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Single Center Results of Concurrent Chemo-Radiotherapy Treatment in Locally Advanced Cervical Cancer

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Abstract:

Objective: *In this study we evaluate our experience with concurrent chemoradiotherapy using three-dimensional conformal radiotherapy (3D-CRT) and high-dose-rate intracavitary brachytherapy with weekly cisplatin in the treatment of patients with locally advanced cervical cancer.*

Methods: *Between Jannuary 2012-December 2016 154 patients' medical records were retrospectively reviewed, and data on patient characteristics, treatment and toxicities were analysed.*

Results: *The median age was 52 years (range:25-86) The median tumour size was 47 mm (range 37-89). Eighty-nine patients (57%) had enlarged lymph nodes on MRI (≥ 10 mm). MRI demonstrated the involvement of the parametrium in 95 patients (62%). The median total treatment time was 55 days .Cisplatin was administered concurrently for a median of five courses. The median follow- up period was 24 months (range: 6-65months). The 3-year loco-regional free survival (LRFS), distant metastasis free survival (DMFS) and overall survival (OSS) rate was 85%, 66% and 89%, respectively. Grade 2-3 acute toxicity was observed in 55 patients (36%). Late grade 3-4 toxicity was observed in 11 patients (7%). Forty-four patients (29) persisted with the disease and eleven died.*

Conclusion: *Concurrent chemo-radiotherapy is an effective regimen, with acceptable toxicity, for patients with locally advanced cervical cancer.*

Keywords: *Carcinoma of the Cervix, Concurrent Chemo-radiotherapy, Radiotherapy*

1. INTRODUCTION

Cervical cancer is the third most common gynaecological cancer and the fourth most common cause of cancer deaths in women (1). Approximately 5 year local recurrence rate was 25-30% and 5 year overall survival rate was 30%. (2). The National Cancer Institute has issued a clinical warning and they reported that survival rates are increased after concomittant chemo-radiotherapy for locally advanced cervical cancer (3).

In the present study, we retrospectively analyzed medical records of patients with FIGO Stages IB-IV carcinoma of the cervix who were treated with concurrent chemo-radiotherapy between 2012-2016 at Kartal Dr Lutfi Kırdar Training and Research Hospital in Radiation Oncology Department.

2. MATERYAL-METODS

We retrospectively analyzed 154 patients with Stages IB–IVA squamous-cell carcinoma of the cervix who were treated with concomittant chemo-radiotherapy between 2012-2016 at our hospital. None of the patients had received prior treatment. All patients provided written informed consent. Patient charts were reviewed for clinicopathological data.

External pelvic radiotherapy was performed with three-dimensional technique (3D) plus high-rate brachytherapy and concurrence with cisplatin as primary treatment. The external beam radiotherapy planning was done computed tomography based simulator, and treatment was delivered to the whole pelvis using 18MV photons with box field. A 50 Gy dose whole pelvis was delivered in 25 fractions. The concurrent chemotherapy consisted of cisplatin 40mg/m^2 weekly with radiotherapy. The brachytherapy was delivered by using three dimensional brachytherapy planning, with 6 Gy per fraction given in five fractions and a total dose of 30 Gy prescribed to target minimum. Two fractions per week were given, making a total of five fractions. The volumes were delineated according to the consensus of the Groupe Européen de Curietherapie and the European Society for Radiotherapy and Oncology (4).The acute and late toxicies were evaluated with The Common Terminology Criteria for Adverse Events v. 4.0 and Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria. After completion of treatment, follow-up examinations were performed at 3 months for response and every 3 months for the next 2 years, as well as every 6 months thereafter for the next 5 years. The survival curves were estimated by Kaplan–Meier method, and the differences were assessed using the log-rank test; a p-value of 0.05 was considered significant.

3. RESULTS

One hundered fifty-four patients were analyzed. Most of the patients presented with bleeding per vaginum. Mean duration of symptoms of 4 months. Most of our patients had Stage II 93 (60.3%) followed byStage III 36 (23.3%) disease.The median fallow-up period was

24 months (range:6-65 months). The median age was 52 years (range 25-86 years). The median cervical tumor size was 47cm (range37-89 cm). The histology was squamous cell carcinoma in 140 (91%) patients and 14(9%) patients had adenocarcinoma. Eighty-nine patients (57%) had enlarged lymph nodes on MRI (≥ 10 mm). MRI demonstrated the involvement of the parametrium in 95 patients (62%).

All patients were treated with external beam radiation followed by intra-cavitary brachytherapy. The mean dose of pelvic radiotherapy was 47,3 Gy. The median course of weekly cisplatinium was five courses (range 4-6 courses) and the median overall treatment time including HDR-brachytherapy and external radiotherapy was 55 days (range 43-68 days). No significant differences were observed in dose intensity of chemotherapy and the overall treatment time of radiation therapy (p=0.13).

Most of the patients had Grade-1 or 2 acute toxicities. Acute Grade ≥3 skin, vomiting, and lower gastrointestinal (GI) toxicity were observed in 5(3.2%), 17 (11%) and 14 (9%) patients,

respectively. Grade-1 and Grade-2 hematological toxicity was seen in 94(63.6%) and 53(34.4%) patients, respectively. Only 7(4.5%) patients had Grade-3 hematological toxicity. Late GI Grade ≥3 toxicity was seen in only 7 (4.5%) patients and 4 (2.5%) had late GU toxicity.

The 3-year loco-regional free survival (LRFS), distant metastasis free survival (DMFS) and overall survival (OSS) rate was 85%, 66% and 89%, respectively (figure 1a,1b,1c). 109 (70.7%) patients were clinically disease-free. Eighteen (11.6%) patients had local residual disease at last follow up. Of the overall 45 relapses, 27 (60%) patients had distant metastasis, 5 (3.2%) had nodal failures and 13 (26.7%) had both local relapses and distant metastasis. We did not find any statistical significant factors for LRFS, DMFS and OSS.

4. DISCUSSION

In 1999 National Cancer Institute made a clinical alert that concurrent chemoradiation became treatment of choice for cervical cancer. The standard treatment of locally advanced cervical carcinoma was radiotherapy with concurrently weekly cisplatin 40mg/m2(5,6). The radiotherapy techniques have evolved from conventional 2-Dimensional planning to 3-DCRT and ıntensity modulated radiotherapy (IMRT). Conventional 2D planning technique based on bony landmarks and pelvic radiotherapy area included total bladder, rectum and small bowel with higher doses of radiation to the organ at risk. In early 1990s, CT based 3-dimentional planning getting popular because of its ability to better spare doses to the organ at risk and better treatment accuracy.

Gerstner and Gulia et al. published that decreased incidences of GI toxicities with the use of 3DRT .The CT-based 4-field plans had a better target volume coverage than the conventional 4 field box technique (7,8). 3DCRT has also been shown to improve overall survival when compared with 2D conventional radiotherapy (9) , although the analysis was a retrospective population-based study. In the current study all locally advanced cervical cancer patients were treated with CT-based 3D conventional pelvic radiotherapy.

Radiotherapy with concurrent chemotherapy has improved the overall survival and local control in comparison with radiotherapy alone, but this treatment modality also increased the treatment related toxicity (10). Around half of locally advanced cervical cancer patients undergoing chemoradiation treatment had ≥Grade 2 acute gastrointestinal toxicity and approximately one-sixth of patients report ≥Grade 2 genitourinary toxicity(11). Mundt et al. showed that IMRT technique significantly improved conformity and decreased doses to the OARs. This study reported that use of IMRT reduce gastrointestinal (p=0.001) and genitourinary (p=0.38) toxicities (12). Gandhi et al. also compared the toxicities and outcomes in locally advanced cervical cancer patients treated with pelvic IMRT and pelvic conventional radiotherapy technique. Their results showed that IMRT technique reduced gastrointestinal toxicity and also reduced doses to the pelvic bone marrow. The clinical outcomes of low doses to the pelvic bone marrow reduced the neutropenia and subsequent treatment breaks. Apart from the acute toxicities, incidences of chronic gastrointestinal and genitourinary toxicities have also been shown to be reduced (13). Our study demonstrated that acute Grade ≥3 skin, vomiting, and lower gastrointestinal (GI) toxicity were observed in 5(3.2%), 17 (11%) and 14 (9%) patients, respectively. Grade-1 and Grade-2 hematological toxicity was seen in 94(63.6%) and 53(34.4%) patients and only 7(4.5%) patients had Grade-3 hematological toxicity. Late GI Grade ≥3 toxicity was seen in only 7 (4.5%) patients and 4 (2.5%) had late GU toxicity. This results were comparable and acceptable with the previous studies. IMRT technique has showed significant reduction in acute and late GI and GU toxicity with previous retrospective data and randomized trials. But survival advantage with the use of IMRT technique has not been established by comparing IMRT with either conventional 4-field box technique or with the use of 3DCRT (14,15). IMRT treatment planning involves complex treatment planning which is time-consuming needs for institutional protocols, meticulous target delineation which there is a high risk of geographical miss of the target volumes.

The 3-year loco-regional free survival (LRFS), distant metastasis free survival (DMFS) and overall survival (OSS) rate in our study was 85%, 66% and 89%, respectively. In the multicentric 'INTERTECC-2' trial treating patients with IMRT, 2-year progression-free survival and overall survival for patients were 78.6% and 90.8%, respectively (16). Gandhi et al.(13) has

reported similar 2-year DFS and OS of 60% and 85.7% respectively, in the IMRT group, which was not significantly different to the conventional RT group (79.4% DFS and 76% OS).

The limitations of this study is retrospective nature but late toxicities is important to impair quality of life and remain the cause of long term morbidity in locally advanced cervical cancer patients. The incidence of acute toxicities is primarily determined by the quality of external beam radiotherapy and the incidence of late toxicities is primarily determined by the quality of brachytherapy. The ideal combination of cervical cancer treatment is use of conformal technique for external pelvic radiotherapy and CT or MRI planning for image based brachytherapy. content here.

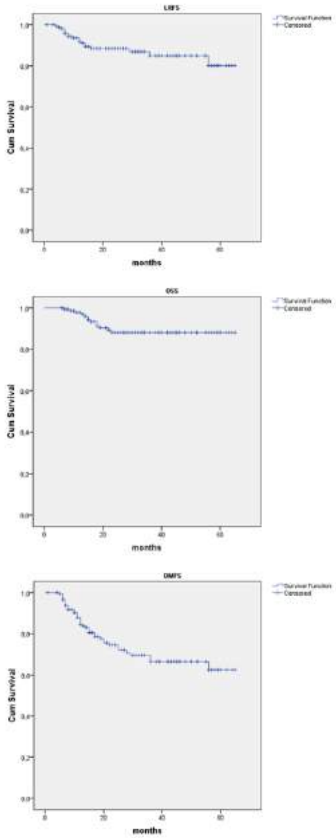

Fig -1a,1b,1c: Survival of LRFS,OSS AND DMFS

3. CONCLUSIONS

Our study demonstrates that concurrent weekly cisplatin based radiotherapy should be considered as the preferred standard of care in patients with locally advanced cervical cancer. The most common acute side effect is gastrointestinal problem. Also hematological toxicities is major problem for treatment breaks. 3DCRT is the ideal treatment modality for cervical cancer with toxicities not significantly higher than the IMRT technique and without compromising the survival outcomes. CT or MRI image based brachytherapy reduce late toxicities. In the future cervical cancer patients will be benefit from new molecular therapies such as immunotherapy with radiation therapy.

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