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To compare the local control and outcome of conventional concurrent CRT and twice weekly concurrent CRT in locally advanced carcinoma cervix

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Abstract

Background: Carcinoma cervix ranks fourth most common malignancy (for both incidence & mortality) globally and third most common diagnosed malignancy in females (~16.5%) in India, (after breast & lip/oral cavity), with about 80% of the total burden occurring in developing countries like India.

Methods- This Prospective comparative study was conducted in the Department of Radiotherapy and Oncology TCC, IGMC, Shimla, in patients suffering from advanced carcinoma of cervix.

Results: Treatment response was assessed at 1st follow up done at six weeks and at the subsequent follow up examinations. At the 1st follow up complete responses were seen in 21 patients (75%) in the study group and, 23 patients (77%) in control group. The difference between the groups was not statistically significant (p =.864). Partial response was achieved in 5 patients (18%) in study arm and 04 patients (13%) in the control arm. Patients of either arm who completed treatment at the shortest possible time period tended to perform better than those who had prolonged treatment times. Patients who completed treatment within 9 weeks of start of RT performed better compared to patients whose treatments were prolonged for 10 or more than 10 weeks from the start of RT, irrespective of the treatment arm. (Complete response rates 77.67% vs. 64.61%) but the difference was not quite significant at p=0.071.

Conclusion Presently we can conclude that both the treatment schedules are equally good, but keeping in view the above mentioned concerns it cannot be recommended as an alternate to the conventional chemoradiotherapy, however as the follow-up time is short, and also the study needs more refinements particularly in terms of reducing the overall treatment time (as it has strong prognostic significance in outcome) its effectiveness needs to be confirmed in larger prospective randomized trials.

Keywords: Chemoradiotherapy, RT, Partial response.

Introduction

Carcinoma cervix ranks fourth most common malignancy (for both incidence & mortality) globally and third most common diagnosed malignancy in females (~16.5%) in India, (after breast & lip/oral cavity), with about 80% of the total burden occurring in developing countries like India.[1]

As per data from GLOBOCAN there were 96922 new cases & 60078 deaths registered in India during the year 2017-2018.

Despite the decrease in incidence of ca. cervix observed from all urban registries of India, it still is considered the leading female neoplasm in India with 70% of its population residing in rural areas.[2]

In Himachal Pradesh it is still the most common gynaecological malignancy in the fairer sex.[3]

In Tertiary Cancer Centre, Shimla, carcinoma of uterine cervix accounts for approximately 58.66 % of all gynaecological malignancies with about 80-90 % patients presenting in advanced stage with bulky central disease.[4]

Material and Methods

This Prospective comparative study was conducted in the Department of Radiotherapy and Oncology TCC, IGMC, Shimla, in patients suffering from advanced carcinoma of cervix.

Signed informed consent was taken from all patients involved in the study prior to enrolment in the study.

Cases Included

Cases included in this study were

1. Staged by FIGO staging 2008, stage II & III A, B
2. Histological proven - Squamous cell carcinoma,
- Adenocacinoma and
- Adenosquamous carcinoma.

Pre-Treatment Work-UP

Each patient enrolled in study underwent complete physical examination, including pelvic examination (under anaesthesia if needed) for clinical staging. Other investigations included complete haemogram, blood biochemistry, urine routine & microscopic examination, chest X-ray (P-A view), ultrasound abdomen & pelvis, & CT-Scan abdomen and pelvis. To exclude the bladder involvement urine cytology, cystoscopy, or Intravenous pyelography was done if needed.

Exclusion Criteria

The following category of patients were excluded

1. Stage – IA, IB and IV A, IVB.
2. Age >65yrs and <18yrs.
3. Histology other than squamous cell, Adenocacinoma or Adenosquamous carcinoma.
4. Patients who had prior pelvic surgery for cancer, pelvic radiotherapy or prior chemotherapy within 5 years.
5. Deranged KFT (BUN or creatinine 2 times above the normal limit).
6. Deranged LFT (Bilirubin 2 times above the normal limit),
7. Karnofsky performance status < or equal to 60,
8. Distant metastasis (disease beyond true pelvis).

Study Design

Control ARM: Patient was subjected to standard cisplatin based chemotherapy given concurrently with radiotherapy on the first day of treatment week (~1hour prior to radiation fraction).

Radiation

EBRT: Dose per fraction was 2Gy

Total dose: 50 Gy in 5 weeks. (5# /week).

Chemotherapy : Injection cisplatin 40 mg/m2 on D1 of every week, given ~1 hr. prior to radiation fraction. (with maximum ceiling of 60 mg / week).

Study arm: Patient was subjected to injection cisplatin 25mg per sqm on day 1 and day 4 every treatment week (depending on tolerability of patients).

Radiation

EBRT: Dose per fractionwas 2Gy

Total dose: 50 Gy in 5 weeks. (5# /wk)

Chemotherapy: Injection Cisplatin 25 mg per sqm. Given i.v. on D1 and D4 every treatment week (depending upon tolerability).

Intracavitary Brachytherapy(ICBT) :- After a gap of 2 to 3 weeks of completion of EBRT, patients in both the arms were reassessed for response and patient were subjected to ICBT using Selectron remote controlled HDR system, Ir192based, giving a dose of 30 Gy (2Gy equivalent) to point A. If they were not fit for ICBT the patients have been subjected to supplement

CRT

Supplement radiation therapy

CONTROL ARM - 20 Gy was given in 10 fractions @ 2 Gy / # over two weeks with inj.cisplatin (@40 mg /m 2) weekly.

STUDY ARM: 20 Gray will be given in 10 fractions @ 2 Gy / # over two weekswith inj.cisplatin given twice weekly on D 1 and D4 of every treatment week.

Control Group

- Dose of 50 Gy was delivered in 5 wks in 25# @ 2 Gy per fraction.
- 5 fractions were administered per week.
- Weekly inj. Cisplatin was given if complete haemogram, liver function & kidney function tests were found to be within normal limits.
- Radiotherapy fraction was delivered after ~1 hr. of inj.cisplatin@ (40mg/m2) on D1 of every treatment week & without chemotherapy on D2-D5 every treatment week.
- Mannitol containing formulations were preferred, if not available, diuresis was achieved with inj. Mannitol, post chemotherapy.
- Anti-emetic like 5-HT3 antagonists (palanosetron 0.25mg), was given 30 minutes before chemotherapy.
- Inj. cisplatin infusion was given over 90-120 minutes with adequate hydration.
- After 2-3 weeks of completion of EBRT, ICBT with (Ir- 192) HDR system was given @ 7Gy in 3 sessions one week apart.
- If patient was not found fit for the same, then supplement EBRT was given in the dose of 20 Gy in 2 wks & 10# @ 2Gy/# with inj. cisplatin 40mg/m2 weekly (with same ceiling as decided previousely).

Study Group

- Total dose 50 Gy was given in 25 #s in 5 weeks @ 2 Gy/ # with concurrent cisplatin@25mg/m2 administered on D1 & D4 of every treatment week if results of blood investigations (CHG, biochemistry) were WNL.
- 5 fractions were delivered per week.
- After 2-3 weeks of completion of EBRT patients were assessed for ICBT.
- Those fit were given ICBT with HDR system using Ir-192.
- If not found fit for ICBT they were subjected to supplement chemo radiation therapy. 20 Gy were given in 10 fractions @ 2Gy/# as 5fractions per week over 2 weeks.

Follow up: First follow up was done at six weeks of therapy. A complete gynaecological examination accompanied with systemic examination was performed and subsequent follow-ups done at every two months intervals. Patients examined locally and for any acute and late toxicity. Late toxicities were graded according to RTOG criteria.*

Secondary treatment

Patients who were having persistent tumor on completion of treatment were considered for salvage surgery if resectable. Adjuvant chemotherapy was administered in patients with un-resectable disease.

Statistical Analysis

Response rate was the primary end point for analysis. The various prognostic factors effecting response were also analysed. The data obtained from both arms was analysed by student "t"-test and chi-square test and p value of < 0.05 was taken as significant.

The statistical significance will be defined as:

- p> 0.05 non-significant
- p 0.05 – 0.01 significant
- p< 0.01 highly significant

Results

Age-Wise Patient Distribution

Age (Yrs)	Study	Control	Total
<40	4	5	9
41-50	9	5	14
51-60	7	12	19
61-65	8	8	16
Total	28	30	58

Age of the enrolled patients ranged between 35 to 65 years, the median age at presentation being 53 years in both the study as well as the control arm.

Stage wise Distribution of Patients

Stage	Twice weekly CRT		CRT CONVENTIONAL		Total
	No	Percentage	No	Percentage	
IIB	16	28.00	19	33.00	35
IIIA	1	2.00	1	2.00	2
IIIB	11	19.00	10	16.00	21
Total	28		30		50

Majority of the patients belonged to stage IIB in both the groups. The number of patients in stage IIIB in study group was 11 and10 in the control group. There was only 1 patient included in stage IIIA.

The planned treatment duration in both the arms was 7-9 week. 29 patients [16 in study and 13 in control arm] i.e. (50%) overall completed their treatment within the planned duration. The difference though was favouring the STUDY arm but was not statistically significant (0.139). When the no. of patients completing treatment within 8 weeks were compared, 16 (57%) had completed their treatment in the study arm while 13 (44%) patients in the control arm completed treatment within 8 weeks, the difference was statistically significant (p =.91).

Response at First Follow UP

Response	Study		Control		Total
	No	Percentage	No	Percentage	
CR	21	75.00	23	77.00	44
PR	5	18.00	4	13.00	9
PD	1	4.00	1	3.00	2
Total	26/28		28/30		55/58

Treatment response was assessed at 1st follow up done at six weeks and at the subsequent follow up examinations. At the 1st follow up complete responses were seen in 21 patients (75%) in the study group and, 23 patients (77%) in control group. The difference between the groups was not statistically significant (p =.864). Partial response was achieved in 5 patients (18%) in study arm and 04 patients (13%) in the control arm.

Patients of either arm who completed treatment at the shortest possible time period tended to perform better than those who had prolonged treatment times.

Patients who completed treatment within 9 weeks of start of RT performed better compared to patients whose treatments were prolonged for 10 or more than 10 weeks from the start of RT, irrespective of the treatment arm.

(Complete response rates 77.67% vs. 64.61%) but the difference was not quite significant at p=0.071.

Patients completing treatment within 8 weeks had better complete responses 23 (40%) vs 35 (60%) but without statistical significant difference (0.235). When the two treatment arms were compared study group had almost equal responses as control in those completing

treatment in less than 8 weeks (84.21% vs 85.71%, p=0.916).

In those completing treatment in more than 8 weeks both the arms had almost equal response (study arm 73.45% vs. 72.05, p = 0.902).

Discussion

Despite the reduction in the incidence of cervical malignancy in western world it still remains the leading cause of female malignancy in the developing world.

Recent times have witnessed the introduction of chemotherapy in the treatment of this disease. Its use in the concurrent setting with radiation has led to improved treatment outcomes. The NCI alert in 1999 heralded concurrent chemoradiation becoming the standard treatment especially in the developed countries as compared to developing countries, where in several problems of cost, medical problems like nephrotoxicity, elderly age group, poor general condition, refusal of the patient etc preclude its administration.

The treatment failure in carcinoma cervix is still predominantly locoregional in two thirds of the cases74, 75 and the improvement in local modalities of treatment would definitely assist in improving the treatment outcome. In an attempt to improve the local control rate, in our study we attempted to increase the therapeutic ratio in carcinoma cervix via exploiting the difference between inherent properties of Radiosensitization through the use of cisplatin twice a week in the management of locally advanced carcinoma of the cervix.

To the best of our knowledge this regimen had not been tested previously in carcinoma cervix in the randomized setting while a phase II trial from China48 had found this regimen to be tolerable and an effective.

Perez et al[5] had stated that in general more extensive tumors with higher local failure rate require longer overall treatment times and their analysis showed that prolongation of overall treatment time did not correlate with pelvic tumor control in stages IB < 3cm in diameter or in patients with extensive parametrial involvement IIB B/L or stage III. These inferences can explain some of the findings of our study. As most of our patients were having bilateral parametrial disease (stage IIB/IIIB i.e.87%/90% respectively)

The differences in between study and control groups in the squamous cell carcinoma group in terms of complete responses did not approach statistical significance (76.19% vs 70.73%, p=0.818) similar to the parent study (by L.C.Wong, Y.C. Choo, D Choy et al) done at department of obstetrics and gynae; university of Hongkong 1988 as were the finding of the study that also showed better outcome in term of initial response.

Conclusion

Presently we can conclude that both the treatment schedules are equally good, but keeping in view the above mentioned concerns it can not be recommended as an alternate to the conventional chemoradiotherapy, however as the follow-up time is short, and also the study needs more refinements particularly in terms of reducing the overall treatment time (as it has strong prognostic significance in outcome) its effectiveness needs to be confirmed in larger prospective randomized trials.

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