



## Comparison of Tumor Regression Rate in Cervical Cancer Patients Treated with Radiotherapy Alone versus Chemoradiotherapy

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### Yalnız Radyoterapi ile Eşzamanlı Kemo-Radyoterapi Alan Servikal Kanserli Hastalarda Tümör Regresyon Oranlarının Karşılaştırılması

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#### ABSTRACT

**Aim:** The aim of the research was to compare the tumor regression rate between Cervical Cancer patients treated with radiation therapy alone or concurrent chemo-radiotherapy.

**Patients and methods:** Seventy-two patients with IIA-IIIB stage cervical cancer were included. Patients were divided to 2 groups. In group I, we used EBRT in total dose of 46-50 Gy and HDR ICBT – two divided doses of 9,0 Gy weekly. In group II, we carried out the same radiotherapy regimen with additionally cisplatin (40 mg/m<sup>2</sup>, weekly, 5 weeks). The longest diameter of the tumor before treatment was compared to measurement after EBRT but prior to ICBT. Treatment response rate was evaluated 1 month after end of the treatment.

**Results:** Tumor regression prior to ICBT varied widely, ranging from 12% to 61%. However, the tumor regression rate was higher in patients treated with chemo-radiotherapy, ranging from 39% to 61% (Mean 53%) compared to radiotherapy alone ranging from 12% to 49% (Mean 35%). In tumors with longest diameter  $\geq 5$  cm, tumor regression rate was ranged between 12% to 42% (median 26,2%) in patients treated with radiotherapy alone, and between 39% to 48% (median 44,8%) in patients treated with chemoradiotherapy.

**Conclusions:** Outcome of this study for advanced cervical cancer treated by EBRT, brachytherapy and simultaneous chemotherapy shows satisfactory tumor shrinkage rate among all patients. Our results show that tumor regression rate is significantly higher in patients treated with concurrent chemoradiotherapy compared to radiotherapy alone.

**Key words:** cervical cancer, brachytherapy, chemoradiotherapy, tumor shrinkage, cisplatin.

#### ÖZET

**Amaç:** Bu araştırmanın amacı, yalnız radyoterapi alan hastalar ile eşzamanlı kemo-radyoterapi alan Servikal kanserli hastalarda tümör regresyon oranlarını karşılaştırmaktır.

**Hastalar ve yöntem:** Evre IIA-IIIB Servikal kanserli 72 hasta çalışmaya alındı. Hastalar iki gruba ayrıldı. Grup I'de, haftalık iki doza bölünmüş olarak 9,0 Gy HDR ICBT ve 46-50 Gy toplam doz EBRT kullandık. Grup II'de, aynı radyoterapi rejimine ilaveten sisplatin (40 mg/m<sup>2</sup>, haftada, 5 hafta) eklendi. Tümörün tedavi öncesi en uzun çapı EBRT tedavisinden sonraki ölçümlerle karşılaştırıldı, ancak ICBT tedavisi öncesi ile karşılaştırılmadı. Tedaviye yanıt oranı, tedavinin sona ermesinden 1 ay sonra değerlendirildi.

**Bulgular:** Tümör regresyonu, ICBT öncesi %12' den %61'e değin geniş ölçüde değişmekteydi. Ancak, tümör regresyon oranı, kemo-radyoterapi alan hastalarda, (%39'dan %61'e kadar değişmekte olup, ortalaması %53), yalnız radyoterapi alan hastalara (%12'den %49'a kadar değişmekte olup, ortalaması %35), göre daha yüksekti.  $\geq 5$  cm'den daha uzun çaplı tümörlerde, tümör regresyon oranı, yalnız radyoterapi alan hastalarda %12'den %42'ye kadar değişmekte olup, medyan %26,2'dir, kemo-radyoterapi alan hastalarda ise %39'dan %48'e kadar değişmekte olup, medyan %44,8'dir.

**Sonuç:** EBRT, brakiterapi ve eşzamanlı kemoterapi yoluyla ileri evre servikal kanserin tedavi edilmesine dair çalışmamızdaki sonuçlar, bütün hastalarda tümör küçülme oranının tatmin edici oranlarda olduğunu göstermiştir. Sonuçlarımız, tümör regresyon oranının eşzamanlı kemo-radyoterapi alan hastalarda, yalnız radyoterapi alan hastalardan belirgin olarak yüksek olduğunu göstermektedir.

**Anahtar kelimeler:** Servikal kanser, brakiterapi, kemo-radyoterapi, tümör küçülme oranı, sisplatin.

## INTRODUCTION

Cervical cancer remains one of the most important causes of death in women worldwide (1). It is the second commonest cancer in women and is the most prevalent malignancy in some low-income countries where the disease frequently presents as large tumours of advanced stage. Over 80% of patients reported to FIGO (International Federation of Gynecological Oncology) with invasive cancer are treated by radiotherapy (2).

According to official data in Azerbaijan cervical cancer is the second leading cancer after breast cancer among women. In spite of high effectiveness of screening and relatively easier diagnostics procedures vast majority of cervical cancer cases in our country have locally advanced stages disease at presentation (3).

Radiotherapy remains an integral component of the standard treatment for the majority of cases, particularly those with bulky early tumors and more advanced disease and a combination of megavoltage external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the accepted definitive mode of treatment. With aim to improve treatment results, radiotherapy was give combined with different physical and chemical radiosensitizing agents (4), and now it is well recognized that cisplatin-based chemoradiotherapy has been shown to improve overall survival in women with advanced cancer of the cervix (5).

We compared the tumor regression rate between radiation therapy alone and concurrent chemoradiotherapy prior to ICBT and analyzed relation of this data with outcome for cancer of the cervix.

## Patients And Methods

Patients with biopsy proven cervical cancer who had stage IIA-IIIB were eligible. Seventy-two patients who were admitted to the department of radiotherapy of National Center of Oncology between January 2008 and January 2009 were included.

All patients were staged according to the FIGO staging system. They were evaluated with, medical history, physical examination, pre-treatment ECOG/WHO performance status, blood test, renal and liver functions tests (i.e. creatinine and bilirubin), chest X-rays, ECG, HIV serology, ultrasound, magnetic resonance imaging of abdomen-pelvis performed for both primary tumor and nodal status (pelvic and para-aortic). Neither laparotomy nor laparoscopy was performed for tumor or nodal assessment. Patients with stage I, stage IV,

ECOG/WHO performance status  $\geq 3$ , older age ( $>70$  years), hydronephrosis, anemia (hemoglobin level  $<8$  g/dL), leucopenia (white cell count  $<2,000$  / $\mu$ L), thrombocytopenia (platelets  $<100,000$ / $\mu$ L), and serum creatinine level  $>100$   $\mu$ mol/L were excluded.

**Statistical Analyses:** Statistical evaluation was made by using the SPSS 11.5 software program. For the analysis of categorical variables the  $\chi^2$  test, and for the multiple group analysis the one way ANOVA test and Post Hoc Bonferroni Test were used.  $p < 0.05$  was considered as significant.

## RESULTS

Age of patients ranged from 32 to 73 years (median 51 years). Histology of the cases was as follows: squamous carcinoma in 68 patients (94,4%); adenocarcinoma in 4 patient (5.6%). All patients were divided into two treatment modality groups. EBRT was performed with Co-60 machine or by linear accelerator in all patients. Dose prescription was performed according to ICRU 38 report. The clinical target volume (CTV) comprised the primary tumour and pelvic lymph nodes. The upper field border was at L4/L5 or L5/S1 level, the lower border was at the obturator foramen, or at least one cm beyond palpable disease. The lateral borders were outside of the pelvis by at least 1–2 cm. Treatment was given by parallel opposed fields or a four-field arrangement (box technique). In the case of four-field technique, the upper and lower borders were identical as above, the ventral field border was the symphysis and the dorsal border parallels the anterior part of the S2/S3 region. The fraction sizes were 2.0 Gy as measured in the mid-plane. The total dose of 46–50 Gy was delivered by 23–25 fractions in an overall time of 5 weeks. Brachytherapy was performed by using Ir-192 source in high dose rate (HDR) regimen to increase the dose in point A to at least 75.0 Gy by application of 2 fractions.

In both groups HDR brachytherapy was initiated at the last week of EBRT (after EBRT dose of 40 Gy) and was consisting of two 9.0 Gy to point A weekly fractions (EQD2 = 29 Gy, EQD2 is the Equivalent Dose in 2 Gy daily fractions, 5 days weekly). In group I (n=35) treatment consisted of radiotherapy alone, group II (n=37) additionally received concurrent weekly infusions of cisplatin (40 mg/m<sup>2</sup>, weekly, 5 weeks). Cisplatin was administered with adequate hydration (1500 ml/day) within 1,5 hours before EBRT. All patients were followed-up with weekly complete blood count, renal and liver tests.

The amount of tumor shrinkage was measured by unidimensional approach suggested by Response

Evaluation Criteria in Solid Tumors Group (RECIST) (9). The longest diameter of the tumor before treatment was compared to measurement after EBRT (40 Gy) but prior to ICBT (at 5-th week). We used magnetic resonance imaging (MRI) for tumor visualization because it is considered that MRI is one of the best modalities to define the tumor mass and to distinct it from the round tissues. Treatment response was evaluated at 1 month after course completion according to RECIST criteria: complete and partial response, stabilization, progression. Complete response (CR) was defined as no evidence of disease on medical examination (in case of negative cytology investigation) or disappearance of lesion on MRI, partial response (PR) – at least 30% decrease of the longest diameter of tumor, progressive disease (PD) – at least 20% increase in longest diameter, stabilization (S) – neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease.

We also analyzed relation between treatment responses (evaluated in 1 month after treatment) with tumor shrinkage rate prior to ICBT (evaluated in 4-th week of treatment). Overall response rates as follow: CR – 79%, PR – 14%, S – 7%, PD – 0%. Treatment response rate according to treatment modality groups are shown in table 1.

## DISCUSSION

The median longest size of tumor in group I was 4,4 cm (ranging from 3,0 to 6,2 cm). In group II the median longest size of tumor was 4,7 cm (ranging from 3,1 to 6,8 cm). Tumor regression prior to ICBT varied widely, ranging from 12% to 61%. However, the tumor regression in patients with chemoradiotherapy was higher, ranging from 39% to 61% (Mean 53%) compared to radiotherapy alone ranging from 12% to 49% (Mean 35%).

In tumors with longest diameter  $\geq 5$  cm, tumor regression rate was ranged between 12% to 42% (median 26,2%) in patients treated with radiotherapy alone, and between 39% to 48% (median 44,8%) in patients treated with chemoradiotherapy.

Locally advanced cervical cancer treated with

curative intent requires radiation doses that can exceed small bowel, rectal and bladder tolerance. This makes brachytherapy a necessary adjunct to external beam radiotherapy (6). Brachytherapy (BT) plays a major role in the therapeutic management of patients with cervix cancer from stage I to IV with an improvement in local control and an increase in overall survival rate. The main principle of ICBT is delivering a high radiation dose directly to the tumor while sparing the surrounding normal tissues. This is possible due to rapid dose fall-off around the radioactive source what allows a very high dose to the central pelvis, while relatively sparing bladder, rectum, sigmoid and small bowel. That is why the main aim of EBRT or concomitant chemoradiation is to achieve maximal tumor shrinkage prior to ICBT (7). According to publications treatment response is related with overall survival rate: better response leads to better survival rate (8).

In conclusion, outcome of this study for advanced cervical cancer treated by EBRT, brachytherapy and simultaneous chemotherapy shows satisfactory tumor shrinkage rate among all patients. Concurrent chemoradiotherapy is well tolerated. There were no grade 3–4 acute gastrointestinal and urogenital side effects. Our results show that significant tumor regression occurs with concurrent chemoradiotherapy compared to radiotherapy alone. Treatment response one month after treatment also was better in chemoradiotherapy group.

Furthermore, carrying out of comparative analysis for all parameters with other radiation treatment methods of cervical cancer with increased number of patients and longer follow-up, we are planning to do conclusive assessment of concurrent chemoradiotherapy by 9.0 Gy two fraction HDR brachytherapy.

In spite the primary endpoint of this study was tumor shrinkage and treatment response rates but not survival rates, we should recognize that response to EBRT and chemo-EBRT may be strong predictor for all outcomes.

**Table 1. Treatment response rate according to treatment modality groups.**

<i>Treatment group</i>	<b>Treatment response 1 month after treatment</b>			
	<b>Complete response</b>	<b>Partial response</b>	<b>Stabilization</b>	<b>Progressive disease</b>
<b>I (Radiotherapy alone)</b>	71,4 % (n=25)	20% (n=7)	8,6% (n=3)	0
<b>II (Chemoradiotherapy)</b>	86,5% (n=32)	8,1% (n=3)	5,4% (n=2)	0
<b>All patients</b>	79% (n=57)	14% (n=10)	7% (n=5)	0

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