Experience in stage IB2 cervical cancer and review of treatment

Serviks evre IB2 kanserinde tecrübe ve literatürün gözden geçirilmesi

Taner Turan[1], Burcu Aykan Yıldırım[1], Gökhan Tulunay[1], Nurettin Boran[1], Ferah Yıldız[2], Mehmet Faruk Köse[1]

[1]*Etlik Zübeyde Hanım Women's Health Teaching and Research Hospital, Gynecologic Oncology Clinic, Ankara, Turkey*

[2]*Faculty of Medicine, Hacettepe University, Department of Radiation Oncology, Ankara, Turkey*

Abstract

Objective: The aim of the study is to evaluate and compare the efficacy of neoadjuvant chemotherapy (NACT), radical hysterectomy (RH) and radiotherapy (RT) in the treatment of stage IB2 cervical cancer.

Material and Methods: Medical records of 86 patients with stage IB2 cervical cancer between 1993 and 2006 were evaluated. Patients who underwent type III RH ± bilateral salphingo-oophorectomy and para-aortic and pelvic lymphadenectomy constituted the RH group (n=18). Patients who received radiotherapy constituted the RT group (n=20). Patients who underwent any of the combination chemotherapies (cisplatin/5-fluorouracyl, cisplatin/UFT® or paclitaxel/carboplatin) followed by RH or RT constituted the NACT group (n=36).

Results: Seventy-four patients were included in the study. The median follow-up was 48.5 months and the mean tumor size was 51.4mm. The groups were similar in terms of follow-up duration and tumor size. However, the mean age of the patients was higher in the RT group and nonsquamous type cervical cancer was more frequent in the RH group. Disease free survival (DFS) and overall survival (OS) were 75.7%. DFS rate was 65% in the RT group, 77.8% in the RH group and 80.6% in the NACT group. OS rates were 65%, 77.8% and 83.3% respectively. The groups were similar in terms of DFS and OS rates.

Conclusion: In our study, none of the treatment modalities were shown to be superior in terms of efficacy. There is need for additional prospective studies comparing multimodal treatment regimens in stage IB2 cervical cancer.

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Key words: Cervical cancer, neoadjuvant chemotherapy, radical hysterectomy, radiotherapy

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Özet

Amaç: Bu çalışmada ever IB2 serviks kanserinde neoadjuvant kemoterapi (NAKT), radikal histerektomi (RH) ve radyoterapinin (RT) tadavi başarısının karşılaştırılması amaçlandı.

Gereç ve Yöntemler: 1993-2006 yılları arasında ever IB2 servikal kanser tanısı olan 86 hastanın tıbbi kayıtları değerlendirildi. RH ± bilateral salpingo-ooforektomi + para-aortik ve pelvik lenfadenektomi yapılan hastalar RH grubunu (n=18), radyoterapiyle tedavi edilen hastalar RT grubunu (n=20) ve kemoterapi kombinasyonlarından (cisplatin/5-fluorourasil, cisplatin/UFT® or paklitaksel/carboplatin) herhangi birini alan ve takiben RH veya RT uygulanan hastalar NAKT grubunu oluşturdu (n=36).

Bulgular: Çalışmaya 74 hasta alındı. Ortanca takip süresi 48.5 ay ve ortalama tümor boyutu 51.4mm'ydi. Gruplar takip süreleri ve tümör boyutu açısından benzerdi. Ancak hastaların ortalama yaşı RT grubunda daha yüksekti ve nonskuamöz tip kanser RH grubunda daha sıktı. Tüm grupta hastalıksız yaşam süresi (HYS) ve tüm yaşam süresi (TYS) %75.7'ydi. HYS RT grubunda %65, RH grubunda %77.8 ve NACT grubunda %80.6'ydı. TYS sırasıyla %65, %77.8 ve %83.3'dü. Gruplar HYS ve TS açısından benzerdi.

Sonuçlar: Bu çalışmada etkinlik açısından tedavi modalitelerinden herhangi birinin diğerine üstün olmadığı görüldü. Evre IB2 serviks kanserinde multimodal tedavi rejimlerinin karşılaştırıldığı prospektif çalışmalara ihtiyaç vardır.

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Anahtar kelimeler: Servikal kanser, neoadjuvant kemoterapi, radikal histerektomi, radyoterapi

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Introduction

There is an ongoing uncertainty about the treatment of early stage cervical cancer. The efficacy of radical hysterectomy and radiotherapy with a 5-year overall survival for stages IB-IIA, estimated to be around 90% in both, are comparable (1, 2). Surgery, the preferred mode of treatment, preserves ovarian function, has fewer adverse effects and allows establishment of radiotherapy as a treatment choice in case of recurrence. However, Landoni et al. showed that 84% of patients with early stage disease who underwent radical surgery also received adjuvant radiotherapy (3).

Chemotherapy given together with radiotherapy (concurrent chemoradiotherapy, [CCRT]) increases the efficacy of radiotherapy. It has been observed that CCRT is associated with an increase in treatment response and improvement in survival rates (4-7). Decrease in distant metastasis rates as well as achievement of local control made neoadjuvant chemotherapy (NACT) more popular. Theoretically, the aim of neoadjuvant chemotherapy is reduction of tumor volume,

Address for Correspondence / Yazışma Adresi: *Uzm. Dr. Taner Turan, Seyranbağları Seyran Caddesi 52/6 06670 Çankaya, Ankara, Türkiye*
Phone: +90 312 322 01 80 Mobile: +90 532 793 33 57 e.mail: turantaner@yahoo.com

elimination of micrometastases and accomplishing optimal tumor size for surgery. Radical hysterectomy or radiotherapy may be applied after chemotherapy to improve survival rates in locally advanced cervical cancer. However, some studies have shown that radiotherapy administered after neoadjuvant chemotherapy did not improve survival rates (8-10), and even displayed a negative effect (11, 12). This effect has been explained by the cross-resistance between chemotherapy and radiotherapy as well as the intracellular changes caused by chemotherapy itself (13). In contrast, these problems do not appear with radical hysterectomy in addition to achievement of excision of focal residual tumor. Hence neoadjuvant chemotherapy followed by radical hysterectomy is expected to improve survival rates. In a meta-analysis of 21 phase III studies, it has been shown that neoadjuvant chemotherapy followed by radical hysterectomy reduced disease specific death rates by 35% and increased survival rates by 14% when compared with radiotherapy only (14). However, in a study by the Gynecologic Oncology Group (GOG) where neoadjuvant chemotherapy followed by radical hysterectomy was compared with radical hysterectomy only, no improvement in surgical-pathologic risk factors or survival rates has been observed (15).

The choice of initial treatment in early stage bulky tumor is not certain. The aim of this study is to evaluate and compare the efficacy of different treatment modalities in stage IB2 cervical cancer.

Material and Methods

Medical records of 86 patients diagnosed with stage IB2 cervical cancer and treated between 1993 and 2006 were evaluated retrospectively. All patients were assessed by pelvic and rectovaginal examination under general anesthesia, computerized tomography of upper abdomen, pelvic magnetic resonance imaging or intravenous pyelography. Measurement of the tumor size was the product of the two greatest tumor diameters. Patients staged clinically according to the FIGO 1988 criteria were treated with radical hysterectomy, radiotherapy or neoadjuvant chemotherapy as the initial treatment. According to the treatment modality, patients were classified into three groups; RH group (radical hysterectomy), RT group (radiotherapy) and NACT group (neoadjuvant chemotherapy).

Patients who underwent type III radical hysterectomy±bilateral salphingo-oophorectomy and para-aortic and bilateral pelvic lymphadenectomy constituted the RH group. Para-aortic lymphadenectomy was performed up to the level of the inferior mesenteric artery. High-risk patients received postoperative radiotherapy. Until year 2001, criteria for postoperative adjuvant radiotherapy were presence of at least one major factor (positive lymph node, parametrial involvement, presence of tumor within surgical border and tumor size ≥4cm) or two minor factors (lymphovascular space involvement [LVSI], stromal invasion greater than ½, tumor size >2-≤4cm, three or more lymph nodes with microscopic metastasis). After year 2001, only patients who had positive lymph node and/or parametrial involvement and/or tumor within surgical border received adjuvant radiotherapy.

The chemotherapy group were initially treated with one of the cisplatin / 5-fluorouracyl (CF) or cisplatin / UFT (CU) or paclitaxel / carboplatin (CbP) combination chemotherapies. CF protocol was administered with 28 day intervals. Patients received cisplatin (75mg/m^2) on the 1st day and 5-fluorouracyl (5-FU) (500mg/m^2) on the 1st-5th day. CU protocol was administered with 21 day intervals. Patients received cisplatin (75mg/m^2) on the 1st day and UFT™ (uracyl [224mg]-tegafur [100mg] capsule, Bristol-Myers Squibb) orally during the first 14 days. CbP protocol was administered with 21 day intervals. Patients received paclitaxel (175mg/m^2) by intravenous infusion in three hours and carboplatin (AUC=6) o the 1st day of therapy. All patients were evaluated prior to therapy and those who had a performance score above two according to the Gynecologic Oncology Group (GOG) criteria, bone marrow suppression or hepatic/renal dysfunction did not receive chemotherapy.

Following two or three courses of chemotherapy, patients were re-evaluated under general anesthesia and those with a tumor size less than 40mm underwent type III radical hysterectomy, while other patients with tumor size ≥40mm received radiotherapy. Clinical response to chemotherapy was evaluated according to World Health Organization criteria (16). Complete clinical response (CCR) was defined as absence of clinically gross tumor; partial clinical response (PCR) was defined as reduction in tumor size of greater than 50%; stable disease (SD) was defined as reduction in tumor size of less than 50% or an increase in size by less than 25% and finally progressive disease (PD) was defined as an increase in tumor size of greater than 25% or appearance of new tumoral foci. Pathological complete response (PatCR) was defined as absence of tumor in postoperative pathological examination of the surgical specimen (type III hysterectomy, ovaries and lymph nodes).

In the RT group, radiotherapy was administered alone or in combination with chemotherapy (CCRT) as the initial treatment. Following radiotherapy, patients who had a tumoral lesion in the cervix underwent adjuvant surgery (type I hysterectomy).

Primary or adjuvant radiotherapy had been the sole treatment until the National Cancer Institute announcement in 1999, after which CCRT was accepted as the standard therapy. Radiotherapy was administrated by the radiation oncology department. External radiotherapy was in the form of four field box technique with 6-18 MV photon beams to a total dose of 4500-5040cGy with conventional daily fractionation. In patients with para-aortic lymph node metastases, 45Gy para-aortic radiotherapy was also added. In case of a close surgical vaginal margin, 21Gy high dose rate vaginal brachytherapy in three fractions was applied. Dose prescription was made 0.5cm below the vaginal mucosal surface and the first 4cm of the vagina was treated.

Patients were evaluated every 3 months for the first two years, every six months for the following three years and annually thereafter. Follow-up included recto-vaginal examination, Pap smear test, abdominal sonography, complete blood count and serum biochemistry. Disease free survival (DFS) and overall

survival (OS) rates during the follow-up period were evaluated. All of the mentioned death events were disease specific deaths. Prognostic factors affecting survival rates within each group were evaluated and groups were compared in terms of survival rates. Statistical analysis was performed with the Chi-Square test and ANOVA Table Test using SPSS (Statistical Package for Social Sciences) 12.0 statistical software. Differences between the groups were considered significant at $p \leq 0.05$.

Results

A total of 86 patients had been treated for stage IB2 cervical cancer. Of these, five patients who had been operated in a different clinic and seven patients who had incomplete follow-up data were excluded. The data of the remaining 74 patients were analyzed.

The mean age of the patients was 48.7 years (range: 29-73, median: 47) and the mean duration of follow-up was 52.5 months (range: 3-167, median: 48.5) (Table 1).The mean pre-treatment tumor size was 51.7mm (range: 40-75, median: 50). Thirty-six patients (48.6%) received neoadjuvant chemotherapy, while 20 patients (27.1%) received radiotherapy and 18 patients (24.3%) underwent radical hysterectomy as the initial treatment. Recurrence developed in 18 patients, hence the DFS rate was 75.7%. The interval between initial treatment and recurrence ranged between 2-80 months (mean: 18.6). Isolated pelvic recurrence developed in 11 patients (61.1%). The localizations of recurrence in relation with modality of treatment are displayed in Table 2.

During follow-up, 18 patients died; hence the OS rate was 75.7%. The interval between initial treatment and death ranged between 6-84 months (mean: 20.8). Of the remaining patients, data about the most recent medical condition of seven patients (9.5%) was missing, one patient (1.4%) was alive with disease and 48 patients (64.9%) were alive without disease. Follow-up duration of patients with unknown latest medical condition ranged between 12-96 months, therefore they were included in the survival analyses.

Radiotherapy group

There were 20 patients in this group. The mean age of these patients was 52.3 years (range: 41-73) and the mean duration of follow-up was 61.9 months (range: 3-127, median: 55). Seventeen patients (85%) had squamous cell carcinoma.<<the mean pre-treatment tumor size was 51.7mm (range: 40-75) (Table 1).

While six patients received CCRT, eleven patients received only radiotherapy. It is not possible to evaluate the acute complications of radiotherapy since it was administrated by a number of radiation oncology departments belonging to other hospitals. Three patients underwent extraperitoneal lymph node dissection followed by CCRT. Two of these patients were node-positive.

Table 1. General characteristics of patients

Parameter		Initial treatment			Total
		RH	NACT	RT	mean / n
		mean / n	mean / n	mean / n	
Number of patients		18	36	20	74
Age (year)		49.4 (38-62) median:49	46.3 (29-66) median:44.5	52.3 (41-73) median:47.5	48.7 (29-73) median:47
Duration of follow-up (months)		53.9 (9-167) median:49.5	46.5 (6-97) median:44	61.9 (3-127) median:55	52.5 (3-167) median:48.5
Pre-treatment tumor size (mm)		52 (40-70) median:50	51.4 (40-70) median:50	51.8 (40-75) median:50	51.7 (40-75) median:50
Pathology	Squamous cell carcinoma	11	34	17	62
	Adenocarcinoma	3	2	2	7
	Adenosquamous carcinoma	4	-	1	5
Presence of recurrence		4	7	7	18
Interval between initial therapy and recurrence (months)		15.5 (6-36)	9 (2-17)	29.6 (6-80)	18.6
Interval between initial therapy and death (months)		25.3 (9-69)	18.8 (6-34)	39.6 (22-84)	20.8
Latest medical condition	No evidence of disease	9	27	12	48
	Alive with disease	-	1	-	1
	Dead	3	8	7	18
	Lost to follow-up	6	-	1	7

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapyn, number of patients

Following radiotherapy, four patients underwent type I hysterectomy+bilateral salphingo-oophorectomy+para-aortic and bilateral pelvic lymphadenectomy as adjuvant surgery. Two of these patients had a tumor in the cervix but all were node-negative. Postoperative pathologic diagnosis was squamous cell carcinoma in these patients and radiotherapy was administered with CCRT preceding type I hysterectomy. Among patients undergoing adjuvant surgery, recurrence developed in one patient 80 months after radiotherapy, who then received palliative treatment but died four months later. Two patients are still alive without disease. Follow-up duration of these patients is 105 and 122 months respectively. One patient was lost to follow-up 12 months after surgery.

Seven patients developed recurrence. During follow-up, the DFS rate was 65%. The duration of the interval between radiotherapy and recurrence ranged between 22 and 84 months (mean: 39.6). The localization of recurrence was only the pelvic region in five patients while it was only the lung in one patient and both pelvis and the lung in another (Table 2). Four of six patients who had recurrence in the pelvis had received only radiotherapy. However, CCRT did not seem to affect pelvic recurrence rate (p=0.550). Of the patients who developed recurrence, four received palliative treatment, two received chemotherapy and one patient underwent surgery.

During the follow-up period, seven patients (35%) with recurrence died and the OS rate was 65%. Twelve patients (60%) were alive without disease. The latest medical condition of one patient was unknown but we had data of 12 months of follow-up.

During follow-up, DSF and OS rates were 66.7% among patients receiving only radiotherapy. These rates were 87.5% and 75% respectively, among patients receiving CCRT. When the two groups were compared, there was no statistically significant difference in terms of DFS (p=0.312) and OS (p=0.707). However, the mean interval between radiotherapy and death was 82.1 months for CCRT, while it was 43.3 months for only radiotherapy.

Radical hysterectomy group

There were 18 patients in this group. The mean age of the patients was 49.4 years (range: 38-62) and the mean duration of follow-up was 53.9 months (range: 3-167, median: 49.5). Postoperative pathology revealed squamous cell carcinoma in 11 patients (61%). The mean pre-treatment tumor size was 52 mm (range: 40-70) (Table 1).

None of the patients died due to surgery-related complications. An intraoperative bladder injury was repaired successfully. During the postoperative period, wound dehiscence was observed in one patient and urinary tract infection was observed in another patient. Postoperative intraabdominal bleeding occurred in one patient but it was not serious and was managed by observation and blood transfusion. Routine suprapubic catheterization was performed intraoperatively and no bladder atonia was observed. Postponement of radiotherapy due to surgery-related complications did not occur.

Postoperative pathology report was unsatisfactory in two patients. Parametrial tumor invasion was detected in 35.3% (6/17), presence of tumor within the surgical border in 23% (4/17), lymph node metastasis in 44.4% (8/18) and deep stromal invasion in 46.2% of patients. The mean number of nodes removed was 51.7 (range: 25-80, median: 48) and the mean number of metastatic lymph nodes was 4.3 (1-19, median: 1). Seventeen patients (94.4%) received adjuvant radiotherapy (14 CCRT and three only radiotherapy) following radical surgery. The histopathologic diagnosis in the patient who did not receive adjuvant radiotherapy was adenocarcinoma.

Information about the current status was not available in six patients. These patients had follow-up durations of 12, 12, 13, 18, 47 and 96 months and were included for survival analyses. Four patients (22.2%) developed recurrence and the interval between radiotherapy and recurrence ranged between 6-36 months (mean: 15.5). Recurrence was detected in only the pelvic region in one patient, only the upper abdomen in one patient, only the lung in one patient and both pelvis and upper abdomen in one patient (Table 2). Three of these patients received palliative treatment, one patient received chemotherapy.

Of the patients who developed recurrence, three died. The fourth patient could not be contacted. Overall survival was 9, 11 and 69 months for the three patients. Parametrial tumor invasion, lymph node metastasis and positive surgical border did not affect survival rates (Table 3) in RH group. However 50% of patients who had a tumor within the surgical border developed recurrence, while this rate fell to 7.7% for those who did not have a tumor within the surgical border (p=0.052). Thirty percent of patients with lymph node metastasis died, while none of the patients without lymph node metastasis had died during follow-up (p=0.090).

Table 2. Localizations of recurrence in relation with modality of treatment

Treatment groups	Pelvic	Upper Abdomen	Lung	Pelvic + Upper Abdomen	Pelvic + Lung	Upper Abdomen + Lung	Total
RH group	1	1	1	1	-	-	4
RT group	5	-	1	-	1	-	7
NACT group	5	-	-	1		1	7
Total	11	1	2	2	1	1	18

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapy

Neoadjuvant chemotherapy group

There were 36 patients in this group. The mean age of the patients was 46.3 years (range: 29-66) and the mean duration of follow-up was 46.5 months (range: 3-97, median: 44). Postoperative pathology revealed squamous cell carcinoma in 34 patients (94.4%). The mean pre-treatment tumor size was 51.4mm (range: 40-70) (Table 1).

Thirty patients (94.4%) received CF, four patients (11.1%) received PC and two patients (5.6%) received CU as neoadjuvant chemotherapy. Following neoadjuvant chemotherapy, the mean tumor size was reduced to 32.7mm and the type of chemotherapy protocol did not affect the reduction in tumor size (p=0.158).

Toxicity of CF combination was tolerable. Only one patient developed grade 3-4 toxicity leading to postponement of chemotherapy for one week. The most common side effect encountered was acute nausea and vomiting, observed in 74% of the cycles (Table 4). Chemotherapy was not cancelled and dose reduction was not indicated in any of the patients because of toxicity. Toxicity of the other two chemotherapy protocols was not evaluated because of the small number of patients. Assessment of toxicity was done according to the criteria of the World Health Organization (16).

Following neoadjuvant chemotherapy, 27 patients (75%) became suitable for surgery in terms of tumor size, but two patients were inoperable for medical reasons and received CCRT. The remaining 25 patients underwent type III radical hysterectomy+bilateral salphingo-oophorectomy+para-aortic and bilateral pelvic lymphadenectomy. Eleven patients were not suitable for surgery after neoadjuvant chemotherapy. Of these patients, six received CCRT and five underwent extraperitoneal lymph node dissection followed by CCRT.

The overall clinical response rate was 33.3% (CCR: 11.1%, PCR: 22.2%). Stable disease was detected in 61.1% of patients while 5.6% had progressive disease. Pathological complete response rate was 8.3%.

The surgical border was tumor-free in all 25 patients who underwent radical surgery, however, five patients (20%) had parametrial tumor invasion and 11 (44%) had lymph node metastasis. Three of five patients (60%) who underwent extraperitoneal lymph node dissection also had positive lymph nodes.

Sixteen (64%) out of 25 patients who underwent radical surgery received postoperative radiotherapy (12 CCRT and four only radiotherapy). So, it was calculated that a total of 27 patients (75%) in this group received radiotherapy.

During follow-up, seven patients (19.4%) developed recurrence; hence the DFS rate was 80.6%. The interval between neoadjuvant chemotherapy and recurrence ranged between 2-17 months (mean: 9). There was recurrence in only the pelvis in five patients while there was both pelvic and upper abdominal recurrence in one patient and upper abdominal and lung recurrence in another patient (Table 2). Of these patients with recurrence, two received radiotherapy and five received chemotherapy.

Table 3. The effect of surgical-pathologic risk factors on DFS and OS rates during follow-up in the RH group

Prognostic Factors		DFS	p	OS	p
Parametrial invasion	Negative	%81.8	0.938	%81.8	0.266
	Positive	%83.3		%100	
Lymph node metastasis	Negative	%87.5	0.375	%100	0.090
	Positive	%70		%70	
Positive surgical border	Negative	%92.3	0.052	%92.3	0.347

DFS: Disease free survival, OS: Overall survival, n: Number of patients

Table 4. Toxicity of CF combinations per courses

Parameters	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	%88.3	%10.4	%1.3	-	-
Leucopenia	%97.4	%1.3	%1.3	-	-
Thrombocytopenia	%97.4	-	%1.3	-	%1.3
ACINV	%26	%54.5	%19.5	-	-
Diarrhea	%89.6	%5.2	%3.9	%1.3	-
Mucositis	%81.8	%13	%3.9	%1.3	-
Elevation of liver enzymes[1]	%98.7	%1.3	-	-	-
Proteinuria	%94.8	%5.2	-	-	-
Hematuria	%88.3	%11.7	-	-	-

ACINV: Acute Chemotherapy Induced Nausea and Vomiting, [1]SGOT/SGPT elevations

Six out of seven patients with recurrence died; hence the OS rate was 77.8%. The mean duration between detection of recurrence and death was 21 months (range: 6-34). One patient is still alive 31 months after recurrence and is receiving chemotherapy.

Two patients (5.6%) not responding to NACT showed progression of disease. These patients died 11 and 14 months after neoadjuvant chemotherapy respectively. During follow-up, eight patients died and the OS rate was 77.8%. The interval between neoadjuvant chemotherapy and death ranged 6-34 months (mean: 18.8).

The effect of chemotherapy type and lymph node metastasis on survival rates was not significant statistically. However factors such as being able to perform radical surgery after neoadjuvant chemotherapy, presence of parametrial involvement, tumor size after chemotherapy and the reduction rate of tumor size had prognostic value for survival (Table 5). The presence of parametrial involvement decreased the OS rate from 95% to 40% (p=0.003). Lymph node metastasis,although being statistically not significant, worsened DFS and OS rates clearly (92.9% vs. 62.5% and 85.7% vs. 50% respectively) (Table 5).

When the three groups were compared, duration of follow-up and pre-treatment tumor size was not different statistically. However, patients in the radiotherapy group were older and the incidence of adenocarcinoma or adenosquamous carcinoma was higher (Table 6).

None of the initial treatment protocols were superior to one another statistically in terms of DFS and OS rates. Responsiveness to neoadjuvant chemotherapy provided no further advantage in terms of survival (Table 7).

Table 5. The effect of surgical-pathologic risk factors on DFS and OS rates during follow-up in the NACT group

Parameter		DFS	p	OS	p
Neoadjuvant chemotherapy modality	Cisplatin/5-fluorourasil	%83.3	0.346	%80	0.473
	Other	%66.7		%66.7	
Treatment after neoadjuvant chemotherapy	Surgery	%80	0.899	%84	0.176
	Radiotherapy#	%81.8		%63.6	
Parametrial involvement	Negative	%90	0.012*	%95	0.003*
	Positive	%40		%40	
Lymph node metastasis	Negative	%92.9	0.076	%85.7	0.070
	Positive	%62.5		%50	
Pre-neoadjuvant chemotherapy tumor size (mm)	≤50	%81.8	0.297	%78.8	0.629
	>50	%66.7		%66.7	
Post- neoadjuvant chemotherapy tumor size (mm)	≤30	%82.4	0.797	%88.2	0.153
	>30	%78.9		%68.4	
Post- neoadjuvant chemotherapy reduction in tumor size	None	%85.7	0.944	%71.4	0.460
	<%25	%75		%62.5	
	≥%25 - <%50	%77.8		%77.8	
	≥%50	%83.3		%91.7	

DFS: Diesase free survival, OS: Overall survival, #RT or CCRT, *: Statistically significant

Table 6. Comparison of age, tumor size and duration of follow-up between the groups

Treatment groups	Age (years), mean	Tumor size (mm), mean	Duration of follow-up (mo's), mean	Histopathology	
				Squamous cell	Others
RH group	49.4 (median: 49)	52 (median: 50)	53.9 (median: 49.5)	%61.1	%38.9
NACT group	46.3 (median: 44.5)	51.4 (median: 50)	46.5 (median: 44)	%94.4	%5.6
RT group	52.3 (median: 47.5)	51.8 (median: 50)	61 (median: 55)	%85	%15
p	0.036*	0.978	0.294	0.007*	

RH: Radical hysterectomy, NACT: Neoadjuvant Chemotherapy, RT: Radiotherapy (RT or CCRT), *: Statistically significant

Discussion

While radiotherapy is the contemporary modality of cervical cancer treatment for stage IIB or later stages, surgery is the choice of treatment for earlier stages. However, treatment of locally advanced early stage tumor (IB2 and bulky IIA) is still controversial; in consequence a multimodal approach is generally preferred. The efficacy of radical hysterectomy and radiotherapy in early stage (IB-IIA) cervical cancer is similar. Five-year OS is approximately 90% in both modalities (1, 2). Neoadjuvant chemotherapy is also associated with similar five-year OS rates (nearly 90%) (17, 18). In the present study, OS rates during follow-up were 77.8% (median follow-up:55 months) in the RT group, 77.8% (median follow-up:44 months) in the NACT group and 83.3% (median follow-up:49.5 months) in the RH group. Survival rate was high in the RH group, although non-squamous type cervical cancer, which is known to have a worse prognosis, was more frequent in this group. The RT group was older. It is known that, with advancing age, survival decreases in cervical cancer. Death rate at age 60 was twice as high as at age 30 (relative index: 1.9) (19). This might explain the recurrence and death rates in the RT group. Despite a higher incidence of recurrence and death in patients receiving radiotherapy, the interval between initial treatment and recurrence and death was longer in this group (for RT group, RH group and NACT group; DSF 29.9 months, 15.5 months and 9 months respectively, OS 39.6 months, 25.3 months and 18.8 months respectively). The limited number of patients or the relationship between treatment modality and cellular kinetics might be the cause of this finding.

Surgical approach has priority in the treatment of early stage tumor as radiotherapy is associated with ovarian and sexual dysfunction. In addition, in case of treatment failure with surgery and recurrence, radiotherapy will be an effective treatment option. However, the likelihood of receiving adjuvant radiotherapy after radical surgery is quite high for stage IB2 tumor. A retrospective analysis by Yessaian et al showed that 52% of patients with stage IB2 tumor had to receive radiotherapy after radical hysterectomy according to GOG criteria (20). In patients with stage IB1 and IB2 cervical cancer treated with radical hysterectomy, Finan et al. found that the rate of adjuvant RT was 72.3% in the stage IB2 group (21). Similarly, another study by Landoni et al comparing radical hysterectomy and radiotherapy in the treatment of stage IB-IIA cervical cancer, demonstrated that 84% of patients with tumor size greater than 4cm received adjuvant radiotherapy (3). In the present study, nearly 95% of patients received adjuvant radiotherapy, which might be explained by the high incidence (40%) of non-squamous cell type cancer in the RH group. Nevertheless, all the patients with squamous cell type cancer (n: 11) received adjuvant radiotherapy in the RH group.

CCRT has been used for the last 20 years to increase the efficacy of radiotherapy. Five studies performed towards the end of 1990s, in which cisplatin based chemotherapy was used, concluded that CCRT improved survival rates (GOG#85, GOG#120, GOG#123, SWOG#8797, RTOG#9001) (22-26). Thereupon NCI made an emergency declaration in 1999 and since then the addition of chemotherapy to radiotherapy has become standard practice (http://rex.nci.nih.gov/massmedia/pressreleases/cervicalcancer.html). Green et al. presented a meta-analysis of 19 studies performed between 1981 and 2000 (n: 4580). They showed that the improvement in the OS rate in the CCRT group was 12% and this was independent of having undergone surgery or not. This effect was most prominent in early stage disease (27). These results were further supported by other studies. In a study by Cetina et al., including 294 patients with stage IB2-IVA cervical cancer treated with weekly cisplatin (40mg/m^2, maximum dose=80mg), the OS was 76.5% during a median 28 month follow-up. This was 86% for stage IB2-IIB (28). In 2007, the long-term results of the GOG#123 study, which evaluated the effect of weekly cisplatin (40mg/m^2) on survival rates in stage IB2 cervical cancer, were presented (29). Preliminary results have demonstrated a reduction rate of 49% for recurrence and 46% for death (25). These rates were 39% and 37% respectively according to the new long-term results. The efficacy of chemoradiotherapy seemed to be diminished in a long-term result of the GOG#123study (29). In the present study, the DFS rate was improved by 20% and the OS rate by 9%, and the OS was increased by two-fold in the CCRT group when compared with the radiotherapy only group. Despite all these results, in the phase III study by the National Cancer Institute of Canada including 259 patients with stage IB-IVA tumor, weekly cisplatin-based CCRT was not found to be superior to radiotherapy only. Five-year OS was 62% in the CCRT

Table 7. The effect of treatment modality on disease-free survival and overall survival rates during follow-up

Treatment modality		Disease-free survival	p	Overall survival	p
NACT vs RT	NACT	%80.6	0.198	% 77.8	0.301
	RT	%65		%65	
NACT vs RH	NACT	%80.6	0.537	%77.8	0.463
	RH	%77.8		%83.3	
RT vs RH	RT	%65	0.307	%65	0.200
	RH	%77.8		%83.3	

RH: Radical hysterectomy, NACT: Neoadjuvant chemotherapy, RT: Radiotherapy (RT or CCRT)

group, while it was 58% in the radiotherapy only group (p=0.42) (30). However, the duration of radiotherapy in that study was shorter than the other studies. Besides, the discrepancy in results is considered to occur as a result of evaluation of the para-aortic region solely with computed tomography and the high incidence of anemia in the chemotherapy group.

The improvement in survival rates with CCRT is explained theoretically by the inhibition of recovery of sublethally damaged cells, the change in cellular kinetics and the increase in radiosensitivity as the result of the reduction in tumor volume (31). The success of CCRT is not limited to prevention of local recurrences only. Studies have also shown that the incidence of distant recurrence was reduced (27). In the present study, 75% of recurrences in the RH group were distant, while 28.6% of recurrences in the NACT and RT group were distant (Table 2). The reduction in distant metastasis is thought to be due to the cytotoxic effect of chemotherapy. In addition to this, it was shown that adjuvant chemotherapy after CCRT did not improve survival (32).

There is an ongoing debate about executing adjuvant type I hysterectomy after radiotherapy. Keys et al., in the GOG#71 study, compared adjuvant hysterectomy after radiotherapy with radiotherapy alone in stage IB2 cervical cancer (19). CCRT was not administered in the two groups. As a result, it was shown that adjuvant hysterectomy improved survival in patients with tumor size smaller than 7cm. Gallion et al. also obtained similar results (stage IB barrel-shaped cancer) (33). However, in the GOG#123 study comparing CCRT followed by adjuvant hysterectomy with radiotherapy followed by adjuvant hysterectomy, it was shown that the incidence of persistent disease decreased significantly in the chemotherapy group. Similarly the DFS and OS were higher in the chemotherapy group (25). As a result, the GOG#123 study states that for patients receiving CCRT, adjuvant hysterectomy has no place in treatment. In the present study, although the number of adjuvant hysterectomies was not high, it was observed that this type of treatment produced improvement in DFS and OS rates by 12% (37.5% vs. 25%, p=0.634).

Neoadjuvant chemotherapy is the standard treatment in many solid tumors, particularly breast tumors and tumors of the head and neck. However, the role of this treatment in cervical cancer is still unclear, even after 25 years. Theoretically, by reducing the size of the tumor, neoadjuvant chemotherapy is expected to increase the chance of resectability. Additionally, surgical prognostic factors are improved by eliminating micrometastases. Some clinical studies and phase II studies with large sample sizes support this hypothesis by demonstrating improvement of surgical prognostic factors with neoadjuvant chemotherapy (34-36). However, more recent studies comparing neoadjuvant chemotherapy followed by radical hysterectomy and only radical hysterectomy did not find any improvement (15, 37).

Complete response rate with neoadjuvant chemotherapy varies between 0-50% (OCR 25-95%) (15, 38-59). After neoadjuvant chemotherapy, surgery became suitable for 28-100% of patients (18, 35, 37-43, 53, 55-58, 60-66). One of the reasons for the diversity of results is the heterogeneity of the study populations. Patients had clinical stage IB2-IIIB locally advanced cervical cancer in most of the studies, although the response to neoadjuvant chemotherapy is directly correlated with the stage of the disease. In the meta-analysis by Eddy et al, CCR was 28% in stage IB2-IIA but fell to 7% in stage IV (67). Similar results have also been reported in other studies (50-52).

The factor that determines operability is the stage of disease. Duenas-Gonzales et al. showed that the operability rate fell from 83% in stage IB2 to 60% in stage IIB and 40% in stage IIIB (52). As a result neoadjuvant chemotherapy, not indicated in the treatment of advanced stage cervical cancer since the need for subsequent radiotherapy is high, should be limited to the treatment of early stage. In the present study, OCR rate with neoadjuvant chemotherapy was 33.3% (CCR: 11.1%, PCR: 22.2%) and 75% of patients became suitable for operation. 75% of patients in the NACT group received adjuvant radiotherapy.

Survival rates are also diverse as are the response and operability rates. Five-year DFS and OS vary between 29-80% and 21-81% respectively (15, 18, 34, 37, 38, 42, 48, 51, 57, 60, 66). Results of this study are within these ranges (median follow-up:44 months, DFS: 80.6%, OS: 77.8%). Prognostic factors found to be important were tumor size following chemotherapy, radiotherapy administration after neoadjuvant chemotherapy and parametrial involvement.

Because of the diversity in the reported results it is difficult to appreciate the status of neoadjuvant chemotherapy. Heterogeneity of disease stages in the studies is one of the reasons. In advanced stages, survival rate with neoadjuvant chemotherapy is lower (63, 64, 68) with no additional benefit (52). However, results of studies including only stage IB2 patients are also variable (15, 17, 18), mainly because of uncertainty of clinical staging. Another reason for the diversity may be the neoadjuvant chemotherapy protocol selected to be administered. Because most neoadjuvant chemotherapy protocols are cisplatin-based, it is considered that chemotherapy protocols do not have any effect on response and survival rates (66). However, in an Italian phase III study which compared cisplatin/iphosphamide/paclitaxel with cisplatin/iphosphamide, it was shown that triple neoadjuvant chemotherapy combination improved CCR significantly (9% vs. 20%) (50). Nevertheless ,there was no difference in terms of operability and survival rates between the two chemotherapy protocols. In the present study, chemotherapy protocol did not affect survival, however CF protocol improved the DFS by 16% and the OS by 13% (p=0.346, p=0.473 respectively).

Neoadjuvant chemotherapy for Cervical Cancer Meta-Analysis Collaboration re-evaluated 21 phase III studies performed between 1975 and 2000 and presented a meta-analysis (14). In this meta-analysis, two groups were created. In the first group, neoadjuvant chemotherapy followed by radiotherapy was compared with radiotherapy only (16 studies, n: 2074) while in the second group neoadjuvant chemotherapy followed by radical hysterectomy was compared with radiotherapy only (five studies, n: 872). In the latter group, neoadjuvant chemotherapy + radical hysterectomy reduced death rate by

35% and increased survival rate by 14%. Only 2 studies in this group consisted of stage IB2 tumor (49, 66). Benedetti-Panici et al., in their subgroup evaluation, observed that neoadjuvant chemotherapy was advantageous in terms of survival in stage IB2 (66), while Chang et al. did not (49).

Aoki et al., in their study comparing neoadjuvant chemotherapy followed by radical hysterectomy with radiotherapy only (locally advanced stage IB-IIB); they observed that, with neoadjuvant chemotherapy, surgical-pathologic risk factors and survival were improved (45). A similar result was reported by Namkoong et al. (locally advanced stage IB-IIB) (69). On the other hand, Serur et al. (stage IB2, squamous cell carcinoma) detected an improvement in surgical-pathologic risk factors but no influence on survival (18). Recently, two studies were reported, one retrospective (37) and a prospective phase III GOG study (15) comparing neoadjuvant chemotherapy followed by radical hysterectomy with radical hysterectomy only in locally advanced early stage cervical cancer. These studies suggest that neoadjuvant chemotherapy has no place in the treatment of locally advanced early stage cervical cancer. In the GOG study, it was shown that neoadjuvant chemotherapy did not improve surgical-pathologic risk factors and survival. Five-year OS was 60.7% in patients receiving neoadjuvant chemotherapy, while it was 63.3% in patients undergoing radical hysterectomy only.

Uncertainty about cervical cancer arises from staging of tumor clinically and debate concerning treatment of stage IB2 tumor continues. It is difficult to create a homogenous patient group and to make a comment about the extent of tumor according to clinical stage. Neoadjuvant chemotherapy, initially a hopeful adjuvant, may be disappointing. In the present study, recurrence developed earlier in the group of patients undergoing neoadjuvant chemotherapy and surgery. However, survival rates were higher in NACT and RH group than in RT group. The percentage of patients receiving adjuvant radiotherapy in RH group and NACT group was quite high (94.4% and 75% respectively). Thus, it was concluded that radical hysterectomy or neoadjuvant chemotherapy as initial treatment had suboptimal efficacy. The comparison of RT and RH groups may be considered as the comparison between radiotherapy versus primary radical surgery followed by radiotherapy, owing to the high rate of adjuvant radiotherapy (94.4%) in the RH group. In this case, it can be concluded that primary radical surgery might be an overtreatment in stage IB2 cervical cancer because the improvement observed in survival was statistically insignificant. On the other hand, the limitations of the present study (retrospective, nonrandomized and relatively small number of patients) must be kept in mind. CCRT and adjuvant hysterectomy improved survival in the RT group.

In conclusion, this retrospective analysis showed that none of the treatment modalities had any superior effect on survival. However, CCRT should be added if radiotherapy will be given as the initial therapy. Furthermore radiotherapy followed by adjuvant hysterectomy must be investigated by further studies and indecision about neoadjuvant chemotherapy should be overcome.

Conflict of interest
None declared

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