"A MATCHED CONTROL STUDY ON THE OUTCOMES OF PATIENTS OF EARLY STAGE CARCINOMA CERVIX TREATED WITH NEOADJUVANT RADIOTHERAPY AND WERTHEIM'S HYSTERECTOMY COMPARED WITH DEFINITIVE RADIOTHERAPY"

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CERTIFICATE

I hereby certify that this dissertation **"A MATCHED CONTROL STUDY ON THE OUTCOMES OF PATIENTS OF EARLY STAGE CARCINOMA CERVIX TREATED WITH NEOADJUVANT RADIOTHERAPY AND WERTHEIM'S HYSTERECTOMY COMPARED WITH DEFINITIVE RADIOTHERAPY"** is a bonafide work done by **Dr. Mayank Pancholi,** in the department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance, supervision and to my satisfaction.

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CERTIFICATE

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CONTENTS

AIMS OF THE STUDY

1. To study the outcome of patients of carcinoma cervix treated with neoadjuvant radiotherapy followed by Wertheim's hysterectomy and bilateral pelvic dissection during a period of five years (2000-2004) in terms of pathological response rate, disease free survival and complications.

2. To compare the outcome of study population with outcome of matched patients treated with definitive radiotherapy during the same time period.

BACKGROUND

Cervical cancer is the second most common cancer in women worldwide and one of the commonest female cancers in many developing countries. The mean age for cervical cancer is 51.4 years. Early diagnosis of cervical cancer can be challenging because of these factors:

1. Frequently asymptomatic nature of early stage disease,
2. Origin of some cancers from within the endocervical canal or beneath the epithelium of the ectocervix, making visualization on speculum examination difficult,
3. Difficult access to health care and socioeconomic factors,
4. Significant false negative rate for Pap smears, even in women having regular screening.

Diagnosis of early stage invasive carcinoma cervix not only has the advantage of favourable outcome for the patients but also allows physicians to choose between treatment options available for a particular case depending on patients' preference and desired side effect profile, whereas in advanced carcinoma cervix the choice of treatment is limited to chemoradiotherapy or chemotherapy.

For early stage carcinoma cervix both radiotherapy and radical surgery are acceptable treatment options with comparable survival in most of the series. However a few studies have reported better survival for those patients who were treated with radical surgery upfront than those who were treated with definitive

radiotherapy in early stage carcinoma cervix. The treatment of such cases is mostly based on institutional practice, preference of the treating physician and the patient.

Surgery as definitive treatment is associated with better staging and identification of high risk features and directing adjuvant treatment to those patients who have indications for adjuvant therapy. Avoiding radical radiation in early stage disease also avoids the long term side effects of radiation like radiation cystitis and proctitis. The post-operative quality of sexual life after radiation is poor because of adhesive vaginitis, loss of lubrication and dyspareunia. Some authors also feel that surgery removes bulky nodes making adjuvant treatment more effective. On the contrary patients who need adjuvant treatment after radical surgery are subjected to morbidity of both modalities.

In the natural history of cervical cancer following treatment the local recurrences are central mostly emphasising the need for radiation to vagina and vault. Brachytherapy serves the purpose with the advantage of avoiding other organs in pelvis.

The role of neoadjuvant chemoradiotherapy and chemotherapy for carcinoma cervix cases is supported by a few trials, however to best of our knowledge no study has ever compared neoadjuvant radiotherapy followed by radical surgery as definitive treatment of carcinoma cervix in early stage.

By this study we aim at analysing the outcomes of those patients of early stage invasive carcinoma cervix treated with combination of both the modalities delivering less than radical radiotherapy before radical surgery, the theoretical advantage being able to avoid crossing tolerance of normal tissues and avoiding long term radiation side effects.

Material and methods

This is a retrospective study of patients of invasive Cervical Cancer stage IA/IB and IIA, who underwent treatment in our institute between years 2000 to 2004. Eligible patients were those who received a course of less than radical radiotherapy by either intracavitary application or external beam radiotherapy. Our operation record registers were searched for the patients who underwent surgery for carcinoma cervix during the foresaid period, all the available records were scrutinized and details were entered in a standard format which was uniform for study and control population except surgery details which were applicable only to the study group. All patients underwent clinical examination before treatment by an experienced clinician, and haemogram, renal and hepatic function tests, coagulation profile as well as cardiac evaluation was done with standard metastatic work up. A biopsy confirmation of the disease was done and a clinical stage was assigned by the same physician to all patients. In the case of discrepancy between the findings of two clinicians, findings of the above mentioned clinician were considered for the purpose of this study. Whenever a single clinical stage could not be assigned due to ambiguous clinical findings and discrepancy occurred, the lower stage assigned was taken as the final stage. All available relevant information as symptoms and their duration, age at presentation, obstetric, reproductive history and family history were noted, comorbidities were noted to subsequently match with the control group, tumour

characteristics such as size, gross morphology and histology with grade were noted, preoperative treatment in form of brachytherapy or external beam radiotherapy was noted, total dose delivered and duration of treatment was also noted. Mean dose of radiation delivered by Intracavitary application was 23Gy whereas median dose of external beam radiation was 40Gy. Subsequently standard Wertheim's hysterectomy with nodal dissection was performed, complications and time of their occurrence was noted till the last available follow up, final histopathology report was assessed for response including pathologic complete response and size of residue, margins on vaginal and parametrial aspect, lymph node yield, lymphovascular invasion and nodal positivity were noted. Adjuvant treatment given was noted, subsequent follow up, disease recurrence site and treatment given on recurrence were noted.

A similarly matched control group who received treatment during the same time period (2000-2004) by definitive radiotherapy were studied using the same variables and compared, late and early complications were noted and compared.

Inclusion Criteria:

1. Women with histologically proven invasive carcinoma of the uterine cervix, stages IA, IB, IIA.

2. Age between 18-70 years.

3. No evidence of visceral, skeletal or distant nodal metastases.

4. No history of past or coexisting second malignancy.

5. Good performance status (Karnofsky performance score > 70 or ECOG PS <2).

6. Normal hematologic & biochemical parameters.

7. No prior treatment for the same cancer elsewhere.

Exclusion criteria:

1. All patients who did not have preoperative diagnosis of invasive cervical carcinoma.
2. All patients who were too elderly to be considered for surgery.
3. All patients who did not undergo standard Wertheim's hysterectomy with bilateral pelvic dissection.
4. Any preoperative uncontrolled comorbidity medical or otherwise which would lead to preference of one treatment over the other.
5. Any patients not satisfying the inclusion criteria.

All those patients who did not match with our study eligibility criteria were excluded from the study. All the patients were followed up by means of clinical examination monthly for the first month, once in two and three months for the second and third year and subsequently 6 monthly during the fourth year and yearly thereafter. Annually ultrasound abdomen, chest radiography were done, any suspicious clinical findings were evaluated further by appropriate tests.

Review of literature

Cervical cancer is a common cancer and is one of the leading causes for which oncology opinion is sought in both developing and developed world. Unfortunately, in countries where penetrance of cervical cancer screening is poor, cervical cancer remains the second most common type of cancer (17.8 per 100,000 women) and cause of cancer deaths (9.8 per 100,000) in women. The burden of disease in developed countries is also considerable, cancer of the cervix was third most common cancer diagnosis as well as cause of mortality among gynecologic cancers in the United States in 2011 [1]. The disease is usually seen at a mean age of around 45 years with peak distribution of cases between 35-39 years and 60-65 years. The five year survival for cases of cervical cancer vary with the stage at diagnosis, which is better for early stage disease and 5 year survival rate ranges from 93%-80% for stage I, 63%-58% for stage II, 35%-32% for stage III and 16%–14.6% for stage IV according to a study of 15070 cases from National cancer database in USA. Most common histology encountered is squamous cell carcinoma and adenocarcinoma, other rare types accounting only for a minority of cases and are generally associated with poor prognosis.

Risk Factors

Human papilloma virus is associated with around 99% of carcinoma cervix cases. Molecular and epidemiological studies have shown a strong correlation

between human papilloma virus infection, intraepithelial neoplasia and invasive cervical cancer. Human papilloma virus infection has gradually been considered a necessary prerequisite for cervical carcinoma.

Numerous other risk factors have been proposed including young age at first intercourse (less than 16 years), sexual promiscuity in both males and females, cigarette smoking, high parity and lower socioeconomic status with a few studies relating significant racial difference among different ethnic and socioeconomic groups which probably reflects the access to health care facilities and screening program, the impact of which is more pronounced with increasing age. AIDS and iatrogenic immunosuppression in transplant patients is also associated with cervical cancer. Several studies also point to the use of oral contraceptives and subsequent adenocarcinoma of cervix.

Clinical Presentation:

In populations where screening penetrance is more the proportion of cases detected by cytology examination of cervical smear is comparatively more and diagnosis is at an earlier age. The most common presentation in symptomatic patients is abnormal bleeding per vagina which may be present for a long time before it comes to attention. In a review of cervical cancer cases by Pretorius et al. 56% of all cases presented with abnormal vaginal bleeding, 28% had an abnormal pap smear, 9% presented with pain, 4% had vaginal discharge and 3% with other symptoms [2]. The presence of a negative pap smear in a screening

program, but in presence of suspicious clinical presentation, should be investigated further as the false negativity rate of pap smear in a case of invasive carcinoma may be as high as 50% [3].

Pathogenesis of Cervical cancer

Human papilloma virus is one of the most frequently sexually transmitted infections, it is associated with condyloma acuminata, anogenital (cervix, vagina and anal) squamous intraepithelial lesions and their progression to malignancy, and head and neck cancer. A study by Richart and Barron suggested that invasive squamous cell carcinoma was the result of progressive intraepithelial dysplastic change. HPV genotypes can be broadly classified into "high-risk" which includes types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68 and "low-risk" including types 6, 11, 40, 42, 43, 44, 53, 54, 61, 72, 73 and 81. Types 16 and 18 are the most commonly isolated HPV types in cervical cancer with type 16 found in approximately 50%of patients [4]. The Viral genome codes for six early (E) proteins which are associated with viral gene regulation and cell transformation, there are other two late (L) proteins which form the shell of the virus, and a region containing regulatory DNA sequences [5,6]. The most important HPV proteins implicated in malignancy are E6 and E7. Their action is exerted through interaction with p53 and Rb gene. In a normal cell p53 regulates apoptosis and cell cycle, when it is degraded by E-6 associated protein it results in loss of cell cycle control and loss of apoptosis

leading loss of control on proliferation of cells harbouring mutations resulting in accumulation of mutations. Same way Rb gene inactivates E2F transcription factor by forming E2F/Rb protein complex. When E7 interacts with this complex it releases E2F this allows uncontrolled continuation of cell cycle and further accumulation of mutations.

HPV infection is transient in most of the women. Acute infection with HPV is latent and characterized by nuclear enlargement, multinucleation, hyperchromasia, and perinuclear cytoplasmic clearing (halos) also called as koilocytic atypia [7]. Neoplastic transformation occurs when the HPV genome integrates with host DNA which usually is seen in high risk HPV.

Historically the changes in cervical epithelial cells were described by terms like mild, moderate and severe dysplasia which were replaced by CIN 1,2,3 which is a histologic diagnosis signifying presence of mitosis, immature cells in lower third, lower and middle third and involvement upto upper third. In addition, LSIL and HSIL are also used by some to describe histologic results although this terminology was originally intended for cytology. For histology, LSIL is equivalent to CIN1 and other abnormalities defined above, HSIL comprises either CIN 2 or 3.

Histologic Types

Squamous cell carcinoma

Invasive cervical carcinoma arises from high-grade dysplasia, which may have a long latent period of up to 10 years before invasive carcinoma develops [8].The incidence of invasive squamous cell carcinoma developing so is about 34% over a period of 10 years [9]. Invasive carcinomaof cervix develops most often after the age of 40 years [10], although younger women may be affected. Invasive squamous carcinomas are classified as keratinizing or non keratinizing, although this classification has no prognostic significance. Keratinizing squamous carcinoma displays classical keratin pearl formation. Nonkeratinizing squamous carcinoma has irregular nests of cells that may display abundant eosinophilic cytoplasm with intercellular bridges but do not contain keratin pearls. Some squamous carcinomas are composed of smaller cells without evidence of neuroendocrine differentiation; these neoplasms are classified as small cell squamous carcinoma and generally thought to have poorer prognosis compared to large cell carcinoma.

Adenocarcinoma

Adenocarcinoma represents about 20% to 25% of cervical cancers in various studies. In a study by Ursin et al. oral contraceptive use has been implicated in the increase in adenocarcinomas in women younger than 35 years of age [11]. A

Canadian study reported presence of HPV in about 70% of cases (53 of 77) with HPV 16 the predominant type [12]. The incidence of human papilloma virus infection in adenocarcinoma of cervix is generally less than that in squamous cell carcinoma. Adenocarcinoma is generally regarded as being more radio-resistant than squamous carcinoma. In the Italian randomized study comparing radical surgery versus radiation therapy for stages IB to IIA cervical cancer, 46 of 343 patients (13.4%) had adenocarcinoma [13]. Surgery and radiation therapy were found to be identical in terms of 5-year survival and disease-free survival rates for the entire group, but in the subgroup of patients with adenocarcinoma, surgery was significantly better in terms of both overall survival (79% vs. 59%, $p = 0.05$) and disease-free survival rates (66% vs. 47%, $p = 0.02$).

Adenosquamous Carcinoma

Adenosquamous carcinoma may form approximately 20% to 30% of all adenocarcinomas of the cervix. Most studies report a poorer outcome. In one of the largest series of surgically staged IB cases by Helm et al. [14], 38 patients with adenosquamous carcinomas were matched and compared with patients with other histologic subtypes of adenocarcinoma. Overall 5-year survival and disease-free survival for the matched adenosquamous and adenocarcinomas were not significantly different (83% vs. 90% and 78% vs. 81%, respectively), however the mean time to recurrence was significantly shorter in the

adenosquamous group: 11 versus 32 months (p = 0.003). Similar findings were also confirmed in the M.D. Anderson Cancer Centre series comparing 29 patients with stage IB1 adenosquamous carcinoma with 97 patients with stage IB1 adenocarcinoma of the cervix undergoing radical hysterectomy. There was no difference in recurrence rates between the two histologic groups, but the time to recurrence was shorter for patients with adenosquamous carcinoma (7.9 months vs. 15 months; p = 0.01) [15].

Glassy Cell Carcinoma

First defined by Glucksman and Cherry in 1956, “glassy cell” carcinoma of the cervix was described as a poorly differentiated adenosquamous carcinoma, microscopically the cells had moderate amount of cytoplasm and a typical “ground glass” appearance. Survival was poor, regardless of the mode of therapy. Subsequently, Tamimi et al. concluded that the poor prognosis ascribed to the classically defined glassy cell carcinoma also holds true for large-cell undifferentiated cervical cancers [16].

Adenoma Malignum

First used by Gusserow in 1870 to describe a very highly differentiated adenocarcinoma. McKelvey and Goodlin reported five cases, four of which succumbed to disease within 4 years of presentation [17]. In 1975, in a report by Silverberg and Hurt, five cases were treated and four of the five were long-term

survivors and authors suggested that the cancer was no more malignant than the usual adenocarcinoma counterpart. These tumours form a minority of all the cervical carcinomas and occur in slightly elderly population.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is a rare tumour. In a report by Musa et al. the sites of origin of these tumours in the female genital tract were Bartholin's gland, the endometrium, and the cervix [18]. Etiology of these tumours is unresolved. Overall survival is poor. Prempree et al. in a review of literature, reported a 3- to 5-year survival rate of only 56.3% (9 of 16) for patients with stage I disease, regardless of the type of treatment. The survival rate for stage II disease was 27.3% (3 of 11), and no patient with stage III or IV disease survived 3-5 years. Lung metastases were common site of distant spread, whereas spread locally was by direct tissue invasion and perineural infiltration.

Adenoid Basal Carcinoma

This is a rare tumour with an excellent prognosis. Most adenoid basal carcinomas have coexistent in situ or invasive squamous carcinoma, and almost half have coexistent in situ or invasive adenocarcinoma. The tumour is almost invariably confined to the cervix, and in a review of 26 cases reported in the literature, only one died of disease due to lung metastases [19]. Tumour

invasion is usually superficial, and simple or radical hysterectomy without lymphadenectomy is a reasonable treatment option.

Clear Cell Adenocarcinoma

The tumourhas a bimodal peak, first in those younger than 24 years and those older than 45 years [20]. The former are related to in utero diethylstilbestrol exposure, but even in these young women, there is no history of hormone exposure in approximately 25% of cases, the prognosis is comparable to that of other adenocarcinomas [20,21].

Villoglandular Papillary Adenocarcinoma

An uncommon type of tumour, occurs in younger women and has a more favourable prognosis. In a report by Young and Scully describing 13 cases, the patients' ages ranged from 23 to 54 years (average 33 years). Treatment was done by cone biopsy for early stage and radical hysterectomy and pelvic lymphadenectomy in others. With follow-up of 2 to 14 years, no recurrences were seen.

Small-Cell Carcinoma

Small-cell cancers are rare representing 0.5% to 5% of all invasive cervical cancers. In a study of 2,201 invasive cervical cancers at the University of Kentucky Medical Centre, Van Nagell et al. noted 25 cases (1.1%) of small-cell carcinoma. 33% of these stained positively for the neuroendocrine markers

(neuron-specific enolase and chromogranin), others stained only for epithelial markers such as cytokeratin and epithelial membrane antigen. In general these tumours have a higher frequency of lymph-vascular space invasion, significantly higher recurrence, metastasis to extrapelvic sites, and a lower survival rate overall.

A later study of SEER data from 1977 to 2003, 0.9% patients were diagnosed with small-cell carcinoma of the cervix, five year survival for small-cell carcinoma (35.7%) was worse compared with squamous cell carcinoma (60.5%) and adenocarcinoma (69.7%) with a predilection for nodal and distant metastases, the poor survival was independent of stage and nodal status. The group at the Chang Gung Memorial Hospital in Taiwan administered adjuvant chemotherapy to 23 consecutive patients with stage IB to II small-cell cervical cancer who had been treated primarily with radical hysterectomy. Ten of 14 patients (71.4%) who received a combination of vincristine, doxorubicin, and cyclophosphamide alternating with cisplatin and etoposide had no evidence of disease during a median follow-up of 41 months, whereas only 3 of 9 (33.3%) who received cisplatin, vinblastine and bleomycin (PVB) survived. The survival rate was 70% for patients with negative lymph nodes and 35% for those with positive nodes ($p = 0.05$). All patients who died of disease had extrapelvic metastases [22].

Papillary Serous Carcinoma

Pathologically tumour resembles papillary serous carcinoma of ovary. In a study by Zhou and colleagues 17 cases were reported. Two peaks were observed one occurring before the age of 40 years and the second peak after 65 years. The outcome for patients with stage I tumours was similar to that of patients with cervical adenocarcinomas of the usual type however, patients with advanced disease were more likely to have rapidly fatal outcome with widespread metastasis.

Sarcoma

In a literature review Rotmensch et al. identified 105 reported cases of cervical sarcomas. A variety of treatment strategies had been used in the management of cervical sarcomas, and generally the overall prognosis was poor [23].

Sarcoma Botryoides

In 1988 a report by Daya and Scully [24] reviewed 13 cases whose ages ranged from 12 to 26 years, with a mean of 18 years. All had polypoid tumour and presented with vaginal bleeding with or without tumour protruding from the introitus. The patients were treated with operative procedures ranging from cervical polypectomy to hysterectomy with pelvic and paraaortic node dissection with and without chemotherapy. Twelve of the 13 patients (92%) were alive and well 1 to 8 years after surgery.

Malignant Mixed Müllerian Tumour

A rare subtype of cervical carcinoma. Most patients present with abnormal vaginal bleeding. Treatment is by radical hysterectomy with or without radiotherapy. Using such an approach in a report of five cases from Iowa, Sharma et al. reported survival of these patients, all were alive and free of disease at 28, 35, 42, and 65 months, respectively [25].

Lymphoma

Cervical lymphomas are rare, in a study by armed forces institute of pathology these constituted about 0.06% of all lymphomas. Presentation is like any other cervical cancer but histologic diagnosis is difficult. Harris and Scully reported that only 15 of 25 cases (55%) referred for consultation were correctly diagnosed by the referring pathologist. Komaki et al. emphasized the importance of distinguishing malignant lymphoma from undifferentiated carcinoma or sarcoma because cervical lymphoma can be successfully treated in spite of locally advanced disease [26].

Verrucous Carcinoma

Usually a slow-growing, locally aggressive, papillomatous lesion. This was first reported in the cervix in 1972.In a literature review in 1988, by Crowther et al., suggested that some of these should be considered papillomas that had undergone malignant change. Radical surgery is the mainstay of treatment.

Melanoma

Malignant melanoma of the cervix is a rare entity. These tumours have, in general, been reported to occur in the seventh and eighth decades and most lesions present with abnormal vaginal bleeding. Treatment is usually radical hysterectomy with or without pelvic lymphadenectomy. Adjuvant radiation may improve local control if the surgical margins are close. The 5-year survival rate is poor, not exceeding 40% for stage I disease and reaching only 14% in stage II [27,28].

Metastatic Carcinoma

Metastasis of malignant epithelial tumours to the uterine cervix is a rare occurrence. A study by Lemoine and Hall reportedonly 33 acceptable cases from 1919 to 1984. Primary sites of disease included stomach, ovary, colon, breast, kidney, renal pelvis, carcinoid, and pancreas.

Patterns of Spread

Direct infiltration: Malignant cells penetrate the basement membrane progressively infiltrating the underlying stroma and tissues in continuity.

Lymphatic Spread: Cervical cancer can spread to all pelvic node groups, although the obturator nodes are most frequently involved. The parametrial nodes, common iliac and paraaortic nodes may be directly involved by aberrant pathways, however, generally the lymph node spread in cervical cancer is in an

orderly fashion from the nodes on the pelvic sidewall to the common iliac and then the paraaortic group. From the paraaortic nodes, spread can occasionally occur through the thoracic duct to the left scalene nodes [29].

The concept of sentinel node identification for cervical cancer was first introduced by Dargent in 2000 [30]. Several authors have subsequently identified sentinel nodes in 70% to 100% of patients. Sentinel nodes have usually been located in the hypogastric, external iliac, obturator, common iliac and paraaortic regions and sometimes in unusual location like in the left groin [31].

Burghardt and Girardi [32] proposed the mechanism of discontinuous paramtrial involvement by tumour emboli held up in lymphatic vessels in parametria grow to become foci of discontinuous parametrial involvement.

Ovarian involvement by cervical cancer is rare but most likely occurs through the lymphatic connection between the uterus and the adnexal structures. In a study of patients with clinical stage IB cervical cancer, the GOG reported ovarian spread in four of 770 patients (0.5%) with squamous carcinoma and in two of 121 patients (1.7%) with adenocarcinoma. All patients with ovarian metastases had other evidence of extracervical spread [33].

Hematogenous Spread: Although spread to virtually all parts of the body has been reported, the most common organs for hematogenous spread are the lungs, liver, and bone.

Overview of management of early stage disease (FIGO IA, IB, IIA)

Early stage disease treatment decision is based on a variety of factors including informed decision making between patient and the treating physician, desired side effect profile, health concerns of the patient and future fertility concerns.

Fertility sparing surgery

Microinvasive disease

Women with stage IA1 disease without lymphovascular space involvement (LVSI) are candidates for treatment with conization or simple hysterectomy, a number of Studies show that recurrence occurs in 3% or fewer of these patients [34,35,36].

A United States national cancer database study (n=1409) of women age less than40 years with stage IA1 cervical cancer found no significant difference in five-year survival between those who underwent conization versus hysterectomy (98 versus 99 %); data regarding LVSI were not available [37].

Vaginal Radical Trachelectomy

The vaginal radical trachelectomy procedure was developed by the late Professor Daniel Dargent from Lyon, France at the end of the 1980s. Suitable candidates should be desirous to preserve fertility, having age less than 40 years, Stage IA1 with vascular space invasion, IA2 or IB1, lesion size less than 2 to 2.5 cm, with limited endocervical extension as assessed by colposcopy and magnetic resonance imaging, squamous carcinoma or adenocarcinoma histology with no evidence of lymph node metastasis.

Abdominal Radical Trachelectomy

The abdominal radical trachelectomy procedurewas developed by Smith et al in 1997 [38].

Radical Hysterectomy

Advantages of surgery over primary chemoradiotherapy for young women are:

1. The ovaries can be left intact, and

2. The sexually active patient may be left with a more functional vagina,

3. If the need for adjuvant RT is anticipated, the ovaries can be transposed out of the RT field.

4. Resection of bulky metastatic lymph nodes may be of therapeutic benefit.

On the other hand, if a primary surgical approach is chosen and adjuvant chemoradiotherapy is required, there may be additional morbidity from this multimodality approach, as compared to definitive chemoradiotherapy or definitive radiotherapy.

Types of Radical Hysterectomy

In 1974, Piver et al. [39] described the following five types of hysterectomies:

Type I Extrafascial Hysterectomy: This is a simple hysterectomy and is suitable for stage IA1 cervical carcinoma.

Type II Modified Radical Hysterectomy: This is basically the hysterectomy described by Ernst Wertheim [40]. The uterine artery is ligated where it crosses the ureter, and the medial half of the cardinal ligaments and proximal uterosacral ligaments are resected with specimen. Removal of upper 1/3rd vagina as described by Piver et al. is usually not necessary. Wertheim described removal of involved enlarged nodes rather than systematic pelvic lymphadenectomy. The modified radical hysterectomy is appropriate for stage IA2 cervical cancer.

Type III Radical Hysterectomy: Performed for stage IB cervical cancer, this operation was originally described by Meigs in 1944 [41]. The uterine artery is ligated at its origin from the superior vesicle or internal iliac artery, allowing removal of the entire width of the cardinal ligaments. Piver et al. described

excision of the uterosacral ligaments at their sacral attachments and resection of the upper half of the vagina.

Type IV Extended Radical Hysterectomy: This differs from the type III operation in three aspects: (i) The ureter is completely dissected from the vesicouterine ligament, (ii) the superior vesicle artery is sacrificed, and (iii) three-fourths of the vagina is excised. The risk of ureteric fistula is increased with this procedure. Piver et al. used this for selected small central recurrences after radiation therapy.

Type V Partial Exenteration: This procedure was intended for removal of a central recurrence involving a portion of the distal ureter or bladder. The relevant organ was partially excised and the ureter reimplanted into the bladder. This procedure may occasionally performed in primary setting if cancer is found to be unexpectedly encasing the distal ureter at the time of radical hysterectomy.

A new classification for radical hysterectomy was described by Shingo Fuji in February 2007 [42]. The classification is based only on the lateral extent of the resection. Four basic types are described, A-D, adding when necessary a few subtypes that consider nerve preservation and paracervical lymphadenectomy. Lymph node dissection is considered separately, and four levels 1,2,3,4 are defined according to the corresponding arterial anatomy and the radicality of the procedure.

Choice of hysterectomy: Type II Versus Type III

The therapeutic efficacy of a type II radical hysterectomy appears comparable to that of a type III procedure for stage IB and IIA cervical cancer, but with lower morbidity. A randomized trial compared type II (modified radical hysterectomy) and type III (radical hysterectomy) procedures in patients with stage IB or IIA disease [43]. The type II operation was associated with a shorter mean operative time (135 versus 180 minutes), less late urologic morbidity (13 versus 28 %), and similar recurrence rates (24 versus 26%), cause-specific mortality (18 versus 20 %), five year overall survival (OS, 81 versus 77 %) and five year disease-free survival (DFS) (75 versus 73 %). Thus, the choice of procedure depends on margins of resection with type II procedure being as good as type III procedure provided safe margins can be obtained.

A number of studies have reported that a minimally invasive radical hysterectomy has a definitive perioperative advantages (decreased blood loss, shorter hospitalization, faster recovery, better cosmetic results) compared with an abdominal radical hysterectomy [44, 45, 46, 47]. However, there are no appropriately powered randomized controlled trials to confirm whether long-term patient survival is equivalent for the two surgical approaches.

No residue after radical hysterectomy

In cases where presumably diagnostic excision biopsy resulted in complete removal of tumour and subsequent radical hysterectomy specimen did not reveal any tumour residue, these patients have an excellent prognosis. In a retrospective review of 594 patients with invasive cervical cancer, 29 % of patients, all with stage IA1 to IB1 disease, had no residual tumour in the pathology specimen [48]. These women have an excellent prognosis with radical hysterectomy and lymph node dissection only.

Lymph node sampling

A primary surgical approach to treatment of cervical cancer allows resection of bulky lymph node metastases, which may be of therapeutic benefit. For paraaortic node metastases, a large retrospective study found that survival was improved in women who underwent lymph node sampling (n = 555) compared with radiographic evaluation (n = 130) [49]. All patients had FIGO stage IIB through IVA disease with no evidence of paraaortic lymph node metastases and were subsequently treated with cisplatin based chemoradiation. Patients who had lymphadenectomy had a better prognosis than those who were evaluated radiographically. Patients with stage III/IV disease had four-year progression-free survival and overall survival of 49% and 54% for the surgically staged patients versus 36% and 40% for the radiographically staged patients.

Indications for adjuvant therapy

High-risk disease

Women with one or more of the following findings are considered to be at high risk for recurrent disease, and should receive adjuvant therapy following hysterectomy [50,51]:

Positive or close resection margins,

Positive lymph nodes,

Microscopic parametrial involvement,

Although increase in the number of positive nodes increases the risk of recurrent disease [52,53], even one microscopically positive node has the same recurrence risk as several positive nodes and adjuvant chemoradiotherapy should be considered [54].

Radiation versus chemoradiotherapy

The superiority of concomitant chemoradiotherapy over adjuvant radiotherapy (RT) alone was initially shown in a trial that randomly assigned 268 women undergoing hysterectomy for high-risk but localized cervical cancer to radiotherapy (49.3 Gy in 29 fractions to a standard pelvic field) with or without chemotherapy (four cycles of cisplatin 70 mg/m2 on day 1, plus 5-fluorouracil [5-FU] 1000 mg/m2 per day by continuous infusion for four days, every three

weeks) [50]. The first and second courses were administered concurrent with radiotherapy. The use of chemotherapy was associated with a significantly better four year overall survival (81 versus 71 %) and progression-free survival (PFS, 80 versus 63 %).

The benefits of chemoradiotherapy over radiotherapy alone were again confirmed in a Cochrane meta-analysis of 13 randomized trials comparing chemoradiotherapy versus radiotherapy alone in women with FIGO stage IA to IVA disease. In this meta-analysis Compared with radiotherapy alone, chemoradiotherapy was associated with a significant 19 % reduction in the risk of death, which translated into an absolute improvement in five-year overall survival from 60 to 66 %. Results from two trials suggested that there was a larger benefit by adjuvant chemotherapy after concurrent chemoradiotherapy.

There was a trend toward greater benefit from chemoradiotherapy in patients with lower stage disease. The hazard ratios for overall survival benefit translated into absolute five-year survival benefits of 10%, 7%, and 3 % for patients with IB/IIA, IIB, and III to IVA disease, respectively.

Benefits were obtained by using non-platinum as well as platinum based chemotherapy concurrently with radiation.

Intermediate-risk disease

The benefit for postoperative radiotherapy in women with factors suggestive of intermediate-risk disease was demonstrated in a randomized GOG trial that assigned 277 such women to pelvic radiotherrapy (without chemotherapy) or no further postoperative treatment. The features that were considered indicative of intermediate risk-disease in this study were as follows [56, 57]:

Large tumour size (>4 cm) [58],

Deep cervical stromal invasion (to the middle or deep one-third),

Lymphovascular space invasion,

Adjuvant RT was associated with a significant improvement in two-year recurrence-free survival (88 versus 79 %), and despite early follow-up, a significant 36 % reduction in the risk of death [59]. In a later publication with 10-year median follow-up, a significant benefit was still evident for radiotherapy in terms of progression-free survival (hazard ratio [HR] 0.58, 95% CI 0.40 to 0.85), but the 30 % reduction in the risk of death was not statistically significant ($p = 0.07$).

Chemoradiotherapy versus RT in intermediate risk patients

There are no randomized trials that specifically address the benefit of chemoradiotherapy versus RT alone in women with intermediate-risk early stage cervical Squamous cell carcinoma. A secondary analysis of the trial (GOG

109) of postoperative RT versus chemoradiotherapy in women undergoing radical hysterectomy and pelvic LND for stage IA2, IB or IIA cervical cancer showed the absolute improvement in five-year survival from the addition of chemotherapy to RT appeared to be less for tumours <2 cm (82 versus 77 %, difference of 5 %) than for those over 2 cm (77 versus 58 %, difference of 19 %), and for patients with only one nodal metastasis compared to more than one. This data supports the view that smaller tumours derive quantitatively less benefit from the addition of chemotherapy to RT.

Definitive radiotherapy and chemoradiotherapy

Oncologic outcomes are similar with either definitive radiotherapy (RT) or radical surgery with or without postoperative radiotherapy for treatment of early stage (stages IA, IB, and IIA) disease. The best available evidence comes from the only randomized trial which directly compared hysterectomy plus adjuvant RT versus RT alone (without concurrent chemotherapy) in 343 women with stage IB1 to IIA disease [61]. Five-year rates of overall survival and DFS were identical in both groups (83 and 74 %, respectively). A subsequent analysis suggested the superiority of surgery over RT [62]. This retrospective review of data on 4885 women with stage IB1 to IIA cervical cancer treated between 1988 and 2005 and included in the United States SEER (Surveillance, Epidemiology and End Results) registry, in multivariate analysis, there was an apparent survival benefit for surgery versus RT alone in women with tumours ≤6 cm

(relative reduction in mortality with surgery versus RT was 62 and 49 % for tumours <4 and between 4 and 6 cm, respectively). However, this study had several major limitations. The most obvious limitation is the inherent bias that impacts treatment selection (ie, healthier women are more likely to be selected for surgery than to radiotherapy). Furthermore, one half of the women in the hysterectomy group also received radiotherapy, and comparisons were not made between women treated solely with surgery versus radiotherapy. Finally, as with the randomized trial described above, the lack of information on use of concurrent chemotherapy limits the interpretation of the results with radiotherapy. The superiority of concomitant chemoradiotherapy over radiotherapy alone in women with both early and locally advanced cervical cancer had been shown in at least five controlled trials and a meta-analysis. These data have led to the adoption of chemoradiotherapy as the preferred approach whenever RT is administered for the treatment of women with cervical cancer, over a broad spectrum of disease stages.

Radiotherapy Techniques

The two main methods of radiotherapy delivery are external photon beam and brachytherapy, brachytherapy in turn can be delivered using an intracavitary approach or via an interstitial approach. Brachytherapy alone is adequate treatment for stage IA1 disease, external beam RT is generally added to brachytherapy to improve pelvic control with more advanced disease.

Intracavitary brachytherapy is the most widely used technique while interstitial brachytherapy is typically considered for women whose disease cannot be optimally encompassed by intracavitary application. In a retrospective series comparing outcomes in 61 patients with stage II (bulky), III, or IVA cervical cancer treated with combined external beam RT and intracavitary brachytherapy versus 70 similarly staged women treated with external beam radiotherrapy and interstitial brachytherapy [63]. Inferior outcomes were found in women treated with interstitial therapy in terms of five-year DFS (21 versus 50 % p = 0.01) and local-regional control (32 versus 61 %, p = 0.01). Morbidity was same in both the groups [63]. Thus, interstitial brachytherapy should be used only in select cases in which the use of intracavitary radiotherapy is precluded.

HDR brachytherapy provides the significant advantage of eliminating exposure of medical personnel to radiation, a shorter treatment period, and the possibility of ambulatory treatment. In at least three randomized trials in women with cervical cancer, HDR was comparable to LDR brachytherapy in terms of oncologic outcomes and complication rates [64,65,66]. The use of external beam RT prior to brachytherapy offers several advantages by decreasing size of bulky endocervical tumours allowing more optimal coverage by the intracavitary dose distribution, while shrinking bulky ectocervical disease improves tumour geometry and therefore optimal brachytherapy placement. The treatment volume for women undergoing adjuvant external beam RT typically

involves the whole pelvis, with larger portals required for higher stage (ie, IIA) disease. Extended field RT, in which the treatment portal is extended to the paraaortic region, is typically considered for women who are known to or suspected of harbouring paraaortic lymph node metastases, typically those with more advanced stage disease.

The use of IMRT and brachytherapy have been compared with conventional radiotherapy and brachytherapy, the results consistently show reduction in toxicity and radiation morbidity with equivalent oncologic control rates.

Role Of Ovarian Transposition

Women who undergo pelvic radiotherapy will develop premature ovarian failure as a side effect of radiotherapy. In an attempt to prevent this ovarian transposition out of the field of radiation has been tried but without much success. The benefits are inconsistent partly due to scatter radiation and also due to theoretical possibility of disease recurrence in the region where ovaries are shielded.

Role Of Postchemoradiotherapy Extrafascial Hysterectomy

Extrafascial hysterectomy confers little, if any, overall survival benefit. The benefit of adjuvant extrafascial hysterectomy after radiotherapy alone was studied in a GOG trial in which 256 patients with tumours measuring more than 4 cm were randomly assigned to radiotherapy alone or radiotherapy followed by

surgery [67]. There was a lower cumulative incidence of local relapse in the surgery group (at five-years, 14 versus 27 %), but not survival benefit.

Surgery Versus Chemoradiotherapy

As discussed above, definitive RT and radical surgery are both accepted treatments of early stage cervical cancer, since oncologic outcomes are similar. Therefore, the decision to proceed with one versus the other is based on other factors, such as childbearing plans, comorbidities, physician and patient preference, and quality of life (QOL) issues.

In general, QOL measures in cancer survivors appear to be higher following surgery than RT; however, it is difficult to draw firm conclusions from the available data due to methodological differences [68]. Ovarian function is more likely to be preserved with surgery than RT, providing a benefit to premenopausal patients. Primary surgery also allows for resection of bulky LN metastases, which may be of therapeutic benefit, through staging lymph node dissection, and it enables the selection of patients for postoperative chemoradiotherapy based upon histopathological review of surgical specimens.

Sexual function and psychosocial well-being

Both hysterectomy and radiotherapy can lead to changes such as vaginal shortening and decreased vaginal lubrication, which adversely influence sexual function, overall QOL, and psychosocial well-being following treatment. The

reported frequency with which these changes occur is quite variable. Vaginal changes after RT include foreshortening, stenosis, and decreased lubrication. These physical changes impact sexual function because they can result in dyspareunia, and influence sexual satisfaction, the ability to have an orgasm, and coital frequency.

The separate contribution of deficits related to surgery or radiotherapy was addressed in a retrospective comparison of 114 women who were interviewed five years after completing treatment for cervical cancer with either surgery (n = 37) or RT (n = 37); a separate control group consisted of age- and race-matched women with no history of cervical cancer [69]. Compared to surgically treated women and controls, irradiated women had significantly worse scores on standardized questionnaires measuring health-related quality of life (physical and mental health), psychosocial distress, and sexual functioning. In contrast, there were no significant differences in any of these measures when women undergoing surgery for cervical cancer were compared to controls.

Prognosis

The major prognostic factors affecting survival among women with cervical SCC are stage, nodal status, tumour volume, depth of cervical stromal invasion, lymphovascular space invasion (LVSI), and to a lesser extent, histologic type and grade. Disease stage is the most important prognostic factor, followed by LN status. After radical hysterectomy and LND, women with stage IB or IIA

disease, who have negative pelvic lymph nodes have a five-year survival of 88 to 96 %, compared to 64 to 74 % for those with similar stage disease and pelvic nodal metastasis. Outcomes are worse for women with involved paraaortic nodes. Among patients who have undergone surgical staging the number of involved lymph nodes also influences prognosis, in one report by Tanaka et al. five-year survival rates for patients with one, two, three to four, and five or more positive lymph nodes were 62, 36, 20 and 0 %, respectively [70]. The prognostic significance of pelvic LN micrometastases in women with early stage disease is unclear [71, 72, 73, 74].

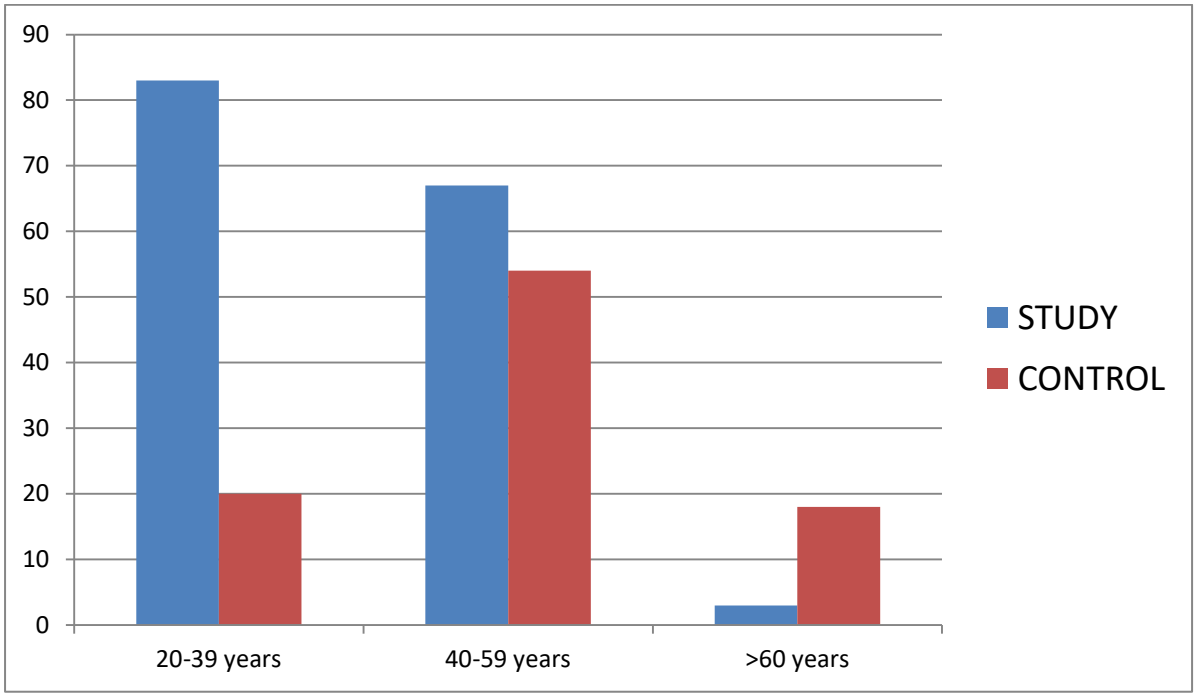
Results

Total patient records studied for the purpose of this study were 300, out of which 153 records were found suitable for the purpose of inclusion in study group and 92 were found eligible for inclusion in the control group.

Age distribution

The distribution of cases in study group is as follows:

Age (years)	Study group	% of total	Control group	% of total
20-39	83	54.2 %	20	21.7%
40-59	67	43.8%	54	58.7%
>60	3	2.0%	18	19.5%
Total	153	100%	92	100%

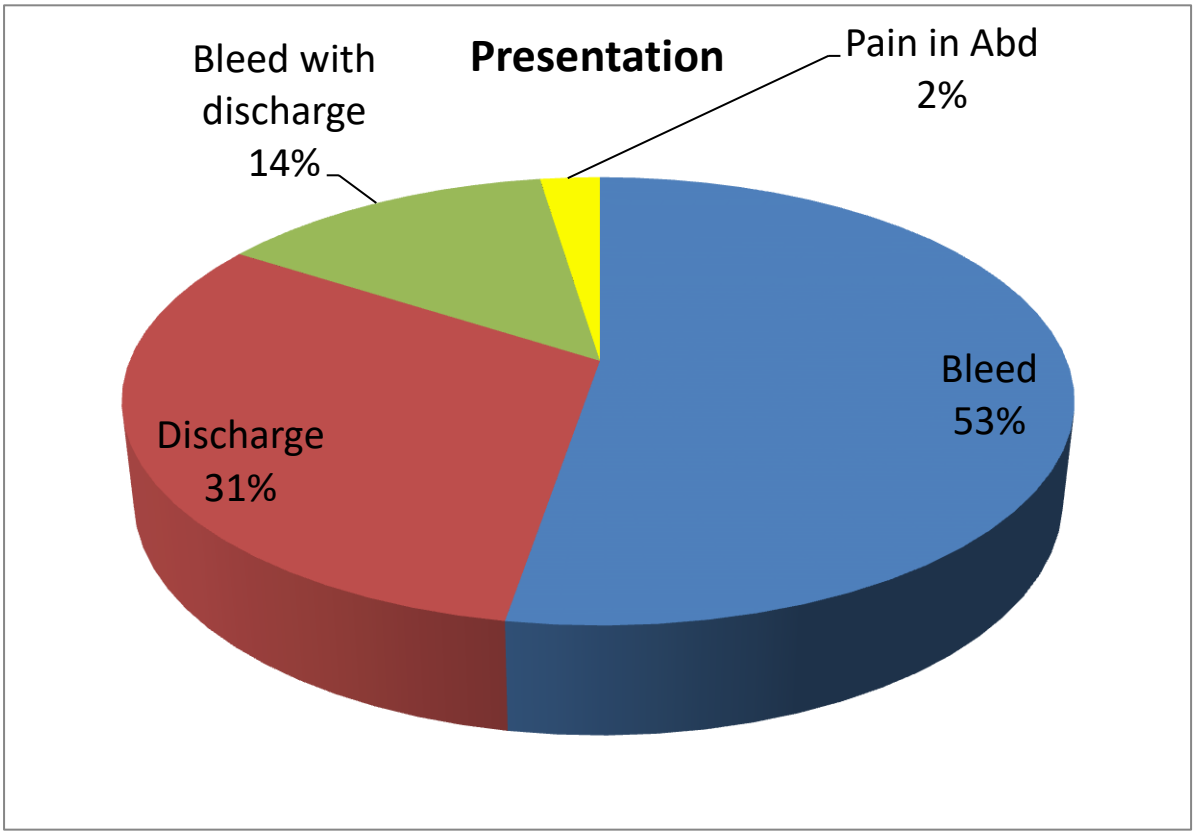


* Representation of absolute numbers

Presentation

Presenting complaints were as follows:

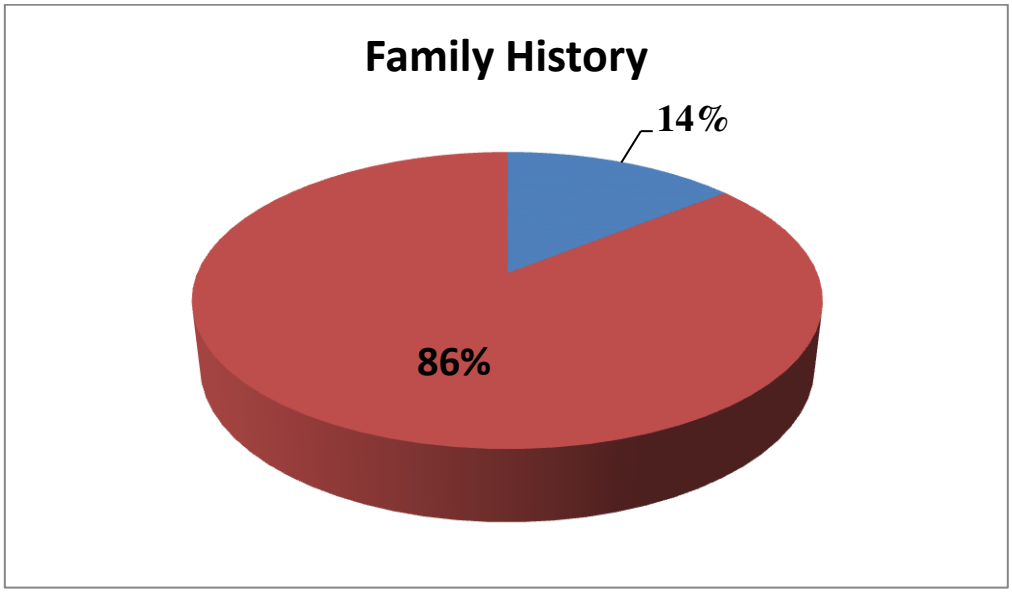
Complaints	Study group	%	Control group	%	Total %
Bleeding PV	81	52.9%	48	52.2%	52.6%
Discharge PV	39	25.5%	38	41.3%	31.4%
Bleed with Discharge PV	30	19.6%	3	3.3%	13.5%
Pain in abdomen	3	2%	3	3.3%	2.4%
Total No.	153		92		245



Family History of cancer

Family history of cancer was present in both groups as follows:

Family History	Study Group	Control Group	Total
Present	23	12	35
Absent	130	80	210
%	15%	13.2%	**14.28%**

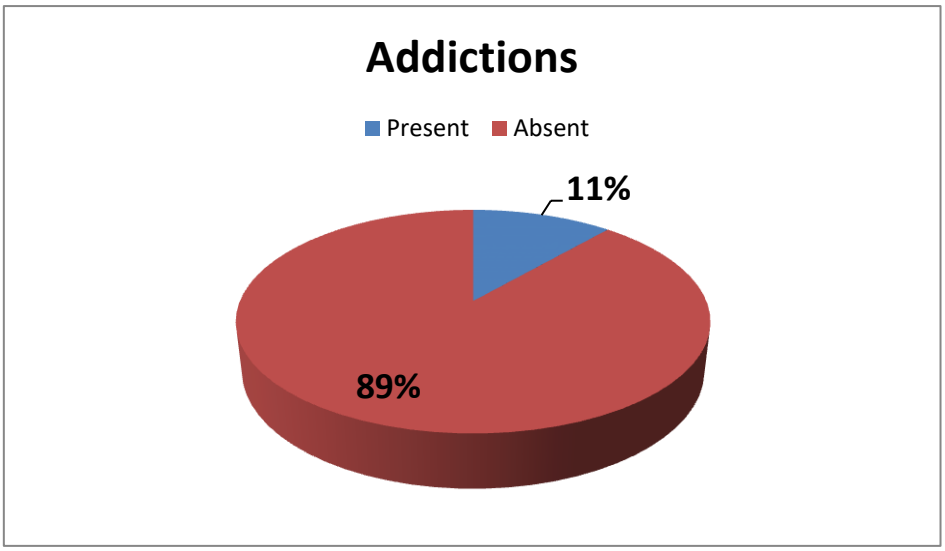


The distribution of family history between cases and controls was not different statistically (p=0.667)

Addictions

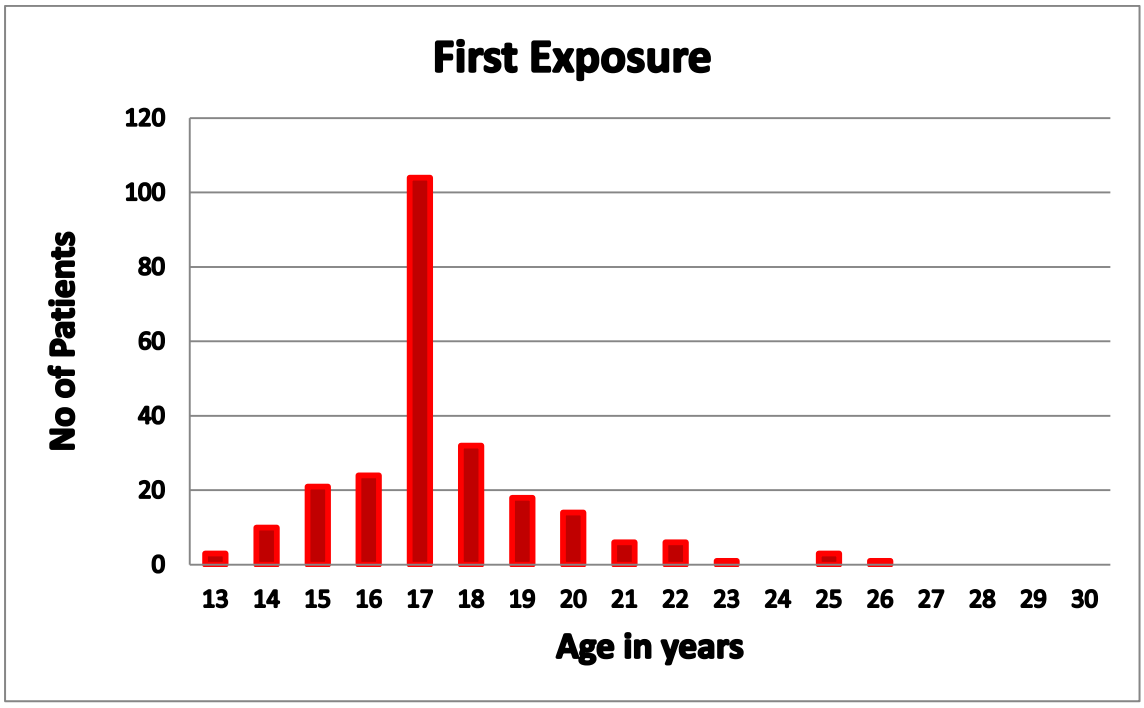
Addictions were present as in the following:

Addictions	Study Group	Control Group	Total
Present	11	17	28
Absent	142	75	217
%	7.2%	18.5%	**11.4%**



Marriage and age at first sexual exposure

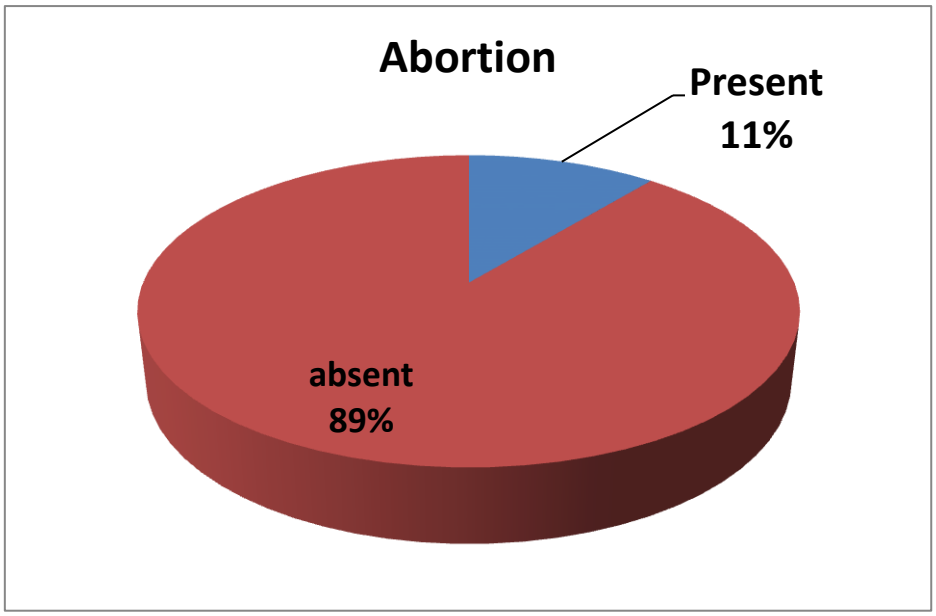
The age at sexual exposure and marriage was coinciding for all patients. The mean age at sexual exposure in study as well as control group was 17 years.



Abortions

History of abortion was present as follows:

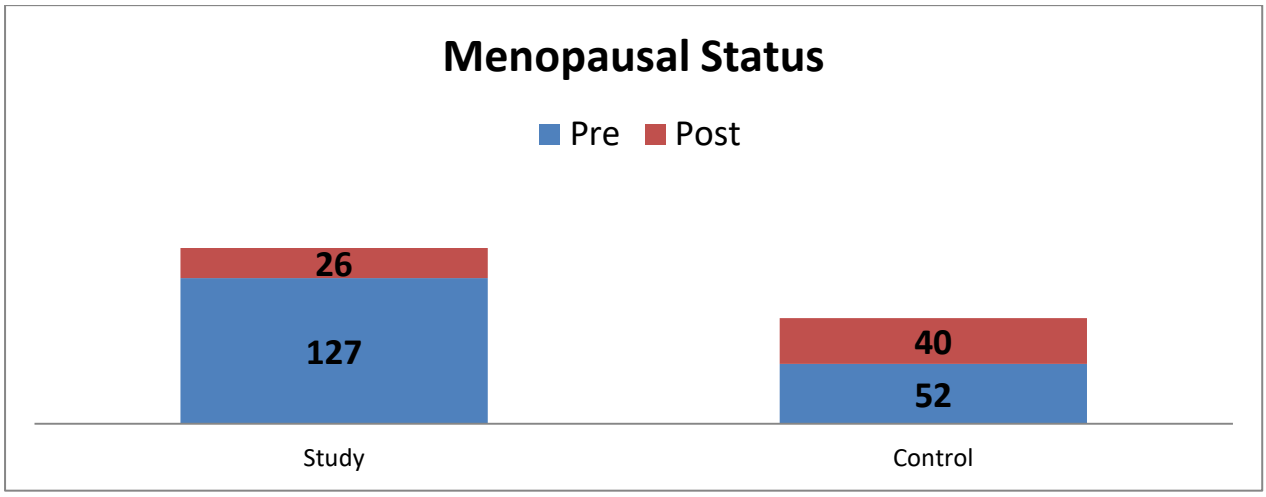
Abortion	Study Group	Control Group	Total
Present	23	3	26
Absent	130	89	210
%	15%	3.3%	**10.61%**



Menopausal Status

The menopausal status between both groups was as follows:

Menopause	Study Group	Control Group	Total
Pre	127	52	179
Post	26	40	66
%Premenopusal	83%	56.5%	**73.06%**



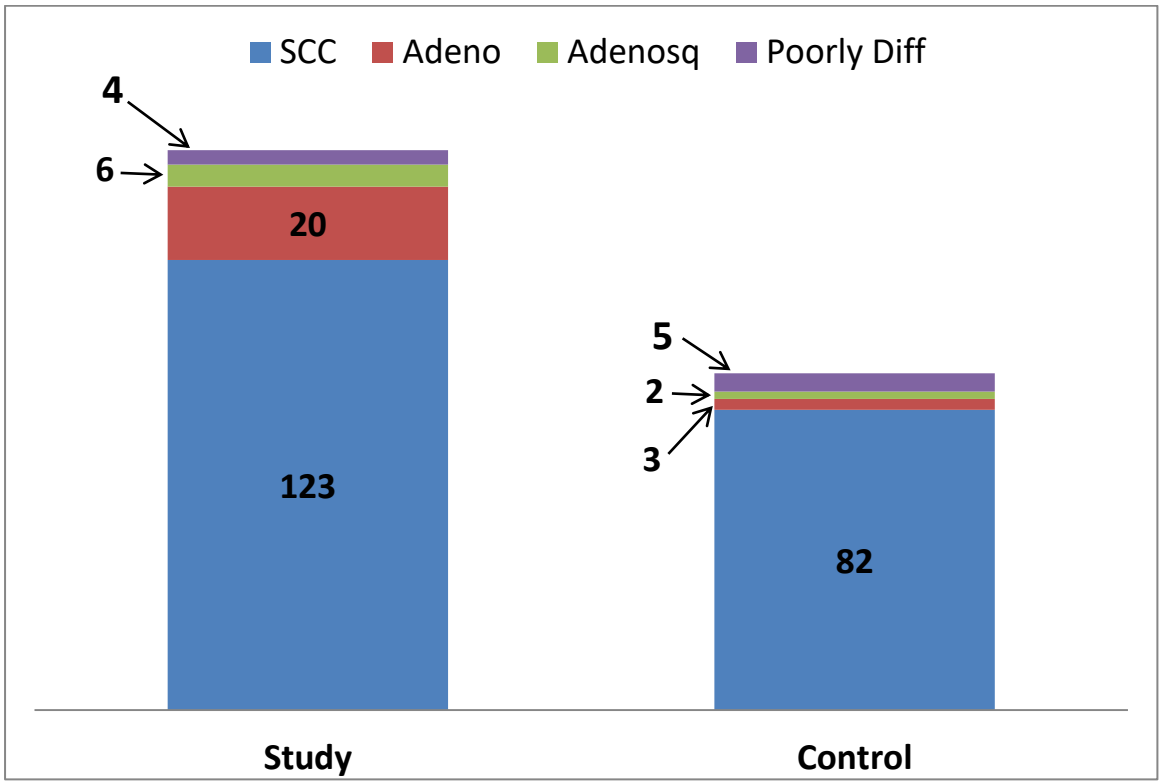
The difference in distribution of pre and post menopausal cases in both the groups was statistically significant (p=0.0001).

Puerperal sterilization was done in 54.2% of patients in study group and history of consanguineous marriage was present in 36% of patients in study group and in 20% of patients in control group.

Biopsy

The distribution of biopsy results was as follows:

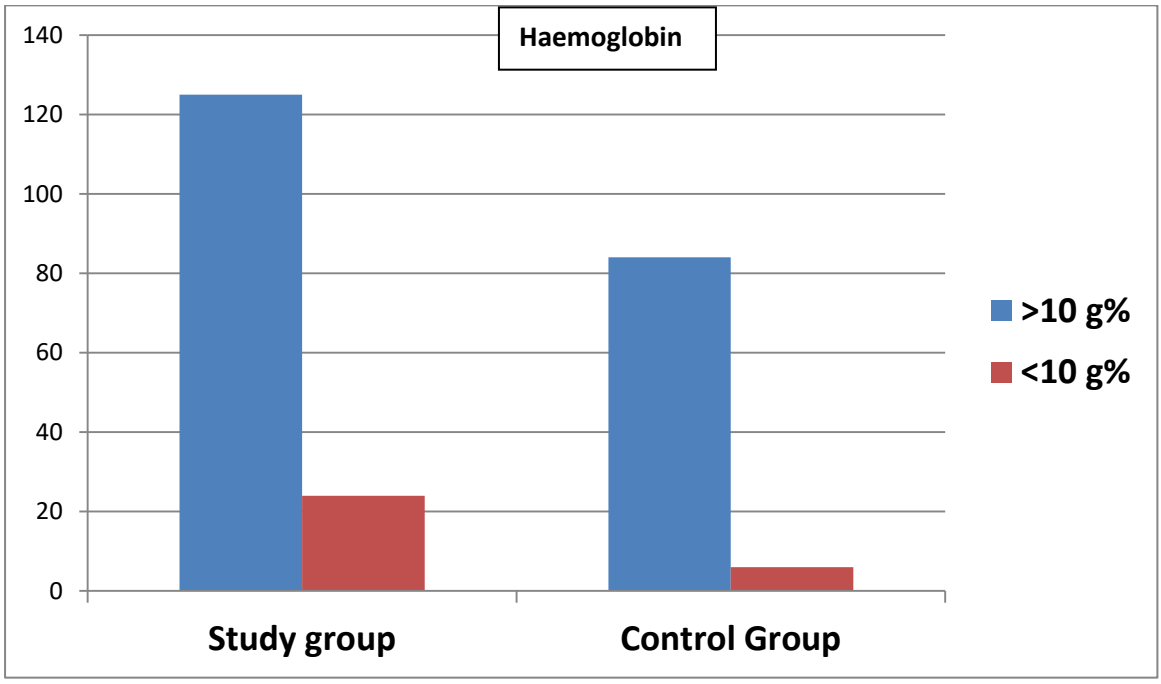
Biopsy	Study Group	%	Control Group	%
Sq. Cell Ca	123	80.4%	82	89%
AdenoCa	20	13.1%	3	3.3%
AdenoSq Cell Ca	6	3.9%	2	2.2%
Poorly differentiated Ca	4	2.6%	5	5.4%



The distribution of pre-treatment histopathology was statistically different (p=0.042).

The relative distribution of tumour in ecto and endocervix was 88% and 12% in study group, whereas 99% tumours in control group were arising from ectocervix.

Similarly, Haemoglobin value in blood was more than 10g% in 125 patients (82%)and less than 10 g% in 24 patients (16%),pretreatmentHaemoglobinwas not available for 2% of patients in study group. In control group Haemoglobin was more than 10 g% in 84 patients (91.3%) ,less than 10 g% in 6 patients (6.5%) and in 2.2% the pretreatment Haemoglobin was not available. The difference distribution of haemoglobin between cases and controls was not statistically significant (p =0.1)



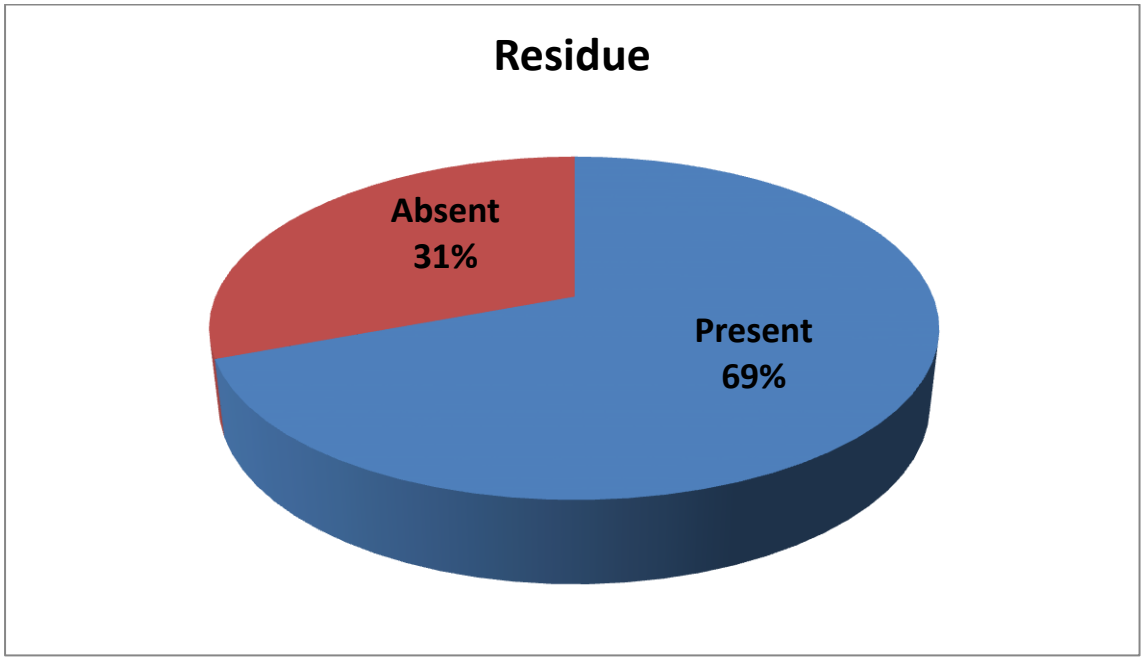
86 (56.2%) cases were stage IB and 67 (43.8%) stage IIA in study group whereas in control group 28 (30.4%) were stage IB and 64 (69.6%) were stage IIA. This distribution of stage IB and II A was found to be statistically different between cases and controls (p= 0.0001)

113 patients (73.9%) were treated with intracavitary application and 40 (26.1%) received external beam radiotherapy before surgery in study group, whereas in control group 3 patients (3.3%) received external beam radiation, 59 (64.1%) a combination of the two and 30 (32.6%) received intracavitary application.

Mean blood loss in surgery group was 445 ml and 73 patients did not require transfusion after surgery, mean blood volume transfused was approximately 200 ml.

Residue

Post neoadjuvant radiotherapy, 47 patients did not have any residue whereas 106 patients had a residue amongst 153 patients in study group.



Mean nodal yield was 13 nodes, the incidence of nodal positivity in the whole study group as in final post-operative histopathology report was 24 (15.7%).

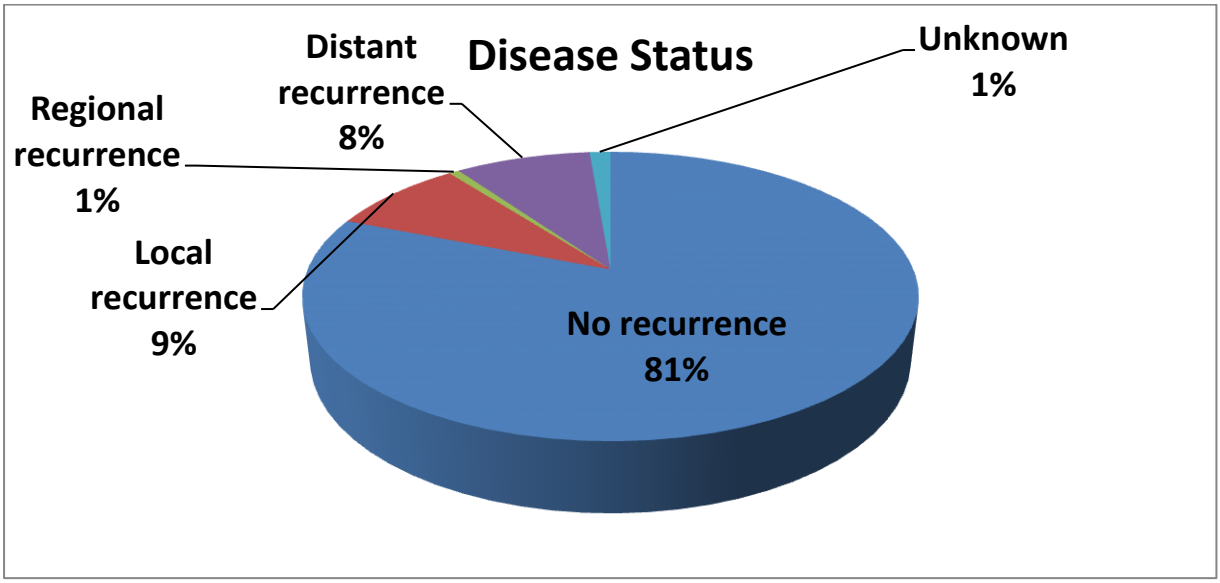
Meananterior vaginal cuff margin was 1.33cms and posterior vaginal cuff margin was 1.9cms. Incidence of microscopically positive margin was 1.3% (2) in the entire study group, 1 (0.7%) margin showed moderate dysplasia.

Mean right parametrial margin was 1.43cms and mean left parametrial margin was 1.44cms.

Disease Status

During the entire period of follow up the following observations were made:

Status	No. of patients	Percentage
No recurrence	124	81%
Local recurrence	13	8.5%
Regional recurrence	1	0.7%
Distant recurrence	13	8.5%
Unknown	2	1.3%



For the purpose of calculating disease free survival patients with unknown status were included in no recurrence group and 82.4% patients (126/153) were disease free at the time of this analysis.

After a follow up of 8-12 years the mean disease free survival in the study group was 85.34 months (approximately 7.11 years) and disease free survival in the control group was 92.18 months (7.7 years).

Univariate Analysis Of Study Group (by Chi square test)

Disease free survival was as follows:

DFS	5 year	10 year
Study Group	85%	75%
Control Group	91%	78%
P value	**0.188; Not Significant**	

Effect of Haemoglobin was as follows:

DFS	**5 year**	**10 year**
< 10 g%	87%	82%
≥10 g%	85%	74%
P value	**0.925; Not Significant**	

Effect of Menopausal status was as follows:

DFS	**5 year**	**10 year**
Premenopausal	87%	76%
Postmenopausal	79%	74%
P value	**0.383 ; Not Significant**	

Effect of histology was as follows:

DFS	**5 year**	**10 year**
Sq Cell Ca	85%	76%
AdenoCa	85%	70%
AdenoSqCa	83%	83%
Poorly Diff Ca	100%	100/%
P value overall	**0.841 ; Not Significant**	

The effect of stage was as follows:

DFS	**5 year**	**10 year**
Stage IB	91%	85%
Stage IIA	77%	64%
P Value	**0.021 Significant**	

The effect of EBRT Vs. ICA was as follows:

DFS	**5 year**	**10 year**
EBRT	78%	73%
ICA	88%	76%
P Value	**0.240 Not Significant**	

The effect of residue in hysterectomy specimen was as follows:

DFS	**5 year**	**10 year**
No residue	98%	78%
Residue	80%	72%
P Value	**0.003 Significant**	

The effect of finding a positive node in final histopathology is as follows:

DFS	**5 year**	**10 year**
Negative Node	88%	78%
Positive node	69%	62%
P Value	**0.015 Significant**	

Effect of resected edge positivity in final histopathology is as follows:

DFS	**5 year**	**10 year**
Negative RE	88%	78%
Positive RE	20%	00%
P Value	**0.0001 Significant**	

Univariate Analysis of control group (by Chi Square Test):

The effect of haemoglobin was as follows:

DFS	**5 year**	**10 year**
< 10 g%	83%	33%
≥10 g%	91%	81%
P value	**0.017 ; Significant**	

The effect of stage on treatment result was as follows:

DFS	**5 year**	**10 year**
Stage IB	96%	61%
Stage IIA	88%	83%
P Value	**0.293 Not significant**	

Effect of Menopausal status was as follows:

DFS	**5 year**	**10 year**
Premenopausal	96%	79%
Postmenopausal	84%	80%
P value	**0.106 ; Not Significant**	

Effect of histology was as follows:

DFS	**5 year**	**10 year**
Sq Cell Ca	91%	80%
AdenoCa	67%	<33%
AdenoSqCa	100%	100%
Poorly Diff Ca	100%	0.71%
P value overall	**0.076; Not Significant**	
P value for SCC VsAdeno CA	**0.013 ; Significant**	

COX REGRESSION ANALYSIS

Variable	**Significance**	**95% CI Lower**	**95% CI Upper**
Case	0.078	0.929	3.98
Menopausal status	0.092	0.903	3.82
Stage	0.02	1.143	4.635
Haemoglobin	0.464	-	-

Hence on multivariate analysis only stage was a significant predictor of disease free survival.

Complications

Early complications unique to study group were:

Complications	**Frequency**	**Percentage**
No complications	139	90.8%
High Residual volume	11	7.2%
Lower limb edema	1	0.7%
Bleeding	2	1.3%

Late complications unique to study group were:

Complications	Frequency	Percentage
No complications	142	92.8%
Incisional hernia	7	4.6%
Lower limb oedema	1	0.7%
SAIO	1	0.7%
Radiation proctitis	1	0.7%
Perforation	1	0.7%

Late complications unique to control group were:

Complications	Frequency	Percentage
No complications	34	37%
Adhesive Vaginitis	38	41.3%
Haematuria	3	3.3%
Proctitis	3	3.3%
Haematuria with Adh Vaginitis	6	6.5%
Lower Limb Oedema	2	2.2%
Proctitis with Adh Vaginitis	1	1.1%
AdhVag with proctitis and cystitis	1	1.1%
Unknown	4	4.3%

Discussion

Cervical cancer is a common cancer affecting our country and world over, but the presentation in our country usually is at a later stage reflecting the lack of effective screening and possible social barriers. The burden of such late diagnosis is more with our rural population.Women of all ages may be affected as in our study the youngest patient was 25 years old, hence age alone should never exclude cervical cancer. The presenting complaint is usually abnormal bleeding per vagina(53% in our study) and many women present with white discharge which may be a nonspecific complaint, women may also present with blood mixed discharge and some of these may present with nonspecific abdominal pain.

A family history of cancer (15% in our study) may be present. Carcinoma cervix and uterus in maternal relatives was a common association in our study population, but its epidemiological significance cannot be commented upon at this time. In our study population 11% of patient used chewable form of tobacco. Age at marriage and first exposure tosexual experience are almost coinciding across both study and control group possibly reflecting our social structure and values.A majority of our patients were premenopausal reflecting the need of keeping long term toxicities of treatment in view and ovarian function preservation when deciding appropriate treatment. Their post treatment quality of life should also be a consideration. Impact of histologic type on

survival in most of the studies is unclear for adenocarcinoma and squamous cell carcinoma. However uncommon histological types like melanoma and small cell carcinoma have a worse outcome.

In our study the disease free survival between both treatment groups was statistically not significant.

The effect of haemoglobin level more than or equal to 10 g% did not have appreciable impact on DFS in our study group, but in definitive radiotherapy group the DFS was significantly lower if haemoglobin level was less than 10 g%.

The impact of menopausal status on treatment outcome (DFS) was not significant statistically in both study and control group.

The effect of histology on DFS was overall not significant in our study group as well as control group, however DFS of adenocarcinoma treated by definitive radiotherapy was significantly lower than DFS obtained for Squamous counterpart.

The effect of stage (IB and IIA) was not statistically significant in control group however, the difference was significant in study group.

In the study group, advantage from use of both the treatment modalities (EBRT and ICA) was similar as regards to DFS. Presence of residue in cervix on final pathologic examination was associated with significantly reduced DFS when compared to no residue on final pathologic examination. Similarly, finding a positive node on final pathologic examination was associated with significantly

reduced DFS. Positive resection margin similarly was associated with a significantly reduced DFS.

On cox regression analysis, only stage at presentation was a significant determinant of DFS with the same being shorter in stage IIA compared with IB.

Complications between the two arms were different, about 91% of patients in study group were free of early post-operative period complications (Within 30 days). Most of the early complications were transient. Similarly about 93% patients were free of late complications in study group, the most common complication being incisional hernia.

In control group about 37% patients were free of late complications and adhesive vaginitis was the most common complication (41.3%) in that group followed by radiation cystitis and proctitis. Hence side effect profile of the study group appears desirable especially in younger patients.

A few interesting observations were made during the data collection process:

A 45 year lady treated for Squamous cell carcinoma cervix stage IIA treated with External beam radiotherapy 40 Gy from 31-01-01 to 27-02-01 followed by Wertheim's hysterectomy with Bilateral pelvic lymphadenectomy on 12-04-01, she developed right lung upper lobe and left lung lower lobe metastatic lesions which were treated with 4 cycles of Cisplatinum, the lesions completely disappeared after 2 cycles and she was progression free till last follow up on 14/11/07.

Another 37 year lady with Squamous cell carcinoma cervix stage IIA treated with 40 Gy external beam radiotherapy from 27-06-03 to 23-07-03 followed by Wertheim's Hysterectomy and Bilateral pelvic lymph node dissection on 01-09-03, a chest radiograph done in November 2011 revealed metastasis in left lower lobe, she underwent thoracotomy and R2 resection as R0 resection would have required pneumonectomy, she was treated by Cisplatinum 4# till 17/7/07 and she survived next two years till July 2009.

These observations suggest than a few patients with metastatic disease may have benefit by aggressive approach at relapse.

Conclusion

The results from this study show that disease free survival is similar in both the study and control group. The factors tosignificantly affect outcome in univariate analysis for study groupwere tumour stage, present of residue after neoadjuvant radiation, positive nodal status on final histopathology and positive resection margin. In control group haemoglobin value less than 10 g% and adenocarcinoma histology were correlating with reduced disease free survival. Haemoglobin level did not have a significant impact on disease free survival in study group. Menopausal status had no effect in both the groups. Stage at treatment was important in study group whereas there was no difference in outcome with stage in control group. In multivariate analysis after balancing confounding factors stage had significant impact on disease free survival. Complications in both the groups are not comparable as both the treatment modalities are different and have complications unique to them, however complications likely to reduce quality of life like adhesive vaginitis with vaginal shortening, dryness were more with definitive radiotherapy, similarly side effects needing evaluation like haematuria and cystitis were more in definitive radiation group, which are likely to be a cause of concern to patient.

In conclusion, the side effect profile should be the directing factor to choice of treatment, in our study on univariate analysis patients with adenocarcinoma of

cervix fared significantly worse than their squamous cell counterpart when treated by definite radiotherapy (p=0.013).

So we conclude that, neoadjuvant radiotherapy followed by radical surgery is the preferred treatment option for early stage carcinoma of cervix, especially so in adenocarcinoma histology where disease free survival is likely to be better and in younger patients where quality of sexual life is likely to be better also long term side effects of definitive radiation would also be avoided.

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