

Original Research Article

Evaluation of the response rate of chemo-radiation and brachytherapy in patients with locally advanced carcinoma cervix in a tertiary care center

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ABSTRACT

Background: Incidence and mortality estimates are used to measure the burden of cancer in a population and survival estimates are ideal for evaluating the outcome of cancer control activities. Survival studies evaluate the quality and quantity of life of a group of patients after diagnosing the disease. The patient survival after the diagnosis of cervical cancer is indirectly influenced by socio-economic factors. The present study was carried out with an aim to evaluate the success rate of chemo-radiation followed by brachytherapy to the patients of locally advanced carcinoma (Ca.) cervix in a tertiary care center.

Methods: All cases were staged according to the International Federation of Gynaecologists and Oncologists (FIGO) staging system. To illustrate the observed survival of cancer patients Kaplan-Meier curve was plotted. All the patients, except one, completed chemo-radiation and were retrospectively analyzed for the presence of local residual disease, local recurrence, distant metastases, radiation reactions, disease-free survival, and overall survival.

Results: There were 22 patients of Carcinoma cervix reported in the radiation oncology department in the year 2018 and 2019. The overall treatment time ranged from 30 days to 178 days, with a median of 63 days. All the patients had a complete response after the treatment. The median follow-up time for all the patients was 15 months. Three patients had a metastatic recurrence and one patient developed distant metastases as well as local recurrence. Overall survival rate was 100% while the disease-free survival rate was 81.82%.

Conclusions: The response to chemo-radiation in the treatment of locally advanced Carcinoma cervix is comparable to historic data and is well tolerated.

Keywords: Brachytherapy, Carcinoma cervix, Chemotherapy, Radiotherapy

INTRODUCTION

Carcinoma of the uterine cervix (cervical cancer) is the second most common malignant tumor among women worldwide and the most common malignancy in developing countries including India. Krishnan et al,

present in their research article that Carcinoma cervix is the leading cause of cancer mortality in India.¹ Disease during which malignant cells form within the tissues of the cervix is known as cervical cancer.² Major risk factor for cervical cancer is Human papillomavirus (HPV).³ Low-grade squamous intraepithelial lesions (LSIL)

associated with certain HPV genotypes may preferentially progress to cervical cancer.⁴ Approximately 70% of cervical cancer is caused by HPV types 16 and 18, which are targeted by the vaccine.⁵ There are usually no signs and symptoms of early stages of cervical cancer such as stage I-IIA, but can be detected with regular check-ups. As most of the cases present at stages such as IIA- IVB, chemo-radiation plays an important role in these patients. Chemo-radiation has been used successfully to treat Carcinoma cervix patients for nearly a century.⁶ Chemotherapy, an aggressive form of chemical drug therapy that destroys rapidly growing cancerous cells. Chemotherapy is primarily used to lower the total number of cancer cells along with the reduced current symptoms. It is designed to kill the cancerous cells, but along with cancerous cells it also affects the cells of blood, skin, hair, and lining of intestinal tract which shows some side effects of therapy, include: diarrhea, dry mouth, hair loss, memory problem, fever, fatigue, loss of appetite, nausea, vomiting, weight loss, infections, anemia, pain from nerve damage, neuropathy, lymphedema, insomnia, etc. Besides cancer treatment, chemotherapy may be used to prepare people with bone marrow diseases for a bone marrow stem cell treatment.⁷ Chemo drug is used for chemotherapy along with the combination of external beam radiation therapy (EBRT) and intracavitary radiotherapy (ICRT) (Brachytherapy). The principle advantage of brachytherapy is its excellent dose distribution. When radioactive sources are appropriately placed, they will deliver a really high dose on to the cervical tumor and a lower dose to the encompassing normal structures, leading to high local tumor control along with minimum normal tissue damage.⁸ The aim of this study is to evaluate the overall outcome of the Ca. cervix cases that are radically treated by chemo-radiation followed by high-dose-rate brachytherapy (HDR brachytherapy).

METHODS

This was the prospective study conducted at tertiary care hospital, New Delhi, India, from July 2019 to January 2020.

All locally advanced squamous cell carcinoma cervix patients who attended the radiation oncology department in our hospital between 1 Jan 2018 to 31 Dec 2019 were enrolled in this study. Those patients who had adenocarcinoma, endometrial carcinoma, or any other histology other than squamous cell carcinoma were excluded. The patients who underwent surgery for carcinoma cervix were also excluded.

Radiation therapy

All the patients had EBRT by IMRT (Intensity Modulated Radiation Therapy) technique employing a linear accelerator (linac). IMRT is an intricate mode of high-precision radiotherapy that uses a computer-controlled linac to deliver acute doses of radiation to a

malignant neoplasm or specific areas within the tumor. IMRT allows the doses of radiation to evolve more accurately to the three-dimensional (3-D) shape of the tumor by modulating or controlling the intensity of the radiation beam in multiple small volumes. This system also allows higher radiation doses to be focused on the tumor while minimizing the dose to surrounding normal critical structures. Treatment is carefully planned by using 3-D computerized tomography (CT) or resonance images (MRI) of the patient with computerized dose calculations to work out the pattern of dose intensity which will best conform to the tumor shape. Basically, combinations of multiple intensity-modulated fields coming from different beam directions produce a radiation dose that maximizes tumor dose while minimizes the dose to adjacent normal tissues. Just because the ratio of normal tissue dose to tumor dose is reduced to a minimum with the IMRT approach, higher and simpler radiation doses can safely be delivered to tumors with fewer side effects. IMRT also has the potential to scale back treatment toxicity, even when doses aren't increased.

LINAC generates the X-rays utilized in this system of EBRT. A dose delivered to the patients of this study was 50 Gy - 50.4 Gy in 25-28 fractions, with 5 fractions per week over 5-6 weeks duration. The treatment profile is shown in Table 1.

Table 1: Treatment profile.

EBRT Dose	
LINAC	50.4 Gy
Duration of EBRT	
Range	33-45 days
Median	36 days
Chemo cycle	Weekly concurrent
Duration between EBRT and brachytherapy	
Range	12-18 days
Median	15 days
Duration between fractions of brachytherapy	
Range	7-15 days
Median	9 days
Overall treatment time	
Range	30-178 days
Median	63 days
Applicator used	
Fletcher Williamson	12 patients
CT/MR	4 patients
Vaginal	4 patients

Chemotherapy

All the patients underwent concurrent chemotherapy. Chemotherapy is usually given along with radiation for cervical cancer. It helps the radiation work well. Chemotherapy could also be used on its own to treat

cervical cancer that has spread to distant areas or that has come after treatment.

Chemotherapy for cervical cancer usually involves a chemo-drug injected into the vein. During this study, 50mg cisplatin is employed for therapy, given weekly during radiation. This drug was given intravenously about 4 hours before the radiation appointment. It's several side effects including oto-toxicity, nephrotoxicity, haemato-toxicity, and is very emetogenic.

Most side effects of chemotherapy subside after treatment gets over. There's the danger of long-lasting effects which will develop even years after the treatment, counting on the sort of chemotherapy used. There's also the prospect of developing second cancer as a result of chemotherapy.

Brachytherapy

After EBRT, all the cases were planned for brachytherapy. The Patients were planned for brachytherapy after a 12-18 days interval. All the cases got 2-3 fractions of HDR brachytherapy with a week's interval.⁹ The method starts with the insertion of the applicator which was done under spinal anaesthesia. The vagina was full of regular Betadine-soaked gauze packs to push the bladder and rectum away and stabilize the applicator. To get the simplest possible dose distribution to the cervix and at-risk tissues, applicator placement must be optimal.

A Foley catheter was inserted and therefore the balloon was inflated with 7cc of normal saline to permit identification of the bladder neck region in CT-scan. After applicator insertion, CT-scan was done. On CT-scan, contouring of rectum, bladder, and high-risk CTV was done. The dose was prescribed to point "A", which is really some extent 2 cm above from the cervical os point of the Fallopian tube and 2 cm lateral to the central axis of the uterus on each side. The doses to the bladder and rectum were calculated with the assistance of an algorithm. Doses delivered were 15-21 Gy in 2-3 fractions at weekly intervals (per fraction dose was either 7 or 7.5 Gy).

All the patients completed their scheduled chemo-radiation followed by brachytherapy except the one patient, she discontinued after EBRT. All patients were even analyzed retrospectively for residual disease, local recurrence, distant metastases, radiation reactions, and disease-free survival.

Histopathological confirmation was finished all the cases. All the cases were investigated with routine biochemical and hematological examination, x-ray chest before starting radiotherapy treatment. All patients were staged clinically by radiation oncologists, consistent with the International Federation of Gynaecologists and Oncologists (FIGO).¹⁰ Patient profiles are shown in Table 2.

Table 2: Patient' profile.

Age		
Range		33-78
Median		50
Haemoglobin %	Range	8.2-11.8 gm.%
	Median	9.5 gm.%
Total number of patients		22
Stage	I	3
	II	11
	III	6
	IV	2
Histology	Squamous cell carcinoma	21
	Adenocarcinoma	1
Follow-up	Range	3-36 months
	Median	15 months

Follow-up

All the patients reviewed weekly during the course of chemo-radiation. Acute reactions were graded in accordance with the radiotherapy Oncology Group (RTOG) criteria. After this, they were reviewed every 3 months for a minimum of two years. On follow-up, patients were examined clinically. Other relevant investigations were done supported the patient's complaints and examination findings. Disease-free survival was calculated from the first day of treatment to the last day of follow-up.

Statistical analysis

The patients who didn't have either local residual lesion or distant metastasis till the last follow-up were counted as disease-free. For overall survival, the duration was calculated from the first day of treatment to the time of the event. All lost to follow-up were considered for survival analysis as censored. Kaplan-Meier method was used for survival analyses by using the SPSS software, version 20.

RESULTS

Carcinoma cervix patients were the subjects for this retrospective analysis. After completion of the treatment, a review is scheduled in one month. Follow-up period ranged from 3 months to at least three years (calculated from the date of registration to the occurrence of an event or loss to follow-up), with a median of 15 months. Out of 22 patients, 3 patients were lost to follow up after completion of treatment. One patient discontinued treatment after completion of EBRT with weekly concurrent chemotherapy. Three patients come up with distant metastatic recurrence and 1 with both (local and distant metastatic) recurrence. The patients lost to follow-up were considered disease-free, so the disease-free survival rate was 81.82% and the overall survival rate was 100%. Details of disease-free survival, follow-up

status, and recurrence pattern/ metastasis according to disease stage are shown in Table 3. The disease-free survival curve is shown in Figure 1.

Table 3: Disease-free survival with pelvic recurrence/ metastasis according to disease stage after radiotherapy.

Stage	Total patients	Disease-free survival	Pelvic recurrence/ metastasis
I	3	3	0
II	11	9	2
III	6	4	2
IV	2	2	0

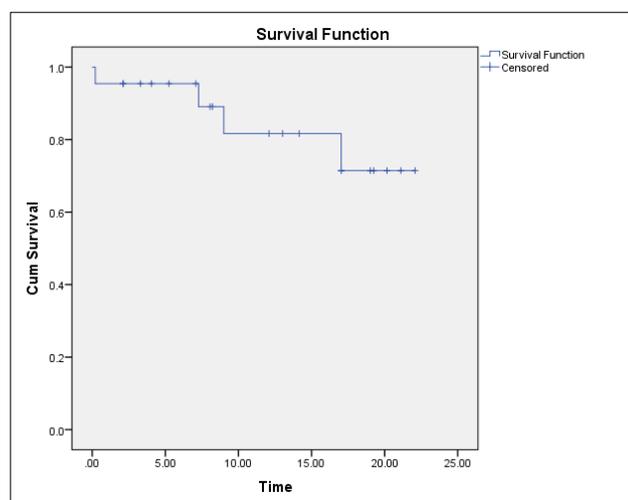


Figure 1: Kaplan-Meier disease-free survival curve.

Complications and reactions

Authors have not come across any severe acute treatment-related complications with EBRT and brachytherapy. Two patients had grade 1 radiation-induced cystitis while one patient had grade 2 cystitis, and eight had grade 1 proctitis while one had grade 2 proctitis. All patients were responded well to conservative management with stool softeners and steroid enemas for proctitis and urinary analgesic for cystitis.

DISCUSSION

Chemo-radiation is an effective and acceptable treatment modality for all stages of Carcinoma cervix and is widely used.⁶ Before the NCI red alert in 1999, people were treated with only radiotherapy. Since NCI red alert chemo-radiation has been the standard treatment for patients with locally advanced Carcinoma cervix. To prove that five trials were conducted by NCI's Clinical Trials Groups which were GOG85, RTOG9001, GOG120, SWOG, and GOG123. Since then chemo-radiation has been practicing in the entire cancer care centers.¹¹

Initially, in chemo-radiation, cisplatin was not only the drug used for chemotherapy. Sometimes, it was used alone, but, other times with the combination of fluorouracil and hydroxyurea. Rose et al, found that survival rate among patients who were treated with cisplatin-based chemo-radiation or cisplatin, fluorouracil, and hydroxyurea based chemo-radiation was higher than those patients who were treated with hydroxyurea based chemo-radiation.¹² Above all cisplatin have some major advantages over other drugs like it enhances the effect of radiation to the cancerous cell and sensitize hypoxic cells to radiation. Nowadays, cisplatin-based chemo-radiation is on practice all over the world in accordance with NCCN guidelines.¹³

Hydroxyurea based chemo-radiation has major acute side effects was bone marrow suppression which was not shown in cisplatin-based chemo-radiation. Other side effects were anorexia nervosa, a psychiatric condition, disorientation, hallucination, seizures, severe kidney problem, and metabolic disturbance.¹⁴ Cisplatin-based chemo-radiation has side effects like anemia, diarrhea, nausea, malaise, and other hematological side effects.¹⁵

Tan et al, in their research found that cisplatin-based chemo-radiation showed several adverse effects and the most adverse were diarrhea, malaise, and nausea with 80.6%, 66.7%, and 62.5% respectively.¹⁵ Derks et al, explained that they performed a retrospective analysis on Carcinoma cervix patients, treated by either chemo-radiation or radiation followed by brachytherapy, between Jan 1997-Jul 2016. The study was observed on the basis of overall survival, local control, and toxicity. One year and 3 years overall local control was 93% and 88% respectively. The overall survival percentage in 3 years and 5 years was 75% and 66% respectively.¹⁶

Jain et al, found in their study that late complications including bowel and bladder for grade 1-4 (RTOG) were seen in 39 patients. Further added to the study, grade 3 radiation-induced cystitis was observed in 1 patient and 2 patients had grade 3 proctitis.⁶

CONCLUSION

The present study evaluated the response rate of chemo-radiation and brachytherapy in patients with locally advanced Carcinoma cervix and showed good survival rate with acceptable toxicity.

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Ethical approval: Not required

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