A DISSERTATION ON

NEW COMBINED MODALITY TREATMENT FOR STAGE II B CERVICAL CANCER

SUBMITTED TO

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY
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BONAFIDE CERTIFICATE

This is to Certify that **Dr.P.Arulraj,** bonafide student of M.Ch., Surgical Oncology (August 2004 to August 2007) in the Department of Surgical Oncology, Government Royapettah Hospital, Chennai - 600 014. has done this dissertation on **"NEW COMBINED MODALITY TREATMENT FOR STAGE II B CERVICAL CANCER "** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M.G.R. Medical University, Chennai for M.Ch. Surgical Oncology Examination to be held in August 2007.

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CONTENTS

INTRODUCTION

Cancer cervix is the second commonest malignancy among women globally, with over 4,50,000 cases detected annually and accounting for almost 2,10,000 deaths per year. During the past 5 decades the incidence of invasive cervical carcinoma has dropped dramatically which is attributed to the development of effective screening techniques for identification of pre-invasive lesions.The scenario, however, is still grim in the developing world wherein a combination of inadequate screening facilities, social stigma and ignorance contribute to patient presenting with locally advanced disease.

NATURAL HISTORY

INCIDENCE

The incidence of cancer cervix varies from country to country and from race to race. The highest incidence rates are reported from Asia, South America and Africa. In India, cancer cervix constitutes 20 – 50% of all cancers detected in women. The incidence of cancer cervix among the various cancer registries of the country ranges from 19 – 44 per 1,00,000 women (mean 31.4 per 1,00,000 women). In Chennai as per MMTR (Madras Metropolitan Tumor Registry) statistics the incidence of cancer cervix is 26.9 / 1,00,000 women which accounts for 21.11% of the total cancer incidence.

PREDISPOSING FACTORS:

The major predisposing factors of cancer cervix include poor physical as well as sexual hygiene.

1. **Female sexual behavior**

a) **Sexual intercourse**-This is the major prerequisite for the development of squamous cell carcinoma of cervix.

b) **Age at first coitus** – Women who start their sexual life at an early age particularly before 18 years are at higher risk (1.4 to 1.9 times increased risk) of developing cancer cervix.

c) **Multiple sexual partners** – Cancer cervix patients usually give a history of multiple sexual partners. The risk is doubled for women with 6 sexual partners.

d) **Parity** – Risk factors related to parity include first child birth at an early age and multiparity.

2. **Male sexual behavior (high risk male) –**

High risk male sexual habits, the presence of which is associated with a higher incidence of cancer cervix in their spouses are:-

a) **Sexual promiscuity**: >3 extra marital partners

b) History of **sexually transmitted disease**

c) **Poor penile hygiene**: Causative role of cigarette smoking in male and the protective effect of male circumcision are controversial.

3. **Lower socio-economic group**

Women from a lower socio-economic group have a higher incidence (about 3 fold) of cervical malignancy due to early marriage, early onset of sexual life and lack of genital hygiene.

4. Viral etiology

a) **HPV** (Human Papilloma Virus) – Among various agents, the HPV virus is considered to be the most likely candidate for etiological responsibility. Infection with HPV serotypes 16 & 18 are highly prevalent in CIN-II, III and invasive cancer cervix. HPV exerts its effect by P-53 gene suppression and inhibition of cell mediated immunity.

b) **HIV** (Human immunodeficiency virus) – Women who are HIV positive have a 10 fold risk of cervical cancer in comparison with matched controls. Prevalence of cancer cervix in HIV positive patients below the age of 50 years is 19%.

c) **HSV** (Herpes simplex virus) – There is much data suggesting an association between cancer cervix and HSV but no conclusive evidence is available.

Smoking – Smoking appears to double the risk of developing cervical cancer. Apart from the above mentioned factors, higher risk of adenocarcinoma of cervix is associated with obesity, diabetes, hypertension and prenatal exposure to Diethyl stilbesterol (clear cell adenocarcinoma).

FIGO Staging: The primary tumor (T) is staged in the following way:

Stage 0 - Carcinoma in situ(Preinvasive carcinoma).

Stage I - Cervical carcinoma confined to uterus.

Stage I A -Invasive carcinoma diagnosed by microscopy with stromal invasion is not > 5 mm in depth and 7 mm wide.

Stage I A 1 -Stromal invasion is <3 mm in depth and <7 mm in width. This is also called micro invasive carcinoma.

Stage I A 2 -Stromal invasion 3 mm -5 mm in depth and <7 mm in width.

Stage I B - Visible tumor only on the cervix or by microscopy is >5 mm in depth and 7 mm wide.

Stage I B1 - Visible tumor is ≤ 4 cm (1.6 in.).

Stage I B2 - Visible tumor is > 4 cm (1.6 in.) in size.

Stage II - Beyond the uterus but not the pelvic wall or the lower third of the vagina.

Stage IIA - Tumor does not involve the parametrium .

Stage IIB -Tumor extends into the parametrium not up to the side wall .

Stage III -The tumor extends to the pelvic wall or involves the lower third of the vagina or causes an obstructed or a nonfunctioning kidney.

Stage IIIA - Tumor involves lower third of vagina but no extension into the pelvic wall.

Stage IIIB - Tumor extends to pelvic wall or causes an obstructed kidney or nonfunctioning kidney.

Stage IVA - Tumor invades the lining of the bladder or rectum, or

extends beyond the pelvis.

Stage IV B – Distant metastasis.

STAGE GROUPING

0	Tis	N0	M0
I	T1	N0	M0
IA	T1a	N0	M0
IA1	T1a1	N0	M0
IA2	T1a2	N0	M0
IB	T1b	N0	M0
IB1	T1b1	N0	M0
IB2	T1b2	N0	M0
II	T2	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
III	T3	N0	M0
IIIA	T3a	N0	M0
IIIB	T1,T2,T3a T3b	N1 AnyN	M0
IVA	T4	AnyN	M0
IVB	AnyT	AnyN	M1

PROGNOSTIC FACTORS

1. **Stage of the disease** – Prognosis in cervical cancer worsens with advancing stage of the disease. The size of the primary tumor (disease bulk) and the depth of invasion into the cervix were found to be associated with increased recurrence rate and poor survival.
2. **Pelvic lymph node involvement** – Several researchers reported increased recurrence rates and decreased survival with lymphovascular invasion and nodal metastasis.
3. **Parametrial involvement** – The extent of parametrial involvement was again found to correlate adversely with survival.

Extent of parametrial involvement and prognosis

Stage	Extent of parametrial disease	Survival (5 yrs)
II B	Unilateral involvement	70%
II B	Bilateral involvement	58%
III B	Unilateral involvement	48%
III B	Bilateral involvement	28%

5) **Histology** – Fuller ***et al.*** reported increased recurrence rates with patients having adenocarcinoma in comparison with those having squamous histology.

6) **Grade** – Fuller ***et al.*** found that the higher histological grade was associated with an increased incidence of recurrence.

7) **Age** – Age at the time of diagnosis was found to have no effect on prognosis, although some researchers observed a decrease in survival for very young patients and for older patients.

8) **Ploidy** – It was found that there were no statistically significant differences in recurrence rates for patients with diploid and aneuploid tumors. More relapses were noted with tumor S-phase fraction greater than 20%.

9) **Overall treatment time** – Perez ***et al.*** have reported that the pelvic control and disease free survival rates are lower for those patients whose treatment time exceeds 7 weeks.

10) **Patient factors** – Mandelblatt ***et al.***. have shown that anemia (Hb <10gm%), platelet count, socio-economic status and smoking were associated with increased pelvic recurrences and decreased survival.

11)

OVERVIEW OF TREATMENT POLICY IN CANCER CERVIX:

All the three standard modalities of treatment namely surgery, radiation and chemotherapy have stamped their role in the different stages of the disease.

Primary Treatment

After careful clinical evaluation and staging, the primary treatment of early-stage cervical cancer is either surgery or radiation therapy. A randomized Italian study compared RT alone versus radical hysterectomy and lymph node dissection. This study used adjuvant RT after surgery for women with surgical stage pT2b (which corresponds to FIGO stage IIB) or more extensive disease. The NCCN panel reached a general agreement, based on the results of five randomized clinical trials, that RT and concurrent cisplatin-based chemotherapy (either cisplatin alone or cisplatin/5-fluorouracil [5-FU]) should be the treatment of choice for stages IIB, IIIA, IIIB, and IVA disease.

Surgery is typically reserved for lower-stage disease and smaller lesions, such as stage 1A and 1B1 and non bulky IIA. Of interest, the French National Federation of Cancer Centers have also updated their guidelines (Standards, Options, and Recommendations [SOR] project) by stating that chemoradiotherapy should be the standard for women with bulky cervical cancer. Extrafascial Type I hysterectomy is recommended for patients with clinical stage IA1 disease; another option is modified radical hysterectomy with pelvic lymph node dissection if lymphovascular invasion is present. However, if the patient is medically inoperable or if fertility is desired, patients with negative margins from cone biopsy could undergo observation. Stage IA2 tumors

can be treated with radical hysterectomy and pelvic lymph node dissection with or without para-aortic lymph node sampling. Brachytherapy with pelvic radiation (point A dose: 75-80 Gy) is another treatment option. These doses are recommended for most patients based on summation of conventional external-beam fractionation and low-dose-rate (40-60 cGy/h) brachytherapy equivalents. Treatment should be modified based on normal tissue tolerance. For patients who desire fertility preservation, radical trachelectomy and lymph node dissection are recommended.

Among panel members, there was some disagreement about the primary approach for stage 1B2/IIA disease. Patients with stage IB1or non bulky IIA tumors can be treated effectively with radical hysterectomy plus bilateral pelvic lymph node dissection with para-aortic node sampling or with combined pelvic radiotherapy and brachytherapy. Substantial discussion occurred about the optimal management of stage IB2 and bulky IIA (greater than 4 cm) disease. For patients with clinical stage IB2 or IIA tumors (greater than 4 cm) who are treated with radiation, concurrent cisplatin-containing chemotherapy has been shown to significantly improve patient survival. The addition of concurrent chemoradiation significantly improves progression-free and overall survival for high-risk patients with early-stage disease (those with positive lymph nodes, parametrial extension, and/or positive margins) who undergo radical hysterectomy and pelvic lymphadenectomy. For stage IB2 or IIA tumors (greater than 4 cm), the panel disagreed about recommending adjuvant hysterectomy for patients undergoing primary chemoradiation.

The EORTC is currently conducting a phase III randomized trial (EORTC 55994) of neoadjuvant cisplatin based chemotherapy followed by surgery compared with RT plus chemotherapy in patients with stage IB or II cervical cancer. For patients with more advanced tumors who are undergoing primary chemoradiation, the volume of RT is critical and is guided by assessment of nodal involvement in the pelvis and para-aortic nodes. Imaging studies (CT or MRI and/or PET scan) are recommended for selected bulky stage IB2 or higher disease.

However, fine-needle aspiration (FNA) is needed to confirm suspicious lymph nodes seen on radiologic imaging. Surgical staging (i.e., extra peritoneal or laparoscopic lymph node dissection) is also recommended for these patients. If node sampling is performed and indicates positive findings, intraoperative radiotherapy (IORT) should be considered for bulky residual nodes. For patients without nodal disease or with disease limited to the pelvis only by surgical staging, treatment consists of pelvic RT with concurrent chemotherapy. However, for patients with positive para-aortic and pelvic lymph nodes, retroperitoneal lymph node dissection should be considered followed by extended-field RT, cisplatin-containing chemotherapy, and brachytherapy. Patients with positive para-aortic lymph nodes who are positive for distant metastases are treated with systemic chemotherapy and individualized RT.

Adjuvant treatment

Adjuvant treatment is indicated after radical hysterectomy depending on surgical findings and disease stage. For small-volume tumors (4 cm or less) in stage IA2, IB1, or IIA, if lymph nodes are found negative in the surgery, patients should undergo close observation or receive pelvic radiation if deep stromal invasion or LVSI is present.

Adjuvant pelvic RT alone versus no further therapy was tested in a randomized trial (Gynecologic Oncology Group [GOG] 92) of selected patients with stage IB carcinoma of the cervix after hysterectomy and pelvic lymphadenectomy. Patients were eligible for this trial after radical hysterectomy and pelvic lymphadenectomy if they had at least two of the following risk factors: (1) greater than one-third stromal invasion; (2) capillary lymphatic space involvement; or (3) large cervical tumor diameters. Patients with positive lymph nodes or involved surgical margins were excluded. A statistically significant decrease in recurrence was found in the RT arm compared with the no additional treatment arm (15% versus 28%). Life-table analysis indicated a statistically significant (47%) reduction in risk of recurrence (relative risk = 0.53;= .008) in the RT group. At 2 years, the recurrence-free rates were 88% for the RT group versus 79% for the no further treatment group. Patients with positive pelvic nodes, positive surgical margin, or positive parametrium should be treated with postoperative pelvic radiation with concurrent chemotherapy.vaginal brachytherapy is also indicated if the vaginal margin is positive. As previously noted, Intergroup Trial 0107 showed a statistically significant benefit of adjuvant pelvic radiation with 5-FU and cisplatin in the treatment

of patients with stage IA2, IB, or IIA disease who had positive lymph nodes, positive margins, or microscopic parametrial involvement found at surgery.

If para-aortic lymph nodes are found positive during surgical staging, patients must undergo further screening with chest CT or PET scan. In women who are positive for distant metastases, biopsy of suspicious areas should be considered as indicated. If all findings are negative, patients should be treated with para aortic lymph node RT, concurrent chemotherapy, and pelvic RT with or without brachytherapy. However, patients with positive results should be treated with systemic chemotherapy and individualized radiotherapy.

Surveillance

Because no definitive study or uniform agreement exists on the best method for post-treatment surveillance for cervical cancer, the NCCN panel combined the practice patterns of member institutions and issued consensus recommendations. Patient follow-up includes interval history and physical examination, with a Pap test every 3 months for 1 year, every 4 months for the second year, every 6 months for another 3 years, and then annually. Chest radiographs can be done annually. Many of the tests remain optional, such as semiannual complete blood counts, blood urea nitrogen, and serum creatinine determinations. Patients with persistent or recurrent disease need to be evaluated using imaging studies (such as pelvic/abdominal/chest CT/PET scan) and surgical exploration in selected cases followed by salvage therapy.

Use of a vaginal dilator is suggested after RT for women who wish to remain sexually active. Patients with a localized recurrence of cervical cancer after surgery should be evaluated for salvage radiotherapy. Salvage rates of approximately 40% have been reported in such situations. For patients who experience pelvic recurrences with no prior RT or who experience recurrences outside of the previously treated field, salvage therapy includes definitive pelvic radiation and platinum based chemotherapy with or without brachytherapy.

Salvage therapy

Patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration, with or without IORT; in carefully selected patients with small lesions (less than 2 cm), options include radical hysterectomy or brachytherapy. Surgical mortality is generally 5% or lower, with survival rates between 20% and 60%. Concomitant measures with such radical procedures include adequate rehabilitation programmes dealing with the psychosocial and psychosexual consequences of the operation as well as reconstructive procedures. Women with recurrence after pelvic exenteration should be treated with platinum-based chemotherapy, best supportive care, or be enrolled in a clinical trial. Patients with isolated recurrences may benefit from surgical resection with or without IORT, tumor-directed RT with concurrent chemotherapy, or chemotherapy. Those with noncentral disease should be treated with pelvic exenteration or resection with IORT for close or positive margins, tumor-directed

RT with or without chemotherapy, platinum-based chemotherapy, best supportive care, or participation in a clinical trial.

Systemic therapy and palliation

Patients with extra pelvic or para-aortic recurrence(s) at multiple sites or with unresectable recurrence(s) should be treated with platinum doublet-based chemotherapy or best supportive care. Isolated site recurrence(s) can be managed with surgical resection with or without IORT, tumor-directed RT with concurrent chemotherapy, or chemotherapy. Patients may then undergo RT (optional), adjuvant chemotherapy (optional), or best supportive care. Occasionally, patients may benefit from radiotherapy to a localized recurrence(s). Generally, these areas would be bone metastases, or painful para-aortic nodal recurrences. Clearly, pain relief of a transient nature may be achieved in responders to chemotherapy. Chemotherapy has a limited role in prolonging survival or improving quality of life and is recommended for patients with extra pelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery.

Cisplatin is generally regarded as the most active agent and is recommended as first-line chemotherapy in recurrent or metastatic cervical cancer; reported response rates are approximately 20% to 30%, with an occasional complete response. However, combination regimens are preferred if cisplatin was previously used as a radio sensitizer. Carboplatin, topotecan, and paclitaxel have also been reported to be tolerable and efficacious. Complete responses were also observed with topotecan and paclitaxel; however, topotecan is associated with more toxicity than carboplatin or paclitaxel.

Therefore, palliation with single-agent cisplatin, carboplatin, paclitaxel, or topotecan is a reasonable approach in patients with recurrent disease not amenable to surgical or radiotherapeutic approaches. Other agents reported to show a partial response include ifosfamide, vinorelbine, irinotecan, epirubicin, mitomycin, and 5-FU. A phase II study evaluating the effectiveness of docetaxel in patients who have persistent or recurrent cervical cancer is ongoing (GOG-0127S). Cisplatin-based combination chemotherapy regimens such as cisplatin/paclitaxel and cisplatin/topotecan have been extensively investigated in clinical studies.

Present study

This prospective non randomized study was performed to evaluate the role of radical surgery in stage II B patients after external beam RT to establish surgery as an useful modality of treatment in prevention of late recurrences and to avoid intracavity RT and its long term complications like adhesive vaginitis, bladder and rectal morbidities. We then assessed the impact of surgery on local control and survival of the patients.

II. LITERATURE REVIEW

Radical hysterectomy is recognized as one of the best treatment methods for stage IB-II invasive uterine cervical carcinoma, and postoperative radiation therapy is preferred for patients with risk factors such as lymph node metastasis, positive surgical margins, and deep stromal invasion. When patients recurred, the most predominant site was the pelvis; distant recurrence alone was rare. In patients with close vaginal margins, Estape ***et al.*** reported that the 5-year survival rate of patients treated by postoperative radiation therapy was 81.3% and that of patients not treated by postoperative radiation therapy was 28.6%. Sedlis ***et al.*** reported that 30 of 140 patients died without postoperative radiation therapy, whereas 18 of137 patients died with postoperative radiation therapy. These findings indicate that postoperative radiation therapy has a significant influence on the prognosis of uterine cervical carcinoma treated with radical hysterectomy. On the other hand, Thomas ***et al.*** reported that postoperative radiation therapy had no significant impact on patients with lymph node metastasis because these patients often relapsed from distant sites. However, it is reported that postoperative radiation therapy was useful for patients even with lymph node metastasis.In the current study, lymph node metastases was recognized as a prognostic factor for all patients with stage IIB. Other prognostic factors for all patients of the current study were tumor size and surgical margin. It was obvious for surgical margin status to reflect the prognosis because of cancer cells left after treatment.

Clinicians have been investigating the use of concurrent chemoradiation in locally advanced cancer cervix for many years. The Gynaecologic Oncology Group (GOG) has been investigating the role of concurrent chemoradiation in cancer cervix since the early 70's. The early studies concentrated on Hydroxyurea a drug used as a radiation sensitizer. The effectiveness of Cisplatin in producing tumour regression is patients with local recurrence or distant metastasis after primary treatment paved the way for its use in combination with radiation at an earlier stage of treatment. From 1979 patients with locally advanced cancer cervix started receiving treatment with concurrent Cisplatin based chemoradiation. The overall 5 year survival of the study conducted by *Blake* ***et al.*** was 49% for all stages. A complete remission rate of 89% was observed for stage III disease. This study suggested that Cisplatin based chemotherapy combined with radiotherapy could be safely used to treat cancer cervix patients at high risk or relapse. Around the same time a number of studies on Cisplatin based concurrent chemoradiation in cancer cervix were published. *Potish* ***et al.*** and *Twiggs* ***et al.*** administered Cisplatin weekly in an effort to increase the percentage of radiation fractions given in proximity to the drug. The starting dose was $10mg/m^2$ gradually escalating to $20mg/m^2$. Both the regimes were well tolerated and the results were promising. Uncontrolled phase II trials in concurrent chemoradiation with single agent Cisplatin in locally advanced cancer cervix were conducted by *Wong* ***et al.*** (dose $25mg/m^2$ weekly), *Micheletti* ***et al.*** (dose$3mg/m^2$/day) and *Malfateno* ***et al.*** (dose 1mg/kg/wk). The results of all these studies showed an improved local control rate with concurrent chemoradiation.

Fields ***et al.*** and *Runowicz* ***et al.*** conducted phase II trials of concurrent chemoradiation using Cis-Platin (Dose: 20mg/m^2 day 1 – 5 at 21 day intervals). The data revealed better disease free survival and overall survival for Cis-platin based regimen.

Souhami ***et al.*** conducted a phase II prospective trial of 50 patients with locally advanced cancer cervix patients stage II_A – IV_A treated with concurrent chemoradiation 30 mg/m^2 weekly on day 1 of every week. The total dose to point A was 75 Gy. A complete response rate 88% was seen. The survival rate at 4 years was 65% with acceptable toxicity.

Perez ***et al.,*** *Pignata* ***et al.****, Meder* ***et al.*** *and Rose* ***et al.*** in their trials have proven the benefits of concomitant chemo-radiotherapy for locally advanced cancer cervix .

The next 5 years (1992-97) proved to be path breaking in cervical cancer treatment with concurrent chemoradiation. Five separate prospective randomized trials conducted in this period have provided compelling evidence that the addition of concurrent Cisplatin containing chemotherapy to radiation improves the local control and long term survival in patients with locally advanced cancer cervix. All of these studies were heterogeneous in that they differed with respect to inclusion criteria and treatment modalities. However each study demonstrated a reduction in the relative risk of recurrence by 30-50% in the arm containing Cisplatin.

Gilani ***et al.,*** conducted a trial using concurrent cisplatin and external radiotherapy prior to radical hysterectomy and lymphadenectomy in patients with stage IB-IIB cervical cancer. The analysis of the surgical specimens revealed complete pathological response in 43.3% of the cases and partial pathological response in 56.7% of patients. According to them the degree of pathological response was not predictable by the degree of clinical response. They have reported that 66.3% of patients showed thirty months disease-free survival and 77.31%, overall survival. Patients with complete and partial pathological response were not significantly different in terms of disease-free survival (p= 0.08) and overall survival (p= 0.3). Cisplatin in preoperative chemoradiation is effective and usually well tolerated in bulky cervical cancer and parametrial invasion, inducing a high rate of clinical and pathological complete responses. When this therapy is followed by radical surgery, disease-free and overall survival rates are higher.

Hall ***et al.*** and Peres ***et al.*** stated that the combined use of surgery and radiotherapy is associated with a complication rate higher than radiotherapy alone. A recent randomized study conducted by Londoni ***et al.*** had also shown a higher complication rate in patients treated with the combined modality compared to that seen inpatients treated with surgery alone. Rouzier ***et al.,*** performed a retrospective study to determine the incidence of residual disease in the hysterectomy specimens of patients with stage I & II B treated with primary radiotherapy or combined with chemotherapy and to identify patient or therapeutic factors associated with pathological response. They reported that pathologically confirmed residual disease on hysterectomy specimen is an

independent factor of both local recurrence and over all survival.

The outcome of early cervical carcinoma treated by Wertheim hysterectomy with selective postoperative radiotherapy was studied by Tay and Tan reported that Wertheim hysterectomy with selective postoperative radiotherapy for selected high risk patients was an effective treatment for stage IB –IIA cervical carcinoma.

Morice ***et al.*** performed a study to evaluate prognostic factors and the role of combination radiotherapy-surgery as treatment for patients with bulky stage Ib and II cervical carcinoma and opined that radical surgery combined with radiotherapy is feasible, with an acceptable rate of complications and yields satisfactory survival results in patients with bulky stage IB and II cervical carcinoma.

III. AIM OF THE STUDY

1. To evaluate the role of radical surgery in stage II B patients after external beam RT.
2. To establish surgery as an useful modality in prevention of late recurrences.
3. To avoid intracavity RT and its long term complications like adhesive vaginitis, bladder and rectal morbidities.
4. To improve local and regional control and possibly survival of the patient.

IV. MATERIALS AND METHODS

STUDY PERIOD: From March 2002 up to April 2007.

TYPE OF STUDY: Prospective non-randomized pilot study.

ELIGIBILITY CRITERIA:

1. Patients with carcinoma cervix FIGO stage II B.
2. Squamous cell carcinoma –Histology.
3. Patients with good performance status -1 (ECOG scales).
4. Patients with Co-morbidities like diabetes, hypertension also included after proper evaluation and control of their illness.

EXCLUSION CRITERIA:

1. Any patients who has received treatment outside this institution (Radiotherapy or chemotherapy).
2. All other histologies except squamous cell carcinoma(All grades included).
3. Patients with either <or> stage II B.

4. Enlarged para-aortic nodes on CT scan.

STUDY PROTOCOL:

1. Informed consent obtained.

2. All patients undergo complete clinical evaluation including pelvic examination.

3. Staged according to FIGO (UICC manual 2002).

4. Biochemical evaluation includes:

   a. Complete hemogram

   b. Urine analysis

   c. Blood sugar, urea, Sr. creatinine

   d. Blood grouping & typing

5. ECG

6. Biopsy - Punch biopsy or slide review if biopsy done outside.

7. Radiology

a. Chest X ray

b. Ultrasound abdomen and pelvis

c. Contrast enhanced CT scan of abdomen &pelvis.

8. Cystoscopy

9. Examination under Anesthesia:

Done by two examiners of which one is a senior teaching faculty.

FIGO staging done on EUA is taken as final stage for treatment.

10. EBRT protocol

RT equipment CO-60 Phoenix for Teletherapy

Dose details:

Total dose delivered : 50 Gy

Dose/# : 2Gy/#

Portals : AP & PA portals. Both portals treated daily

No of fractions : 25

Total duration : Usually 5-6 weeks(Not more than 6 weeks)

Treatment days / week : 5

Treatment planning : EBRT

The whole pelvis including the cervix, vagina and parametria with the pelvic and iliac group of nodes was treated.

RT portal margins for EBRT

1. Superior:	L4-L5 interspace (to include all the iliac and hypogastric nodes).
2. Inferior:	If vagina is free – lower margin of Obturator foramen. If vagina is involved – the entire vagina up to the introitus was included.
3. Lateral:	2cm lateral to bony pelvis.

11. Clinical reassessment : Assess for parametrial disease regression and feasibility for surgery.

12. Type II modified radical hysterectomy at 4 to 6 weeks after surgery.

13. Recording of intraoperative and postoperative course and complications.

14. Histopathological evaluation of specimen includes:

a. Presence of residual tumor.

b. Parametrial, vaginal margins.

c. Evaluation of pelvic nodes.

15. Residual urine evaluation with USG before discharge.

16. Follow-up

Clinical examination every month for 1st year

every 2 months – 2nd & 3rd year

every 3 months – 4 rd year

yearly – 5th year onwards

CXR/USG and vaginal cytology annually

17. Adjuvant treatment:

For node positive patients only.

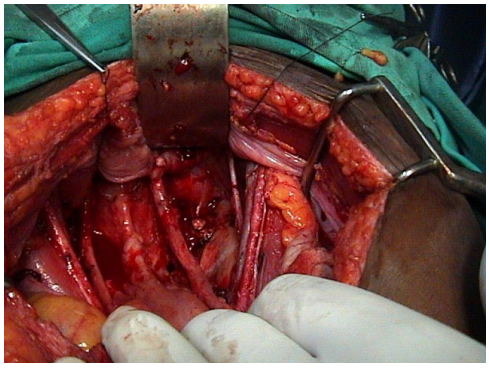
Six cycles of cisplatin and 5FU.

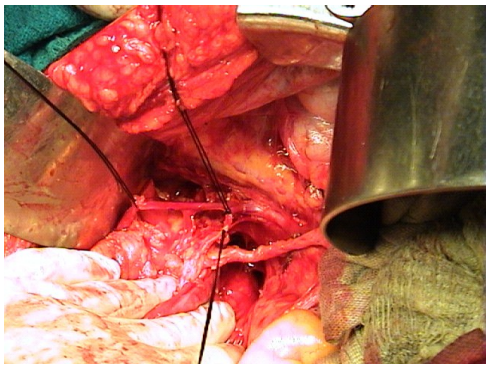
After completing the radiation and surgery , the patients were reviewed every month for the first one year followed by every 2 months for the next 2 years followed by once every 3 months thereafter for local recurrence and distal metastases with clinical and radiological assessment. The degree of pathologic response was assessed in the surgical specimens and lymph nodes. Complete pathological response (path CR) was defined as either a tumor-free specimen or just a few microscopic scattered tumoral foci in the cervix which are not quantified.

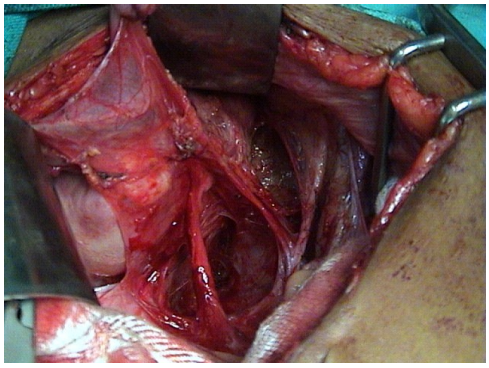
Statistical analysis

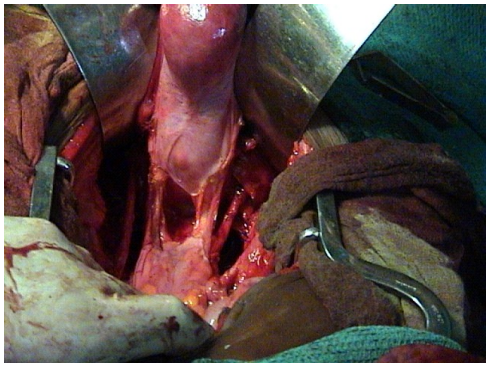
The Chi-Square test was used to evaluate the relationship between residual disease on surgical specimen and clinico-pathologic characteristics. We used logistic regression model to analyze independent factors associated with residual disease. Local recurrence free survival and over all disease free survival were calculated using the Kaplan-Meier method. We assessed the influence of clinical, pathologic and therapeutic factors on outcome in multivariate analysis using the Cox regression model. Results with a P value of<0.05 were regarded as statistically significant. Statistical analyses were performed with SPSS version 9 **.**

PER-OP STEPS









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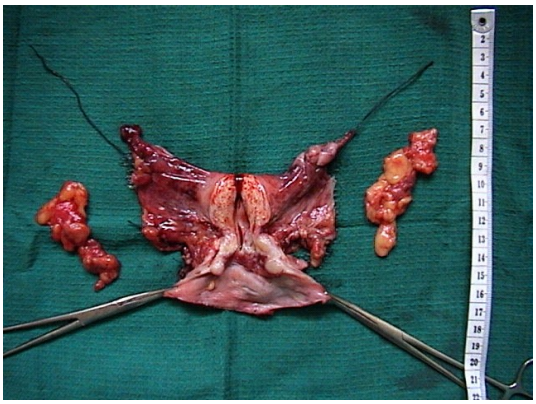

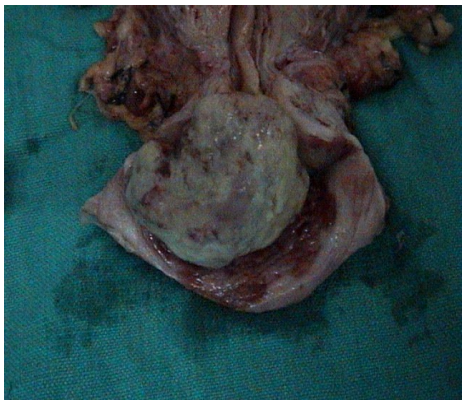

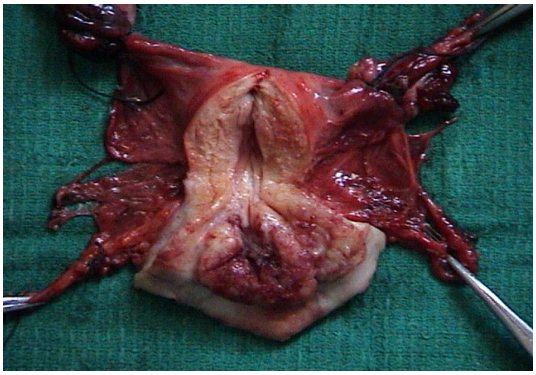

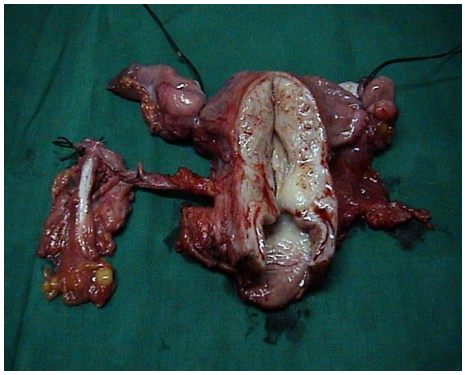

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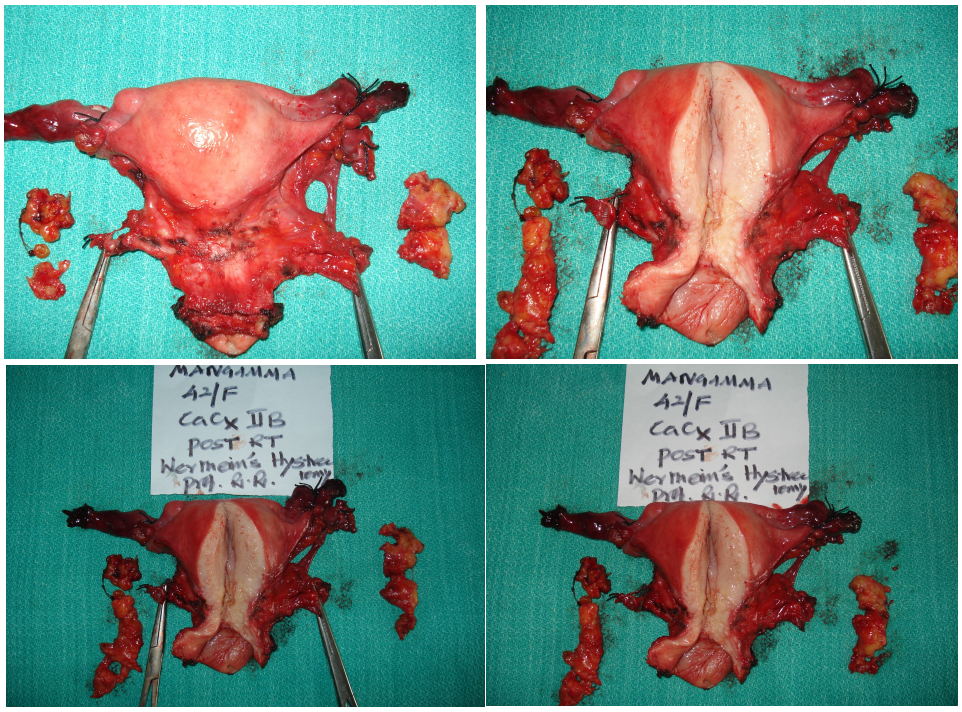
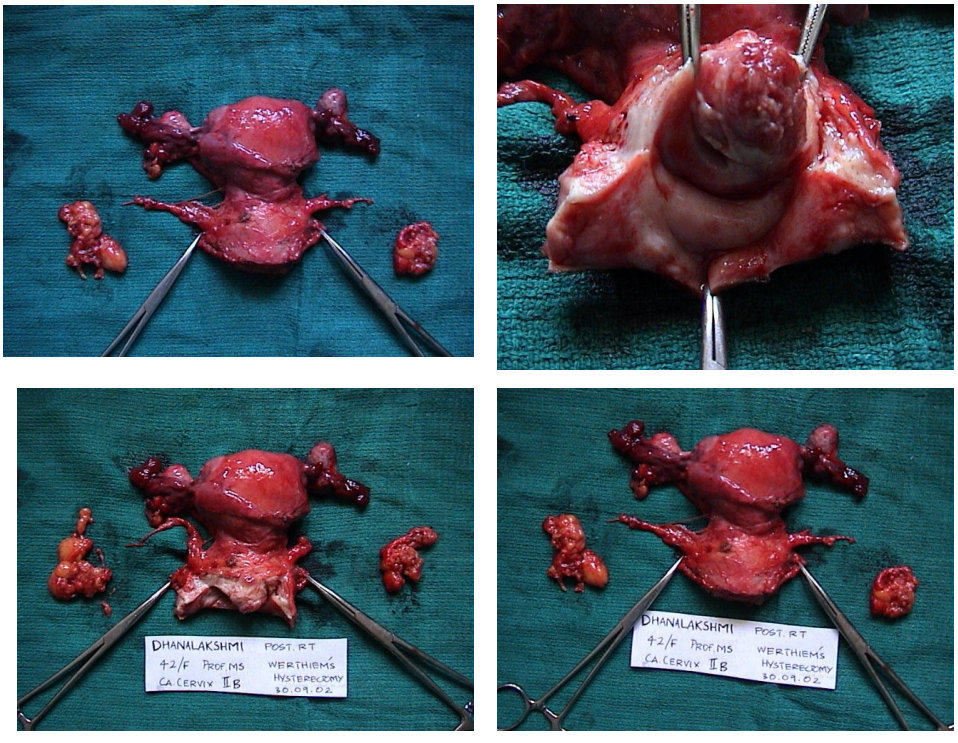
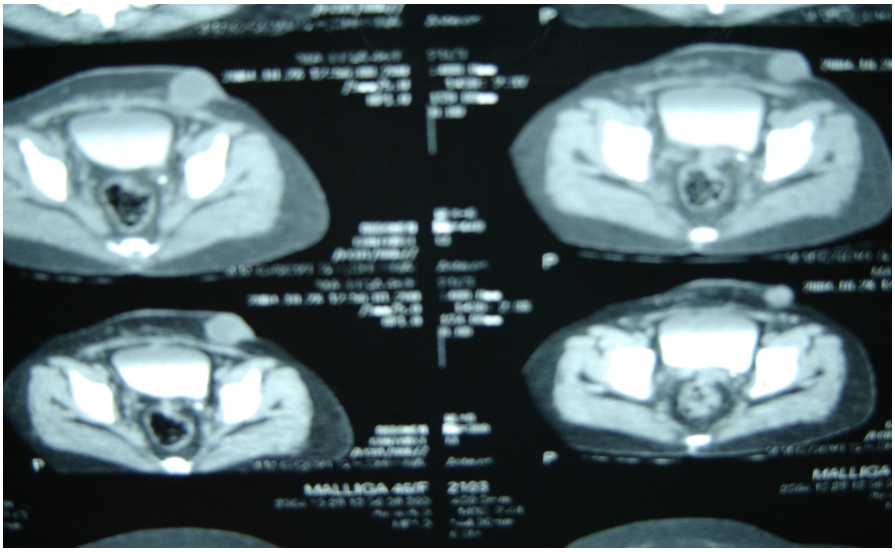




RECURRENCE



V. OBSERVATIONS AND RESULTS

From March 2002 to April 2007 a total of 83 patients with previously untreated locally advanced cancer cervix IIB fulfilled the criteria for inclusion in this trial. Seven patients were excluded because they defaulted for radiation or surgery. The median period of follow up was 24 months.

PATIENT CHARACTERISTICS

In this study, we enrolled 39 (51.32%) patients belonging to the age group of ≤ 45 years and 37 (48.68%) patients belonging to the age group of > 45 years. The median age of patients in this trial was 45 years.

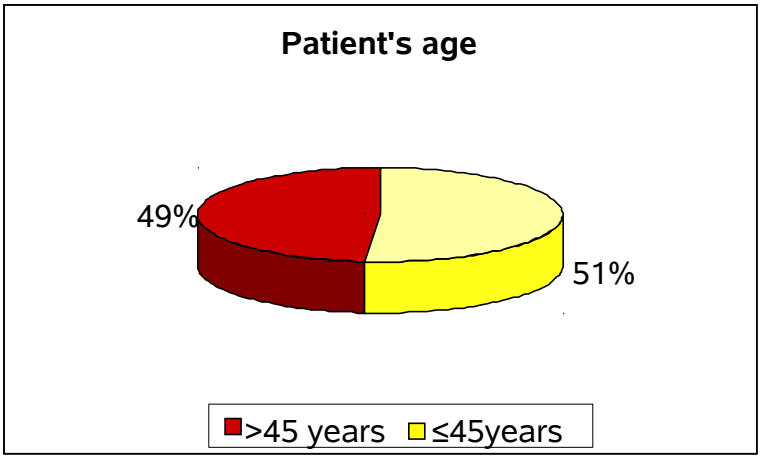
HISTOLOGICAL GRADE

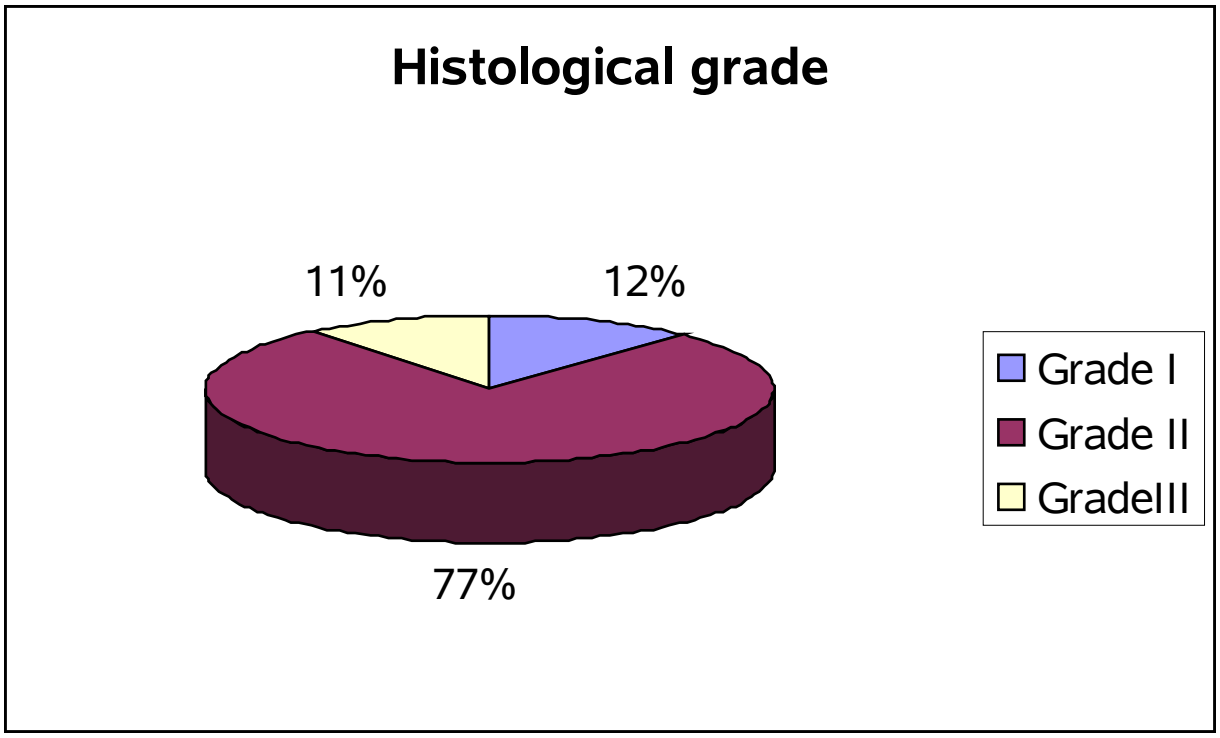
Only squamous cell cancers were included in this trial. Of which 12 % of patients had well differentiated squamous cell cancer, 78% of patients had moderately differentiated squamous cell cancers and 10% of patients in the trial had poorly differentiated squamous cell cancer.

Forty-one (54%) had tumor size > 4cm and 35 (46%) had tumor size ≤4cm.

Table 1. Patient characteristics

S.No	Characteristics	Number of Patients(n)	Percentage (%)
1	Patient's age:		
	≤45 Years	39	51.32
	>45 Years	37	48.68
2	Histological Grade:		
	Well Differentiated SCC	9	11.84
	Moderately Differentiated SCC	59	77.63
	Poorly Differentiated SCC	8	10.53
3	Tumor size:		
	>4cm	41	53.95
	≤4cm	35	46.05




Histological grade
11%
12%
77%
Grade I
Grade II
GradeIII

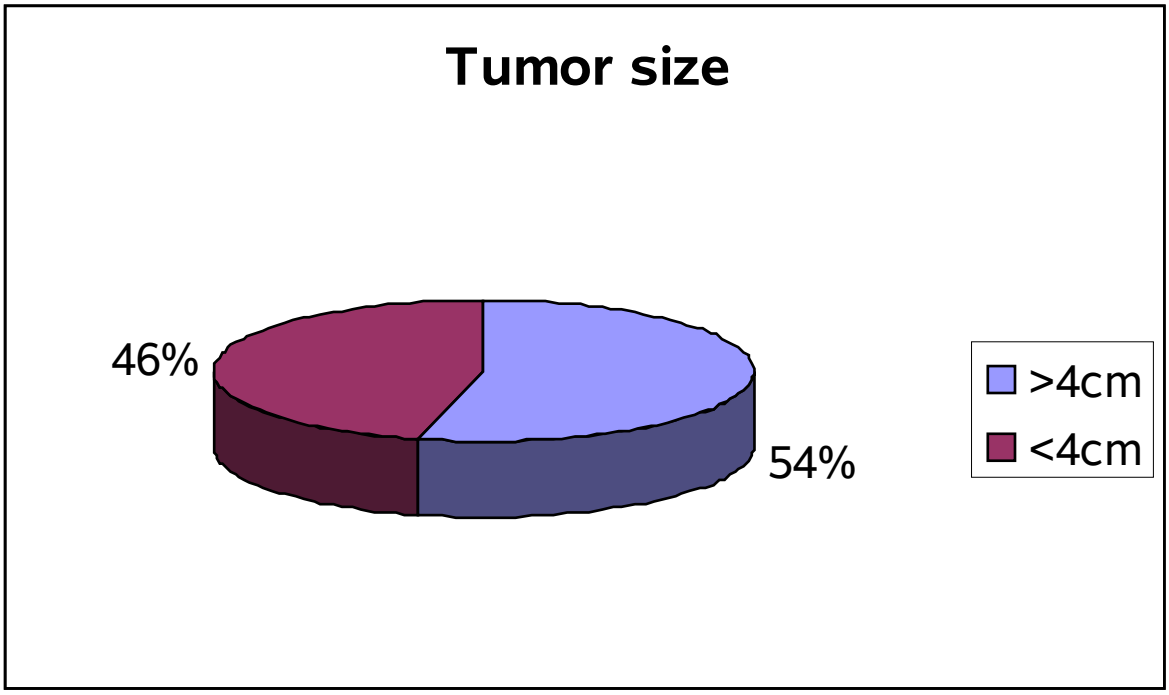
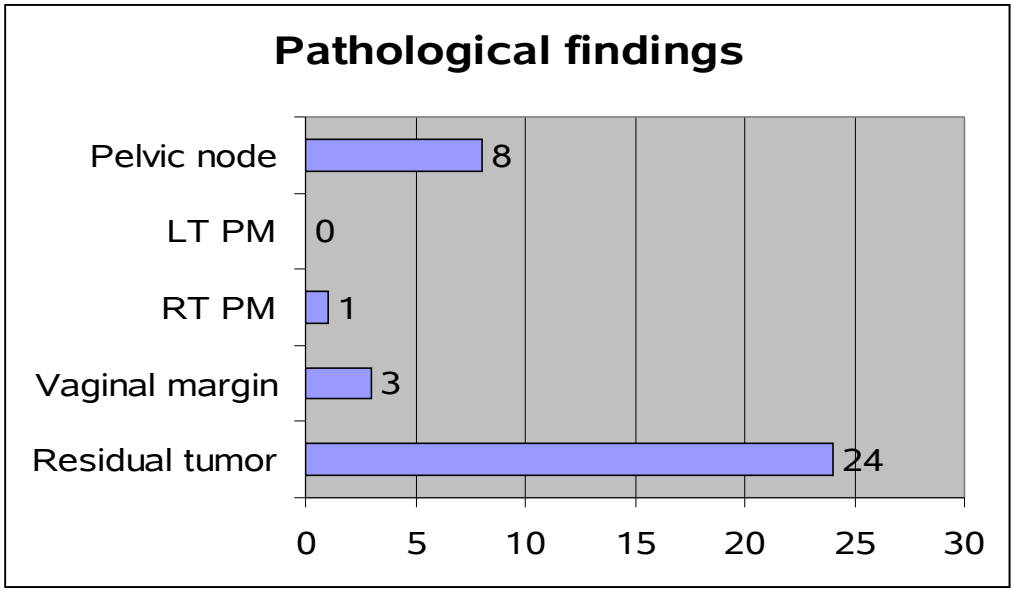

Tumor size
46%
54%
>4cm
<4cm

Table 2 . Pathological findings

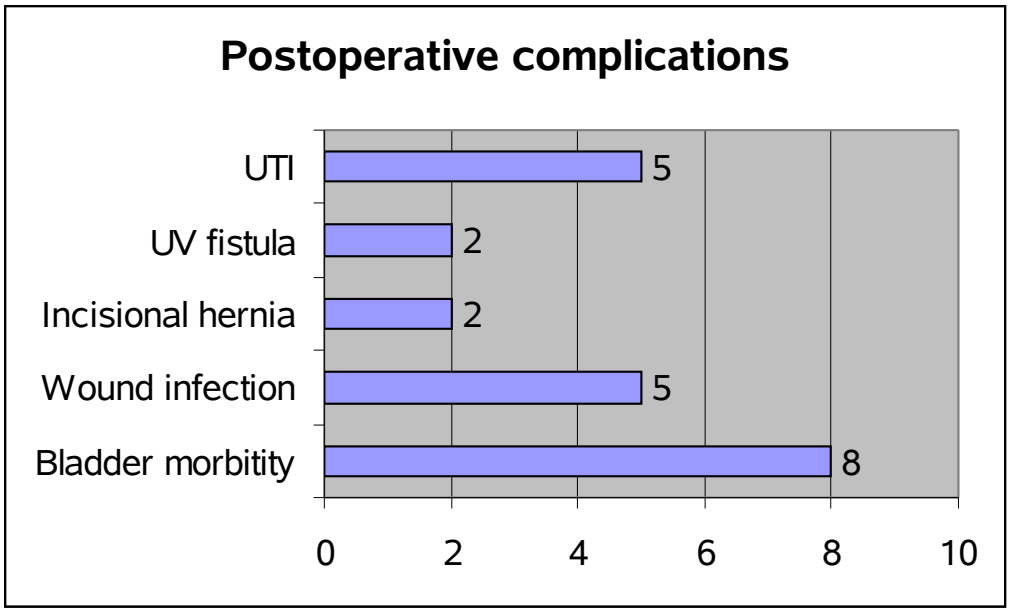
S.No.	Characteristics	Number of patients(n)	Percentage(%)
1	Residual tumor	24	31.58
2	Vaginal margin	3	3.95
3	RT PM	1	1.32
4	LT PM	-	-
5	Positive pelvic nodes	8	10.33



Residual tumor was detected in 24 patients (32%) . Of these 3 patients (4%) had positive vaginal margin and one patient had positive unilateral parametrium. Pelvic node was positive in 8 patients (10%).

Table 3. Postoperative complications

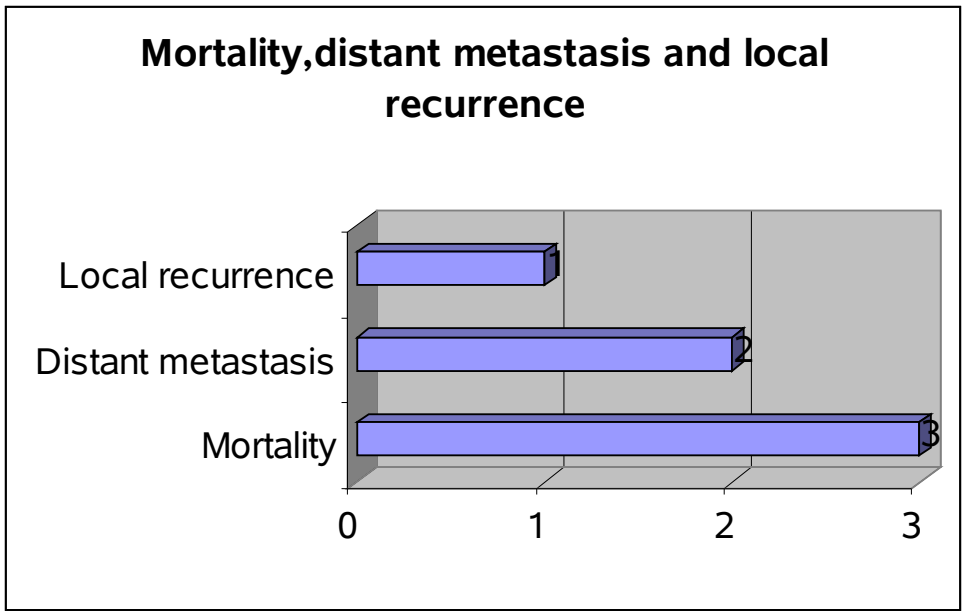
S.No.	Characteristics	Number of Patients(n)	Percentage(%)
1	Bladder morbidity	8	10.53
2	Wound infection	5	6.58
3	UV fistula	2	2.63
4	Incisional hernia	2	2.63
5	UTI	5	6.58



Mild to moderate bladder morbidities were seen in 8 patients (10%) (Table 3). Intra-operative complications included one case of significant bleeding. Postoperative complications included two cases of ureterovaginal fistula which required secondary stenting. Long-term complications included two cases of incisional herniae that needed mesh repair .

Table 4.Outcome after radiotherapy and surgery

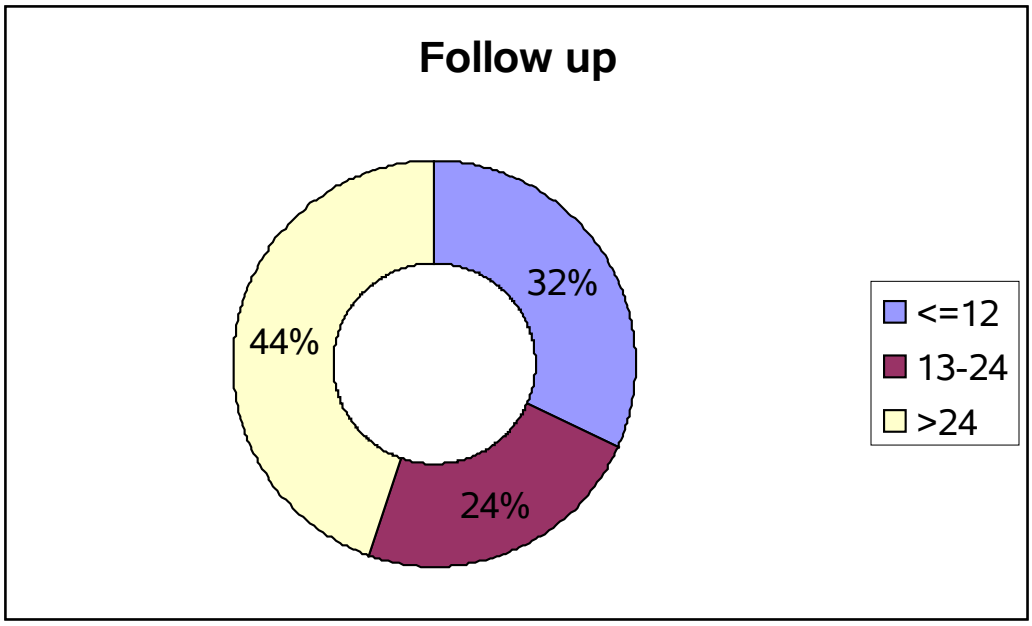
S.No.	Characteristics	Number of Patients(n)	Percentage (%)
1	Local recurrence	3	3.95
2	Distant metastasis	2	2.63
3	Mortality	1	1.32



Local recurrences were detected in three patients (3.95%).There were two cases of distant metastasis: one to the lung, and one to left supraclavicular nodes. One patient died as a result of progressive disease.

Table 5. Survival after radiotherapy and surgery

S.No.	Follow up duration (months)	Number of patients(n)	Percentage(%)
1	<=12	24	31.58
2	13-24	18	23.68
3	>24	34	44.74



Median period of follow up was 24 months. Twenty four patients completed one year follow up. Eighteen patients completed two years follow up. All other patients falls in > 24 months category.

Table 6. Predictive factors of residual disease

Parameter	Number of patients(n)	Residual disease	Percentage(%)	P Value
Histological Grade: I	9	1	11.1	0.223
II	59	19	32.2	
III	8	4	50	
Tumor size: >4cm	41	17	41.5	<0.003
≤4cm	35	7	20	
Age:				

≤45 years	39	15	38.46	0.185
>45years	37	9	24.3	

Incidence and predictive factors of residual disease:

Twenty four patients in this study had residual disease in the hysterectomy specimen. Incidence and predictive factors of residual disease are reported in Table 6 . Tumor size was significantly correlated with residual tumor. Seventeen patients (41.5%) with tumor size > 4cm showed evidence of residual disease verses seven patients(20%) with tumor size≤4cm (P<0.003). Histological grade (P=0.223) and Age(P= 0.185) fell short of reaching statistical significance.

Table 7. Predictive factors of nodal residue

Parameter	Number of patients(n)	Pelvic node	Percentage(%)	P Value
Histological Grade: I	9	1	11	0.359
II	59	5	8.47	
III	8	2	25	
Tumor size: >4 cm	41	5	12.1	0.323
≤4 cm	35	3	8.57	
Age: ≤45 years	39	4	10.25	0.937
>45 years	37	4	10.81	

Incidence and predictive factors of nodal residue :

The predictive factors associated with nodal involvement with respect to the histological grade , tumor size, residual disease and age were reported to be statistically not significant . In the logistic regression model, the tumor size ($P < 0.003$) was an independent predictive factor of residual disease in the hysterectomy specimen.

Table 8. Predictive factors of local recurrence

Parameter	Number of patients(n)	Local recurrence	Percentage(%)	P Value
Histological Grade: I	9	-	-	<0.005
II	59	1	1.69	
III	8	2	25	
Tumor size: >4 cm	41	1	2.43	0.652
≤4 cm	35	2	5.71	
Age: ≤45 years	39	2	5.12	0.587
>45 years	37	1	2.7	
Pelvic node: Yes	8	2	25	<0.001
No	68	1	1.4	
Residual Tumor: Yes	24	3	12.5	<0.009
No	52	-	-	

Incidence and predictive factors of local recurrence:

The histological grade (P = <0.005) , positive pelvic node (P = <0.0001)and residual tumor (p = < 0.009) were significantly associated with local recurrence.

Table 9.Predictive factors of distant metastasis

Parameter	Number of patients(n)	Distant metastasis	Percentage (%)	P Value
Histological Grade: I	9	-	-	0.743
II	59	2	3.3	
III	8	-	-	
Tumor size: ≤4cm	41	1	2.4	0.909
>4cm	35	1	2.8	
Age: ≤45years	39	1	2.5	0.570
>45years	37	1	2.7	
Pelvic node: Yes	8	1	12.5	0.065
No	68	1	1.5	
Residual tumor: Yes	24	1	4.1	0.570
No	52	1	1.9	

Incidence and predictive factors of distant metastasis:

The predictive factors associated with distant metastases with respect to the histological grade, tumor size, residual disease, positive pelvic node and age were reported to be statistically not significant.

Table 10.Predictive factors of morbidity

Parameter	Number of patients(n)	Morbidity	Percentage(%)	P Value
Histological Grade: I	9	1	11.11	0.70550
II	59	13	22.33	
III	8	1	12.5	
Tumor size: >4 cm	41	9	21.95	0.29127
≤4 cm	35	6	17.14	
Age: <45 years	39	7	17.94	0.64620
≥45years	37	8	21.62	
Pelvic node: Yes	8	2	25	0.76512
No	68	9	13.23	
Residual tumor: Yes	24	4	16.66	0.71479
No	52	11	21.15	

Incidence and predictive factors of morbidity:

The predictive factors associated with morbidities with respect to the histological grade , tumor size, residual disease, positive pelvic node and age were reported to be statistically not significant.

Response:

Clinical response: All 76 patients were evaluated clinically 4 weeks after radiotherapy. Seventeen patients(22.36%) showed complete clinical response, and 59 (77.63%) partial clinical response.

Pathological response: Fifty two out of 76 surgical specimens had no residual disease (68.42%).Twenty four patients(31.58%) had microscopic residual disease. Eight patients had positive pelvic nodes in surgical specimens (10.53%).One patient had parametrial involvement (1.33%) and three had vaginal margin positive in the pathology report (3.95%). There were two cases of distant metastasis: one to the lung, and one to left supraclavicular nodes.

Survival:

After a median follow-up of 24 months (range:1- 37 months), overall survival was 89.6% . Thirty-month survival for path CR was 88.89% and for path PR, 62.2%, which was not statistically significant (Fig. 1). Thirty-month disease-free survival was 66.3%.

Kaplan – Meier : Survival curve

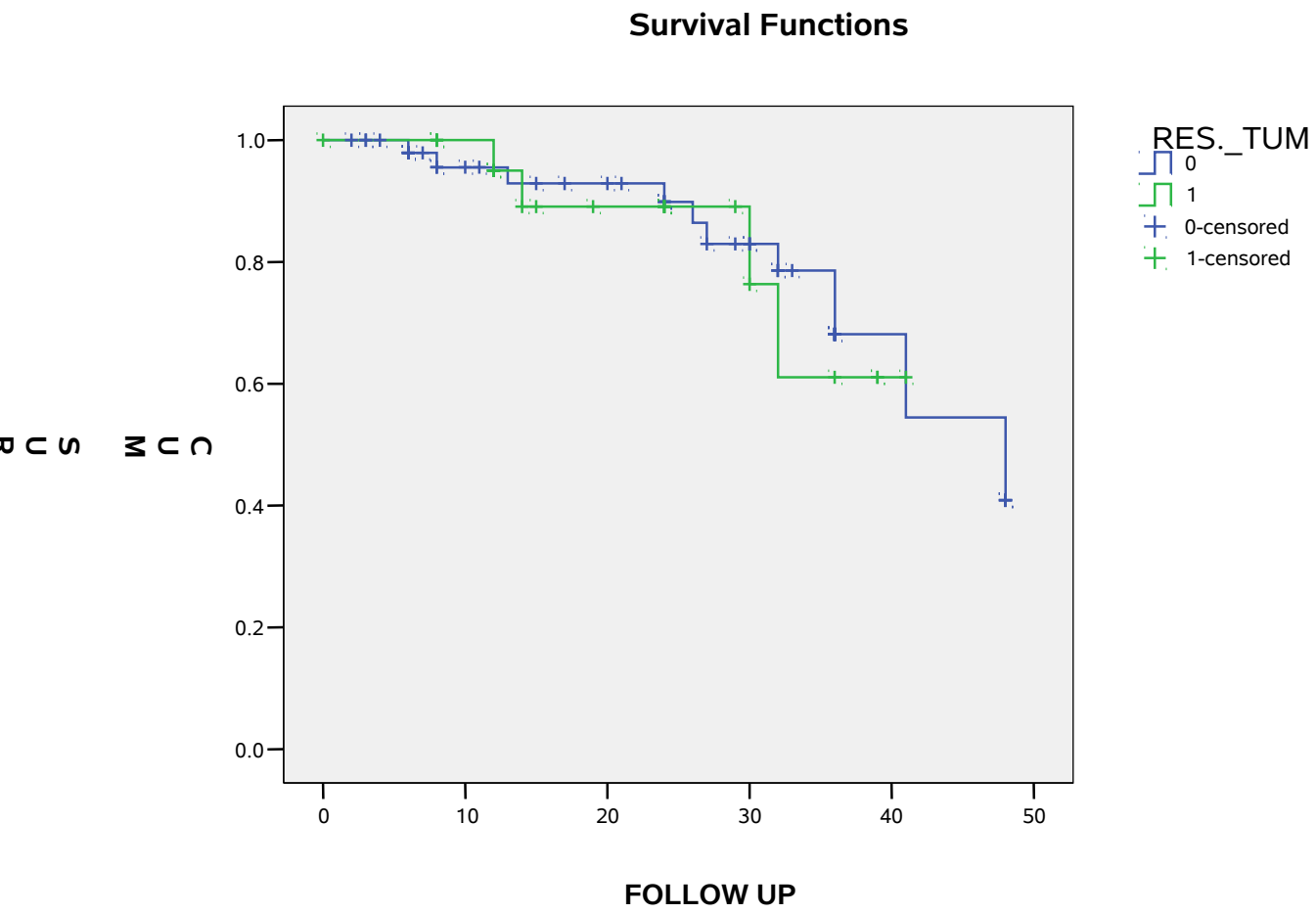


Fig. 1. Overall survival rate

VI. DISCUSSION

Invasive cervical cancer is the commonest cause of death from cancer among women in India. The constraints of the single modality treatment in achieving a "cure" forces us to venture into newer modalities of treatment to achieve this goal. The present study is an attempt to establish the feasibility of new combined modality of treatment in stage IIB cervical cancer- radiation followed by radical surgery to be an ideal treatment to achieve maximal benefit within the "window of curability".

Lack of local control is a major cause of treatment failure in patients with bulky or advanced carcinoma of the cervix. Several studies have confirmed that bulky cancer and extensive parametrial invasion are

poor prognostic features (Twiggs ***et al.,*** Wongs ***et al.*** and Potish ***et al.***). After a point dose of 85 Gy, pelvic failure rates of 25-37% in bulky (> 4cm) stage Ib-IIa tumors, and 35-50% for stages IIb-III are considered standard results

. Bulky tumors have significant level of hypoxic cell populations that are radio resistant. This mechanism has been implicated as a major cause of treatment failure. The radiation doses that would be needed to overcome the radiation resistance of hypoxic populations may exceed the normal tolerance of the surrounding healthy tissues. Radical surgery could play a role in this scenario by eliminating radio resistant populations remaining after radiation.

In other organs and other histological types,(Peter ***et al.***) when chemotherapy and radiotherapy are followed by surgery, pathologic evaluation of residual disease has been demonstrated to provides precious information about tumor behavior and sensitivity to tailor adjuvant therapies. However, in most of the cervical cancer trials, hysterectomy was not included in the treatment schedule or was performed before radiation or chemoradiation. It has been reported that the presence of residual disease in the hysterectomy specimen may provide prognostic information, but surgery was limited to extrafascial hysterectomy with bilateral salpingo-oophorectomy in most of the studies and the series included a limited number of patients (Beskow ***et al.*** and Calais ***et al.***). Moreover, little information is available concerning the pathologic assessment of residual disease on hysterectomy specimen after chemoradiation.

This prospective non randomized study was performed to evaluate the role of radical surgery in stage II B patients after external beam RT and to establish surgery as an useful modality in prevention of late recurrences. We then assessed the impact of surgery on local control and survival of the patients.

Out of twenty four patients (31.5%) of the 76 patients with residual disease on the hysterectomy specimen only four patients had metastatic pelvic lymph nodes. Factors significantly associated with lymph node involvement are reported in the Table-7. In the logistic regression model, tumor size is independent predictive factor of residual disease.

Residual disease and local control

In our study, 31.5% of patients had residual disease on the hysterectomy specimen. In other studies, rates of residual disease on hysterectomy specimens after preoperative radiotherapy for cervical carcinoma have ranged from 21 to 78 %(Calais ***et al.***, Mauryama ***et al.,*** Moyses ***et al.***, Mundt ***et al.*** and Keys ***et al.***). Factors associated with residual disease on hysterectomy specimens have been poorly studied. However, as residual disease is correlated with lower rates of local control; those factors may be used to better select patients who may benefit from hysterectomy. In our series,80% of patients with tumors smaller than 4 cm displayed total eradication of their tumor by radiotherapy vs. 59% of patients with tumors 4cm or larger (P=<0.003).The correlation between size and the rate of residual cervical disease has been contradictorily reported in the literature. Beskow ***et al.*** found a significant effect of size, whereas Moyses ***et al.*** did not. Tumor grade may influence the presence of residual tumor on the hysterectomy specimen. In our series the histological grade (P=0.223) and age(P= 0.185) fell short of reaching statistical significance.

There are obvious limitations in this prospective study design that must be acknowledged. First, during the study period, seven patients did not have adjuvant surgery or preop radiation because of co morbidity or refusal. As they were not recorded prospectively in the database, we cannot provide further information concerning these patients. Keys ***et al.***. have evaluated ,in a randomized clinical trial, the role of adjuvant hysterectomy after standardized radiation for patients with ‘bulky’ stage II B cervical

cancer. In their study, there was a lower cumulative incidence of local relapse in the group of patients that had adjuvant hysterectomy compared to the radiation only group(at 5years,27 vs. 14%).But there were no statistical difference in outcomes.

In our study, the local recurrence rate of the patients treated with preoperative radiotherapy and radical surgery was 3.95%. Univariate analysis of various clinical and pathologic factors associated with local control and survival is presented in Table-8.Tumor size, residual disease on hysterectomy specimen, and pathological nodal disease were significantly associated with local recurrence. In the multivariate analysis using Cox regression model, the data pertaining to tumor size, residual disease and pathologic node involvement were found to be independent predictive factors of local recurrence.

The correlation between residual disease and nodal status also has been reported by Timmer ***et al.*** This correlation may be related to the selection of poor prognosis tumors which are less radiosensitive. But it also raises the question of metastasis seeding during the time interval between radiotherapy and surgery, explaining the weak impact of hysterectomy on survival in previous publications(Gallion ***et al.***, Sundford ***et al.***, Perez ***et al.***, Keys ***et al.***, Resbeut ***et al*** **.**and Rotman ***et al.***).

The median duration of follow-up after surgery was 24 months (range, 1–37 months). Eight patients were lost to follow-up one month after the surgical procedure. Fig. 1 shows the survival curve. Disease recurred loco regionally in three patients, two patients at a distant sites (Table 4). Only one patient (the only one with involved

margins) had a massive pelvic recurrence that invaded the vagina, bladder, and lateral pelvic walls, 6 months after the surgical procedure.

Whether performing pelvic surgery in patients treated with primary radiotherapy continues to be debated. The use of surgery as adjuvant after preoperative radiation or chemoradiation has gained acceptance because of experience in the combined treatment of rectal and other malignancies during the past two decades. Several retrospective analyses have compared patients who underwent hysterectomy or no pelvic surgery after radiotherapy (without concomitant chemotherapy) (Gallion ***et al.,*** Keys ***et al.*** and Resbeut ***et al***.). Only one randomized trial (closed 10 years ago) comparing patients treated with initial external radiotherapy and randomly allocated to hysterectomy (completion pelvic surgery) versus no hysterectomy (whatever the presence of residual disease) has recently been published(Keys ***et al***.). This study does not seem to demonstrate a benefit for overall survival. Nevertheless, a trend toward an increase in disease-free survival was observed in patients who underwent hysterectomy (62% vs. 53% at 5 years; P = .09). The potential advantages of hysterectomy after external radiotherapy are 2-fold: any residual disease can be removed with the prospect of improving (ideally) event-free survival, and the nodal status can be adequately assessed, thus allowing adjuvant treatment in patients with nodal involvement. None of the published series has evaluated the value of hysterectomy after RT. In the randomized trial about CRT conducted by Keys ***et al.***, hysterectomy was performed in both arms. The rate of residual disease after CRT was lower compared with those treated with

external radiotherapy alone (48% vs. 59%; P = .04). In the case of patients without macroscopic residual disease confirmed at clinical examination and on MRI (8 weeks after the end of CRT), a randomized trial is ongoing in France to evaluate the effect of hysterectomy. Patients with a very small residuum (<1 cm) are probably in a situation similar to that of patients without residual disease; if the surgical procedure had been performed a few weeks later, this residuum would have been totally sterilized by CRT.

But in this study, after a median follow-up of 24 months (range: 1-37 months), overall survival was 89.6 %; 30 months survival for complete and partial pathological responders was 88.89% and 62.22%, respectively. Thirty months disease-free survival was 66.3%.

In the present series, 15 of 76 patients (19.73%) developed complications. The combined use of surgery and radiotherapy is associated with a complication rate higher than radical radiotherapy alone or chemoradiation. But our study had shown acceptable complication rate in patients treated with the combined modality compared to that seen in patients treated with radical radiotherapy alone or chemoradiation .

CONCLUSION

Tumor size, grade of disease and positive pelvic node residue are well recognized prognostic factors which influence therapeutic outcome in cancer of the cervix. The high failure rates seen in locally advanced cancer cervix with radiotherapy alone may be attributed to the presence of relatively radio-resistant hypoxic cells within the tumor mass. The following conclusions can be drawn from this preliminary phase III trial which showed the benefit of addition of surgery with radiation in stage IIB cervical cancer patients. Combined radiotherapy and radical surgery give the following benefits:

1. Pathologic evaluation of residual disease provides precious information about tumor behavior and sensitivity to tailor adjuvant therapies
2. Lesser complication rate compared with radical RT or chemoradiation
3. Better local control and disease free survival

In the current study, the use of radical surgery 4 weeks after completion of EBRT with the dose of 50 Gy had shown an increased locoregional control which was demonstrated with statistically significant values. This radical surgery not only shown added benefit in the treatment of stage II B disease but also increased the local control with acceptable complications. The benefits are more pronounced in

1. Young patients

2. Tumor size ≤ 4 cm size

3. Pelvic node negative patients

The patients are on regular follow up for accrual of long term results. The impact of this study on long term survival as well as the long term morbidity associated with this protocol are to be analyzed in the future with a larger sample size in a randomized study.

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MASTER CHART

A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T
1	Sajeevamma	47	747/06	2	2	1	0	0	0	0	0	0	0	0	0	0	8	0	0
2	Thayammal	55	16/06	2	2	0	0	0	0	0	0	0	1	0	0	0	13	0	0
3	Andal	50	389/02	1	1	0	0	0	0	0	0	0	1	0	1	0	48	0	0
4	Alice	35	1146/05	2	1	1	0	0	0	0	0	0	0	0	0	0	14	0	0
5	Vasanthi	35	1000/06	2	1	0	0	0	0	0	0	1	0	0	0	0	6	0	0
6	Vasantha	42	127/05	3	2	0	0	0	0	0	0	0	0	0	0	0	24	0	0
7	Dhanalakshmi	48	761/06	2	1	0	0	0	0	0	0	0	1	0	0	0	8	0	0
8	Kanchana	35	519/05	1	1	0	0	0	0	0	0	0	0	0	0	0	20	0	0
9	Rajeswari	43	677/06	2	2	1	0	0	0	0	0	0	0	0	0	0	8	0	0
10	Adilaksmi	45	379/05	2	1	1	0	0	0	0	0	0	0	0	0	0	24	0	0
11	Latha	25	942/05	1	1	0	0	0	0	0	0	0	0	0	0	0	21	0	0
12	Ananathavalli	62	11168/05	3	1	1	0	0	0	1	0	0	0	0	0	0	15	1	0
13	Chinnaponnu	55	1283/04	2	1	0	0	0	0	0	0	0	0	0	0	0	27	0	0
14	Lakshmi	55	856/04	2	1	1	0	0	0	0	0	1	0	0	0	0	30	0	0
15	Santhi	40	66/06	2	1	0	0	0	0	0	0	0	0	0	0	0	15	0	0
16	Nagammal	50	29/07	2	2	0	0	0	0	0	0	0	0	0	0	0	2	0	0
17	Dhanalakshmi	35	1258/06	3	2	0	0	0	0	1	1	0	0	0	0	0	6	0	0
18	Muniamma	52	118/04	2	2	1	1	0	0	1	0	0	0	0	0	0	-	0	1
19	Seetha	40	141/04	2	2	1	0	0	0	0	0	0	0	0	0	0	39	0	0
20	Nagammal	45	1250/06	2	1	0	0	0	0	0	0	0	0	0	0	0	7	0	0
21	Padmavathi	64	1151/06	2	1	0	0	0	0	0	0	0	0	0	0	0	8	0	0
22	Lakshmi	40	1297/06	2	1	0	0	0	0	0	0	0	0	0	0	0	6	0	1

23	Valarmathi	40	62/07	2	1	0	0	0	0	0	0	0	0	0	0	3	0	0
24	Parvathi	48	1136/06	1	2	0	0	0	0	0	0	0	0	0	0	4	0	0
25	Sornammal	43	148/07	3	1	0	0	0	0	0	0	0	0	0	0	3	0	0
26	Sarojiniamma	45	78/06	2	2	1	0	0	0	0	0	0	0	0	0	14	0	0
27	Padmavathi	31	756/06	2	1	0	0	0	0	0	0	1	0	0	0	41	0	0
28	Pushpa	44	924/06	2	2	0	0	0	0	0	0	0	0	0	0	17	0	0
29	Pachayammal	50	678/06	2	1	0	0	0	0	0	0	0	0	0	0	11	0	0
30	Dhanalakshmi	42	284/02	2	2	1	0	0	0	0	0	0	0	0	0	41	0	0
31	Guna ammal	47	875/02	2	2	0	0	0	0	0	0	0	0	0	0	36	0	0
32	Vasanrha	40	710/02	2	2	1	0	0	0	0	0	0	0	0	0	39	0	0
33	Thankammal	54	374/06	1	2	1	0	0	0	0	0	0	0	0	0	8	0	0
34	Valliammal	55	780/06	2	1	0	0	0	0	0	0	0	0	0	0	8	0	0
35	Nagammal	78	318/05	2	2	1	1	0	0	0	0	0	0	0	0	24	0	0
36	Dhanalakshmi	55	529/06	2	2	0	0	0	0	0	0	0	0	0	0	10	0	0
37	Palaniammal	60	593/04	1	2	0	0	0	0	0	0	0	0	0	0	32	0	0
38	Gangai	45	996/04	2	2	1	1	0	0	0	0	0	0	0	0	29	0	0
39	Asirvatham	65	1471/04	2	1	0	0	0	0	0	0	0	0	0	0	29	0	0
40	Adilakshmi	60	1383/04	2	2	1	0	0	0	1	0	0	0	0	0	19	0	0
41	Sulochana	55	1334/04	2	1	0	0	0	0	0	0	0	1	0	1	27	0	0
42	Kani	45	1245/06	2	1	0	0	0	0	0	0	1	1	0	0	26	0	0
43	Mary	30	417/03	2	1	1	0	0	0	1	0	0	0	0	0	12	1	0
44	Muniamma	45	970/03	1	1	0	0	0	0	1	0	0	0	0	0	36	0	0
45	Kasthuri	49	1187/03	2	2	0	0	0	0	0	0	1	0	0	0	36	0	0
46	Lakshmi	50	2338/03	2	1	0	0	0	0	0	0	0	0	0	0	36	0	0

47	Rani	42	1164/05	2	1	0	0	0	0	0	0	0	0	0	0	0	24	0	0
48	Ponnamma	50	765/02	2	1	0	0	0	0	0	0	0	0	0	0	0	36	0	0
49	Pencilamma	45	189/03	2	1	0	0	0	0	0	0	0	0	0	0	0	36	0	0
50	Dhanalakshmi	48	216/03	2	2	1	0	0	0	0	0	0	0	0	0	0	36	0	0
51	Rani	40	236/03	3	2	1	0	0	0	0	0	0	0	0	0	0	24	0	0
52	Sowrajamma	54	589/01	2	2	0	0	0	0	0	0	0	0	0	0	0	48	0	0
53	Lakshmi	63	406/02	3	2	0	0	0	0	0	0	0	0	0	0	0	48	0	0
54	Umayal	50	213/02	2	1	0	0	0	0	0	0	0	0	0	0	0	48	0	0
55	Fathima Mary	49	1357/03	2	2	0	0	0	0	0	0	0	0	0	0	0	36	0	0
56	Guna Bhusanam	57	433/03	2	1	0	0	0	0	0	0	1	0	0	0	0	36	0	0
57	Alamelu	55	274/05	1	1	0	0	0	0	0	0	0	0	0	0	0	30	0	0
58	Salomi	38	370/05	2	1	0	0	0	0	0	0	0	0	0	0	0	24	0	0
59	Asmath	44	226/05	2	1	0	0	0	0	0	0	0	0	0	0	0	24	0	0
60	Lakshmi	55	1438/05	2	2	0	0	0	0	0	0	0	0	0	0	0	30	0	0
61	Ponnammal	45	1007/04	2	2	0	0	0	0	0	0	1	0	0	0	0	32	0	0
62	Saratha	35	675/04	2	1	1	0	0	0	0	0	0	0	0	0	0	30	0	0
63	Muniammal	52	1512/04	2	1	0	0	0	0	0	0	0	0	0	0	0	32	0	0
64	Pushpa	33	1064/04	1	2	0	0	0	0	0	0	0	0	0	0	0	33	0	0
65	Sasikala	30	606/02	3	1	1	0	0	0	0	0	0	0	0	0	0	12	0	0
66	Lakshmi	37	328/03	2	2	1	0	0	0	0	0	0	0	0	0	0	24	0	0
67	Vasantha	42	127/05	2	1	0	0	0	0	0	0	0	0	0	0	0	30	0	0
68	Seeniammal	42	1177/05	2	1	0	0	0	0	0	0	0	0	0	0	0	24	0	0
69	Kanthi	30	1154/05	3	2	1	0	0	0	0	0	0	0	0	0	0	12	1	0
70	Mallika	42	434/02	2	2	1	0	0	0	0	0	0	0	1	0	0	32	0	0

71	Ambujam	50	960/04	2	1	0	0	0	0	0	0	0	0	0	0	0	36	0	0
72	Karpagam	46	508/02	2	2	0	0	0	0	1	0	0	0	0	0	0	36	0	0
73	Varalakshmi	45	774/03	2	2	0	0	1	0	1	0	0	0	0	0	0	6	0	0
74	Gowri	53	682/02	2	2	1	0	0	0	0	0	1	0	0	0	1	12	0	0
75	Devaki	34	334/05	2	1	0	0	0	0	0	0	0	0	0	0	0	24	0	0
76	Sathyavathi	65	910/03	2	1	0	0	0	0	0	0	0	0	0	0	0	6	0	0

A-Serial No. B-Name C-Age D-C.D.No. E-Histological grade F-Tumor size

G - Residual Tumor H-Vaginal margin I-Right parametrium J-Left parametrium

K-Pelvic nodal residue L-Mortality M-Bladder morbidity N-Wound infection

O-Uretero vaginal fistula P-Incisional herenia Q-UTI R-Follow up(Months)

S-Local recurrence T-Distant Metastasis 0-No 1-Yes Tumor size: 0- ≤4 & 1- >4