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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 medicated 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

	Location	Dose
1	PT-A	83.2
2	PT-B	65Gy
3	Bladder	<80Gy
4	Rectum	<70Gy

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

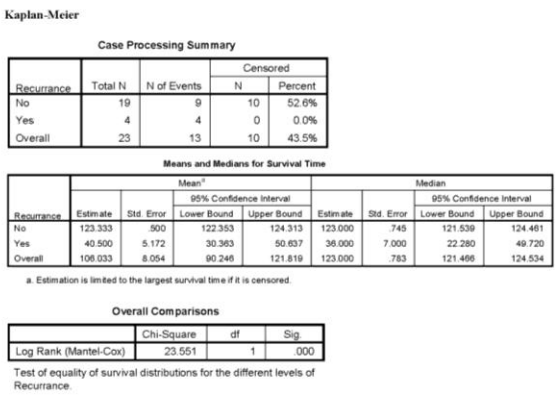
- 3 patients had recurrence locally and undergone hysterectomy
- 1 patient had skeletal metastasis and undergone chemo and RT to spine but locoregionally NAD

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

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



Kaplan-Meier

Case Processing Summary

Recurrance	Total N	N of Events	Censored N	Censored Percent
No	19	9	10	52.6%
Yes	4	4	0	0.0%
Overall	23	13	10	43.5%

Means and Medians for Survival Time

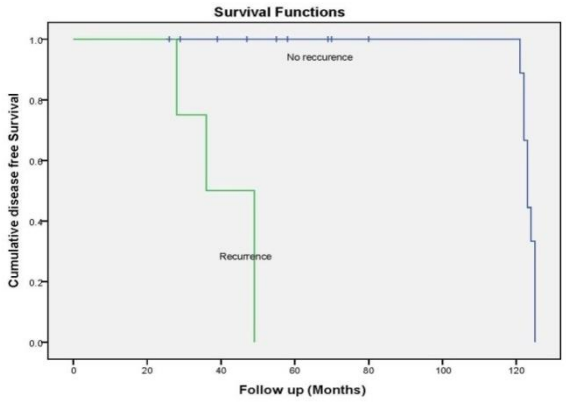
Recurrance	Mean[a] Estimate	Mean[a] Std. Error	Mean[a] 95% Confidence Interval Lower Bound	Mean[a] 95% Confidence Interval Upper Bound	Median Estimate	Median Std. Error	Median 95% Confidence Interval Lower Bound	Median 95% Confidence Interval Upper Bound
No	123.333	.500	122.353	124.313	123.000	.745	121.539	124.461
Yes	40.500	5.172	30.363	50.637	36.000	7.000	22.280	49.720
Overall	106.033	8.054	90.246	121.819	123.000	.783	121.466	124.534

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	23.551	1	.000

Test of equality of survival distributions for the different levels of Recurrance.



Kaplan-Meier

Case Processing Summary

Stages	Total N	N of Events	Censored N	Censored Percent
II B	14	10	4	28.6%
III B	9	3	6	66.7%
Overall	23	13	10	43.5%

Means and Medians for Survival Time

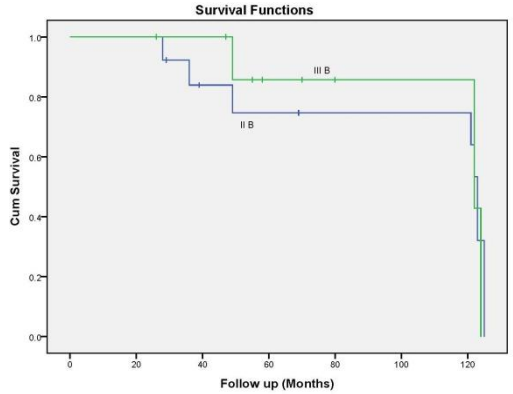
Stages	Mean[a] Estimate	Mean[a] Std. Error	Mean[a] 95% CI Lower Bound	Mean[a] 95% CI Upper Bound	Median Estimate	Median Std. Error	Median 95% CI Lower Bound	Median 95% CI Upper Bound
II B	101.812	11.452	79.366	124.257	123.000	.938	121.162	124.838
III B	112.429	12.010	88.889	135.968	122.000	52.834	18.446	225.554
Overall	106.033	8.054	90.246	121.819	123.000	.783	121.466	124.534

a. Estimation is limited to the largest survival time if it is censored.

Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	.000	1	.990

Test of equality of survival distributions for the different levels of Stages.



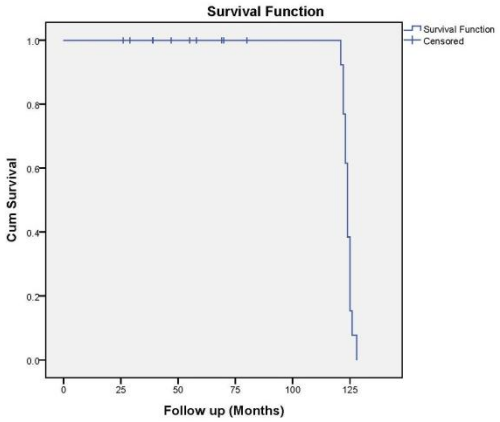
Case Processing Summary

Total N	N of Events	Censored N	Censored Percent
23	13	10	43.5%

Means and Medians for Survival Time

Mean[a] Estimate	Mean[a] Std. Error	Mean[a] 95% CI Lower Bound	Mean[a] 95% CI Upper Bound	Median Estimate	Median Std. Error	Median 95% CI Lower Bound	Median 95% CI Upper Bound
124.000	.519	122.983	125.017	124.000	.585	122.854	125.146

a. Estimation is limited to the largest survival time if it is censored.



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.

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