10.5005/jp-journals-10006-1647

RESEARCH ARTICLE

Comparison of Neoadjuvant Chemotherapy Followed by Radical Hysterectomy and Neoadjuvant Chemoradiation Followed by Radical Hysterectomy with Concurrent Chemoradiation in Locally Advanced Carcinoma Cervix (FIGO Stages IB2, IIA2, IIB): Interim Results of a Randomized Control Study

[1]Subbiah Shanmugam, [2]Gopu Govindasamy, [3]Syed A Hussain, [4]Jagadeesan G Mani

ABSTRACT

Objectives: To investigate the therapeutic efficacy, toxicity profile and quality of life in locally advanced cervical carcinoma treated with concurrent chemoradiation therapy (CCRT), preoperative chemoradiation (PCRT) and preoperative chemotherapy (PCHEMO) followed by surgical implications

Materials and methods: A total of (N = 100) locally advanced cervical cancer patients (FIGO stages IB2, IIA2 and IIB) was treated between June 2014 to March 2018, Out of 100 patients, 33 patients treated with CCRT arm (50Gy EBRT and 21Gy brachytherapy), 33 patients treated with PCRT arm (50Gy EBRT) followed by radical hysterectomy, 34 patients with PCHEMO arm followed with radical hysterectomy using 3 weekly cisplatin (75 mg/m^2 and paclitaxel (175 mg/m^2). Patient's Quality life was recorded with a standard questionnaire. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 22.

Results: The median follow-up period was found to be 28 months. However less statistical significance was obtained between various parameters such as age, FIGO stage, performance status, perioperative morbidities, and symptoms scales among three arms ($p > 0.05$). 97%, 94%, 88% of overall response rates noted in CCRT, PCRT and PCHEMO arm patients respectively. But 55% and 24% of PCRT and PCHEMO arm patients had pathological complete responses with the significance of $p = 0.0016$. CCRT arm patients had a larger amount of symptom expertise, difficulties in sexual functioning and sexual agony.

Conclusion: We observed equivalent therapeutic response, better toxicity profile and better quality of life among the patients treated with PCRT arm than the standard CCRT arm patients.

Clinical significance: This approach could be feasible in developing countries wherein brachytherapy resources are scarce.

[1]Professor and Head, [2]Professor, [3]Assistant Professor, [4]Resident

[1-4]Department of Surgical Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai, Tamil Nadu, India

Corresponding Author: Subbiah Shanmugam, Professor and Head, Department of Surgical Oncology, Government Royapettah Hospital, Kilpauk Medical College, Chennai, Tamil Nadu, India, e-mail: subbiahshanmugam67@gmail.com

Keywords: Brachytherapy, Locally advanced cervical cancers, Preoperative chemoradiotherapy, Randomized control trial, Toxicity profile, Quality of life.

How to cite this article: Shanmugam S, Govindasamy G, Hussain SA, Mani JG. Comparison of Neoadjuvant Chemotherapy Followed by Radical Hysterectomy and Neoadjuvant Chemoradiation Followed by Radical Hysterectomy with Concurrent Chemoradiation in Locally Advanced Carcinoma Cervix (FIGO Stages IB2, IIA2, IIB): Interim Results of a Randomized Control Study. J South Asian Feder Obst Gynae 2019;11(1): 35-43.

Source of support: Nil

Conflict of interest: None

Date of received: 02 July 2018

Date of acceptance: 27 December 2018

Date of publication: March 2019

INTRODUCTION

Carcinoma of the uterine cervix is one of the 7th most common disease worldwide and considered as a malignant disease among the South Indian women with an affected population rate of about 19.4–43.5/100,000/year.[1,2] Locally advanced cervical tumors (characterized by FIGO stages IB2, IIA2, IIB) forms a particular subset of "curable" disease having greater 5-year survival rates (around 70%) with satisfactory treatment.[3] Concurrent cisplatin-based chemoradiotherapy is considered as the standard treatment for locally advanced cervical malignancies based on five clinical trials (GOG 85, radiation therapy oncology group RTOG 9001, GOG 123, GOG 120, SWOG 8797).[4,5] Conversely, when pelvic recurrences develop, the morbidity of salvage surgery after Irradiation is frequently greater than the morbidity of salvage irradiation following radical surgery. The benefits of downsizing the disease by using PCHEMO or preoperative chemoradiotherapy without using brachytherapy are appealing and also open up a totally new outlook in radical treatment for curable locally

advanced cervix malignancies. Radical hysterectomy after chemoradiation therapy without brachytherapy has been appeared to come up with similar outcomes with concurrent chemoradiation.[6] This strategy is more attractive in low and middle-income countries wherein the cervix related cancers burden is higher and also brachytherapy resources are limited. Numerous studies demonstrated that cisplatin and paclitaxel with concurrent radiotherapy have offered to raise response rates and desired tolerability.[7-12]

The aim of this interim analysis was to investigate the therapeutic efficacy, toxicity profile, and quality of life in locally advanced cervical carcinoma treated with CCRT, PCRT, and PCHEMO followed by surgical implications.

MATERIALS AND METHODS

Inclusion Criteria

(a) Histologically confirmed patients with cervical squamous cell carcinoma (FIGO stages IB2, IIA2, and IIB); (b) age 18–65 years; (c) ECOG performance score less than or equal to 2.

Exclusion Criteria

Patients with (a) non-squamous histologies; (b) other systemic diseases, comorbidities precluding full participation in this trial; (c) concomitant treatment with any experimental drugs; (d) pregnant or nursing women; (e) previous irradiation or concomitant malignant diseases

All patients were evaluated before starting treatment with history and physical examination (examination under anesthesia to confirm the stage), biopsy, complete blood analysis, chest X-ray, ultrasonography (USG) abdomen and pelvis, CECT abdomen and pelvis, Cystoscopic examination (for tumors involving anterior fornix) and proctoscopy examination (tumors involving posterior fornix).

Treatment Schemes and Response Evaluation

The patients were randomized to three arms as standard CCRT, PCRT followed by a radical hysterectomy and PCHEMO followed by radical hysterectomy. For CCRT arm patients, cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2) were given with 3 weeks interval between the two cycles along with concurrent Radiotherapy of 50 Gy EBRT (2 Gy of 25 #) followed by brachytherapy of 21 Gy (7 Gy for 3 doses) completed within 8 weeks. For PCRT arm patients, cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2) were given with 3 weeks interval between the two cycles along with concurrent Radiotherapy of 50 Gy EBRT (2 Gy of 25 #) within a time span of 5 weeks and followed by Radical hysterectomy within 3 weeks after completion of radiotherapy, for PCHEMO arm patients, cisplatin (75 mg/m^2) and paclitaxel (175 mg/m^2) was given with 3 weeks interval for 3 cycles followed by radical hysterectomy within 3 weeks after completion of chemotherapy.

During the course of treatment, all the patients underwent weekly hematology as well as blood chemistry laboratory tests for safety and dosage modification purposes. Treatment response and operability were evaluated by WHO criteria with physical examinations (examination under anesthesia at the time of radical hysterectomy) and imaging before brachytherapy, after Neo-adjuvant chemoradiotherapy and neoadjuvant chemotherapy in CCRT, PCRT and PCHEMO arms respectively. Patients with advancing disease were termed as treatment failure and taken care of with conventional chemoradiotherapy. Safety was compared by documenting clinical adverse events (AEs) by utilizing the National Cancer Institute Common Toxicity Criteria (version 3.0). Quality of life was assessed by means of two validated questionnaires (EORTC QLQ-C30 and EORTC QLQ-CX24) formulated by the European Organization for Research and Treatment of Cancer (EORTC). The association of clinical manifestations between the two groups was determined by *t* test for continuous variables, and Pearson's Chi-square test was adapted to estimate the associations between independent variables. A probability (*p*) value of < 0.05 was regarded as statistically significant. All statistical comparisons were performed using IBM SPSS version 22.0. Bonferroni adjusted Mann–Whitney test was used for various correlations in the evaluation of personal gratifications among three treatment arms.

Clinical Trial ID

NCT01917695

RESULTS

Patients' Characteristics

From July 2014 to March 2018, 100 women with age from 18 to 65 years old were enrolled and randomly allocated to CCRT arm (*n* = 33), PCRT arm (*n* = 33) and PCHEMO arm (*n* = *34*). Of 33 patients randomized to CCRT arm, 6% defaulted during treatment (EBRT) and 6% defaulted for brachytherapy. Of 33 patients randomized to PCRT arm, 6% were defaulted for surgical treatment (after completing EBRT and two cycles of chemotherapy) and of 34 patients randomized to PCHEMO arm, 3% defaulted for surgery.

The follow-up period was until June 2018 with a median follow-up period of 28 months. Clinical characteristics were well adjusted at baseline between treatment arms and depicted in Table 1.

There was no statistically significant difference between age group, FIGO stage and performance status of the patients dispersed among three groups (p >0.05).

Oncological Outcomes

The overall response rate for CCRT, PCRT and PCHEMO arm patients were 97%, 94%, and 88%, respectively. Complete clinical response was seen in 72%, 45% and 26% of CCRT, PCRT and PCHEMO arms respectively. Partial clinical response was seen in 12%, 42% and 59% of CCRT, PCRT and PCHEMO arms respectively. At the time of response assessment 3% of CCRT,6% of PCRT and 12% patients of PCHEMO arms had progressive disease and changed over to Radical chemoradiation treatment.

At the time of this interim analysis, 70% of CCRT, 88% of PCRT and 85% of PCHEMO arm patients were alive without disease and 12% of CCRT and 6% of PCRT arms 0% of PCHEMO were dead. Of 85% alive patients in PCHEMO arm, 9% had local and 3% had distant recurrence who were treated with surgical/medical methods. Of these alive patients, 2 of CCRT and 4 of PCHEMO arm patients had recurrent disease. Two patients of CCRT arm expired due to distant recurrence. No death was noted in PCHEMO arm.

Clinical response rates among the treatment arms were found statistically significant (p = 0.0022), as shown in Table 2.

Pathological Outcomes

Pathological Response Rate

Sixty-three percent of PCRT and 27% of PCHEMO patients had a complete pathological response which shows a statistically significant difference (p = 0.0016). Unlike in PCRT arm patients, where no positive lymph node disease, 6 of PCHEMO arm patients had lymph nodal positive disease (0% *vs.* 21%). there was no statistically significant relationship found between 2 arms in Lymphovascular space invasion and depth of stromal invasion. In both arms, vaginal margins and parametrial margins were not involved by the tumor cells (Table 3).

Perioperative Outcomes

Totally 58 patients were operated from PCRT and PCHEMO arms including 29 patients in each arm. Mean duration of hospital stay for both arms were similar (14 days) but the operating time was longer for PCRT patients than PCHEMO patients (170 mins *vs.*155 mins) (p >0.05). Also, the conversion rate from laparoscopic to open radical hysterectomy was higher among PCRT than PCHEMO arm patients (21% *vs.* 18%) (p >0.05). There was no statistically significant difference found in the average amount of blood loss during surgery even though PCHEMO arm patients bled more than PCRT arm patients (255 mL *vs.* 275 mL).

Table 1: Characteristics of patients

Characteristics	*CCRT arm*	*NACRT arm*	*NAC arm*	*p value*
Number of patients	33	33	34	–
Mean age in years (SD)	47.76 (6.185)	47.58 (5.385)	47.68 (5.492)	0.992
FIGO stage	*No. (%)*	*No. (%)*	*No. (%)*	
Stage IB2	2 (6.1%)	5 (15.2%)	5 (14.7%)	0.155
Stage IIA2	3 (9.1%)	4 (12.1%)	9 (26.5%)	
Stage IIB	28 (84.8%)	24 (72.7%)	20 (72%)	
ECOG Performance status				
P.S. 1	26 (78.8%)	30 (90.9%)	29 (85.3%)	0.385
P.S. 2	7 (21.2%)	3 (9.1%)	5(14.7%)	

Table 2: Response assessment and oncological outcomes

	Clinical response of treatment arms			
	CCRT arm no. (%)	*NACRT arm no. (%)*	*NAC arm no. (%)*	*p value*
Response category				
Overall response rate	97%	94%	88%	
Complete response	24 (72%)	15 (45%)	9 (26%)	
Partial response	4 (12%)	14 (42%)	20 (59%)	0.0022
Progressive disease	1 (3%)	2 (6%)	4 (12%)	
Not evaluable	4 (12%)	2 (6%)	1 (3%)	
Oncological outcomes				
Alive without disease	23 (70%)	29 (88%)	29 (85%)	
Alive with recurrence	2 (6%)	0 (0%)	4 (12%)	
Dead without disease	2 (6%)	2 (6%)	0 (0%)	0.571
Dead due to recurrence	2 (6%)	0 (0%)	0 (0%)	
Not evaluable	4 (12%)	2 (6%)	1 (3%)	

Postoperative Outcomes

Both PCRT and PCHEMO arm patients tolerated the surgery well and no treatment-related death was reported. Equal number of patients had Urinary tract infection (6%) and sustained urinary bladder injury (3%) but PCRT patients had significantly increased incidence of acquisition of Delayed Urinary bladder control (18% *vs.* 10%) than PCHEMO arm patients.3% of PCRT arm patients had rectum injury, and 3% of PCHEMO arm patients had an incisional hernia within 6 months.

Overall there were no statistically significant post-operative morbidities between the two arms (Table 3).

TOXICITY PROFILE

There were no treatment-related deaths. The types and frequencies of adverse effects are shown in Table 4.

Eleven percent of CCRT, 9% of PCRT and 13% of PCHEMO patients had grade 3 anemia, 8% of CCRT, 5% of PCRT and 8% of PCHEMO had grade 3 leukopenia, 3% of CCRT, 2% of PCRT and 2% of PCHEMO had grade 3 thrombocytopenia, 6% of CCRT, 5% of PCRT and 4% of PCHEMO had grade 3 neutropenia during treatment. 7% of CCRT, 6% of PCRT and 6% of PCHEMO patients had grade 3 nausea and vomiting. Thirty-five percent of CCRT, 28% of PCRT and 32% of PCHEMO Patients had Grade 2 alopecia. Two percent of arm CCRT, 3% of PCRT and 6% of PCHEMO Patients had grade 3 hypersensitive reactions 2% of CCRT, 2% of PCRT and 2% of PCHEMO patients had grade 3 ototoxicity, 10% of CCRT, 8% of PCRT and 11% of PCHEMO patients had grade 3 peripheral neuropathy during treatment.

Radiotherapy-induced short-term severe toxicities reported in 14 patients. Six percent of CCRT and 3% of PCRT had grade 3 proctitis 12% of CCRT and 6% of PCRT.

Patients had grade 3 cystitis. grade 3 skin reactions reported in 6% patients and 3% patient of CCRT and PCRT respectively. Lymphedema reported in a higher number, 4 pts (12%) in PCRT than CCRT (1 pt.) and arm PCHEMO (1 pt).

Quality of Life

Results Eortc QLQ–30

Of total 100 patients incorporated in this interim analysis, total 81 (25 from CCRT, 27 from PCRT and 29 patients from PCHEMO arm fulfilled the list of questions.

One question-form was analyzed per patient by the end of three months after completion of respective

Table 3: Histopathological and operative outcomes–analysis

Histopathological parameters	*NACRT arm*	*NAC arm*	*p value*
Pathological response			
Complete	21 (63%)	9 (27%)	0.0016a
Partial	8 (24%)	20 (60%)	
Lymph nodal status			
Positive	0 (0%)	6 (21%)	0.0392
Negative	29 (100%)	23 (79%)	
Stromal invasion			
Less than 1/3 depth	23 (79%)	26 (90%)	0.3708
1/3 to 2/3 depth	4 (14%)	1 (3%)	
Full thickness	2 (7%)	2 (7%)	
Lympho-vascular space invasion			
Present	3 (10%)	24 (83%)	0.002
Absent	26 (90%)	5 (17%)	

Perioperative outcomes			
Parameters	*NACRT arm (N = 29)*	*NAC arm (N = 29)*	*p value*
Type of surgery			
Open radical hysterectomy	13 (39%)	8 (24%)	0.3107
Lap conversion to open RH	7 (21%)	6 (18%)	
Laparoscopic radical hysterectomy	9(27%)	14 (41%)	
Mean duration of surgery (in minus)	171.5 ± 31.5	155.3 ± 35.6	0.068
Mean blood loss (mL)	254.8 ± 136.7	274.1 ± 115.4	0.764
Mean postoperative hospital stay (days)	13.7 ± 3.1	13.24 ± 3.4	0.912
Postoperative outcomes			
Morbidities			
Urinary sepsis	2 (6%)	2 (6%)	*
Delayed urinary bladder emptying (>3 weeks)	6 (18%)	3 (10%)	*
Urinary bladder injury	1 (3%)	1 (3%)	*
Rectum injury	1 (3%)	0 (0%)	*
Incisional hernia	0 (0%)	1 (3%)	*

*Small sample size and outcomes are not mutually exclusive, statistical tests could not be applied

Table 4: Toxicity profile

Toxicities due to chemotherapy	*CCRT arm (N=62 cycles) No.of pts(%)*	*NACRT arm (N = 66 cycles) No.of pts (%)*	*NACarm (N = 102 cycles) No.of pts(%)*	*p value (CHI-SQ)*
Anemia				
Grade 2	29 (47%)	24 (36%)	36 (35%)	0.686 (0.7534)
Grade 3 and more	7 (11%)	6 (9%)	13 (13%)	
Leukopenia				
Grade 2	21 (34%)	19 (28%)	29 (28%)	0.748 (0.5798)
Grade 3 and more	5 (8%)	3 (5%)	8(8%)	
Thrombocytopenia				
Grade–2	5 (8%)	5 (8%)	11 (11%)	0.762 (0.5424)
Grade–3 and more	2 (3%)	1 (2%)	2 (2%)	
Neutropenia				
Grade–2	12 (20%)	12 (18%)	20 (20%)	0.811 (0.4167)
Grade–3 and more	4 (6%)	3 (5%)	4(4%)	
Nausea and vomiting				
Grade–1and 2	52 (84%)	60 (91%)	91 (89%)	0.979 (0.0418)
Grade–3 and more	3 (7%)	4 (6%)	6(6%)	
Alopecia				
Grade–1	40 (65%)	47 (72%)	69 (68%)	0.719 (0.6595)
Grade–2	22 (35%)	19 (28%)	33(32%)	
Hypersensitivity				
Grade–1 and 2	19 (31%)	21 (32%)	30(29%)	0.373(1.9674)
Grade–3 and more	1 (2%)	2 (3%)	6(6%)	
Nephrotoxicity				
Grade–1 and 2	12 (19%)	14 (21%)	22(22%)	0.908(0.1914)
Grade–3 and more	0 (0%)	0 (0%)	0(0%)	
Ototoxicity				
Grade–1 and 2	7 (11%)	9 (14%)	10(10%)	0.897(0.2163)
Grade–3 and more	1 (2%)	1 (2%)	2(2%)	
Peripheral neuropathy				
Grade–1 and 2	28 (45%)	32 (48%)	55(55%)	0.650(0.8611)
Grade–3 and more	6 (10%)	5 (8%)	11(11%)	
Radiation toxicities	*No. of patients*	*No. of patients*	*No. of patients*	
Cystitis				
Grade 2	12	8	2	0.887 (0.2385)
Grade 3 and more	4	2	0	
Proctitis				
Grade 2	8	5	2	0.840 (0.3483)
Grade 3 and more	2	1	0	
Skin reactions				
Grade 2	4	4	0	0.726 (0.638)
Grade 3 and more	2	1	0	
Lymphedema				
Grade -1 and 2	1	4	1	0.870 (0.2778)
Grade 3 and more	0	2	0	

treatment method. For items relating to sexual performance, only sexually active women (13 from CCRT, 16 from PCRT and 11 from PCHEMO arms) replied for the questions. For the items relating to functioning scales, women in CCRT arm disclosed lower scores for physical and social functioning and women in PCHEMO arm revealed reduced emotional functioning and global health QOL. There was no significant difference among symptom scales, but CCRT arm patients disclosed an increased degree of symptom experience, difficulties in relation to sexual functioning/vaginal functioning and sexual agony. Women in PCHEMO arm disclosed lot more sexual activity and Lymphedema was more frequently recorded in PCRT arm patients. Peripheral neuropathy was more experienced by the patients in PCHEMO arm (Table 5).

Bonferroni Adjusted Mann–Whitney Test for Multiple Comparison

There was significant declination of physical functioning among CCRT patients than other two arms and poor sexual functioning among patients of CCRT and PCRT than PCHEMO arm patients.

Table 5: Quality of life

QLQ-30 Functioning scales	CCRT arm (N = 25) Mean rank	NACRT arm (N = 27) Mean rank	NAC arm (N = 29) Mean rank	p value
Functioning scales				
Physical functioning	37.02	42.00	43.5	0.043[a]
Role functioning	41.00	41.0	41.00	1.00
Emotional functioning	41.38	41.61	40.10	0.869
Cognitive functioning	41.00	41.0	41.00	1.000
Social functioning	40.40	41.11	41.41	0.957
Global health–QOL	41.78	45.33	36.29	0.278
Symptom scales				
Fatigue	41.98	38.37	42.60	0.685
Nausea and vomiting	40.00	43.00	40.00	0.132
Pain	39.36	38.67	44.59	0.414
Single item scales				
Dyspnea	41.00	41.00	41.00	1.000
Insomnia	41.00	41.00	41.0	1.000
Appetite loss	41.00	41.00	41.00	1.000
Constipation	38.60	41.00	43.07	0.657
Diarrhea	42.86	42.50	38.00	0.167
Financial difficulties	40.36	41.22	41.34	0.951

Parameters	Treatment arms	p value
Physical functioning	CCRT arm *vs.* NACRT arm	0.202
	CCRT arm *vs.* NAC arm	0.046[a]
	NACRT arm *vs.* NAC arm	0.999
Sexual enjoyment	CCRT arm *vs.* NACRT arm	0.999
	CCRT arm *vs.* NAC arm	0.070
	NACRT arm *vs.* NAC arm	0.010[a]
Sexual/ vaginal functioning	CCRT arm *vs.* NACRT arm	0.107
	CCRT arm *vs.* NAC arm	0.232
	NACRT arm *vs.* NAC arm	0.001[a]

QLQ-24 multi-item scales				
Symptom experience				
Body image	41.00	41.00	41.00	1.000
Sexual/vaginal functioning	21.62 (N = 13)	14.00 (N = 16)	28.64 (N = 11)	0.001[a]
Single item scales				
Lymphedema	40.00	44.00	39.09	0.640
Peripheral neuropathy	40.50	40.50	41.90	0.408
Menopausal symptom	41.00	41.00	41.00	1.000
Sexual worry	22.65 (N = 13)	22.24 (N = 19)	24.46 (N = 13)	0.618
Sexual activity	16.85 (N = 13)	20.00 (N = 16)	26.83 (N = 12)	0.069
Sexual enjoyment	19.00 (N = 13)	17.50 (N = 16)	25.30 (N = 10)	0.011[a]

DISCUSSION

Multimodality treatment modalities have focused on radical concurrent chemoradiotherapy, preoperative chemoradiotherapy followed by radical surgery and PCHEMO followed by radical surgery in recent years.[13-18]

To our knowledge, this is the first study from our institution exploring the efficacy of preoperative chemoradiotherapy and PCHEMO followed by radical surgery having conventional chemoradiation as the control arm.

Concurrent Chemoradiation Arm

A study by Brunner et al. showed 72% of patients with stage II B cervix malignancies were treated with definitive chemoradiation.[13] Also, when studied among Southeast Asian population, radical surgeries has been considered as better effective treatment strategy rather than concurrent chemoradiation. But various studies need to be explored to know the efficacy of surgical treatment benefits for these patients.

Disilvestro et al. performed an identical clinical study choosing cisplatin (40 mg/m^2/week) and paclitaxel (40 mg/m^2/week) for 6 cycles in conjunction with concurrent radiotherapy reported 94.7% patients experienced clinical complete response including 89.4% had a complete response, 5.3% had a partial response and 5.3 % had stable disease. With 14 months of median follow-up period, 84% of patients were alive without any disease,

5.3 % alive with disease and 10.5% had expired. At the same time 1.8%, 17.7% and 11.5% of the total cycles exhibited grade 3 or 4 anemia, leukopenia and neutropenia respectively.

Miglietta et al. conducted a similar study choosing cisplatin (75 mg/m^2) plus paclitaxel (175 mg/m^2) every 3 weeks for 4 cycles documented 100% of patients experienced complete response with 88% obtained persistent complete remission at a median follow up of more than 23 months.[11] About 3.7% of patients had bone metastasis and 7.4% suffered from distant nodal recurrence after 24 months of follow up time frame. Furthermore, 8%, 25 % and 16% of total chemotherapy cycles present grade 3 or 4 anemia, leukopenia and neutropenia respectively. No single patient came up with any late toxicities pertaining to radiotherapies like grade 3 cystitis, proctitis, and enteritis.

Our cohorts exhibited more desirable hematological adverse reaction profile and poor results in regards with the response and survival outcomes than Disilvestro et al. and Miglietta et al. reports, which might be attributable to the dissimilarities in the number of cycles, timing and dosage strength of cisplatin and paclitaxel provided in conjunction with concurrent radiotherapy.

Preoperative Chemoradiotherapy

In phase III randomized controlled trial performed by Cetina et al. in stage IB2 to II B patients using gemcitabine and cisplatin, 72% had a complete pathological response, and 22% had a partial pathological response along with 66% f patients with the microscopic disease. Our cohorts showed 63% and 23% complete and partial pathological response, respectively. About 2.3% had positive parametrial margin, and 10% had lymph node-positive disease. But none of our study population had positive parametrial margins and positive lymph node diseases. The median length of hospital stay was 5 days (4–6 days), median operative duration was 4 hours (4–6 hours), median blood loss was 450 mL and 3.4% had a vascular injury. 1.5% had a urethral injury and 2.3% had a ureteral injury. 1,5% had wound dehiscence, and 1.5% had unilateral lymph cysts. Our clinical trial outcomes revealed 3% of urinary bladder and 3% of rectum injury. Furthermore, less amount of blood loss and less duration of surgery in comparing with L.cetina et al. results.

Similarly, a prospective analysis performed by Huguet et al., in which all the patients were given a tumor-free resection margins[19] and at histological assessment complete response was recognized in 54.5%, cervical microscopic disease with significant tumour cells <5 mm in dimension was identified in 17,5% and cervical residual disease >5 mm in dimension was identified in 28% of patients. However, when zero vaginal, as well as the parametrial residual disease, was noted which is similar to our study results. 7.8% of patients were been treated with bilateral pelvic lymph node dissection came up with pelvic lymph node-positive disease, 1.29% with isolated central recurrence, 3.89% with pelvic nodal recurrence, 3.89% with isolated metastatic diseases, 6.49% were with pelvic recurrences with synchronous metastasis as well as 1.29% metastasis with synchronous paraaortic nodal metastasis. Hardly any treatment-related deaths were noted. Chemotherapy side-effects, as well as acute radiation side-effects, were tolerable with a minimal number of cases of serious grades 3 –4 acute side effects.[20]

Our findings having said that, despite achieving a path complete response rate of 63% which is within the range 52–77.5%, signifies that there is a definite role of radical surgery after chemoradiation.[21]

Not surprisingly, many appealing challenges were evolved from our analysis. First, an RH after chemoradiation is feasible as well as not harmful to the patients. Operative risks are within the spectrum documented even for radical surgery performed as primary treatment of early-stage cervical cancer. additionally, a tendency for significantly fewer rates of long-term toxic outcomes. Second, the chemoradiation regimen of 3 weekly cisplatin–paclitaxel is well tolerated.[22]

Preoperative Chemotherapy Arm

This strategy was based on neoadjuvant chemotherapy's "ability to downstage disease, facilitate surgical resection and potentially eradicate systemic metastasis,"

In a study conducted by Park et al., clinical phase II trial showed neoadjuvant paclitaxel and cisplatin, clinical responses occurred in 90.7% of patients, including 39.5% with complete response, 11.6% with a pathologically determined complete response, 51.2% with a partial response and 9.3% of patients showed stable disease and none of them demonstrated active disease. Besides, Hematologic toxicity was noted in 39.5% of patients and most of them observed was anemia, but there were nil patients observed with grades 3 or 4 toxicities. But when observed grade 1 peripheral neuropathy was seen in 29 patients despite there is no delayed treatment of toxicities.[23] In comparison to Park et al. results, our study showed a better response rate (complete pathological response–27% and partial pathological response–60%) and as well as fewer toxicities among the patients.

In a comparative analysis of chemoradiation and neoadjuvant chemotherapy results before radical hysterectomy in stage IB–IIB bulky cervical cancer and with tumour dimensions more than 4 cm performed by Modarress et al., making using cisplatin 50 mg/m^2 and

vincristine 1 mg/m^2 every 7–10 days, for three courses exhibited Complete clinical response in NACT group was seen in 16.7% of patients, partial clinical response to treatment in NACT was observed in 83.3% of patients.[25] Lymph node involvement was identified in 23.4% of patients. Parametrial involvement was observed in 20% of patients of NACT group. A residual tumor in NACT was detected in 46.7% of patients. After treatment, there was just one patient with hydronephrosis grade 2 in NACT group.[24]

Similar to Modaress et al. study, our cohorts experienced 21% lymph node positive diseases, but in contrast, no single patient had parametrial positive diseases.

A recently published randomized controlled trial (RCT) by Gupta et al. from Tata Memorial hospital comparing neoadjuvant chemotherapy followed by surgery (NACT-surgery) versus CTRT in patients with stage IB2 to IIB squamous carcinoma of cervix showed that neoadjuvant chemotherapy arm patients experiencing a significantly higher rate of grades 3–4 thrombocytopenia within 42 days than the chemoradiation-treated patients but a lower rate of grades 1–2 symptoms such as diarrhea, dysuria, skin reactions, and renal toxicity. After 3 months, CCRT was associated with higher rates of rectal, bladder, vaginal, and other toxicities than neoadjuvant chemotherapy.[25] Our cohorts' toxicity profiles are staying in parallel with this study population.

Pertaining to the quality of life, in our interim analysis, there seemed to be no significant difference among symptom scales, but CCRT patients disclosed considerably more amount of symptom experience, difficulties in sexual functioning/vaginal functioning and sexual agony. However, Women in PCHEMO arm disclosed an increase in sexual activity. Lymphedema was more frequently noted in PCRT arm patients. Peripheral neuropathy was highly experienced among the patients in PCHEMO arm.

Similar to our study, showed long-term morbidity as well as better quality of life among cancer survivors. Among which 64% were found to be sexually active, 67% responded with radical hysterectomy and 50% with primary radiation therapy.[26] However, our study also showed lower scores among patients treated with CCRT having social, functional and financial difficulties. Furthermore, Women treated with CCRT showed higher level of symptom experience, sexual or vaginal functioning as well as sexual worry. Also,women treated with PCHEMO followed by radical hysterectomy also showed higher sexual activity and lymphedema as well as peripheral neuropathy. It was also observed that sexual activity in women with increased age and longer follow up study showed effective positive results on sexual activity.

Thus, from our study, we observed equivalent therapeutic, better toxicity profile and quality of life among patients treated with peroperative chemoradiation followed by radical surgery than the standard concurrent chemoradiation arm patients. Even though the patients treated with preoperative chemotherapy in this interim analysis had good quality of life than the other two arms, almost half of them treated with adjuvant vault brachytherapy during treatment, hence its therapeutic efficacy should be viewed with caution.

CONCLUSION

Though it is premature to decide on this interim report, results show that chemoradiation without brachytherapy followed by surgery has been learned to have equivalent outcomes as well as associated with tolerable morbidity. It seems sensible to make use of a modified therapeutic protocol of chemoradiation followed by radical hysterectomy as an alternative treatment option in low-resource countries wherein brachytherapy is not easily accessible. Long-term outcomes of this randomized control trial are currently being evaluated.

CLINICAL SIGNIFICANCE

This approach could be feasible in developing countries with higher incidence of cervical cancers wherein brachytherapy resources are scarce.

ACKNOWLEDGMENTS

Authors would like to acknowledge the Professors and Assistant Professors of Departments of Medical Oncology and Radiation Oncology of Royapettah Government Hospital, Chennai for providing necessary supports and guidance for conducting this clinical trial.

REFERENCES

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 2006;24: 2137-2150.
2. Rajkumar R, Sankaranarayanan R, Esmi A, Jayaraman R, Cherian J, Parkin DM. Leads to cancer control based on cancer patterns in a rural population in South India. Cancer Causes Control 2000;11:433-439.
3. Markman M. Chemoradiation in the management of cervix cancer: current status and future directions. Oncology 2013; 84:246-250.
4. Jemal A, Bray F, Center MM, FerlayJ,Ward E, Forman D. Global Cancer Statistics. CA Cancer J Clin 2011; 61:69-90.
5. Rose PG. Concurrent chemoradiation for locally advanced carcinoma of the cervix: where are we in 2006? Ann Oncol 2006;17(Suppl. 10):x224-229.
6. Chuang L, Kanis MJ, Miller B, Wright J, Small W, Creasman W. Treating locally advanced cervical cancer with concurrent chemoradiation without brachytherapy in low-resource

countries. American Journal of Clinical Oncology. 2016 Feb 1;39(1):92-97.

7. Pignata S, Frezza P, Tramontana S, Perrone F, Tambaro R, Casella G, Ferrari E, Iodice F, De Vivo R, Ricchi P, Tramontana F. Phase I study with weekly cisplatin-paclitaxel and concurrent radiotherapy in patients with carcinoma of the cervix uteri. Annals of Oncology. 2000 Apr 1;11(4):455-459.
8. Petera J, Odrážka K, Frgala T, Špaček J. External beam radiotherapy and high-dose brachytherapy combined with cisplatin and paclitaxel in patients with advanced cervical carcinoma. Gynecologic Oncology. 2005 Nov 1;99(2):334-338.
9. Prasad E, Viswanathan PN, Rangad VF, Pavamani S, Ram TS. Maximum tolerated dose and early response-results of a phase I trial of paclitaxel and cisplatin with radiation therapy in carcinoma of the cervix. Clin Oncol (R Coll Radiol) 2009; 21:488-493.
10. Chen MD, Paley PJ, Potish RA, Twiggs LB. Phase I trial of taxol as a radiation sensitizer with cisplatin in advanced cervical cancer. Gynecol Oncol 1997; 67:131-136.
11. Miglietta L, Franzone P, Centurioni MG, Boni L, Tacchini L, Cosso M, et al. A phase II trial with cisplatin-paclitaxel cytotoxic treatment and concurrent external and endocavitary radiation therapy in locally advanced or recurrent cervical cancer. Oncology 2006;70:19-24.
12. DiSilvestro PA, Walker JL, Morrison A, Rose PG, Homesley H, Warshal D, et al. Radiation therapy with concomitant paclitaxel and cisplatin chemotherapy in cervical carcinoma limited to the pelvis: A phase I/II study of the Gynecologic Oncology Group. Gynecol Oncol 2006;103:1038-1042.
13. Brunner TB, Grabenbauer GG, Klein P, Baum U, Papadopoulos T, Bautz W, et al. Phase I trial of strictly time-scheduled gemcitabine and cisplatin with concurrent radiotherapy in patients with locally advanced pancreatic cancer. Int J Radiat Oncol Biol Phys 2003;55:144-153.
14. Zarba JJ, Jaremtchuk AV, Gonzalez Jazey P, Keropian M, Castagnino R, Mina C, et al. A phase I–II study ofweekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical carcinoma. Ann Oncol 2003;14:1285-1290.
15. Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. Lancet 2001; 358:781-786.
16. Choi CH, Lee YY, Kim MK, Kim TJ, Lee JW, Nam HR, et al. A matched-case comparison to explore the role of consolidation chemotherapy after concurrent chemoradiation in cervical cancer. Int J Radiat Oncol Biol Phys 2011; 81:1252-1257.
17. DiSilvestro PA, Ali S, Craighead PS, Lucci JA, Lee YC, Cohn DE, et al. Phase III randomized trial of weekly cisplatin and irradiation versus cisplatin and tirapazamine and irradiation in stages IB2, IIA, IIB, IIIB, and IVA cervical carcinoma limited to the pelvis: a GynecologicOncology Group study. J Clin Oncol 2014;32:458-464.
18. Duenas-Gonzalez A, Zarbá JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. J Clin Oncol 2011;29:1678-1685.
19. Cetina L, Garcia-Arias A, Candelaria M, Cantú D, Rivera L, Coronel J, et al. Brachytherapy versus radical hysterectomy after external beam chemoradiation: a non-randomized matched comparison in IB2-IIB cervical cancer patients. World Journal of Surgical Oncology. 2009 Dec;7(1):19.
20. Huguet F, Cojocariu OM, Levy P, Lefranc JP, Darai E, Jannet D, et al. Preoperative concurrent radiation therapy and chemotherapy for bulky stage IB2, IIA, and IIB carcinoma of the uterine cervix with proximal parametrial invasion. International Journal of Radiation Oncology Biology Physics. 2008 Dec 1;72(5):1508-1515.
21. LENT SOMA scales for all anatomic sites. Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1049-1091
22. Morice P, Uzan C, Zafrani Y, Delpech Y, Gouy S, Haie-Meder C. The role of surgery after chemoradiation therapy and brachytherapy for stage IB2/II cervical cancer. Gynecologic oncology. 2007 Oct 1;107(1):S122-S124.
23. Park DC, Kim JH, Lew YO, Kim DH, Namkoong SE. Phase II trial of neoadjuvant paclitaxel and cisplatin in uterine cervical cancer. Gynecologic Oncology 2004 Jan 1;92(1):59-63.
24. Modarress M, Maghami FQ, Golnavaz M, Behtash N, Mousavi A, Khalili GR. Comparative study of chemoradiation and neoadjuvant chemotherapy effects before radical hysterectomy in stage IB–IIB bulky cervical cancer and with tumor diameter greater than 4 cm. International Journal of Gynecological Cancer. 2005 May;15(3):483-488.
25. Gupta S, Maheshwari A, Parab P, Mahantshetty U, Hawaldar R, Sastri S, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. Journal of Clinical Oncology. 2018 Feb 12;36(16):1548-1555.
26. Derks M, van Lonkhuijzen LR, Bakker RM, Stiggelbout AM, de Kroon CD, Westerveld H, et al. Long-term morbidity and quality of life in cervical cancer survivors: a multicenter comparison between surgery and radiotherapy as primary treatment. International Journal of Gynecological Cancer. 2017 Feb 1;27(2):350-356.