

THE COMPARISON OF FOUR DIFFERENT TREATMENT MODALITIES IN BULKY STAGE IB AND IIA CERVIX CANCERS

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SUMMARY

Objective: To compare the effectiveness of four different treatment modalities in International Federation of Gynecology and Obstetrics (FIGO) IB2 and IIA2 bulky cervical cancers.

Material and methods: Totally, n = 70 eligible women with bulky (≥ 4 cm) FIGO IB2 - IIA2 cervical cancer that diagnosed and treated at our clinic between the years of 1/1994 - 1/2010 were reviewed retrospectively. Data regarding demographic and disease related characteristics were obtained for analysis from patients' files. Different treatment modalities (radical hysterectomy followed by adjuvant chemoradiation (RH + CTRT); primary chemoradiotherapy (CTRTR); neoadjuvant chemotherapy followed by radical hysterectomy (NACT + RH) and neoadjuvant chemoradiotherapy followed by radical hysterectomy (NACRT + RH) were compared in terms of disease-free survival (DFS) and overall survival (OS) by Kaplan-Meier test. A p value of less than 0.05 was accepted as statistically significant.

Results: Sixty-three patients (90%) had Stage IB2 and seven (10%) had stage IIA2 disease. (RH + CRT), (CTRTR), (NACT + RH) and (NACRT + RH) were performed to 32, 23, 10 and 5 patients, respectively. Mean follow-up period was 78.1 ± 51.6 months [range: 10-210]. Thirteen patients (18.6%) developed recurrence and 10 (14.3%) died from disease. Mean disease-free (DFS) and overall survival (OS) were 64.6 ± 46.7 [4-210] and 68.2 ± 47.3 [10-210] months; respectively. No statistically significant difference was found in terms of survival between four treatment methods ($p = 0.85$ for DFS and $p = 0.9$ for OS).

Conclusion: The effectiveness of four treatment modalities were similar in terms of survival for patients with bulky FIGO stage IB2 and IIA2 cervical cancers.

Key words: Bulky stage 1b-2a cervix cancer, primary chemoradiotherapy neoadjuvant chemotherapy, neoadjuvant radiotherapy, radical hysterectomy, Journal of Turkish Society of Obstetrics and Gynecology, (J Turk Soc Obstet Gynecol), 2013; Vol: 10, Issue: 1, Pages: 42- 7

EVRE IB VE IIA BULKY SERVİKS KANSERLERİNDE DÖRT FARKLI TEDAVİ MODALİTESİNİN KARŞILAŞTIRILMASI

ÖZET

Amaç: Uluslararası Jinekoloji ve Obstetri Federasyonu (FIGO)'ya göre evre Ib2 evre Iia2 bulky serviks kanserlerinde dört farklı tedavi modalitesinin etkinliğinin karşılaştırılmasıdır.

Gereç ve yöntemler: Kliniğimizde, 1/1994 ve 1/2010 yılları arasında FIGO IB2 - IIA2 serviks kanseri tanısı alan ve tedavi edilen toplam 70 uygun hasta retrospektif olarak incelendi. Demografik veriler ve hastalıkla ilişkili karakteristikler analiz için hasta dosyalarından elde edildi. Farklı tedavi modaliteleri, radikal histerektomi ve adjuvan kemoradyoterapi (RH + KTRT), primer kemoradyoterapi (KTRT), neoadjuvan kemoterapi takiben radikal histerektomi (NAKT + RH), neoadjuvan kemoradyoterapi takiben radikal histerektomi (NAKRT + RH) hastalüksüz sağkalım (HS) ve genel sağkalım

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(GS) açısından Kaplan-Meier testi kullanılarak karşılaştırıldı. $P < 0.05$ istatistiksel olarak anlamlı kabul edildi.

Sonuçlar: Altmış-üç (%90) hasta evre Ib2 ve 7 hasta evre IIA2 idi. (RH + KRT), primer (KTRT), (NAKT + RH) ve (NAKRT + RH) sırası ile 32, 23, 10 ve 5 hastaya uygulandı. Ortalama takip süresi 78.1 ± 51.6 ay [dağılım: 10-210] olarak tespit edildi. Onüç (%18.6) hastada rekürrens gelişti ve 10 (%14.3) vaka hastalıktan kaybedildi. Ortalama HS ve GS sırasıyla 64.6 ± 46.7 [4-210] ve 68.2 ± 47.3 [10-210] idi. Yaşam süreleri açısından dört tedavi yöntemi arasında istatistiksel anlamlı fark bulunmadı (HS için $p = 0.85$ ve GS için $p = 0.9$).

Tartışma: Bulky FIGO evre IB2 ve IIA2 serviks kanserli hastalarda dört farklı tedavi modalitesinin etkinliği sağkalm açısından benzerdir.

Anahtar kelimeler: Bulky evre 1b-2a serviks kanseri, neoadjuvan kemoterapi, neoadjuvan radyoterapi, primer radyokemoterapi, radikal histerektomi *Türk Jinekoloji ve Obstetrik Derneği Dergisi, (J Turk Soc Obstet Gynecol), 2013; Cilt: 10, Sayı: 1, Sayfa: 42- 7*

INTRODUCTION

Cervix cancer is the second highest mortality rate of cancer after breast among women all over the world and the course of patients with advanced stage disease is worse⁽¹⁻³⁾. Radical hysterectomy with systematic pelvic and paraaortic lymphadenectomy is considered to be the standard therapy for patients with early stage cervical cancer. But the rate of recurrence is as high as 30 percent in only surgery performed patients⁽²⁻³⁾. The optimal management of locally advanced cervical tumors measuring ≥ 4 cm diameter is controversial in the literature. In locally advanced cervix cancers, there are four different treatment modalities are put into practice including radical hysterectomy followed by adjuvant chemoradiation (RH + CTRT), primary chemoradiotherapy (CTRT), neoadjuvant chemotherapy followed by radical hysterectomy (NAKT + RH), and neoadjuvant chemoradiation therapy followed by radical hysterectomy (NART + RH)⁽¹⁻⁵⁾.

In a randomised study of radical surgery versus radiotherapy in stage IB-IIA cervical cancers, the cure rate of each options yield similar 5 year survival rates ranging between 70-95%⁽⁴⁾. Adjuvant radiotherapy treatment is carried out when postoperative pathological examinations reveal risk factors for recurrence, including deep stromal invasion (DSI), lymphovascular space invasion (LVSI), parametrial invasion (PI), lymph node metastasis (LNM), and bulky tumor⁽³⁻⁵⁾. Regardless of treatment, patients with ≥ 4 cm bulky tumors had more recurrence and worse survival rates than patients with stage IB1⁽⁵⁻⁸⁾. The 5 year survival rate for patients with tumor size greater than 3 cm was only 30-60% compared to 5 year survival of 70-90% in patients with tumor size less than or equal to 3 cm^(7,9,10). There is no clear consensus in terms of

treatment modalities for stage IB2 and IIA2 cervical cancers between centers in the worldwide. In the light of these attainments, the goal of this retrospective study was to compare the effectiveness of four different treatment methods in the management of stage IB2 and IIA2 cervical cancers.

MATERIAL AND METHODS

In this retrospective study, totally 70 eligible women with complete information and bulky (≥ 4 cm) FIGO stage IB2 and IIA2 cervical cancer that diagnosed and treated at Department of Gynecologic Oncology, Aegean Obstetrics and Gynecology Education and Research Hospital, Izmir, Turkey between the years of 1/1994 - 1/2010 were analyzed. Data regarding demographic and disease-related characteristics were obtained from patient's files. Four different treatment modalities; adjuvant chemoradiation after radical hysterectomy (RH + CTRT) $n=32$; primary concomitant chemoradiation (CTRT) $n=23$; neoadjuvant chemotherapy followed by radical hysterectomy (NAKT + RH) $n=10$; neoadjuvant chemoradiation followed by radical hysterectomy (NACRT + RH) $n=5$ were compared in terms of disease-free survival (DFS) and overall survival (OS). Institutional Review Board approval was obtained from our center.

The patients who had histologically proven cervical cancer, stage IB2-IIA2 bulky (≥ 4 cm in diameter) according to International Federation of Gynecology and Obstetrics new (FIGO) 2009 criteria, adequate hematologic, renal, and liver function tests and no evidence of secondary neoplasm were included to the study. Stage of disease and tumor dimension were evaluated with rectovaginal examination, colposcopy, abdominopelvic

ultrasound, combination of magnetic resonance (MRI) and computerized tomography (CT).

Primary adjuvant chemotherapy (cisplatin 40 mg/m² weekly) were administered 3-5 times and radiotherapy was performed as brachytherapy and externally to all patients. As neoadjuvant chemotherapy; three cycles paclitaxel 60 mg/m² plus cisplatin 40 mg/m² every ten days and as neoadjuvant chemoradiotherapy external-beam radiotherapy to 45 Gy plus weekly cisplatin 50 mg/m² were administered. Surgery was performed 3-4 weeks after completion of the preoperative treatments. After surgery adjuvant chemotherapy + brachytherapy + pelvic radiotherapy was administered to all patients. Adjuvant extended field radiotherapy was performed to 9 patients. Statistical analysis was performed with SPSS 16.0 statistical package program (SPSS, Inc., IL, Chicago, USA) by using Kaplan-Meier test. A p value of less than 0.05 was accepted as statistically significant.

RESULTS

Sixty-three patients (90%) had bulky FIGO Stage IB2 and 7 (10%) had stage IIA2 cervical cancer. The clinical tumor size ranged from 4.1 to 10 cm, with a mean tumor

diameter of 5 cm. Patients' clinical and surgicopathologic characteristics are presented in Table 1. Histologic cell types include n= 60 (85.7%) squamous cell carcinomas, n= 6 (8.5%) adenocarcinoma, and n = 4 (5.8%) adenosquamous carcinoma. Pathologic research showed parametrial involvement in 2 (2.85%) patients. Seven (10%) patients had LVSI, and only one patient had positive surgical margins. Nine (12.8%) patients had pelvic and/or paraaortic nodal metastases.

RH + CTRT, primary CTRT, NACT + RH and NACRT + RH were performed to n = 32, n = 23, n = 10 and n = 5 patients, respectively. Mean follow-up period was 78.1 ± 51.6 months [range: 10-210 months]. Thirteen patients (18.6%) developed recurrence and 10 (14.3%) died from disease. Mean disease free (DFS) and overall survival (OS) were 64.6 ± 46.7 [4-210] and 68.2 ± 47.3 [10-210] months; respectively. In NACRT + RH group, one patient developed vesicovaginal fistula, and in RH + CTRT one patient developed long-term hydronephrosis that needed urethral stenting. Five year disease free and overall survival rates for (RH + CTRT); (CTRTR); (NACT + RH); (NACRT + RH) groups are found as 88 ± 6%; 80 ± 8%; 100%; 80 ± 8% and 93 ± 4%; 86 ± 4%; 100%; 84 ± 4%, respectively. No statistically significant difference was found in terms of survival between four treatment methods (p = 0.85 for DFS and p = 0.9 for OS), (Table II, Fig.1 and 2).

Table I: Clinical and surgicopathologic characteristics of the study patients.

	RH + CTRT (n = 32)	CTRTR (n = 23)	NACT + RH (n = 10)	NACRT + RH (n = 5)
Age*	50 [34-65]	48 [36-70]	48 [42-59]	48 [42-50]
Tumor Type**				
Squamous cell cancer	26 (81.25)	19 (82.6)	10 (100)	5 (100)
Adenocancer	4 (12.5)	2 (8.7)	-	-
Adenosquamous cancer	2 (6.25)	2 (8.7)	-	-
Tumor Size***				
4 cm	12	11	6	2
5-6 cm	17	8	4	2
7-8 cm	2	1	-	-
9-10 cm	1	2	-	1
>10 cm	-	1	-	-
FIGO Stage***				
IB2	31	17	10	5
IIA2	1	6	-	-
LVSI***	5	-	2	-
Parametrial involvement***	2	-	-	-
Positive surgical margin***	1	-	-	-
Pelvic and/or paraaortic nodal metastases***	8	-	-	1

Values are expressed as *: median with range, **: n (%), ***: n

RH + CTRTR: radical hysterectomy followed by adjuvant chemoradiation; **CTRTR:** primary chemoradiotherapy;

NACT + RH: neoadjuvant chemotherapy followed by radical hysterectomy; **NACRT + RH:** neoadjuvant chemoradiotherapy followed by radical hysterectomy

LVSI: Lymphovascular space involvement

Table II: Disease free and overall survival rates with respect to treatment modalities.

	Tahmini 5 yıllık HS	Tahmini 5 yıllık GS
RH + KTRT	88 ± 6	93 ± 4
KTRT	80 ± 8	86 ± 4
NAKT + RH	100	100
NAKRT + RH	80 ± 8	84 ± 4
Log Rank (Mantel Cox) p	0.85	0.9

Values are expressed as rate (%) ± standart deviation, **DFS:** Disease free survival, **OS:** Overall survival

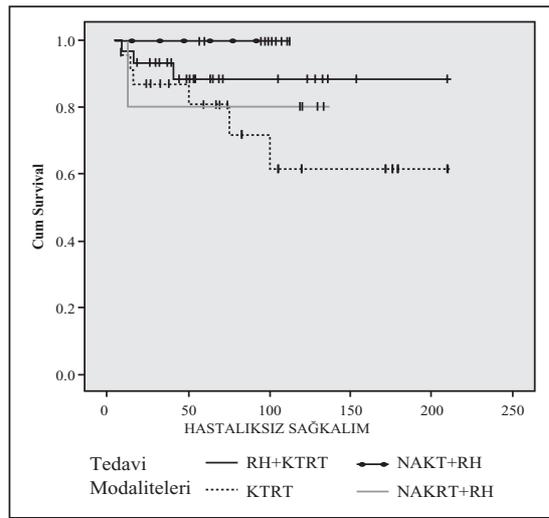


Figure 1: Disease free survival curve regarding to four different treatment modalities.

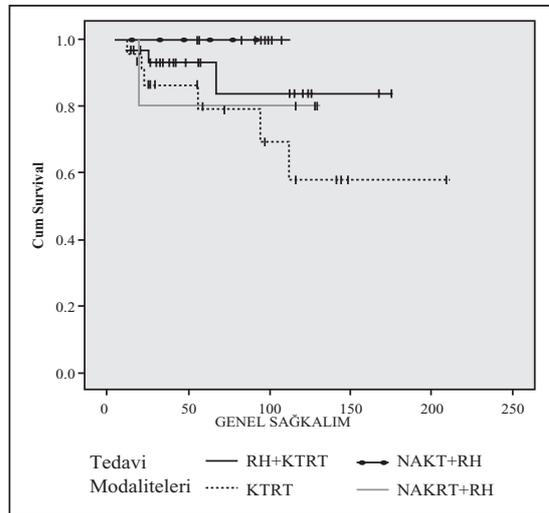


Figure 2: Overall survival curve regarding to four different treatment modalities.

DISCUSSION

The ideal management of bulky cervical tumors shows differences between centers in the worldwide. Patient factors like age, fertility desire, medical status, tumor characteristics (tumor volume, depth of invasion, lymphovascular space invasion, lymph node metastases status, histopathologic type) and the experience of clinicians are the factors concerning treatment modality. Both radical surgery and radiotherapy have proven to be equally effective, but differ in terms of morbidity and complications. Radical surgery has some advantages as ovarian function sparing and avoid the effects of early menopause in young women when compared with radiotherapy. Patients who have comorbidities and contraindications for surgery also benefit from radiotherapy. There are some conflicting published datas regarding the treatment of bulky stage IB-IIA cervical cancer^(3,8,9,11). While some centers are performing primary surgery for stage IB2 disease followed by tailored postoperative radiation with or without chemotherapy, the others are in favor of primary chemo-radiation therapy. Today there is no agreement for the treatment of bulky cervical cancers and there are few studies to evaluate the efficacy of different type of treatments in the literature.

The 5-year survival rate of radical hysterectomy and radiation therapy was 78-92% versus 65-90%⁽¹¹⁾. Because of unfavorable survival rates with single treatment method like radical surgery or radiation therapy alone in patients with bulky stage IB, other treatment modalities have been required to achieve and improve the local control and enhance survival. Rushdan et al.⁽¹²⁾ reported that treatment with surgery and radiotherapy significantly decreased the recurrence rate and improved overall survival in patients with cervical carcinoma compared to surgery alone. CTRT is one of the most used treatment modality in bulky cervical cancers. In this context chemotherapeutic agents (especially cisplatin) are effective in eradicating the subclinical metastasis and act as a radiosensitizer. However, 5-fluorouracil (5-FU), hydroxyurea, ifosfamide, mitomycin-C, and bleomycin have also been used for this purpose^(13,14). Moris et al. showed that the CTRT is superior to the radiation alone in the treatment of locally advanced cervical cancer with 5-year overall survival rate 58% and 73% respectively⁽¹⁵⁾. The original cochrane review which include 4580

patients strongly suggested that chemoradiation improves overall survival, progression free survival and also demonstrated significant benefit for local and distant recurrence⁽¹⁶⁾.

Positive lymph node status, positive/close surgical margins, and parametrial invasion are the risk factors for recurrence in cervical cancers. The patients with these risk factors benefited from adjuvant chemo/radiation after radical hysterectomy^(2,3,16,17). Adding concurrent chemoradiotherapy to patients who have tumor size greater than 2 cm has been found more advantageous and has shown 19% improvement in 5 year survival⁽¹⁷⁾.

For improving resectability rate, neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy can be used prior to surgery. Adminstrating chemotherapy before radical surgery might shrink the tumour. This could make surgery easier and it may also help to remove any tiny tumours that cannot be easily seen^(18,19). There was no randomized phase III trial between neoadjuvant chemotherapy and concurent chemoradiation in bulky stage IB cervical cancers. Modaress et al. noted that neoadjuvant chemotherapy and chemoradiation had similar effects in survival prognostic factors⁽²⁰⁾. Panici et al. showed statistically significant survival rates between neoadjuvant chemotherapy followed by radical hysterectomy + pelvic lymphadenectomy group and radiation therapy alone group in locally advanced cervical cancer (5 year OS and DFS rate of 59% and 55% in neoadjuvant chemotherapy arm, 44% and 44% in radiotherapy arm)⁽²¹⁾. Moreover; the first randomized trial using neoadjuvant chemotherapy in stage IB squamous carcinoma showed significantly improved survival rates⁽²²⁾. In a retrospective study performed in Turkey, Turan et al. evaluate and compare the efficacy of three treatment modalities NACT + RH, RH + CTRT and primary radiotherapy in 74 patients with stage IB2 cervical cancer and concluded that none of the treatment modalities had any superior effect on survival⁽²³⁾. In another study by Özgül et al. including 36 cases evaluated the factors determining response to neoadjuvant chemotherapy in stage IB2 cervix cancer and reported that neoadjuvant chemotherapy is more effective only in elderly patients but such factors like tumor size and pathology, chemotherapy protocol and number of cycles are not effective⁽²⁴⁾. In our series, 5 year OS was $93 \pm 4\%$ for RH + CTRT, 100% for

NACT + RH and, $86 \pm 4\%$ for primary CTRT respectively. In the light of these premices, it can be concluded that our results are in concordance with previous published large sampled studies.

Although the weak point of this study is the small number of patients especially in NACRT + RH group, our results represent important clues in terms of treatment decision for bulky stage IB2 and IIA2 cervical cancers. According to the best of authors' knowledge, the different side of this article is the first performed study in Turkey that searching the efficacy of four treatment modalities in the management of bulky cervix cancers.

CONCLUSION

We demonstrated that the effectiveness of four treatment modalities were similar in terms of survival for patients with bulky FIGO stage IB2 and IIA2 cervical cancers. Moreover; the treatment decision and type should be individualized by evaluating multiple factors including the stage of disease, age, medical condition of the patient, tumor-related factors for yielding the best cure with minimum complications. Further large sample sized studies are needed to evaluate the efficacy of treatment modalities in patients with bulky stage IB2 and IIA2 cervical cancer.

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