

The Outcome of Locally Advanced Cervical Cancer in Patients Treated with Neoadjuvant Chemotherapy Followed by Radical Hysterectomy and Primary Surgery

Azamsadat Mousavi¹, MD; Mitra Modarres Gilani¹, MD; Setareh Akhavan¹, MD; Shahrzad Sheikh Hasani¹, MD; Abbas Alipour², MD; Hamideh Gholami³, MD

¹Department of Oncology, Emam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran;

²Thalassemia Research Center, Mazandaran University of Medical Sciences, Sari, Iran;

³Department of Oncology, Mousavi Hospital, Zanjan University of Medical Sciences, Zanjan, Iran

Correspondence:

Hamideh Gholami, MD;
Ayatollah Mousavi Hospital, Gavazang,
Postal code: 45139-63615, Zanjan, Iran
Tel: +98 24 33130981

Fax: +98 24 33130001

Email: gholami@zums.ac.ir

Received: 13 July 2019

Revised: 26 July 2019

Accepted: 01 September 2019

What's Known

- As an alternative treatment for locally advanced cervical cancer, neoadjuvant chemotherapy (NACT) has been administered before radical hysterectomy to shrink large tumors.
- NACT before surgery reduces the need for postoperative radiotherapy in patients with locally advanced cervical cancer.

What's New

- Lower rate of postoperative adjuvant radiotherapy is required after preoperative NACT, particularly in young patients.
- NACT reduces the recurrence rate and increases the overall survival of patients. Favorable clinical and pathological response to NACT before radical hysterectomy according to disease stage was observed.

Abstract

Background: In recent years, before radical hysterectomy, neoadjuvant chemotherapy (NACT) has been administered to patients with locally advanced cervical cancer to shrink large tumors. It has been reported that this treatment significantly reduces the need for radiotherapy after surgery. The current study aimed to assess the outcome (survival, recurrence, and the need for adjuvant radiotherapy) of locally advanced cervical cancer in patients treated with NACT followed by radical hysterectomy and primary surgery.

Methods: In a retrospective cohort study, the records of 258 patients with cervical cancer (stage IB2, IIA, or IIB), who referred to Imam Khomeini Hospital (Tehran, Iran) from 2007 to 2017 were evaluated. The patients were assigned into two groups; group A (n=58) included patients, who underwent radical hysterectomy and group B (n=44) included those, who underwent a radical hysterectomy after NACT. The outcome measures were the recurrence rate, 5-year survival rate, and the need for adjuvant radiotherapy.

Results: The median for overall survival time in group A and B was 113.65 and 112.88 months, respectively (P=0.970). There was no recurrence among patients with stage IB2 cancer in group B, while the recurrence rate in group A was 19.5% with a median recurrence time of 59.13 months. Lymph node involvement was the only factor, that affected patients' survival. The need for postoperative adjuvant radiotherapy in group B was lower than in group A (P=0.002).

Conclusion: Neoadjuvant chemotherapy before the hysterectomy was found to reduce the need for postoperative radiotherapy in patients with locally advanced cervical cancer according to disease stages. As a direct result, adverse side effects and the recurrence rate were reduced, and the overall survival rate of patients with stage IIB cervical cancer was increased.

Please cite this article as: Mousavi A, Modarres Gilani M, Akhavan S, Sheikh Hasani S, Alipour A, Gholami H. The Outcome of Locally Advanced Cervical Cancer in Patients Treated with Neoadjuvant Chemotherapy Followed by Radical Hysterectomy and Primary Surgery. Iran J Med Sci. doi: 10.30476/ijms.2020.81973.0.

Keywords • Uterine cervical neoplasms • Hysterectomy • Recurrence • Survival

Introduction

Cervical cancer is the most frequent gynecologic malignancy and the fourth most common cancer in women worldwide. Over 5 million new cases of cervical cancer are diagnosed annually, and more than 2.5 million women die from the disease.¹ In 2012,

cervical cancer among Iranian women was ranked the twelfth leading cause of death with just under 1,000 new cases and 370 deaths.²

Primary radical hysterectomy with bilateral pelvic lymphadenectomy or primary chemoradiotherapy is the gold standard treatment for the IA2, IIA, and IIB stages of cervical cancer. Adjuvant radiotherapy is administered if the surgical pathology report indicates lymph node (LN) or parametrial involvement, positive surgical margin, or deep cervical stromal invasion. On the other hand, large cervical tumors (lesion diameter >4cm) and stage IIB cervical cancer are mainly treated with chemoradiation.³

The side effects of radiotherapy are premature ovarian dysfunction, sexual dysfunction, vaginal fibrosis, and obstructive endarteritis. These may lead patients to perceive the therapy as ineffective, and that the radiation may even be the cause of a new type of cancer.³ In recent years, as an alternative treatment for locally advanced cervical cancer, neoadjuvant chemotherapy (NACT) has been administered before radical hysterectomy to shrink large tumors.¹⁻⁹ It has been reported that this treatment significantly reduces the need for radiation therapy after surgery.¹⁰ However, it is also reported that NACT has no effect on the overall survival rate, even though it limits tumor size, lymph node involvement, and far metastasis.¹¹

NACT has become the main alternative treatment at Iranian oncology centers due to the limited accessibility of patients to radiotherapy and subsequent treatment delays. The present study aimed to assess the outcome of NACT therapy, followed by radical hysterectomy and primary surgery, in locally advanced cervical cancer according to disease stage. In addition, we evaluated the recurrence rate, 5-year survival rate, and the need for adjuvant radiotherapy.

Materials and Methods

In a retrospective cohort study, the records of 258 patients with cervical cancer (stages IB2, IIA, or IIB), who referred to Imam Khomeini Hospital (Tehran, Iran) from 2007 to 2017 were evaluated. The study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (registration code: IR.TUMS.IKHC.REC.1396.4552). Written informed consent was obtained from all participants.

Based on a Magnetic resonance imaging (MRI) scan and clinical examination, all patients had been classified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.³ The

exclusion criteria were concurrent malignancies or other comorbidities, that had an adverse effect on cancer survival as well as incomplete records. The inclusion criteria were patients aged <80 years with performance status <2; normal liver, cardiovascular, renal, and bone marrow function, normal complete blood count (CBC) test, no other malignancies, coagulation disorders, or previous chemotherapy; and willingness to undergo NACT. The patients were assigned into two groups. Group A (n=58) included patients with cancer stages IB2 and IIA, who underwent radical hysterectomy with negative margins. Group B (n=44) included patients, who underwent a radical hysterectomy after NACT. Demographic information from the records included parity, age at marriage, disease stage, LN involvement, lymph-vascular space invasion (LVSI), type of tumor, radiotherapy requirement, adjuvant hysterectomy, vaginal involvement, response to chemotherapy, survival time, and recurrence rate.

The NACT procedure included three cycles of 80 mg/m² cisplatin (Milan®, France) and 60 mg/m² paclitaxel (Stragen-Sobhan®, Iran) at 10 days intervals followed by radical hysterectomy, if the patient achieved a complete or partial response. Two weeks after the final chemotherapy cycle, patients with no clinical parametrial involvement underwent surgery. Patients underwent three cycles of chemotherapy with paclitaxel and cisplatin postoperatively.

Based on a pelvic MRI scan, the clinical response of a tumor was evaluated and categorized as:

- Complete response: Total disappearance of the tumor and elimination of all pathologic lymph nodes.
- Partial response: At least 30% decrease in tumor size.
- Permanent disease: Less than 30% decrease in tumor size.
- Progressive disease: At least 5 mm or 20% increase in tumor size or emergence of a new tumor.
- Suitable response: Combination of complete and partial responses.

The pathological response of a tumor was categorized as:

- Complete response: Disappearance of the tumor with negative lymph nodes
- Optimal partial response: Disease with less than 3 mm stromal invasion
- Sub-optimal partial response: Tumoral invasion into stroma more than 3 mm
- Suitable pathologic response: Combination of complete and optimal responses

Statistical Analysis

Data analysis was performed using SPSS software version 21.0. The data were analyzed for normality using the Kolmogorov-Smirnov test. The hypothesis test was carried out on two variable groups using *t* test for numerical data or Mann-Whitney test for non-parametric data. Chi-square test or Fisher's exact test was used for data on nominal group depending on appropriateness. Progression-free survival (PFS) and overall survival (OS) were analyzed using the Kaplan-Meier method and log-rank test. Independent prognostic factors were determined using Cox regression modeling. $P < 0.05$ was considered statistically significant. The confidence interval was considered 0.95 to obtain a study power of 80% beside 0.05 as significance with type one error (α) of 0.05.

Results

Out of the 258 records of patients with cervical cancer, 140 patients underwent chemoradiation

(not the main topic of our study), 52 received NACT followed by a hysterectomy, and 66 underwent primary radical hysterectomy. Sixteen records were excluded due to incomplete information or comorbidities, that affected survival. Eventually, 58 records of patients with primary radical hysterectomy were assigned into group A and 44 records with NACT followed by radical hysterectomy were assigned into group B. Table 1 presents demographic and basic information about the patients. There was no statistically significant difference in age, age at marriage, and parity between the groups. However, the groups differed significantly in terms of cancer stage, type of tumor, vaginal invasion, lymph node involvement, and LVSI.

Survival

The median follow-up time was 63.50 ± 39.94 months. Mortality rate and survival time in both groups are presented in table 2. The median for overall survival time in group A and B was 113.65 and 112.88 months, respectively ($P = 0.970$) (figure 1).

Table 1: Demographics and basic information of the patients

Variable		NACT+RS (n=44)	Surgery (n=58)	P value
Age (mean±SD)		46.09±12.07	48.04±10.14	0.38 [†]
Age at marriage (mean±SD)		18.25±4.5	16.77±4.1	0.09 [†]
Parity median (IQR)		3 (2-6)	5 (2.75-6.25)	0.28 [‡]
Stage (n, %)	Ib2	13 (29.5)	41 (70.7)	0.001 [§]
	Ila	11 (25)	16 (27.6)	
	Ilb	20 (45.5)	1 (1.7)	
Vaginal invasion (n,%)	None	16 (36.4)	40 (69)	0.002 [§]
	Fornix	11 (25)	9 (15.5)	
	1/3 upper	11 (25)	9 (15.5)	
	2/3 upper	6 (13.60)	0 (0)	
LN (n,%)	Yes	23 (52.27)	16 (27.59)	0.01 [§]
	No	21 (47.72)	42 (72.41)	
LVSI (n, %)	Yes	15 (34.09)	41 (70.69)	<0.001 [§]
	No	29 (65.91)	17 (29.31)	
Tumor type (n, %)	SCC	41 (93.20)	41 (70.70)	0.02 [§]
	Adenocarcinoma	3 (6.80)	16 (27.60)	
	Others	0 (0)	1 (1.70)	

NACT: Neoadjuvant chemotherapy; RS: Radical surgery; LN: Lymph node; LVSI: Lymph-vascular space invasion; SCC: Squamous cell carcinoma; IQR: Interquartile range=Q3-Q1; [†]*t* test; [‡]Mann-Whitney U test; [§]Chi-square or Fisher's exact test; * $P < 0.05$ was considered statistically significant

Table 2: Death rate and survival time in both study groups

Stage	Outcome	NACT+RS (n=44)	Surgery (n=58)	P value
Total	Death (n, %)	5 (11)	12 (21)	<0.001 [§]
	Survival time (median, 95% CI)	113.65 (100.56-126.76)	112.88 (103.35-112.42)	
Ib	Death (n, %)	0 (0)	7 (17.1)	0.18 [§]
	Survival time (median, 95% CI)	94.33 (84.21-104.46)	56.46 (35-77.93)	
Ila	Death (n, %)	1 (9.10)	4 (25)	0.62 [§]
	Survival time (median, 95% CI)	104.40 (79.24-129.59)	104.77 (85.5-124.05)	
Ilb	Death (n, %)	4 (20)	1 (100)	0.24 [§]
	Survival time (median, 95% CI)	80.7 (66.93-94.48)	22 (22-22)	

[†]Log-rank test; [§]Chi-square or Fisher's exact test; * $P < 0.05$ was considered statistically significant

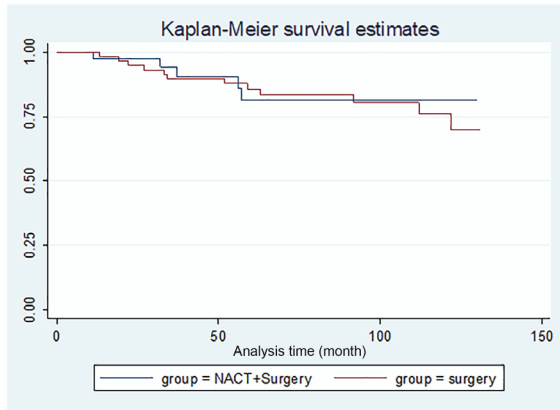


Figure 1: Overall survival analysis of patients with locally advanced cervical cancer among those treated with neoadjuvant chemotherapy followed by radical hysterectomy and primary surgery (P=0.97). NACT: Neoadjuvant chemotherapy

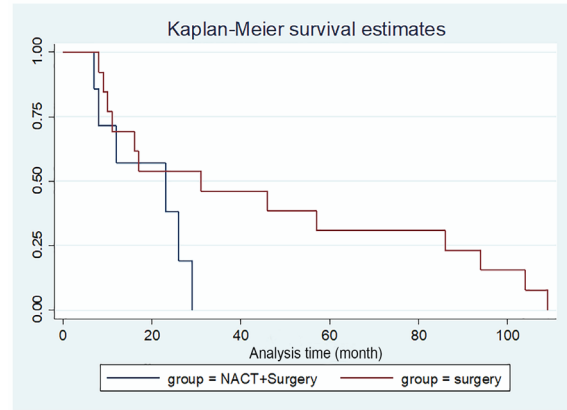


Figure 2: Progression-free survival Analysis in patients with locally advanced cervical cancer among patients treated with neoadjuvant chemotherapy followed by radical hysterectomy and primary surgery (P=0.12). NACT: Neoadjuvant chemotherapy

Although the mortality rate in different disease stages was not significant between the groups, the median survival time in stage IIB in group B was four times greater than in group A, and the difference was statistically significant (P=0.008). Lymph node involvement affected almost 50% of the patients and was statistically significant (P<0.001). No deaths were reported among patients with cervix stromal invasion <3 mm, while all patients with stromal invasion >3 mm deceased. The type of tumor, LVSI, and vaginal involvement did not affect the survival of patients. Survival time in cases with squamous cell carcinoma (SCC) and adenocarcinoma was 97.13 (89.86-104.40) and 95.28 (76.86-113.69) months, respectively, and the difference was not statistically significant (P=0.880). The PFS for SCC and adenocarcinoma was 39.46 (29.93-48.98) and 23.22 (13.64-32.81), respectively, and the difference was not statistically significant (P=0.110). The depth of invasion in groups A and B was 12.69±6.15 mm and 6.14±7.20 mm, respectively (P=0.001). However, when correlated with LN involvement, the depth of invasion in patients with and without LN involvement was 12.21±7.7 mm and 9.80±6.86

mm, respectively (P=0.040).

Recurrence

The number of cases with progressive disease after treatment in groups A and B was 13 (22.40%) and 6 (13.60%), respectively, and the difference was not statistically significant (P=0.260) (table 3). The first recurrence in group A occurred seven months after completion of treatment, while it occurred two months earlier in group B. The difference in the median of recurrence time between the groups was not statistically significant (P=0.120) (figure 2). There was no recurrence in stage IB2 patients of group B, however, the recurrence rate in those of group A was 19.5% with a median recurrence time of 59.13 months. The rate of recurrence grew in both groups as the disease stage advanced. However, there was less recurrence in group B compared to group A. Table 4 indicates the survival time and PFS of all patients with respect to disease progression.

Response to Therapy and 5-Year Survival

The clinical and pathological response to NACT are presented in table 5. Pathologic

Table 3: Recurrence rate and progression free survival time in both study groups according to disease stages

Stage	Outcome	Group		P value
		NACT+RS (n=44)	Surgery (n=58)	
Total	Recurrence rate (n, %)	6 (13.6)	13 (22.4)	0.26 [§]
	PFS time (median, 95% CI)	23 (4.37-45.56)	31 (6.37-66.23)	0.12 [†]
Ib	Recurrence rate (n, %)	0	8 (19.5)	0.08 [§]
	PFS time (median, 95% CI)	0	59.13 (28.68-89.57)	NA
IIa	Recurrence rate (n, %)	1 (9.1)	4 (25)	0.62 [§]
	PFS time (median, 95% CI)	23 (23-23)	28.5 (7.97-49.03)	0.39 [†]
IIb	Recurrence rate (n, %)	5 (25)	1 (100)	0.29 [§]
	PFS time (median, 95% CI)	16.4 (7.32-25.48)	11 (11-11)	0.07 [†]

NA: Not applicable; PFS: Progression free survival; [†]Log-rank test; [§]Chi-square or Fisher's exact test

Table 4: Survival and progression-free survival time in both study groups according to vaginal, LN, deep stromal invasion, and LVSI conditions. Data are expressed as mean and 95% CI

		Condition		P value [†]
		No	Yes	
Vagina	Survival time	102.1 (90.71-113.49)	94.26 (86-102.52)	0.22
	PFS	38.94 (28.35-49.53)	32.1 (19.59-44.53)	0.32
LN	Survival time	117.48 (110.86-124.1)	74.97 (64.75-85.19)	<0.001
	PFS	38.27 (21.11-55.42)	36.22 (26.74-45.69)	0.72
>3 mm invasion	Survival time	NA	110 (100.47-119.54)	NA
	PFS	NA	39.23 (21.84-56.62)	NA
LVSI	Survival time	116.07 (105.09-127.05)	112.77 (102.37-123.18)	0.67
	PFS	33.8 (1.21-66.39)	41.5 (20.14-62.86)	0.47

NA: Not applicable; PFS: Progression-free survival; LN: Lymph node involvement; LVSI: Lymph-vascular space invasion; [†]Log-rank test

Table 5: Response rate to chemotherapy before radical hysterectomy

Clinical* (n, valid %)	Complete response	14 (31.82)
	Partial response	21(47.73)
	Permanent disease	5 (11.36)
	Progressive disease	4 (9.09)
Pathologic** (n, valid%)	Complete response	16 (43.20)
	Optimal partial response	3 (8.10)
	Suboptimal partial response	18 (48.60)

*Number out of 44; **Number out of 37 (unavailable data for 7 patients)

Table 6: Five-year survival and death risk in both study groups

Group	5-year survival				Hazard ratio	SE	Significance
	Ib2	Ila	Iib	Total			
NACT+RS	91%	81%	61%	81%	1	-	-
Surgery	93%	81%	NA	86%	1.195 (0.42-3.41)	0.54	0.74

NA: Not applicable

complete response, optimal partial response, and sub-optimal partial response were observed in 43.2%, 8.1%, and 48.6% of the patients, respectively (data from 7 patients were unavailable). The 5-year survival rate and the risk of mortality were similar in both groups (table 6).

Adjuvant Radiotherapy Requirement

Patients in both groups received adjuvant radiotherapy, if the surgical pathology report indicated LN or parametrial involvement, positive surgical margin, or deep cervical stromal invasion. Postoperative radiotherapy was needed in 21 out of 44 cases of radical hysterectomy following chemotherapy and in 50 out of 58 cases of primary surgery (P=0.002). There was a higher need for radiotherapy in approximately 30% of IB2 patients, who underwent primary radical surgery (P=0.008), whereas the need in other cancer stages was similar in both groups.

LVSI and LN Involvement

Of the 94 overall radical hysterectomy cases, 38 had negative LVSI and LN involvement. Of

the remaining 56 cases of positive LVSI, 20 had LN involvement, and the rest were negative. There was a significant correlation between LVSI and LN involvement (P=0.002). We also found a correlation between LN involvement and the disease stage (P<0.001); LN involvement increased as the disease stage advanced.

Tumor Size

Three cycles of NACT treatment significantly reduced tumor size from a median of 50 mm to 14.5 mm. The results showed that chemotherapy limited tumor invasion (P=0.001) such that parametrial (P=0.004), vaginal (P<0.001), and LN (P<0.001) involvement significantly decreased after chemotherapy.

Discussion

The risk of cervical cancer is higher in women aged 70 and older. Radiotherapy and chemotherapy are the treatment of choice. However, primary radical hysterectomy is often performed in developing countries due to the high number of patients and inadequate radiotherapy equipment.¹²

The need for postoperative adjuvant radiotherapy in group B was lower than that of group A (48% vs. 86%) in our study. Clinical findings showed lower recurrence and higher DFS in group B. Due to the low sample size, the results showed no significant difference in mortality rate between the groups, although 17% of the patients in group A deceased compared to no deaths in group B.

Despite the difference in cancer stages between the groups, there was no statistical difference in terms of age, age at marriage, and parity. Some patients, who underwent primary surgery mainly suffered from IB2 stage cervical cancer, whereas those in group B had IIB stage. This meant that the groups were statistically different in terms of disease stages IB and IIB. Considering the definition of the disease stages, a significant difference was expected between LN and vaginal invasion. Hence, the novelty of our study was in analyzing the results based on the disease stage rather than patients in each group. In 2016, Lee and colleagues studied a group of patients of different age, disease stage, and LN involvement. Although they analyzed data based on the disease stage, their evaluation was negatively affected by the mismatch in age and LN involvement of their patients.¹³ Other studies also used NACT in the IIB cancer stage.^{14, 15}

The results of optimal clinical and pathologic response to chemotherapy were 79% and slightly higher than 50%, respectively, and were directly correlated. The need for radiotherapy significantly decreased in disease stage IB. However, despite statistically similar results, the clinical response for disease stages IIA and IIB indicated that NACT reduced the need for radiotherapy and its subsequent adverse effect; an important issue among young patients.

The mortality rate and survival rate in disease stage IIA did not differ between the groups. Only one patient in group A died 22 months after primary surgery. Based on the pathology report, this patient suffered from stage IIB cancer. The results showed a statistically significant number of deaths (n=4, 20%) in group B after 7-8 months following NACT and radical surgery (RS). A study in Italy investigated the effect of NACT+RS on stage III cervical cancer.⁹ They reported 44% response rate (77% complete response and 36.5% partial clinical response) compared with 79.1% in our study. Di Donato and colleagues used NACT+RS and recommended this approach as a valid and acceptable method.⁹ They reported 56.4% and 29.5% overall survival (OS) rate for three and five years, respectively. Compared with our 5-year rate at 80%, it appears

that their patients had cervical cancer of the more advanced stages. Note that patients in disease stage III are hardly suitable choices for curative intent mainly due to their uropathy and chronic renal failure.⁹ In line with our findings on NACT and radical hysterectomy, a previous study of 90 patients with locally advanced cervical cancer reported a 5-year OS of 81% and disease-free survival (DFS) of 70%.¹⁴ They reported 24% vaginal involvement, which is similar to our result for the NACT group (25%) but higher than the primary surgery group (15.5%).

In a 10-year follow-up, Luvero and colleagues compared two groups similar to our study. They used adjuvant chemotherapy after surgery in patients, who had already undergone NACT and found no correlation between LN involvement and survival.¹⁵ In our study, LN involvement was the only factor, that affected the OS of patients (figure 1) despite non-significant DFS. We found that patients without deep invasion had significantly lower LN involvement, which in turn highlights the effect of chemotherapy in reducing invasion and consequently less LN involvement. We also found that chemotherapy was a valuable alternative, since the tumor size and parametrial invasion were significantly affected by NACT.

Gong and colleagues proposed NACT+RS as an alternative treatment when radiotherapy is not accessible.¹⁶ In a 1-year retrospective study, they collected the records of 414 Chinese patients with stage IB2-IIB cervical cancer. The reported clinical response to chemotherapy for complete response, partial response, and suitable response was 32.6%, 46.5%, and 90%, respectively, which differed from our results (4%, 86%, and 80%, respectively). Similar to our findings on 5-year survival, they could not confirm any improvement in 2-year survival between the NACT+RS and RS group.¹⁶ However, despite an insignificant increase in 5-year survival and DFS in our study, the 81% survival rate is comparable to other studies using NACT before surgery.^{15, 17, 18} In another study, Fu and colleagues suggested that NACT did not affect the 2- and 5-year survival rate and DFS in patients with cervical cancer, if the disease stage and type of hysterectomy were not considered.¹⁹ However, Landoni and colleagues suggested that optimal response did not require postoperative chemotherapy to improve survival.²⁰

We found that NACT had significant effects on vaginal and parametrial invasion and LN involvement since there were no patients with grade 3+ vaginal invasion after treatment. LVSI frequency in group A was slightly higher than 70% compared with the 40% in group B. This indicated a positive effect of NACT on LVSI due to an acceptable response to the treatment. Kim

and colleagues showed that NACT could limit some intermediate to high-risk factors for survival (e.g., tumor size, lymph-vascular invasion, parametrial invasion, and deep stromal invasion), and thus reduce the need for postoperative radiotherapy.¹¹ A meta-analysis study by Robova and colleagues showed the efficacy of NACT+RS on the survival of malignant cases, especially in large tumors with stage IB.²¹ Marchetti and colleagues reported that more than 70% of the overall 5-year OS was associated with FIGO classification. Using univariate analysis, they identified smoking habit, tumor size, LVSI, parametrial invasion, and LN involvement as other prognostic factors for OS which included tumor size, grading, and parametrial invasion in a multivariate analysis.²² Another study by Benedetti-Panici and colleagues suggested that NACT+RS significantly improved survival in stage IB2-IIB cervical cancer.²³

In the present study, the most common type of cancer was SCC followed by adenocarcinoma. After a complete cycle of NACT before RS, the tumor size was significantly reduced even to the level of complete eradication. Various studies have shown a significantly higher survival rate in long-term SCC cases with stages higher than IIB compared to non-SCC tumors.^{24, 25} They indicated that the histological nature of a tumor is an important factor for the identification of suitable cases for NACT before surgery. Namkoong and colleagues identified SCC of the cervix as a tumor sensitive to chemotherapy.²⁶

The main limitations of our study were incomplete medical records, insufficient information, and incomplete follow-up. However, we managed to obtain the required information by tracing the majority of patients. The records of those patients, who could not be reached were excluded from the study.

Conclusion

Neoadjuvant chemotherapy before the hysterectomy was found to reduce the need for postoperative radiotherapy in patients with locally advanced cervical cancer. As a direct result, adverse side effects and the recurrence rate were reduced, and the overall survival rate of patients with stage IIB cervical cancer was increased. Further clinical trials are recommended to assess the effectiveness of preoperative NACT in gynecologic surgery and other surgical procedures.

Acknowledgment

The authors appreciate the support provided by

the personnel of the Obstetrics and Gynecology Department of Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Conflict of Interests: None declared.

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