period, 381 patients (86%) survived. The 5-year PFS and OS rates did not differ between groups. The 5-year PFS rates in NACT+S versus CCRT patients were 75.6% vs. 74.0%, respectively (p=0.819) (**Fig. 2B**). Univariate analysis showed that PFS was influenced by histopathologic type (p=0.023), tumor size (p=0.005), FIGO stage (p=0.003), and lymph node status (p=0.017). Multivariate analysis revealed that histopathologic type
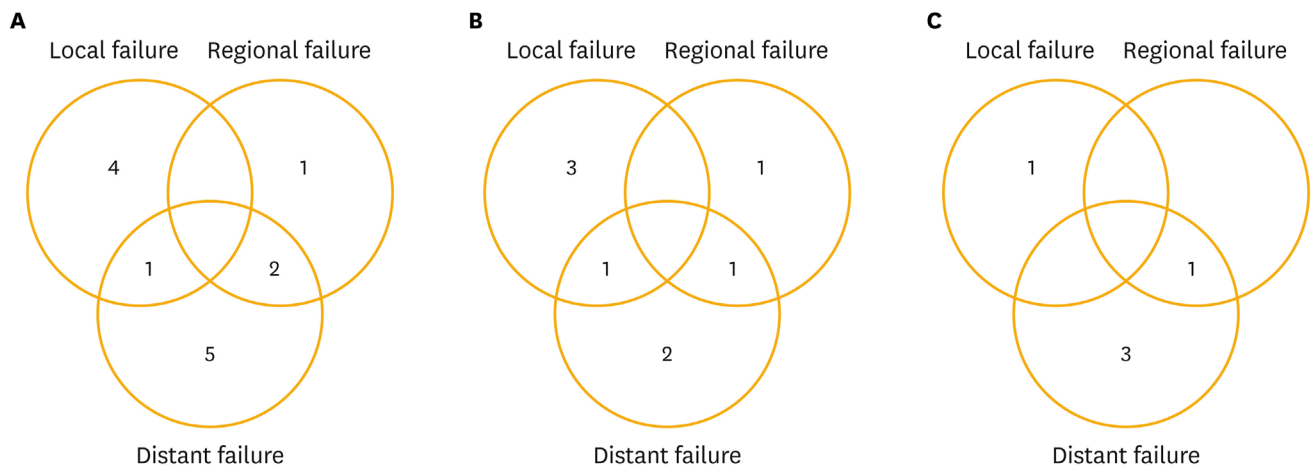
Fig. 1. Patterns of failure in patients treated with neoadjuvant chemotherapy followed by surgery (NACT+S). (A) All patients treated with NACT+S (n=85), (B) patients treated with NACT+S without postoperative radiotherapy (PORT; n=63), and (C) patients treated with NACT+S followed by PORT (n=22).

(p<0.001), tumor size (p=0.015), FIGO stage (p=0.008), and lymph node status (p=0.025) were prognostic factors related to PFS (**Table 2**). There was no significant difference in the 5-year OS between the NACT+S and CCRT groups (92.1% vs. 84.9%, p=0.184) (**Fig. 2C**), although the NACT+S group had more favorable characteristics. Clinical FIGO stage was an independent prognostic factor of OS on both univariate (p=0.002) and multivariate (p=0.002) analyses (**Table 3**). On the other hand, lymph node status did not show a statistically significant difference in OS with respect to total cohorts or individual treatment groups (**Fig. 3**).

DISCUSSION

Historically, NACT has been used based on the following rationales: (1) systemic chemotherapy inhibits distant metastasis by eradicating latent micrometastases, and (2) both pCR and surgical complete resection, which are achieved by reducing tumor volume and tumor extent after NACT, improve LRC [4,6].

Debates on whether these rationales for NACT apply equally to cervical cancer are still ongoing. The dominant pattern of failure of cervical cancer has been known to be locoregional recurrence [7]. Distant metastasis is seldom detected in cervical cancer patients at initial diagnosis [8]. Therefore, it is more important to control overt locoregional disease with upfront radiotherapy rather than to prevent latent micrometastasis with NACT. Furthermore, the effect of NACT on downstaging for purposes of enhancing resectability appears to be exaggerated [9-12]. Because most cases show residual disease on pathologic analysis after NACT+S, most physicians have no choice but to administer adjuvant radiotherapy in clinical practice. Finally, patients are subjected to a triple therapy that prolongs overall treatment time, which is reported to be a negative prognostic factor with respect to local control [13-15].

The present study showed that NACT was administered to patients for three main purposes: enhancement of resectability, presence of adenocarcinoma pathology, and preservation of fertility. However, it is difficult to conclude that NACT showed an advantage over upfront radiotherapy. Additionally, uneven distribution of baseline characteristics was likely to
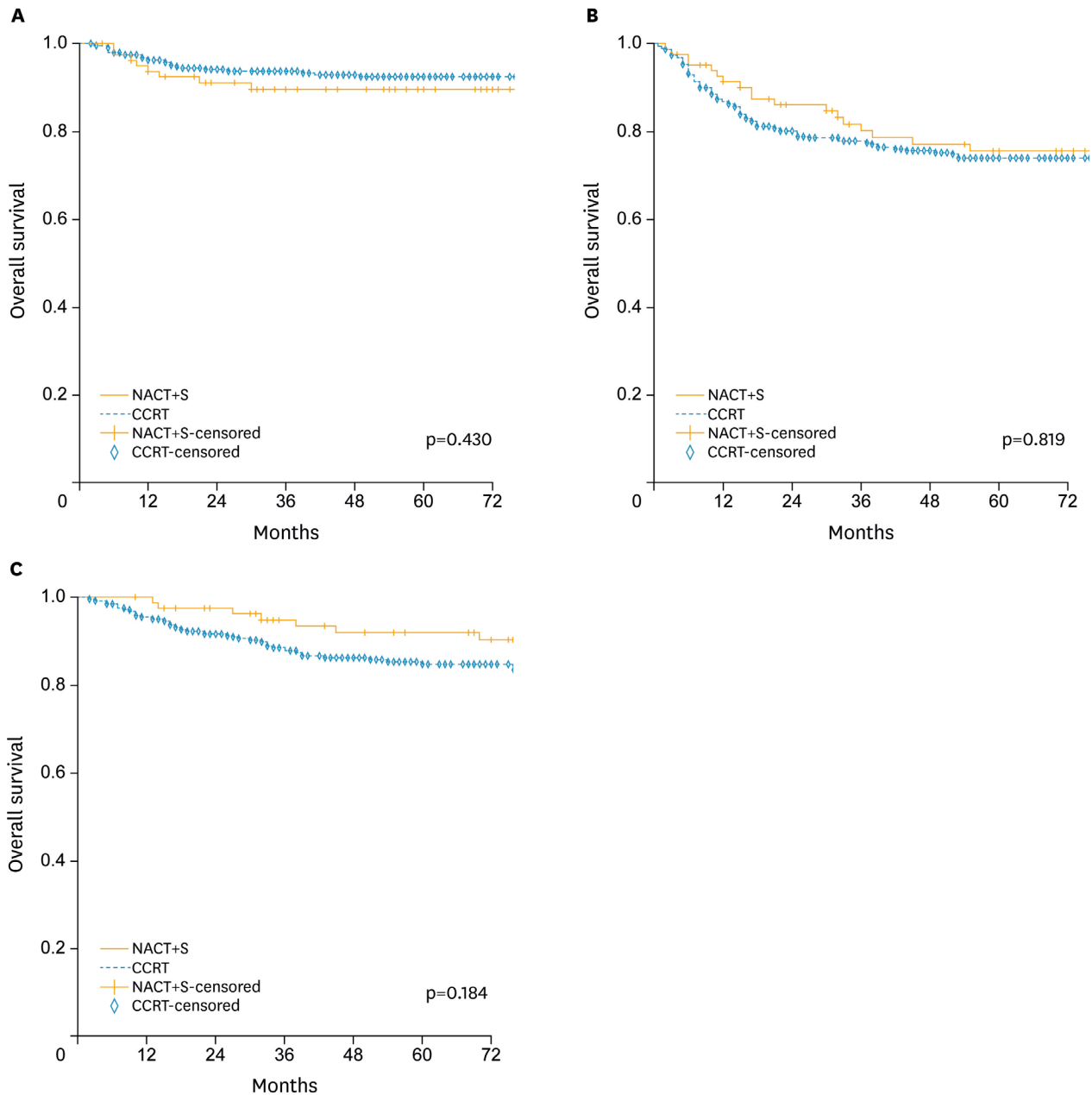
Fig. 2. (A) Locoregional control, (B) progression-free survival, and (C) overall survival according to treatment group. CCRT, concurrent chemoradiotherapy; NACT+S, neoadjuvant chemotherapy followed by surgery.

affect treatment outcomes between the NACT+S and CCRT groups. NACT+S administration was associated with lower stage and lower lymph node metastasis than CCRT; however, no statistically significant differences in terms of LRC, PFS, and OS were found between both groups. Ultimately, NACT+S as an investigational treatment did not outweigh CCRT as standard treatment with respect to clinical benefits and efficacy, despite the uneven distribution of patients in both groups. It is still questionable whether the efficacy of NACT as judged by the aforementioned three clinical aspects would be acceptable as a standard treatment in clinical practice.

Table 2. Univariate and stepwise multivariate Cox regression analyses of predictors for progression-free survival

Variable	UVA		MVA*	
	5-Year PFS	p-value	HR (95% CI)	p-value
Age (yr)		0.604		
<50	72.5			
≥50	75.4			
Histopathologic type		0.023		<0.001
SCCa	76.3		Reference	
Adenoca/AdenoSCa	62.4		2.396 (1.495–3.840)	
Tumor size (cm)		0.005		0.015
<4	81.1		Reference	
≥4	69.5		1.648 (1.103–2.462)	
FIGO stage at diagnosis		0.003		0.008
IB	85.5		Reference	
IIA/B	70.9		2.089 (1.215–3.589)	
Clinical LN status		0.017		0.025
Negative	77.6		Reference	
Positive	70.9		1.552 (1.057–2.278)	
OTT (day)		0.017		
<65	78.7			
≥65	68.7			
Treatment group		0.819		
CCRT	74.0			
NACT+S	75.6			

Adenoca, adenocarcinoma; AdenoSCa, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; MVA, multivariate analysis; NACT+S, neoadjuvant chemotherapy followed by surgery; OTT, overall treatment time; PFS, progression-free survival; SCCa, squamous cell carcinoma; UVA, univariate analysis.

*Variables were entered into the multivariate regression model in a stepwise method if p≤0.10 and were removed at any point if p>0.10.

Table 3. Univariate and stepwise multivariate Cox regression analyses of predictors for overall survival

Variable	UVA		MVA*	
	5-Year OS	p-value	HR (95% CI)	p-value
Age (yr)		0.624		
<50	85.4			
≥50	87.1			
Histopathologic type		0.231		0.069
SCCa	87.9		Reference	
Adenoca/AdenoSCa	78.3		1.782 (0.956–3.323)	
Tumor size (cm)		0.075		
<4	90.6			
≥4	83.3			
FIGO stage at diagnosis		0.002		0.002
IB	95.7		Reference	
IIA/B	83.8		3.505 (1.563–7.861)	
Clinical LN status		0.239		
Negative	87.8			
Positive	84.7			
OTT (day)		0.034		0.101
<65	88.9		Reference	
≥65	83.1		1.527 (0.921–2.531)	
Treatment group		0.184		
CCRT	84.9			
NACT+S	92.1			

Adenoca, adenocarcinoma; AdenoSCa, adenosquamous carcinoma; CCRT, concurrent chemoradiotherapy; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; LN, lymph node; MVA, multivariate analysis; NACT+S, neoadjuvant chemotherapy followed by surgery; OS, overall survival; OTT, overall treatment time; SCCa, squamous cell carcinoma; UVA, univariate analysis.

*Variables were entered into the multivariate regression model in a stepwise method if p≤0.10 and were removed at any point if p>0.10.
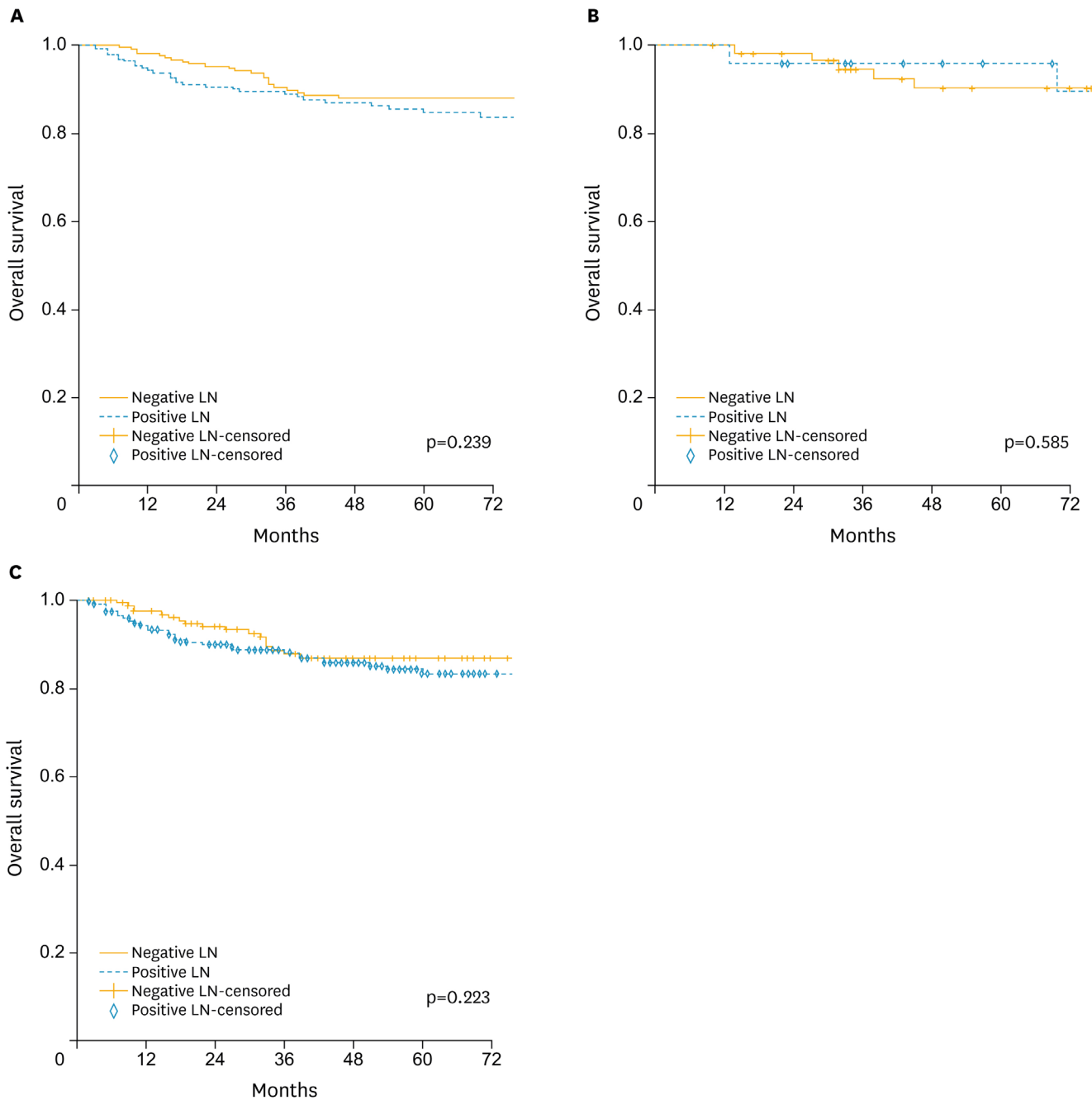
Fig. 3. Overall survival according to lymph node (LN) status. (A) Total patients (n=443), (B) patients treated with neoadjuvant chemotherapy followed by surgery (n=85), and (C) patients treated with concurrent chemoradiotherapy (n=358).

To date, NACT+S is not recommended for the treatment of cervical cancer. Some studies concluded that NACT showed a high response rate and might be an option for locally advanced cervical cancer [16-18]. However, several concerns were raised regarding their conclusions. First, the proportion of non-responders defined as stable or progressive based on the World Health Organization criteria was consistently reported to be 50% to 80% after administering 3 to 6 cycles of NACT [9-11]. Several regimens have been tried, such as vincristine, ifosfamide, and even paclitaxel, in addition to platinum. However, no remarkable

improvements in response were observed in these trials. Instead, treatment-related grade five toxicities occurred, as these potent agents were added to induce favorable response. Second, most reports suggested that NACT might be a possible option because responders have more favorable survival outcomes than non-responders. However, the control group for the responders should not be non-responders, but rather a patient group treated with standard treatments like CCRT so as to elucidate the effects of delayed effective local treatment. Additionally, meta-analysis failed to show the improvement of survival with NACT compared to the primary surgery group [19,20]. In the present study, our results did not support the hypothesis that the administration of NACT+S was superior to CCRT, although the former had more favorable characteristics compared to the latter. We are awaiting the results of an ongoing trial by the European Organization for Research and Treatment of Cancer Gynecologic Group (EORTC 55994) that is designed to compare NACT+S to CCRT in stage IB2–IIB cervical cancer. For the time being, primary CCRT remains the standard treatment for patients with locally advanced cervical cancer.

NACT has produced comparable survival outcomes in responder groups, as has been demonstrated in several clinical trials. Until now, we have no reliable biomarkers related to the efficacy of NACT despite several investigations. If a biomarker is developed and validated in clinical trials, NACT+S could be considered as a treatment option in locally advanced cervical cancer. Otherwise, NACT+S ought to only be considered cautiously within clinical trials.

A limitation of our study is its retrospective nature. In particular, this study has a selection bias regarding the treatment approach, and its two arms are imbalanced. Patients were treated with a heterogeneous chemotherapy regimen, which might have affected treatment outcomes. The results should therefore be interpreted conservatively.

In conclusion, although NACT+S has been investigated in several settings for decades, NACT+S has no therapeutic advantages over CCRT in FIGO stage IB–IIB cervical cancer. Therefore, NACT+S should be considered only in selected patients through multidisciplinary discussion or clinical trial settings. The upcoming EORTC 55994 trial is expected to answer several questions regarding the clinical significance of NACT+S compared to CCRT.

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