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A Prospective Randomized Study to Compare Clinical Outcome of External Beam Radiotherapy (EBRT) and Sequential High Dose Rate Intracavitary Brachytherapy (HDRICBT) With or Without Concurrent Cisplatin on the Day of ICBT Insertion in Treatment of Locally Advanced Carcinoma CervixD

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Abstract

The study reviews that cervical cancer is among the most commonly diagnosed cancers in women worldwide. In 2018, according to the GLOBOCAN estimates there were 569,847 new cases of cervical cancer worldwide (4th most common cancer in women worldwide, accounting for 6.9% of all cancers in women apart from non-melanoma skin cancers). Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer (for incidence), and vice versa (for mortality); cervical cancer ranks fourth for both incidence and mortality. In contrast to developed countries, cervical cancer is a public health problem in developing countries.

Keywords: Cervical cancer; GLOBOCAN; Lung cancer; Melanoma; Brachytherapy

Introduction

Cervical cancer is among the most commonly diagnosed cancers in women worldwide. In 2018, according to the GLOBOCAN estimates [1] there were 569,847 new cases of cervical cancer worldwide (4th most common cancer in women worldwide, accounting for 6.9% of all cancers in women apart from non-melanoma skin cancers). Among females, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death, followed by colorectal and lung cancer (for incidence), and vice versa (for mortality); cervical cancer ranks fourth for both incidence and mortality. In contrast to developed countries, cervical cancer is a public health problem in developing countries like India, so much so that India alone accounts for one-quarter of the worldwide burden of cervical cancers. It is the one of the leading cause of cancer mortality, accounting for 17% of all cancer deaths among women aged between 30 and 69 years. It is estimated that cervical cancer will occur in approximately 1 in 53 Indian women during their lifetime compared with 1 in 100 women in more developed regions of the world [2].

Estimates indicate that >90% of cervical cancers are due to the presence of Human Papilloma Virus (HPV) and are contracted as STD [3]. The most common subtypes in human cervical cancers are HPV-16 and 18, which are found in 70% of cases. Social factors related to cervical cancer include those associated with HPV transmission, such as early age at first intercourse; a history of multiple sexual partners; a male partner with a history of multiple sexual partners; a large number of pregnancies. Squamous cell carcinoma of the uterine cervix usually originates at the squamous columnar junction (transformation zone) of the end cervical canal and the portion of the cervix.

For women who develop locally advanced cervical cancer, the standard of care has evolved from External Beam Radiation Therapy (EBRT) alone, to EBRT plus brachytherapy, to combined EBRT plus brachytherapy with concurrent chemotherapy [4,5]. The addition of chemotherapy serves predominantly as a radio sensitizer, resulting in improvements of about 5% in overall survival [4].

Regarding the dose, American brachytherapy society recommends, point A dose with BED 80 to 85 Gy for early stage disease and 85 to 90 Gy for advance stage disease. Pelvic side wall recommendations are 50 to 55 Gy for early stage and 55 to 65 Gy for advance disease [6]. Bladder and rectal dose should be less than 100 Gy and 70 Gy respectively. External Beam Radiotherapy (EBRT) is used to treat the whole pelvis. Structures treated include the uterus and cervix (or in the postoperative cases, the tumor bed), the vagina, the parametrical tissue, and the pelvic lymph nodes, including the internal, external, and common iliac nodes. In selected cases the Para-aortic lymph nodes may be treated. In treatment of invasive carcinoma of the uterine cervix, it is important to deliver adequate doses of irradiation not only to the primary tumor, but also to the pelvic lymph nodes to maximize tumor control.

In patients with locally advanced disease, in addition to EBRT, treatment of central disease (cervix, vagina, and medial parametria) relies heavily on dose given with Intracavitary Sources through Brachytherapy (ICBT). Evidence confirms that brachytherapy used for dose escalation after EBRT for cervical cancer significantly improves survival [7-11]. Therefore, brachytherapy is a standard part of the treatment of locally advanced (stages IB2 to IVA) cervical cancer after external beam radiation. However, brachytherapy alone may be used as

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primary treatment for selected cases with early-stage (stages IA to IB1) cervical cancer [12]. In recent years, HDRICBT has become popular in the management because of its advantages of a short treatment time, rigid immobilization, patient convenience, and out-patient procedure. However, the optimum time-dose-fractionation of HDRICBT remains controversial [13]. A variety of dose/fraction schedules are practiced worldwide.

In many countries where there is a great incidence of this pathology, the cost of treatment increased proportionally to the number of fractions used individually and the design of an optimal treatment program depends on the requirements of each particular centre.

Although 40% of radiation treatment is delivered by brachytherapy, chemotherapy is combined with EBRT and not with brachytherapy due to fear of increased toxicity. The scepticism about the enhanced risk of CCBT-induced complications is mainly theoretical and not supported by evidence, and therefore, concurrent use of chemotherapy during brachytherapy can potentially improve the results.

Materials and Methods

It was a prospective randomised study conducted on diagnosed and untreated patients of locally advanced carcinoma cervix registered in Department of Radiotherapy, JNMCH, AMU, and Aligarh during January 2017 to July 2018.

Study was explained and informed consent was taken from each eligible patient. Patients were grouped in two arms Arm 1 as the study group and Arm 2 as the control group by randomization. After treatment completion patients of both arms were evaluated and compared for acute and late toxicities and response (Tables 1-4). Staging was according to International Federation of Gynaecological and Obstetric (FIGO) criteria (2009). Integration of concurrent chemotherapy with EBRT in the cervical cancer patients is well established and Cisplatin is the most commonly used radio sensitizer in this setting [14]. However, the idea of concurrent use of radio sensitizers or chemotherapy drugs with brachytherapy is still evolving and it has a sound theoretical basis and seems to be a rational and a potentially effective approach for locally advanced CA cervix patients.

As we know, forty percent of total tumor dose is delivered in brachytherapy in uterine cervix and parametria, and the minimum dose to the rectum and bladder is achieved by accurate treatment planning it is logical that the optimal time to integrate chemotherapy during the course of radiotherapy is during the brachytherapy insertions. The two most important reasons for this assumption are discussed. Firstly, the dose of radiation applied during one brachytherapy insertion is much higher than external radiation, due to that difference we can expect that the effects of the combination of brachytherapy and chemotherapy are substantially greater than either of both, and the second reason is that the dose rate of brachytherapy is decreasing by inverse-square law and thus potentially results in less toxicity to surrounding normal tissues [14].

Patient characteristics	Study arm (Concurrent CDDP with ICBT)	Control arm (only ICBT)
Median age (YEARS)	49.89(± 7.89)	51.83 (± 8.91)
Stage (FIGO 2009)	IIB (43.3%)	43.30%
	IIIB (26.7%)	20%
Menstrual profile	Pre-menop-50%	33.33%
	Post-menop-50%	66.70%
Residence profile	Urban-43.3%	43.30%
	Rural-56.7%	56.70%
Socioeconomic status	Lower 26.7%	43.30%
	Lower middle 33.3%	36.70%
	Middle 26.7%	10%
	Upper 3%	6%
Parity	Nulliparous-3.3%	10%
	Multiparous-96.7%	90%

Table 1: Patient characteristics, results of ICBT.

	Study arm	Control arm
Response after ICBT		
CR	22(73.3%)	22(73.3%)
PR	8(26.7%)	8(26.7%)
SD	0	0
PD	0	0
Status at 3 months follow up		
CR	26(86.7%)	24(80%)
PR	1(3.3%)	2(6.7%)
SD	0	0
PD	3(10%)	4(13.3%)
Status at last follow up (August 2019)		
CR	27(90%)	24(80%)
PD	3(10%)	6(20%)
Toxicity (Post ICBT)		
Grade III Skin	0	3.30%
Grade III Vaginl	6.60%	0
Grade III GI	6.60%	0
Grade III Hematological	3.30%	0

Table 2: Response after ICBT and before ICBT.

At last follow up	Study arm	Control arm
Local(cervical/pelvic)	1	3
Distant mets	2 (Lung)	2 (Lung and brain)
Local and distant	0	1
Total	3	6

Table 3: Progressive disease.

At last follow up	Study arm	Control arm
Post RT proclitic	2	0
Post RT colitis	0	0
Post RT cystitis	1	1
Post RT cervicitis	0	0
Post RT vaginitis	1	1
Rectovaginal fistula	0	0
Vesicovaginal fistula	0	0
TOTAL	4	2

Table 4: Late reactions after the treatment.

Results

The optimum timing of integration, single agent or combination of drugs, best radio sensitizer agent, optimum dose, patient compliance, risk of increased toxicity and feasibility are the major issues and concerns related to the CCBT and are addressed in this study. Regarding the timing of integration we have used chemotherapy 1 hour prior to the ICBT delivery. However, there is no suggestion in the literature for this issue and most of the data available, used chemotherapy, one day prior to the ICBT insertion. Chemotherapy is not given on the days of

brachytherapy in these studies because of potential risk of increased toxicity. On the contrary, our integration of same day is based on the pharmacokinetics that maximum drug should be present in the body at the time of ICBT delivery for maximum radio sensitization.

As far as optimum drug and combination of drugs for CCBT is concerned, various combinations with different schedules and doses were reported in the literature with Cisplatin as the commonest agent used [15] used concurrent paclitaxel 40 mg/m^2 and carboplatin AUC2 on the days of ICBT implants [16] used Cisplatin 50 mg/m^2 as continuous infusion for first brachytherapy course and carboplatin 300 mg/m^2 was used for second course. Cisplatin 50 mg/m^2 intravenous day 1 and protracted infusion of 5-fluorouracil 750 mg/m^2 was used by [17] with each of the brachytherapy courses [18] treated 40 patients of LACC with CCRT followed by LDR brachytherapy (two sessions of 12 Gy each) with concurrent Cisplatin 35 mg/m^2 given just before brachytherapy insertion [19] treated patients with Cisplatin 75 mg/m^2 (1 hour infusion) and ifosfamide 2 gm/m^2 (24 hour infusion) given concurrently with two LDR brachytherapy insertions of 30 Gy each.

We used Cisplatin (35 mg/m^2) on the same day before brachytherapy insertion. The basis for the use of single agent Cisplatin was the successful integration of this agent with EBRT and we used the similar dose and delivery schedule as used in EBRT. Cisplatin is considered the most effective single agent as systemic therapy in eradicating micro metastasis and moreover as a radio sensitizer in uterine cervical carcinoma [20,21]. The suggested mechanisms of concurrent use of Cisplatin with EBRT with the concurrent use of Cisplatin before radiation can be through modification of the initial radiation damage, inhibition of repair of radiation damage in tumor cells, exploitation of induced cell synchrony, re oxygenation following drug treatment and before irradiation, improved drug access following irradiation, shrinking of the tumor by radiation leading to more rapid proliferation and greater chemo sensitivity of tumor cells, enabling smaller radiation field-sizes and higher radiation doses to be used [20].

The major concern however associated with CCBT use of Cisplatin is increased toxicity (hematological as well as systemic). Hematological toxicity may postpone the CCBT; delay the timely insertion of ICBT, which may further lead to increase in overall treatment duration. The skin and vaginal toxicities present after EBRT may be further enhanced with CCBT. On review, it is found that response rate in carcinoma cervix is highly promising with the use of concurrent chemo radiation (EBRT followed by brachytherapy) [14,22,23]. We have reported a similar outcome with 73.33% complete response rate and mostly grade 1 and 2 acute toxicities, evaluated at the end of 1 month after completion of treatment.

In CCBT arm, 22/30 (73.3%) patients had complete response (CR) rate at post 1 month of brachytherapy which converted to 26/30 (86.7%) at 3 months and 25/30(83.3%) at 6 months. In control arm, complete response was present in 22/30 (73.3%) patients post 1 month after brachy, whereas only in 24/30 (80%) at 3 months and 23/30(76.6%) at 6 months. this observation, although not statistically significant, is encouraging for our basic concept of this study that the addition of concurrent Cisplatin with ICBT, may result in increased response rate.

Discussion

We compared our results with other similar studies which have addressed the question of CCBT. Strauss treated 27 patients with stage IIB-IIIB cervical cancers with concurrent Cisplatin and brachytherapy in Germany [24]. Complete response rate was 92.3% and 80% of the patients were disease free in 20 months follow-up. Acute effects including grade III hematological toxicities and late effects were seen in 29.6% and 7.4% of cases, respectively. These toxicities were more common in comparison with our study. Compared with Strauss [24], complete response in our study was seen in 88% *vs.* 86.7% respectively. Acute effects like grade III hematological toxicities 29.6% *vs.* 6.6%. Acute effects especially hematological toxicities, subjective complaints and response rate were acceptable in our study.

Conclusion

We have few limitations in this study. Our study period was short; mean follow up in our study was 8 months. We analyzed the result after a short duration of follow up (maximum 1 year follow up), short study period implying short follow up period, may not suffice for addressing an important issue of adding an intervention to an established treatment. Further long term follow up is needed for better analysis of results in terms of response and toxicities. The number of patients enrolled were also less (60) so if we increase the number of patients, it could lead to statistically better results. Application of CCBT in locally advanced carcinoma cervix needs further integration and combination of Cisplatin with other drugs may be suggested topic for future studies in this direction.

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