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Long Term Outcome after Concurrent Chemo radiation with Cisplatin in Carcinoma Cervix

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Abstract
Aim: *The aims of this study were to examine treatment outcomes (survival, local control and toxicity) in patients with cervical cancer treated with chemoradiation in stage 1B2-1VA carcinoma of cervix in Department of Radiotherapy, Government Medical College, Kottayam.*
Materials and Methods: *Between January 2012 to December 2013, 46 patients with cervical cancer were treated with chemoradiation. Case notes were reviewed retrospectively. Acute and late toxicity were recorded, with toxicity graded using the Common Toxicity Criteria Version 4. The mean age was 56 years. All patients were staged with examination under anaesthesia by FIGO staging. The chemotherapy used was cisplatin 40 mg/m2 weekly with radiotherapy. External beam radiotherapy was given to the pelvis (45-46 Gy/23 fractions/4 1/2weeks) followed by high dose rate brachytherapy (18 Gyto point A, 9 Gy per fraction weekly in 2 fractions). Optimal dose of radiation (ORT) was defined as a minimal cervical dose exceeding 70 Gy, point A dose of 80–90 Gy, and duration not exceeding 56 days. Optimal dose of radiation was received by 45.7% of patients. Bulky disease, anaemia, advanced stage, non optimal radiation dose and prolonged treatment time affected local failure rate.*
Results: *The 3-year overall survival rate was 93.5%. The 3-year disease-free survival was 87%.. There were 5 patients (10.9%) with acute toxicities and 21cases (45.8%) of chronic toxicities. Local failure rate was 4.3%*
Conclusion: *There was a trend towards improved survival and local control with concurrent chemoradiation in this cohort of patients that may become significant with longer follow-up. Patients with anaemia, bulky and locally advanced, cervical cancer treated with weekly cisplatin, teletherapy, and high dose-dose rate brachytherapy have poorer outcomes when treatment duration is prolonged.*
Keywords: *Cervix carcinoma, chemoradiotherapy, outcome, survival, toxicity.*

Introduction

Among women worldwide, cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death, accounting for 8% [275,100] of total cancer deaths among women in 2008[1]. In India cervical cancer is the most common women related cancer followed by breast cancer. 80% of new cervical cancer cases occur in developing countries like India. Every year in India, 122,844 women are diagnosed with cervical cancer and 67, 477 die from the disease. Five randomised phase III trials [(2-7)] that showed that platinum chemotherapy given concurrently with radiotherapy improved 3-year survival by 8 to 19%. This survival benefit was seen in women with locally advanced cancer, FIGO stages IB2—

IVA. Treatment outcomes (survival and toxicity) were studied in 183 patients from Christie Hospital, Manchester treated in 1993and 5-year overall survival was 49% and grade 3 and 4toxicity 3.4%][8].. Concurrent chemoradiation was introduced as standard treatment for locally advanced cervical cancer in 2000.

Materials and Methods

Patient Selection and Characteristics

Between January 2012 and December 2013, 46 patients with cervical carcinoma (1B2-1VA) were treated with concurrent chemoradiation. Case notes were reviewed retrospectively. The median age of the patients was 55 years (range 33-81years). All patients had World Health Organization performance status 0-2 at presentation, adequate renal function and a mean haemoglobin level maintained above 11.4 g/dl. 9 women had FIGO stage I B2 disease (19.6%), 2 (4.3%) had stage IIA,14 (34.8%) patients11B, 20 (43.5%%) had stage IIIB, 1 (2.2%) had stage IVA.43 women (93.48%) had squamous cell carcinomas,1 (2.2%) adenocarcinoma, 1 (2.2%) squamotransitional carcinoma, one (2.2%) carcinoma in situ. Of the squamous cell carcinomas, 15 (32.6%) were large cell keatinizing, 14(30.4%) large cell non keratinizing, 3(6.5%) were moderately differentiated and 11 (23.9%) were squamous cell carcinoma, subtype not specified. All patients were staged with examination under anaesthesia by FIGO staging. All patients were treated with chemoradiation.

Fig.1 Stage wise distribution

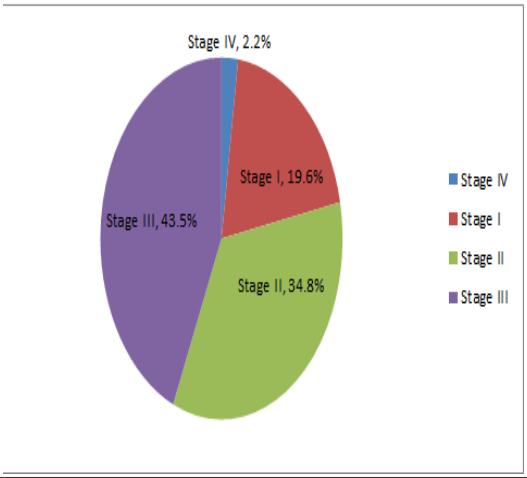

Fig.2 Histology wise distribution

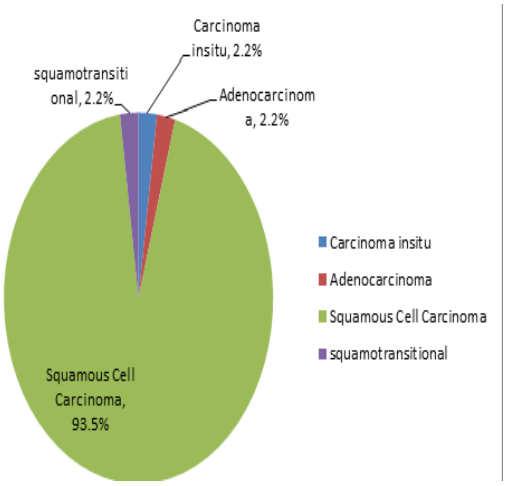

Table 1: Patient Characteristics

Characteristics	n= 46	%
Median AGE	55	
Histology		
Squamous Cell Carcinoma	43	93.48%
Adenocarcinoma	1	2.2%
Squamotransitional	1	2.2%
Carcinoma in situ	1	2.2%
Performance Status		
1	44	95.7%
2	2	4.3%
Mean haemoglobin	11.4%	
Stage		
1	9	19.6%
11	16	34.7%
111	20	43.5%
1V	1	2.2%
Tumour Size		
➢ 4cm	15	32.6%
< 4cm	14	30.4%

Radiotherapy

Patients were treated with a combination of external beam radiotherapy followed by brachytherapy. External beam radiotherapy was delivered using Co 60 photons using a four-field technique by 2D planning. Patients were treated supine with arms folded across the chest. The superior border was at the L4-5 intervertebral space to include the common iliac nodes. The inferior border was bottom of the obturator foraminae ensuring there was an adequate margin below disease. Laterally the field was 1.5 cm outside the true bony pelvis, anteriorly midway through the symphysis pubis and posteriorly at the S2-3 junction. The dose administered was 45-46 Gy in 23 fractions, 5 fractions a week over four

and a half weeks. Brachytherapy was given using the Manchester system using high dose rate iridum 192 in remote after loading equipment after completion of external beam radiation. The dose was 9 Gy per fraction weekly for two fractions, so that point A received low dose rate equivalent of 32GyBiological equivalent doses were calculated. Patients receiving 45Gy in 23 fractions/4 $^{1/2}$weeks followed by a brachytherapy dose of 32Gy had a biological equivalent dose of 85Gy and patients receiving 46Gy/23 fractions/4 weeks followed by a brachytherapy dose of 32 Gy had a biological equivalent dose of 87 Gyat point A Overall treatment time is limited to 7-8 weeks. Most patients completed phase I around 30 days, except for 2 for whom treatment was prolonged due to non-compliance or side effects of concurrent chemotherapy.40 patients completed their treatment in 50-60 days. The other 6patients completed their treatment within 70 days. This delay was due to failed insertions or waiting period of brachytherapy.

Chemotherapy

All patients were World Health Organization performance status 0-2 and all had adequate renal function. Forty-six patients were treated with concurrent chemoradiation alone and 3 patients were treated with radiation alone. One among radiation alone patient has a histology of carcinoma in situ with FIGO stage 11 and above 70 years, others, 75 years with Stage 1V A disease and 81 years of age. Concurrent treatment was given as weekly cisplatin 40 mg/m2. Patients were reviewed weekly during their treatment with assessment of gastrointestinal symptoms, blood tests and serum creatinine. 26 (56.5%) patients received four cycles of concurrent chemotherapy, 14(30.4%) received three cycles, 2(4.3%) received 5 cycles,1(2.2%) received two cycles and none with one cycle. This difference in number of cycles received was due to increased gastrointe-stinal toxicity, renal impairment or neutropenia. Chemotherapy skiped in advanced age and poor performance status.

Statistics

Overall Survival and disease-free survival rates were analysed using Kaplan-Meier methods. Stage distribution was assessed using the chi-squared test. Toxicity was assessed using Fisher's exact test. 1 patient was lost to follow-up. The median follow- up was 55months (range 24-64 months).

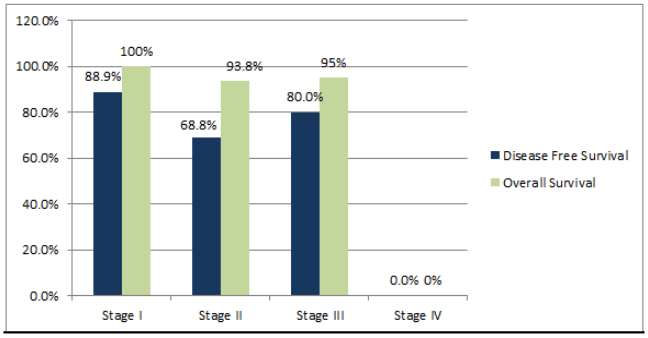

Fig.3. Stage wise three year survival rate

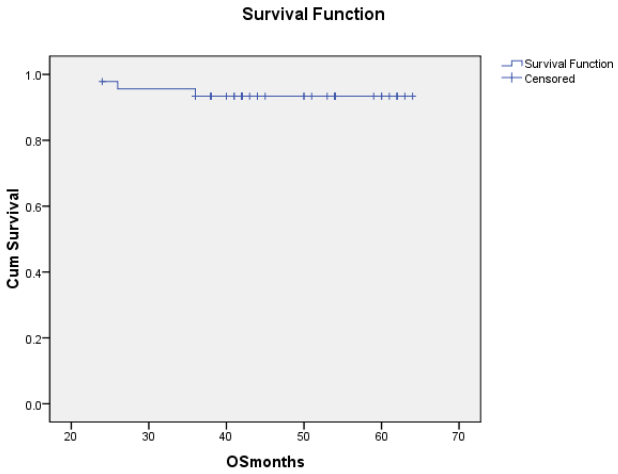

Fig.4 Kaplan Meir Curve of Overall Survival

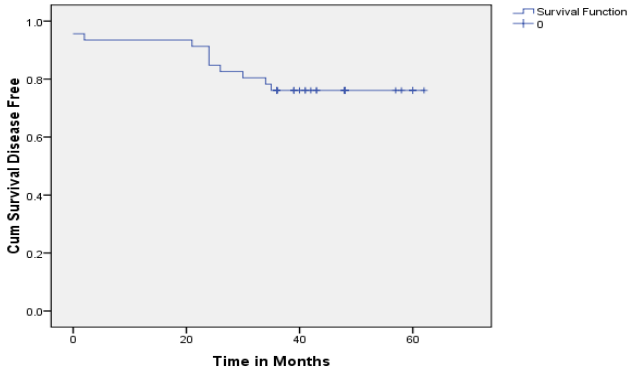

Fig.5 Kaplan Meir Curve for Disease free Survival

Table 2 - Three-year survival rate with respect to stage

	DFS	OS
Stage 1	88.9%	100%
Stage 2	68.8%	93.8%
Stage 3	80%	95%
Stage 4	0%	0%

DFS, disease-free survival OS, Overall survival

Results

Survival and Progression

The 3-year overall survival rate was 93.5%. The 3-year disease-free survival was 87%. There were 5 patients (10.9%) with acute toxicities and 21 cases (45.8%) of chronic toxicities. Local failure rate was 4.3%

Local failure was observed in 1 (11.1%) of Stage 1, 1 (6.25%) of Stage 11 and distant failure was noted in 3(15%) of Stage 111.Residual disease was observed in Stage 1VA with progression of disease to distant failure in supraclavicular nodes over two months with overall survival of 24 months. On analysis of failures, in Stage1, bulky disease and prolonged overall treatment time were the contributory factors. In the Stage11 with local failure haemoglobin level was below 9mg/dl. 5 patients failed distantly of which 2 had supraclavicular lymph node metastasis,(I each of stage 11 and 111), 2 lung metastases(1 each of 111and 1V), 1 of stage 11 liver metastases, and other of stage 111 had lung and bone metastases.

Late Toxicity

Late toxicity was defined as that occurring more than 90 days after the first day of radiotherapy. It was scored using the common toxicity criteria version 4. There were five patients (11.6%) with grade 3 toxicity and no cases of grade 4 toxicity. Of the patients with grade 3 toxicity, two(4%) had proctitis, three (6.5%) had vaginal stenosis. Grade 1 vaginal stenosis was reported in four(8.6%), Grade 2 in six (13%).Only one patient had grade 1 cystitis .Patients with grade 3 vaginal stenosis were counselled, use of lubricating gel encouraged and frequent sexual intercourse advised if they are of sexually active age.

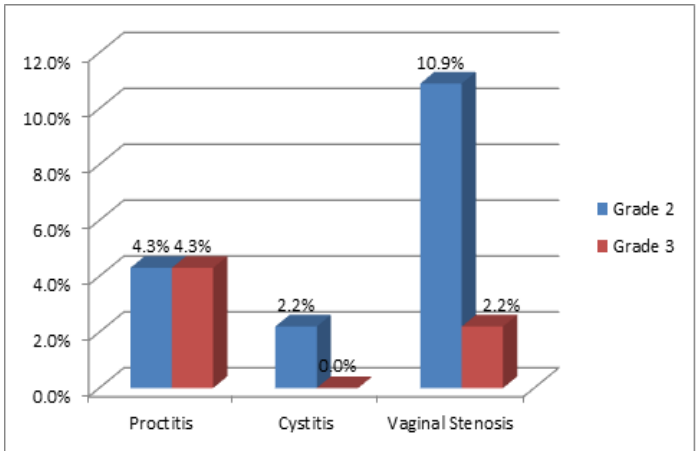

Fig.6 Grade 2&3 late toxicity

Discussion

Chemotherapy and radiation are standard components of therapy for patients with stage1B-1VA carcinoma of the cervix.[2.]Five randomized, phase III trials (GOG-85, RTOG-9001, GOG-120, GOG-123, and SWOG-8797) have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy .An absolute survival benefit of 12% by Green etal and 11% by Leukaetal were shown in their study.[9,10] Compared to the study by Spensleyetal. in Christie Hospital, Manchester,23%survival benefit was gained in our study.[11] Our disease staging was exclusively clinical FIGO staging and all patients irrespective of their stage received ,18Gy high dose rate brachytherapy weekly once in two fractions ,might explain the difference. The risk of prolongation of treatment time has been reported as an estimated loss of local control ranging from 0.3 to 1.6% per day of treatment prolongation[12]. Radiobiological models show that increased waiting time to commencing radio-therapy can have an adverse effect on tumour control and there is plenty of evidence that shows that delay in starting radiotherapy leads to reduced local control and hence metastases and reduced survival[13,15,16].Two patients of our study who failed distally had a prolongation of treatment time more than 54 days.On multivariate analysis, in our study there is a significant association between local failure and prolongation of treatment time(p=0.000). Regression analysis confirms previous reports that prolongation of

overall treatment time results in decreased pelvic tumor control rate of 0.85% per day for all patients, 0.37% per day in Stages IB and IIA, 0.68% per day in Stage IIB, and 0.54% for Stage III patients treated with greater than or equal to 85 Gy to point A).[17] According to study by Girinsky T, Rey A, Roche B, et al. overall treatment time of 8–9 weeks may effectively reduce proctitis without adversely affecting prognosis in patients undergoing Concurrent chemoradiation. They suggested a waiting period of more than 5 days before performing HDR-ICBT in patients undergoing concurrent chemoradiation[16].

[17]In the study by Meenakshi Mittal, Bikramjit et al. group 1 received intracavitary applications of two fractions of 9.5 Gy each separated by 10 days, while in Group II patients received three fractions of 7.5 Gy each separated by 7 days. Corresponding total planned biologically equivalent dose$_{10}$ (without proliferation correction) and biologically equivalent dose$_3$, for EBRT plus HDR ICBT, at point A were 90.15 Gy and 151.17 Gy for Group receiving 9.5X2 fractions, and 92.47 Gy and 150.75 Gy for 7.5 for 3 fractions, respectively.

In the meta-analysis of the eight randomised studies by Lukka etal.[10,18] late toxicity data were reported only in four. No significant increase in late toxicity was detectd with the addition of cisplatin chemotherapy to radiotherapy. The late toxicity rate was reported as 12% .In this particular study, the late toxicities attributed was fairly high compared elsewhere. Radiobiologically, increasing the dose rate in brachytherapy will increase late effects much more than it increases tumor control. Thus the therapeutic ratio increases as the dose rate decreases.[14,18]

Conclusion

Concurrent chemo radiation has shown a trend towards improved overall and disease-free survival. There was also a trend towards increasing toxicity, especially late toxicity at the expense of tumor control which may become significant with longer follow-up.

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