Original Research Paper

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Oncology

"RESPONSE EVALUATION IN HIV INFECTED CARCINOMA CERVIX PATIENTS"

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ABSTRACT

Back Ground: Carcinoma cervix is the most common gynecological cancer. It is second most common cancer in women. Invasive cervical carcinoma appears at the age of 44 and 52 years. It was observed that HIV patients with cervical cancer presented a decade earlier than un HIV cancer cervix patients. Primary treatment is guided by International Federation of Gynaecology and Obstetrics (FIGO) stage. Stage IA, Primarily treated with surgery Radical Hysterctomy, Stage IA2 to IIA with surgery (or) radiation; Stage II B to IV B is treated with definite radiation (External beam radiotherapy brachy therapy).

Aims: This study is carried out to asses.

- The response to radiotherapy in HIV seropositve cancer cervix.
- To compare the responses to radiotherapy in HIV positive and no HIV cancer cervix patients.
- Addition of concurrent chemotherapy to radiation in medical fit HIV patients can replicate the same beneficiary effects as non-HIV cancer cervix counter parts.

Methods: Total of 52 HIV positive (HIV was screened with ELISA) and 52 non HIV cases cervix were selected depending upon the histopathological report. All patients were given only RT and concurrent chemo-radiation.

Results: Stage wise distribution of cancer cervix in HIV and non HIV patient was compared in either groups Stage III B (35.46% in HIV and 40.38% in non HIV) followed by Stage-IIB (34.61% in both HIV and non HIV groups) . Stage wise response to only RT and CONCURRENT CHEMORADITION in HIV and non HIV cancer cervix patients. The comparative analysis of RTVS CONCURRENT CHEMORADITION in HIV positive group has shown that stage IB to II A and III A all the patients have complete response to only radiotherapy. All patients received only radiotherapy with minimal side effects like diarrhea and vomiting in concurrent chemo radiotherapy these side effects increased.

Conclusion: This study is four arm study conducted in basically HIV and non HIV cancer cervix patients receiving only RT and CC RT. Responses assessed with only RT and CONCURRENT CHEMORADITION in HIV and non HIV groups shows additional benefit with addition of chemotherapy.

KEYWORDS : Only Radiotherapy and Concurrent Chemotherapy, Stage, Histopathological features.

I. INTRODUCTION

Carcinoma cervix is the most common gynaecological cancer and is second most common malignancy in women. Invasive cervical carcinoma appears at the age of 44 and 52 years. It was observed that HIV patients with cervical cancer presented a decade earlier than Non-HIV cancer cervix patients.

It was observed that HIV patients with cervical cancer presented a decade earlier than non HIV cancer cervix patients primary treatment guided by International Federation of Gynaecology and Obstetrics (FIGO) Stages IB2 to IVA cervical cancer treated with Primary radiation therapy and women with FIGO stages I to II A disease who at time of primary surgery were found to have poor prognostic factors including metastatic disease in pelvic hymphnodes, para metrial disease and positive surgical margins treated with can current chemo radiotherapy. Used in selected can depending the histopathological report.

Both pelvic external beam radiotherapy and intra cavitary brachy therapy (To) carries the risk of acute toxic effects and long term complicating the acute side effects of pelvic radiotherapy (on the skin gastrointenstinal (GI) tract and genitourinary tract. These acute side effects also increased in concurrent chemo radiotherapy. Settle down in the majority of patients following treatment.

II. AIM & OBJECTIVES

This study is carried out to asses

- The response to radiotherapy in HIV seropositive cancer cervix.
- To compare the resonse to radiotherapy in HIV positive and non HIV positive cancer cervix patients.
- Addition of concurrent chemotherapy to radiation in medical fit HIV patients can replicate the same beneficial effects as non HIV cancer cervix counter parts.

III. MATERIALS AND METHODS

The study is case control type of observational study. The study was to asses treatment response to radiotherapy which is a standard of care for cancer cervix (stages IB to IVB) either in radical or palliative setting. Total of 52 HIV positive (HIV was screened with ELISA) and 52 non HIV pathologically confirmed cancer cervix. Out of 52 patients HIV arm only 35 patients (30 patients without CD4 counts at the time of diagnosis were given only radiotherapy and 5 patients with CD4 counts >200/mm3 received concurrent chemoradiation). Two non-HIV cancer cervix control arms. Arm one consists of 33 non-HIV cancer cervix, treated with only radiotherapy and arm two consists of 15 non-HIV cancer cervix patients treated with concurrent chemoradiation.

All cases and contols had advanced stage cancer cervix(IB to IVB) as per IAEA guidelines where definitive radiotherapy was employed, radiotherapy was given to a total dose of 80 to 85 GY (50GY with external beam radiotherapy in 2GYper day/ 5 fractions per day total 25# another 30GY BED were given through intracavitary radiation with LDR or HDR). EBRT to pelvis was planned conventionally with AP/PA parallel opposed fields or Four field box technique (AP/PA/LL/RL) based on patients characterstics to doses of 50-50.4GY in 180-200CGY/# IN 5.5 to 6 weeks, another 30GY were substituted with Intracavitary radiation either HDR (900CGY IN 2# OR 700CGY IN 3#) or LDR (it was done in only 2 patients in non-HIV only RT control group with same BED as HDR). In subset of patients where Concurrent chemoradiation was given, chemotherapy with inj. cisplatin 40mg/ m2 was given every week to a total of 3 to 5 cycles during EBRT, chemotherapy was not given with intracavitary radiation.

Response to radiotherapy was assessed twice, first at the end of EBRT i.e, interim response and second at 6weeks post ICR i.e, follow up response. Response was assessed in terms CR(complete response), PR (partial response), SD (stable disease)as per revised RECEST (Response Evaluation Criteria in Solid Tumors) guidelines. CR-disappearance of all the visible leisions PR- about 30% decrease in sum of diameters of all the visible leisions SD-between less than 30% decrease in size or less than 20% increase in size of lesion.

Inclusion criteria:

1) Age upto 80 years
2) Histologically confirmed by biopsy – sqamous cell carcinoma.
3) FIGO staging I – IV B
4) ECOG performance status 2(or) below

Exclusion criteria:

1) Age above 80 years
2) Any evidence of distant metastatis

3) Previous treated case of carcinoma cervix
4) PSECOG

Diagnostic work up:
Pre-treatment evaluation:
Initial clinical evaluation consists of careful history and physical examination platelets.

CBP including platelets, CD4 count:
Diagnostic procedures:
- Papanicolaon smear is mainly used for screening
- Cervical biopsy
- Dialation and curettage
- Cystoscopy and restosigmoid as copy (as clinically indicated)

Imaging – Chest x-ray,

CT Scan or
MRI of abdomen & pelvis

Optional- LFT
RFT

All cases and controls had advanced stage cancer cervix (IB to IV B) were taken. As per International Atomic Energy Agency (IAEA) guidelines where definitive radiotherapy was employed. Radiotherapy was given to a total dose of 80-85 Gy. EBRT to pelvis was planned conventionally with (AP/PA/LL/RL) based on patients charactestics to doses of 50-54 GY in 180-200 GY/Day/5 praction in week/5-6 liters. Another 30Gy were substituted with intracavitary radiation either HDR 900 CGY/ weekly with gap of / week between 2 practions. Concurrent chemoradiation was given, chemotherapy with Inj. Cisplatin 40mg/m2 was given every week to a total of 3 to 5 cycles during EBRT (External Beam Radiotherapy).

Response to radiotherapy was assessed twice
- First at the end of EBRT i.e., interim response
- Second at 6 weeks post ICR i.e., follow up response

Response was assessed interms
CR (Complete response)
PR (partial response)

SD (Stable response as per revised RECEST (Response Evaluation Criteria in solid tumors)

IV. RESULTS

Stage wise distribution of cancer cervix in HIV and non HIV patient was compared in either groups Stage III B (35.46% in HIV and 40.38% in non HIV) followed by Stage-IIB (34.61% in both HIV and non HIV groups)

But in HIV patients stage-IV disease constitute of 9.61% of cases compared to non HIV group where none of the presented in Stage-IV.

Stage wise distribution of HIV+ ca.cervix & un HIV ca.cervix

Interim response compare to follow up response.

Stage wise response to only RT and CONCURRENT CHEMOR ADITION in HIV and non HIV cancer cervix patients. The comparative analysis of RTVS CONCURRENT CHEMORADITION in HIV positive group has shown that stage IB to II A and III A all the patients have complete response to only radiotherapy.

Stage II B -87.5%
Stage III B – 50% complete response.
Stage IV – Intent of treatment was palliatice.

CONCURRENT CHEMORADITION (concurrent chemoradi otherapy)

Stage-II A 100% response
Stage II B & III A complete response (IIB 87.5% Vs 100%, IIIB 50% Vs 100%)

In Non-HIV cancer cervix stage IB to IIIA – Complete response to RT in follow OP assessment (87.5% in IB and 33.34% in III B – had complete response). Addition of concurrent chemotherapy can increase the rate of complete responses in higher stages in early stage benefit is not significant Non HIV cancer cervix patient have shown that from Stage IB to III A – Complete response to only RT – follow up assessment. Stage II B 87.5%, Stage III A 33.34% - Complete response in CONCURRENT CHEMORADITION

Stage II A - Stage III A - 100% response in CONCURRENT CHEMORADITION

Concurrent chemotherapy can increase the rate of complete responses in higher stages specially with involved parametric through in early stage benefit is not significant.

All patients received only radiotherapy with minimal side effects like diarrhea and vomiting in concurrent chemo radiotherapy these side effects slightly increased.

Stage wise comparison of responses to only radiotherapy and CCRT in HIV+ CA.CERVIX patients only RT

Stage	No. cases	CR	PR/SD	CR	PR/SD
IB	1	1(100%)	0	1(100%)	0
MA	3	0	3(100%)	3(100%)	0
MB	9	3(33.34%)	6(66.67%)	7(87.5%)	1(12.5%)
III A	2	0	2 (100%)	1(100%)	0
HIE	12	3(25%)	9(75%)	5(50%)	5(50%)
IVA	1	0	1(100%)	0	0
IVB	2	0	2(100%)	0	0

Stage wise comparison of responses to only radiotherapy and CCRT in HIV+ CA.CERVIX patients CCRT

Stage	No. cases	CR	PR/SD	CR	PR/SD
IIA	2	2(100%)	0	2(100%)	0
[IB	1	0	1	1(100%)	0
111 A	0	0	0	0	0
NIB	2	1	1	2(100%)	0

Stage wise responses to only RT and CCRT in non-HIV CA. CERVIX patients

STAGE	NO.CASES	CR	PR/SD	CR	PR/SD
I B	3	3(100%)	0	3(100%)	0
II A	4	0	4(100%)	4(100%)	0
II B	9	1(11.11%)	8(88.89%)	7(87.5%)	1(12.5%)
III A	3	1(33.34%)	2(66.67%)	2(100%)	0
III B	12	2(13.34%)	10(86.67%)	3(33.34%)	6(66.66%)

Stage wise responses to only RT and CCRT in non-HIV CA. CERVIX patients

STAGE	NO.CASES	CR	PR/SD	CR	PR/SD
II A	1	1(100%)	0	1(100%)	0
II B	5	2(40%)	3(60%)	4(100%)	0
III A	1	1(100%)	0	1(100%)	0
III B	8	1(12.5%)	7(87.5%)	7(100%)	0

Comparitive analysis of interim response and follow-up response to only RT versus CCRT in HIV positive CA.CERVIX patients

Group HIV+	Number of cases	Mean age ± SD years	Response interim			Follow up Response		
			CR	PR	SD	CR	PR	SD
HIV + ve only RT	30	42.0±8.49	7 (26.66 %)	12 (40%)	11 (36.6 %)	16 (72.63 %)	-	5 (22.72%)
HIV +ve CCRT	5	47.80± 9.93	3 (66%)	2 (34%)	-	5(100 %)	-	-

HIV positive patients who received only RT were diagnosed with HIV on evaluation and their CD4 counts were not available and the other group of HIV patients who received CCRT were on HAART and their CD4 counts were >200/mm at the time of diagnosis of ca.cervix.

Comparitive analysis of interim and follow-up responses to CCRT (concurrent chemo-rt) and only RT in non-HIV CA.CERVIX patients.

Group Non-HIV+	Number of cases	Mean age ± SD years	Response interim			Follow up Response		
			CR	PR	SD	CR	PR	SD
Non- HIV + ve only RT	33	53.08± 13.10	8 (24.4 %)	15 (45.45 %)	10 (30.15 %)	22 (73.33 %)	2 (6.67 %)	6 (20%)
Non- HIV +ve CCRT	15	45.86± 8.49	5 (33.34 %)	10 (66.66 %)	-	13(100 %)	-	-

V. DISCUSSION

Study is basically a case-control study of observational type, which had a main aim of detection of treatment response to radiotherapy in HIV positive cancer cervix patients.

HAART (Highly Active Anti Retroviral Therapy) may not actually prevent the development of cancer but may delay the progression.

Under controlled setting as per IAEA (International Atomic Agency guidelines concurrent chemoradiation is given in HIV positive cancer cervix patients with good human status (CD4 counts >200/mm3).

Confirmation of diagnosis using pap smears and biopsy should be done subsequently

STAGE OF CA.CERVIX	5 YEAR SURVIVAL RATE
IA	93%
IB	80%
IIA	63%
IIB	58%
IIIA	35%
IIIB	32%
IVA	16%
IVB	15%

Other study :

Three randomized, Phase-III trials have shown an OS advantage for cisplatin based therapy given concurrently with radiation therapy, while one trial that examined this regimen demonstrated no benefit. Although the positive trials vary some what in terms of the stage of disease, dose of radiation and schedule of cisplation and radiation, the trials demonstrate significant survival benefit for this combined approach. The risk of death from cervical cancer was decreased by 30% to 50% with the use of concurrent chemo radiation therapy.

Meta-analysis confirmed that the combination of chemotherapy and radiation therapy was associated with improved survival for patients with stage IB2- IVA cervical cancer

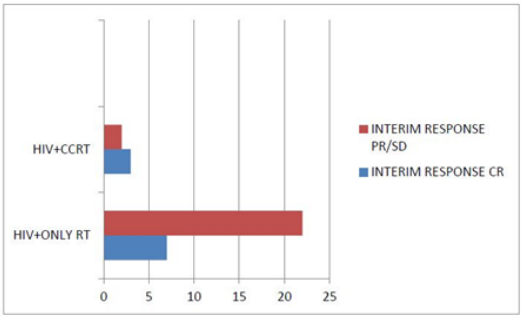
Our study :

Study is basically a case control study of observational type, which had a main aim of detection of treatment response to radiotherapy in HIV positive cancer cervix patients.

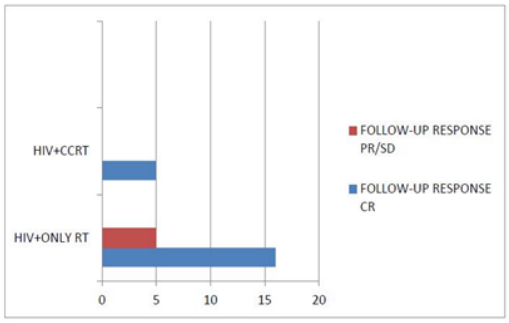
Stage wise distribution of cancer cervix in HIV and non HIV patient was compared in both group.

Stage wise response to only RT and concurrent chemo-radiation in HIV and non HIV cancer cervix patients.

INTERIM RESPONSE ASSESMENT



FOLLOW-UP RESPONSE ASSESMENT



VI. CONCLUSION

This study is a four arm study conducted in basically HIV and non-HIV cancer cervix patients receiving only RT and CCRT.

Study group – Total of 52 HIV positive (HIV was screened with ELISA) and 52 non HIV pathologically confirmed cancer cervix. Out of 52 patients HIV arm only 35 patients (30 patients without CD4 counts at the time of diagnosis were given only radiotherapy and 5 patients with CD4 counts >200/mm3 received concurrent chemoradiation). Two non-HIV cancer cervix control arms. Arm one consists of 33 non-HIV cancer cervix, treated with only radiotherapy and arm two consists of 15 non-HIV cancer cervix patients treated with concurrent chemoradiation.

Major stage at presentation in both HIV and non HIV cancer cervix presents was Stage III B followed by stage II B but in HIV sub set stage IV disease was present in 9% of cases and 0% in non HIV suggesting the relatively late presuctation in HIV

Response to only RT in HIV and non HIV cancer cervix patients was similar and the statistically significant difference was observed. It is concluded that patients in either group who completed the whole course of treatment irrespective of HIV status has similar response. Similarly response to CONCURRENT CHEMORADITION in HIV and non HIV cancer cervix patients were similar no statistical significance was observed.

Response assessed with only RT and CONCURRENT CHEMORADITION in HIV and non HIV groups showed additional benefit with addition of chemotherapy, with P value of 0.001 in either group, especially in III B sub set (as the numbers were less the statistical analysis, stage wise was not done only percentage were compared).

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