



Treatment Response and Acute Toxicity of Concurrent Chemoradiotherapy for Uterine Cervix Cancer in Comparison with Radiotherapy Alone

Serviks Uteri Kanseri Tedavisinde Eş Zamanlı Kemoradyoterapi ve Yalnız Radyoterapinin Tedaviye Yanıt ve Akut Toksisite Açısından Karşılaştırılması

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SUMMARY

Introduction: To assess treatment response, feasibility, safety and effectiveness of radiotherapy by different regimens of HDR-brachytherapy and external beam radiotherapy (EBRT) with and without concurrent cisplatin in the treatment of advanced cervical cancer.

Patients and Methods: A total of 95 patients with advanced cervical cancer were included for analysis. All patients were divided to 3 groups. In the I group we used EBRT in total dose 46-50 Gy, HDRBt - four 7.5 Gy weekly fractions. II group patients received 46-50 Gy EBRT, two weekly 9.0 Gy HDRBT fractions. In the III group we carried out the same radiotherapy regimen plus concurrent cisplatin (40 mg/m² of body surface per week for five weeks).

Results: All patients completed radiotherapy as planned and in the III group 96% patients received at least four cycles chemotherapy. Complete response (CR) was obtained at 88.8%, 90%, 96.6% patients in I, II, III groups correspondingly. Treatment related toxicity (particularly hematological) which was assessed according to CTC RTOG scale was significantly higher in the III group.

Conclusion: EBRT, HDRBt plus cisplatin appears to be safe and effective, although acute hematological toxicity is increased but appears to be acceptable.

Key Words: Cervical cancer, brachytherapy, chemoradiotherapy, cisplatin.

ÖZET

Giriş: İleri evre serviks kanseri tedavisinde yüksek doz oranlı brakiterapi (HDR-brakiterapi) ve dıştan odaklamalı radyoterapi (external beam radiotherapy) rejimlerinin tek başına ve eş zamanlı sisplatin kemoterapisi ile uygulandığında uygulanabilirlik, güvenlik, tedaviye yanıt ve etkinlik açısından karşılaştırılması.

Hastalar ve Yöntem: İleri evre serviks kanseri olan toplam 95 hasta incelemeye dahil edildi. Hastalar 119 gruba ayrıldı. Birinci gruptaki hastalara total doz 46-50 Gy olacak şekilde dıştan odaklamalı radyoterapi (external beam radiotherapy), yüksek doz oranlı brakiterapi (HDR-brakiterapi)-7.5 Gy'lik dörde bölünmüş haftalık fraksiyonlar halinde uygulandı. İkinci gruptaki hastalar 46-50 Gy dıştan odaklamalı radyoterapi (external beam radiotherapy), iki haftalık 9.0 Gy yüksek doz oranlı brakiterapi (HDR-brakiterapi) aldı. Üçüncü gruptaki hastalara ise aynı radyoterapi rejimleri ile birlikte eş zamanlı sisplatin (haftalık 40 mg/m² beş hafta boyunca) kemoterapisi uygulandı.

Bulgular: Bütün hastalar planlanan radyoterapiyi aldı ve üçüncü gruptaki hastaların da %96'sı en az dört siklus kemoterapi aldı. Tam yanıt oranları Grup 1, Grup 2 ve Grup 3'te sırasıyla %88.8, %90 ve %96.6 olarak tespit edildi. Tedavi ile ilişkili toksisite (özellikle hematolojik) CTC RTOG Skalası ile değerlendirildi ve Grup 3'te belirgin olarak yüksekti.

Sonuç: Dıştan odaklamalı radyoterapi (external beam radiotherapy) ve yüksek doz oranlı brakiterapi (HDR-brakiterapi)'nin sisplatin ile eş zamanlı uygulandığında akut hematolojik toksisitedeki kabul edilebilir artışa rağmen güvenli ve etkin görünmektedir.

Anahtar Kelimeler: Servikal kanser, brakiterapi, kemoradyoterapi, sisplatin.

INTRODUCTION

Uterine cervical cancer is one of the widespread gynecological malignancies and the main cause of oncogynecological mortality all over the world (1). According to WHO data annually 500.000 patients with cervical cancer are registered in the world what makes 5% of all oncological diseases and about 200.000 women die from this cancer (2,3).

Many present with locally advanced disease, although in developed countries the mortality is falling as tumours are diagnosed earlier, in part due to cervical screening programmes (4).

According to official data in Azerbaijan cervical cancer is in the second place after breast cancer among women. In spite of high effectiveness of screening measures and relatively easy diagnostics the vast majority of cervical cancer cases in our country at first visit to physician are already in late, locally advanced stages (5).

Selection of treatment method is an individual issue and depends on spread of the cancer process and also on co-morbid conditions. Early disease can be curatively treated either by surgery or irradiation but patients with locally advanced cervical cancer have a poor prognosis mainly due to failure to control the local disease with radiotherapy even though technique and methods of treatment have improved over the last decade. In spite of the various efforts to enhance the efficacy of irradiation, local failure is still the main problem in these cases. Radiotherapy remains an integral component of the standard treatment for the majority of cases, particularly those with bulky early tumors and more advanced disease. With aim to improve treatment results last years radiotherapy is done under action of different physical and chemical radiomodifying agents (6).

The advantage of concurrent chemoradiotherapy over radiotherapy alone in patients with cervical cancer

has now been well documented in a series of prospective randomized trials (7).

PATIENTS and METHODS

We conducted a prospective study to assess the eligibility of patients presenting with cervical cancer in the developing world for chemoradiotherapy. Patients with biopsy proven cervical cancer of IIA-IIIIB stages were eligible. We investigated treatment results of 95 patients applied to the department of radiotherapy of National Center of Oncology from January of 2008 to January of 2009. All patients were staged according to the FIGO staging system, after a workup, including medical history, physical examination, pre-treatment ECOG/WHO performance status, blood test, renal and liver functions tests (mostly creatinine and bilirubin concentrations), chest X-rays, ECG, HIV test, US, computed tomography scans or MRI of abdomen and pelvis performed both for primary tumor and for nodal status (pelvic and para-aortic). Laparotomy or laparoscopy was not performed for tumor or nodal assessment. Exclusion criteria: stage IA, stage IV, ECOG/WHO performance status < 3, age > 70 years, hydro-nephrosis, hemoglobin level < 8 g/dL, white cell count < 2.000/ μ L, platelets < 100.000/ μ L, serum creatinine level > 100 μ mol/L.

Depending on treatment method all patients were divided into three groups. External beam radiation therapy (EBRT) was similar in all groups and was performed with Co-60 machine or by linear accelerator. Dose prescription was performed according to ICRU 38. The treatment volume comprised the primary tumor 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 bony 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 was 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 4-5 weeks. This variety of doses and fractions is due to the individual participant's standard therapy taking into consideration missing days and was maintained throughout the study. Brachytherapy was performed by HDR (source: Ir) aiming to increase the dose in point A to at least 75.0 Gy by application of 2-4 fractions.

In the I group (45 patients) after 16-30 Gy of EBRT HDR brachytherapy was initiated consisting of four 7.5 Gy to point A weekly fractions (EQD2¹ = 44 Gy). In the II group (20 patients) HDR brachytherapy was initiated at the last two weeks of EBRT and was consisting of two 9.0 Gy to point A weekly fractions (EQD2 = 29 Gy). In the III group (30 patients) radiotherapy was similar to the II group plus concurrent weekly infusions of cisplatin in dose 40 mg/m², total 5 infusions. Cisplatin was administered on Mondays with adequate hydration (1500 mL) no later 1.5 hours to EBRT.

During all the treatment course patients underwent periodical medical examination including weekly blood count, renal and liver tests.

RESULTS

Studentized statistic method was used for statistical evaluation of the results. For all statistical tests $p < 0.05$ was considered significant.

Treatment response was evaluated at three month after course completion according to WHO criteria: complete (CR) and partial response (PR), stabilization, progression. Complete response was defined as no evidence of disease on medical examination (in case of negative cytology investigation) or on MRI.

Median duration of treatment course was 54 days (± 7 days). All patients received radiotherapy as planned in spite of some toxicity.

From all 95 patients CR was in 87, PR-in six and only in two patients treatment led to stabilization. In the group I at 40 (88.8%), in the group II at 18 (90.0%) and in the group III at 29 (96.6%) cases was registered CR. PR was achieved at 4 (8.8%), 1 (5.0%), 1 (3.3%) cases in the groups I, II, III accordingly.

Comparative analysis of close results in different groups showed that in the group III (concurrent chemoradiotherapy) no case of stabilization was registered.

Also in this group CR cases were more than in other groups ($p < 0.05$).

Comparative analysis did not reveal differences in treatment results depending on patients' age. Whereas it was significant dependence on histological type of tumor. So, in six patients with adenocarcinoma the treatment completed by PR in 2 (33.3%) cases.

Stage of disease also had influence on effectiveness of treatment. Independently on treatment method patients with IIIB stage of disease had worse results than patients applied in earlier stages. So, all 8 (8.4%) patients with PR and stabilization had IIIB stage cervical cancer.

Acute side effects were assessed at time of each evaluation according to RTOG Acute Toxicity Criteria and are more detailed showed in Table 1.

CONCLUSION

In conclusion, outcome of this study for advanced cervical cancer treated by EBRT, brachytherapy and simultaneous chemotherapy shows satisfactory CR rate-91.5% among all patients. Weekly cisplatin 40 mg/m² concurrent with radiotherapy is well tolerated when given to an unselected population of patients. While no grade 3-4 acute gastrointestinal and urogenital side effects occurred. 96% of patients in III group received all 5 cycles of cisplatin and in 4% cases received only 3-4 cycles, but in all patients radiotherapy was carried out as planned.

Further, by increase of patients amount and prolongation of follow up period, carrying out of comparative analysis for all parameters with other radiation treatment methods of cervical cancer we are planning to do conclusive assessment of concurrent chemoradiotherapy by 9.0 Gy two fraction HDR brachytherapy.

Also we consider that independently on treatment results the introduction of national screening programmes and the provision of accessible radiotherapy facilities should be the major priorities in the developing world setting.

¹ EQD2 is the EQuivalent Dose in 2 Gy daily fractions, five days weekly.

Table 1. Types and frequencies of acute adverse effects.

Organ, tissue	Group II														
	Group I					Acute toxicity grade (RTOG)					Group III				
	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Skin	17.8% (8)	77.8% (35)	4.4% (2)	-	-	15% (3)	80% (16)	5% (1)	-	-	13.3% (4)	80% (24)	6.7% (2)	-	-
Upper GI (nausea, vomiting)	91.1% (41)	8.9% (4)	-	-	-	90% (18)	10% (2)	-	-	-	-	93.3% (28)	6.7% (2)	-	-
Lower GI (rectitis)	31.1% (14)	68.9% (31)	-	-	-	15% (3)	80% (16)	5% (1)	-	-	10% (3)	73.3% (22)	16.7% (5)	-	-
Genitourinary (cystitis)	82.2% (37)	17.8% (8)	-	-	-	80% (16)	20% (4)	-	-	-	76.6% (23)	23.4% (7)	-	-	-
Leukocytes	86.7% (39)	13.3% (6)	-	-	-	85% (17)	15% (3)	-	-	-	3.3% (1)	33.3% (10)	60% (18)	3.3% (1)	-
Hemoglobin	88.9% (40)	11.1% (5)	-	-	-	90% (18)	10% (2)	-	-	-	10% (3)	70% (21)	20% (6)	-	-

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