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ORIGINAL ARTICLE

Induction Chemotherapy Followed by Concurrent Chemoradiation in the Management of Different Stages of Cervical Carcinoma: 5-year Retrospective Study

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Dr. Kamlesh Kumar Harsh is a Junior specialist in the Department of Radiation Oncology in the Regional Cancer Center at Bikaner. He has always shown keen interest in research and improvement of patient care. He is the author of many national and international publications. Besides being dedicated physician, he is of jolly nature and enjoys his duties and works. His zeal to continuous improvement has resulted in improved patient care and services to cancer sufferers.

Abstract

Aim The data of survival for Indian cervical cancer patients treated by indigenous modifications of the protocol are scarce. The objective of this retrospective study was to analyze the efficacy and tolerability in patients of cervical carcinoma treated by neoadjuvant chemotherapy followed by concurrent chemoradiation.

Materials and Methods Three hundred and thirty two cases of squamous cell carcinoma of cervix who received 3 cycles of neoadjuvant chemotherapy followed concurrent chemoradiation were retrospectively analyzed for overall survival (OS), disease-free survival (DFS), and local pelvic control rate.

Results The 3-year OS and DFS were 93.7 % for stage I-B, 88.0 and 84.0 % for stage II-A, 82.8 and 79.7 % for stage II-B, 70.0 and 64.9 % for stage III-A, 59.3 and 52.4 % for stage III-B, and 53.6 and 32.1 % for stage IV-A disease. The 5-year OS and DFS rates were 93.7 and 87.5 % for stage I-B, 84.0 % for Stage II-A, 79.7 and 76.6 % for stage II-B, 67.6 and 59.5 % for stage III-A, 48.4 and 41.9 % for stage III-B, and 28.6 and 14.3 % for stage IV-A disease.

Conclusion Neoadjuvant chemotherapy followed by concurrent chemoradiation is feasible and produces impressive disease-free and overall survival. This protocol is especially helpful for busy cancer centers with long waiting lists on radiotherapy machines.

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Keywords Cervical carcinoma · Neoadjuvant chemotherapy · Concurrent chemoradiation · Squamous cell carcinoma

Introduction

Cervical cancer is the fourth most common cancer affecting women worldwide after breast, colorectal, and lung cancers. India accounts for one-fifth of cervical cancer globally and 130,000 new cases are added every year, and the number of new cervical cancer cases in India is projected to increase to 226,084 by 2025 and accounts for nearly one-third of global cervical cancer deaths [1, 2]. In India, the patients commonly present with locally advanced disease and the prognosis is directly related to the stage at presentation. Approximately 70–90 % of mortality occurs within 5 years of diagnosis. In an effort to improve the overall survival rates in advanced stage, NACT has been tried as an additional treatment to the current standard of care of concurrent chemoradiotherapy. The role of NACT in cervical cancer is that it arrests the further growth of the tumor by causing shrinkage of primary tumor and also controls the micro-metastasis. This prevents a significant proportion of relapses, radiobiologically it can be explained as it decreases the hypoxic cell fraction thereby considerably increases the radio-sensitivity of the tumor. Several studies have endorsed the role and response of NACT. It has been identified as an important prognostic factor [3, 4].

The data of survival for Indian cervical cancer patients treated by indigenous modifications of the protocol are scarce. The role of NACT is further bolstered by the facts that in a country like India where more than 70 % of the population from rural areas is generally illiterate, they may not agree for radiotherapy on the first visit, so NACT can be considered as an option of treatment followed by concurrent chemoradiation. NACT not only alleviates the symptoms, but also helps the patients to come to terms with the disease and accept radiotherapy as modality of treatment. Besides this, busy cancer centers across the country with long waiting lists for treatment on radiotherapy machines cannot accommodate the patients on their first visit. So the use of NACT is a viable option before concurrent chemoradiation. In this retrospective study, we have assessed the results of three cycles of NACT followed by concurrent chemoradiation.

Materials and Methods

The present study was conducted in the department of Radiotherapy and Oncology Acharya Tulsi Regional Cancer Treatment & Research Institute, Bikaner, Rajasthan, India. Over a period of 1 year (1st January–31st December 2008) 332 histologically confirmed squamous cell carcinomas of cervix were reviewed for the study. Staging procedures were done as per the protocols prescribed by FIGO (International federation of gynecology and obstetrics). Routine hematological and radiological investigations were done before starting the treatment.

Chemotherapy

Patients were initially treated with three cycles of NACT cisplatin 75 mg/m^2 IV on day$_1$ and day$_2$ in divided doses and 5-fluorouracil 1000 mg/m^2 IV at an interval of 21 days, i.e., day$_1$, day$_{22}$, and day$_{43}$ followed by weekly cisplatin 40 mg/m^2 with radiotherapy (Table 1).

Radiotherapy

After completion of NACT, the patients were treated with a combination of EBRT and HDR-ICBT. HDR-ICBT was delivered by GAMMAMID-12i (I^{132}). For stage I-B and II-A non-bulky disease, 20 Gy EBRT was delivered to whole pelvis, 200 cGy per fraction, 5 days a week using ^{60}CO γ-rays followed by HDR-ICBT 4 fractions of 6 Gy each, twice weekly for a total dose of 24 Gy, and then 30 Gy by central shielding EBRT. For stage II-B to IV-A bulky disease after 2 weeks of NACT, 25 fractions of EBRT were given (200 cGy per fraction, 5 days a week, total dose of 50 Gy with central shielding after 40 Gy). The total dose to be delivered to the parametrium and pelvic lymph node was 45–50 Gy. When patients had bulky parametrical tumors or macroscopic lymph node metastasis, an additional 10–15 Gy was applied to boost the external dose to a total of 60–65 Gy followed by HDR-ICBT 3 fractions of 7.5 Gy every 3rd day, twice weekly for a total dose of 22.5 Gy (Table 2).

The overall treatment time of radiotherapy was approximately 6–8 weeks in the majority of patients. HDR-ICBT was based on Manchester System.

Standard treatment protocols for cervical carcinoma

Disease stage	EBRT (Gy)		ICBT dose/fr. to point-A	EQD2
	Whole pelvic	Central shielding		
I-B/II-A	20	30	6 Gy/fr × 4 fr.	80 Gy
II-B/IV-A	40	10	7.5 Gy/fr × 3 fr.	83 Gy

Follow-Up

After completion of radiotherapy, the patients were followed up monthly for 1st year, every 3 months for the next 2 years, every 6 months for the next 2 years (total 5 years),

Table 1 The baseline characteristics of the patients

Characteristics	Observation	Percentage (%)
Total no. of patients		
Total	332	
Rural	239	72
Urban	93	28
Age		
(30–50 years)	206	62
(31–75 years)	126	38
Stage (FIGO)		
I-B	16	5
II-A	25	8
II-B	64	19
III-A	37	11
III-B	162	49
IV-A	28	8
KPS score		
70	96	29
80	150	45
90	86	26
Morphology		
Ulcerating	90	27
Proliferative	164	49
Infiltrative	78	24
Histopathology (sq. cell ca.)		
Well differentiated	106	32
Moderately differentiated	146	44
Poor differentiated	80	24
Pelvic nodal status		
Positive	60	18
Negative	272	82
Para-aortic nodal status		
Positive	27	8
Negative	305	92

Table 2 Stage wise survival of the patients

Stage FIGO	No. of patients	At 3-years				At 5 years			
		O.S.	%	D.F.S.	%	O.S.	%	D.F.S.	%
I-B	16	15	93.7	15	93.7	15	93.7	14	87.5
II-A	25	22	88.0	21	84.0	21	84.0	20	80.0
II-B	64	53	82.8	51	79.7	51	79.7	49	76.6
III-A	37	26	70.0	24	64.9	25	67.6	22	59.5
III-B	162	96	59.3	85	52.4	79	48.8	68	41.9
IV-A	28	15	53.6	9	32.1	8	28.6	4	14.3
Total	332	227	68.4	205	61.7	199	59.9	177	53.3

OS overall survival; *DFS* disease free survival

and once a year thereafter. Routine hematological and radiological investigations were done as per the standard schedule. Cervical smear was obtained in suspected cases of recurrence; in cases with gross residual/recurrent disease, biopsy was taken for confirmation. Cystoscopy, proctoscopy, and barium enema were performed only when clinically indicated. The median follow-up time in surviving patients was 5 years. Late complication and toxicity were assessed using the Radiation Therapy and Oncology Group (RTOG) Criteria. The data were extracted from the admission and follow-up record files and radiotherapy files of the treated patients.

Statistical Analysis

Overall survival, pelvic control rate, and disease-free survival were calculated from the date of initiation of treatment to the last day of follow-up. Patients who did not have either local residual/recurrent lesion or distant metastases till the last follow-up were counted as disease free. The results were analyzed using simple statistical values like mean, mode, and median. The survival estimates were calculated using Kaplan–Meier method. All statistical calculations were performed using SPSS version 20.0 (IBM corp, Armonk, USA).

Results

Three hundred and thirty two patients were included for this retrospective analysis. The patients were followed up till 31st December 2013. The results were calculated from the date of initiation of treatment to the occurrence of any event or lost to follow-up. The mean age of patients was 52 years (range, 30–75 years). All patients were staged according to the International federation of Gynecology and obstetrics (FIGO) staging system, 16 patients had stage I-B disease, 25 patients had stage II-A disease, 64 patients had stage II-B disease, 37 patients had stage III-A disease, 162 patients had stage III-B disease, and 28 patients had stage IV-A disease.

Survival Rates

The OS and DFS at 3 and 5 years are depicted in Table 2.

The 3-year OS and DFS rates were 93.7 % for stage I-B, 88.0 and 84.0 % for Stage II-A, 82.8 and 79.7 % for stage II-B, 70.0 and 64.9 % for stage III-A, 59.3 and 52.4 % for stage III-B, and 53.6 and32.1 % for stage IV-A disease.

The 5-year OS and DFS rates were 93.7 and 87.5 % for stage I-B, 84.0 % for Stage II-A, 79.7 and 76.6 % for stage II-B, 67.6 and 59.5 % for stage III-A, 48.4 and 41.9 % for stage III-B, and 28.6 and 14.3 % for stage IV-A disease.

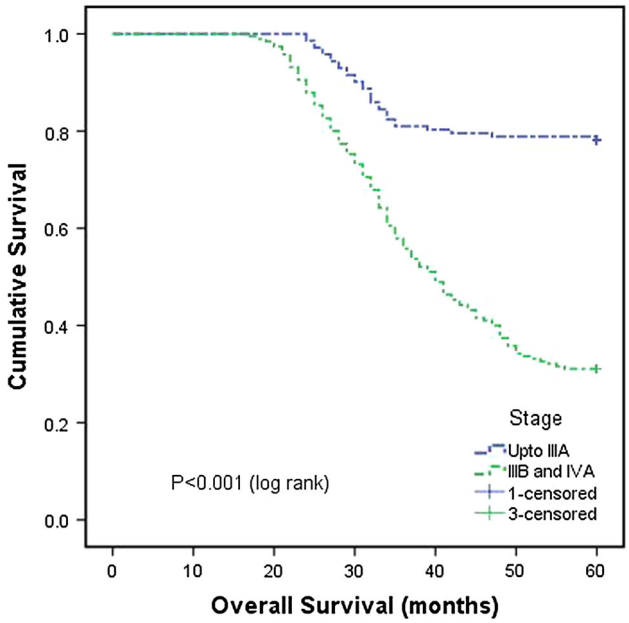

Fig. 1 Kaplan Meier curve showing the overall survival of the patients

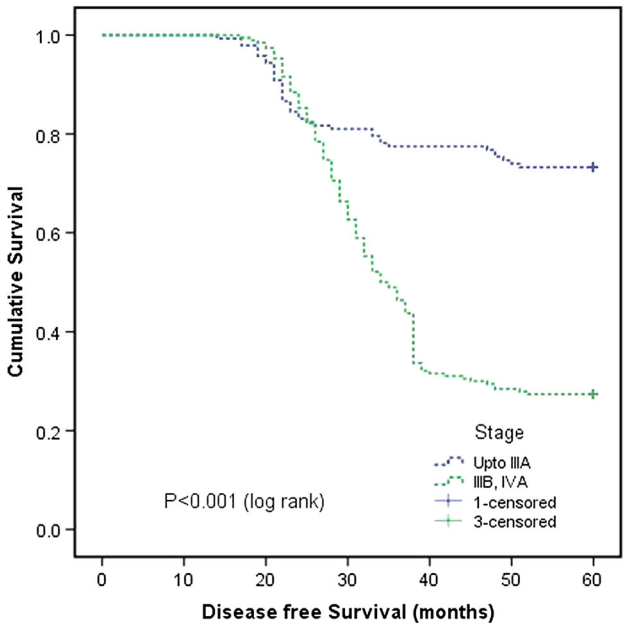

Fig. 2 Kaplan Meier curve showing the disease free survival of the patients

Figure 1 shows the Kaplan–Meier curve for OS at 5 years comparing stage I-A, I-B, II-A, II-B, and III-A versus stage III-B and IV-A ($p < 0.001$), whereas Fig. 2 shows the Kaplan–Meier curve for DFS at 5 years comparing stage I-A, I-B, II-A, II-B, and III-A versus stage III-B and IV-A ($p < 0.001$).

Local Pelvic Control Rates

The local pelvic control rates at 3 and 5 years are depicted in Table 3. The 3- and 5-year local pelvic control rates were 93.7 and 87.5 % for stage I-B, 84.0 and 80.0 % for Stage II-A, 79.7 and 76.6 % for stage II-B, 64.9 and 59.5 % for stage III-A, 52.5 and 41.9 % for stage III-B, and 32.0 and 14.3 % for stage IV-A disease.

Lost to Follow-Up and Death

The total number of patients who lost follow-up at 3 and 5 years were 66 (19.8 %) and 84 (25.3 %), respectively and total number of deaths 3 and 5 years were 39 (11.7 %) and 49 (14.7 %) respectively.

Patterns of Disease Recurrence

The patterns of disease recurrence at 3 and 5 years are depicted in Table 3. The 3- and 5-year overall/total incidences of pelvic recurrence were 4.5 and 6 %, pelvic and distant metastasis were 4.2 and 6 %, the total pelvic recurrences were 8.7 and 12 %, and distant metastasis were 3.6 and 4.8 %, respectively.

Tumor Response After 3 Cycles of Neoadjuvant Chemotherapy

The patterns of tumor response after 3 cycle of neoadjuvant chemotherapy is depicted in Table 4. In our study, NACT reduced 30–50 % of the tumor bulk and 80 % patients got symptomatic relief. Approximately 10 % patients did not respond to NACT and had progressive disease, 28 % patients had stable disease, 52 % patients showed partial response, and remaining 10 % patients showed complete response.

In most of the patients, the recurrence was at the primary site and occurred within 2 years of completion of the treatment; a second primary malignancy developed in breast in one patient and in gall bladder in another patient (Table 4).

Complication and Reactions

According to the RTOG criteria, incidence of acute radiation reaction were as follows: cutaneous reaction of perineum developed in 48 % (grade-0), 28 % (grade-I), 18 % (grade-II), and 6 % (grade-III). Mucosal reactions of rectum developed in 80 % (grade-0), 20 % (grade-I) and no case developed grade II to IV reactions; mucosal reactions of vagina developed in 52 % (grade-0), 34 % (grade-

Table 3 The local control rate and the patterns of failure of the patients

Stage FIGO	Nos. of patients	Local pelvic control rate				Pelvic recurrence				Pelvic and distance metastasis				Distance metastasis				Total pelvic recurrence			
		3 year	%	5 year	%	3 year	%	5 year	%	3 year	%	5 year	%	3 year	%	5 year	%	3 year	%	5 year	%
I-B	16	15	93.7	14	87.5	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
II-A	25	21	84.0	20	80.0	1	4	2	8	–	–	–	–	–	–	–	–	1	4	2	8
II-B	64	51	79.7	49	76.6	2	3.1	4	6.3	–	–	1	1.6	–	–	–	–	2	3.1	5	7.8
III-A	37	24	64.9	22	59.5	2	5.4	4	10.8	–	–	1	2.7	–	–	–	–	2	5.4	5	13.5
III-B	162	85	52.5	68	41.9	8	4.9	8	4.9	9	5.5	11	6.8	8	49	10	6.1	17	10.5	19	11.7
IV-A	28	9	32	4	14.3	2	7.1	2	7.1	5	17.8	7	25	4	14.3	6	2.1	7	25	9	32
Total	332	205	61.7	177	53.3	15	4.5	20	6.0	14	4.2	20	6.0	12	3.6	16	4.8	29	8.7	40	12

I), 14 % (grade-II) and no case developed grade III and IV reactions. Late complications involving the rectum, small bowel, leg edema, or urinary tract were observed in 47 (14.15 %) cases (31 cases of the stage III-disease). Bladder complications were seen in 16 (4.8 %) patients out of which 1 (3.31 %) patient developed hematuria/severe cystitis and 5 (1.5 %) patients developed vesicovaginal fistula; rectum complications were seen in 24 (7.2 %) patients out of which 16 (4.8 %) patients developed rectal ulcer/radiation proctitis and 8 (2.4 %) patients developed rectovaginal fistula. Mostly rectal toxicities appeared within 12–24 months, and bladder toxicities appeared between 18 and 42 months. 4 patients developed acute intestinal obstruction for which surgery was done, and 3 cases developed severe leg edema. One patient developed uremia and succumbed to the recurrent disease and two patients developed uncontrolled bleeding per rectum due to radiation proctitis and expired. Two patients developed severe hydronephrosis for which ureteric stents were inserted. Remaining patients were managed symptomatically.

Discussion

The tumor size is an important prognostic factor in cervical carcinoma. Large tumors tend to be less radiosensitive as they have relatively large hypoxic tumor cell population and lesser tumor vascular supply, and are thus likely to respond poorly to radiotherapy [3]. To overcome these shortcomings, NACT followed by concurrent chemoradiation is being adopted for bulky locally advanced disease. The symptoms like foul smelling discharge, vaginal bleeding, and abdominal pain were revealed in up to sixty percent of patients following chemotherapy and this forms an important symptomatic response. Once down-staged following NACT, residual disease may become highly sensitive to concurrent chemoradiation followed by ICBT which is the accepted definitive mode of treatment.

In recent years, several groups have reported that NACT improved the survival of patients with locally advanced cervical carcinoma. Significant activity (20–25 % tumor response) in well-designed studies with adequate patients number has been documented for cisplatin and 5FU [5]. Sadri et al. reported ($n = 71$) NACT and radiotherapy in stage II-B (7-year follow-up) with a response of 54 % compared to only 48 % with radiotherapy alone. OS improved in tumor greater than 5 cm from 36 % in radiotherapy to 66 % in NACT and radiotherapy. In NACT group, grade 3 or 4 toxicity was not observed and OS was statistically better in chemo-responders [6]. Huang et al. also showed that NACT is effective in tumor size > 3 cm [7]. Moris et al. reported ($n = 403$) a significant benefit provided by chemo-radiotherapy versus radiotherapy alone

Table 4 Tumor response after 3 cycles of neoadjuvant chemotherapy

Stage FIGO	Nos. of patients	Tumor response after 3 cycles of neoadjuvant chemotherapy							
		C.R.	%	P.R.	%	S.D.	%	P.D.	%
I-B	16	8	50	6	37.5	1	6.25	1	6.25
II-A	25	12	48	8	32	3	12	2	8
II-B	64	6	9	39	61	11	17	8	13
III-A	37	5	13	23	62	5	13	4	12
III-B	162	3	2	88	54	62	38	9	6
IV-A	28	0	0	8	28	10	36	10	36
Total	332	34	10	172	52	92	28	34	10

in bulky I-B, II-A, and all II-B to IV Stage. The 5-year cumulative data of OS and DFS rates were 73 versus 58 % and 67 versus 40 %, respectively [8]. Symonds et al. showed ($n = 204$) 3-year survival rates to be 40 % for radiotherapy alone and 47 % for the combined therapy. Acute and late toxicities of radiation therapy were not increased by the addition of chemotherapy [9]. Napolitano et al. showed ($n = 106$) that the 5-year OS rates for the NACT were 78.6 % in stage IB-IIA and 68.37 % in stage II-B, and 5-year DFS rates for the NACT were 77.1 % in stage IB–IIA and 56.2 % in stage IIB [10]. Thomas et al. ($n = 200$) reported that the 3-year pelvic tumor control rates in the patients with stage I-B/II and stage III/IV diseases were 8 and 50 % and survival rates were 71 and 42 %, respectively; the 3-year pelvic control rates for historic control patients treated with irradiation alone were 58 % [11]. Chang et al. showed the bulky (primary tumor greater then 4 cm) stage I-B or II-A cervical cancer with the median follow-up of 39 months, where 31 % of patients in the neoadjuvant arm and 27 % in the radiation therapy arm had relapse or persistent disease after treatment and 21 % of patients in each arm died of disease. Estimated cumulative survival rates at 5 years were 70 and 61 %, respectively [12]. The NACT regime is relatively non-myelo suppressive with no major side effect, prevents heavy loss of blood due to disease itself, reduces tumor bulk, and gives symptomatic relief. Unfortunately, not all patients responded to NACT in our study. NACT reduced 30–50 % tumor bulk and 80 % patients had symptomatic relief.

In case of concurrent chemoradiation, Rose et al. showed that weekly cisplatin is ideal chemotherapy regimen, including high anti-tumoral activity, acceptable tolerance with concurrent radiation, lower cost, and demonstration of a survival benefit in randomized trials [13]. A meta-analysis showed that chemo-radiotherapy resulted in 6 % improvement in 5-year survival ($p < 0.001$), with significant survival benefit from platinum-based ($p = 0.017$) and non-platinum-based ($p = 0.009$) chemo-radiotherapy, reduced local and distant recurrences, and improved DFS and short-term side effects [14]. Our results in this study are similar to that of the other studies mentioned above.

EBRT (whole pelvis) reduces the risk of microscopic disease, to achieve tumor shrinkage, and makes more favorable anatomic geometry for applicator placement before brachytherapy. ICBT can treat the target volume with high dose sparing normal tissue. In this study, we followed the American Brachytherapy society recommendation for HDR-ICBT for carcinoma cervix [15].

The ABS recommended keeping the total treatment (EBRT and HDR-ICBT) duration to less than 8 weeks, because prolongation of total treatment duration can adversely affect local control and survival but in our study total duration of treatment is 9 weeks. The use of NACT in advanced stage is of potential advantage and results were not affected although it increases treatment duration. Due to lack of screening programs for early diagnosis, about 60 % of cases are reported in advanced stages. Early detection with screening programs, cancer awareness, and education programs in the surrounding rural area, along with more financial assistance from the government and support from non-government organization, is required for early stage diagnosis and prompt treatment.

Complication

It has been asserted that early radiation reactions occur within 6 months and late radiation complications generally occur within the first 2–4 years after treatment, after which the incidence is decreased markedly. Hareyama et al. reported the 5-year major complications rates of 3.5 % in the rectum, 4.0 % in the bladder, and 2.4 % in the small bowel in patients treated with doses similar to those that we used [16]. Nakano et al. also reported the 5-year late toxicity of radiation therapy rates being 3.8 % in rectosigmoid colon, 0.8 % in the small bowel, and 2.6 % in the bladder [17]. In a study by Perez et al., the most frequent grade 2 sequelae were cystitis and proctitis (0.7–3 %); the most common grade 3 sequalae were vesicovaginal fistala (0.6–2 %),

rectovaginal fistula (0.8–3 %), and intestinal obstruction (0.8–4 %) [18]. In the present study, major complication rates were 24 (7.2 %) in the rectum, 16 (4.8 %) in the bladder, and 4 (1.2 %) in the small bowel in the patients; other rare complications were leg edema, etc.

Conclusion

Neoadjuvant chemotherapy followed by concurrent chemoradiation is feasible and produces significant response and significant improvement in the rates of overall survival and provides immediate symptomatic relief; although it increases the overall treatment duration, it increases the treatment compliance of rural patients. Acute and late complications of radiotherapy were almost acceptable.

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