Concurrent Chemoradiotherapy without Brachytherapy in Locally Advanced Cervical Cancer

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Abstract

Background: Concurrent chemoradiotherapy (EBRT + cisplatin) plus intracavitary brachytherapy is the standard of care in patients with advanced cervical cancer. However, a number of patients could not undergone brachytherapy due to massive residual tumor or anatomical distortion. In this study, we have evaluated the treatment outcome in patients with locally advanced cervical cancer, undergone conventional EBRT plus cisplatin based chemotherapy.

Methods: In this study, we have selected patients with locally advanced cervical carcinoma (stage: IIB to IIIB) undergone external beam radiotherapy and chemotherapy without brachytherapy at our institute between October of 2007 and October of 2009. The patients have received 50 Gy within 5 weeks to whole pelvic that has followed by a localized boost dose on tumor to 70 Gy concurrently with cisplatin 35 mg/m2 weekly. The treatment has related toxicities, and survival (overall and disease free) have evaluated.

Results: 30 cases with a median age of 55 (range; 40 to 73) have been studied. According to FIGO classification, the clinical stages were as follows: stage: IIB 23, IIIA 4, and IIIB 3 cases. Three months after treatment, 19 patients (63.3%) have achieved complete response. With a median follow up time of 18 months (range; 10-33 months), 8/23 cases (34.7%) with stage IIB and 2/7 (28.5%) among stage IIIA-IIIB remained disease free at the end of follow up. Data have shown a 2-year overall survival rate of 58.7% ± 9% and 2- year disease free survival of 37.7% ± 9% . Most toxicities were grade I and II. 2 (6.6%) grade III diarrhea and 4 (13.3%) grade III neutropenia have recorded.

Conclusion: Although a considerable number of patients have achieved complete response using concurrent chemoradiotherapy without brachytherapy, the overall treatment outcomes especially for stage IIIA-IIIB were unsatisfactory. Using modern radiation therapy techniques with increased delivered boost dose could improve treatment results.

Keywords: Cervical cancer; Radiotherapy; Concurrent chemoradiotherapy

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Introduction

Cervical cancer is the fifth common cancer between the Iranian women [1, 2]. In spite of achieving major advances in screening, prevention and treatment of cervical cancer during past decades, it has remained an important public health issue especially in developing countries. Due to lack of national screening program in these countries, most patients have diagnosed with advanced stages. Therefore, this cancer is the leading cause of cancer death in women in developing countries including Latin America, Asia and Middle East [2].

While Surgery is the standard treatment method in stages I_a-IIA, locally advanced cases are generally selected for radiotherapy which usually includes External Beam Radiotherapy (EBRT) plus intracavitary brachytherapy [3, 4].

The addition of chemotherapy to radiotherapy (concurrent chemoradiotherapy) has been introduced to improve treatment outcomes in women with advanced cervical cancer. Following the results of five randomized trials, the National Cancer Institute has issued a clinical alert in 1999

and has recommended concurrent radiotherapy and chemotherapy (typically containing cisplatin) as the standard of care in women with locally advanced cervical cancer [5]. A randomized trial which has conducted by Radiation Therapy Oncology Group (RTOG) on four hundred three women with stage IIB-IVB cervical cancer has shown that the addition of cisplatin and 5FU to radiotherapy has significantly improved survival rate without increasing toxicity [6]. Some other randomized trials have also reported significant improved outcome with concomitant platinum-based chemotherapy and radiotherapy in comparison to radiotherapy alone [7, 8]. Finally, systematic review and meta-analytic studies compared concurrent chemoradiotherapy versus radiotherapy alone, and led to an improvement in local control and overall survival rates with concurrent chemotherapy and radiotherapy [9-11].

Patients who have undergone concurrent chemoradiotherapy might experience urgent treatment related toxicities including neutropenia or gastrointestinal toxicities which potentially interfere with the treatment protocol. There are also concerns about late gastrointestinal and/or genitourinary side effects which might affect the quality of life in survivors. The late treatment related sexual dysfunction is another critical issue, particularly in young patients [10].

Some patients with advanced stages of cervical cancer could not be suitable for intracavitary brachytherapy after receiving 45Gy to 50 Gy EBRT due to massive tumor bulk and/or anatomical distortion. These women typically continue on localized EBRT. The delivered boost dose to the tumor using conventional EBRT instead of brachytherapy has limited by adjacent organs tolerance such as bladder and rectum. This study has designed to evaluate the efficacy and toxicity of concurrent chemoradiotherapy to whole pelvic which has followed by localized boost dose that delivered to tumors, using conventional 4-field box technique in advanced cervical cancer.

Materials and Methods

This study has conducted at Radiation Oncology Department of Ghaem Hospital affiliated to Mashhad University of Medical Sciences, Iran. It has registered by Research Council of Mashhad University of Medical Sciences (code number:2124).

The inclusion criteria during this study were as follows: patients with cervical Squamous Cell Carcinoma whose have confirmed by pathology, stage IIB-IIIB, without any history of any previous treatment for cervical cancer, at least 3 months duration of life expectancy, normal liver and kidney functions, and have treated by concurrent chemotherapy and radiotherapy without intracavitary brachytherapy due to anatomical problems from October 2007 to October 2009. The exclusion criteria were: presence of simultaneous malignancies, para-aortic lymph nodes in CT scan and/or distant metastases, severe ischemic heart disease, not complying with the complete radiation protocol.

After receiving approval from the Ethic Committee of Mashhad University of Medical Sciences, suitable patients have enrolled in this study from 2007 to 2009. After explaining the treatment protocol and possible side effects, a written consent has taken from each patient before commencing the treatment.

All patients have physically examined by a radiation oncologist and a gynecologist. The pretreatment investigations have included lab tests as below: Complete Blood Count (CBC), serum electrolytes, biochemical laboratory tests, chest X-ray and abdominopelvic CT-scan.

Treatment Protocol

EBRT has administered using cobalt 60 unit. All patients had supine position during simulation and treatment. During simulation, radiopaque markers have placed at the cervical orifice and at the distal margin of tumor in vagina. The patients have treated using four-field box with SSD at 80 cm technique. Irradiation has delivered to whole pelvic encompassing uterus and cervix, common iliac, external iliac, hypogastric and blocked lymph nodes. The lower margin has defined depending upon the tumor extension to vagina. A dose of 50 Gy in 25 fractions concomitant with cisplatin 35 mg/m^2 weekly has prescribed. We have checked CBC and kidney function tests, weekly before chemotherapy session. The patients have also assessed for gastrointestinal and dermal toxicities every week. After receiving 50 Gy, all cases had gynecological examination. Suitable patients for brachytherapy have excluded from this trial. Women who could not undergone intracavitary brachytherapy due to massive residual tumor and/or anatomical distortion have selected for continuing on localized field external beam radiotherapy to 70 Gy/7 weeks with weekly chemotherapy. Chemotherapy has postponed in case of neutrophil count <1500per cubic-millimeter

and/or creatinine clearance <60 ml/min and sever GI or dermal toxicities.

The patients have examined every 3 months up to 2 years and every 6 months thereafter. Chest X-ray and abdominopelvic ultrasound have ordered annually. Treatment response has evaluated based on RECIST criteria and it has confirmed by bimanual examination, Pap smear and biopsy [12]. The treatment has related toxicities have graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4, published by National Cancer Institute (NCI).

Statistics:

Frequency tables and diagrams have used for data description. We have utilized Chi-square test to compare frequencies between different groups. Kaplan-Meier method has used for assessing survival rates. The overall survival has calculated from time of the diagnosis to time of the death, from every cause till the last visit. Disease free survival has measured from the time of diagnosis to the time of recurrence or the last visit with no evidence of disease. The survival curves have compared between different groups by means of log-rank test. We have considered p-values less than 0.05 as statistically significant. The data have analyzed using SPSS software.

Results

30 patients with a median age of 55 (range; 40-73) have enrolled in this study. FIGO stages were as follows: 23 (76.6%) IIB, 4 IIIA, and 3(10%) IIIB. The treatment response has assessed 3 months after irradiation. 19 patients (63.3%) have achieved complete response with no evidence of disease. 4 cases had partial response (> 50% reduction in tumor diameter) and 7 cases (23.3%) have obtained no significant response. In comparison with patients with stage IIIA-IIIB, significantly higher number of patients with stage IIB disease has enjoyed complete response (28.5% vs. 73.9%, p: 0.02). The median follow up time for all patients was 25.5 months (range; 11-56 months). 10 cases (33.3%) have remained disease free at the end of follow up; meanwhile, 19 instances of death (all cancer related) have recorded. The proportion of patients who have remained disease free at the end of follow-up was 8/23 (34.8%) among cases with stage IIB and 2/7 (28.5%) among those with stage IIIA-IIIB disease. All patients with stage IIIB have failed the treatment. Table 1 reveals treatment results according to different stages.

Table 1. Treatment outcome according to different stages

Stage	Total number	Achieving CR Number (%)	Disease free at the end of follow Number (%)	Median Overall survival Months(95% CI)
Stage IIB	23	17 (73.9)	8 (34.8)	26.2 (22.4-29.9)
Stage IIIA	4	2 (50)	2 (50)	18.2 (12.6- 23.8)
Stage IIIB	3	0	0	12.6 (11.6-13.7)

The median overall survival was 27 months (95% CI, 16.7 – 37.4) with a 3-year overall survival rate of 39.1%±9% (Figure 1). The median survival time was relatively longer in patients with stage IIB disease in comparison to those with stage IIIA-IIIB (30 vs. 18 months, P=0.32); however, the difference has not reached statistical significance. There was also no significant difference in median overall survival between patients younger than 56 and older cases (30 vs. 18 months, P:0.12).

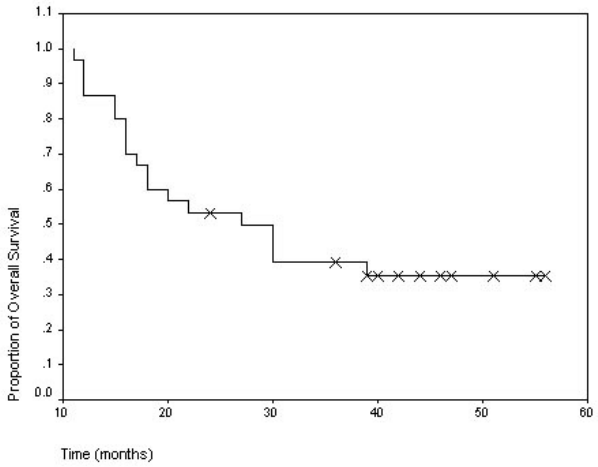

Figure 1. It shows the overall survival among 30 patients with Stage IIB, IIIA, IIIB cervical cancers whose have undergone chemo-radiotherapy without brachytherapy.

Complications

Themostcommonacutecomplicationwashematological toxicities. As shown in Table 2, most acute complications were mild to moderate and did not significantly interfere with the protocol. We have observed no instance of neutropenic fever duringthetherapy.Wehaveobserved rectovaginal fistula in 3 and vesicovaginal fistula in 2 cases which all have accompanied with active local tumor. There was no intestinal obstruction during the follow-up.

Table 2. Frequency of acute hematological and gastrointestinal toxicities

Parameters	Grade I	Grade II	Grade III	Grade IV
Anemia	10 (33.3%)	7 (23.3%)	0	0
Neutropenia	9 (30%)	10 (33.3%)	4 (13.3%)	0
Nausea and vomiting	1 (3.33%)	3 (10%)	0	0
Diarrhea	2 (6.66%)	1 (3.33%)	2 (6.66%)	2 (6.66%)

Discussion

The standard treatment of advanced cervical cancer is EBRT to primary tumor and lymph nodes at risk to a total dose of 45-50 Gy concurrent with cisplatin based chemotherapy plus a boost dose to primary tumor using intracavitary brachytherapy for a total dose to point A of 80 Gy. The incorporation of chemotherapy has significantly improved survival [6-11]. Brachytherapy has also an integral role in improving local control and enhancing survival in these patients [13]. However, in rare cases, brachytherapy is not feasible due to insufficient tumor regression and/or anatomical distortion. These patients might continue on EBRT delivered to the gross tumor, keep using 4-field box technique. Our series have included 30 patients with stage IIB-IIIB cervical cancer, undergoing EBRT alone to a total boost dose of 70 Gy concomitantly with cisplatin, based on chemotherapy. A significant number of stage IIB patients have achieved complete response following treatment (17/23, 73.9%); however, with a median follow up of 25.5 months, only 8 (34.7%) remained disease-free till the end of follow up.

Patients with stage III disease had worse outcome with only 2 from 7 patients (28.5%) remained disease-free during the follow up. Barraclough et al, in a study on 44 patients have received external beam boost instead of intracavitary brachytherapy, has shown a 3-year cancer specific survival rate of 70% and 42% for stage II and III respectively [14]. Historically, studies have revealed that patients, who have undergone conventional EBRT without brachytherapy, have a poorsurvival and local control [15].

The total dose which could be delivered using EBRT 4-field box technique has limited by the tolerance of surrounding organs including bladder and rectum. Modern radiation techniques such as Intensity-Modulated Radiation Therapy (IMRT) and stereotactic radiotherapy, allowed enhancing the dose to the tumor volume while sparing the normal tissue from receiving high doses [16]. Thus, these techniques could be potentially a proper substitute for brachytherapy and would increase the chance of local control and survival while reducing toxicity in patients whose could not be brachytherapy candidates [17-21]. Jarcano et al. in a trial on 26 patients with gynecological cancers have not undergone EBRT with a final boost dose using hypofractionated extra-cranial Stereotactic Radiotherapy (SRT) as a substitute to brachytherapy, reported encouraging toxicity and treatment results [22].

IMRT techniques are much more complex than traditional EBRT. Higher dose gradients make this treatment more sensitive to geometric uncertainties. Inter-and intra-fraction movements of cervix which have increased the risk of geometrical miss, should be considered [23]. Repeated IMRT planning during the treatment could improve the sparing of sensitive normal tissues, especially in patients with substantial tumor regression [24]. Image Guided Radiation Therapy (IGRT) with daily online imaging and repeated planning, could compensate for inter-fraction target movement as stated for treatment of prostate cancer [25, 26] enhance advantages of IMRT.

In conclusion, probably the treatment results of using conventional EBRT for delivering boost dose in patients with advanced cervical cancer whose could not be suitable for brachytherapy is not satisfactory. However, in regions that modern radiotherapy techniques such as IMRT and stereotactic radiotherapy are unavailable, continuing external beam radiotherapy using three dimentional conformal radiotherapy to 70 GY concomitant with chemotherapy might be acceptable. Modern external radiotherapy techniques have brought the opportunity for increasing the dose into the tumor volume, at the same time reducing local radiation toxicities.

Although these techniques have not still replaced brachytherapy for delivering the boost dose, but it seems reasonable to consider IMRT or SRT in patients who could not be candidate for brachytherapy.

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Conflict of Interest

The authors have no conflict of interest in this study.

Authors' Contribution

SimaKadkhodayan and FatemehHomaeiShandiz designed and wrote this article, FarnooshFarshidi and ParvaneDehghan collected the data, Mehdi SeilanianToussi and Monavar Afzal Aghaee analyzed the data. All authors read and approved the final manuscript.

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