Experimental
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Clinical Article

Is the Initial Treatment in Stage IB2 Cervical Carcinoma Neoadjuvant Chemothreapy or Primary Surgery?

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OBJECTIVE: It is expected that neoadjuvant chemotherapy (NACT) decrease tumor size, increase the operability and improve surgical-pathologic risk factors so that improve the survival. In this study we evaluated the effect of NACT on surgical-pathologic risk factors and survival.
STUDY DESIGN: Between 1993 and 2007, the data of patients with stage IB2 cervical cancer were reviewed. Twenty-four patients who were treated with NACT followed by radical surgery (RS) were compared with 15 patients underwent primary RS. After two or three courses of chemotherapy patients were reassessed and RS was performed to patients whose tumor size was less than 40mm. In both groups all patients underwent type III radical hysterectomy + bilateral salpingo-oophorectomy + systematic paraaortic and bilateral pelvic lymphadenectomy.
RESULTS: The mean size of the tumor mass was 50.1mm. Nine patients were acccepted as responder (complete clinical response + partial clinical response) and 15 patients as unresponder (stabile disease) after NACT. The surgical-pathologic risk factors didn't improve with NACT except for stromal invasion. The median follow-up was 48 months. Overall survival and disease free survival was 86.7% in RS group, this ratio was 80% in NACT unresponder group and 66.7% in NACT responder group (p=0.501).
CONCLUSION: NACT didn't improve either the surgical-pathologic risk factors expect for stromal invasion or survival in patients with stage IB2 cervical carcinoma. It appears that we have disappointment with this treatment modality.

Key Words: Neoadjuvant chemotherapy, Cervical carcinoma

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Introduction

NACT is one of the initial therapy choices in stage IB2 cervical carcinoma. Theoretically, NACT is expected to decrease tumor size, increase the operability and improve surgical-pathologic risk factors by eliminating micrometastasis so that improve the survival. However it couldn't be possible to show this theoretical advantage during last 25 years.

It has been designated that NACT followed by radiotherapy (sequential radiotherapy) has no contribution to survival,[1-3] even it worsens.[4,5] However, NACT followed by radical surgery (RS) improves overall survival by %14, when compared to only radiotherapy (RT).[6]

It is unclear if NACT followed by RS has superiority to only RS. Aoki et al. and Namkoog et al. reported that use of NACT before RS decreases pathologic risk factors and improves survival.[7,8] Contrary to this, Serur et al. reported that although NACT decreases surgical pathologic risk factors in stage IB2, it doesn't improve the survival.[9] In two recently published studies, one of them performed by Gynecologic Oncology Group (GOG), no beneficial effect as shown on survival and surgical-pathologic risk factors compared to primary RS.[10,11]

At the present time, the importance of NACT in cervical carcinoma is unclear. In this study we evaluated the effect of NACT on surgical-pathologic risk factors and survival.

Material and Method

Between 1993 and 2007, the data of patients with stage IB2 cervical cancer were reviewed from a computerized database. The patients whose datas are adequately recorded were included into the study. Twenty-four patients who were treated with NACT followed by RS were compared with 15 patients treated with primary RS. Effect of NACT on surgical-pathologic risk factors and survival were evaluated.

Patients were staged clinically according to 1988 FIGO staging system by using CT, MRI, (if need with IVP) and recto-vaginal pelvic examination under general anesthesia.

The NACT protocols were as follows; 1- cisplatin (75mg/m²)+5-fluorourasil (500mg/m²) (28 days interval), 2- carboplatin (AUC=6, maximum dose: 750mg)+paclitaxel (175mg/m², 3 hours infusion) (21 days interval). After two or three courses of NACT patients were reassessed by pelvic ex-

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amination under general anesthesia and RS was performed to patients whose tumor size was less than 40mm. The other patients received RT.

Clinical response after chemotherapy was evaluated according to World Health Organization (WHO) criterias.[12] Complete clinical response (CCR) was defined complete disappereance of gross tumor. A partial clinical response (PCR) required more then 50% reduction or less than 25% increase in tumor size. Stabile disease (SD) was defined as a less than 50% decrease or less than 25% increase of tumoral mass. Progressive disease (PD) was accepted as increase in tumor size more than 25% or appereance of a new tumor.

The all patients underwent type III radical hysterectomy + bilateral salpingo-oophorectomy + systematic bilateral pelvic and para-aortic lymphadenectomy. Para-aortic lymphadenectomy was performed to arteria mesenterica inferior. Patients with high-risk (surgical margin positive, parametrial and lymph node invasion) received adjuvant RT after radical hysterectomy.

After treatment, patients were followed-up every 3 months for the first two years and every 6 months for the next 3 years and than annually. They were assessed by recto-vaginal pelvic examination, pap smear, abdomino-pelvic ultrasonoghraphy, complete blood count and biochemical tests. If clinically indicated CT or MRI was done.

Disease free survival (DFS) was defined as the time between the initial therapy and recurrence, overall survival (OS) was defined as the time between the initial therapy and death. In RS group we couldn't get information about the final status of three patients. But these patients were included into the survival evaluation because we had their 12, 36, 48 months follow-up records.

Statistical datas were analyzed by SPSS (Statistical Package for Social Sciences) 12.0 program working under Windows XP operative system using Annova Table Test and Chi-Square Test. Statistical significance was defined as $p<0.05$.

Results

The mean age of the patients was 49.3 (33-66, median: 48) and the mean tumor size was 50.1mm (40-90, median: 50). After NACT, nine patients were acccepted as a responder (CCR+PCR) and 15 patients as nonresponder (SD). In whole group, 28 patients received adjuvant radiotherapy after RS (Table I). Clinical characteristics of patients and surgical-pathologic risk factors are illustrated on table I.

Table I. Patients' characteristic, histopathologic results

Parameters		Mean (min-max) / n (%)
Age		49.3 (33-66, median: 48)
Tumor size (mm)		50.1 (40-70, median: 50)
Follow-up (month)		51.3 (8-102, median: 48)
Pathology	Squamous	34 (87.2)
	Adenocancer	3 (7.7)
	Adenosquamous	2 (5.1)
Treatment modality	RS	15 (38.5)
	NACT followed by RS	24 (61.5)
Parametrium invasion	Negative	26 (66.7)
	Positive	13 (33.3)
Positive surgical border	Negative	36 (92.3)
	Positive	3 (7.7)
LVSI	Negative	20 (51.3)
	Positive	19 (48.7)
Stromal invasion	<1/2	22 (56.4)
	>1/2	17 (43.6)
Ovarian metastasis	Negative	38 (97.4)
	Positive	1 (2.6)
Vaginal invasion	Negative	31 (79.5)
	Positive	8 (20.5)
Lymph node metastasis	Negative	19 (48.7)
	Positive	20 (51.3)
Number of removed lymph node		58.4 (19-160, median:53)
Number of positive lymph node		2.7 (1-15, median:1)
Adjuvant RT	Not received	11 (28.2)
	Received	28 (71.8)

BSO: Bilateral salphingooophorectomy, LVSI:Lymphovascular space invasion
NACT: Neoadjuvant chemotherapy, RS: Radical surgery, RT: Radiotherapy

Both of the groups were similar according to tumor size, number of removed lymph node and pathologic diagnosis (Table II). But the number of patients diagnosed as adenocancer or adenosquamous cancer was higher in RS group.

NACT improved deep stromal invasion. On the other hand this response was not related to the response of NACT (Table III). Lymph node metastasis, parametrial invasion, surgical margin invasion, LVSI, ovarian and vaginal metastasis was similar in all three groups (Table III, Table IV). While the surgical margins were clear in all patients in NACT group, invasion was observed 20% of patients in RS group.

The mean follow-up was 51.3 months (8-102, median: 48) in all patients. There were no diffences in follow-up time between groups (Table V). In this study eight of 39 (20.5%) patients had recurrence and all of them had died. NACT didn't affect the survival. The ratio of death and recurrence was 13.3% in RS group, this ratio was 20% in NACT unresponder group (stabile disease) and 33.3% in NACT responder group (CCR+PCR) ($p=0.501$).

Table II. The distrubition of age, tumor size, number of removed lymph nodes and pathology results among the groups

Treatment modality	Age mean (range)	Tumor size (mm) mean (range)	Number of removed lymph nodes mean (range)	Pathology	
				Squamous	Nonsquamous
RS	49.1 (34-64) median:48	46.7 (40-60) Median:40	59.6 (19-93) Median:64	11 (73.3%)	4 (26.7%)
NACT + RS unresponder	48.3 (33-63) median:48	53.7 (40-90) median:50	58.1 (19-160) median:50	15 (100%)	-
NACT + RS Responder	51.4 (44-66) median: 49	50 (40-65) median:50	57.1 (33-93) median:50	8 (88.9%)	1 (11.1%)
p	0.669	0.272	0.974	0,091	

NACT: Neoadjuvant chemotherapy, RS: Radical surgery, Unresponder: Stabile Disease Responder: Complete Clinical Response + Partial Clinical Response

Table III. The effect of NACT on parametrial invasion, lymph node metastasis, surgical margin invasion and stromal invasion

Treatment modality	Parametrial invasion		Lymph node metastasis		Positive surgical margin		Stromal invasion	
	Negative	Positive	Negative	Positive	Negative	Positive	≤1/2	> 1/2
RS	10 (66.7%)	5 (33.3%)	6 (40%)	9 (60%)	12 (80%)	3 (20%)	4 (26.7%)	11 (73.3%)
NACT + RS unresponder	9 (60%)	6 (40%)	8 (53.3%)	7 (46.7%)	15 (100%)	-	11 (73.3%)	4 (26.7%)
NACT + RS responder	7 (77.8%)	2 (22.2%)	5 (55.6%)	4 (44.4%)	9 (100%)	-	7 (77.8%)	2 (22.2%)
p	0.670		0.686		0.074		0.012	

NACT: Neoadjuvant chemotherapy, RS: Radical surgery, Unresponder: Stabile Disease Responder: Complete Clinical Response + Partial Clinical Response

Table IV: The effect of NACT on LVSI, ovarian metastasis, vaginal metastasis and adjuvant RT

Treatment modality	LVSI		Ovarian metastasis		Vaginal invasion		Adjuvant RT	
	Negative	Positive	Negative	Positive	Negative	Positive	No	Yes
RS	6 (40%)	9 (60%)	14 (93.3%)	1 (6.7%)	12 (80%)	3 (20%)	4 (26.7%)	11 (73.3%)
NACT + RS unresponder	10 (66.7%)	5 (33.3%)	15 (100%)	-	11 (73.3%)	4 (26.7%)	5 (33.3%)	10 (66.7%)
NACT + RS responder	4 (44.4%)	5 (55.6%)	9 (100%)	-	8 (88.9%)	1 (11.1%)	2 (22.7%)	7 (77.8%)
p	0.308		0.440		0.657		0.831	

NACT: Neoadjuvant chemotherapy, LVSI: Lymphovascular space invasion, RS: Radical surgery, RT: Radiotherapy, Responder: Complete Clinical Response + Partial Clinical Response, Unresponder: Stabile Disease

Table V: The effect of NACT on survival

Treatment modality	Follow-up (month) mean (range)	Recurrence		DFS (month) mean (range)	Last Status		OS (month) mean (range)
		Negative	Positive		Live	Ex	
RS	51.5 (8-102) median:48	13 (86.7%)	2 (13.3%)	9 (6-12) median:9	13 (86.7%)	2 (13.3%)	11.5 (8-15) median:11
NACT+RS unresponder	53.5 (14-100) median:46	12 (80%)	3 (20%)	11.3 (9-15) median:10	12 (80%)	3 (20%)	23.7 (14-30) median:27
NACT+RS responder	47.3 (10-101) median:50	6 (66.7%)	3 (33.3%)	8.3 (1-17) median:7	6 (66.7%)	3 (33.3%)	23.5 (13-34) median:23.5
p	0.901	0,501		0.814	0,501		0.423

NACT: Neoadjuvant chemotherapy, RS: Radical surgery, DFS: Disease free survival, OS: Overall survival Responder: Complete Clinical Response + Partial Clinical Response Unresponder: Stabile Disease

Discussion

In this retrospective study we couldn't find out what we expect from NACT. Except the stromal invasion, NACT didn't improve either the surgical-pathologic risk factors or the survival. Although the adenocancer and adenosquamous was more in number in RS group, survival was better (86.7% vs 80% and 66.7%) in this group.

CCR to NACT ranges 0-50% (overall clinic response 25-95%) and operability ranges 28-100%.[10,13-37] Survival ratio is also variable like response and operability. 5-year DFS and OS survival rates are reported as 29-80% and 21-81%, respectively.[9,11,13,17,23,26,32,35,37,38] The main reason of variability in results is that there is no standardisation of stage between groups. The clinic response, ratio of operability and survival rates decreases in advanced stage.[25,27,39,40] On the other hand the clinical staging of cervical cancer has uncertanity. The other reason of variability might be the chemotherapy protocols. It is thought that chemotherapy protocols are not effective on response and survival because many of them are cisplatin-based.[37] In a multi-center randomized phase III study from Italy of which compares cisplatin/ifosfamide/paclitaxel combination with cisplatin/ifosfamide showed that triple NACT protocol improves the CCR significantly (20% vs 9%).[25] Also it was reported that pathologic diagnosis, surgical-pathologic risk factors, age and intracellular structures effect clinic response and survival.[8,41-45]

Randomized trials with sequential radiotherapy have failed to improve the prognosis[1-3] and may even be worse for survival[4,5] These negative results are explained by the cross-resistance between two treatment modalities and intracellular alterations.[46] On the other hand cross-resistance is not problem in RS which removes the residue tumor. Consequently RS after NACT is expected to improve the survival. According to a meta-analysis of 21 phase III studies performed between 1975 and 2000, RS after NACT decreases deaths by 35% and improves survival by 12% when compared to only RT.[6]

The studies in which NACT + RS compared with primary RS are limited in number. Aoki et al. reported (stage IB-IIB) that NACT improved surgical-pathologic risk factors and survival.[7] Namkoong et al. (stage IB-IIB) and Cai et al. also reported similar results.[8,47] Sardi et al. showed that NACT nonresponder groups' surgical-pathologic risk factors and survival rates are similar to primary surgery group.[36] They also reported improvement on survival and surgical-pathologic risk factors in NACT responder group. In our study we determined that NACT response didn't improve pathology results and survival. Serur et al. and Chen et al. found out an improvement in surgical-pathologic risk factors in NACT group but this doesn't reflect to survival.[9,48] Two studies about comparision of NACT+RS with RS in early cervical carcinoma are recently published. One of them is retrospective,[11] the other one is prospective phase III study (GOG study).[10] According to these studies NACT doesn't have any importance in early cervical carcinoma. In GOG study, they reported that NACT (cisplatin/vincristine, every 10 days, three courses) didn't improve survival and surgical-pathologic risk factors in stage IB2 tumors. 3-years OS was 67.7% in NACT group and 69.3% in RS group. 5-years OS was respectively 63.3% and 60.7%.[10] Behtash et al. reported (stage IB2-IIA) that lymph node metastasis and parametrial invasion was significantly worse in NACT group.[11] 3-years OS was 56% in NACT group and 75% in primary surgery group while 5-years OS was 28% and 68% respectively. Similarly in our study pathology results and survival didn't change with NACT. Although more than one fourth of patients had nonsquamous pathology (adenocancer and adenosquamous cancer) among patients underwent primary RS, OS was 86.7% in this group. However the ratio of nonsquamous pathology was 11.1% in patients received NACT and OS was 66.7% in these patients.

As a conclusion, we have results of nonhomogen studies and nonhomogen disease. It is not easy to manage this disease with datas from these studies. NACT which was a hopefull treatment choice at past, has now high risk of disappointment. If we could understand the factors that affect the response to NACT, we think that new drugs and new protocols of NACT can achieve the success in cervical cancer in the future.

IB2 Servik Kanserinde Başlangiç Tedavisi Neoadjuvant Kemoterapi mi Primer Cerrahi mi Olmalı?

AMAÇ: Teorik olarak neoadjuvant kemopterapiden (NAKT) beklenilen; tümör boyutunu küçültüp operabiliteyi arttırması, patolojik prognostik faktörlerde iyileşme sağlaması ve sonuçta daha iyi sağ kalım oranları elde edilmesidir. Bu çalışmada NAKT uygulanmasının cerrahi-patolojik risk faktörleri ve yaşam oranları üzerindeki etkisi değerlendirildi.

GEREÇ ve YÖNTEM: 1993-2007 yılları arasında evre IB2 serviks kanseri tanısı alan hastaların verileri gözden geçirildi. NAKT ve takiben radikal histerektomi (RH) yapılan 24 hastayla primer RH uygulanan 15 hasta karşılaştırıldı. NAKT'yi takiben hastalar genel anestezi altında tekrar değerlendirildi ve tümör boyutu 40mm'nin altında olanlara RH uygulandı. Her iki grupta radikal cerrahi olarak; tip III radikal histerektomi + bilateral salpingo-ooforektomi + sistematik para-aortik ve bilateral pelvik lenfadenektomi yapıldı.

BULGULAR: Ortalama tumor boyutu 50.1 mm' ydi. NAKT sonrası 9 hasta cevaplı (tam klinik cevap + parsiyel klinik cevap), 15 hasta cevapsız (stabil hastalık) olarak kabul edildi. Derin stromal invazyon haricinde NACT uygulananlarda cerrahi-patplojik risk faktörleri iyileşmemekkteydi. Ortanca takip süresi 48 aydı. Tüm sağ kalım ve hastalıksız yaşam oranı RH grubunda %86.7, NAKT'ye cevapsız grupta %80, NAKT'ye cevaplı grupta %66.7'ydi (p=0.501).

SONUÇ: NAKT stromal invazyon derinliği dışında cerrahi-patolojik risk faktörlerini ve sağ kalım oranlarını iyileştirmemekteydi. Öyle görünüyor ki, umut vaat eden NAKT'yle ilgili hayal kırıklığı yaşama olasılığımız yüksektir.

Anahtar Kelimeler: Neoadjuvant kemoterapi, Servikal karsinoma

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