Radiotherapy in Locally Advanced Cancer of the Cervix

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Summary

Radical radiotherapy is considered as the treatment of choice in locally advanced cancer cervix. In late stages radiotherapy produce optimum palliation and to some extent cure. Three hundred cases of cancer cervix (stage I-IV) comprising stage-I (7), stage-II (144), stage-III (145) and stage IV (4) were evaluated and treated with radiotherapy between April 1990 to July 1994. FIGO stage IB, IIA and IIB (early), were treated with predominant intracavitary radiotherapy (34 Gy X 2 fractions; within one week) followed by external pelvic radiotherapy to a dose of 36 Gy in 18 fractions; treating 200 cGy per fraction, 5 days a week. The late stage (stage-IIB, IIIA and IIIB, IVA) of disease were managed with initial external radiotherapy to a dose of 50 Gy, followed by a single intracavitary dose of 30 Gy to point-A. The median follow up was 33 months (range 12-72 months). The tumor volume less than 100 cc were associated with better survival than volume more than 100 cc (p < 0.05). The five year actuarial survival was 83%, 68% and 58% respectively in FIGO stage I-III disease. There were 0.33% and 2.6% late grade-III bladder and rectal complications. Our experience shows effectiveness of radiotherapy in the management of locally advanced cancer of the cervix.

Key Words: Cancer of the cervix, Radiotherapy, Malignancy

Introduction

Carcinoma of the uterine cervix is still the leading cause of mortality and morbidity in Indian women. The reported age adjusted incidence rate varies between 19.4 to 43.3 cases per 100,000 women population[1]. In Delhi cancer registry in particular, the incidence rate is as high as 30.1 cases per 100,000 population, whereas the incidence in Bombay cancer registry is low. Some current reports shows decreased trend of cervical cancers in rural India[2]. Late stage disease predominates. The stage II and III disease constitute more than 90% of the cases[3,4]. Late stage disease presentation is mainly due to the suboptimal early detection measures, ignorance, illiteracy and lack of treatment facilities. Other important factors are early marriage and sexual exposure, multiparity, poor genital hygiene and genital viral infections.

Radiotherapy is considered as the treatment of choice in all stages of cervical cancer. Surgery is an alternative to radiotherapy in early stage low volume disease. The standard cure rate with radical radiotherapy are 85%, 66%, 39% and 11% respectively in stage I-IV cervical cancer[5]. Radiotherapy is usually given as a combination of external and intracavitary components. The older radium system is now changed to non-radium sources (cobalt, iridium or caesium), which have higher dose rates than the standard radium system in intracavitary radiotherapy. In order to compensate for the increased dose rate of non-radium sources, various dose rate correction factors are used to match the classical radium system[6]. Significant late complication rates of rectum and bladder were 1.5% to 11% respectively[7,8]. In our Institute, low dose rate (LDR) Selectron system facility is being used since 1987 and at the time of analysis about 1200 cases have been treated.

Materials and Methods

Between April 1990 to July 1994, three hundred cases of cervical cancer patients were treated with radical radiotherapy in our department. Patients with age ranging between 21 to 70 years with good performance status were included. All patients were jointly evaluated by the radiation oncologists and gynecologists. The tumor volume was estimated by the digital estimation in three dimensions in a relaxed pelvis. All patients had complete blood count, liver and renal function tests, urinalysis, chest x-ray, intravenous urography or ultrasound of the abdomen and pelvis. In some cases CT scan and MRI scan of the abdomen and pelvis were done. In appropriate cases, cystoscopy and proctosigmoidoscopy were performed. The early stage low volume disease were managed with predominant intracavitary radiotherapy and the late stage large volume disease were managed with initial external radiotherapy (Table I). The initial external radiotherapy are aimed at the reduction of the bulky cervical disease to make subsequent intracavitary radiotherapy easier. In early stages [FIGO stage IB, IIA and IIB (*low volume*) two fractions of intracavitary radiotherapy (ICRT) were delivered within a week, and a dose of 34 Gy each was prescribed to the Manchester point-A. To compensate for the increased dose rate of caesium system, a dose reduction of 15% was applied. Within a gap of 2-3 weeks, an external radiotherapy dose of 36 Gy in 18 fractions over 4 weeks was delivered to the pelvis by split field in order to protect the rectum and bladder. In *large volume* and late stage disease, an external radiotherapy dose of 50 Gy in 27 fractions over 5.5 weeks were delivered. The last 10 Gy was delivered along with a 5 half value layer (HVL) mid-line shield. Within a gap of 2-3 weeks, a single insertion of intracavitary radiotherapy was delivered and a further dose of 30 Gy was delivered to point-A.

External radiotherapy was delivered by a telecobalt unit or a 15 MV linear accelerator (Clinac-20), utilizing four field brick technique or antero-posterior opposed portal. The daily tumor dose was limited to 180-200 cGy, treating 5 days a week. Intracavitary radiotherapy was given by low dose rate (LDR) Selectron system (Nucletron Int, The Netherlands) utilizing 40 mCi each of caesium-137 pellet sources (total active sources = 36). In order to compensate for the higher dose rates of the caesium system (180 cGy/hour), over standard radium system (53 cGy/hour), a dose rate correction of 15% was applied in all cases. The acute radiation morbidity was graded according to the RTOG grading system[9]. The response to the radiation were assessed at the end of 6 weeks post radiotherapy. Patients with optimum tumor regression were considered for ICRT, otherwise were supplemented with further external radiotherapy by a reduced portal. The intracavitary dosimetry were done as per the recommendations of ICRU-38[10]. The rectum and bladder doses were limited to 60% and 75% of the point-A dose respectively.

Following radiotherapy, patients were followed up

Table I
Radiotherapy schedule

Stage	Radiotherapy		
	External radiotherapy		Intracavitary brachytherapy
	Whole pelvis	Parametrium (with MLS)	
Early stage (IB-IIB early)	Nil	36 Gy/18 #	34 Gy x 1 # (at point-A)
Late stagw (IIB-IVA)	40 Gy/22 #	10 Gy/5 #	30 Gy x 1 # (at point-A)

Abbreviations: Gy = Gray; # = Fractions; MLS = Mid line shield

bimonthly for 2 years and three monthly thereafter. Clinical examination were done in every follow up visit, vaginal cytology every six months and evaluation of abdomen and pelvis by ultrasound or CT scan every year. The follow up was aimed at early detection of recurrence and radiation complications. The late rectal and bladder morbidity was graded as per the Crook's grading system[11]. All patient details were analyzed by a computerised database. The disease free survival was analyzed according to the Kaplan-Meier non-parametric method[12]. The parameters like digital tumor volumetry, hemoglobin percentage, inter-radiotherapy interval were estimated against the overall survival. The grade-I late complications were managed with symptomatic treatments, but the grade-II and III rectal morbidities were treated with steroid retention enemas. In refractile cases, with severe rectal bleeding intrarectal formalin (4%) application was done. Moderate to severe bladder complication treated with intravesical irrigation of 1% alum or formalin.

Results

The final analysis of the results were evaluated in August 1995. A total of 300 cases were evaluated. The age distribution of the patients ranged between 21 to 70 years with a median age of 38 years [Fig. 1]. The performance status of patients were above 80 as per the KPS scoring system. The pretreatment hemoglobin concentration was 11 gm/dl (range 6-15 gm/dl). Patients with hemoglobin level below 10 gm/dl were transfused to raise the level above 10 gm/dl. The tumor volume varied between 8 cc to 800 cc with a mean volume of 107 cc amongst 146 (49%) recorded patients. The patients were distributed as per the FIGO staging system as 7 cases in stage-I, 144 cases in stage-II, 145 cases in stage-III and only 4 cases in stage-IV [Fig. 2]. Stage-IV cases with early bladder invasion were irradiated with an indwelling catheter in situ to reduce vesico-vaginal fistula formation. The five year actuarial survival were 83% for stage-I, 68% for stage-II, 58% for stage-III and 38% for stage-IV [Fig. 3]. The percentage of the patients censored in stage II and III were 71% and 64% respectively. The analysis of overall survival against the hemoglobin level above and below 10 gm/dl did not demonstrate any statistically significant survival difference [Fig. 4]. Similarly the inter-radiotherapy interval (between
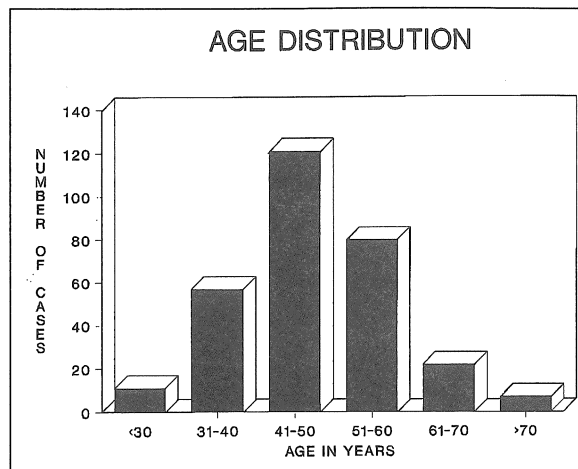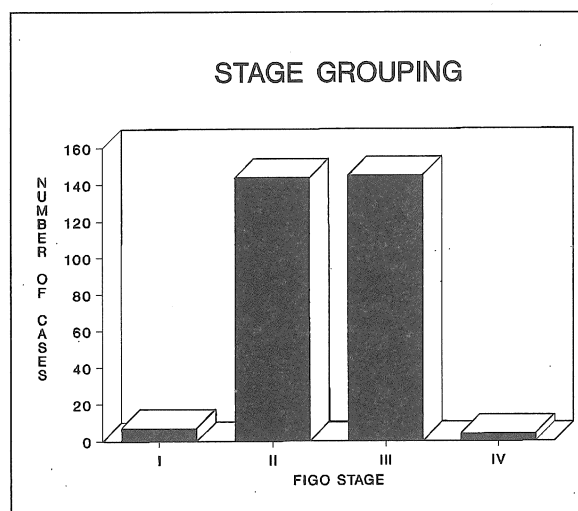

Fig. 1: Age distribution of patients

Fig. 2: FIGO stage profile

intracavitary and external radiotherapy) more or less than 3 weeks did not demonstrate any significant difference against overall survival [Fig. 5]. While comparing the overall survival of the tumor volume less than 100 cc or more than 100 cc, the former group showed better survival (p<0.05) [Fig-6].

The complication analysis revealed the rectal complication of 10%, 6.3% and 2.6% respectively for grade I, II and III morbidities. The comparable complication for bladder were 2.6, 1.6 and 0.33% respectively [Table II]. The rectal complications were
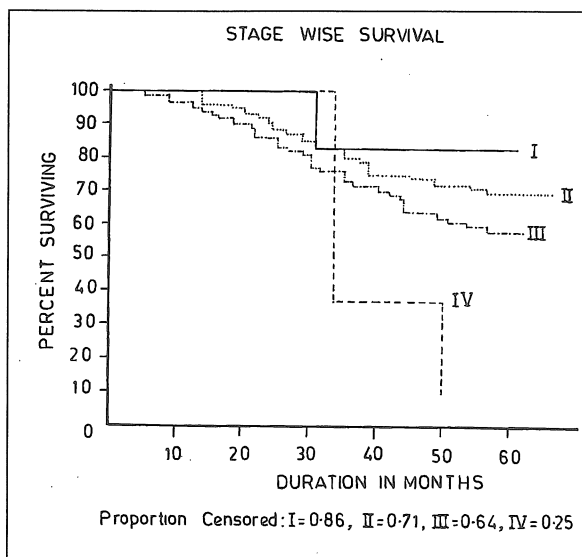
STAGE WISE SURVIVAL

Proportion Censored: I= 0·86, II=0·71, III=0·64, IV= 0·25

Fig. 3: Five year stage wise actuarial survival
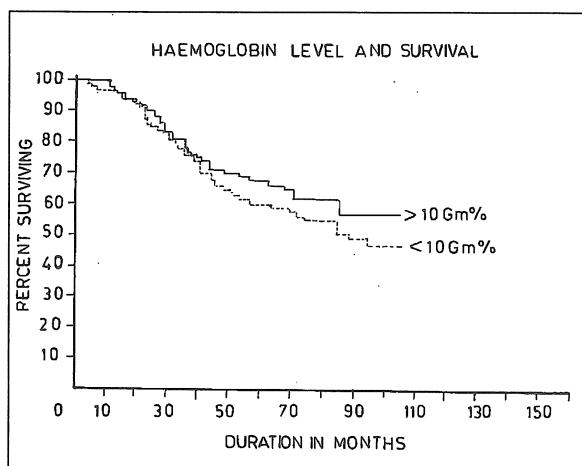
HAEMOGLOBIN LEVEL AND SURVIVAL

Fig. 4: Comparative overall survival between pretreatment hemoglobin level above and below 10 gm/dl

Table II
Late complications

Viscera	Late complications		
	Grade-I	Grade-II	Grade-III
Rectum	10%	6.3%	2.6%
Bladder	2.6%	1.6%	0.3%

very common and appears early, whereas the bladder complication was seen later in the follow up. The 80% rectal complication was seen at 12 months and bladder at 21 months respectively [Fig. 7].

The commonest cause of failure in our series were tumor persistence or local pelvic recurrence. The local pelvic failure were recorded maximum before 24 months of follow up. Metastatic disease were seen in the later part of the disease course. They were in the lungs (24%), retroperitoneum (16%), supraclavicular nodes (14%) and inguinal nodes (12%). The other less common sites were bone (8%), mediastinum (4%), second primary (4%), liver, brain, skin and soft-tissue (one each) [Fig. 8].

Discussion

India has the highest incidence of cervical cancer making up one-fourth to one-third of all female cancers. The FIGO stage II and III disease constitutes more than 90% of the patients[3]. Lack of optimal early detection facility, higher mean child birth and early sexual exposures are a few contributory causes of this vary high incidence. Of course the introduction of 'clinical down staging' at community level has resulted
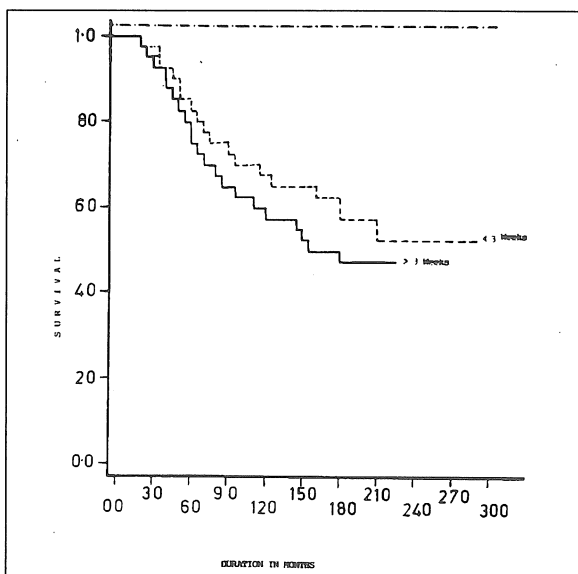

Fig. 5: Comparative overall survival between inter-radiotherapy interval above and below 3 weeks
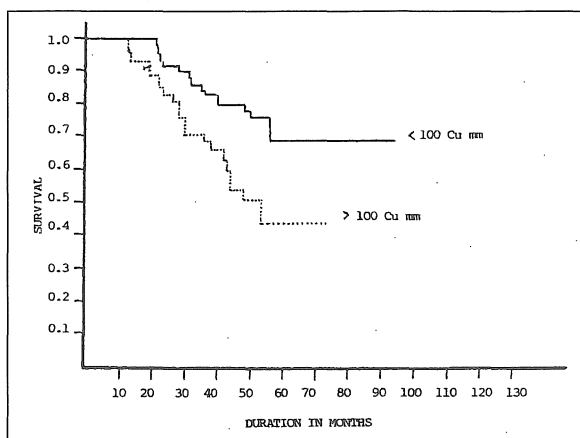
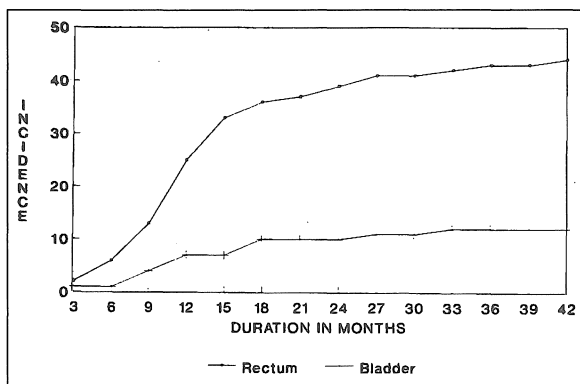Fig. 6: Tumor volume more or less than 100 cc and overall survival

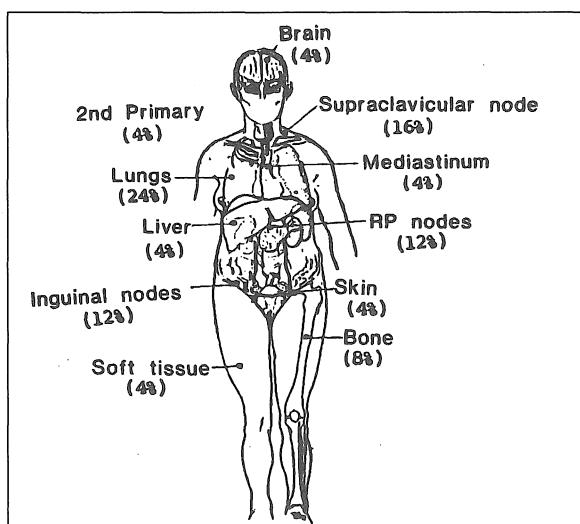Fig. 7: Patterns of rectal and bladder complications

Fig. 8: Distribution of the distant metastases

in shift to left in some studies[13], but the majority centers see patients in late stages. Out of 300 cases in our series, stage II and III cases constitute 48% and 48.3% respectively. The stage I and IV disease represents only 2.3% and 1.3% respectively. Our results are similar to the other reported series from India[3]. The late stage disease usually have large volume disease, pelvic inflammatory disease and associated intra-tumoral hypoxia. The mean tumor volume in our series was 107 cc. Increased tumor volume results in lesser radiological healing of the cervical growth[14]. While analyzing the outcome of radiotherapy above or below 100 cc of tumor volume, there was a statistically significant survival difference in favor of low volume disease [Fig. 6].

The mean age incidence of the cervical cancer is between 52.8 years[5]. Particularly in India, the age incidence rate are a decade earlier[15], primarily due to early age at marriage[4]. Hence they present at a younger age, and at a late stage. The age adjusted incidence rate are documented as 43.5 per 100,000 female population in Madras cancer registry, India[1]. Young age has a poorer prognosis[16], though the later is not consistently reported[17]. Poorly differentiated tumor, late stage presentation and large tumor volume are usually associated with cervical cancer of the young; ofcourse we did not observe any difference in the outcome in our series.

Bleeding cancer cervix, antecedent pelvic inflammatory disease lead to blood loss and nutritional anemia. Low hemoglobin level lead to poor oxygen delivery and further complicate the tumor hypoxia. The mean tumor volume in our study was 107 cc and with the mean hemoglobin level of 11 gm/dl. Lower hemoglobin level cause lower local control rate and survival is a controversial issue. Dische[15] reported higher pelvic failure rate and low survival rates in patients with lower pretreatment hemoglobin level. In our patients we were not able to demonstrate statistically significant difference between hemoglobin level above or below 10 gm/dl (fig. 4).

Inter-radiotherapy interval is an important determinant of the therapeutic outcome for radical radiotherapy in cervical cancer [19]. The interval between external and intracavitary radiotherapy lead

to increased proliferation of the tumor resistant clonogens. The latter in turn cause local failure. While comparing the inter-radiotherapy interval at less or more than 3 weeks there was no difference in the survival (fig. 5), hence the optimum interval between intracavitary and external radiotherapy can be kept between 3-4 weeks.

The survival of cervical cancer patients treated with radical radiotherapy alone or with a combination of chemotherapy has not improved the survival figures since last four decades[20]. In our study, the survival figures ranged from 83%, 68%, 58% and 38% respectively in stages I-IV respectively [Fig. 3]. The standard cure rates in one of the largest meta-analysis reported are 85%, 66%, 39% and 11% respectively in various stages (I-IV)[5]. Higher survival figures are projected in many American series reported in the literature [8]. Perez et al reported a five year disease free survival rate of 83%, 75%, 62%, 44% and 10% in FIGO stage IB, IIA, IIB, III and IV respectively[7]. The higher figure in stage IV disease (38%) in our series might be a coincidence and therefore the above figure should not be interpreted seriously; moreover the number of patients are very few (four only). Addition of prior chemotherapy has not improved the survival much as the complete response rates are very low[21]. Hence radical radiotherapy remains the treatment of choice in all stages of cervical cancer. The addition of parametrial interstitial implantation improve the survival figures[22]. Increased radiation dose improve local control rates.

Complications are the normal accompaniments of radical radiotherapy. Minor radiation related acute side effects are easily managed with symptomatic treatment, but the late complications are more troublesome. In the past, when all cervical cancer patients were treated with radium, the complication rates were insignificant and reported as less than 1%[23]. Use of higher specific activity sources (more than 3.5 times of radium), has made complication rates relatively higher[6]. The late bowel complications were 10%, 6.3% and 2.0% in grade I-III respectively in our patients. Similarly the grade I-III bladder morbidities were 2.6%, 1.6% and 0.3% respectively [Table II]. Perez et al[7] evaluated

more than 1000 cases of cervical cancer of various stages, who were treated with radical radiotherapy and reported higher complication rates for bowel and bladder. The grade-3 late bowel complication were 6.1%, 14.5%, 12.1%, 10.7% and 11.1% respectively in FIGO stage IB, IIA, IIB, III and IVA respectively. In our series, the bowel complications started at about 6 months and increased to a maximum of 24 months; whereas the bladder late morbidities begin at 12 month and attend nadir around 24-30 months. The complication rates are related to the point-A dose, inadequate posterior packing, small ovoids, displaced applicators, narrow vagina and few other factors related to increased rectal dose.

Failure of treatment increases at higher stages of the disease. Higher tumor volume and bulky parametrial disease are the commonest cause of pelvic failure. The pelvic failure were distributed as residual disease (tumor persistence) and or local recurrence. The pelvic recurrence appeared within the first 24 months of the follow up. The main limitation of the optimum tumor control is because of failure to deliver higher tumor dose as per the volume. Interstitial implantation to the parametrium might improve the local disease control in the future. The distant failure rate (outside pelvis), is common and appear late. The metastatic disease constituted 10% of the total cases. The main sites of the metastases are lung, supraclavicular and retroperitoneal lymph nodes. The other reported series showed lung as the most frequent site for distant metastases.

In conclusion, radical radiotherapy was given to 300 cases of cancer cervix resulted in an 5 year actuarial survival of 83%, 68%, 58% and 38% respectively in stage I-IV disease respectively. The severe grade-III complication rate were 2.6% and 0.3% espectively rectum and bladder. The tumor volume study was found to be an important predictor of the out come of radiotherapy. Pretreatment hemoglobin level was not crucial contrary to the other reported series. An optimum combination of external and intracavitary radiotherapy is essential for favorable local control and survival with least complication rates.

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