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Radical radiotherapy treatment (EBRT + HDR-ICRT) of carcinoma of the uterine cervix: Outcome in patients treated at a rural center in India

ABSTRACT

Aim: To report the outcome of carcinoma of the uterine cervix patients treated radically by external beam radiotherapy (EBRT) and high-dose-rate (HDR) intracavitary radiotherapy (ICRT).

Materials and Methods: Between January 1997 to December 2001, a total of 550 newly diagnosed cases of carcinoma of the uterine cervix were reported in the department. All cases were staged according to the International Federation of Gynecologists and Oncologists (FIGO) staging system, but for analytical convenience, the staging was limited to stages I, II, III, and IV. Out of the 550 cases, 214 completed radical radiotherapy (EBRT + HDR-ICRT) and were retrospectively analyzed for presence of local residual disease, local recurrence, distant metastases, radiation reactions, and disease-free survival.

Results: There were 7 (3.27%), 88 (41.1%), 101 (47.1%), and 18 (8.4%) patients in stage I, II, III, and IV, respectively. The median follow-up time for all patients was 43 months (range: 3-93 months) and for patients who were disease free till the last follow-up it was 59 months (range: 24-93 months). The overall treatment time (OTT) ranged from 52 to 73 days (median 61 days). The 5-year disease-free mean survival rate was 58%, 44%, 33%, and 15%, with 95% confidence interval of 48 to 68, 37 to 51, 24 to 35, and 6 to 24 for stages I, II, III, and IV, respectively. There were 62 (28.97%) cases with local residual disease, 35 (16.3%) developed local recurrence/distant metastases, 17 (7.9%) developed distant metastases, and 9 (4.2%) had local recurrence as well.

Discussion and Conclusion: The overall outcome was poor in advanced stage disease, but might be improved by increasing the total dose, decreasing overall duration of treatment, and by adding chemotherapy in patients with disease limited to the pelvis.

KEY WORDS: Carcinoma cervix, high-dose-rate brachytherapy, radiotherapy

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INTRODUCTION

Carcinoma of the uterine cervix (Ca Cx) is the most common malignancy in women in developing countries such as India.[1] As most of the cases present at advanced stages, such as stage III and IV, in which surgery is not possible, radiotherapy plays an important role in these patients.[2-8] Radiation has been used successfully to treat cervical cancer for nearly a century. The combination of external beam irradiation and brachytherapy has been shown to be an effective treatment for Ca Cx patients. The success of brachytherapy requires delivery of a high radiation dose to the tumor while sparing, to some degree, the surrounding normal tissue. Ca Cx is the commonest malignancy in females at our center.

Our hospital is situated in a rural area of Maharastra, India, with the facility of one tele-cobalt unit, HDR/PDR (high dose rate/pulse dose rate) remote afterloader unit, and a treatment planning system. The department was started in August 1996. This study aimed to evaluate the overall outcome of the Ca Cx cases treated radically by external beam radiation (EBRT) and high-dose-rate intracavitary radiotherapy (HDR-ICRT).

MATERIALS AND METHODS

A total of 550 newly diagnosed cases of Ca Cx were reported in the department of radiotherapy from January 1997 to December 2001. Out of this, only 214 patients completed their scheduled EBRT + HDR-ICRT treatment; they were analyzed retrospectively for residual disease, local recurrence, distant metastases, radiation reactions, and disease-free survival. There were 97 post-operated patients, in whom ICRT was given by vaginal cylinder or by two ovoid, and these cases are analyzed

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separately. One hundred and seven patients were not given ICRT due to poor anatomy and large residual growth. These cases were given only EBRT with reduced field size, with a total dose of up to 60-66 Gy. All the above 204 cases were excluded from the study. One hundred and thirty-two cases discontinued their treatment during EBRT or did not report for HDR-ICRT (in spite of patient and relative counseling for disease and nature of treatment); these patients were also excluded from the study. Histopathological confirmation was done for all patients. All cases were investigated with routine hematological and biochemical examination, x-ray chest, and ultrasonography of the abdomen and pelvis before starting radiotherapy treatment. All patients were examined and staged clinically by a radiation oncologist, according to the International Federation of Gynecologists and Oncologists (FIGO) staging system. Pretreatment hemoglobin level was not taken into consideration for survival analysis, but was kept above 10 gm%, by giving blood/packed red cell transfusion. Patient characteristics are shown in Table 1.

Radiation therapy

All patients had EBRT by anterior-posterior/posterior-anterior (AP/PA) or four-field box technique with a cobalt-60 unit. The upper border of the pelvic field was at the L5-S1 junction; the lower border was at the lower most part of the obturator foramen, which was modified according to the vaginal extent the disease. The lateral borders were kept 1.5 cm beyond the Widest part of pelvic brim. For the four-field box technique, the anterior and posterior borders of the lateral portals were kept at the anterior part of the pubic symphysis and the S2-S3 junction, respectively. Patients were treated to mid-plane dose on AP/PA and at isocenter on the four-field box technique. Dose delivered was 50 Gy - 54.4 Gy in 25-28 fractions, with 5 fractions per week over 5-6 weeks duration, without any midline block. The treatment profile is shown in Table 2.

Brachytherapy

After completion of external radiotherapy, all the cases were examined for fitness for brachytherapy. Patients were planned for brachytherapy after a 12-18 day interval. All cases were given two fractions of HDR-ICRT with a weeks interval. Applicator insertion was done under general/spinal anesthesia. The vagina was packed with regular Betadine-soaked gauze packs to push the bladder and rectum away and stabilize the applicator. A Foley's catheter was inserted and the balloon was inflated with 7 cc of diluted Urograffin to allow identification of the bladder neck region. A rectal catheter with a lead wire inside it was inserted in the rectum to visualize the rectal mucosa for rectal points. After applicator insertion, AP and lateral semi-orthogonal marker x-ray films with the help of jig were taken for pelvic dosimetry. Planning was done with the help of the Abacus treatment planning system (version 3.1; Germany). The dose was prescribed to point "A." Point "A" is described as a point 2 cm up from the cervical os point of the uterine tube (tandem) and 2 cm lateral to the uterine source on both sides. Bladder reference points were marked on the anterior radiograph at the center of the balloon; on the lateral radiograph an anteroposterior line was drawn through the center of the Foley's catheter balloon and the bladder reference point was taken on this line at the posterior surface of the balloon as per the recommendations given in Report 38 of the International Commission for Radiation Units (ICRU). For rectal reference points we used, for convenience and cost effectiveness, a rectal catheter with a marker lead wire inside, although this is not the ideal recommendation as per ICRU-38.[9] Multiple rectal reference points were delineated on the lateral radiograph. For the R1 rectal point

Table 1: Patient profile

Age	
Range	28-83 years
Median	46 years
Hemoglobin %	
Range	5.6-13.9 gm%
Median	10.2 gm%
Total no. of pts.	550
Pts. Defaulting treatment	132
Pts. For only EBRT	107
Post operated pts.	97
Total patients for study	214
Stage	
I	7 (3.27%)
II	88 (41.13%)
III	101 (47.19%)
IV	18 (8.41%)
Histology	
Squamous cell carcinoma	187 (87.38%)
Adenocarcinoma	15 (7.0%)
Adenosquamous cell carcinoma	3 (1.41%)
Others	9 (2.21%)
Follow-up	
For all 214 pts.	
Range	3-93 months
Median	43 months
For disease-free pts.	
Range	24-93 months
Median	59 months

Pts. - patients

Table 2: Treatment profiles

EBRT dose	
AP/PA	5000 cGy (198 pts.)
Four-field box	5040 cGy (16 pts.)
Duration of EBRT	
Range	33-47 days
Median	36 days
Duration between EBRT and HDR-ICRT	
Range	12-18 days
Median	15 days
Duration between two fractions of ICRT	
Range	7-21 days
Median	9 days
Applicator used	
Fletcher suit type	207 pts.
Ring tandem	7 pts.
Overall treatment time	
Range	52-73 days
Median	61 days

EBRT: External beam radiotherapy; AP/PA: Anterior-posterior/posterior-anterior; HDR-ICRT: High dose rate - intracavitary radiotherapy; Pts.: Patients

in the lateral radiograph, an anteriorposterior line was drawn through the lower end of the uterine source to a point 5 mm anterior to the rectal marker. Four more rectal points R2, R3, R4, and R5 were taken 1-1 cm above and below the R1 point, respectively. In the anterior radiograph, rectal point R1 was taken at the lower end of intrauterine source and four more rectal points R2, R3, R4, and R5 were taken 1-1 cm above and below the R1 point, respectively. All points were in the line of the rectal marker. The doses to the urinary bladder and rectum were calculated on the bladder and rectal reference points. Doses delivered were 15 Gy in two fractions at weekly interval (per fraction dose was 7.5 Gy). Bladder and rectum doses were limited to 80% of the prescribed point "A" dose, as per the ICRU-38 recommendations, but in a few patients doses exceeded the limit due to poor anatomy. Brachytherapy treatment was delivered by HDR/PDR remote afterloader unit, in which a single high-stepping iridium source was used. A 3-channel Fletcher-Suit applicator was used in 207 patients. A ring-tandem applicator was available from August 2001 and was used in only 7 patients until December 2001. Computerized planning, the dose prescribed, and the dose distribution was the same as with the 3-channel applicator. Procedural complications were seen only in three patients. Two patients had a vaginal tear at the time of packing; both were above 70 years of age. In one patient, tandem was not in the uterine cavity; this was confirmed by ultrasonography. The procedure was repeated and the position confirmed.

Follow-up

All the patients reviewed monthly, after completion of treatment, for 6 months for the assessment of treatment response and treatment-related complications. After this they were reviewed every 2-3 months for 1 year and 3-4 months up to 3-4 years; following this review was every six months. On follow-up, patients were examined clinically and ultrasonographically; Pap smears were taken every 4-6 months for 3 years initially and then yearly. Other relevant investigations were done based on the patient's complaints and examination findings. Late complications were graded in accordance with the Radiation Therapy Oncology Group (RTOG) criteria, especially for bladder, rectum, and bowel complications. Disease-free survival was calculated from the date of registration till the last follow-up in July 2006. The follow-up period ranged from 3-93 months.

Statistical analyses

Patients who did not have either local residual/recurrent lesion or distant metastases till the last follow-up were counted as disease free. The different results were analyzed using simple statistical values like mean, mode, and median. For overall survival, disease-free survival, and pelvic control, the duration was calculated from the date of registration to the time of the event. All losses to follow-up were considered as an event for survival analysis. Kaplan-Meier method was used for survival analyses by using the SPSS software, version 10.0.

RESULTS

Two hundred and fourteen patients were the subjects for this retrospective analysis. Follow-up period ranged from 3 months to 93 months (calculated from the date of registration to the occurrence of an event or loss to follow-up), with a median of 43 months. For patients who were disease free till the last follow-up, the follow-up period ranged from 24 months to 93 months, with a median of 59 months. Overall, 27 (12.61%) patients were lost to follow-up (after completion of radiotherapy) and 90 (42.05%) were disease free. Overall pelvic control rate was 42.05%. In stage I there were only seven patients: one patient was lost to follow-up and the other six were disease free till the last follow-up. In stage II there were 88 patients, 46 (52.27%) were disease free till the last follow-up and 9 patients were lost to follow-up. In stage III there were 101 patients, out of which 16 were lost to follow-up and only 35 (34.65%) were disease free. In stage IV there were 18 patients, of which one was lost to follow-up and only 3 (16.66%) were disease free. Details of disease-free survival, follow-up status, and pattern of failure according to disease stage are shown in Table 3.

Survival

The 5-year disease-free mean survival rate (Kaplan-Meier method) was 58%, 44%, 33%, and 15%, with 95% confidence intervals of 48 to 68, 37 to 51, 24 to 35, and 6 to 24 for stage I, II, III, and IV, respectively. The overall disease-free survival was 58%, 49%, 37%, and 23%, with 95% confidence intervals of 48 to 68, 44 to 55, 33 to 42, and 16 to 31 for stage I, II, III, and IV, respectively. The overall survival and disease-free survival curves for all stages are shown in Figures 1 and 2.

Recurrence pattern

In most of the patients recurrence was at the primary site and this tended to occur within 2 years of completion of treatment. Out of the 214 patients in the study group 62 (28.97%) had local disease on routine monthly follow-up in the initial 3-6 months. Thirty-five (16.35%) patients were found to have recurrence/metastasis in subsequent follow-ups.

Table 3: Disease-free survival, follow-up status, with pattern of failure (persistent D/pelvic recurrence/metastasis) according to disease stage after radiotherapy

Stage	Total Pts (214)	Disease free till last f/U (%)	No F/up	Persistent D*	Pelvic recurrence + Metastasis
I	7	6 (85)	1	-	-
II	88	46 (52.27)	9	21	12
III	101	35 (34.65)	16	32	18
IV	18	3 (16.66)	1	9	5

*Persistent D: Persistent disease (<6 month after treatment); F/up: Follow-up

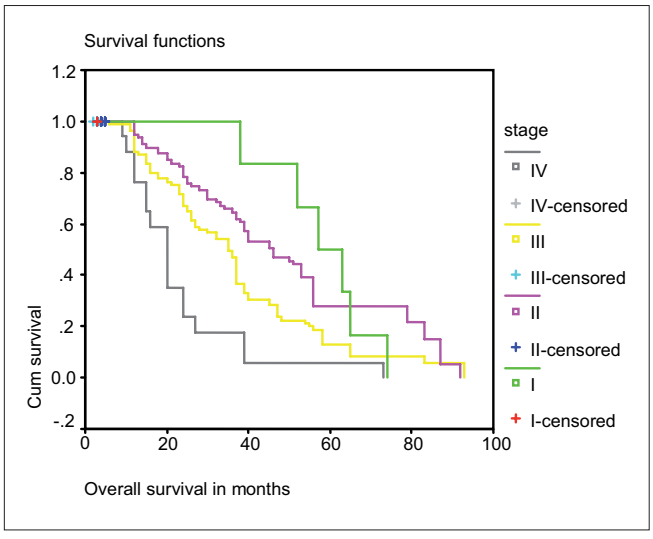

Figure 1: Overall survival according to disease stage

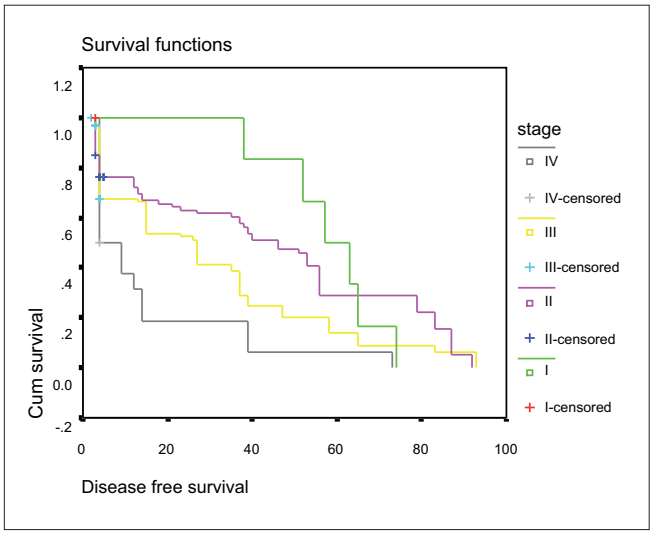

Figure 2: Disease-free survival according to disease stage

Distant metastasis was detected in 17 patients, out of which 9 had local disease also. The remaining 18 patients had only local recurrence. Two patients developed a second primary malignancy (not included in the metastasis list). One patient developed a second primary malignancy in her breast, 1 year after completion of radiotherapy for Ca Cx; this patient is still surviving after receiving treatment for both the malignancies. Another patient developed a second primary in the tonsil 6 years after completion of radiotherapy; she completed her radiotherapy for carcinoma tonsil 6 months before. Details of the recurrence pattern and metastasis sites are shown in Tables 3 and 4.

Complications and reactions

We have not come across any severe acute treatment-related complications with EBRT and HDR-ICRT. Late complications involving the bowel and bladder according to RTOG criteria (grades 1-4) were found in 39 (18.22%) patients. For grades 1-4, bladder complications were seen in 13 (6.07%) patients and rectum complications in 19 (8.88%). One patient had grade 3 radiation-induced cystitis and two had grade 3 proctitis. All patients were managed symptomatically, with stool softeners and steroid enemas for proctitis and urinary analgesics, bladder irrigations, and plenty of oral fluids for cystitis. Rectal toxicities appeared within 6-20 months and bladder toxicities appeared between 16-36 months. Two patients developed acute intestinal obstruction (one after 11 months and the other after 18 months); both required surgery. One expired in the postoperative period; the other is still disease free. Five patients developed severe hydronephrosis (on ultrasonography); ureteric stents were inserted in two patients, as they were disease free locally. One expired in uremia and the other two had local disease for which palliative chemotherapy was started. Bowel and bladder complications were seen more often in patients who received more than 100% of the prescribed point "A" dose to the bladder/rectum. Late vaginal toxicities were not evaluated, as this is subjective, and the follow-up evaluation is not documented properly for vaginal shortening, adhesions, and stenosis. Details of the late radiation toxicities are shown in Table 5.

Table 4: Various sites for metastases

Metastasis sites	No. of patients	Recurrence at primary site
Liver	5	(3)
Para-aortic failure	3	(2)
S. C. node	3	(2)
Brain	2	-
Bone	2	(1)
Lung	2	(1)

S. C. node: supraclavicular node

DISCUSSION AND CONCLUSION

Radiotherapy is an effective treatment modality for all stages of Ca Cx and is widely used in developing countries.[1] Centers in the UK use two fractions of HDR-ICRT, with 7 Gy to point A in each fraction.[2] The American Brachytherapy Society (ABS) recommends multiple HDR insertions to allow progressive tumor volume reduction, allowing more effective disease coverage with subsequent applications. Four to eight fractions of HDR-ICRT, with the dose ranging from 5.3 to 7.5 Gy per fraction and the total dose by EBRT from 20 Gy to 50.4 Gy for early and late stages of the diseases and ICRT is given during EBRT (but EBRT is not given on the day of HDR).[3] As this department is new, the total radiation doses were kept on the lower side and the dose schedule used was similar to that used at various places in the UK. In our setup, where patients are uneducated and poor, a treatment plan for ICRT, after completion of EBRT was preferred.

The comparison of the results of the present study with that reported by other authors with respect to 5-year survival rate, cause-specific survival rate, and disease-free survival rate are shown in Table 6. Our results in this study are inferior to that of the other studies mentioned in Table 6. Important

Table 5: Late complications with radiotherapy

Complications	No. of patients (%)	Grades of severity			
		1	2	3	4
Cystitis	13 (6.07)	5	7	1	-
Proctitis	19 (8.88)	8	9	2	-
Acute intestinal obstruction	2 (0.93)	-	2	-	-
Severe hydronephrosis with uremia	5 (2.33)	-	2	3	-
Total	39 (18.22)	13	20	6	-

Table 6: Five-year survival rate for Ca Cx with EBRT + HDR-ICRT, as reported by different authors

Author/year	Stage-I	Stage-II	Stage-III	Stage-IV
FIGO Annual/1987[11]	422 (76.9%)	798 (58.1%)	588 (38.1%)	50 (15.2%)
Arai/1992[8]	147 (88.1%)	256 (71.6%)	515 (52.2%)	104 (19.6%)
Ellic/1988[12]	232 (93%)	463 (73%)	430 (54%)	34 (18%)
Ito/1994[13]	62 (84%)	204 (71%)	366 (47%)	27 (12%)
Joslin/1989[14]	95 (94%)	170 (62%)	106 (38%)	-
Macleod/1997[15]	22 (IB 78%)	22 (IIA 72%) 36 (IIB 42%)	17 (IIIB 29%)	6 (0%)
Patel/1994[16]*	35 (74.6%)	90 (62.5%)	111 (43%)	-
Selke/1993[17]	15 (72%)	35 (IIA 65%)	54 (IIIB 45%)	-
Lorvidhaya/2000[7]*	208 (79.5%)	882 (IIB 59.4%)	638 (32.3%)	28 (15.2%)
Jain V S*,#	7 (58%)	88 (44%)	101 (33%)	18 (15%)

*5-year disease-free survival; Ca Cx: Carcinoma cervix; EBRT: External beam radiotherapy; HDR-ICRT: High dose rate-intracavitary radiotherapy; #Present series

prognostic factors in our study are stage of the disease, total dose to the parametrium and point "A" by EBRT and HDR-ICRT, overall treatment time and, less significantly, histology and pretreatment hemoglobin. Though there are several factors affecting the results in this study, only a few important ones merit discussion. As HDR-ICRT was planned after completion of EBRT, with a gap of 12-18 days, the overall treatment time (OTT) was more than 52 days for all the patients; however, if the ICBT had been planned as per ABS recommendations it would have been less than 52 days. Petereit *et al*.[18] showed that survival decreased by 0.6% a day and pelvic control by 0.7% a day for each additional day of treatment beyond 55 days for all stages of cancer of the cervix. In our study OTT was 52-73 days with a median of 61 days. One hundred and thirteen (52.8%) patients completed treatment within 55 days. Pretreatment hemoglobin was less than 10 gm% in 83 (38.78%) patients and all were given blood transfusions/packed cell transfusions; in spite of this, 43 (20.09%) patients had hemoglobin in the range of 8.5-10 gm% when they were on treatment. We used 10 gm% of hemoglobin as the cut-off level because Girinski *et al*,[8] in his retrospective analyses, has reported that a hemoglobin reading of less than 10 gm% during or before radiation treatment was associated with reduced cause-specific survival and locoregional control. However, transfusion during treatment did not alter the prognosis.

Kapp *et al*. reported 74.5% pelvic control at the 3-month post-treatment evaluation and persistent tumor in 24.5%.[10] In our study, persistent tumor was present in 29.4% patients at the 6-month post-treatment follow-up and pelvic control was 70.5%, which is less than that reported by Kapp *et al*.;[10] however, the total dose delivered was higher than in our study. Similarly, actuarial 5-year disease-free survival rate reported by Lorvidhaya *et al*.[7] was 79.5%, 70.0%, 59.4%, 46.1%, 32.3%, 37.8%, and 23.1% for stages IB, IIA, IIB, IIIA, IIIB, IVA, and IVB, respectively, which were better than our results but, again, the total dose by EBRT and HDR-ICRT was more, and duration of overall treatment was less, due to HDR insertions started early, after 30-40 Gy.

When EBRT and HDR brachytherapy are combined, the goals are to treat point A (or Point H) to an LDR equivalent of 80-85 Gy for early-stage disease and 85-90 Gy for advanced stage.[3] The pelvic side wall dose recommendations are 50-55 Gy for smaller lesions and 55-60 Gy for larger lesions. At our rural setup, more than 2-3 insertions of ICRT will again increase the chances of irregularities in treatment by the patient. We have now started (since April 2003) giving three fractions of HDR-ICRT (7 Gy/fraction), but this is done after completion of EBRT.

Concurrent chemoradiotherapy in the treatment of cervical cancer offers definite improvement in pelvic control and overall survival and this is the acceptable treatment modality for advanced cases. The Cochrane Collaborative meta-analysis included data from 19 trials, 12 of which used platinum-based chemotherapy. The second, a Canadian study, based on 8 randomized trials, exclusively examined platinum-based chemoradiation. An absolute improvement in survival was estimated as 12% by the Cochrane group and 11% in the Canadian study.[6,19,20] Controversy persists about the most appropriate drug for chemotherapy, and its dose and schedule with optimally delivered radiotherapy, to get similar or better results for tumor control and minimum toxicity. Use of concurrent chemoradiation, with weekly cisplatin, for advanced cancer cervix cases is ideal for developing countries and is already in use at our center since 2003.

CT- and MRI-based 3-D CRT (three-dimensional computerized radiotherapy) and intensity-modulated radiotherapy (IMRT)

has shown improved results in locally advanced cervical cancer, but its routine use in developing countries is limited in the present scenario.[21] Use of interstitial brachytherapy to achieve better dose distribution in cases with a narrow vagina, inability to enter the cervical os, extension to the parametrium and lower vagina, and bulky lesions (where ICRT is not possible or possible only with suboptimal dose distributions) is yet to be started at our center.

A relatively large number of patients receiving EBRT/ICRT discontinued treatment. The most probable causes were poor financial status, illiteracy, and ignorance about the disease. Post-operated cases were analyzed separately due to the problem of preoperative diagnosis, staging, improper surgery, and delayed postoperative radiation treatment.[22] Analysis of cases who received only external radiotherapy was also done but is not included in this report.

In the present study, the difference between disease-free survival and overall survival is very little as most of the patients, after the diagnosis of local residual disease, recurrence, or distant spread, were not willing for further palliative therapy and did not report for review after being informed about the prognosis. In most of the cases with residual/recurrent lesion the patient record till death is not available to permit overall survival analyses.

In this retrospective study on the outcome in Ca Cx treated radically by EBRT and HDR-ICRT, we came to the conclusion that the 5-year disease-free survival results are poor in all stages when analyzed by the Kaplan-Meier method (due to the small number of cases with stages I and II), but advanced stage disease results might be improved by increasing the total dose, decreasing overall duration of treatment, by adding chemotherapy in patients with disease limited to the pelvis, and by increasing the overall dose to point "A" by CT/MRI-based 3-D treatment planning and by using perineal templates in cases with poor anatomy and involvement of the parametrium.

In spite of the problems present in this rural population (illiteracy, ignorance, poverty, and poor transport facilities) we achieved good follow-up for the patients who completed their treatment but, at the same time, the number of cases discontinuing treatment as well as the number of patients with advanced stage disease were quite high. Due to lack of screening programs for early diagnosis, around 60% of cases reported in advance stages. Early detection with screening programs, cancer awareness and education programs in the surrounding rural areas, along with more financial assistance from the government and non-governmental organizations, is required for early stage diagnosis and early treatment.

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