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Original Articles

A Comparative Study of Result of Treatment of Cancer Cervix Patients Treated by Two Separate Schedules of Radiotherapy

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Abstract

Background: *Cervical cancer is the most common cancer of Bangladeshi women diagnosed mostly (>80%) at stage II and stage III. Rdaiotherapy (both teletherapy and brachytherapy) is the most important modality of treatment at these stages.*

Objective: *To compare the local control, diseases free survival and overall survival between the (cancer cervix) patients treated randomly by two schedules of radiotherapy.*

Method: *From June 1996 to June 2005, patients with histologically confirmed carcinoma cervix (Ca.cervix) were treated by external beam therapy (EBRT) as well as intra cavitery brachytherapy (ICRT) along with concurrent/sequential chemotherapy with cisplatin and 5-Fluorouracil. EBRT was given by cobalt^{60} teletherapy machine and ICRT by caesium^{137} low dose rate machine. The patients were divided into two groups according to treatment schedules. Group I: the patients in this group received EBRT in whole pelvis in two steps, first with open field upto 10-20 Gy then by applying midline shield with lead block 30-40Gy in 25-28 total fractions, five days a week; they also received 50-70 Gy to point A by ICRT in 2-4 weekly fractions. Group II: patients in this group received with open field a dose of 45-50Gy in 25-28 fractions, 5 days a week by EBRT and 25-30 Gy at point A by ICRT in 1-2 weekly fractions.*

Result: *In Group I, 96 out of 101 and in Group II, 104 out of 118 patients were eligible for evaluation. In both groups patients were distributed according to stages and age more or less equally; their age range were 30-70 years and mean age was 47.2 years in Group I and age range were 25-80 years and mean age was 46 years in Group II. Squamous cell carcinoma were found (90%) and performance status was WHO grade 0-1 (>75%) in both groups. Local control of disease at 5 years was 65% in group I and 51% in group II. Overall survival at 2 years, 5 years, 7 years and 9 years in group I, was 71%, 64%, 55%, 46% and in group II, 54%,50%, 43%,32% respectively. Distant metastasis occurred in 22% in-group I and 28% in-group II. Lymph node, lung, liver, peritoneum were common site of metastasis. Proctitis, cystitis, vaginal stenosis in group I was 80%, 33% 16% and in Group II 29%, 13% and 5% respectively.*

Conclusion: *External beam therapy and brachytherapy was effective treatment in carcinoma. Cervix in both operable and inoperable stages. In small volume of tumor, both schedules of radiotherapy were more or less equivalent but in bulky diseases Group I schedule that was higher dose by brachytherapy at point A showed better result; though the complication was more:*

Introduction:

The effectiveness of radiotherapy alone as curative treatment for carcinoma of uterine cervix is well recognized. There are two techniques of irradiation such as external beam photon therapy (EBRT) by Cobalt^{60} Teletherapy or Linear accelerator machine and internal source of treatment (Intracavitary brachytherapy) used for radical radiotherapy. Several

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sources of brachytherapy are available; although caesium^{137} source is the most popular for low dose rate (LDR) and iridium^{192} for high dose rate (HDR). In the treatment policy evolved by Fletcher[1], initial EBRT is given to whole pelvis to induce primary tumor shrinkage and to sterilize microscopic disease within the pelvic lymph nodes. Intracavitary brachytherapy is then used to treat the central diseases (cervix, vagina, medial parametria).

The most common brachytherapy techniques used in the treatment of cervical cancer are based on Manchester triple source system comprising of intrauterine tube and two vaginal ovoids. This arrangement gives the classical pear shaped isodose distribution with widest part of distribution located around the cervix. The brachytherapy dose is calculated at point A, reference point corresponds to the paracervical triangle in the medial edge of the broad ligament where the uterine vessels cross the ureter; demarcated in the point at 2cm lateral to the centre of the uterine canal and 2cm from the mucous membrane of lateral fornix in the plane of the uterus. In current practice, point A dose is used to approximate the average or minimum dose to the tumor[2].

In stage II and above, radiotherapy is the standard treatment of choice. Surgery and radiation therapy are equally effective for early-stage small-volume disease[3]. Younger patients may be benefited from surgery in regard to ovarian preservation and avoidance of vaginal atrophy and stenosis.

Five randomized phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy. The risk of death from cervical cancer was decreased by 30% to 50% with the use of concurrent chemoradiation therapy. Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer[4].

Methods & Materials:

Histologically confirmed cases of carcinoma of cervix uteri (FIGO stage Ib, stage IIa, IIb and stage IIIb) were selected for the study between the periods June 1996 to June 2005 in different Institutions. Clinical evaluation including gynecological examination was done. The laboratory investigations such as complete blood picture, urea, creatinine, SGPT, SGOT, alkaline phosphatase, bilirubin, blood sugar and serum electrolytes and serum protein, albumin in relevant cases were done. Radiological and imaging studies such as X-ray chest P-A view, USG of whole abdomen, IVU, CT scan of abdomen, cystoscopy, and proctoscopy in relevant cases were carried out. According to selection criteria, cervical cancer patients of any age group, stage Ib stage IIa, stage IIb and stage IIIb, performance status not more than WHO grade 2, hemoglobin level >9gm/dl, bilirubin within normal limit, SGPT < double of normal value, alkaline phosphatase < triple of normal value, without any prior anticancer treatment were included for the study.

Radiotherapy:

All the patients received radiotherapy by two modalities External beam radiotherapy

(EBRT) and Intracavitary radiotherapy (ICRT). EBRT was applied by Cobalt^{60} machine

and was applied by Caesium^{137} low dose rate machine. The patients were divided into two

Groups in accordance with radiotherapy schedules, Group I and Group II.

Group I: the patients in this group received EBRT in whole pelvis in two steps, first with open field upto 10-20 Gy then by applying midline shield with lead block 30-40Gy in 25-28 total fractions, five days a week; total duration of 5-5.5 weeks, they also received 50-70 Gy to point A by ICRT in 2-4 weekly fractions.

Group II: patients in this group received radiotherapy to whole pelvis with open field a dose of 45-50Gy in 25-28 fractions, 5 days a week by EBRT and 25-30 Gy at point A by ICRT in 1-2 weekly fractions.

The pelvic field both anterior and posterior extends from upper margin of L-5 vertebra above to the level of mid portion of the obturator foramen or the lowest level of disease, with a three-cm marg**in**, and laterally 1.5 to 2 cm beyond the lateral marg**in**s of the bony pelvic wall (at least 7 cm from the midl**in**e). The two lateral fields extends from the level of anterior border of pubic symphysis anteriorly upto the level of space S2 and S3 and the upper and lower limit remains the same as that of anterior and posterior fields. Patients having radiologically enlarged para-aortic lymph nodes underwent extended field Radiotherapy with a dose 44Gy in 22 fractions in 4.5 weeks duration.

The duration of the radiotherapy was 8-10 weeks. Radiotherapy was withheld if a patient had a leukocyte count of less than 2000 per cubic millimeter, and delays of up to one week were also allowed **in** the event of radiation-related gastro**in**test**in**al or genitour**in**ary toxicity. The length of delays **in** radiotherapy, **in** days, was calculated by subtract**in**g the planned duration of radiotherapy (the number of prescribed fractions plus 2 weekend days for every five fractions) from the actual duration of radiotherapy.

Chemotherapy:

Concurrent chemotherapy during radiotherapy was given in both groups of patients. Chemotherapy schedule was combination of cisplatin 25mg/m2 and 5 Flourouracil 400mg/m2 weekly for 6 weeks. Further chemotherapy was prescribed and carried out in bulky and suspected residual disease after completion of concurrent chemoradiotherapy. The patients more than 70 years were treated by only radiotherapy. Chemotherapy was discont**in**ued if the leukocyte count dropped below 3000 per cubic millimeter or the platelet count dropped below 100,000 per cubic millimeter. Eighty four cases in Group I and 91 in Group II patients. Cisplatin (25mg/m2) and 5 Flourouracil (400mg/m2) weekly for six weeks were given during radiotherapy treatment. Further four cycles of chemotherapy were given in 15 cases of Group I and 12 cases in Group II.

Medical management:

Every week, clinical examination including gynecological examination was done and laboratory investigations such as complete blood count, SGPT, creatinine was carried out. Cervical/ vaginal lesion with fungating growth was treated with antiseptic dressing and endometrial collection was drained out by dilating the cervical os. Blood transfusion was given if Hb level less than 9gm/dl and thrombocytopenia developed; Neutropenia was corrected by postponing specific treatment or by administering colony stimulating factors. Antibiotics, antiemitic, analgesic, vitamins, anti fungal drugs and intravenous fluid were given in relevant cases. Gastrointestinal problem such as nausea, vomiting, diarrhea, dysentery, mucositis, proctitis, cystitis, were managed. Every patient was advised to take high protein, extra 8-10 glasses of liquid and avoid sun light.

Survival

Survival of each patient was calculated from the date of therapy was started to the date of the last follow-up examination. Complete response was defined as absence of cancer cells as determined by smear cytology and biopsy of the uterine cervix. Recurrence was defined as reappearance of cancer cells.

Local control rate

Complete response was defined as no remaining cancer cells according to cytologic and histologic assessment for over 3 months after radiotherapy. Local control was defined as absence of recurrence in the pelvic cavity.

Acute and late complications

Acute complication such gastrointestinal, cuteneous, hematological and late rectal and bladder complications and non-rectal gastrointestinal sequelae (small bowel complications) were graded according to the Radiation Therapy Oncology Group (*RTOG*)/ the European Organization for Research and Treatment of Cancer (*EORTC*) scoring system[5].

Second cancers

Cancer either in the radiation field or outside that differed histologically from the primary cancer, as distinguished from recurrence or metastasis from the primary tumour, was considered a second cancer.

Follow up

After the completion of treatment, follow up schedule was: monthly check up for first three months, once per three months for three years, once per six months for 3-5 years and once per year after 5 years of treatment. All patients were followed up for more than 5 years after radiation therapy.

In follow up clinic, complaints of the patients were recorded, then clinical examination, relevant investigation (laboratory, radiological and imaging studies) were done and noted.

All these data were compiled and analyzed.

Result:

From June/1996 to June/2005, the patients were treated according to the program schedule and completed the treatment within 8 weeks to 14 weeks period. Follow up period was 5 years to 13 years median 9 years.

After completion of treatment, 96 patients out of 101 in group I and 104 out of 118 patients in group II were evaluated by clinical examination according to follow up schedule. In local control of disease, there was no

Table-I

Charecteristics of patients

	Group I	Group II
Toal no. of patients	101	118
Eligible	96	104
Age range (years)	30-70	25-80
Mean age (years)	47.2	46.5
Stage (no. of patients)		
IB	5 (5.2%)	4(3.84%)
IIA	7 (7.29%)	8(7.7%)
IIB	55 (57.29%)	52(50%)
IIIB	29 (30%)	40(38.46%)
Bilateral parametrial involvement in stage IIb and IIIB	26/84 (30%)	36/92 (39.1%)
Histopathology (no. of patients)		
squamous cell ca	85(88.54%)	98(94.23%)
adenocarcinoma	6(6.26%)	4(3.84%)
adenosquamous	3(3.12%)	2(1.92%)
small cell carcinoma	2(2.08%)	0
WHO Performance status (no. of patients)		
Grade0 (Asymptomatic)	53(55.2%)	36(34.62%)
Grade1 (Symptomatic but completely ambulatory)	21(21.87%)	42(40.38%)
Grade2 (Symptomatic, <50% time in bed during day)	15(15.62%)	15(14.42%)
Grade 3 (Symptomatic,>50% time in bed but not bed bound)	7(7.30%)	11(10.58%)

Table-II

Radiotherapy treatment shedule

	Group I (n=96)	Group II (n=104)
Technique	Site	Site
	Whole pelvis	*Whole pelvis*
EXT by Co60	45-50 Gy (10-20GY	45-50 Gy in 25-30 fractions
	open field and 30-40 Gy	
	with midline lead shield) in 25-28 fractions	
	5 weeks to 6 weeks duration	5 weeks to 6 weeks duration
Brachy by LDR	At point A*	At Point A*
Cs137 (At point A*)	55-70 Gy in 2-4 fractions	25-30 Gy in 1-2 fractions
Duration treatment (8-10) weeks	88 patients (91.67%)	78 patients (75%)
10-14 weeks	8 patients (8.34%)	26 patients (25%)

*Point A: reference point corresponds to the paracervical triangle in the medial edge of the broad ligament where the uterine vessels cross the ureter.

disease detectable in cervix or pelvis either clinically or pathologically (pap's smear cytology or biopsy). Average local control of disease was 64.58% in Group I and 50.91% in group II. Local control of disease at 5 years is given in figure 1.

Survival: Overall survival of patients with ca. cervix at 2 years, 5 years, 7 years and 9 years was 71%, 64%, 55%, 46% in group I patients and that was 54%, 50%, 43%, 32% in group II respectively (Figure 2). Disease free survival at 2 years, 5 years, 7 years and 9 years was 62%, 56%, 48%, 42% in Group I and that was 50%, 47%, 38%, 29% in Group II respectively (Figure 3).

Toxicities: Regarding early toxicities, Grade 0-2 toxicities occurred more or less equal in patients of both Groups but Grade 3 toxicities occurred in 24 cases (25%) in patients of Group I and 11 patients (10.57%) in Group II patients. In late toxicities, vaginal stenosis, skin fibrosis, haematuria, per rectal bleeding were more common in group I patients. (Table 3).

Metastasis and second malignancies: Metastais developed in 22 patients (22.91%) in group I and 30 (28.84%) in group II patients. Second cancer developed in 4 patients (Table 4).

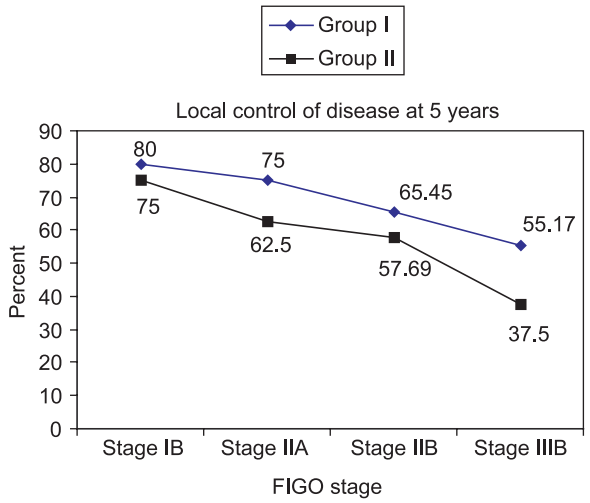

Fig.-1:

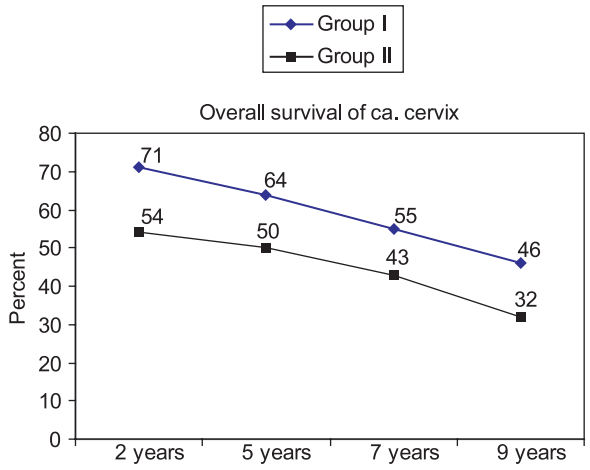

Fig.-2:

Group I: Stage Ib 4/5, IIa 6/8, IIb 36/55, IIIB 16/29

Average 62/96 (64.58%)

Group II: Stage Ib 3/4, IIa 5/8, IIb 30/52, IIIB 15/40

Average 53/104 (50.96%%)

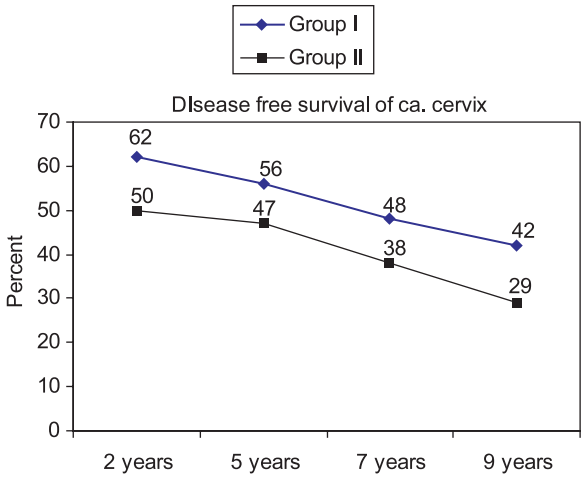

Fig.-3:

Table-III

Early toxicities (during treatment and within six months of completion of treatment)

EORTC Grade 0-2	Group I	Group II
Nausea	43 (44.79%)	45 (43.26%))
Vomiting	18 (18.75%)	12 (11.53%)
oral mucositis	21 (21.87%)	25 (24.03%)
Diarrhea	17 (17.70%)	14 (13.46%)
cystitis	17 (17.70%)	15 (14.42%)
proctitis	78 (81.25%)	43 (41.36%)
leucopenia	14 (14.5%)	16 (15.38%)
Thombocytopnea	2 (2.08%)	0

EOTC Grade 3

Group I : 15 cases with proctitis and 9 cases with cystitis — No. of patients 24 (25%)

Group II : 8 cases with proctitis and 3 cases with cystitis — No. of patients 11 (10.57%)

Late toxicities (after six months)

	Group I	Group II
Proctitis	18 (18.75%)	5 (4.80%)
Haematuria	12 (12.50%)	10 (9.61%)
Vaginal stenosis	24 (25.00%)	17 (16.34%)
Skin fibrosis	15 (15.62%)	18 (17.30%)
Constipation	26 (27.08%)	12 (11.53%)
Urethral sticture	4 (04.16%)	0

Table-IV

Metastasis and second malignancies: Total 52 patients developed metastasis

	Group I	Group II
Metastasis	22 (22.91%)	30 (28.84%)
Second malignancy	2	2

Sites of metastasis:

sites of mets	No. of patients n= 52 (26%)
Lymph node	26 (13%)
Lung	12 (6%)
Liver	6(3%)
Bone	4 (2%)
Peritoneum	4 (2%)

Single site mets= 15, multiple sites mets=37

Second malignancy	No. of patients (n=4)
Gall bladder cancer	01 (after 5 years)
U. bladder cancer	01 (after 4 years)
Gastro esophageal cancer	01 (after 7 years)
Lung cancer	01 (after 3 years)

Discussion:

Five randomized phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy in ca. cervix patients[6-11] . In the presents study, the patients with ca. cervix of both groups were treated by cisplatin and 5FU concurrently with radiotherapy. About 88% of patients in both groups were with advanced stage (IIB and IIIB) disease (Table 1). Standard treatment for ca. cervix of advanced stage is concurrent cisplatin based chemotherapy and radiotherapy; local control rate was 72% at 2 years and 67% at 5 years[12]. In the present study, local control rate at 5 years was 65% in group I and 51% in Group II. In both groups of patients with stage IB, IIA and IIB, the local control rate was more or less equal but in stage IIIB cases, it was better in group I patients; 55% vs 37% (Figure 1).

The size of the primary tumor is an important prognostic factor[13]. In the present study, the patients of group II were with comparatively bulky tumor; 40 patients (38%) with stage IIIB and where as in group I, 29 patients (30%) were stagIIIB disease. About 40% of group II patients of stage IIB and IIIB was with

bilateral involvement but that was 30% among the group I patients. Intracavitary brachytherapy dose that was given at point A in the patients of group I was more than that of patients in group II (Table 2). Patterns-of-care studies in stage IIIA/IIIB patients indicate that survival is dependent on the extent of the disease, with unilateral pelvic wall involvement predicting a better outcome than bilateral involvement[14]. These studies also reveal a progressive increase in local control and survival paralleling a progressive increase in paracentral (point A) dose and use of intracavitary treatment. The highest rate of central control was seen with paracentral (point A) doses of more than 85 Gy [15].

Timely completion of RT is essential for good outcomes, whether chemotherapy is used or not[16-20]. Women who required over nine weeks to complete treatment had significantly higher rates of pelvic failure and poorer disease-specific survival at 10 years as compared to those whose treatment was administered over a shorter time period[16]. In the present study, more than 90% of the patients in group I and 75% of group II completed radiotherapy within 10 weeks (Table.2).

Overall survival (Figure 2) of two years, five years, seven years and nine years in group I patients was better that of group II. (71%, 64%,55%,46% and 54%, 50%, 43%,32% respectively) and disease free survival was 62%, 56%, 48%,42% and 50%, 47%, 38%,29% respectively (Figure 3). According to Rose at el , 10 years survival of concurrent cisplatin based chemoradiotherapy of ca. cervix was 43-46%[21]. According to Spensly et al the 3-year overall survival rate was 70%, with an estimated 5-year overall survival rate of 60%. The 3-year disease-free survival was 63.6%, with an estimated 5-year disease-free survival rate of 55% [22].

Acute and subacute side effects occur during and for the first six months after treatment and include injury to the skin and mucosal surfaces, fatigue, edema, and sequelae of implantation such as fever, thromboembolism, uterine perforation, and vaginal laceration. Late effects, occurring after six months, include fibrosis, stricture, fistula, second malignancies[23-25], radiation enteritis, and intestinal malabsorption. In the present study, grade 0-2 toxicities occurred more or less equal in patients of both groups. But grade 3 toxicities (proctitis and cystiytis) occurred in 24 cases (25%) in patients of Group I and 11 patients (10.57%) in Group II patients. The early toxicities were nausea, vomiting, oral mucositis, cystitis, proctitis, leucopenia, thrombocytopenia. In late toxicities, vaginal stenosis, skin fibrosis, haematuria, per rectal bleeding were more common in group I patients (Table 3).

In a large series of cervical cancer patients treated by radiation therapy, the incidence of distant metastases (most frequently to lung, abdominal cavity, liver, and gastrointestinal tract) was shown to increase as the stage of disease increased, from 3% in stage IA to 75% in stage IVA[26]. In the present study, 52 patients out of 200 cases developed distant metastasis, of them lymph node (13%), lung (6%), liver (3%), bone (2%) shown in Table 4. Imachi et al observed that lung metastais developed 6.1% of treated cervical cancer patients[27]. The incidence of bone metastasis was 2% approximately[28]. In the present study second malignancy developed in four patients within 3 -7 years of treatment. A review of 1048 patients with cancer of the cervix treated with radiation, either alone or combined with surgery, disclosed 32 cases of second primary malignancies occurring from 1 to 16 years subsequent to treatment[29].

Conclusion: External beam therapy and brachytherapy was effective treatment in ca. cervix in operable and inoperable stages. In small volume of tumor, both schedules of radiotherapy were more or less equivalent but in bulky disease Group I schedule with higher dose by brachytherapy at point A showed better result; though the complication was more but can be treated.

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