Neoadjuvant chemotherapy for locally advanced stage (IB2-IIA2-IIB) cervical carcinoma: Experience of a tertiary center and comprehensive review of the literature

Lokal olarak ileri evre (IB2-IIA2-IIB) servikal karsinom için neoadjuvan kemoterapi: Tersiyer merkez deneyimi ve literatürün kapsamlı incelemesi

 Caner Çakır, Fatih Kılıç, Rıza Dur, Dilek Yüksel, Mehmet Ünsal, Vakkas Korkmaz,
 Çiğdem Kılıç, Günsu Kimyon Cömert, Nurettin Boran, Osman Türkmen, Sevgi Koç, Taner Turan

Etlik Zübeyde Hanım Women's Health Training and Research Hospital, Clinic of Obstetrics and Gynecology, Ankara, Turkey

Abstract

Objective: This study aimed to evaluate neoadjuvant chemotherapy (NACT) for locally advanced stage cervical carcinoma.

Materials and Methods: Data of 43 patients with locally advanced cervical carcinoma who had NACT were reviewed. NACT protocols implemented included cisplatin/5-fluorauracil, cisplatin/UFT, and carboplatin/paclitaxel. After NACT, the patients were re-examined, and patients who had a tumor size ≤40 mm underwent Piver-Rutledge type III radical hysterectomy, while other patients received radiotherapy. Following NACT, clinical responses were assessed according to the criteria of the World Health Organization.

Results: The mean age of the patients was 49.4 years, and the median follow-up duration was 48 (range, 5-228) months. The median tumor sizes were 50 and 30 mm before and after NACT, respectively. Complete clinical response was observed in 4 (9.3%) patients, partial clinical response in 8 (18.6%), and pathologic complete response in 3 (6.9%). Stable disease was noted in 30 (69.9%) patients and progression in 1 (2.3%) patient. After NACT, 31 patients have undergone radical surgical procedures. The 5-year disease-free survival rate was 72%, and the 5-year disease-specific survival rate was 91%. Age, International Federation of Gynaecology and Obstetrics 2009 stage, histopathologic type, NACT protocol, rate of decrease in tumor size after NACT, clinical response, number of courses, tumor size before NACT, tumor size after NACT, and lymph node metastasis were not associated with disease-free survival.

Conclusion: Following NACT, a significant reduction in tumor dimension was observed, and the probability of radical surgery is increased. However, clinical response was not predictive of survival.

Keywords: Cervical carcinoma, locally advanced stage, neoadjuvant chemotherapy, survival

Öz

Amaç: Bu çalışmada neoadjuvan kemoterapinin (NACT) etkinliği değerlendirilmiştir. NACT, lokal olarak ilerlemiş servikal karsinomda başlangıç tedavisi için yöntemlerden biridir.

Gereç ve Yöntemler: Lokal olarak ilerlemiş servikal karsinomlu, NACT olan 43 hastanın verileri gözden geçirildi. NACT protokolleri sisplatin/5-fluorourasil, sisplatin/UFT ve karboplatin/paklitaksel idi. NACT sonrası hastalar tekrar muayene edildi ve tümör boyutu 40 mm ve altı olan hastalar ameliyat edildi (Piver-Rutledge tip III radikal histerektomi) ve diğer hastalara radyoterapi verildi. NACT klinik yanıtı, Dünya Sağlık Örgütü kriterlerine göre değerlendirildi.

Bulgular: Hastaların ortalama yaşı 49,4 yıl ve ortanca takip süresi 48 (aralık, 5-228) aydı. Ortalama tümör boyutu NACT'den önce 50 mm ve NACT'den sonra 30 mm idi. Yanıt oranları aşağıdaki gibidir; dört hastada (%9,3) tam klinik yanıt, sekiz hastada (%18,6) kısmi klinik yanıt ve üç hastada (%6,9) patolojik tam yanıt. Otuz hastada (%69,9) stabil hastalık ve bir hastada (%2,3) progresyon görüldü. NACT'den sonra 31 hasta radikal cerrahi prosedür geçirdi. Beş yıllık hastalıksız sağkalım %72,5 yıllık hastalığa özgü sağkalım %91 idi. Yaş, Uluslararası Jinekoloji ve Obstetrik Federasyonu 2009 evresi,

PRECIS: This study evaluated the outcomes of neoadjuvant chemotherapy in cervical carcinoma.

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histopatolojik tip, NACT protokolü, NACT sonrası tümör boyutundaki azalma oranı, klinik yanıt, kurs sayısı, NACT öncesi tümör boyutu, NACT sonrası tümör boyutu ve lenf nodu metastazı hastalıksız sağkalım ile ilişkili değildi.

Sonuç: NACT sonrası tümör boyutunda önemli bir azalma oldu ve radikal cerrahi olasılığı arttı. Ancak klinik yanıt, sağkalımı tahmin etmedi.

Anahtar Kelimeler: Serviks kanseri, lokal ileri evre, neoadjuvan kemoterapi, sağkalım

Introduction

Cervical carcinoma (CC) is the fourth most common cancer in women worldwide, and it is the fourth leading cause of cancer-related deaths[1]. The type of treatment type is based on the disease stage. Surgery, radiotherapy (RT), and chemotherapy (CT) have been suggested as standard treatment approaches[2]. The effectiveness of radical hysterectomy (RH) and RT in early-stage CC is comparable[3]. Owing to the preservation of ovarian activity, having lesser sexual dysfunction in surgery than in RT, and leaving RT as an alternative treatment for recurrence, surgery is currently the preferred method of treatment CC. However, after RH, the need for RT increases. Landoni et al.[4] reported that 84% of patients with stage IB-IIA disease received postoperative RT.

Concurrent chemoradiation used to enhance the effect of RT on the treatment of recurrence and locally advanced CC improves the response rate and survival of the patients[5]. This treatment modality not only controlled the course of a localized tumor but also decreased distant metastasis; thus, neoadjuvant chemotherapy (NACT) becomes a current issue. The main objectives of NACT are to eliminate micrometastasis, make the tumor smaller enough for surgical removal, and increase the survival of patients following the RF or RT. However, RT following NACT (sequential RT) had no effect on survival[6,7] and even worsened it[8,9]. These negative results are explained by the cross-resistance between the two treatment modalities and intracellular alterations[10]. By contrast, the cross-resistance problem does not exist in RH and the residual tumor is removed. Therefore, RF following the NACT is expected to increase patient survival. In a meta-analysis of 21 phase III trials, NACT followed by RH improved overall survival (OS) by 14% in comparison with RT alone[11]. However, in a study of the gynecologic oncology group (GOG), compared with NACT followed by RH, RH alone did not show any improvement[12].

The value of NACT in the treatment of CC is not appropriately defined until now; especially, in early-stage CC, uncertainty is much more common. Thus, this study aimed to evaluate the effect of NACT on the outcomes of patients with locally advanced CC (stage IB2, IIA2, and IIB).

Materials and Methods

Medical records of patients with stage IB2, IIA2, or IIB CC between 1998 and 2020 were reviewed retrospectively. This study included 43 patients who received NACT. These patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO 2009) staging system. In all patients, diseases were staged using upper abdominal tomography, pelvic magnetic resonance imaging (intravenous pyelography as needed), and gynecologic examination under general anesthesia. Histopathological evaluation was carried out according to the 2014 World Health Organization (WHO) criteria[13]. This study was approved by the local ethical committee (file no. 90057706-799/08; 05.06.2020).

Cisplatin/5-fluorouracil (5-FU) (CF), cisplatin/UFT™ (CU), and carboplatin/paclitaxel (CbP) combinations were applied as NACT protocols. The CF protocol started with cisplatin at a dose of 75 mg/m², given as an infusion within 1 h, followed by 5-FU at a dose of 500 mg/m² given within 6 h. The 5-FU dose was repeated at days 2-5 of the protocol. CT was given at 28 days intervals. The CU protocol was started with cisplatin at a dose of 75 mg/m², given as an infusion within 1 h. UFT™ [urasil (224 mg)-tegafur (100 mg) capsule, Bristol-Myers Squibb, NY, USA] was started at the same day as one capsule administered orally for 14 days. CT was given at 21 days intervals. The CbP protocol started with paclitaxel at a dose of 175 mg/m², given as an infusion within 3 h, followed by carboplatin dose calculated by using an area under curve of 6 (maximum dose of 750 mg) given within CT, the following criteria were supplied: (i) performance status ≤2 according to the Eastern Cooperative Oncology Group standards, (ii) adequate bone marrow function (leukocytes ≥3.000/mL, neutrophils ≥1.500/mL, platelets ≥100.000/mL, and hemoglobin ≥10 mg/dL), (iii) adequate hepatic function (total bilirubin, alanine aminotransferase, and aspartate aminotransferase levels were below twice of the upper limits), and (iv) adequate renal function (glomerular filtration rate >60 mL/min). Patients were evaluated for CT toxicity and adjustment of the next dose based on the complete blood counts and biochemical tests at every 10 days. Toxicity was assessed according to the WHO criteria[14].

Patients were re-examined under general anesthesia after two or three cycles of NACT. Patients who had tumors ≤40 mm underwent to Piver-Rutledge type III hysterectomy, while other patients received RT. Adjuvant treatment decisions for all patients were made by a gynecologic oncology council after RH. Patients with high-risk status received postoperative RT. Up until 2001, the criterion for postoperative adjuvant RT was the presence of at least one of the major risk factors (i.e., positive lymph nodes, parametrial involvement, presence of a tumor within the surgical margins, and tumor size ≥4 cm) or two of the minor risk factors (i.e., lymphovascular space invasion, stromal invasion of ≥1/2, tumor size 2-4 cm, and ≥3 lymph nodes with microscopic metastasis). After 2001, only patients with positive lymph nodes and/or parametrial involvement and/or a tumor within the surgical margins received adjuvant RT. RT was administered alone or in combination with CT (concurrent chemoradiation).

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Following the CT, clinical responses were assessed according to the WHO criteria[14]: complete clinical response (CCR), absence of gross tumor; partial clinical response (PCR), >50% decrease in tumor size; stable disease (SD), <50% decrease or <25% increase in tumor size; progressive disease (PD), >25% increase in tumor size or new tumor foci were found. The absence of tumor in the pathology specimen (RH, ovaries, and lymph nodes) was defined as pathologic complete response (Pat CR). Patients were followed by a pelvic examination, vaginal smear, abdominal ultrasonography, whole blood count, and blood biochemistry tests in the first 2 years after treatment in every 3 months, every 6 months up to the fifth year, and then once a year. Chest X-ray imaging was requested annually or when clinically suspicious recurrence was detected. Advanced imaging techniques (computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography) were performed when necessary. If recurrence was detected during follow-up, the time and site of recurrence were recorded. Deaths were also recorded.

The time from the first dose of NACT to any cause of death because of disease or last follow-up visit was defined as OS. The time from the first dose of NACT to death because of the disease or last follow-up visit was defined as disease-specific survival (DSS). Disease-free survival (DFS) was defined as the period from the first dose of NACT to confirmed recurrence or refractory disease with clinical examination and/or radiological imaging or the period from the initial surgery to the last follow-up visit in those who did not develop refractory/recurrence disease.

Statistical Analysis

SPSS 20.0 (SPSS Inc., Chicago, IL) was used for data review and statistical analysis. Descriptive statistics were expressed as mean ± standard deviation and median (minimum-maximum) for continuous variables and n (%) for categorical variables. The defining effect of surgical-pathologic factors on clinical response was assessed using the chi-square test. The Kaplan-Meier method was used to evaluate survival results. Survival curves were compared in the log-rank test. Significance was defined as p<0.05.

Results

The mean age of the patients was 49.4±8.67 (range, 33-70) years. According to the FIGO 2009 staging system, 28 (65.1%) patients had stage IB$_2$ disease, 11 (25.6%) had stage IIA2 disease, and 4 (9.3%) had stage IIB disease. Histopathologic diagnosis was squamous cell carcinoma in 39 (90.7%) patients. The median tumor size was 50 mm (range, 30-70 mm) before NACT and 30 mm (range, 0-70 mm) after NACT. In one patient, the tumor size was <40 mm before NACT, although this patient had stage IIB disease. As a NACT regimen, 36 (83.7%) patients received CF, 3 (7%) received CbP, and 4 (9.3%) received CU.

Moreover, 27 (62.8%) patients received three cycles of CT and 16 (37.2%) received two cycles (Table 1).

The control treatment after NACT showed that the mean tumor size decreased to 32.4±15.26 mm. Moreover, 4 (9.3%) patients obtained CCR. The rate of decrease in tumor size was >25% in 30 (69.8%) patients and >50% in 12 (27.9%) patients. The decrease in tumor size was <25% in six patients, but in 7 (16.3%) patients, there was no change in the tumor size. Accordingly, the calculated overall clinical response (OCR) rate was 27.9% (CCR, 9.3%, n=4; PCR, 18.6%, n=8). The SD rate was 69.9% (n=30), whereas the PD rate was 2.3% (n=1) (Table 1).

After NACT use, a surgical approach was feasible in 31 (72.1%) patients. This rate was 69.4% in patients who received CF and 66.7% in patients who received CbP. Four of the patients who received CU became operable. Finally, after NACT, 31 patients underwent surgery, and Piver-Rutledge type III RH + bilateral salpingo-oophorectomy + para-aortic-bilateral pelvic lymphadenectomy was performed. Moreover 5 (11.7%) of the remaining 12 patients received RT alone or concurrent chemoradiation, and the other 7 (16.3%) patients received concurrent chemoradiation after extraperitoneal/transperitoneal lymph node dissection (Table 1).

The tumor size was <4 cm during clinical examination in all patients who underwent surgery. However, in the postoperative pathological evaluation, the tumor size ranged from 4 to 6 cm in eight patients. After radical surgery of these 31 patients, 6 (19.4%) were found to have parametrial involvement and 1 (3.2%) had surgical border invasion. Lymph node metastasis was evaluated in 38 patients (31 patients underwent RH + lymphadenectomy and seven patients underwent extraperitoneal/transperitoneal lymphadenectomy + RT). Therefore, lymph node metastasis was detected in 17 (44.7%) of these 38 patients. Moreover, 3 of 7 patients who underwent extraperitoneal/transperitoneal lymph node dissection were found to have lymph node metastasis. In the assessment after NACT, three of the four patients who had no tumor in the cervix were also tumor negative after the pathological examination. However, in one patient, although no tumor was seen in the cervix, lymph node metastasis was detected. Consequently, the Pat CR rate was 6.9% (3/43). In addition, 24 (77.4%) of the 31 patients received concurrent chemoradiation after radical surgery. As a result, 36 of the 43 patients received RT (Table 2).

The factors determining clinical response to NACT were investigated. We compared 31 patients who had no clinical response (SD + PD) following NACT with 12 patients who had clinical response (CCR + PCR) following NACT. Age, FIGO 2009 stage, tumor size before NACT, NACT combination, number of NACT cycles, and histopathologic type were found to be not predictive of clinical response (p>0.05) (Table 3).

The median duration of follow-up in the entire cohort was 48 (range, 5-228) months. During follow-up, 11 patients had recurrence and six patients died. Three patients died of the disease during the study period. The 5-year DFS rate was 72%,

Table 1. Characteristics of the patients (n=43)

Characteristics		Mean ± SD	Median (range)
Age (years)		49.4±8.67	48 (33-70)
Tumor size before NACT (mm)		54.2±9.81	50 (30-70)
Tumor size after NACT (mm)		32.4±15.26	30 (0-70)
		n	%
FIGO 2009 stage	IB2	28	65.1
	IIA2	11	25.6
	IIB	4	9.3
Tumor size according to FIGO 2018 stage	<2 cm	-	-
	≥2 cm to <4 cm	1	2.3
	≥4 cm	42	97.7
Pathology	Squamous cell carcinoma	39	90.7
	Adenocarcinoma	3	7
	Adenosquamous	1	2.3
NACT protocol	Cisplatin and 5-fluorouracil	36	83.7
	Carboplatin and paclitaxel	3	7
	Cisplatin and UFT™	4	9.3
Number of cycles	2	16	37.2
	3	27	62.8
Tumor size after NACT	Increased	1	2.3
	Not changed	6	14
	Reduce in size of <25%	6	14
	Reduce in size among ≥25% to <50%	18	41.9
	Reduce in size by ≥50% (with gross tumor)	8	18.6
	No gross tumor (clinically)	4	9.3
Clinical response of NACT	Complete clinical response	4	9.3
	Partial clinical response	8	18.6
	Stabile disease	30	69.9
	Progressive disease	1	2.3
Curative intend primary treatment after NACT	Surgery	31	72.1
	Radiotherapy	12	27.9
Curative intend primary treatment after NACT in detailed	Surgery	31	72.1
	Only radiotherapy	2	4.7
	Concomitant chemoradiotherapy	3	7
	Extraperitoneal LND+radiotherapy	6	14
	Transperitoneal LND+radiotherapy	1	2.3

SD: Standard deviation, NACT: Neoadjuvant chemotherapy, LND: Lymphadenectomy, FIGO: Federation of Gynecology and Obstetrics

the 5-year DSS rate was 91%, and the 5-year OS rate was 87% in the study group.

The effects of the clinical and pathological parameters on DFS were evaluated. Age, FIGO 2009 stage, histopathologic type, NACT protocol, treatment after NACT, rate of decrease in tumor size after NACT, clinical response (Figure 1), number of courses, tumor size before NACT, tumor size after NACT, and lymph node metastasis were not associated with DFS (Table 4). Table 5 and 6 represent the clinical response and survival rates of relevant studies investigating the efficacy of NACT in early-

Table 2. Surgical and pathologic characteristics of patients who underwent surgery (n=31 patients)

Characteristics		Mean ± SD	Median (range)
Age (year)		48.7±7.28	48 (33-66)
Tumor size before NACT (mm)		55.5±9.95	50 (30-70)
Pathological tumor size after NACT (mm)		31±16.50	30 (0-60)
Number of removed lymph node[1]		55.1±27.49	51 (11-160)
Number of metastatic lymph node[1]		4±3.98	2.5 (1-15)
		n	%
FIGO 2009 stage	IB2	26	83.9
	IIA2	3	9.7
	IIB	2	6.5
Tumor size according to FIGO 2018 stage	<2 cm	-	-
	≥2 cm to <4 cm	1	3.2
	≥4 cm	30	96.8
Pathology	Squamous cell carcinoma	28	90.3
	Adenocarcinoma	2	6.5
	Adenosquamous	1	3.2
NACT protocol	Cisplatin and 5-fluorouracil	25	80.6
	Carboplatin and paclitaxel	2	6.5
	Cisplatin and UFTTM	4	12.9
Number of cycles	2	11	35.5
	3	20	64.5
Shrinking in tumor size	Tumor size increased	1	3.2
	Tumor size not changed	3	9.7
	<25%	2	6.5
	≥25% to <50%	16	51.6
	≥50%	9	29
Lymph node metastasis[1]	Negative	21	55.3
	Positive	17	44.7
Site of metastatic lymph node[1]	Only pelvic	10	23.3
	Only para-aortic	1	2.3
	Pelvic and para-aortic	3	7
	Not reported	3	7
Parametrial involvement	Negative	25	80.6
	Positive	6	19.4
Surgical border invasion	Negative	30	96.8
	Positive	1	3.2
Lymphovascular invasion	Negative	16	51.6
	Positive	11	35.5
	Not reported	4	12.9

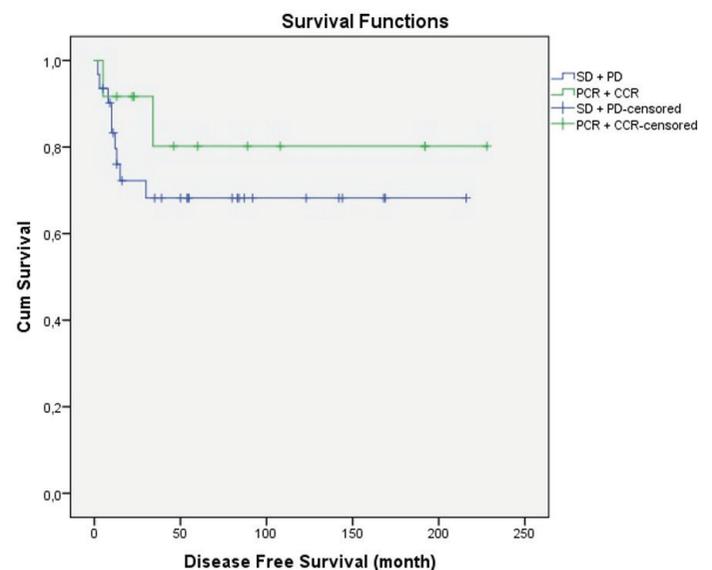|			
Adnexal metastasis	Negative	25	80.6
	Positive	1	3.2
	Not reported	5	16.1
Depth of the stromal invasion	≤1/2	12	38.7
	>1/2	16	51.6
	Not reported	3	9.7
Endometrial/uterine invasion	Negative	24	77.4
	Positive	4	12.9
	Not reported	3	9.7
Adjuvant radiotherapy	Not received	7	22.6
	Received	24	77.4
Type of adjuvant radiotherapy	Only radiotherapy	2	6.8
	Concomitant chemoradiotherapy	19	61.3
	Not reported	3	9.7

[1] Lymph node metastasis evaluated in 38 patients (31 patients underwent radical hysterectomy+lymphadenectomy and seven patients underwent extraperitoneal/transperitoneal lymphadenectomy+radiotherapy), SD: Standard deviation, NACT: Neoadjuvant chemotherapy, FIGO: Federation of Gynecology and Obstetrics

Table 3. Factors predicting clinical response

Factors		SD+PD n (%)	CCR+PCR n (%)	p
Age[1]	≤48 years	16 (72.2)	6 (27.3)	0.845
	>48 years	14 (70)	6 (30)	
FIGO 2009 stage	I	18 (64.3)	10 (35.7)	0.119
	II	13 (86.7)	2 (13.3)	
Tumor size before NACT[1]	≤50 mm	19 (79.2)	5 (20.8)	0.245
	>50 mm	12 (63.2)	7 (36.8)	
NACT combination	CF	27 (75)	9 (25)	0.335
	Others[2]	4 (57.1)	3 (42.9)	
Number of NACT cycles	2	14 (87.5)	2 (12.5)	0.083
	3	17 (63)	10 (37)	
Histopathologic type	Squamous cell	28 (71.8)	11 (28.2)	0.892
	Others[3]	3 (75)	1 (25)	

[1]Median value, [2]Carboplatin and paclitaxel, cisplatin and UFT™, [3]Adenocancer+adenosquamous cell cancer, CCR: Complete clinical response, PCR: Partial clinical response, SD: Stabile disease, PD: Progressive disease, NACT: Neoadjuvant chemotherapy, CF: Cisplatin and 5-fluorouracil, FIGO: Federation of Gynecology and Obstetrics

Figure 1. Disease-free survival and clinical response

CCR: Complete clinical response, PCR: Partial clinical response, SD: Stable disease, PD: Progressive disease

Discussion

NACT is the standard treatment in especially breast and head-neck cancers and in many other solid tumors. Despite years of experience, the value of NACT in the treatment of CC is still undetermined.

In theory, NACT is expected to increase the operability by decreasing the tumor size and to improve the surgical prognostic factors by destroying micrometastasis. CT given before the RH and RT, which damage the circulation of the tissues, is thought

stage CC. After NACT, these studies have reported that the CCR rates ranged from 0% to 50%, whereas CCR + PCR rates ranged from 45% to 95%[12,15-46]. In the survival analysis, the 5-year OS and DFS rates varied between 28% and 92.1% and from 29% to 85%, respectively[12,15,19,20,24-26,28,30,34,35,39-42,44-52]. The results of the present study were analyzed in the light of these literature data.

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Table 4. Effects of clinical and pathological parameters on disease-free survival

Clinical and pathological parameters		5-year disease-free survival (%)	p
Age[1]	≤48 years	86	0.141
	>48 years	61	
FIGO 2009 stage	I	73	0.710
	II	72	
Histopathologic type	Squamous cell cancer	72	0.866
	Others2	67	
NACT protocol	Cisplatin and 5-fluorouracil	76	0.233
	Others3	57	
Treatment after NACT	Surgery	72	0.841
	Radiotherapy	74	
Rate of decrease in tumor size after NACT	Did not decreased	86	0.304
	<25%	50	
	≥25%, <50%	70	
	≥50% (with gross tumor)	73	
	No gross tumor (clinically)	100	
Clinical response	SD+PD	68	0.374
	CCR+PCR	80	
Number of courses	2	67	0.530
	3	74	
Tumor size before NACT (mm)[1]	≤50	77	0.396
	>50	66	
Tumor size after NACT (mm)[1]	≤30	78	0.238
	>30	64	
Lymph node metastasis[4]	Negative	67	0.326
	Positive	81	

[1]Median value, [2]Adenocancer+adenosquamous cell cancer, [3]Carboplatin/paclitaxel, cisplatin/UFT™
[4]Lymph node metastasis evaluated in 38 patients (31 patients underwent radical hysterectomy+lymphadenectomy and seven patients underwent extraperitoneal/transperitoneal lymphadenectomy+radiotherapy), NACT: Neoadjuvant chemotherapy, SD: Stable disease, PD: Progressive disease, CCR: Complete clinical response, PCR: Partial clinical response, FIGO: Federation of Gynecology and Obstetrics

to be having more robust antitumoral effects.

Some of the studies have supported this theoretical approach. These studies, which were generally phase II studies, have shown that NACT improved surgical prognostic factors[19,47,49,53]. However, recent reports that compare the NACT followed by RH and RH alone do not show this improvement[12,19,40,46-49,54].

Studies have reported that CCR obtained by NACT ranged from 0% to 50% (OCR, 25-95%) (Table 5). After NACT, 28-100% of the patients became eligible for surgery[16-21,28,29,31,33,40,42,46,48,49,55]. One of the reasons of the variability of these rates is the non-homogeneity of the stages analyzed in the studies. In most of these studies, patients had locally advanced CC ranging from stage IB2 to IVA. However, the response after NACT is directly correlated to the disease stage. In a meta-analysis, Eddy et al.[15] reported that the CCR of 28% in stage IB2-IIA decreases to 7% in stage IV. Similar results were reported in other studies[23,25,30,43,50].

The operability rates change parallel to the clinical response, and stage is also a determining factor. Dueñas-Gonzales et al.[30] showed that operability is 83% in stage IB2, 60% in stage IIB, and 40% in stage IIIB. Gadducci et al.[43] also reported that operability decreases in the advanced stage. These studies have revealed that NACT is inappropriate for CC in advanced stage because of the high probability of RT need, which should be limited to early disease stages.

In the study by Li et al.[46], the DFS [hazard ratio (HR) 0.4, 95% confidence interval (CI) 0.1-08%; p=0.027] and OS (HR: 0.1, 95% CI: 0.01-0.8; p=0.026) rates were better in complete clinical responders than in non-responders. In the present study, the 5-year DFS rate was 80% in responders and 68% in non-responders. Similar results are demonstrated in other studies[8,56]. By contrast, Pat CR determines the survival, which varied from 0% to 26%[12,16,17,19,20,23,25,34,36,46,55].

Similar to response and operability, reported survival rates are varied (Table 6). The 5-year DFS and OS rates varied between 29% and 85% and 28% and 92.1%, respectively[12,19,25,40,42,46,48,51,52]. Our results are within this wide range (5-year DFS, 72%; 5-year OS, 87%). Lymph node metastasis, disease stage, parametrial involvement, stromal invasion, surgical border positivity, lymphovascular space invasion, histologic type, Pat CR, and tumor size before and after treatment carry prognostic significance for survival. An et al.[57] reported that deep stromal invasion, lymph node metastasis, and tumor size after NACT affect the OS rate (p<0.05). The authors also showed that stromal invasion was an independent risk factor of DFS rate (p<0.05), and the OS rate was significantly affected by tumor size >3 cm after NACT in a multivariate analysis. In the present study, none of risk factors were significant in the survival analysis.

Understanding the place of the NACT is difficult owing to the variability of the reported results. The non-homogeneity of the study group in terms of stages is one of the reasons of the variability. Survival after NACT is lower in advanced stages[25,58-60], and NACT has not any contribution to survival in these stages[30]. Results of the studies in which study group consisted of patients with only stage IB2 disease were very variable (Table 6)[12,15,19]. One of the reasons is the uncertainty of the clinical staging.

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Table 5. Clinical response rates after NACT reported in studies

Author	Stage	Neoadjuvant chemotherapy protocol	Interval (day)	CCR (%)	PCR (%)	SD (%)	PD (%)
Eddy et al., 1995[15]	IB2	Cis+vinc, 3 cycles	10 d	6	76	15	3
Lacava et al., 1997[16]	IIB-IVA	Vineralbine, 12 doses	7 d	5	40	38	17
Giardina et al., 1997[17]	IB2-IIIB	Cis, 4 doses	7 d	28	57	15	
Fujiwaki et al., 1997[18]	IIB	Cis+peplo or doxo, 1 cycle	-	4	75	21	
Serur et al., 1997[19]	IB2	Cis+MTX+bleo, 3 cycles / Cis+vinc+bleo, 3 cycles	21 d / 10 d	10	80	10	
Zanetta et al., 1998[20]	IB2-IVA	Cis+ifos+pacli, 3 cycles	21 d	28.9	55.3	13.2	2.6
Sugiyama et al., 1999[21]	IIIB	Cis or carb+peplo, 2 cycles	21 d	7.1	60.7	32.1	0
Sugiyama et al., 1999[22]	IB2-IIIB	Cis+irinotecan, 2 or 3 cycles	28 d	13	65	17	4
Pignata et al., 1999[23]	IB2-IVB	Cis+vineralbine, 3 cycles	21 d	22	42	18	18
Chang et al., 2000[24]	IB2-IIA	Cis+vinc+bleo, 3 cycles	10 d	23.5	55.8	13.2	4.4
Etcheverry et al., 2000[25]	IB2-IIIB	Cis+ifos+5-FU, 3 cycles	21 d	30	55	10.6	4.4
Hwang et al., 2001[26]	IB2-IIB	Cis+vinc+bleo, 3 cycles	21 d	50	43.7	6.3	0
Aoki et al., 2001[27]	IB2-IIB	Cis+vinc+peplo, 2 cycles	21 d	0	86	14	0
Aoki et al., 2001[28]	IB-III	Cis(IA)+5-FU(IA), 2 or 3 cycles	21 d	0	64	27	9
Porzio et al., 2001[29]	IB2-IIB	Cis+vinc+bleo, 3 doses	7 d	70		30	0
Dueños-Gonzales et al., 2001[30]	IB2-IIIB	Cis+gemci, 3 cycles	21 d	7.5	87.5	5	
D'Agostino et al., 2002[31]	IB2-IVA	Cis+pacli+epir, 2 or 3 cycles	21 d	19	59.5	12	9.5
Napolitano et al., 2002[32]	IB-IIIB	Cis+vinc+bleo, 3 cycles	21 d	22.6	56.6	20.8	
Dueños-Gonzales et al., 2003[33]	IB2-IIIB	Oxalip+gemci, 3 cycles	21 d	30	50	10	10
Dueños-Gonzales et al., 2003[34]	IB2-IIIB	Carb+pacli, 3 cycles	21 d	9	86	5	
Huang et al., 2003[35]	IB2-IIA	Cis+vinc+bleo, 3 cycles	10 d	18.1	61.3	20.6	0
Termrungruanglert et al., 2005[36]	IB2	Cis+gemci, 2 cycles	21 d	33.3	55.5	11.1	0
Fuso et al., 2005[37]	IB2-IIB	Cis-based CT*, 3 cycles	21 d	24.7	39.7	35.6	
Choi et al., 2006[38]	IB1-IIA	Cis+5-FU, 2 or 3 cycles	21 d	16	50	34	0
Eddy et al., 2007[12]	IB2	Cis+vinc, 3 cycles	10 d	15	37	45.5	2.3
Gong et al., 2012[39]	IB2-IIB	Cis-based protocols, 1 or 3 cycles	Change*	4	86	10	
Katsumata et al., 2013[40]	IB2-IIB	Cis+mit+bleo, 2 or 4 cycles	21d	66		34	
Angioli et al., 2015[41]	IB2-IIB	Cis+pacli, 3 cycles	21 d	84.6		15.3	
Lee et al., 2016[42]	IB-IIB	Cis-based protocols (1 or 8 cycles)	Change*	84.6		15.3	
Gadducci et al., 2017[43]	IB-IVA	Cis+pacli, 6 cycles	7 d	35.2	47.1	17.7	0
Gadducci et al., 2018[44]	IB2-IIB	Cis-based protocols, 3 or 6 cycles	Change*	11	70.7	18.3	
Mori et al., 2019[45]	IB2-IIB	Irinotecan+nedaplatin, 2 cycles	21d	62.5		9.4	
Li et al., 2019[46]	IB2-IIB	Cis-based protocols	Change*	9	57	37	
Our study	IB2, IIA2, IIB	Cis-based protocols, 2 or 3 cycles	Change*	9.3	18.6	69.9	2.3

* Interval changes according to protocols, CCR: Complete clinical response, PCR: Partial clinical response, SD: Stable disease, PR: Progressive disease, Cis: Cisplatinum, Vinc: Vincristine, Peplo: Peplomycin, Doxo: Doxorubicin: Ifos: Ifosfamide, Bleo: Bleomycin, Pacli: Paclitaxel, MTX: Methotrexate, 5-FU: 5-fluorouracil, Gemci: Gemcitabine, Epir: Epirubicin, Mit: Mitomisin, IA: Intra-arterial infusion

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Table 6. Survivals rates obtained by neoadjuvant chemotherapy

Author	Stage	Neoadjuvant chemotherapy protocol	Interval (day)	Time for survival	DFS (%)	OS (%)
Eddy et al., 1995[15]	IB2	Cis+vinc, 3 cycles	10 d	2 years	85	88
Kim et al., 1989[47]	IB2-IIIB	Cis+vinb+bleo, 3 cycles	21 d	2 years	94	94
Behtash et al., 2006[48]	IB2-IIA	Cis+vinc, 3 cycles	10 d	3 years	44	56
				5 Years	29	28
Eddy et al., 2007[12]	IB2	Cis+vinc, 3 cycles	10	3 years	59.7	NR
				5 years	56.2	NR
Etcheverry et al., 2000[25]	IB2-IIIB	Cis+ifos+5-FU, 3 cycles	21 d	5 years	78	78
Serur et al., 1997[19]	IB2	Cis+MTX+bleo, 3 cycles	21 d	5 years	80	80
		Cis+vinc+bleo, 3 cycles	10 d			
Sardi et al., 1997[49]	IB1-IB2	Cis+vinc+bleo, 3 cycles	10 d	7 years	88	82
Hwang et al., 2001[26]	IB2-IIB	Cis+vinc+bleo, 3 cycles	21 d	10 years	80	97.5
Zanetta et al., 1998[20]	IB2-IVA	Cis+ifos+pacli, 3 cycles	21 d	Median f-u:16 months	76	94
Duenas-Gonzales et al., 2003[34]	IB2-IIIB	Carb+pacli, 3 cycles	21 d	Median f-u:21 months	79	79
Duenas-Gonzales et al., 2001[30]	IB2-IIIB	Cis+gemci, 3 cycles	21 d	Median f-u:28 months	55	62
Aoki et al., 2001[28]	IB-III	Cis+5-FU (IA), 2 or 3 cycles	21 d	Median f-u:30 months	18.2	27.3
Chang et al., 2000[24]	IB2-IIA	Cis+vinc+bleo, 3 cycles	10 d	Median f-u:39 months	69	79
Buda et al., 2005[50]	IB2-IVA	Cis+ifos+pacli, 3 cycles	21 d	Median f-u:43 months	74	75
		Cis+ifos, 3 cycles			70	63
Huang et al., 2003[35]	IB2-IIA	Cis+vinc+bleo, 3 cycles	10 d	Median f-u:49 months	65	69
Yin et al., 2011[51]	IB2-IIB	Cis-based protocols, 2 or 3 cycles	Change*	5 years	85	88.7
Gong et al., 2012[39]	IB2-IIB	Cis-based protocols, 1 or 3 cycles	Change*	2 years	93	95.5
Katsumata et al., 2013[40]	IB2-IIB	Cis+mit+bleo, 2 or 4 cyles	21 d	5 years	59.9	70
Angioli et al., 2015[41]	IB2-IIB	Cis+pacli, 3 cycles	21 d	4 years	80	84
Lee et al., 2016[42]	IB-IIB	Cis-based protocols (1 or 8 cycles)	Change*	5 years	75.6	92.1
Gupta et al., 2018[52]	IB2-IIB	Cis+pacli, 3 cycles	21 d	5 years	69.3	75.4
Gadducci et al., 2018[44]	IB2-IIB	Cis-based protocols, 3 or 6 cycles	Change*	Median f-u:89 months	72	77
Mori et al., 2019[45]	IB2-IIB	Irinotecan+nedaplatin, 2 cycles	21 d	5 years	78.8	89.7
Li et al., 2019[46]	IB2-IIB	Cis-based protocols	Change*	5 years	70	75
Our study	IB2, IIA2, IIB	Cis-based protocols, 2 or 3 cycles	Change*	5 years	72	87

*Interval changes according to protocols, DFS: Disease-free survival, OS: Overall survival, NR: Not reported, median f-u, median follow-up, Cis: Cisplatinum, Vinc: Vincristine, Vinb: Vinblastine, Ifos: Ifosfamide, Bleo: Bleomycin, Pacli: Paclitaxel, MTX: Methotrexate, 5-FU: 5-fluorouracil, Gemci: Gemcitabine, IA: Intra-arterial

The diversity of the CT protocols may be another reason for the variability of the results. CT protocols do not affect response and survival because many of them are cisplatin-based[55]. A multicenter randomized phase III trial in Italy comparing cisplatin/ifosfamide/paclitaxel combination with cisplatin/ifosfamide showed that triple NACT protocol improved the CCR significantly (20% and 9%)[50]. No difference was found between the two C protocols in terms of the operability and survival. In a randomized controlled study by Yang et al.[61], NACT combination irinotecan plus cisplatin (IP group) and paclitaxel plus cisplatin (TP group) were compared. The authors reported no difference between the two groups in terms of OS and DFS (OS, p=0.212; DFS, p=0.296).

Data related to the CF combination are generally derived from concurrent chemoradiotherapy. The reported Pat CR changed from 40% to 67.5%[62-64]. However, there is a limited number of

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studies that have used this NACT. Choi et al.[38] reported that the CCR was 16% in stage IB1-IIA, the 5-year OS rate was 80.7%, and the 10-year OS was 77%. Etcheverry et al.[25] reported CCR and Pat CR of 30% and 13%, respectively (stage IB2-IIIB), in which ifosfamide was added to the CF combination. The 5-year OS was 78% in this study.

In a meta-analysis, Zhu et al.[65] included 4727 patients, in which the patients had FIGO stage IB and IIB CC and NACT combination consisted of platinum and/or taxane-based CT. Their clinical response rate ranged from 58.49% to 86.54%, and the pathological response rate ranged from 7.5% to 78.81%. Moreover, Zhu et al.[65] indicated that clinical and pathologic responses were associated with a favorable prognosis. Meng et al.[66] compared NACT+RH with RH. As NACT combination, cisplatin plus paclitaxel were implemented. The clinical response rate (CCR+PR) was 80.5% in the RH group and 91.2% in the NACT+RH group (p=0.048). In our study, which includes stage IB2-IIB, the CCR was 9.3%, the Pat CR was 6.9%, and the 5-year OS rate was 87%.

NACT for cervical cancer meta-analysis collaboration reevaluated the data of 21 phase III trials performed between 1975 and 2000 and reported them in a meta-analysis[11]. Results are divided into the two groups. Studies that compared NACT followed by RT (NACT+RT) and RT alone (16 studies, n=2.074) were included in the first group, and studies that compared NACT+RH and RH (5 studies, n=872) were included in the second group. After the assessment of the second group, NACT + RH decreased the mortality rate by 35% and improved the survival by 12% when compared with the RT group. Only two of the five studies in the second group included stage IB2 tumors[24,55]. Benedetti-Panici et al. [55] defined the survival advantage by NACT in stage IB2 disease in the subgroup analysis, but Chang et al.[24] did not show any advantage. In addition, Chang et al.[24] showed that clinical response was higher in the RT group, but Sardi et al.[49] showed that the clinical response was better in the NACT group than in NACT+RH+adjuvant RT and RH+adjuvant RT groups. Recently, Zou et al.[67] published a meta-analysis involving 2.270 patients with stage IB2-IIB CC and evaluating the efficacy of concurrent chemoradiation and NACT followed by radical surgery (NACT+RH). They stated that compared with the concurrent chemoradiation group, the NACT+RH group did not have a survival advantage (OS, p=0.07; DFS, p=0.82)[67]. Patients receiving NACT with concurrent chemoradiation were compared in another randomized phase II study, and authors revealed that prognosis in the concurrent chemoradiation group was more favorable than that in the NACT group (DFS, HR 1.84, 95% CI 1.04-3.26, p=0.033; OS, HR 2.79, 95% CI 1.29-6.01, p=0.006)[68]. European Organisation for Research and Treatment of Cancer (ClinicalTrials.gov identifier: NCT00039338) investigated the effect of NACT+RH against concurrent chemoradiation in patients with stage IB2-IIB disease using cisplatin-based CT regimens. Unfortunately, some of its data are still not yet published. The results of this study will shed light on the management of these patient groups.

Aoki et al.[27] compared NACT+RH and RH alone (stage IB-IIB) and reported that the pathological prognostic factors and survival were better in the NACT group. Similar results were also reported by Namkoong et al.[69] (stage IB-IIB). By contrast, in their randomized controlled trial, Yang et al.[61] showed that pathologic prognostic factors were improving in the NACT group, but it does not affect the survival. Yang et al.[54] found similar survival results between the NACT+RH and RH groups in their meta-analysis of 16 studies. A retrospective study[48] compared NACT+RH and RH alone in early-stage CC, and a prospective phase III study by GOG[12] was published. These studies concluded that NACT has no place in the treatment of early-stage CC. In the study of GOG, surgical prognostic factors and survival in stage IB2 tumors were not improved by NACT (cisplatin/vincristine, every 10 days, three courses). The 5-year OS was 56.2% in the NACT group and 53.8% in the RH group[12].

An article compared the effectiveness of NACT or primary RH in patients with stage 1B2 CC previously treated in our clinic[70]. In this study, 24 patients who received NACT followed by radical surgery were compared with 15 patients who underwent primary radical surgery. Patients were divided into three groups, including RH alone, NACT unresponder group, and NACT responder group. No difference was found between these groups in terms of recurrence, DFS, and OS.

Study Limitations

The retrospective design is the most critical limitation of the present study. Moreover, improvements in surgical and adjuvant therapy modalities over years may affect the results. In addition, the small sample size and the fact that NACT was not compared with other treatment methods (RH, CCRT, etc.) also limited the interpretation of the results. As strengths, detailed clinical-pathological characteristics and adjuvant treatments of the patients were evaluated. Pathologic examinations were performed by experienced gynecological pathologists. Follow-up periods of the patients were long. Additionally, the results were revised in the light of various relevant studies published in the literature.

Conclusion

The value of NACT in the treatment of CC is still being debated and discussed. At present, it is thought that NACT may be used in locally advanced CC, but results reveal that this is not feasible. By contrast, we think that new drugs, new combinations, and new protocols of NACT could achieve successful treatment of CC, as in theory.

Ethics

Ethics Committee Approval: This study was approved by the Etlik Zübeyde Hanım Women's Health Training and Research Hospital Ethical Committee (file no. 90057706-799/08; 05.06.2020).

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Informed Consent: Medical records of patients with stage IB2, IIA2, or IIB CC between 1998 and 2020 were reviewed retrospectively.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Concept: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Design: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Data Collection or Processing: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Analysis or Interpretation: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Literature Search: C.Ç., F.K., R.D., D.Y., M.Ü., V.K., Ç.K., G.K.C., N.B., O.T., S.K., T.T., Writing: C.Ç., R.D., V.K., O.T., T.T.

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