International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Impact Factor (2012): 3.358

A Comparison between Intracavitary Brachytherapy and Interstitial Brachytherapy in Carcinoma Cervix (Stage IIB and Stage IIIB) - Prospective Randomized Study

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Abstract: ***Objective:*** ***In locally advanced cervical cancer, the management consists of external beam radiotherapy and brachytherapy. The impact of intracavitary brachytherapy versus interstitial brachytherapy on local tumor control, survival and complications were prospectively investigated in this study.*** ***Methods:*** ***A total of 60 patients with stage IIB, IIIB cervical cancer were treated using a combination of Teletherapy and Brachytherapy at our institution. Patients were similar with respect to age, FIGO stage, tumor size, histology subtype in both groups. Patients were randomized to receive external beam irradiation followed by either intracavitary or interstitial irradiation. They also received concurrent chemotherapy -Cisplatin (100mg/sq.mtr, three weekly- 2 cycles). Patients treated with interstitial therapy received a mean external dose of 4600cGY and interstitial irradiation HDR-600cGy * 3 fractions using a transperineal Syed-Neblett template with mean tumor dose of 2900cGY. Patients treated with intracavitary therapy received a mean external dose of 4600cGy and mean cumulative dose of 2700cGY to point A using Fletcher-Suit HDR applicators- 600cGy*3 fractions.*** ***Results:*** ***The local control rates were 70% for interstitial Brachytherapy and 80% for intracavitary Brachytherapy. The complication rates were 33% for interstitial Brachytherapy of which 10% was bladder and 23.33% was rectum. In patients who received intracavitary Brachytherapy, the complication rates were 13.33% of which 6.66% was bladder and 6.66% was rectum. All complications were managed conservatively.*** ***Conclusion:*** ***More relapses are seen in patients with stage IIB, IIIB treated with interstitial irradiation,compared to patients treated by intracavitary Brachytherapy. The bladder and rectal complication rates are higher in patients treated with interstitial irradiation,compared to that of patients treated by intracavitary Brachytherapy.***

Keywords: Intracavitary Brachytherapy, Interstitial Brachytherapy, High dose rate, Low dose rate, Chemoradiation.

1. Introduction

Chemoradiation is the treatment of choice for locally advanced cervical cancer [(1)]. By the combination of teletherapy and brachytherapy, adequate tumoricidal doses with minimal toxicity to bladder and rectum can be delivered [(2)]. Bulky stage IIB, IIIB tumors are treated initially with whole pelvic external radiation followed by intracavitary or interstitial irradiation. In spite of advances in radiation technology and treatment methods such as combined chemotherapy, the patterns of failure are seen as increase in both local, as well as distant failure with advancing stage of disease. The 5-year survival rates for patients with stage IIB is 65% and for stage IIIB is 45% [(3)].

Syed and colleagues introduced the practice of interstitial radiation in the treatment of locally advanced carcinoma. The Syed-Neblett perineal template standardizes to implant even the parametrial disease and improve the local control rates. In this technique the entire volume of tumor can be treated by placing the needles and treating them, unlike in intracavitary technique where the tandem and ovoids are used to treat the cervical tumor [(4)].

There is no systematic comparison between the intracavitary and interstitial techniques till date. So we did a randomized study to know the local tumor control rates, survival and complication rates from these two brachytherapy methods in carcinoma cervix stage IIB and stage IIIB.

2. Methods

All patients were treated between March 1,2007 to December 1,2008 registered at Kidwai Memorial Institute of Oncology and diagnosed as carcinoma cervix, FIGO (International Federation of Gynecology and Obstetrics) stages IIB and IIIB[(5)]. They were clinically staged according to FIGO criteria after an examination under anaesthesia, proctoscopy and cystoscopy. All patients were treated initially with whole pelvic external beam radiation using Telecobalt therapy with AP/PA portals or a four field box technique. All fields were treated daily, (five fractions per week) with 180-200 cGy per fraction, totally amounting to 4500-4600cGy by external beam irradiation.

The patients were assessed weekly and the response and complications were noted [(6)]. Patients were randomized after completion of external beam irradiation to either intracavitary Brachytherapy or interstitial Brachytherapy. Patients received concurrent chemoradiation with Cisplatin chemotherapy 100mg/ sq mtrs,three weekly 2-cycles. External beam irradiation of 4500cGy/25# or 4600cGy/23# was delivered.

In the intracavitary group, Fletcher-suit applicators were used and then after loaded with Ir.192 seeds [(7)], 6 Gy* 3# was delivered to point A[(8)]. In the interstitial group, the entire tumor volume was implanted with 17 gauge hollow needle guides using the Syed-Neblett template, 20 needles were implanted and then after loaded with Ir-192 seeds, the dose delivered was 6 Gy * 3# [(9,10)]. The mean tumor volume

in interstitial brachytherapy was 74 cc and in intracavitary group it was 89 cc [11,12]. The mean over all treatment time in interstitial group was 55 days compared to intracavitary group which was 49 days (p=0.001*) [13-16].

Table 1: Patient characteristics.

	Interstitial group	*Intracavitary group*
Mean Age-(yrs)	45.73	47.43
Clinical stage%		
II B	6	8
III B	24	22
SCC grade (%)		
I	1	2
II	11	10
III	18	18
USG (size)		
<5 sq cm	26	27
>5 sq cm	4	3
Total	30	30

After the completion of brachytherapy, patients were examined at 6 weeks interval for first 6 months and every 3 months till 2 years and every 6 months interval, until 5 years of follow up. The symptoms suggestive of recurrence were evaluated by physical examination, radiographic imaging and documented by biopsy.

Statistics were compiled and analyzed using descriptive method in the present study. Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance.

The Chi-square /Fisher exact test has been used to find the homogeneity of samples on categorical scale. Survival curves were calculated using the Kaplan-Meier method.

3. Results

The patient data, tumor characteristics, tumor size were not different between the two groups (Table-1). All patients were treated with chemoradiation. External beam irradiation of 46 Gy using Telecobalt therapy was delivered and concurrent chemotherapy-cisplatin 100 mg/sq m, three weekly- two cycles was given.

30 patients received intracavitary brachytherapy.-HDR 6 Gy*3#(Table-2) mean LDR Eq.dose to point A – 27 Gy, (Table-3) bladder dose- 15.19 Gy and rectal dose-10.27 Gy [17].

30 patients received interstitial brachytherapy -HDR 6 gy*3# mean LDR Eq. tumor dose- 29 Gy, bladder dose-20.23 Gy and rectal dose-19 Gy [18,19].

A complete response to radiation was achieved in 24 of the 30 (80%) patients treated with intracavitary group and 21 of the 30 (70%) patients treated with interstitial group. 6 patients had progressive disease in intracavitary brachytherapy and 9 patients in interstitial brachytherapy.

The complication was seen in 10/30 (33%) in interstitial brachytherapy of which 3/30 (10%) was cystitis and 7/30 (23.33%) was proctitis. In intracavitary brachytherapy, the complication was seen in 4/30 (13.33%) of which 2/30 (6.66%) was cystitis and 2/30 (6.66%) was proctitis. The mean tumor volume in interstitial brachytherapy group was 74 cc and 89 cc in intracavitary brachytherapy group. 4 patients developed distant metastasis in interstitial brachytherapy and 5 patients in intracavitary brachytherapy. The maximum follow-up period in interstitial brachytherapy was 65 months and in intracavitary brachytherapy it was 67 months. The mean follow-up was (42.5 m Vs 49.3 m). P value= 0.03.

Table 2: Comparison of HDR - Dose per fraction in Gy in two groups of patients studied

HDR - Dose per fr in Gy	Group I ISBT	Group II ICBT	P value
POINT A	5.97±0.24	5.56±0.57	0.001**
BLADDER	4.59±0.44	3.73±0.84	<0.001**
RECTUM	4.35±0.59	2.83±0.34	<0.001**

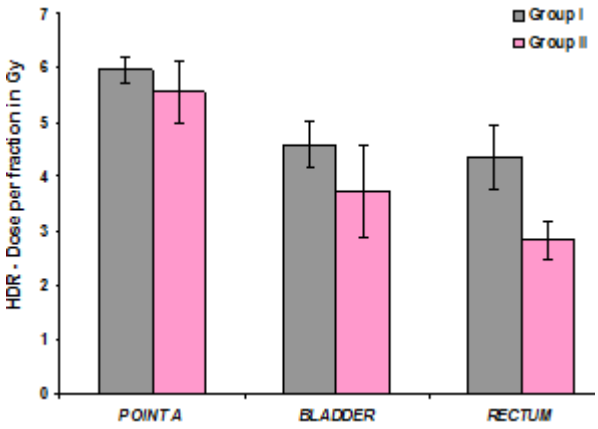


Table 3: Comparison of LDR - Equivalent Doses in Gy in two groups of patients studied

LDR - Eq Doses in Gy	Group I ISBT	Group II ICBT	P value
POINT A	29.58±1.67	26.85±3.53	<0.001**
BLADDER	20.23±2.64	15.19±4.58	<0.001**
RECTUM	18.95±3.57	10.27±1.43	<0.001**

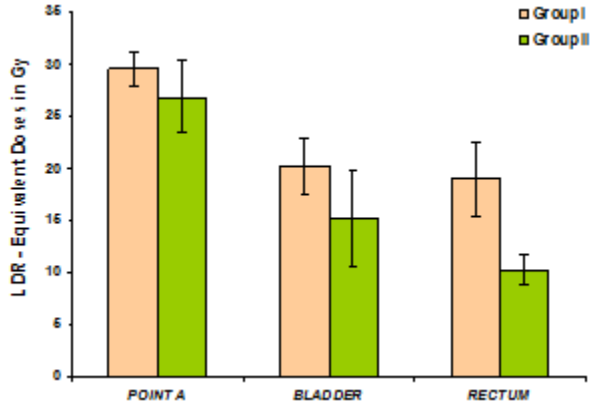


Table 4: Comparison of Total Dose - In Gy in two groups of patients studied

Total Dose - In Gy	Group I ISBT	Group II ICBT	P value
POINT A	75.41±1.61	72.84±3.53	0.001**
BLADDER	66.20±2.56	61.19±4.58	<0.001**
RECTUM	64.95±3.45	56.27±1.43	<0.001**

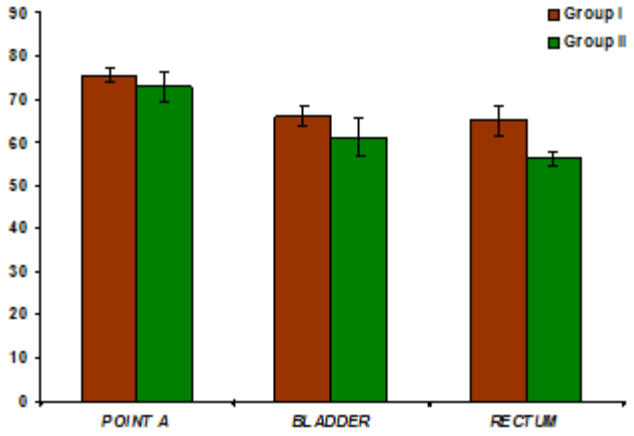


Table 5: Comparison of OTT in two groups of patients studied

OTT	Group I ISBT	Group II ICBT	**P value**
Range	39.0-74.0	41.0-63.0	
Mean ± SD	55.57±8.37	49.23±5.03	
95%CI	52.44-58.68	47.35-51.11	0.001**

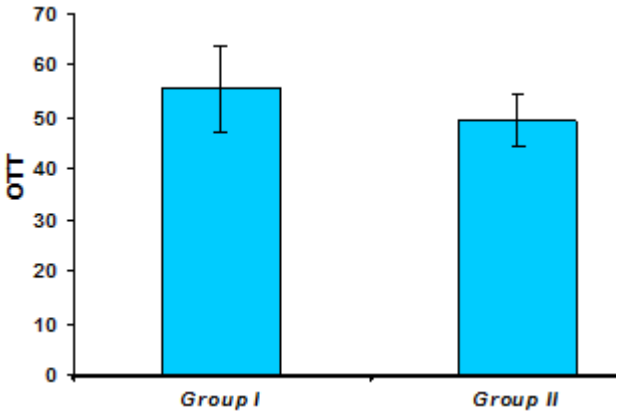
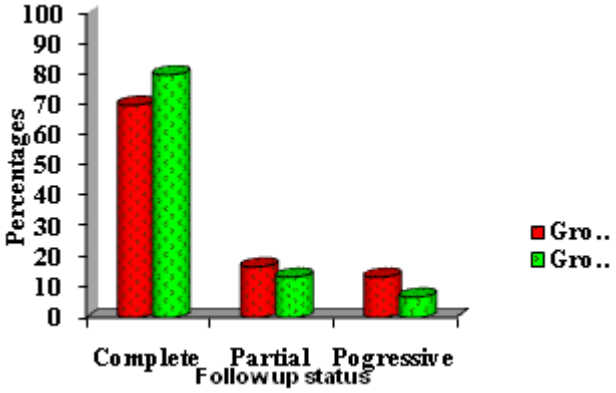


Table 6: Comparison of Follow up status in two groups of patients studied

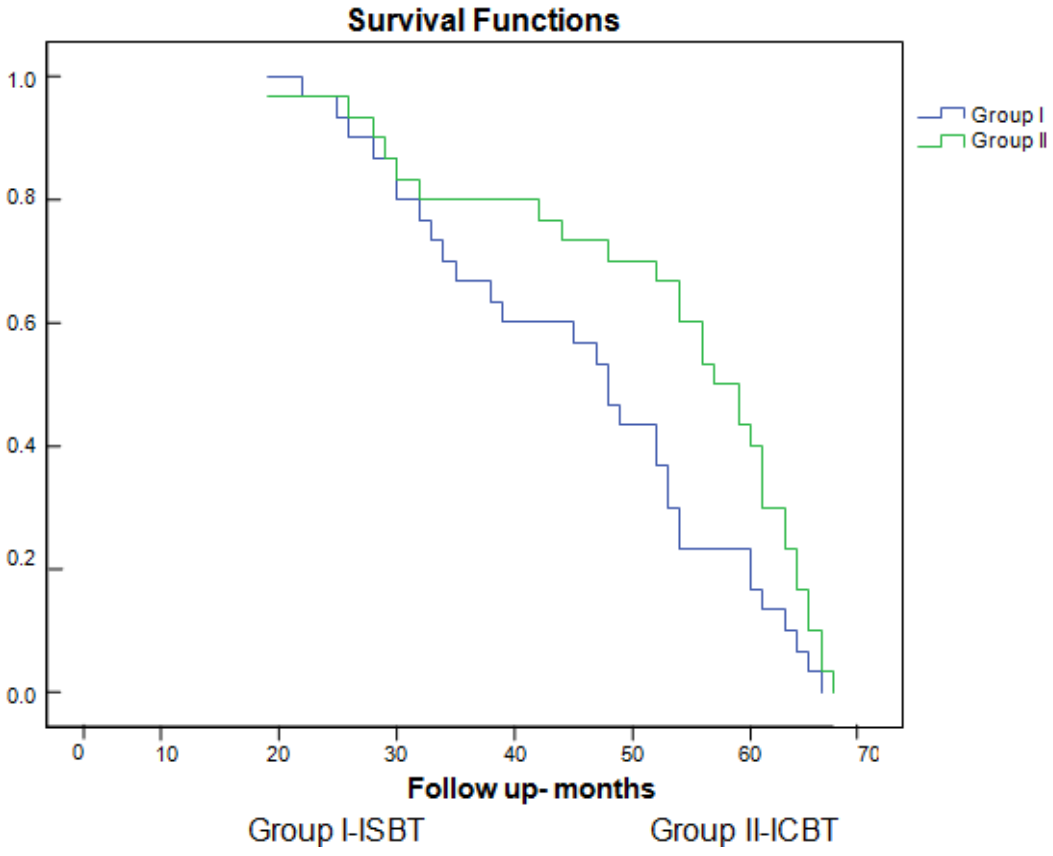
Follow up status	*Group I-ISBT*		*Group II-ICBT*	
	No	*%*	*No*	*%*
Complete response	21	70.0	24	80.0
Partial Response	5	16.7	4	13.3
Progressive disease	4	13.3	2	6.7
Total	30	100.0	30	100.0



Distribution of Response of patients is statistically similar in two groups with P=0.693

Table 7: Comparison of Follow up in months by survival analysis using Kaplan Meier function in two groups of patients studied

Follow up in months	*Group I-ISBT*	*Group II-ICBT*	P value
Mean ± SE	42.53±2.47	49.37±2.61	Log rank test
95%CI	40.79-49.06	48.12-59.36	χ*030.0=Π ;107.4=2



4. Discussion

Cervical cancer is the leading cause of cancer death in rural population of our country. A large proportion of these deaths will occur in women diagnosed with cervical lesions, who do not achieve adequate pelvic control with primary radiotherapy. Interstitial Brachytherapy has been proposed to increase local control due to improving dosimetry. The advantage of Interstitial Brachytherapy involves homogenous irradiation, even though there is distorted anatomy. We can increase the dose to parametrial tissue and pelvic side wall disease by inserting the needles directly and reducing the dose to bladder and rectum. The local control and complications rate of Interstitial irradiation are variable due to differences in dosimetry and technique.

In this Study with 67 months of maximum follow up, the local control rates with Intracavitary Brachytherapy were higher by 10 %,(80% Vs 70%). The control rates achieved with Intracavitary Brachytherapy are comparable with those reported in the literature.

In the study by Monk BJ et al, the 5 year disease free survival (50% Vs 21% p = 0.01) and 5 year Local control (61% Vs 32% p=0.01) were observed in stage II patients treated by intracavitary irradiation and no statistical difference in survival was detected among stage III and IVA patients. Major complications occurred in 21 % patients in each group [(20)].

The reason for reduced local control rates with Interstitial Brachytherapy could be probably due to considerable decrease in the tumor volume coverage by prescribed isodose lines. The tumor coverage volume for interstitial brachytherapy was 74 cc and with that for Intracavitary Brachytherapy was 89cc. When the interstitial needles are not placed perfectly parallel in the tumor tissue, the dose is inhomogenous and local control rates are decreased. The estimated dose to points A and B can be more accurately calculated compared to isodose curves in interstitial implants which are more variable. The use of tandem with interstitial implant needles increases dose to the central tumor and decreases the central recurrances.

When toxicity was considered, our study has shown that late rectal and bladder complications were high with Interstitial Brachytherapy arm,though the tumor volume coverage was less. In Intracavitary Brachytherapy, the rectal complications were 2 out of 30 patients accounting to 6.66% and bladder complication were 2 out of 30, accounting to 6.66%. In Interstitial Brachytherapy, the rectal complications were 7 out of 30 patients accounting to 23.33% and bladder complication were 3 out of 30, accounting to 10%(Table-4).This mandates the implementation of 3D conformal dosimetric version in brachytherapy.

5. Conclusion

This study has shown that Interstitial Brachytherapy is not superior over Intracavitary Brachytherapy. The therapeutic ratio with Intracavitary Brachytherapy is optimal as the local control rates were better (80% Vs 70%). The complication rates were higher (33% Vs 13.33%) in interstitial Brachytherapy due to high BED doses to bladder and rectum.

The late normal tissue toxicities remained high in interstitial brachytherapy arm, though the tumor volume coverage by prescribed isodose volume were smaller when compared with that of Intracavitary Brachy therapy. This mandates the implementation of Brachyvision for dosimetry and 3D CT-based volumetric tumor coverage, dose assessment and sparing of normal tissues.

The survival rates are better with Intracavitary Brachytherapy than Interstitial Brachytherapy (Table-7). Good local tumor control can be achieved by decreasing the overall treatment time. Further validation with studies including larger accrual of patients with longer duration of follow-up would give better results.

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