RESEARCH COMMUNICATION

Evolution in the Management of Locally Advanced Cervical Cancer: The Experience of Cancer Institute (WIA), Chennai, India

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Abstract

Objective: To conduct a retrospective analysis of disease free survival (DFS) of locally advanced cervical cancer (LACC) in relation to evolution of treatment and related factors. Methods: A total of 3,892 cases of LACC treated at the Cancer Institute (WIA), Chennai, India, during 1990-1999 were analyzed. Management of LACC including concurrent chemo-radiation (CCRT) has evolved through trials conducted at the institute. DFS and risk of second cancer were elicited using actuarial and Kaplan-Meier methods, respectively. Results: A majority belonged to stage III (54%) and complete follow-up at 5-years was 90%. DFS at 5, 10 and 15-years were 58%, 49% and 42% for stage IIB and 43%, 35% and 31% for stage III, respectively. External beam radiotherapy (EBRT) alone as treatment modality reported the poorest 5-year DFS (37%). Addition of chemotherapy to EBRT resulted in marginal increase in survival (41%) but inclusion of brachytherapy to EBRT enhanced survival (58%) significantly ($p<0.001$). CCRT with brachytherapy as a planned component resulted in the best DFS (69%), irrespective of disease stage. In a carefully selected group of patients who were suitable for salvage surgery, the long-term DFS was 71%, 63% and 63% at 5, 10 and 15 years, respectively, for stages IIB and III together. Complete response was achieved in 67% and 15% of them recurred. Remote metastasis occurred in 13%. The cumulative risk of developing any second cancer was 0.5% at 5 years, 1.9% at 10 years and 2.8% at 15 years of follow up. Conclusion: Our data indicates satisfactory treatment outcome even in advanced disease and with the present state of knowledge, the recommended standard treatment for LACC is careful pre-treatment evaluation followed by CCRT which includes brachytherapy.

Keywords: Locally advanced cervical cancer - chemo-radiation - disease free survival - recurrence - remote metastasis

Asian Pacific J Cancer Prev, **11**, 1091-1097

Introduction

Cancer of the uterine cervix is the commonest cancer among rural women and occupies the second rank among urban women in India (National Cancer Registry Programme, 2008). The estimated number of new cancers of the cervix per year globally is 500,000 of which India's contribution is nearly 100,000 (Ferlay et al., 2004). The burden of cervical cancer is compounded by late disease at presentation which constitutes our major therapeutic problem. Over the last two decades there has been only a small change in the stage distribution of cervical cancers. Locally advanced cervical cancers (LACC) which include IIB, III and IVA, according to FIGO classification (Hermanek and Sobin, 1987), constitute over 70% of all cases (Shanta et al., 2008). This study is based on the largest series of cervical cancer cases from a single institution and presents a retrospective analysis of disease free survival and other outcomes in relation to evolution of treatment protocol and various other related factors.

Materials and Methods

Cases

A total of 3,892 LACC cases treated at the Cancer Institute (WIA), Chennai, India, between 1990 and 1999 formed the study material. For the present purposes, cases in stages IB, IIA and IVB were excluded from the analyses.

Variables

The variables analyzed in relation to 5, 10 and 15-year survival were age at diagnosis, histology type, stage and treatment modality.

In addition, patterns of recurrence in those who achieved a complete response at 8 weeks, survival in cases that recurred as against those who never recurred, outcome of salvage treatment, remote metastases and second cancers in survivors were studied.

Morbidity and late complications did not form part of the present study.

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Evolution of treatment for LACC

Management of LACC at the institute has evolved on the basis of experience from randomized controlled clinical trials conducted at the Institute, the world experience data and our own data on survival. This has enabled the formulation of a standard protocol with minimal variation wherever necessary for individual cases in the treatment of LACC.

Pre-treatment evaluation Careful pre-treatment evaluation can make a significant difference in overall survival. In the years under study (1990-1999), only the traditional staging work-up was done consisting of careful pelvic and bimanual pelvic examination and if necessary an examination under anesthesia by an experienced gynecologist. Complete hematology, biochemical profile, radiogram chest, either IVP radiograph or ultra sonogram of the kidney for evidence of obstructive uropathy and evaluation of pelvic and para-aortic nodal enlargement to the extent possible by ultra sonogram only were advised. Although CT scan was available, we did not use routine CT scan. During this period, we did not have MRI.

Biopsy and histological study were mandatory. Any co-morbid conditions like hypertension, diabetes, were evaluated and stabilized. Cytology was a routine follow-up procedure. Surgical staging at the institute was done only as a study project in stages I, IIA and IIB disease. The upstaging in stage IIB at the institute was 28% (unpublished data). Gynecologic Oncology Group (GOG) has documented para-aortic nodal disease in 21% of IIB cases (Heller et al., 1990). We had not practiced routine surgical staging in LACC.

Radiotherapy Radiotherapy (RT) is accepted as the primary treatment of locally advanced cervical cancers. Using conventional dose with acceptable morbidity, RT in LACC failed to eradicate pelvic disease in nearly 60% of cases. Dose escalation enhances morbidity significantly. Bulk of disease (tumor volume) increases the proportion of patients with residual pelvic disease. A fallacy in the FIGO staging is that it does not provide for volume of disease in staging (Lee et al., 2010). Nodal disease is not evaluable clinically and does not form a part of FIGO staging (Hermanek and Sobin, 1987). Today, volume determination and nodal status are evaluated by CT and MRI and recommended for treatment planning.

Enhancing Radiation Responses Efforts to enhance or improve radiation response commenced at the institute in 1966 and consisted of a series of randomized controlled clinical trials. It was initially radio-sensitization studies

Table 1. An Overview of Trials on Locally Advanced Cervical Cancers at Cancer Institute (WIA)

Calendar period	Trial details	Number of cases	5-year DFS	Survival benefit
	2-arm trials: Stages IIB and III			
1966	Radiotherapy (RT) only	74	14.8	
	RT+SPI/SPG	71	31.0	p<0.001
1966	RT only	20	30.0	
	RT+Peptichemo	20	40.0	↑
1978	RT only	24	37.5	
	RT+BLM	23	56.5	↑
1995-96	RT only	71	46.6	
	RT+BLM+Etoposide	76	56.7	↑
1996-98	RT only	100	46.0	No change
	RT+Hydroxy	100	48.0	
1999	RT only	50	74.0	
	RT+Hyperthermia	50	82.0	↑

Calendar period	Trial details	Number of cases	5-year DFS% by stage	
			IIB	IIIB
1995-1996	4-arm randomized trial in Stages IIB & IIIB: RT vs. RT+Chemotherapy			
	RT only	96	46.1	30.4
	RT+BLM+CDDP	90	52.1	42.8
	RT+BLM+Iphos+CDDP	91	47.8	44.8
	RT+BLM+Endoxan+CDDP	85	59.5	32.5

Calendar period	Trial details	Number of cases	3-year DFS% by stage	
			IIB	IIIB
1999-2003	2-arm trial: Intracavitary in LCCR			
	Low dose rate (LDR)	182	68.0	68.2
	High dose rate (HDR)	155	53.7	60.3
	All stages together	337		
	LDR	176	61.4	
	HDR	161	64.6	

followed by chemo-radiation. All our randomized trials were concurrent chemo-radiation (CCRT) (Krishnamurthi et al., 1967; Shanta, 2001; Vasanthan et al., 2005) as opposed to adjuvant or neo-adjuvant therapy. The advantages of CCRT were avoiding delay in starting definitive treatment (RT), avoiding prolongation of treatment period and the two modalities could be additive. This has been subsequently confirmed by meta-analysis in head and neck cancers (Pignon et al., 2009) and experience in cervical cancers (Green et al., 2005). Cervical cancer trials at the Cancer Institute (WIA) were all randomized double blind controlled clinical trials of RT only vs. CCRT in LACC comprising stages IIB and III only. Early stage disease was not included.

The SPI-SPG, BLM and BLM + Etoposide and Hyperthermia trials (1965 onwards) did show a survival benefit to the chemotherapy arm but the series were small (Table 1). Moreover they were single centre trials. The four arm trial in 1996-99 (Table 1) showed both complete response and survival benefit only for stage IIB but not for stage III. The morbidity in the multiple drugs arm was significant and therefore not considered acceptable. A study of RT vs. RT+CDDP was being planned when the National Cancer Institute alert came in 1999 (National Cancer Institute, 1999).

Our trial comparing LDR vs. HDR did not document any significant change in survival (Nag et al., 2002) (Table 1). The morbidities were minimally different but acceptable.

Conclusions from Cancer Institute (WIA) trials and global trials Chemo-radiation did enhance radiation response and this was related to tumor volume. The response was more in stage IIB than in stage III. Multiple drugs increased morbidity but did not enhance response. The most quoted major world trials with remarks are summarized in Table 2: RTOG 9001 trial (Morris et al., 1999) included stages IB-IV of which, 70% belonged to Stages IB & IIB. GOG 85 trial (Whitney et al., 1999) included stages IIB to IV and GOG 120 trial (Rose et al., 1999) included Stages IIB to IV of which, 75% were IIB. The chemotherapy drug used, dose and mode of administration were different and not comparable. The RT protocol, the dose delivered and overall time showed considerable variations. All stages were grouped together and the percentage of LACC (stage III) was small. In majority of trials, there was no control arm of RT only and the comparison was based on retrospective conventional RT results. It was at that time that the NCI alert recommending weekly cisplatin for all LACC came in 1999 (National Cancer Institute, 1999).

Concurrent Radiation + Chemotherapy Appendix 1 gives the details of radiation therapy including ICRU-38 recommendations (ICRU Report 38, 1985) and chemotherapy protocols practiced at the institute during 1990-99. This includes external beam radiation delivered using 4 or 6 mv X-rays from a linear accelerator and intra-cavitary application during external beam radiation. During this period, chemotherapy schedules were not uniform. However, the modality was always concurrent chemo-radiation. The radiotherapy schedule was uniform for each group.

Statistical methods

The descriptive statistics of the variables studied are represented as two-way tables giving the number and frequency (%) of cases. The differences in the proportions were tested for statistical significance using non-parametric Chi-square test. Cases were followed up until December 31, 2007. Disease free survival (DFS) time was computed in months between date of diagnosis and date of death or recurrence or remote metastasis or second cancer or loss to follow up or closing date of follow up, whichever was earlier. DFS was estimated by actuarial method (Cutler and Ederer, 1958). Differences between survival curves were tested using the log-rank test (Mantel, 1966). Cumulative risk of getting second cancer was estimated using Kaplan-Meier method (Kaplan and Meier, 1958).

Results

Frequency of cas es by treatment modality and stage

Majority belonged to stage III (54%) followed by stage IIB (44%) and IVA (2%) (see Table 3). The treatment modalities were external beam RT only (EBRT; 1371 cases), EBRT + concurrent chemotherapy (CCRT; 386), EBRT + Brachytherapy (1991), EBRT+ concurrent chemotherapy + Brachytherapy (CCRT + Brachytherapy; 78) or EBRT followed by salvage surgery (62).

DFS by treatment modality and stage (Table 3)

Complete follow up at 5 years was available for 90% of

Table 2. An Overview of Major World Trials on Chemo-Radiation in Locally Advanced Cervical Cancers

Study group (Stage)	Trial arm	Result	Remarks
RTOG 9001[14] (IB-IV)	Pelvic RT + CDDP + 5FU	Benefit to IB and IIB only	No RT only control arm; 70% cases belonged to stages IB and IIB
A number of small trials (IIB-IV)	RT + weekly CDDP (or) RT + twice-weekly CDDP	No benefit	Series small
GOG 85[15] (IIB-IV)	RT + HU vs. RT + CDDP + 5 FU	Benefit to CDDP arm	No RT only control arm; Toxicity significant; Not confirmed by other studies
GOG 120[16] (IIB-IV)	RT + 3 chemotherapy regimen: HU, HU+CDDP, HU+CDDP+5 FU	Benefit to CDDP arm	No RT only control arm; 75% of IIB cases; Benefit by stage not available

RT: Radiotherapy

Table 3. Disease Free Survival % by Modality of Treatment and Stage for Locally Advanced Cervical Cancer Cases in Chennai Treated During 1990-1999

Modality of treatment	Stage	Cases		Disease free survival%		
		Number	%	5-year	10-year	15-year
External Beam RT (EBRT) only		1371	35.2	37	29	24
	IIB	414	30.2	49	39	32
	III	871	63.5	32	26	21
	IVA	86	6.3	23	20	20
Concurrent chemoradiation (CCRT) (EBRT+chemotherapy)		386	9.9	41	35	31
	IIB	168	43.5	50	44	38
	III	218	56.5	34	28	26
EBRT+Brachytherapy		1990	51.1	58	48	42
	IIB	1028	51.7	61	51	44
	III	954	47.9	54	45	40
	IVA	8	0.4	50	-	-
CCRT + Brachytherapy		78	2.0	69	69	63
	IIB	45	57.7	77	77	67
	III	33	42.3	58	58	58
EBRT+Surgery (Salvage)		67	1.7	71	63	63
	IIB	62	92.5	74	65	65
	IIIB	5	7.5	40	-	-
All modalities together						
	IIB	1717	44.1	58	49	42
	III	2081	53.5	43	35	31
	IVA	94	2.4	25	22	22
All modalities and stages together	IIB-IVA	3892	100.0	49	41	36

RT: Radiotherapy

the cases with a median follow up of 93 months for those alive in this series. EBRT alone, in the doses delivered in this study, resulted in a 5-year DFS of 49% and 32% in stages IIB and III respectively. Concurrent chemo-radiation (CCRT: EBRT + chemotherapy) increased 5-year DFS only marginally to 50% in stage IIB and 34% in stage III which was not statistically significant. Brachytherapy + EBRT as treatment modality enhanced the DFS to 61% in stage IIB and 54% in stage III patients ($p<0.001$) while CCRT + brachytherapy resulted in the best DFS: 77%, 77% and 67% at 5, 10 and 15 years respectively for stage IIB and 58% for stage III ($p<0.001$).

Role of Salvage Surgery (Table 3)

The number of patients who were suitable for salvage surgery was small and applicability was low. In a carefully selected group, the long-term DFS was 71%, 63% and 63% at 5, 10 and 15 years respectively for stages IIB and III together. Surgery, of course, was not easy and carried significant morbidities which could be reduced with experience. Surgery in stage IIB cases could be Wertheim's hysterectomy but in Stage III, it had to be an exenterative procedure. A planned pre-operative chemo-radiation and surgery is certainly a good option.

This highlights an important fact that in oncologic care, the first treatment is the best and the best salvage treatment can never be as good as the initial treatment.

Complete response and recurrence by stage of disease and treatment modality (Table 4)

Complete response (CR) at 8 weeks, characterized as not having clinical local pelvic or cytological residue in 3892 LACC cases treated by radiation, irrespective of modality was achieved in 2617 patients (67.2%). There was residual disease in the rest (32.8%). CR and residual disease at 8 weeks were directly related to stage of disease and modality of treatment. CR was the lowest (63.9%) in EBRT only (stage IIB:76.8%; stage III:59.9%) and the highest (82.1%) in CCRT + Brachytherapy (stage IIB:88.9%; stage III:72.7%). The data more than clearly reiterated the fact that whatever combination of treatment was used, tumor volume or stage of disease continued to be the major factor in CR and therefore in DFS. The CR and DFS have been significantly improved by combination of CCRT + Brachytherapy.

Among 2617 patients who achieved CR at 8 weeks, 395 (15.1%) recurred and 2222 patients never recurred (84.9%). Recurrences were significantly lower among stage IIB than stage III patients who received EBRT only ($p=0.01$). Recurrences among all stages together were significantly lower ($p=0.04$) among those who received CCRT + brachytherapy (7.8%) than EBRT only (17.7%). The differences were either minimal or were statistically not significant in the rest (Table 4). The DFS at 5, 10 and 15 years for patients of all stages together who never recurred were 70%, 61% and 56% respectively. The corresponding DFS figures were 78%, 67% and 57% for stage IIB and 70%, 58% and 57% for stage III respectively. Survival in those who recurred was dismally poor with a DFS of 13% at 5 years (data not shown).

Pattern of recurrence, remote metastasis and second cancer (Figure 1)

Of the 395 who recurred, 329 (83.3%) had only local recurrence, 66 had a local recurrence with remote metastasis and 4 patients had recurrence with second

Table 4. Complete Response and Recurrence Pattern by Modality of Treatment and Stage of Locally Advanced Cervical Cancer in Chennai, 1990-99

Treatment modality	Stage	Total number of cases	Complete response (CR)		Recurrence (out of CR cases)	
			Number	%	Number	%
External Beam RT (EBRT) only		1371	876	63.9	155	17.7
	IIB	414	318	76.8	43	13.5
	III	871	522	59.9	106	20.3
	IVA	86	36	41.9	6	16.7
Concurrent chemo-radiation (CCRT) (EBRT + chemotherapy)		386	252	65.3	52	20.6
	IIB	168	125	74.4	31	24.8
	III	218	127	58.3	21	16.5
EBRT + Brachytherapy		1990	1373	69.0	178	13.0
	IIB	1028	828	80.5	101	12.2
	III	954	541	56.7	77	14.2
	IVA	8	4	50.0	0	0.0
CCRT + Brachytherapy		78	64	82.1	5	7.8
	IIB	45	40	88.9	3	7.5
	III	33	24	72.7	2	8.3
RT + Surgery (Salvage)		67	52	77.6	5	9.6
	IIB	62	48	77.4	4	8.3
	IIIB	5	4	80.0	1	25.0
All modalities and stages together	IIB-IVA	3892	2617	67.2	395	15.1

cancer. Of 2222 who never had any recurrence, 262 (11.8%) developed remote metastasis and 20 (0.9%) reported with second cancers on follow up. On the whole, 498 (12.8%) developed remote metastasis with the following pattern: Lung only (94; 19%), liver only (23; 4.6%), bone only (46; 9.2%), multiple sites (13; 2.6%), nodes involving supraclavicular, mediastinal and para-arotic (316; 63.4%) and peritoneum (6; 1.2%). A total of 36 (0.9%) patients developed second cancers: pelvis (10: bladder, endometrium, vagina, vulva and urethra), breast (7), thyroid (6), lung (3), leukemia (2), skin (2) and one each of sarcoma, parotid, stomach, rectum, esophagus and sigmoid colon. The cumulative risk of developing any second cancer was 0.5% at 5 years, 1.9% at 10 years and 2.8% at 15 years of follow up (Figure 2).

DFS by age at diagnosis and histology type (Table 5)

A majority of cases were between 30 and 59 years of age (83.2%) and with squamous cell carcinoma and its variants (95.1%). DFS at 5, 10 and 15 years were decreasing with increasing age groups but the trend was statistically not significant (p=0.989). DFS was significantly higher in squamous cell carcinoma compared to adeno and adenosquamous carcinomas (p<0.001). Metastatic potential in adeno or adenosquamous carcinomas (17%) was significantly higher (p=0.05)

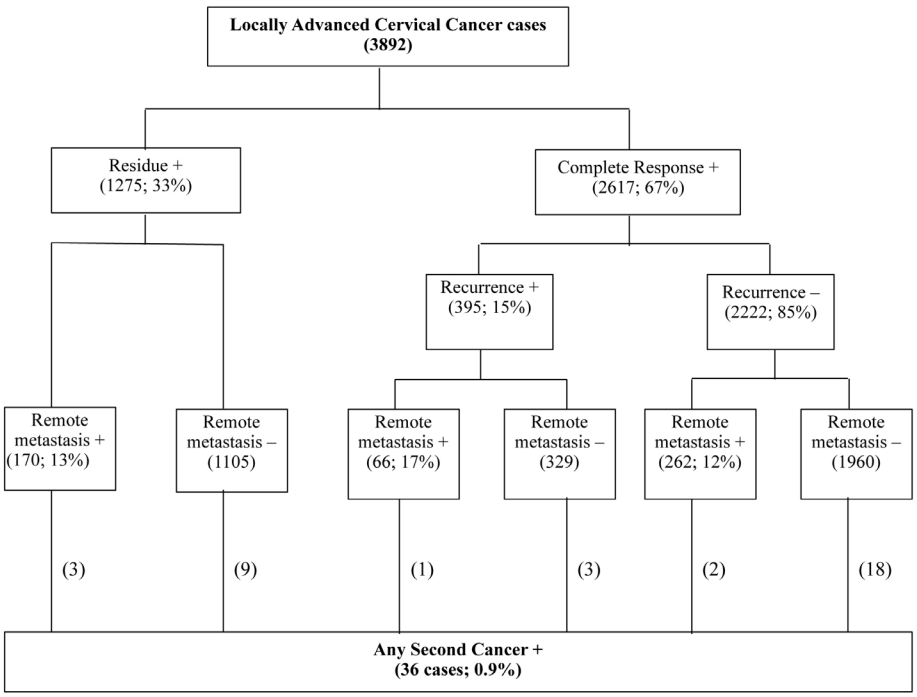

Figure 1. Pattern of Complete Response, Recurrence, Remote Metastasis and Second Cancer Among Cervical Cancers in Chennai, 1990-1999

Table 5. Disease Free Survival % of Age at Diagnosis and Histology Type for Locally Advanced Cervical Cancer Cases in Chennai Treated During 1990-1999

Modality of treatment	Cases		Disease free survival%		
	Number	%	5-year	10-year	15-year
Age at diagnosis					
Less than 30 years	68	1.7	54.5	47.6	47.6
30-59 years	3239	83.2	49.5	42.0	36.6
60 years and above	585	15.1	46.5	34.5	28.3
p-value				0.989	
Histology type					
Squamous cell carcinomas	3702	95.1	50.1	42.1	36.5
Adenosquamous carcinoma	76	2.0	31.4	18.0	18.0
Adenocarcinomas	114	2.9	28.9	22.8	22.8
p-value				<0.001	

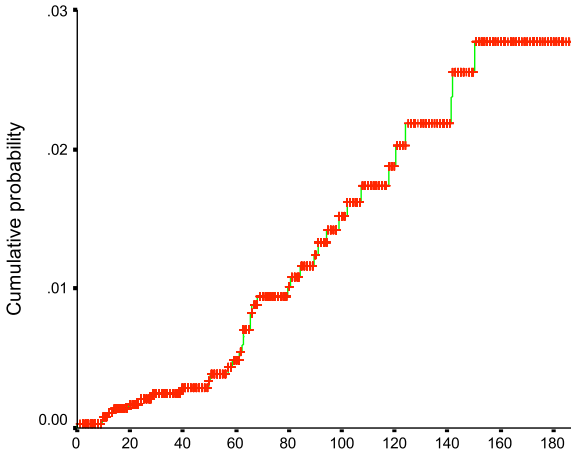

Figure 2. Risk of Second Cancer Following Cervical Cancer in Chennai (Cases Registered in 1990-1999 and Followed Through 2007)

than in squamous cell carcinomas (12%). Small cell and neuro-endocrine carcinomas started appearing only after the year 2000. We are unable to explain this.

Discussion

Follow up is often the impediment in the conduct of long-term survival studies in a developing environment. Passive follow up is often inadequate when population mortality data registration and linkage facilities are depleted. To counter the lacunae, the hospital cancer registry at the Cancer Institute (WIA), Chennai, had evolved an effective active follow up system that is integrated with registry operations. In this case series, the completeness of follow-up at 5-years was 90% which was the highest among all registries in India.

The most credible yardstick to measure treatment outcome is long-term disease free survival. Clinical trials that provide only short term overall survival and projected DFS can be misleading. The trials conducted at the institute and the DFS of retrospective data by stage of disease and modality of treatment received over the years formed the basis of our present therapeutic strategy for LACC. The results speak for themselves in this case series. EBRT alone as a treatment modality reported the poorest survival and therefore was inadequate as a curative option. While concurrent chemo-radiation (CCRT: an addition of chemotherapy to EBRT) resulted only in a marginal increase in DFS, inclusion of brachytherapy to EBRT enhanced the DFS significantly. Also, brachytherapy as a planned component of radio-therapeutic management of LACC consisting of concurrent chemo radiation (CCRT + brachytherapy) resulted in the best DFS in this series irrespective of disease stage. It was also observed that both of these treatment modalities (EBRT + brachytherapy and CCRT + brachytherapy) emerged as independent prognostic factors for DFS after adjusting for the effects of age at diagnosis, histological type and stage of disease in the multifactorial analysis in this series. Thus, with careful planning and sequencing of treatment, a gradual but significant improvement both in overall and DFS can be achieved.

A limited analysis of treatment time in this case series in relation to response and survival at the institute stresses the importance of overall treatment period in survival. When the treatment time was less than 56 days, residual disease was seen in 2% of cases whereas when the treatment time was over 56 days residue was seen in 7.5% cases. This confirms the pattern of cancer care study (Lanciano et al., 1991).

In conclusion, based on the data accrued and with the present state of knowledge, the recommended standard treatment for locally advanced cancers of the cervix is careful pre-treatment evaluation followed by concurrent chemo-radiation (CCRT: EBRT + chemotherapy) which includes CCRT +Brachytherapy. The addition of brachytherapy significantly enhances survival. The standard chemotherapy in our experience will be weekly Cisplatin 40mgm/m^2 IV infusion for 4 - 6 weeks based on patient tolerance.

The overall treatment time is an important component in survival and the recommended period is 56 days. The end result of treatment will depend on careful pre-treatment evaluation and planning based on volume of disease. Today, imaging (CT and MRI) plays an important role in planning RT for LACC. This was not done in the period 1990-1999 for this case series.

Our results have enhanced significantly following a standard protocol that has been evolved based on the above experience. Currently, the 3-year DFS of 413 LACC cases registered in 2006 is nearly 75%. Thus, our data indicate a very satisfactory treatment outcome even in advanced disease.

Acknowledgment

The authors are grateful to the team of medical and para-medical staff of gynecology oncology department, staff of the tumor registry and related departments at the institute for their diligence in patient care and documentation of data.

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Appendix 1. Concurrent Radiation + Chemotherapy Protocols Followed during 1990-99 at the Cancer Institute (WIA), Chennai, India.

A. Radiation Therapy: External beam radiation was delivered using 4 or 6 mv X-rays from a linear accelerator. A four field box technique was generally used, superiorly at L4, L5 interspace to include iliac nodes and extending up to L3, L4 interspace if common iliac coverage was planned or indicated. The lateral margins were beyond the pelvic brim by 1 cm and the lower margin was the inferior border of the obturator foramen. Vaginal coverage was based on extent of vaginal involvement. The anterior margin of the lateral portal was the symphysis pubis and posterior margin designed to cover the sacral hollow. Treatment was on five days per week with a fractionation of 200 CG per day.

B. Intra-cavitary Treatment: Patients were assessed for feasibility of intra-cavitary application during external beam radiation, initially at 40 Gy. Whole pelvic irradiation of 4000 cGy was followed by one LDR application to deliver a dose of 30 Gy at point A or three HDR applications of 800 cGy each delivering a total dose of 24 Gy. When whole pelvic irradiation was given to a dose of 5000 cGy initially, 1 LDR application was done to deliver a dose of 23 Gy at point A or 2 HDR applications of 800 cGy each delivering a total dose of 16 Gy. The supplementary parametrial irradiation takes into account the dose received by Point B from the intra-cavitary applications and raises the dose given to achieve a dose of 65–70 Gy. Intra-cavitary application is usually done within a period of 5–7 days from the completion of external beam radiation therapy. The overall treatment time is between 56–60 days. Dose to Point A, Point B, bladder and rectum were reported as per International Commission on Radiation Units and Measurements (ICRU–38) recommendations [17].

C. Chemotherapy Protocol: During this period chemotherapy schedules were not uniform. However, the modality was always concurrent chemo-radiation. The radiotherapy schedule was uniform for each group.

C.1 4-arm double blind controlled clinical trial

C.1.1 Arm 1: Radiation therapy with placebo. Days 1 to 3: Two units of dextrose normal saline were infused as placebo. Radiation was started on day 8 and the placebo cycle was repeated at 30Gy external radiation and radiation was not given during those 3 days.

C.1.2 Arm 2: Radiation therapy with Bleomycin and Cisplatin. Day 1: Bleomycin 30mg was given as 24 hours intravenous infusion. Day 2: Cisplatin 50mg/m2 was given as 24 hours infusion. Day 3: Two units of dextrose normal saline as hydration.Radiation was started on day 8. Chemotherapy cycle was repeated at 30 Gy of external radiation and radiation was not given during those 3 days.

C.1.3 Arm 3: Radiation therapy with Bleomycin, Cisplatin and Ifosphomide. Day 1: Bleomycin 30mg was given as 24 hours intravenous infusion. Day 2: Cisplatin 50mg/m2 was given as 24 hours infusion.Day 3: Ifosphamide 3gm/m2 was given as 24 hours infusion along with mesna. Radiation was started on day 8. Chemotherapy cycle was repeated at 30 Gy of external radiation and radiation was not given during those 3 days.

C.1.4 Arm 4: Radiation therapy with Bleomycin, Cisplatin and Cyclophosphomide. Day 1: Bleomycin 30mg was given as 24 hours intravenous infusion. Day 2: Cisplatin 50mg/m2 was given as 24 hours infusion. Day 1 to 5: Cyclophosphamide 500mg was given as intravenous bolus. Radiation was started on day 8. Chemotherapy cycle was repeated at 30 Gy of external radiation and radiation was not given during those 5 days.

C.2 Hydroxyurea as a radiation sensitizer. The patients in the st udy arm received hydroxyurea at a dose of 80 mg/kg body weight, per oral, two hours prior to radiation, every Monday and Thursday. The patients in the control arm received placebo tablets at the same time. A total of 200 patients were entered into the trial.

C.3 Etoposide trial. This was a randomized clinical trial to determine the response rates, duration of response and survival after the treatment of long-term twice daily low-dose oral etoposide and 5-week low-dose bleomycin with concomitant use of hyperfractionated radiotherapy.
Arm 1: Radiotherapy + chemotherapy
Arm 2: Radiotherapy + placebo
Radiotherapy: Radiotherapy was given daily, 5 days/week (1.8 Gy/fraction) to a total dose of 50.4 Gy in 28 fractions over a period of 5 weeks. After 1 week rest, intra-cavitary brachytherapy was given, 2 days/week (5 Gy/fraction) to a total dose of 25 Gy in 5 fractions.
Chemotherapy: Oral etoposide (25 mg twice daily) for 3 weeks followed by no drug for 1 week, 6 such cycles were given. 5 mg/m2 of bleomycin in 500 ml of saline was infused for 5 days a week during the days of external beam radiation up to 50.4 Gy.