Original Research Paper

Volume - 11 | Issue - 09 | September - 2021 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Oncology

COMPARISON OF COMPLIANCE AND RESPONSE FOR NEOADJUVANT CHEMOTHERAPY FOLLOWED BY CONCURRENT CHEMO RADIATION VERSUS CHEMO RADIATION ALONE IN CARCINOMA CERVIX FIGO STAGE IVA- A SINGLE INSTITUTION EXPERIENCE.

Dr M.Pandu ranga kumari — Assistant professor, Rangaraya medical college, Kakinada, Andhra Pradesh.

Dr.G Sateesh kumar* — Associate professor, Rangaraya medical college, Kakinada, Andhra Pradesh.
*Corresponding Author

ABSTRACT

Aims/Objectives: Cervical cancer is the second most cancer in women in India. Patients presenting with stage IVa have 5 year survival rates of only 16% and are not able to complete the full course of radiation due to advance disease.
The aim of this retrospective study is to study the compliance of the stage IVa patients to neoadjuvant chemotherapy (NACT) followed by concurrent chemo radiotherapy and their completion of radical dose of radiation and subjective response in comparison to patients without NACT.

Materials and Methods: We retrospectively studied stage IVa cervical cancer patient's case sheets from January 2019 to June 2020.
The patients are divided in to 2 arms:

Arm-A : 11 patients - who received NACT with Paclitaxel 175mg/m2 and carboplatin AUC 6 every 3 weeks of 4 cycles followed by external beam radiotherapy(EBRT) of 50 Gy/25 fractions with weekly cisplatin of 40 mg/m2, followed by brachytherapy of 700cGy of 3 fractions.

Arm-B: 9 patients-who received external beam radiotherapy (EBRT) of 50 Gy/25 fractions with weekly cisplatin of 40 mg/m2, followed by brachytherapy of 700cGy of 3 fractions.

The compliance to complete radical dose of radiotherapy with concurrent chemotherapy and response in patients with and without NACT were compared

Results:

Arm A: 10 patients (91%) completed radical dose of RT and weekly cisplatin, one patient (9%) defaulted for EBRT, all patients tolerated 4 cycles of NACT.
During 3 months follow up 1 patient (9%) developed liver secondaries and 1 patient (9%) developed other complication (jejunal obstruction) 2 patients suffered dysuria(18%) and 7 (64%) patients asymptomatic.

Arm B: 4 patients (44.5%) completed radical dose of RT and 5 patients (55.5%) defaulted radiation [one for EBRT and 4 for HDR]
During 3 months follow up one patient (11%) developed liver secondaries and 1(11%) developed uraemia and died (both these patients completed radical dose), 2 (22.2%) patients with dysuria,2 (22.2%) patients with bleeding p/v and 3(33.3%) patients are asymptomatic.
Patients who defaulted for radical dose of concurrent RT were more in arm -B (55%) when compared to arm- A(9%)
More patients are asymptomatic in arm-A(64%) than arm-B(33%).

Conclusions: Response and compliance to treatment was better in the patients who received NACT followed by concurrent chemo radiation and are able complete treatment and majority of them are asymptomatic.
From this it may be concluded that NACT may be considered in stage IVa cervical cancer.
However a prospective trial with large number of patients is needed to come to a conclusion.

KEYWORDS : Cervical cancer stage IV A ,NACT, Compliance, Response.

INTRODUCTION

In India cervical cancer is the 2 nd most common female genital tract malignancy and cause of death[1]. India being a developing country with lack of accessible and affordable preventive, screening and medical facility on one side and illiteracy and social inhibition makes women with cervical cancer to present with advanced stage[2]

According to FIGO stage IV A survival rate is 16% only and it poses a challenge to oncologist to improve it. Standard treatment for stage IV a is with concurrent chemo radiotherapy [3] and brachytherapy but the compliance to it is very poor

The intention of this study is to treat stage IV A disease patients with neoadjuvant chemotherapy to down stage tumor followed by CCRT(concurrent chemoradiotherapy) and study compliance compared to standard therapy.

Materials and Methods:

We retrospectively studied stage IVa cervical cancer patient's case sheets from January 2018 to September 2020.

Patient selection:

Inclusion criteria:

1. Age □ 70 yrs
2. Histological confirmation by biopsy: Squamous Cell carcinoma,
3. ECOG performance status ≤2
4. Stage IVA (radiological)
5. Hemoglobin (Hb) > 10 gm%.
6. Complete blood picture, renal function tests, liver function tests within normal limits.

All the patients having less than 10 gm% of Hb were given transfusion prior to Radiation.

Exclusion criteria:

1. Age □ 70 yrs.
2. ECOG performance status > 2
3. Stage I.II,III
4. Previously treated case.
5. Other co-morbid conditions

All patients were given a course of antibiotics before starting therapy.

Staging

Patients were staged according to the system adopted by FIGO i.e International Federation of Gynaecologist and Oncologist Staging for carcinoma of the cervix.[4]

ECOG Performance status

ECOG performance status scale was followed, patient with ECOG 0, 1, were included in the study[5]

Pre-treatment Evaluation -

1. A complete detailed history which includes presenting complaints, past history,
   Family history, personal history and socioeconomic history with emphasis on
   Sexually transmitted infections.
2. General physical examination
3. Local examination: Includes Abdomen, pelvic, rectal examination
4. Systemic examination
5. Haematological investigations:

- Complete Blood picture
- Renal function tests
- Liver function tests.

6. Screening for HIV/HBs Ag
7. Biopsy from the primary tumor (edge of gross tumor or 4

quadrants)
8. X-ray Chest (PA view)
9. Ultrasound abdomen & pelvis
10. CT scan: Abdomen & Pelvis.
11. MRI/PET CT (optional)

Protocol design:
The patients are divided in to 2 arms:

Arm-A:
11 patients - who received NACT with Paclitaxel 175mg/m2 and carboplatin AUC 6 every 3 weeks of 4 cycles followed by external beam radiotherapy(EBRT) of 50 Gy/25 fractions with weekly cisplatin of 40 mg/m2, followed by brachytherapy of 700cGy of 3 fractions.

Arm-B:
9 patients-who received external beam radiotherapy (EBRT) of 50 Gy/25 fractions with weekly cisplatin of 40 mg/m2, followed by brachytherapy of 700cGy of 3 fractions.

EBRT
All patients received external beam radiotherapy (EBRT) based on International commission on radiation units and measurements ICRU-50[6] EBRT was given with LINAC machine using 6 MV photons at 100cm SAD..

Total dose of 50 Gy in 25 fractions at the rate of 2 Gy per fraction in 5weeks 5 days a week was given to whole pelvis.. Parallel opposed anterior and posterior portal (or) Box technique were used.

RT TECHNIQUE
- Simulation

Position: Supine (comfortable and easily reproducible)
Bladder should be full to reduce dose to the small intestine
- **CTV:** Gross disease, Uterus, Cervix, Vagina with sufficient margin, Parametrial tissue, Pelvic lymph nodes including internal, external and common iliac lymph nodes, para aortic lymph nodes (selected cases),pre sacral nodes, utero-sacral ligament.
- Beam energy- 6 MV photons
- **Portals:** Two portals AP / PA or four fields box technique by AP, PA and 2 laterals.
- **Superior:** L4 - L5 interspace
- **Inferior:** Inferior border of obturator foramen or if there is a vaginal extension, 3cm clear margin below lower extent of the lesion
- **Lateral:** 1.5 cm lateral to the bony pelvis
- **Anterior:** Pubic symphysis
- **Posterior:** sacral hollow

All portals were treated at each session and dose was calculated at mid plane.

BRACHYTHERAPY
ICA Procedure
1. Bowel preparation
2. Short acting sedation.
3. Perineum cleaned
4. Foleys catheterisation with 7ml of 1:2 diluted urografin inflated in balloon.
5. Cervical canal found by gentle probing and dilated
6. Uterine canal length measured with sound and appropriate intrauterine tandem inserted.
7. Ovoids inserted
8. Anterior and posterior packing done.
9. Rectal tube inserted
10. Patients were treated with HDR brachytherapy.
11. Dose fractionation: 700 cGy / Fr. / 3 Fr

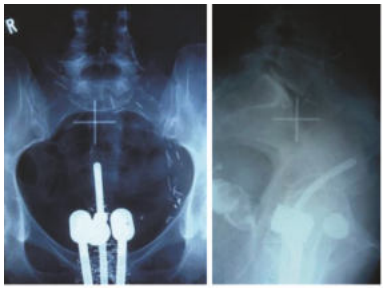

Fig.23 - ICA procedure and Orthogonal films

PELVIC DOSIMETRY
The dose was calculated using 3D computerized treatment planning system and two orthogonal radiographs of the pelvis with the applicators containing dummy sources in situ. The isodose distribution was plotted and the dose calculated at point A. dose calculations were also made for rectum and bladder according to the ICRU – 38 recommendations[8]

Plan Evaluation:
- Point A: 100% dose
- Bladder Dose:
- Bladder dose to 90% of point A. Total bladder dose below 80 Gy (LDR equivalent at 50 cGy/hr)
- 65-75% of point A for HDR
- Rectal dose:
- Total rectal dose below 75 Gy
- 55-65% of point A for HDR.

Cisplatin Regime
- Injection Ranitidine 50mg IV 8 hourly.
- Injection Dexamethasone 16mg IV stat.
- Injection Granisetron 3mg IV stat.
- IV fluid 1 pint DNS with 1 ampoule of KCL.
- IV fluid 1 pint DNS with 1 ampoule of MgSO4.
- IV 20% Mannitol 100 ml IV stat.
- IV normal saline 1 pint with Cisplatin 40 mg/ m2 over 3 hrs infusion.
- IV fluid 1 pint DNS

NACT regime
- Injection Ranitidine 50mg IV 8 hourly.
- Injection Dexamethasone 16mg IV stat.
- Injection Granisetron 3mg IV stat.
- Injection Avil IV stat
- *Inj.Paclitaxel* 175 mg/m2 I.V Infusion In glass bottle NS for 3 hrs
- *Inj.Carboplatin* AUC 5 I.V Infusion in 5D for 3 hrs
- Iv Fluids

FOLLOW UP
The compliance to NACT followed by complete radical dose of radiotherapy with concurrent chemotherapy,3 months follow up were compared

RESULTS:
In this retrospective comparative study of total 20 patients, with squamous cell carcinoma of cervix following strict selection criteria as outlined previously and treatment protocol as mentioned before, the following observations were made.

Table 1- AGE DISTRIBUTION

AGE	ARM A	ARM B
31-40	2	1
41-50	3	3
51-60	5	1
61-70	1	4
TOTAL	11	9

Table 2 During Treatment

	ARM A	ARM B
COMPLETED RADICAL DOSE RT	10	4
DEFAULTED FOR EBRT	1	1
DEFAULTED FOR HDR	0	4
TOTAL DEFAULTERS FOR RADICAL DOSE OF RT	1	5
TOLERATED 4 CYCLES OF NACT	11	
TOLERATED MINIMUM 4 CYCLES OF CONCURRENT CT	11	4

Table 3 During 3 months follow up of Treatment

	ARM A	ARM B
LIVER SEC DURING FOLLOW UP	1	1
OTHER COMPLICATONS	1 jejunal obs	1 uremia and death
Asymptomatic	7	3
dysuria	2	2
Bleeding p/v	0	2
Death	1 (liver sec)	1

Arm A:
10 patients (91%) completed radical dose of RT and weekly cisplatin, one patient (9%) defaulted for EBRT, all patients tolerated 4 cycles of NACT.

During 3 months follow up 1 patient (9%) developed liver secondaries and 1 patient (9%) developed other complication (jejunal obstruction) 2 patients suffered dysuria(18%) and 7 patients aymtomatic(64%)

Arm B:
4 patients (44.5%) completed radical dose of RT and 5 patients (55.5%) defaulted radiation [one for EBRT and 4 for HDR]

During 3 months follow up one patient (11%) developed liver secondaries and 1(11%) developed uraemia and died (both these patients completed radical dose),2 (22.2%)patients with dysuria,2 (22.2%) patients with bleeding p/v and 3(33.3%) patients asymptomatic.

Patients who defaulted for radical dose of concurrent RT were more in arm -B (55%) when compared to arm- A(9%)

More patients are asymptomatic in arm-A(64%) than arm-B(33%)

DISCUSSION

McCormack et al[9] did a single-arm phase II trial of 46 patients, with locally advanced cervical cancer (stage Ib2-IVa). Patients received dose-dense carboplatin (AUC2) and paclitaxel (80 mg m^{-2}) weekly for six cycles followed by CRT (40 mg m^{-2} of weekly cisplatin, 50.4 Gy, 28 fractions plus brachytherapy). The primary end point was response rate 12 weeks post-CRT.

Complete or partial response rate was 70% (95% CI: 54–82) post-NACT and 85% (95% CI: 71–94) post-CRT. The median follow-up was 39.1 months. Overall and progression-free survivals at 3 years were 67% (95% CI: 51–79) and 68% (95% CI: 51–79), respectively and concluded that good response rate is achieved by dose-dense weekly NACT with carboplatin and paclitaxel followed by radical CRT. This treatment regimen is feasible as evidenced by the acceptable toxicity of NACT and by the high compliance to radiotherapy

Singh RB et al [10] studied 28 patients with locally advanced cervical cancer received NACT using paclitaxel (60 mg/m(2)) and carboplatin (AUC-2) weekly for 6 doses followed by definitive CCRT with weekly cisplatin (40 mg/m(2) for 6 doses). Response to concurrent chemo-radiation and toxicity were end points.

Following NACT, complete (CR) - 2(7.1%), Partial (PR) - 17 (60.7%), stable 7 (25.0%) and 2 patients (7.1%) progressed and concluded tha NACT followed by CCRT is feasible and high response rate in locally advanced cervical cancer.

Rony Benson et al [11] studied 25 patients who received 6 weekly doses of NACT Paclitaxel (60 mg/m^2) and carboplatin (AUC 2), followed by CRT and brachytherapy. The analysis of epidermal growth factor receptor (EGFR) expression was carried out by immunohistochemistry. Gefitinib (250 mg daily) was given as maintenance therapy for 1 year after completion of chemoradiation.

Comparison of EGFR expression and survival outcomes was done. Nineteen (76%) patients had a radiological complete response to NACT and concluded that NACT is associated with good response.

Vikas et al [12] studied 113 patients with FIGO stage IIB-IIIB, were randomized to receive either two cycles of cisplatin and 5-flourouracil(CT) followed by radiotherapy(RT) (CT-RT group ,n=58) or RT alone (RT alone group , n=55).

In the CT-RT group 54 evaluable patients 52 responded: clinical complete response (cCR) in 1(1.85%) and partial response in 51(94.45%). Remaining 2 patients (3.70%) had progressive disease (PR). Of 52 patients completed RT as planned. Following RT 38(73.08%) achieved clinical CR, 13(25%) had residual disease, and 1(1.92%) had progressed at first follow up after 1 month.. In the RT group, 54 patients were evaluable 41(75.93%) patients achieved clinical CR, 12(22.22%) had residual disease, and 1(1.85%) progressed.

Conclusions:
In this study response and compliance to treatment was better in the patients who received NACT followed by concurrent chemo radiation and are able complete treatment and majority of them are asymptomatic.

From this it may be concluded that NACT may be considered in stage IVa cervical cancer.

However a prospective trial with large number of patients is needed to come to a conclusion.

REFERENCES

1. GLOBOCAN 2020.
2. Cervical cancer-Incidence. Medindia.net/patients/ patientinfo/cervicalcancer-incidence.html.
3. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: Individual patient data meta-analysis. Cochrane Database Syst Rev 2010;(1):CD008285
4. AJCC Cancer Staging manual; 6 edition. Green FL, page DL network; springer - verlage 2002.
5. Handbook of cancer chemotherapy. Seventh Edition. Ronald T Skeel. Lippincott Williams and Wilkins.
6. ICRU Report 50: Prescribing.recording and reporting photon beam therapy. Bethesda, MD: International Commission on Radiation Units and Measurements,1993.
7. Nag S, Erickson B, Thomadren B. the American Brachytherapy Society recommendation for high dose rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncology Biol Phys. 2000; 48: 201-111.
8. ICRU. Dose and volume specification for reporting intracavitory therapy in gynecology: Report 38.Bethesda, MD: International Commission of Radiation Units and Measurements, 1985.
9. McCormack M, Kadalayil L, Hackshaw A, Hall-Craggs MA, Symonds RP, Warwick V, *et al.* A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. Br J Cancer 2013;108:2464-9.
10. Singh RB, Chander S, Mohanti BK, Pathy S, Kumar S, Bhatla N, *et al.* Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma: A pilot study. Gynecol Oncol 2013;129:124-8.
11. Rony Benson 1, Sushmita Pathy 1, Lalit Kumar 2, Sandeep Mathur 3, Vatsla Dadhwal 4, Bidhu Kalyan Mohanti Locally advanced cervical cancer - neoadjuvant chemotherapy followed by concurrent chemoradiation and targeted therapy as maintenance: A phase II study
12. Vikas Fotedar1 , Dr Rajeev K Seam2 , Dr Manoj K Gupta3 , Dr Anupam Jhobta4 ,Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced carcinoma cervix: a prospective randomized study.