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Assessment of primary radical hysterectomy and neoadjuvant chemotherapy followed by radical hysterectomy in Stage IB2, IIA bulky cervical cancer

A. Musaev[1], A.B. Guzel[1], G. Khatib[1], U.K. Gulec[1], M.A. Vardar[1], A. Altıntas[1], D. Gumurdulu[2]

[1] Department of Obstetrics and Gynecology, Faculty of Medicine, Cukurova University, Adana
[2] Department of Pathology, Faculty of Medicine, Cukurova University, Adana (Turkey)

Summary

Objective: Uncertainty concerning the treatment of Stage IB2-IIA (bulky) cervical cancer is still continuing. In this study, an analysis of Stage IB2-IIA (bulky) cervical cancer was performed. The efficacy of primary radical surgery and neoadjuvant chemotherapy followed by a radical surgery was investigated. *Materials and Methods:* Medical data of 50 patients who were diagnosed with Stage IB2-IIA (bulky) cervical cancer and treated between 2002-2009 were retrospectively assessed. In the radical surgery group, radical hysterectomy + bilateral pelvic + para-aortic lymphadenectomy were performed. In the neoadjuvant chemotherapy group, a combination of cisplatin/topotecan or paclitaxel/carboplatin was given to the patients and then radical surgery was performed. Each group was evaluated individually. Prognostic factors were determined and survival rates were compared between the groups. A p value was taken < 0.05 for the statistical significance level for all results. *Results:* Radical surgery after neoadjuvant chemotherapy was performed in 21 and primary radical surgery in 29 patients. Median follow-up time was 36.0 ± 14.0 months. Average of the tumor size before treatment was 50.2 ± 7.6 mm. In the radical surgery after neoadjuvant chemotherapy group, lymphovascular space invasion (LVSI) and tumor size (before and after treatment) were determined to be significant factors for each of disease-free survival (DFS) and overall survival (OS). On multivariate analysis, tumor size (before treatment) was found to be an independent prognostic factor for both of DFS ($p = 0.006$) and OS ($p = 0.010$). No significant difference in survival periods was observed among the groups. *Conclusion:* There was no significant superiority among the two treatment options. Nonetheless, further studies are needed to compare the multimodal approaches in these stages of cervical cancer.

Key words: Stage IB2-IIA (bulky) cervical cancer; Neoadjuvant chemotherapy; Radical hysterectomy.

Introduction

The treatment modality for cervical cancer depends on the status of the disease at the time of diagnosis. Whereas surgery is the current treatment approach for early-stage cervical cancer (Stage IA-IB1), the optimal treatment modality for Stage IB2 and bulky IIA (locally advanced) cervical cancers is not clear yet [1]. The five-year survival rate exceeds 90% in patients with Stage IA-IB1, while it ranges from 31% to 48% in Stage IB2 and bulky IIA [2]. Therefore, it seems necessary to improve novel treatment modalities in locally-advanced cervical cancer cases.

The current treatment strategies for the locally-advanced cervical cancer (LACC) are; primary chemoradiation primary radical hysterectomy (PRH) ± chemoradiotherapy and neoadjuvant chemotherapy followed by radical hysterectomy (NACT-RH) ± chemoradiotherapy [3]. The ability to protect the ovaries is the main advantage of PRH treatment modality against radiotherapy. However, adjuvant radiotherapy (ART) should be considered according to the final pathologic result. In order to improve the outcomes of PRH in locally-advanced cervical cancers, NACT-RH has been studied over the past two decades. NACT was suggested to achieve shrinkage in tumor size and thus make the surgery more appropriate, which in turn would yield ART to be avoided. On the other hand, a delay in surgery, protracted treatment, and increased repopulation of resistant cancer cells should be noticed as disadvantages of NACT-RH treatment modality [4].

In this study, the authors reviewed retrospectively the cervical cancer patients who were operated at their center between 2002-2009. Stage IB2-IIA (bulky) cases' medical data were screened and those who underwent PRH or NACT-RH were evaluated individually. Subsequently, prognostic factors affecting survival were determined and survival rates were compared between the groups.

Materials and Methods

Approval to conduct this study was provided by the Research Ethics Committee at Çukurova University Faculty of Medicine. In this study, patients in Stage IB2-IIA (bulky) cervix cancer who were treated with PRH or with RH after NACT at the Gynecologic Oncology Unit of the University Hospital of Çukurova University between January 1, 2002 and December 30, 2009 were investigated.

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Table 1. — *Patient characteristics.*

Parameter		PRH n (%)	NACT-RH n (%)	*p*	Total n (%)
Age (year)		53.3 ± 9.9	52.9 ± 8.8	0.882	53.1 ± 9.4
Stage	IB2	21 (71.4)	15 (72.4)	0.765	36 (72)
	IIA	8 (28.6)	6 (27.6)		14 (28)
Grade	1	5 (17.2)	1 (4.8)	0.768	6 (12)
	2	21 (72.4)	18 (85.7)		39 (78)
	3	3 (10.3)	2 (9.5)		5 (10)
Number of removed lymph nodes		35.8 ± 12.6	36.2 ± 16.0	0.415	36.0 ± 14.0
Tumor size before treatment (mm)		49.8 ± 7.8	50.7 ± 7.4	0.661	50.2 ± 7.6
Histology	Squamous carcinoma	25 (86.2)	20 (95.2)	0.438	45 (90)
	Adenocarcinoma	2 (6.9)	0 (0.0)		2 (4)
	Adenosquamous carcinoma	2 (6.9)	1 (4.8)		3 (6)
Recent status	Alive free disease	21 (72.4)	15 (71.4)	0.549	36 (72)
	Alive with disease	1 (3.4)	0 (0.0)		1 (2)
	Died	7 (24.2)	6 (28.6)		13 (26)
Follow-up (months)	61.9 ± 35.4	36.2 ± 16.0	0.827	36.0 ± 14.0	
Stromal invasion	No n (%)	0 (0.0)	5 (23.8)	0.019	5
	< 1/2 n (%)	12 (41.4)	8 (38.1)		20
	> 1/2 n (%)	17 (58.6)	8 (38.1)		25

Patients' archival files were reviewed. Their demographic, clinical and surgical characteristics, pathological findings, and treatment modalities were evaluated. Patients were divided into two groups: PRH group and NACT-RH group. Fifty patients, 29 from the PRH group and 21 from the NACT-RH group, were included.

Clinical stage was determined by clinical evaluation, magnetic resonance imaging (MRI), and chest X-ray. Intravenous pyelography, cystoscopy, and proctosigmoidoscopy were performed as deemed appropriate. Tumors were staged according to the International Federation of Gynecology and Obstetric (FIGO) 1995 criteria. In the PRH group, type III hysterectomy + bilateral salpingo- oophorectomy (except one patient whose ovaries were preserved) + bilateral pelvic para-aortic lymphadenectomy (BPPLND) were performed. Para-aortic dissection was applied to the renal vein on the left side and to the gonadal vein on the right. In the NACT-RH group, a combination of cisplatin/topotecan or paclitaxel/carboplatin was given to the patients. The combination of cisplatin/ topotecan was repeated every 28 days. Cisplatin (50 mg/m²) was given in the first day and topotecan (0.75 mg/m²) was given in the first three days. On the other hand, the combination of paclitaxel (175 mg/m²) /carboplatin (5 AUC) was repeated every 21 days and both of the agents were applied in the first day. Patients underwent radical surgery following three cycles of NACT. The same surgical procedure described for the PRH group was performed. Postoperative ART was given to the high-risk patients in both groups. High-risk patients were defined as those who had at least one of the following major findings: positive lymph nodes, parametrial invasion, positive surgical margin and ≥ four cm tumor size, or two or more of the following intermediate findings: lymphovascular space invasion (LVSI), > 1/2 stromal invasion, and two to four cm tumor size.

Follow-up controls were made every three months in the first two years and, subsequently, every six months until the fifth year and then annually. Disease-free survival (DFS) was considered as the period between the operation time and relapse or recurrence dates. Overall survival (OS) was considered as the period between the pathological diagnosis and death dates. Survival times were expressed in months. Each group was assessed individually. Their prognostic factors were determined and then survival rates were compared between the groups.

Statistical methodology

SPSS 17.0 Evaluation Version (Statistical Package for Social Sciences) software package was used in the statistical analysis of the data. Categorical variables were compared using Chi-square or Fisher test. Continuous variables with normal distribution were analyzed using the *t* test. Mann Whitney U test was used in the analysis of the continuous variables with abnormal distribution. Univariate analysis of survival rates were carried out by the Kaplan-Meier method and multivariate analysis by the Cox regression method. Log rank test was performed to compare the survival curves between groups. For all tests, $p < 0.05$ was considered statistically significant.

Results

A total of 50 patients were enrolled for this study: 29 were in the PRH and 21 in the NACT-RH group. Patients' characteristics are demonstrated in Table 1. The average age for all patients was 53.1 ± 9.4 (31 - 73) years . Mean of follow-up period was 36.0 ± 14.0 (4 - 119) months. There was no significant difference between groups according to age, stage distribution, grade, removed lymph nodes' number, tumor size before treatment, histological type, and follow-up period.

There were 29 cases in the PRH group and the mean age of these patients was 53.3 ± 9.9 (31 - 73) years . The average of follow-up period was 61.9 ± 35.4 (4 - 119) months . Twenty-five (86.2%) of the cases were with squamous carcinoma histology. Mean of the tumor size before treatment was 49.8 ± 7.8 (40-70) mm. FIGO stage was IB2 in 21 (71.4%) cases and bulky IIA in eight (28.6%) patients. Mean number of the removed lymph nodes (LN) was 35.8 ± 12.6 (15-64) and mean number of the metastatic ones was seven. As adjuvant treatment, only RT was given to 11 (37,9%) patients and chemoradiotherapy (CRT) was administered to ten (34.5%) patients.

Table 2. — *Pathologic findings of PRH group.*

Pathological risk factors		Recurrence		*p*	DFS (months)	*p*	OS (months)	*p*
		Negative n (%)	Positive n (%)					
Parametrial involvement	Negative	21 (72.4)	8 (27.6)	-	58.7 ± 38.6	-	61.9 ± 35.4	-
	Positive	0(0)	0(0)			-		-
LN metastasis	Negative	19(76)	6(24)	0.692	56.9±38.2	0.539	59.8 ± 36.1	0.355
	Positive	2(50)	2(50)		70.0±453		77.5 ± 30.6	
Positive surgical margin	Negative	21(72.4)	8(27.6)	-	58.7±38.6	-	61.9 ± 35.4	-
	Positive	0(0)	0(0)		-		-	
LVSI	Negative	9(90)	1(10)	0.135	75.2±39.2	0.096	77.2 ± 35.9	0.094
	Positive	12(47.1)	7(87.5)		50.1±36.4		53.9 ± 33.3	
Endometrial involvement	Negative	16(76.2)	5(23.8)	0.382	57.3±39.5	0.752	60.6 ± 36.4	0.738
	Positive	5(62.5)	3(37.5)		62.5±38.5		65.6 ± 34.7	

Table 3. — *Treatment and pathological features of NACT-RH group.*

Parameter		Recurrence		*p*	DFS (months)	*p*	OS (months)	*p*
		Negative n (%)	Positive n (%)					
NACT regimen	Cisplatin + topotecan	11(74.7)	6 (35.3)	0.228	57.3 ± 36.4	0.938	60.8 ± 31.7	0.788
	Paclitaxel + carboplatin	4 (100)	0 (0)		55.7 ± 39.5		55.7 ± 39.5	
Parametrial involvement	Negative	15 (71.4)	6 (28.6)	-	57.1 ± 35.9	-	59.8 ± 32.3	-
	Positive	-	-		-		-	
LN metastasis	Negative	13 (76.5)	4 (23.5)	0.316	61.5 ± 36.0	0.203	64.5 ± 31.8	0.172
	Positive	2 (50)	2 (50)		37.5 ± 30.9		39.2 ± 29.7	
Positive surgical margin	Negative	15 (71.4)	6 (28.6)	-	57.1 ± 35.9	-	59.8 ± 32.3	-
	Positive	-	-		-		-	
LVSI	Negative	10 (100)	0 (0)	0.009	75.1 ± 24.5	0.024	75.1 ± 24.5	0.035
	Positive	5 (45.5)	6 (54.6)		40.6 ± 37.6		45.9 ± 33.2	
Endometrial involvement	Negative	13 (86.7)	2 (13.3)	0.031	65.1 ± 34.1	0.104	67.1 ± 30.8	0.105
	Positive	2 (33.3)	4 (66.7)		36.8 ± 35.0		41.7 ± 31.5	
Tumor size (mm) before NACT	≤50	14 (93.3)	1 (16.7)	0.002	72.5 ± 26.1	0.008	72.8 ± 25.4	0.014
	>50	1 (16.7)	5 (83.3)		32.0 ± 36.9		38.6 ± 32.5	
Tumor size (mm) after NACT	≤ 30	12 (92.3)	1 (7.7)	0.014	68.1 ± 29.8	0.042	69.1 ± 28.2	0.061
	>30	3 (37.5)	5 (62.5)		34.8 ± 38.9		41.3 ± 34.1	

Table 4. — *Multivariate analysis of the clinicopathological prognostic factors.*

Parameter	DFS		OS	
	p	% 95 CI	*p*	% 95 CI
LVSI	0.113	0.022 - 1.500	0.122	0.024 - 1.554
Endometrial involvement	0.643	0.238 - 2.426	0.361	0.184 - 1.851
Depth of stromal invasion (superficial)	0.989	0.000	0.989	0.000
Depth of stromal invasion (deep)	0.759	0.391 - 3.625	0.372	0.524 - 5.617
Tumor size before treatment (mm)	0.006	1.710 - 25.427	0.010	1.548 - 25.146
Group	0.784	0.256 - 2.797	0.902	0.278 - 3.097

During follow-up, recurrence was determined in eight (27.6%) cases and DFS was 15 (2-58) months in these patients. Recurrences were pelvic in five and extra-pelvic in three cases (one liver, two liver + lungs). Patients with recurrence were treated with RT (two cases) or CT (six cases). Seven of these patients died and OS in these patients was 29.7 (4-61) months . According to the pathological assessment, neither positive parametrial involvement nor positive surgical margin was found. As pathological risk factors parametrial involvement, LN metastasis, positive surgical margin, LVSI, and endometrial involvement were evaluated. No significant impact of these factors was determined on DFS or OS (Table 2).

A total of 21 patients were included in the NACT-RH group and their mean age was 52.9 ± 8.8 (31 - 71) years . The average of follow-up period was 36.2±16.0 (11-11.5) months. Except one adenosquamous carcinoma case, all the 20 cases were in squamous carcinoma histology. A regimen of cisplatin/topotecan was administered to 17 patients and paclitaxel/carboplatin to the other four patients. Before NACT, mean tumor size was 50.7 ± 7.4 (40-70) mm and after NACT it decreased to 35 mm. Clinical stage was assessed as FIGO IB2 in 15 (72.4%) and bulky IIA in six (27.6%) cases. Mean number of dissected LN was 36.2 ± 16.0 (14 - 73) and mean number of the metastatic ones was

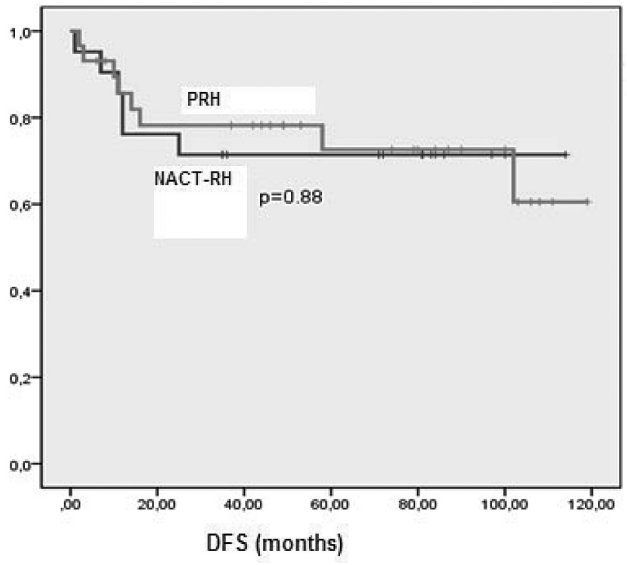

Figure 1. — Disease-free survival of the groups.

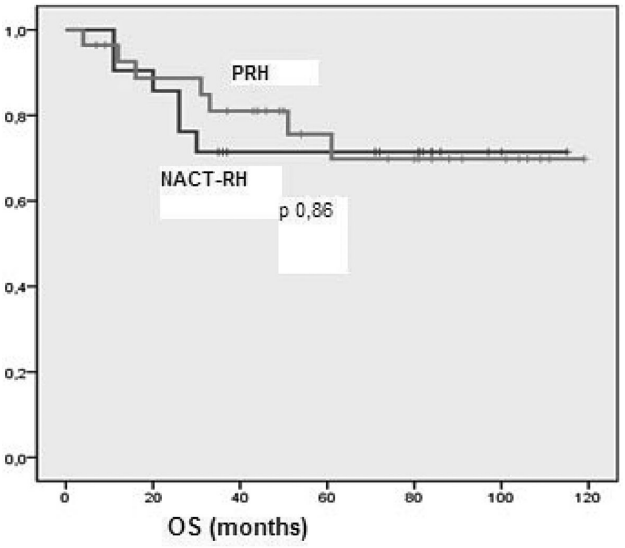

Figure 2. — Overall survival of the groups.

ten. After surgery adjuvant RT was applied to ten (47.6%) patients and CRT to four (19.0%) patients. During follow-up six (28.6%) recurrence cases were reported. DFS was calculated as 11.2 (1 - 25) months in these patients. Recurrences were determined in the pelvis in two cases. The remaining four cases' recurrences were multicentric. Recurrences were treated with RT (two cases) or CT (four cases). All patients with recurrence died and their OS was 20.7 (11- 30) months. All patients had no parametrial or surgical margin involvement, but there were positive LN in four (19%) and LVSI in 11 (52.4%) patients according to the pathological report. Whereas LVSI had significant effect on survival rates, LN involvement had none (Table 3).

While DFS and OS were found to be 58.7 ± 38.6 months and 61.9 ± 35 months in the PRH group, it was determined as 57.1 ± 35.9 months and 59.8 ± 32.3 months in the NACT-RH group, respectively. During follow up period OS rates were calculated as 75.9% in the PRH and 71.4% in the NACT-RH group. There was no significant difference in recurrence, DFS or OS between the two groups (Figures 1, 2). Among various clinicopathological factors, only tumor size before treatment had significant impact on the DFS and OS according to the multivariate analysis (Table 4).

Discussion

Efficacy of radical surgery and RT or CRT treatments in the early stage cervical cancer are similar. Five-years OS rates are about 90% for both treatment modalities [5, 6]. Recent studies have reported that patients treated with NACT-RH had close rates of OS [7, 8]. Ability of protection of the ovarian functions, less sexual dysfunction, and the possibility of keeping RT as treatment option for recurrences are important advantages of surgery in the early-stage cervical cancers. However, the probability of receiving ART in the LACC is still high. Yessaian *et al.* reported that ART was performed to 52% of Stage IB2 cervical cancer patients after radical surgery [9]. Also, a study by Finan *et al.* showed that ART was needed for 72.3% of Stage IB2 after radical surgery [10]. Further, ART was used to 84% of > four cm Stage IB2-IIA in a study by Landoni *et al.* [11]. NACT was suggested to shrink tumor volume as well as decrease metastasis. Thus, surgery would be more convenient and necessity for RT would be reduced. Hereupon, survival would be improved also. A 22-44% response rate (especially in the LACC cases), reduced metastatic LN, and increased DFS rates were reported with NACT treatment modality in the cervical cancers. Nevertheless, despite approximately 25 years of experience with NACT, its efficacy in the cervical cancer has not yet been elucidated. While some studies supported this approach, [12,13] others did not [14,15]. Complete clinical response obtained with NACT ranged between 0-50% [14, 16, 17]. NACT is given in two to four cycles before surgery and various agents have been described for this purpose. Platin-based regimens are widely used because of their well-known cytotoxic activity in the cervical cancer [18]. In the SNAP 01 and SNAP 02 named, multicentric, randomized phase III study, cisplatin/ifosfamide/paclitaxel (TIP) and cisplatin/ifosfamide (IP) combinations were compared and clinical response was found to be significantly improved with TIP protocol (9% *vs* 20%) [19]. Park *et al.* have used paclitaxel/cisplatin combination for three cycles as neoadjuvant therapy in Stage Ib2-IIb cervical cancer. After ten days from the last cycle, patients were evaluated with clinical examinations and MRI. Complete and partial

response rates were found to be 40% and 51%, respectively [20]. Cisplatin + vinkristine + bleomycin (VPB) combination was administered to the patients with ≥ Stage Ib2 cervical cancer in a study conducted by Bermudez *et al.* Authors have indicated that the response was less than 50% in the Stages IIb - IIIb and >50% in Ib2, IIa [21]. In the present study, cisplatin/topotecan and carboplatin/paclitaxel protocols were used and the response was similar to the two protocols. Complete response rate of neoadjuvant CT in the present study was 33.3%.

Various survival rates with NACT treatment modalities in the LACC are reported. Five-year DFS and OS ranged between 29-80% and 21-81%, respectively [8, 12, 15, 16, 22, 23-26]. Aoki *et al.* compared NACT-RH and PRH treatment modalities in Stage IB-IIB cervical cancer and they recorded that survival rates, surgical, and pathological risk factors were improved in the NACT-RH group [16]. Similar results were reported by Namkoong *et al.* [27] Nevertheless, Serur *et al.* stated that surgical and pathological risk factors were improved in Stage Ib2 patients, but survival was not [8]. On the other hand, according to a retrospective study by Behtash *et al.*, no positive impact was obtained with NACT in the early-stage cervical cancer [15]. Furthermore, NACT-RH *vs* PRH was assessed in a prospective phase III GOG study and authors declared that surgical, pathological risk factors, and survival was not improved in Stage Ib2 tumors with NACT arm. Five-years OS was 60.7% in the NACT and 63.3% in the PRH arm [14]. Also, in the present study no significant difference was noticed in DFS ($p = 0.877$) or OS ($p = 0.827$) rates among PRH and NACT-RH groups. Variability of the reported results and studies' not being homogeneous in terms of stage make it difficult to understand the real effect of NACT. Survival obtained from NACT arms was found to be lower in the advanced stages [27, 28]. Results of the studies conducted with only Stage IB2 are variable also [7, 8, 14]. Uncertainty created by the clinical staging might be the main reason for this condition. Applied NACT protocol also can be considered as another reason. However, most of the NACT regimens are platin-based, so it is believed that its effect on survival is minimal [22].

Rates of recurrence and survival for LACC depend on several factors including lymph node metastasis, surgical margin status, parametrial infiltration, deep stromal invasion, LVSI, and tumor size. Even though LN status does not change the stage in the cervical cancer; it has an important effect on prognosis and decision of the adjuvant therapy. Metastatic lymph nodes were associated with lower survival rates in many studies [29, 30]. There was no significant difference in DFS and OS according to the LN status in the present study. This result can be explained by the small number of patients and the fact that patients were in early stages.

Deep stromal invasion is associated with increased recurrence rate and decreased survival period [31, 32]. Salmal *et al.* found that recurrence rate was 13% in 77 cases who had > ten mm stromal invasion compared with 4% of 119 cases had < ten mm stromal invasion. Researchers stated that stromal invasion was a significant factor affecting prognosis [31]. The difference of stromal invasion between the two groups was statistically significant in the present study ($p = 0.019$). However, this observation was not confirmed by the multivariate analysis for DFS or OS.

Kristensen *et al.* have investigated the prognostic significance of the tumor size on survival and they detected that a five-year survival was 94% in the < two cm tumors and 47% in the ≥ four cm tumors [32]. In accordance with the literature, by the multivariate analysis, the present authors determined that tumor size was a significant prognostic factor for their cases.

Conclusion

In this study, no significant superiority was observed between the PRH and NACT-RH treatment options. Lack of sufficient randomized controlled studies, poor prognosis of the patients whose surgery could not be applied after NACT, and the necessity of ART after NACT for a substantial proportion of the patients were important factors which evidently decreased the tendency to apply NACT. Nevertheless, there is a need for further studies to compare the multimodal approaches in these stages of cervical cancer.

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Address reprint requests to:
G. KHATIB, M.D.
Department of Obstetrics and Gynecology
Faculty of Medicine, Çukurova University
01330 Adana (Turkey)
e-mail: ghanim.khatib@gmail.com