DOI: https://doi.org/10.53350/pjmhs22166718

ORIGINAL ARTICLE

Assessment of Response Rate and Toxicity in Locally Advanced Squamous Cell Carcinoma Cervix with Induction Chemotherapy Followed by Radiotherapy in Comparison with Concurrent Chemoradiation

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ABSTRACT

Objective: To compare the toxicity, response rate, and survival of concurrent chemo radiotherapy and induction chemotherapy followed by radiotherapy alone in squamous cell cervical cancer patients.

Place and duration of study: Radiation Oncology Department of Nishtar Hospital for 1 year

Study design: A comparative retrospective study

Methodology: A total of 60 women were included in the study who have been diagnosed with stage IB2 to stage IIIB squamous cell cervical carcinoma. After passing the inclusion and exclusion criteria, patients were divided into two groups, a concurrent chemo radiotherapy group (30 patients) and a radiotherapy group (30 patients) by consecutive data sampling.

All the patients were subject to external beam radiotherapy to the 45 Gy to whole pelvis with 15 MV X-rays 5 days/week by using the four-field technique. The patients in the radiotherapy group were given induction chemotherapy with cisplatin 50 mg/m2 every 21 days with paclitexal 175mg/m2 (2 cycles) followed by radiotherapy alone. For the patients of concurrent chemo radiotherapy, patients were administered 40 mg/m2 cisplatin weekly with radiations for 5 cycles.

Results: The overall response rate for CCRT group and RT group was 65% (n=30) and 50% (n=30) respectively. The overall survival rate was 12 months and 8 months for the CCRT group and RT group respectively. Similarly, relapse-free survival was 10 months in CCRT patients and 6 months in RT patients. The rate of hematological toxicities was more in CCRT patients. The most common adverse effect was diarrhea with 3 (10%) patients in the CCRT and 2 (6.6%) patients in the RT group. No deaths occurred due to treatment.

Conclusion: The efficacy and toxicity of CCRT show promising results in squamous cell cervical carcinoma patients as compared to induction chemotherapy followed by radiotherapy treatment alone.

Keywords: Concurrent chemoradiotherapy. Radiotherapy, squamous cell cervical carcinoma, toxicity

INTRODUCTION

Cervical cancer is one of the leading causes of death in females in developing countries and its risk is increasing over time[1, 2]. In Pakistan, the mortality rate of cervical cancer is high as almost 70% of the cases are diagnosed at a very late stage. The exact causes of this disease are not unknown in the country as not much attention is paid to its screening and prevention. Generally, if carcinoma of the cervix is diagnosed at an early stage there is a 98% chance of survival[3]. However, the survival rate is further increased by treatment with chemotherapy and radiation combined[4, 5]. Currently, the most commonly used treatment for cervical cancer is surgery[6], radiation [7] and chemotherapy with hyperthermia, carboplatin[8], bevacizumab[9], cisplatin[10], mitomycin[11], paclitaxel[12], docetaxel[13], irinotecan[14], topotecan[15], 5-fluorouracil[16], gemcitabine[14] and ifosfamide[17]. The treatment method is chosen according to the stage of cancer and the minimum rate of morbidity.

The former literature proposed radiotherapy as the treatment of cervical cancer but the dose intensity needed to be limited in that case due to tolerance of normal tissues[18]. Therefore, a number of studies have been conducted to test the effectiveness of concurrent chemoradiotherapy, which has revealed better results than radiotherapy alone[19, 20]. This treatment is now a preferred method for stage II or higher cancer.No study has been conducted in Pakistan till now to test the efficacy of concurrent chemoradiotherapy in patients with late-stage cervical cancer. This study aims to compare the toxicity, response rate, and survival of concurrent chemoradiotherapy and induction chemotherapy followed by radiotherapy alone in squamous cell cervical cancer patients.

METHODOLOGY

A retrospective comparative study was conducted in the Radiation Oncology Department of the Nishtar Medical Hospital from May 2021- to May 2022. A total of 60 women, who have been diagnosed with stage IIB and IIIB squamous cell cervical carcinoma were included. Only those women were included who were aged between 30 to 60 years, had Karnofsky performance of equal to or more than 70, had hemoglobin equal to or more than 10 g/dL, leukocyte count equal to or more than 3000/mm3, absolute neutrophil count equal to or more than 1500/mm3, platelet count equal to or more than 100,000/mm3, creatinine clearance more than or equal to 50 mL per minute and had a normal hepatic function. All the patients provided their informed consent to become a part of the study. The patients who had non-squamous cervical carcinoma, stage IA, IB1 and IV tumors, distant metastasis, synchronous/metachronous tumors, prior history of chemotherapy, radiotherapy and malignancy were not included. The study was approved by the Ethical Committee of the hospital.

After passing the inclusion and exclusion criteria, patients were divided into two groups, a concurrent chemoradiotherapy group (30 patients) and an induction chemotherapy followed by radiotherapy group (30 patients) by consecutive data sampling.

All the patients were subject to external beam radiotherapy to the pelvis with 15 MV X-rays. These radiations were given in 2Gy fractions every day for 5 days per week by using four field techniques, the total dose being 45Gy for 25 radiation fractions. The upper and lower border of the pelvic portal was at the L4-5 junction and lowest point of the obturator foramen respectively. While the lateral border was 1.5-2 cm lateral to the pelvis girdle. While using the four-field technique, the anterior border of the lateral portal was positioned at the pubic cortex and the posterior border was in the mid of the S2 vertebrae. These were confirmed by CT scan and were moved if necessary. A cervical boost was given by using HDR brachytherapy with a 10Gy total dose. Orthogonal films were captured at 35 degrees and 315 degrees to confirm the doses, applicator positioning, and delivery of the dosimetric plan. The standard dose for the bladder was kept at 75% and 70% for the rectum.

The patients in the radiotherapy group were given induction chemotherapy with cisplatin 50 mg/m2 every 21 days with paclitexal 175mg/m2 (2 cycles) followed by radiotherapy alone.

For the patients of concurrent chemoradiotherapy, patients were administered 40 mg/m2 cisplatin weekly with radiation for 5 cycles.

All the data were analyzed by SPSS version 17. CTCAE version 3 was used for evaluating toxicity. Kaplan-Meier method was used to assess overall survival and relapse-free survival. 2-tail t-tests were used to calculate the p-value if p was less than or equal to 0.05, it was considered statistically significant.

RESULTS

Out of 60, 30 patients were treated with CCRT and 30 with induction chemotherapy followed by radiotherapy alone. The baseline characteristics of study patients are presented in Table I.

The overall response rate for CCRT group and RT group was 65% (n=30) and 50% (n=30) respectively. The overall survival rate was 12 months and 8 months for the CCRT group and RT group respectively. Similarly, relapse-free survival was 10 months in CCRT patients and 6 months in RT patients.

Adverse effects of the treatment for both groups are shown in Table II. The rate of hematological toxicities was more in CCRT patients. Leukopenia was presented in 3 patients (10%) in the CCRT group and 2 patients (6.6%) in the RT group. The most common AE was diarrhea with 3 (10%) patients in the CCRT and 2 (6.6%) patients in the RT group. No deaths occurred due to treatment.

Table 1: Baseline characteristics of study patients

Variable	CCRT (n=30)	RT (n=60)	P
Age (SD)	46.1		0.8
FIGO stage			
IIB	12 (40%)	13 (43.3%)	0.7
IIIA	10 (33.3%)	9 (30%)	0.8
IIIB	8 (26.7%)	8 (26.7%)	0.8
Tumor size (cm) (SD)			
Median	3.9 (2.2-6.1)	3.8 (1.9-5.7)	0.8
Average	4.2 (1.6)	4.1 (1.5)	0.6
Deaths due to cervical carcinoma (n)	7 (23.3%)	10 (33.3%)	0.1

Table 2: Adverse events

Adverse events	CCRT (n=30)	RT (n=30)
Leukopenia	3 (10%)	2 (6.6%)
Thrombocytopenia	1 (3.3%)	0 (0%)
Nausea	2 (6.6%)	1 (3.3%)
Diarrhea	3 (10%)	2 (6.6%)
Anemia	1 (3.3%)	1 (3.3%)

DISCUSSION

The primary treatment used for cervical cancer was radiotherapy. However, this treatment was not effective enough as more than half of the stage IIB and stage III patients suffered a relapse. For that purpose, treatments like chemotherapy and hyperthermia were used in combination with radiotherapy to increase their effectiveness[20]. For example, for late-stage uterine cancer, cisplatin chemotherapy has now been used as the primary treatment method[21]. Neoadjuvant chemotherapy is useful in lowering the size of the tumor, accelerating the eradication of micro metastases, enhancing operability, and surgically down staging the disease. In addition, the combination of chemotherapy followed by surgery is associated with a lower risk of adverse effects compared to chemotherapy and radiotherapy given at the same time.[23]

Tumor size was evaluated by pathological examination and MRI in the CCRT group ad RT group respectively. The medication dose range for CCRT was within the therapeutic range.

Our study used CCRT as the standard treatment of advanced cervix cancer. Many other studies have also supported its efficacy in their results. Morris et al[22] conducted a randomized trial to compare radiotherapy and CCRT. In this trial, 403 patients were randomly treated with either of the treatment. Comparing the toxicity results of our study and that of Morris et al[22], there is a significant difference. 17.6% patients in the latter study showed toxicity after 43 months at grade 3 and 4 late toxicity and the major adverse effects included rectal dysfunction and large bowel. Other studies with long follow up period reported worse late toxicity after treatment with concurrent chemoradiotherapy[23, 24]. In our study diarrhea was the major adverse effects in patients of both groups.

Our study opted for cisplatin based chemotherapy and it achieved better results. The use of cisplatin has also been advocated by Lorusso et al[25] which compared the results of cisplatin chemotherapy and carboplatin chemotherapy in patients diagnosed with cervical cancer.

Our study has some limitations. The sample size and the study duration were small. Longer CCRT trials are needed to confirm the study results.

CONCLUSION

The efficacy and toxicity of CCRT show promising results in squamous cell cervical carcinoma patients as compared to induction chemotherapy followed by radiotherapy treatment alone.

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