Research Article

Ten years follow up study in Locally advanced Cancer Cervix treated with Hyperfractionated Radiotherapy, Concurrent Chemotherapy and HDR Brachy Therapy

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Abstract

Aim: Cancer cervix is common malignancy among women globally spanning various continents in the world. The incidence of invasive cervical carcinoma has dropped dramatically due to effective screening techniques. But in India Women present at a locally advanced stage due to lack of awareness and ignorance. The patients are treated and are lost follow up mostly. This study was a continued effort to follow up a group of patient treated in March 2006 to September 2006. Their course of disease and toxicities and their present conditions were analyzed at the end of 10 years.

Patients and Methods: The 24 patients with locally advanced cancer underwent Hyperfractionated radiotherapy and concurrent chemotherapy and brachytherapy during the period March 2006 to September 2006. One patient opted out of study at the end of treatment. The rest 23 patients were followed up and condition analyzed at the end of 10 years. Overall survival disease free survival, toxicities and recurrence patterns. Among 13 patients available were analyzed. The various assessments done were detailed history, symptoms clinical examination, USG abdomen, Ct abdomen and pelvis, cystoscopy and Proctoscopy.

Results: Of the 23 patients 7 were lost follow up, 3 expired. Overall survival 13 patients disease free for survival 10 patients, 3 patients had local recurrence and undergone Wertheim’s hysterectomy, 1 patient had skeletal metastasis and undergone RT to spine.

Conclusion: The improvement in the treatment response obtained soon after treatment in our study compared with conventional protocol was sustained even after 10 years which showed a definite improvement in overall survival and disease free survival with acceptable late toxicities. We recommend a randomized study with large number of patients to prove that we achieve in our study are significant.

Keywords: Hyperfractionated Radiotherapy, Concurrent chemotherapy, brachytherapy, cancer cervix, cistplatin.

Introduction

Age at first coitus – Women who start their sexual life at an early age particularly before 18 years are at higher risk (1.4 to 1.9 times increased risk) of developing cancer cervix. Multiple sexual partners - cancer cervix patients usually give a history of multiple sexual partners. Multiparty, Lower socio – economic group – women form a lower socio – economic group had a higher incidence (about 3 fold) of cervical malignancy due to early
marriage, early onset of sexual life and lack of genital hygiene. Viral etiology – HPV (Human Papilloma virus) – infection with HPV serotypes 16 and 18 are highly prevalent in CIN – II, III and invasive cancer cervix. HPV exerts its effect by P-53 gene suppression and inhibition of cell mediated immunity. Smoking – Smoking appears to double the risk of developing cervical cancer. Various treatment modalities tried - Hyperfractionated EBRT, concomitant boost in EBRT, Neo – adjuvant chemotherapy prior to surgery, Role of concurrent chemo radiation.

Previous study
The previous study was conducted 10 years back in March 2006 to September 2006.

Hyperfractionated ebrt-Concurrent Chemotherapy: Hyperfractionated radiotherapy, 57.6Gy of EBRT 120cGy per fraction, twice daily at 6 hours interval for 5 days a week with Cisplatin based concurrent chemotherapy weekly, followed by Brachytherapy.

EBRT PROTOCOL

Dose details
Total dose delivered 57.6 Gy
Dose /# 1.2 Gy / #, 2# a day 6 hours interval by AP portals, both portals treated twice daily
No of fractions 48
Total duration 4 weeks and 4 days
Treatment days /week 5
Patients were assessed for ICA at the end of 48 fractions of external beam radiation.

Procedure of chemotherapy administration
Patient is pre- hydrated with one liter of Ringer lactate solution, 24 hours prior to commencement of chemotherapy during every cycle. On the day of chemotherapy, before administering the drug the patient is hydrated with 500 ml of ringer Lactate solution. This was followed by injection of 4 mg of Ondansetron, 50 mg of Inj. Ranitidine and Inj Dexamethasone 8mg given. Mannitol 30 minutes prior to onset of Cisplatin administration. This was followed by infusion of 40 mg/m2 of Cisplatin dissolved in 1 litre of normal saline infused in 2 hours. This was followed by post chemo hydration with 1 litre of Normal saline. Finally 20 mg of Inj. Frusemide was given i.v.

The entire chemo procedure was completed in 4 hours. External beam radiation was delivered within 1 hour of chemotherapy then second fraction 6 hours later. Overall treatment time per patient is 52 days. The patients were to be reviewed every one month for the first six months followed by every 2 months for the next 2 years followed by once every 3 months thereafter.

HDR Brachytherapy protocol
Technique: Remote after loading with Iridium-192
No of #: TWO (1 week after EBRT –1 week apart)

Dose delivered to Point A 800cGy /# -2# (26Gy LDR equivalent)

Summated Dose: EBRT & HDR ICCA in the Study

<table>
<thead>
<tr>
<th>Location</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT-A</td>
<td>83.2Gy</td>
</tr>
<tr>
<td>PT-B</td>
<td>65Gy</td>
</tr>
<tr>
<td>Bladder</td>
<td>&lt;80Gy</td>
</tr>
<tr>
<td>Rectum</td>
<td>&lt;70Gy</td>
</tr>
</tbody>
</table>

The immediate response and the toxicities were analyzed separately at the end of treatment and patients were followed up for period of 10 years.

Present study
The 23 patients followed up for the past 10 years were analyzed during the period June 2016 to October 2016 and various parameters analyzed. The clinical tools used were

1. Detailed clinical history
2. Symptom Analysis
3. Clinical examination of patients
4. USG abdomen and pelvis
5. CT Scan Abdomen and Pelvis
6. Cystoscopy and protoscopy

Results
Of the 23 patients accrued in study, 3 expired and 7 were lost for follow up. Patients expired due to disease progression and not due to radiation.
toxicity. Of the 3 expired 1 cast stage IIB and 2 cases State IIIB, Of the 7 lost follow up cases 3 patients were Stage IIB and 4 patients Stage IIIB, Those Patients were also included in analysis to access the feasibility of studying general population. For the remaining 13 patients workup done along with the toxicity assessment.

**Overall survival**
- Stage IIB – 10 patients
- Stage IIIB – 3 patients.

**Disease free Survival**
- 3 patients had recurrence locally and undergone hysterectomy

**Late Toxicities**
- 2 patients had Grade 2 subcutaneous fibrosis.
- 1 patient had Grade 1 bowel toxicity.
- 1 patient had Grade 1 Bladder toxicity.
- Other patients are normal with no specific symptoms and no abnormality Locoregionally.

**Rtog/Eortc Late Radiation Morbidity**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Slight atrophy; Pigmentation change; some hair loss,</td>
<td>Patch atrophy; moderate telangiectasia total hair loss</td>
<td>Marked atrophy; gross telangiectasia</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>Slight induration (Fibrosis) and loss of subcutaneous fat</td>
<td>Moderate fibrosis but asymptomatic; slight filed contracture ; &lt;10% linear reduction</td>
<td>Severe induration and loss of subcutaneous tissue; field contracture &gt; 10% linear measurement.</td>
<td>Necrosis</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>Slight atrophy and dryness</td>
<td>Moderate atrophy and telangiectasia ; little mucous</td>
<td>Marked atrophy with complete dryness</td>
<td>Ulceration</td>
</tr>
<tr>
<td>Small / Large intestine</td>
<td>Mild diarrhea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding</td>
<td>Moderate diarrhea and colic; bowel movement &gt; 5 times daily; excessive rectal mucus or intermittent bleeding</td>
<td>Obstruction or bleeding, requiring surgery</td>
<td>Necrosis / perforation fistula</td>
</tr>
<tr>
<td>Bladder</td>
<td>Slight epithelial atrophy ; minor telangiectasia (microscopic hematuria)</td>
<td>Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria</td>
<td>Severe frequency and dysuria; severe telangiectasia (often with petechiae) ; frequent hematuria, reduction in bladder capacity (&lt;150 cc)</td>
<td>Necrosis / contracted bladder (capacity &lt;100 cc) ; severe hemorrhagic cystitis.</td>
</tr>
<tr>
<td>Bone</td>
<td>Asymptomatic ; no growth retardation ; reduced bone density</td>
<td>Moderate pain or tendeness ; growth retardation; irregular bone sclerosis.</td>
<td>Severe pain or tenderness; complete arrest of bone growth ; dense bone sclerosis</td>
<td>Necrosis / spontaneous fracture.</td>
</tr>
</tbody>
</table>
Conclusion

Current chemo-radiation with cisplatin has shown to have benefit over conventional RT alone. With the aim to further increase the response the dose escalation of RT using Hyperfractionated schedule has been tried. The improvement in treatment response obtained soon after treatment in our study compared with the conventional protocol, was sustained even after 10 years also, which showed a definite improvement in OS and DFS with acceptable late toxicities. We recommend a randomized study with large number of patients to prove that the results we achieved in our study are significant.

References