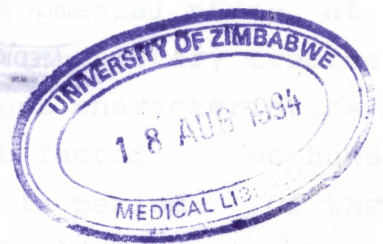


CARCINOMA OF THE CERVIX IN ZIMBABWE
A REVIEW OF PATIENTS' CHARACTERISTICS
AND OUTCOME OF TREATMENT

BY
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ABSTRACT

Carcinoma of the cervix accounts for over 30% of female malignancies in Zimbabwe. Aetiological factors include early age at first coitus, multiple sexual partners, poor hygiene and the human papilloma virus. Radiotherapy (RT) is the definitive treatment for most patients with this disease and involves both external beam therapy (EBT) and intracavitary treatment (ICT).

A retrospective study was undertaken of all patients who presented to the Parirenyatwa Radiotherapy Centre (RTC) between November 1990 and December 1991 with a diagnosis of cervical carcinoma. This was an important developmental phase at the centre including the re-introduction of intra-cavitary treatment. The aim of the study was to document patient characteristics and outcomes of therapy and identify prognostic factors. Two hundred and seventy-three patients presented in this period. Of these, 52 were excluded leaving 221 patients who could be evaluated. Of the patients whose age was known ($n = 190$), 60% of these were in the age group 35-54 years with a range for the whole group of 21-80 years. Patients were divided into two groups according to whether they received radical RT including I.C.T. (group 1, 93 patients) or received EBT only (group 2, 128 patients).

Fifty-one percent of the 221 patients presented with Stage III disease. In group 1, 77.4% were Stages I and II and 22.6% Stage III, whereas in group 2 the percentages were 12.5 and 72 respectively. The proportion of Stage III patients treated with ICT increased during the study period. Thirty-one percent of the whole group had no biopsy. Of those biopsied 95.4% had squamous cell carcinoma and 4.6% adenocarcinoma. Group 1 patient details were more reliable and so were analysed in more depth. Fifty-nine percent of group I patients gave a history of 3-8 months of

symptoms and 21.5% symptom duration longer than 1 year. The mean length follow-up time was 13.4 months for group 1 and 7.1 months for group 2. Complete remission (CR) rates at last follow-up were 49% for group 1 and 19% for group 2. Ninety-seven percent of group 1 patients achieving a CR had received 70Gy or more total dose to Point A. The CR rate was clearly inversely related to stage in group 2. In group 1 this trend was also seen though less clearly defined. Patients with both pelvic wall and lower one third vaginal involvement did more poorly than other Stage III patients.

Treatment was in general well tolerated: 78.5% of group 1 patients had no or only mild acute complications (mainly gastrointestinal) and only 2.1% had severe acute complications. The acute complication rate was higher in those who completed treatment in under 7 weeks. Follow-up was insufficient in the majority of the patients to assess late effects. Most local recurrences and metastases which occurred were seen within 1 year of completion of treatment.

Health measures which could improve treatment results include: public education regarding early symptoms, medical education in early diagnosis and referral, accurate staging, more frequent use of a combination of EBT and ICT, avoiding prolonged treatment times, improved follow-up, better co-operation between gynaecologists and radiotherapists and more widespread cervical visualisation procedures in rural and district health centres areas to be reinforced in future by cytological screening.

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TABLE OF CONTENTS

	PAGE
List of figures	v
List of tables	vi
List of abbreviations	vii
Introduction	1
Literature Review	4
Demographical Considerations	25
Patients and Methods	26
Results	32
Discussion	43
Conclusions	53
Recommendations	56
Tables and Figures	59
References	83

FIGURES

	<u>PAGE</u>
1. Age Distribution	62
2. Staging of the patients	64
3. Histological diagnosis for 153 groups 1 and 2 patients	67
4. Disease status group 1	71
5. Outcome vs duration of treatment: group 1	73
6. Outcome vs duration of treatment: group 1	74
7. Nature and frequency of acute complications ...	79

TABLES

	<u>PAGE</u>
1. Criteria for exclusions	59
2. Staging of carcinoma of the cervix	60
3. Age distribution of 190 patients	61
4. Stage groups of the patients	63
5. Staging by month first seen: group 1 only	65
6. Duration of symptoms by stage: group 1 only ...	66
7. Histological diagnosis in 221 patients	66
8. Total doses to point A: group 1 only	68
9. Length of follow-up: group 1	69
10. Length of follow-up : group 2	69
11. Disease status: group 1	70
12. Disease status at last follow-up: group 2	70
13. Outcome vs duration of treatment: group 1	72
14. Outcome of treatment vs dose: group 1 (n=93) .	72
15. Outcome of treatment vs dose: group 2	75
16. Outcome at second follow-up vs stage: group 1.	76
17. Outcome vs stage: group 2	76
18. Outcome vs follow up time in months: group 1 .	77
19. Outcome vs follow-up time in months: group 2 .	77
20. Acute complications: group 1	78
21. Nature and frequency of acute complications: group 1 (n=93)	78
22. Acute complications vs dose in cGy: group 1 ...	80
23. Risk of acute complications vs dose: group 1 ..	80
24. Acute complicatons vs duration of radiotherapy in weeks: group 1	81
25. Risk of acute complications vs duration of radiotherapy in weeks: group 1	81
26. TDF distribution in the 24 CR patients: group 2.	82

ABBREVIATIONS

Adeno	-	Adenocarcinoma
AIDS	-	Acquired immunodeficiency syndrome
AWD	-	Alive with disease
cGy	-	centiGray
CIN	-	Cervical intraepithelial neoplasia
COMPS	-	Complications
CR	-	Complete remission
CXR	-	Chest X-ray
EUA	-	Examination under anaesthesia
FBC	-	Full blood count
F/up	-	Follow up
g/dl	-	Grams per decilitre
Gy	-	Gray
EBT	-	External beam treatment
HIV	-	Human immunodeficiency virus
HPV	-	Human papilloma virus
HSV	-	Herpes simplex virus
ICT	-	Intracavitary treatment
LFT	-	Liver function test
LOST	-	Lost to follow up
METS	-	Metastases
PAP	-	Papanicolau
RD	-	Residual disease
REC	-	Recurrence
RT	-	Radiotherapy
RVF	-	rectovaginal fistula
SCC	-	Squamous cell carcinoma
TDF	-	Time-dose factor
U + E	-	Urea and electrolytes
VVF	-	Vesico-vaginal fistula
WD	-	With disease

INTRODUCTION

Carcinoma of the cervix is a problem of great magnitude in Zimbabwe as in many other developing countries (Stein, 1984; Rogo et al, 1990; Machoki and Rogo, 1991).

Although it is difficult in this country to obtain accurate incidence and mortality statistics, previously published data showed an incidence of 8.7/100000 in the Bulawayo area between 1963 and 1977, (Skinner, 1993) with a total of 611 new cases recorded at the Harare and Bulawayo Cancer Registries in the two year period of 1971 and 1972 (Frost, 1981).

It has been shown in the National Cancer Registry quarterly analysis that carcinoma of the cervix is the commonest cancer in the female population of Zimbabwe, accounting for 32.3 percent of all female cancers in the period 1986 to 1990, with breast cancer as the second commonest tumour accounting for only 9.9 percent of all female cancers (Zimbabwe National Cancer Registry, 1991).

There is a possibility that the incidence of carcinoma of the cervix is rising as compared to the 1986 to 1990 incidence. The National Cancer Registry figures for January 1991 to June 1991 show a rise to nearly 40 percent of all female malignancies.

A study done in 1963 - 1977 also showed a rise in the incidence of carcinoma of the cervix in the Bulawayo area over that period (Skinner, 1993).

However the figures quoted may not reflect the true picture since many patients, especially rural, with advanced or untreatable disease and those not biopsied may not be registered.

A high proportion of our patients with carcinoma of the cervix present with advanced disease (Frost, 1981; Kasule, 1989; Rogo et al, 1990). This is because of delays due to traditional beliefs, delays in the referral system and poor basic knowledge of the causes of abnormal vaginal bleeding and discharge (Machoki and Rogo, 1991). Several to many months may elapse from the time of the first symptom until a tissue diagnosis and subsequent referral to a central hospital for definitive treatment.

This study is a retrospective analysis of all patients who were referred to the Parirenyatwa Hospital Radiotherapy Centre between November 1990 and December 1991 with a diagnosis of carcinoma of the cervix. This period was marked by the re-introduction of caesium intracavitary treatment for cervical cancer which had not been used for some years due to unavailability of sources and problems with staffing.

The aim of this analysis was to document the patient characteristics, treatment policies and treatment outcomes for patients with carcinoma of the cervix in order to identify how best to improve early diagnosis and management of this problem in Zimbabwe.

LITERATURE REVIEW

Incidence and Epidemiology

Cervical carcinoma is the commonest malignancy in women in developing countries and the second commonest malignancy in women in the world as a whole (Miller, 1992). Three quarters of all women with cervical cancer are in the developing world. There is a declining incidence of invasive cervical cancer in industrialised countries (and a rise in CIN) mainly due to effective screening measures (Yule, 1978).

In Zimbabwe, carcinoma of the cervix is the predominant female malignancy accounting for 78% of all gynaecological malignancies referred to Harare Central Hospital between January 1981 and December 1983 (Kasule, 1989). In the southern region of the country cervical cancer accounted for 31.5% of all female cancers during the period of 1963 to 1977 and this was the most common malignancy in females (Skinner, 1993). This compares strikingly with an industrialised country such as England and Wales where invasive carcinoma of the cervix constitutes less than 8% of all female malignancies. This geographical variation is mainly due to socioeconomic factors, sexual habits, lifestyle and the impact of effective screening measures. There is a rise in the incidence of carcinoma in situ with a fall in the incidence of

invasive carcinoma in industrialised countries (Miller, 1992).

Anatomy and Lymphatic Drainage

The cervix forms the distal part of the uterus which is a muscular organ in the pelvis with a body and fundus which opens into the vault of the vagina. The supravaginal part of the uterine cervix is closely related to the base of the bladder. The rectum lies immediately posterior to the vagina 3cm below the external cervical os.

The region where the squamous epithelium of the vagina and the stratified columnar epithelium of the ectocervix meet is commonly known as the squamo-columnar junction. This junction is also known as the transformation zone and can be readily visualised using a colposcope in premenopausal women. However, with increasing age it tends to ascend into the cervical canal. This transformation zone is the site of origin of most cervical cancers (Cotran et al, 1989; Coulter and Mason, 1990).

The lymphatic drainage of the cervix follows a well-defined pattern. Lymphatic spread of tumours is usually via the parametrial lymphatics to the obturator, internal iliac, external iliac and common iliac nodes, and then to the para aortic nodes at the lower border of the fourth lumbar vertebrae (Coulter and Mason, 1990). There is also drainage to pre-sacral nodes and

rarely the inguinal nodes may be involved.

Age at Presentation

Although cervical intraepithelial neoplasia (CIN) presents at an early age - 17 years onwards, with a peak incidence at 25-39 years -invasive carcinoma is seen in the older women with a peak incidence at 40-50 years (Cotran et al, 1989).

Invasive cancer presenting in patients below 35 years of age may be a more aggressive subgroup requiring special attention (Harte and Atkinson, 1990; Murrel et al, 1990).

Frost (1989) demonstrated that 77% of patients with invasive carcinoma of the cervix in Zimbabwe are in the 30-59 year age group with 30% of the total in the 40-49 year age group.

Aetiology

Coitus

Cervical cancer is extremely rare in women assumed to be virgins. Coitus is therefore a pre-requisite for the development of this tumour (Coulter and Mason, 1990).

First intercourse at age below 17 years carries a higher risk of developing carcinoma of the cervix (Frost, 1981). In Bombay, India, the incidence of cervical cancer has been shown to have declined in Hindus as the mean age at marriage increased from 12 years to 17 years (Yeole et al, 1989).

In Africa the average age at marriage and at birth of first child is generally much lower than in Western countries.

Parity

The mean parity of women with cervical cancer is higher than controls. It is as yet unknown whether this only reflects early age at start of sexual activity or whether parity is an independent factor in aetiology (Emembolu and Ekwempu, 1988).

Transmissible Agent

Cervical cancer is five times more common among prostitutes than controls reflecting the role of multiple sexual partners in aetiology. There is also a relative risk of 1.7 of developing cervical cancer in women married to a man whose first wife died of the disease (Coulter and Mason, 1990).

Human Papilloma Virus (HPV)

Evidence that HPV could be a causative transmissible agent for cervical cancer is very strong. DNA hybridisation techniques have detected HPV DNA in 75-100% of precancerous dysplasia and invasive carcinoma (Kitchener, 1988; Schiffman, 1992).

HPV types commonly associated with invasive cancer are known as high-risk HPVs. They are mainly types 16,18 and 31. HPV 6 and 11 are most frequently found in condylomata and are termed low-risk HPVs. Both low and high-risk HPVs are found in dysplasia (Syrjanen et al, 1988).

High risk HPVs tend to be integrated into the host genome near a proto-oncogene and induce cell transformation. This is through co-operation with the ras oncogene. HPV may act as a promoter which, together with initiators such as other viruses (eg Herpes Simplex Virus II (HSV II), bacteria and environmental agents, result in neoplasia. Low-risk HPVs only result in unintegrated episomal DNA in the host cell. Male partners of women with cervical cancer have been shown to have small penile and posterior urethral lesions harbouring HPV (Cotran et al, 1989).

HPV infection is also found in women without cervical cancer. Why these women do not develop carcinoma of the cervix is still unclear. However, there is evidence that there may be a local

immunodeficiency within the cervical epithelium of women who develop this cancer, which makes them more susceptible to the carcinogenic effects of HPV. This local immunosuppression has been shown to manifest as a selective depletion of Langerhans cells (Tay et al, 1987a) and a specific depletion of the T4 helper inducer and T8 suppressor cytotoxic lymphocytes (Tay 1987b).

Human Immunodeficiency Virus (HIV)

Symptomatic HIV infected women with HPV infection are at a higher risk of developing cervical intraepithelial neoplasia (CIN) than women who are HIV seronegative. The disease also tends to have a rapid evolution and poor prognosis in these individuals (Spina and Tirelli, 1992.)

Cervical carcinoma in HIV infected women has been formally recognised as an AIDS-defining diagnosis since January 1, 1993. These women also have a higher incidence of HPV infection compared to HIV seronegative women from the same population (Levine, 1993.)

Socio Economic Factors

There is a higher incidence of cervical cancer in the lower socio economic groups (Kasule, 1989; Coulter and Mason, 1990). This is

clearly shown in Zimbabwe where the majority of patients seen are rural and in the low socio-economic group. There is evidence of a link between this factor and early age at first coitus and marriage, and multiple sexual partners.

Smoking - This doubles the risk of developing carcinoma of the cervix.

Racial Factors

The increased incidence of cervical cancer in African women may not be racial but may be due to an increased rate of HPV infection (Schiffman, 1992). It may also be closely linked to socio economic factors as seen in black women in America (Freeman, 1991). However, Jewish women have a low incidence of this cancer which has been attributed to male circumcision in infancy (Coulter and Mason, 1990). More recently it has been suggested that it is the regulation of sexual life by adherents of orthodox Jewish religious laws that contributes to the low incidence.

Contraception

The influence of the oral contraceptive pill on the incidence of cervical cancer remains controversial. Some studies show an association while others contradict this. It is thought a

definitive study is probably impossible because of bias.

Herpes Simplex Virus II

Although HSVII has been isolated from cervical tissues in women with various grades of dysplasia and in invasive cancer, its causative role remains inconclusive.

Pathology

Most cervical cancer is the end-stage of a continuous process of progressively more atypical changes in which one stage merges with the next.

Cellular transformation begins with the activation of oncogenes at a cellular level in the p53 gene and the retinoblastoma (RB) gene. This may be caused by interaction of the viral oncoprotein E6 and E7 from HPV with these suppressor genes or result from a spontaneous mutation in HPV negative individuals (Kitchener, 1988; Riou et al, 1992).

At the earliest stage, atypical cells appear in the basal layer of the squamous epithelium and show changes in the nucleocytoplasmic ratio, loss of polarity, and increasing mitotic figures and pleomorphism, which are the hallmark of malignancy. This process proceeds until the epithelium is totally replaced by

these atypical cells (Cotran et al, 1989). These pre-invasive changes are termed cervical intraepithelial neoplasia (CIN) and are graded 1 to 3.

Grade 1 CIN is defined as less than one third involvement of the epithelial surface.

Grade 2 CIN is when one third to two thirds of the epithelium is involved.

Grade 3 CIN is full thickness involvement of the epithelium and is also termed carcinoma in situ.

These changes almost always begin at the transformation zone. The more severe the change the shorter the time span for progression into carcinoma in situ.

It is accepted that 40-60% of all CIN will progress to invasive carcinoma while 25% will remain unchanged and 25% partially or completely regress (Cotran et al, 1989).

However 75% of all carcinoma in situ will progress to invasive carcinoma. The average time for CIN 1 and II to progress to invasive carcinoma is 1 to 20 years, with an average of 10 years (Miller, 1992).

Once the stage of carcinoma in situ has been reached, an invasive clone of cells has to develop for progression to invasive carcinoma. It takes another clone of cells with a metastatic potential to dedifferentiate before the tumour can metastasize.

Macroscopically, cervical cancer can be fungating or exophytic, ulcerative or infiltrative. The most common is the exophytic type which grows outwards and can be easily felt expanding the cervix.

Direct extension is to contiguous structures such as vagina, bladder, rectum, ureters, and peritoneum.

Lymphatic spread to pelvic nodes can occur early in the disease process but has a higher incidence in higher stages of the disease. Pelvic node involvement occurs in 16% of Stage I, 30% of Stage II, 44% of Stage III and 55% of Stage IV. Para-aortic node involvement occurs in less than 10% of stage I, 10% of stage IIA, 20% of stage IIB, 30% of stage III and more than 50% of stage IV.

Haematogenous spread is relatively uncommon. When it occurs, the principal sites affected are liver, lungs and bone.

Histology

Ninety percent of all cervical cancer are squamous cell carcinoma. Of these, 65% are large cell non-keratinizing and usually moderately well differentiated, 25% large cell keratinizing and usually well differentiated and 10% small cell non-keratinizing and usually poorly differentiated. Adenocarcinoma accounts for only 10% or less of cervical tumours.

Less common histological variants are adenosquamous, verrucous, clear cell and undifferentiated carcinomas.

Clinical Course

The most common presenting features of cervical cancer are post coital bleeding and/or intermenstrual or postmenopausal bleeding. In Zimbabwe, vaginal bleeding in postmenopausal women may be mistaken by the patient, consequent to cultural beliefs, for a return of fertility (Martin, 1990), leading to late presentation.

A foul smelling vaginal discharge is also a common presenting symptom. Pain is usually associated with advanced disease. This can be due to local infiltration, nerve compression or direct invasion of the lumbosacral plexus.

Direct extension anteriorly into the bladder may cause haematuria, frequency and eventually a vesico-vaginal fistula (VVF). Similarly extension posteriorly into the rectum may cause rectal bleeding tenesmus and a recto-vaginal fistula (RVF). Laterally the pelvic bones may be involved.

The ureters can be involved by cervical cancer as it spreads in the pelvis due to their close anatomical relationship with the cervix. This can lead to obstructive renal failure and death.

Diagnosis

The diagnostic work-up for cervical cancer includes a good history and physical examination with bimanual vaginal and rectal examinations.

Laboratory studies are done, which are a full blood count (FBC), urea and electrolytes (U+E) Liver function tests (LFT) and urinalysis.

Standard radiographic studies are chest X-ray and intravenous urography. Barium enema should be done if there is a suggestion of involvement of the rectum or colon.

Complementary radiological investigations are bipedal lymphangiography, ultrasound scan, computed tomography or

magnetic resonance imaging, all aimed at defining the local extent of disease and any pelvic or para-aortic lymph node involvement.

Examination under anaesthesia (EUA) is carried out to assess local tumour extent, involvement of adjacent organs, lymph node involvement and for biopsies of the tumour. Cystoscopy and less often rectosigmoidoscopy is indicated in stage IIB onwards. Areas of possible tumour involvement may be biopsied during these procedures.

For microinvasive cancer (Stage Ia) diagnosed by cytology (PAP smear) colposcopically directed biopsy or conization is done at EUA.

In Zimbabwe not all the radiological investigations outlined above are done due to limited resources and a high patient load. Most commonly, FBC, U+E, LFT, chest X-ray, EUA and biopsy are carried out in the majority of the patients, especially those with early stage disease. Other investigations are done at the discretion of the clinician and/or if the patient can afford payment. Lymphangiography and computerised tomography although available, are not routinely carried out due to limited personnel and expense. Magnetic resonance imaging is not yet available in Zimbabwe.

Treatment

The treatment of cervical cancer principally involves the use of RT, surgery or a combination of both modalities, depending on the stage of the disease and other patient factors. The role of chemotherapy has yet to be clearly established (see below).

RT is usually in the form of intracavitary treatment (ICT) and/or external beam treatment (EBT). Surgery generally is by a Wertheim's hysterectomy which involves the removal of uterus, a cuff of vagina, both tubes and ovaries and a pelvic lymphadenectomy. Other less extensive surgical procedures are used for early stage disease (see below)

ICT was first described in 1903 by Cleaves and later various techniques were developed using radium applicators (Coulter and Mason, 1990)

The Stockholm technique was developed by Fasell and Heyman between 1910 and 1930. The Paris system, based on the low dose rate concepts of Regaud and Chassagne, came into use in 1926.

The Manchester technique was initially described in 1938 and combined the best of the Stockholm and Paris methods. This was later modified by Todd and Meredith to standardise treatment doses to point A and point B (Rotman and Aziz, 1991).

Later on in 1953 Fletcher further modified the system to allow for limited staff exposure to radiation (Coulter and Mason, 1990).

Point A is defined as the point 2cm lateral to the central uterine canal and 2cm above the external cervical os. Point B is 3cm lateral to point A. The dose to point B with ICT is usually approximately one third of that to point A.

More recently, manual and remote control afterloading systems, have been used. The Amersham system based on the Manchester technique, is one of the commonly used manual afterloading systems.

Remote control afterloading systems have the main advantage of reducing staff radiation exposure. They may be low dose rate (0.4-2Gy per hour), medium dose rate (2-12Gy per hour) or high dose rate (greater than 12Gy per hour). They also enable more accurate positioning of applicators as the clinician can take more time to do this without fear of radiation exposure.

EBT is used to give a homogeneous dose to the pelvis and in particular to treat the pelvic lymph nodes which receive little dose from ICT. It can be given before or after ICT.

Various field arrangements are used ranging from simple parallel

opposing fields to complex rotational fields. The principal dose limiting organ is the rectum which must not receive a total dose in excess of 60Gy. Extended field irradiation to include the para-aortic nodes increases small bowel morbidity and is of limited value (Haie et al, 1988; Vigliotti et al, 1992).

Staging

The uterine cervix was among the first sites to be classified by the TNM system. The categories have been defined to correspond to the FIGO stages which is the system more commonly used. Histological confirmation of disease is mandatory. Staging is usually clinical, with pathological staging only possible in those cases treated surgically when the pTNM nomenclature is preferred.

The staging of carcinoma of the cervix is shown in Table 2.

Treatment by Stage

Stage 0 - Removal of the abnormal transformation zone is the treatment of choice. This is done by local ablation, for example using a carbon dioxide laser or cryosurgery. If there is endocervical extension of CIN, a cone biopsy is done as accurate colposcopic evaluation is not possible.

Stage Ia - The treatment for micro-invasive cervical cancer is colposcopically directed conization. In an older woman whose family is complete, hysterectomy is the treatment of choice (Photopoulos, 1990).

Stage Ib - Here either RT or surgery can be used with a similar cure rate of over 80%. The definitive surgical treatment is a Wertheim's hysterectomy. In young women hysterectomy has advantages in that there is an option of ovarian conservation, long term bladder and bowel complications due to radiation are avoided and there is preservation of a near normal vaginal (Photopoulos, 1990).

Post-operative RT is indicated if the margins are narrow or if there are multiple lymph nodes involved with tumour. Post-operative RT reduces pelvic recurrence.

RT may be ICT only or in combination with EBT (45-50 Gy in 22-25 fractions in 4.5-5 weeks) to deliver a total dose to point A of 75-80Gy.

Bulky Ib and IIa - EBT may be given pre-operatively in those under going surgery or given to reduce the tumour bulk prior to ICT to achieve a satisfactory dose distribution in those treated with RT. There is an increased risk of nodal involvement with bulky tumours (Thomas et al, 1992) making treatment of the whole

pelvis essential.

Stages IIB to IVa - RT is the mainstay of treatment. EBT to the whole pelvis is given to a total dose of 50Gy in 25 fractions in 5 weeks or equivalent. This is followed by ICT where possible, to give an additional 20-25Gy to point A. There is increasing evidence that fractionated ICT is more effective than a single application (Rotman and Aziz, 1991; Marcial et al, 1992).

Stage IVb - As the disease already extends outside the pelvis at this stage, local treatment is directed at relieving symptoms such as bleeding, offensive discharge and pain. Small volume fields are used to deliver the RT in the shortest possible time which relieves symptoms with minimal side-effects. Symptomatic metastases are also treated appropriately

Chemotherapy

Chemotherapy is of no proven value in the curative treatment of cervical cancer even though it can cause tumour regression. The role of chemotherapy is principally in the palliation of advanced and metastatic disease. Recently adjuvant and neoadjuvant chemotherapy has been investigated. In one study, neoadjuvant chemotherapy was found to be of value in stage IIB and to a lesser extent in stage IIIb disease by increasing the complete remission rates (Sardi et al, 1990).

Chemotherapy can also be given concurrently with radiotherapy in advanced and bulky disease with acceptable toxicity (Suggs et al, 1989; Chang et al, 1992).

Cisplatinum is the single most effective agent but bleomycin, methotrexate and vincristine have also shown significant response rates, which generally range between 25% and 65%. These agents are usually used in combination or with other drugs (Chang et al, 1992).

Simple combinations or single agents may have the advantage of being less toxic and therefore more tolerable especially in a palliative setting. Low dose methotrexate has been shown to be as effective as methotrexate and adriamycin combination, with low-dose methotrexate being less toxic (Sabir et al, 1989).

Prognosis

Stage

Stage is an established prognostic indicator. In one study the 5 year disease free survival rates by stage were , 100% for stage IA, 87.7% for stage IB, 70% for stage IIA, 66.3% for stage IIB, 36.7% for stage III and 0-15% for stage IV with radiotherapy treatment. (Perez, 1992). Results for surgically treated patients with Stage I to IIA are similar.

Tumour Volume

Tumour volume correlates to survival within each stage. It has been demonstrated that bulky tumours do worse (Thoms et al, 1992). In stage 3, unilateral parametrial involvement carries a better prognosis than bilateral parametrial involvement (Kovalic, 1991; Lanciano, 1991). Several studies have demonstrated that endometrial extension carries a poorer prognosis (Perez, 1992).

Histology

No significant correlation between tumour histology and survival has been shown although studies tend to demonstrate a poorer but non-significant survival with adenocarcinoma (Lowrey et al, 1992). Small-cell tumours tend to be more aggressive and metastasize early.

Anaemia

There is good evidence that survival is poorer in patients who have low haemoglobin values (less than 10g/dl) during treatment (Dische, 1991). Blood transfusions given during treatment may be an adverse prognostic factor (Girinski et al, 1989).

Immunity

Infiltration of the cervical intercellular spaces by Langerhans' cells has been demonstrated to carry a good prognosis. The presence of Langerhans' cells relates to stage. Early stage tumours have a higher rate of infiltration than late stage tumour

(Nakano et al, 1989).

HIV related tumours tend to be more aggressive and have a poorer prognosis.

Age

Some authors suggest that women under 35 years have a poorer prognosis than others (Harte and Atkinson, 1990; Murrell et al, 1990; Lowrey et al, 1992), and that patients over 50 years of age have a better prognosis than those under 50 years (Lowrey et al, 1992).

Follow-up

Upon completion of therapy patients are usually followed up three monthly for 2 years, 4 monthly for 2 years, then 6 monthly thereafter. At each visit general and pelvic examinations and a PAP smear are done. Other investigations eg. CXR, FBC may be done if indicated.

DEMOGRAPHIC CONSIDERATIONS IN ZIMBABWE

The Parirenyatwa Hospital Radiotherapy Centre (RTC) is situated in Harare, the capital city of Zimbabwe and is a referral Centre for the Northern and Eastern part of the country. It is also a referral centre for neighbouring countries without Radiotherapy facilities, such as Zambia and to a lesser extent Mozambique and Malawi. The RTC is closely linked to the National Cancer Registry situated in the same hospital.

During the period November 1990 to December 1991 a total of 793 cases of carcinoma of the cervix were registered with the National Cancer Registry. (Zimbabwe National Cancer Registry, 1991). This figure includes invasive carcinoma, carcinoma in situ, micro-invasive carcinoma and also very advanced tumours given palliative treatment other than radiotherapy.

PATIENTS AND METHODS

The subjects of the study were 273 patients who presented at the Parirenyatwa Hospital Radiotherapy Centre with a diagnosis of carcinoma of the cervix during the 14 month period, November 1990 to December 1991.

Of these 273 patients, 52 were excluded from the analysis. These included patients who refused to have RT (14 patients), absconded during treatment (24 patients), were found not suitable for RT treatment (10 patients) and those whose treatment was stopped before the prescribed RT dose was completed due to complications (4 patients) (see Table 1).

All 10 patients in this study found not to be suitable for radiotherapy (RT) presented with Stage IV disease. In four patients treatment was stopped due to severe acute complications. Of these four patients, three developed intractable diarrhoea during treatment. Two out of three with intractable diarrhoea tested positive for the human immuno deficiency virus (H.I.V). One patient had severe congestive cardiac failure and could not lie flat on the radiotherapy treatment table.

All data was obtained from the patients' case files kept in the Radiotherapy Centre. The case files included referral letters, EUA findings, histology reports and radiotherapy treatment details.

All patients were Africans except for three, of whom two were Caucasians and one was of mixed race. Two hundred and fifty-four of 273 (93%) patients were housewives and illiterate or semi-literate, living in the rural areas.

After exclusion 221 patients had radiotherapy and completed the course of treatment as originally prescribed. These 221 patients were divided into two groups for analysis, according to whether they received both EBT and ICT (group 1) or EBT only (group 2). There were 93 patients (42.1%) in group 1 and 128 patients (57.9%) in group 2.

Diagnosis and Staging

Biopsy was done in 153/221 (69.2%) of patients before referral for treatment. In the remaining 68 patients (30.8%), a diagnosis of carcinoma of the cervix was made on clinical grounds by digital examination in the clinic. This only applied to patients with advanced disease in the stage IIIB to IVB category. The F.I.G.O. staging system was used (see Table 2).

The term Stage IIIA+B was also used as a subgroup of Stage IIIB in order to distinguish those patients with both lower one third vaginal and pelvic side wall involvement by tumour. The majority of patients had a full blood count, LFT and blood urea and electrolytes done before referral.

Due to limited radiological resources intravenous urography was done only in 43 patients (19.5%), where there was a clinical indication such as a mildly raised blood urea (31 cases) a mass in the flank (8 cases) or other urinary symptoms (4 cases). Similarly, in the majority of patients a chest X-ray was ordered only in symptomatic cases (i.e. a few had routine CXR).

Lymphangiography was not performed in all these cases, again due to limited radiological resources and a high patient load.

Computerised tomography, although available in the private sector was not done routinely for non-paying patients.

Treatment

Group 1 patients (93/221) were treated with a RT technique which consisted of 2 phases of EBT followed by ICT.

In phase 1, of EBT anterior and posterior parallel opposing fields to the whole pelvis were used. The field borders varied slightly from patient to patient according to the various preferences of the radiotherapists. Most commonly, the superior margin of the field was at the upper border of the 5th lumbar vertebra, though in some cases it was at the lower border of the 5th lumbar vertebra. The lateral borders were placed 1cm outside the bony pelvic side walls. The inferior border was placed at

the lower border of the obturator foramina unless there was vaginal extension of the tumour, when the inferior border was placed to encompass all tumour with a 1cm margin. With marked vaginal extension, the superior border was often lowered to avoid irradiating an extensive field.

Phase 2 of the treatment consisted of lateral parallel opposing fields to the pelvis with a field width of 8-10cm, but the length of the field remaining the same as for Phase 1 in the majority of patients. The anterior border was chosen to pass through the mid symphysis pubis and the posterior border to take in the anterior one third of the rectum. For planning Phase 2, a radio opaque marker was placed in the posterior fornix and barium sulphate paste introduced into the rectum for tumour localisation.

The dose for Phase 1 ranged from 40Gy in 20 fractions in 4 weeks to 50Gy in 25 fractions in 5 weeks, in the midplane. For phase 2, 6-20Gy was given at 2Gy per fraction to a total dose of 46-60Gy in the midplane. All patients were treated with 5 fractions per week.

After a break of 3 to 7 days patients received an intracavitary treatment using a caesium manual after loading system of low dose rate (Amersham). Some patients had ICT during the EBT necessitating a 2-3 day break from EBT. Recalibration of sources and dosimetric calculations were done in October 1990. However

no individual dosimetry for ICT was performed due to lack of facilities for pelvic radiography after insertion of applicators. A dose of 20-30Gy was delivered to point A over 2-3 days. The dose rate of this system was 42,28 to 44,36cGy per hour depending on the combination of sources used.

Forty nine of the ninety three (52.7%) patients had intracavitary treatment during the external beam treatment and 44/93, (47.3%) after completion of EBT. The duration of ICT was 2 to 3 days in a single application.

For the EBT, none of the patients had outlines drawn nor isodose distribution charts plotted for dose distribution. This was before computerised treatment planning was available in the department.

The treatment of group 2 patients differed from the previous group in that none of the patients had an intracavitary caesium application. The external beam treatment was usually given in fractions greater than 225cGy, but in most patients' treated to 60cGy total, 200cGy fractions were preferred.

Most patients were treated with an anterior and posterior parallel opposing pair of fields to the pelvis. Only 25/128 patients (19.5%) had phase 2 treatment using two lateral field. The total external beam doses ranged from 21Gy in 7 fractions in

one and half weeks to 66Gy in 33 fractions in six and half weeks. In this group 16/128 patients (12.5%) were in stages 1 to 2B. These patients had EBT only although they presented with early disease. Of these 16 patients, 7 refused intracavitary treatment of whom two were stage 1, two stage 2A and three stage 2B. Two patients developed metastases during treatment, one to the supraclavicular lymph nodes (previously stage 2A) and one to the lumbar spine (previously stage 2B). Seven patients who were all stage 2B had bulky tumours which did not respond well to external beam RT.

The first follow up was usually at 4 to 6 weeks after the completion of all treatment. Subsequent follow up was usually at 2 monthly to 3 monthly intervals. Follow up time ranged from 0-27 months in the all 221 patients.

Acute complications were graded as mild, moderate or severe. Mild complications were those which responded to simple medical management without a need for a break in the treatment. Moderate complications were those which necessitated a break from treatment but without need for hospitalisation. Severe complications were those which required termination of treatment, hospitalisation or surgical management.

RESULTS

Patients' Age:

The age distribution of the patients whose age was known (n=190) is shown on Table 3 and Fig. 1

The age range was 21-80 years for Group 1 and 29-80 years for Group 2. There was no difference in the mean age of the two groups, i.e. 46.81 years for group 1 and 47.33 years for group 2.

Thirty one of the 221 patients (14.0%) were of unknown age. All of these patients were in group 2.

More than half of the patients 114/190 (60.0%) were in the age group 35-54 years, with 26/190 (13.7%) patients aged 34 years and below and 35/190 (18.4%) patients aged 60-80 years.

There was no significant difference in age distribution of the two groups.

Staging

The stage groups of the patients are shown in Table 4 and Fig. 2. The whole group of 221 patients who completed RT are presented.

Over half of the patients 113/221 (51.1%) presented with stage III disease. About one sixth of the patients 37/221 (16.7%) were in the stage IIIA+B category.

In the group of 93 patients who received both EBT and ICT (group 1) 72/93 (77.5%) were in stage I or II, 21/93 (22.6%) in stage III and none in stage IV.

By contrast, in the group of 128 patients who received EBT only (group 2) 16/128 (12.5%) were in stages I and II whereas 92/128 (71.9%) were in stage III and 20/128 (15.6%) in stage IV.

The various stage groupings for group 1 patients are shown against the month of initial presentation in Table 5. In the first half of the study period only 6/93 (6.5%) patients with stage III disease had EBT and ICT, whereas in the last seven months of the study period 15/93 (16.1%) patients with stage III disease had both EBT and ICT.

Duration of symptoms

The duration of symptoms by stage as recorded from the histories are shown on Table 6.

This was recorded for group 1 patients only because records for symptom duration were less reliable in group 2 patients.

The majority of patients, 55/93 (59%) gave a history of 3-8 months,

while 20/93 (21.5%) gave a history of longer than 1 year.

There was no obvious correlation between duration of symptoms and stage.

Histological Diagnosis

The histological diagnosis of all 221 patients is shown on Table 7 and Fig. 3. In both group 1 and group 2, squamous cell carcinoma was the most frequent histological diagnosis.

Of the 153 tumours biopsied, in 146/153 (95.4%) a diagnosis of squamous cell carcinoma was made. Of these 9/153 (5.9%) were well differentiated, 73/153 (47.7%) moderately differentiated, 38/153 (24.8%) poorly differentiated and differentiation was not stated in 26/153 (17.0%) (see Fig. 3).

Sixty eight (30.8%) of all the evaluable 221 patients were treated following clinical diagnosis with no biopsy done prior to referral. Of these 68 patients, 22/221 (10.0%) were in group 1 but twice as many, 46/221 (20.8%) were in group 2.

Only 7/153 (4.6%) patients biopsied had adenocarcinoma.

Radiotherapy Doses

In group 1 the total doses delivered to Point A in the patients who received both EBT and ICT are shown in Table 8.

Fifty nine of 93 patients (63.4%) received total doses between 75-79Gy to Point A and 25/93 (26.9%) received 70-74Gy.

Only 3 patients received 69Gy or less in this group. Of these three patients, one was HIV positive and developed severe pelvic inflammatory disease which necessitated a discontinuation of intracavitary treatment after 59Gy to Point A.

In one other patient the caesium applicators were displaced at 69Gy before completion of treatment. The third patient received 6145cGy instead of the 70Gy prescribed due to an error in dosimetry.

In group 2 total pelvic doses received by patients ranged from 10Gy to 92Gy (see Table 15). The majority of the patients, 117/128 (91.4%) received doses between 30-69Gy. Only 3 patients received total doses in excess of 70Gy. These patients had their treatment protracted over several months, with one to three months break in between short courses.

Length of Follow-up

In group 1, the length of follow up is shown in Table 9. It is seen that 48/93 patients (51.6%) had been followed up for over one year. Only 18/93 (19.0%) were followed up for less than 6 months.

In group 2, 83/128 (64.9%) of patients were followed up for less than 6 months and only 15/128 (11.7%) were followed up for more than one year (see Table 10).

Disease Status at Follow-up

The disease status of patients in group one, at first and second follow up is shown on Table 11 and Fig. 4.

It is seen that 16/93 (17.2%) of patients had been lost to follow-up by the second follow up.

At first follow-up 72/93 (77.4%) of group 1 patients were in complete clinical remission but 10/93 (10.7%) had residual disease. However by the 2nd follow-up the number of patients in complete clinical remission had fallen to 49/93 (52.7%) and there was a significant number of local recurrences, 18/93 (19.4%) by this time.

Only one patient who achieved a complete clinical remission after treatment had a recurrence of disease by the time of first follow up.

By contrast, Table 12 shows that a much higher proportion of patients were lost to follow-up in group 2, 44/128 (34.4%) at the last follow up, i.e. these patients did not attend the follow up clinic at the RTC at all.

At last follow-up only 24/128 (18.8%) of patients in this group had achieved a complete remission; the majority of the patients, 47/128 (36.7%) had residual disease.

Duration of Treatment vs Outcome

The outcome at second follow up as a function of the total treatment time for group 1 patients is shown in Table 13 and Fig. 5 and Fig. 6. The time from start to completion of all treatment ranged from 4 to 15 weeks. Since 16 patients were lost to follow-up (Table 11), the total number of patients in Table 13 is 77.

The majority of patients, 70/77 (90.9%) completed their treatment in 4-7 weeks. The one patient who had treatment over 15 weeks had intracavitary treatment after the 1st follow up as the patient had initially refused this treatment.

There was no significant difference in the complete remission rate (61.4%) between the two groups that had a total treatment time of 4-5 weeks and 6-7 weeks, respectively. In the remaining 7 patients treated in 8-15 weeks the number was too small for any meaningful analysis.

The Impact of Dose, Stage and Follow-up Time on Treatment Results

In group 1, of the patients receiving a total dose to Point A of 70-74Gy, 15/25 (60%) went into complete remission compared to 30/59 (51%) in the sub-group that received 75-79Gy. Similarly 16% and 20%, respectively recurred (see Table 14). The treatment results in these two sub-groups were not significantly different.

In group 2, all complete remissions are seen in the dose range 30 to 69Gy but 75% of these patients (18/24) received total doses of 50-69Gy (see Table 15).

None of the 3 patients who received doses of 70Gy or more had a complete remission. All had persistent, non-metastatic disease. These 3 patients were treated unconventionally eg. 21Gy in 7 fractions in 3 weeks repeated after a break of 1-3 months.

The proportion of patients lost to follow-up increased with decreasing dose being 0/3 in those receiving above 70Gy, 18/67 (27%) with 50-69Gy, 18/50 (36%) with 30-69Gy and 8/8 (100%) with

10-29Gy, respectively.

In group 1, 6/7 (86%) of patients in Stage I achieved complete remission, compared with 32/54 (59%) in Stage II and 11/16 (69%) in Stage III (see Table 16).

Of all the stage groupings, Stage IIIB (excluding subgroup Stage IIIA+B) had the highest complete remission rate of 89% (8/9 patients). This may be related to the small numbers (9) in this group. Altogether 49/77 (64%) patients achieved a complete remission (see also Table 11).

In group 2, the complete remission rate for all Stage II patients was 8/14 (57%) and for all Stage III patients 15/92 (16%). Within Stage III a complete remission rate of 10/54 (19%) was observed for Stage IIIB compared to 3/34 (9%) for Stage IIIA+B (see Table 17).

For group I, all local recurrences were detected within the first 20 months of follow-up; of these 11/18 (61%) presented within 1 year of completing treatment (see Table 18).

Similarly all patients who developed metastases were diagnosed within the first 18 months of completing treatment. All the other patients followed up for more than 2 years were disease free at the time of writing this manuscript.

Table 19 shows the outcome of treatment in relation to follow-up time in months for group 2 patients. Of the 24 patients achieving complete remission 6/24 (25%) had been followed up for over one year.

Of the patients who had local recurrence, 5/6 (83%) developed it within one year of completing RT. Of the 7 patients who developed metastases, 6/7 (86%) did so within 5 months of completing RT.

Acute Complications in Patients Treated with EBT and ICT

Data on acute complications were available for group 1 patients only because their records were more comprehensive. Most complications were mild or moderate, occurring in 42/93 (45.2%) patients. Severe complications occurred in 2 patients only (2.1%); one of these patients was HIV positive (see Table 20).

Gastrointestinal complications were the most frequently occurring, 28/93 (30.1%) with diarrhoea being the most common 24/93 (25.8%). Dysuria and skin reactions had almost the same incidence of 7/93 (7.5%) and 6/93 (6.5%), respectively (see Table 21 and Fig 7).

Most patients with acute complications 26/44 (59.1%) had total doses to Point A of 75Gy to 79Gy (see Table 22). No acute

complications were seen with total doses below 70Gy except in one patient (HIV positive).

The % complication rate increased from 52% (13/25) at 70-74Gy to 67% (4/6) at doses greater than 80Gy (see Table 23).

Of all acute complications 42/44 (95.5%) occurred in patients who completed treatment in 7 weeks or less. All severe (2/2) and all moderate (18/18) complications also occurred in those treated in 7 weeks or less (see Table 24).

Acute complications occurred in 18/39 (46%) of the patients whose course of RT was 5 weeks or shorter, 24/46 (52%) when the RT course was 6-7 weeks and 1/6 (17%) with a course of 8-9 weeks (see Table 25).

The Group 2 patients with complete remission at follow-up

Twenty four (19%) patients who were treated with EBT only went into complete remission. They were further analysed as a subgroup of group 2.

The mean age of these 24 patients was 48 years with a range of 30-65 years. Only 2/24 (8.3%) were under the age of 35 years. Age was unknown in 5/24 (21%) of the patients.

The staging of the 24 patients was as follows:- Stage I - 1/24 (4%), Stage IIA - 1/24 (4%), Stage IIB - 8/24 (33%), Stage IIIA - 1/24 (4%), Stage IIIB - 10/24 (42%), Stage IIIA+B - 3/24 (13%). None of the patients had Stage IV disease.

The histological diagnosis was unknown in 12/24 (50%) of these patients. Of the other 12 patients who had a histological diagnosis all had squamous cell carcinoma of which 6/12 (50%) were moderately differentiated, 3/12 (25%) poorly differentiated, 1/12 (8%) well differentiated and 2/12 (17%) of unknown differentiation.

The total doses received by the 24 patients varied greatly. The TDFs ranged from 66 to 130. Table 26 shows the TDF distribution in these 24 patients.

In this subgroup 17/24 (70.8%) of patients had a TDF of 80-99 and only 3/24 (12.5%) of patients has a TDF of less than 80. Similarly only 4/24 (6.7%) of patients had a TDF of more than 99. (TDF 99 = 60Gy in 30 fractions in 6 weeks).

DISCUSSION

This study shows clearly that cervical cancer is a serious problem in Zimbabwe, presenting a high patient load on the radiotherapy facilities available. Most patients are from the rural areas, of low socio-economic background, illiterate and with advanced disease at presentation, as noted previously in other studies (Du Toit, 1988; Kasule, 1989). Illiteracy may contribute to a significant proportion of patients refusing treatment even when offered (5.1%) and an even higher proportion absconding during treatment (8.8%). It also makes it difficult to explain in detail a complex treatment such as the one usually offered in a way that the patient will understand. This results in a number of misconceptions about radiotherapy and also a vicious circle, since patients who refuse treatment or abscond will of course have a poor prognosis, possibly resulting in other rural patients subsequently refusing RT.

Patients Age

The peak age incidence for invasive cervical cancer of 35-54 years in our study correlates with previously published data (Frost, 1981; Contran et al, 1989; Azhar and Lopez, 1989).

All patients of unknown age were in the group that received EBT only. Patients who do not know their age are usually illiterate and unaware of the early symptoms of cervical cancer. This could explain why they tend to present with more advanced disease.

Diagnosis and Staging

In those patients staged without EUA, staging may not have been accurate especially in those patients experiencing a lot of discomfort during examination. This bias may have influenced the results of the Group 2 patients who were mostly staged clinically.

Du Toit (1988) describes a need for a different staging protocol for developing countries which is similar to the one used at the Parirenyatwa Radiotherapy Centre. For example he states that examination under anaesthesia should only be done when in doubt of the diagnosis and no X-rays and cystoscopy are necessary in Stage I and II. He, however, goes on to point out that non recognition of such a protocol may lead to inability to compare treatment results with other centres. In our opinion this would be a major disadvantage of adopting such a protocol.

FBC was not routinely repeated at specific intervals after the start of treatment. It is known that a haemoglobin level of less than 10g/dl during RT carries a poor prognosis due to

radioresistant hypoxic cells within the tumour. There is also a tendency towards severe anaemia with advancing disease (Girinski, 1989; Dische, 1991). It will therefore be essential to establish the frequency of doing a FBC in our RTC.

Most patients in our study were of advanced stage. Patients in group 2 were of a more advanced stage (71.9% in Stage III) compared to group 1 (68.8% in Stage II). This is similar to the findings of Du Toit (1988) in South Africa and Azhar and Lopez (1989) in Malaysia in that the highest proportion of patients in the Third World is in Stage III (see Table 4 and Fig 2).

The staging of patients by the month first seen showed an increasing number of patients in Stage III being offered ICT throughout the year 1991 (Table 5). This reflects an increased use of the facility of brachytherapy which had been re-introduced at this centre. The distribution of the stages had not changed much during this period.

Duration of Symptoms

Although there was no obvious correlation between stage and duration of symptoms in group 1 patients (Table 6), Frost (1981) showed a correlation between the duration of symptoms and patients stage with 74% of Stage I, 63% of Stage II and 53.5% of Stage III having had symptoms for less than 6 months. In our

study group 1, 47/93 (50.5%) of patients in Stage II had symptom duration 8 months or less.

Duration of symptoms was less reliably recorded in patients who received EBT only (Group 2). Many of these illiterate patients did not give reliable information, if any at all.

Histological Diagnosis

The 68/221 (30.8%) of patients with no histological diagnosis could represent a group of patients with rapid disease progression, such that the clinical diagnosis was obvious and clinicians chose to refer these patients for treatment without a biopsy. About 2/3 (46/68) of these patients were in group 2 (Table 7).

The distribution of the various histological types in the biopsied patients is similar to that in previous work (Contran et al, 1989), with squamous cell carcinoma representing 95.4% of biopsied tumours and adenocarcinoma 4.6%.

Follow-up

Follow up was better for the group 1 patients than the group 2 patients and none of the patients was recorded as having died in either group. This is due to the practice of discharging very

sick patients to the district hospitals and to hospice care for palliative and terminal care, and feedback information is rarely received.

The better follow up for group 1 may also reflect the possibility that patients with early stage disease are more aware of their illness and the need to attend review clinics compared to those who present with late stage disease (group 2). Better follow up with increasing total RT dose in group 2 probably reflects the fact that lower doses were used with higher stages of the disease i.e. palliative treatment and these patients were then discharged to the district hospitals.

Of those patients followed-up, all local recurrences and metastases were detected within the first two years of follow-up in both groups (Tables 18 and 19). This corresponds to previous findings for Stage II cervical carcinoma where 78% of all locoregional relapses occurred within the first 2 years following treatment. The author therefore recommended that patients be followed up at least 2 monthly during this period, if surgical salvage can be offered (Kunkler et al, 1991).

None of the patients had cervical cytology done during subsequent visits after treatment. Although this is a reliable test for detecting early recurrence which can be salvaged surgically (Whitaker, 1990), in our setting this would overload our cytology

services. Reliance is put, therefore, on meticulous clinical assessment to detect any early local recurrence that may be suitable for salvage surgery.

Outcome of Treatment

The higher overall complete remission rate in group 1, 49/93 (52.7%) versus 24/120 (18.8%) is to be expected since group 2 patients had more advanced disease and were treated with EBT only; ICT improves local control. Similarly the residual disease rate was much higher in group 2, 47/128 (36.7%) versus 3/93 (3.2%) in group 1. The metastatic rate was similar for both groups.

There was a decrease in the complete remission rate with increasing stage in either group (Tables 16 and 17) which was more readily demonstrated in group 2. In group 1, stage IIIB had the highest complete remission rate of 89%. This is probably not true as the numbers in Stages I, and IIA and IIIB were too small.

Stage is established as the most important prognostic indicator. A lot of interest has been focussed on FIGO Stage III disease. It has been shown for stage IIIB, for example, that the outcome is worse if both parametria are involved than if there is unilateral parametrial involvement (Kovalic et al, 1991). For Stage IIIA, lower one third vaginal lesions which are continuous

with the cervical lesion were shown to have a better prognosis than discontinuous or skip lesions (Kavadi et al, 1992).

In this study the subgroup of Stage IIIA+B, in which there is pelvic wall involvement with extension of tumour to the lower one third of the vagina also, has been shown to have a worse outcome compared to Stage IIIB in either group.

Of all patients in group 2 with Stage I and Stage II disease, 10/16 (62.5%) went into complete remission whereas only 14/92 (15.2%) with Stage III did so. Of the Stage III patients that went into complete remission, 3/92 (3.3%) were Stage IIIA+B and 10/92 (10.9%) were in Stage IIIB. This further illustrates that the subgroup of Stage IIIA+B has a much poorer prognosis than the remainder of Stage IIIB.

There was a correlation between complete remission and increasing total dose for group 2 patients (Table 15). Such a correlation was not clear for group 1 patients as most received doses in a narrow dose range of 70-79Gy to Point A. Those receiving doses less than 70-79Gy did so due to unfortunate circumstances already stated and their outcome was thus expected to be less favourable.

Physical dose was used for most analyses in this study but it has been shown that time-dose factor (TDF) calculations are a better predictor of pelvic control and sequelae of treatment (Perez et

al, 1991). They showed that doses to Point A were not predictors of local control in Stage I and IIA, but for Stage IIB and Stage III doses below 60Gy were associated with a high local recurrence rate. External beam treatment was used in conjunction with intracavitary treatment in their study as was the case in our group 1 patients.

No correlation between duration of treatment and outcome could be shown in our study (Table 13). Most patients in group 1 were treated in 4-7 weeks, 70/93 (75%). The numbers were too small in the other treatment duration categories for comparisons to be made. However, a study done on Stage I-III patients showed that for Stage III patients survival was significantly decreased when overall treatment time was increased from less than 6, 6-7.9, 8-9.9 and 10 weeks (Lanciano et al, 1993).

In group 2, 24/128 patients went into complete remission (Tables 17 and 26). In these group 2 patients a strong correlation between stage and outcome is seen.

There was an obvious correlation between TDF and outcome (see Table 26). It was expected that patients with TDF values of over 80 would have a better prognosis. 21/24 (87.5%) patients had TDF values in the 80-130 range. This shows the need for high dose palliation in most patients with advanced stages except some Stage IV.

Complications

As expected with pelvic radiotherapy, gastrointestinal complications were the most common. The increase in the risk of acute complications with decreasing duration of treatment demonstrates the predictive role of the TDF. Most patients treated in 4-5 weeks had more than 200cGy per fraction. This may be expected also to predispose to a higher risk of late damage (Perez, 1991; Deore et al, 1992).

All severe (2/2) and all moderate (18/18) acute complications occurred in those treated in 7 weeks or less. Treatment at conventional fractionation (200cGy per fraction) is preferred as this decreases the risk of severe complications. These results conflict with the findings of Lanciano et al, (1993) in which there was no change in the rate of major complications with increasing treatment time.

Prevention and early diagnosis

Most patients in Zimbabwe present with advanced disease. When detected early carcinoma of the cervix is highly curable. Prevention and early diagnosis is thus of great importance in Zimbabwe, as in other countries.

It is recommended that the general public and health workers be given health education to be aware of the early symptoms of the disease. A method of screening of the group at risk is also important i.e. rural women whose risk status can be checked on a check list kept by the village health worker, especially women over 35 years and/or with a history of abnormal vaginal bleeding or discharge.

Screening has improved the mortality from cervical cancer in industrialised countries especially in women of 35-54 years (Yule 1978). It has also been shown that women with 2 negative pap smear results had a 50% higher protection against lethal invasive carcinoma than controls (Van Oortmarssen et al, 1992).

In the African setting, although screening as practised in developed countries is desirable lack of resources and costs make widespread use of cytology and colposcopy impractical. However digital examination, preferably combined with cervical visualisation can be valuable for downstaging the disease, especially in countries such as Zimbabwe where cervical cytological screening may take long to be introduced (Miller, 1992).

CONCLUSIONS

Our study demonstrated that the peak age incidence of cervical cancer in Zimbabwe is 35-54 years. There were 114/190 (60%) patients in this age group. There was no difference in the mean age of patients in group 1 and group 2.

The majority of patients presented with advanced disease. One hundred and ninety-eight of 221 (89.6%) of all patients had stage IIB to stage IV disease. In group 1, 64/93 (68.8%) of patients were in stage II whereas in group 2, 92/128 (71.9%) were in stage III.

There was no correlation between the duration of symptoms in group 1 patients and their stage. However most patients in group 1 had a symptom duration of 8 months or less. In group 2, patients histories relating to duration of symptoms were less reliable and so was not analysed.

The histological pattern was principally squamous cell carcinoma. Of all tumours biopsied, 95.4% were squamous cell carcinoma. The remainder (4.6%) were adenocarcinoma. Most of the squamous cell carcinoma were moderately differentiated (47.7%), with 24.8% poorly differentiated, 5.9% well differentiated and differentiation unknown in 17%. The various histological

subtypes were distributed similarly between the two groups.

As expected there was a higher complete remission rate (52.7%) in group 1 patients than in the group 2 patients (18.8%). Although most patients with CR were treated within 7 weeks, the numbers in the other time categories were too small for comparison.

There was a tendency for higher stages to be associated with a worse prognosis. This was shown more clearly in group 2. Stage IIIA+B was demonstrated to have an especially poor prognosis.

In group 2 there was an increase in the complete remission rate with increasing total pelvic dose. Most patients (70.8%) who achieved complete remission in group 2 had time-dose factors of 80-99. The relationship between dose and outcome was less clear for group 1 because most patients received similar radical doses.

Follow-up was better for group 1 (mean 13.4 months) than group 2 (mean 7.1 months).

In group 1, 15/25 (60%) of all local recurrences and metastases had been detected within one year of follow-up, and all occurred within 2 years of follow-up. In group 2, 11/13 (84.6%) of all recurrences and metastases were detected within one year of follow-up.

Overall, treatment was well tolerated with 52.7% of group 1 patients experiencing no complications. Severe complications occurred in only 2.1% of the patients. The risk of acute complications increased with increasing total dose to Point A (especially beyond 79Gy) and with shorter treatment time less than 7 weeks.

RECOMMENDATIONS

1. Early presentation should be promoted. Health education to increase the awareness of early symptoms such as post-coital bleeding, intermenstrual and postmenopausal bleeding and vaginal discharge is essential and should be directed at the rural population at risk, especially in women over 35 years of age.
2. Increased awareness is needed by medical staff in rural and district Hospitals of the value of early diagnosis and referral for definite treatment. Patients should be sent for a specialist opinion even before the histology report is available to decrease the delay time between diagnosis and treatment.
3. Examination under anaesthesia and biopsy should be done on all patients to ensure accurate staging. This aids in deciding the most appropriate treatment for patients and in documenting data that can be compared with centres in other countries. In all Stage IIIB cases, it must be clearly stated whether there is unilateral or bilateral pelvic wall involvement and for Stage IIIA whether there is any continuous or discontinuous involvement of the lower third of the vagina.

4. Intracavitary treatment should be offered to all patients where possible except for most patients in Stage IV.
5. The total treatment time must be kept at 7 weeks or below to improve outcome. It is thus preferable to give the first I.C.T. before completion of E.B.T. However, in trying to shorten total treatment times, TDF values should not exceed 99 in order to avoid a high proportion of late bladder and rectal complications.
6. Since most of our patients present with late disease palliative chemotherapy should be investigated in these often young women with large families. The aim should be to improve quality of, and occasionally prolong, life in their remaining lifespan. Cheap and simple chemotherapy regimes such as low dose single agent methotrexate would be most relevant in our setting, because of limited resources.
7. Follow-up can be improved by educating patients, rural health workers and family physicians on the need for the patient to be seen regularly. Outreach clinics could help to update our records on those patients discharged to the district hospitals for palliative care. The minimum length of follow-up at the radiotherapy centre in those patients treated radically should be at least 5 years, before discharging them to the rural or district hospitals.

8. There must be closer co-operation between gynaecologist and radiotherapist in the form of joint meetings and clinics to provide optimum patient management and to facilitate quick treatment decisions such as surgical intervention in early local recurrence or RT for pelvic recurrence following primary surgery.

9. A national screening programme is necessary in Zimbabwe. It should be directed at the population most at risk i.e. women of 35-55 years, mostly in the rural areas. The frequency of screening a subject should be every 5 years initially in view of the long natural history of cervical cancer. The frequency of screening can be reduced and population coverage increased with increasing resources. Large amounts of resources will need to be mobilised before cytological screening can be made available nationwide.

10. Before cytological screening can be employed to cover the whole population of the country, downstaging by regular digital and speculum examination should be carried out, initially at district levels, for the population at risk.

TABLES AND FIGURES

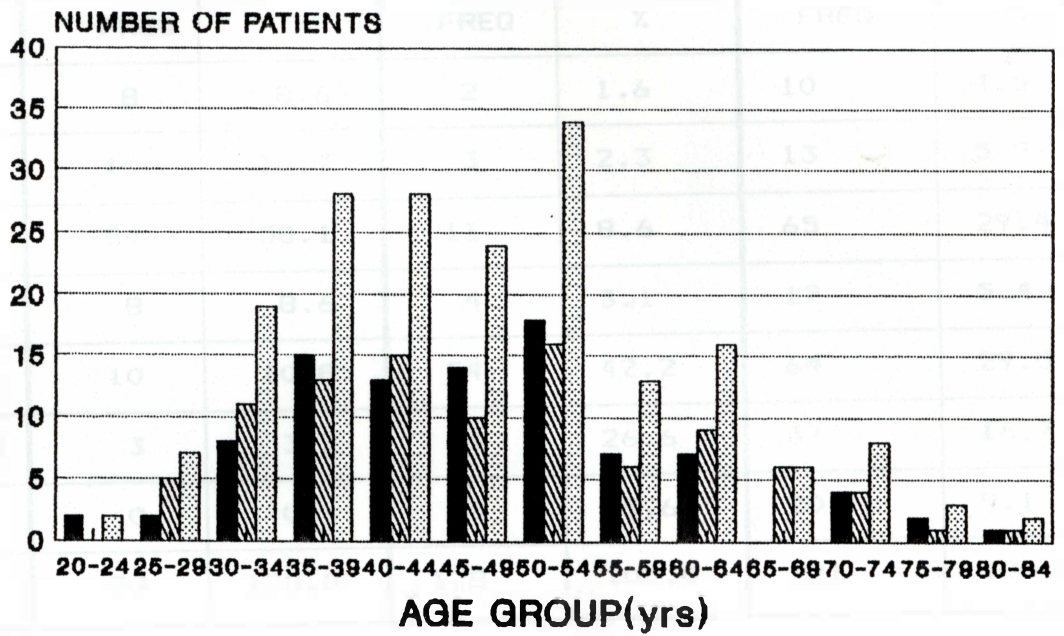
TABLE 1: CRITERIA FOR EXCLUSIONS

CATEGORY	NO	% ALL PTS (273)
REFUSED TREATMENT	14	5.1
ABSCONDED	24	8.8
STOPPED TREATMENT	4	1.5
NOT SUITABLE	10	3.7
TOTAL	52	19.1

TABLE 2: STAGING OF CARCINOMA OF THE CERVIX

<u>FIGO</u>	<u>TNM</u>	<u>DEFINITION</u>
-	Tx	Primary tumour cannot be assessed
-	To	No evidence of primary tumour
0	Tis	Carcinoma <u>in situ</u>
I	T1	Tumour confined to cervix (extension to the corpus should be disregarded.)
Ia	T1a	Preclinical invasive carcinoma diagnosed by microscopy only
Ia1	T1a1	Minimal microscopic stromal invasion
Ia2	T1a2	Tumour with invasive component 5mm or less in depth taken from the base of the epithelium and 7mm or less in horizontal spread
Ib	T1b	Tumour larger than T1a2
II	T2	Tumour invades beyond uterus but not to pelvic wall or lower third of the vagina
IIa	T2a	Without parametrial invasion
IIb	T2b	With parametrial invasion
III	T3	Tumour extends to pelvic wall and/or involves lower third vagina and/or causes hydronephrosis or non functioning kidney
IIIa	T3a	Tumour involves lower third of vagina, no extension to pelvic wall
IIIb	T3b	Tumour extends to pelvic wall and/or causes hydronephrosis or non functioning kidney
IVa	T4	Tumour invades mucosa of bladder or rectum and/or extends beyond true pelvis
IVb	M1	Distant Metastases
	Nx	Regional nodes cannot be assessed
	No	No regional node metastases
	N1	Regional lymph node metastases
	Mo	No distal metastases
	M1	Distant metastases

Fig. 1 AGE DISTRIBUTION



Series 1 Series 2 Series 3

SERIES 1-GP1 SERIES 2-GP2 SERIES 3-GP1&2

TABLE 4: STAGE GROUPS OF THE PATIENTS

Fig. 2 STAGING OF THE PATIENTS

STAGE	GROUP 1 (n=93)		GROUP 2 (n=128)		GROUP 1&2 (n=221)	
	FREQ	%	FREQ	%	FREQ	%
I	8	8.6	2	1.6	10	4.5
IIA	10	10.7	3	2.3	13	5.9
IIB	54	58.1	11	8.6	65	29.4
IIIA	8	8.6	4	3.1	12	5.4
IIIB	10	10.8	54	42.2	64	29.0
IIIA+B	3	3.2	34	26.6	37	16.7
IV	0	0	20	15.6	20	9.1
TOTAL	93	100.0	128	100.0	221	100.0

Fig. 2 STAGING OF THE PATIENTS

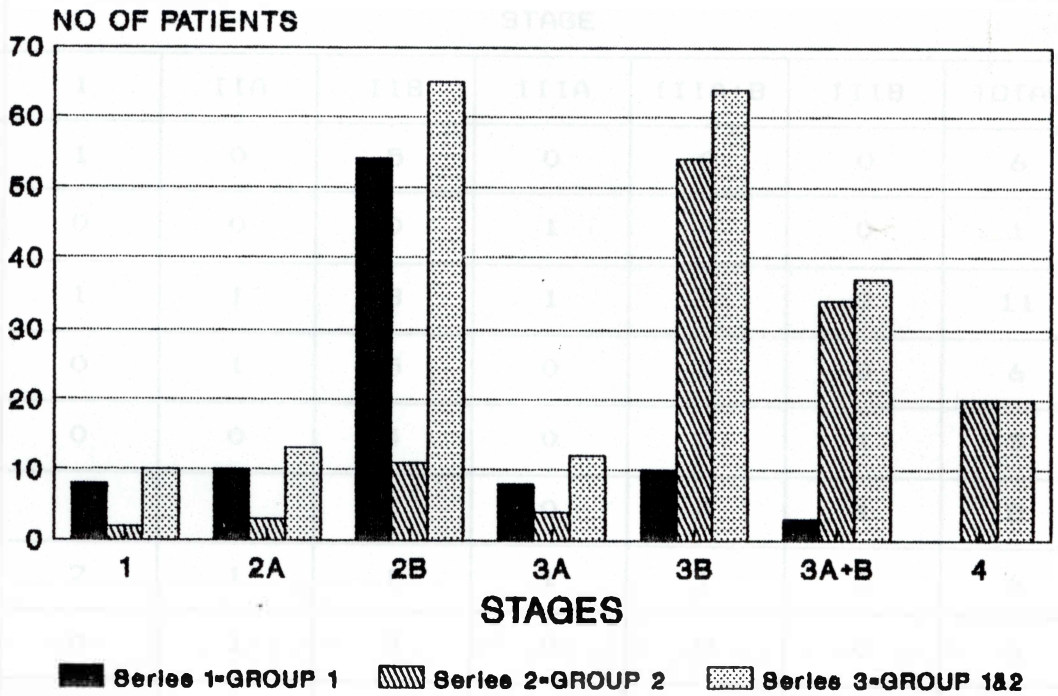


TABLE 5: STAGING BY MONTH FIRST SEEN : GROUP 1 ONLY

MONTH	STAGE						TOTAL
	I	IIA	IIB	IIIA	IIIA+B	IIIB	
NOV 90	1	0	5	0	0	0	6
DEC 90	0	0	0	1	0	0	1
JAN 91	1	1	8	1	0	0	11
FEB	0	1	5	0	0	0	6
MARCH	0	0	4	0	0	1	5
APRIL	1	1	5	0	0	1	8
MAY	2	1	1	1	1	0	6
JUNE	0	1	5	0	0	0	6
JULY	2	0	6	1	0	0	9
AUGUST	0	4	4	1	1	3	13
SEPT	0	0	2	1	1	2	6
OCT	0	0	5	0	0	0	5
NOV 91	0	0	2	1	0	1	4
DEC 91	1	1	2	1	0	2	7
TOTAL	8	10	54	8	3	10	93
%	8.6	10.7	58.1	8.6	3.2	10.8	100.0

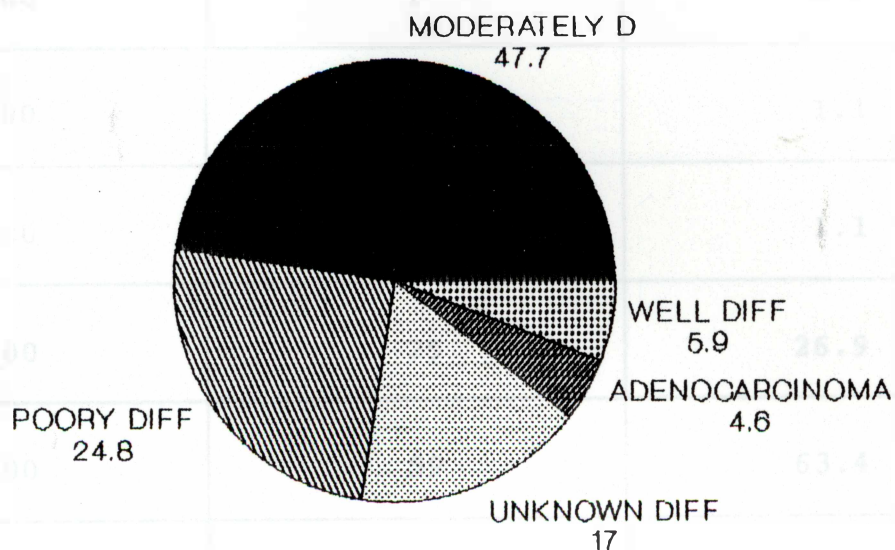
TABLE 6: DURATION OF SYMPTOMS BY STAGE: GROUP 1 ONLY

SYMPTOM DURATION (MONTHS)	STAGE						TOTAL (n=93)	PERCENT
	I	IIA	IIB	IIIA	IIIB	IIIA+B		
0 - 2	0	1	9	0	1	1	12	12.9
3 - 5	2	2	15	3	3	0	25	26.9
6 - 8	4	3	17	2	2	2	30	32.2
9 -11	1	0	4	1	0	0	6	6.5
12 and above	1	4	9	2	4	0	20	21.5
TOTAL	8	10	54	8	10	3	93	100.0

TABLE 7: HISTOLOGICAL DIAGNOSIS IN 221 PATIENTS

HISTOLOGY	GROUP 1 (n=93)		GROUP 2 (n=128)		GROUP 1&2 (n=221)	
	FREQ	PERCENT	FREQ	PERCENT	FREQ	PERCENT
WELL DIFF. SCC	4	4.3	5	3.9	9	4.0
MODERATELY D. SCC	32	34.4	41	32.0	73	33.0
POORLY DIFF. SCC	16	17.2	22	17.2	38	17.2
UNKNOWN DIFF. SCC	14	15.1	12	9.4	26	11.8
NO HISTOLOGY	22	23.7	46	35.9	68	30.8
ADENOCARCINOMA	5	5.4	2	1.6	7	3.2
TOTAL	93	100.0	128	100.0	221	100.0

Fig. 3 HISTOLOGICAL DIAGNOSIS FOR 153 GROUPS 1 AND 2 PATIENTS



NB.Pts.with[NO HISTOLOGY] are excluded

TABLE 8: TOTAL DOSES TO POINT A: GROUP 1 ONLY

DOSE	FREQUENCY	PERCENT
5500 - 5900	1	1.1
6000 - 6400	1	1.1
6500 - 6900	1	1.1
7000 - 7400	25	26.9
7500 - 7900	59	63.4
8000 and above	6	6.4
TOTAL	93	100.0

TABLE 9: LENGTH OF FOLLOW-UP: GROUP 1

TIME (MONTHS)	FREQUENCY	PERCENTAGE
0 - 2	11	11.9
3 - 5	7	7.5
6 - 8	15	16.1
9 - 11	12	12.9
12 and above	48	51.6
TOTAL	93	100.0

MEAN = 13,4 months
RANGE = 0 - 27 months

TABLE 10: LENGTH OF FOLLOW-UP: GROUP 2

TIME (MONTHS)	FREQUENCY	PERCENT
0 - 2	53	41.5
3 - 5	30	23.4
6 - 8	17	13.3
9 - 11	13	10.1
12 and above	15	11.7
TOTAL	128	100.0

MEAN = 7.1 months
RANGE = 2 - 22 months

TABLE 11: DISEASE STATUS: GROUP 1

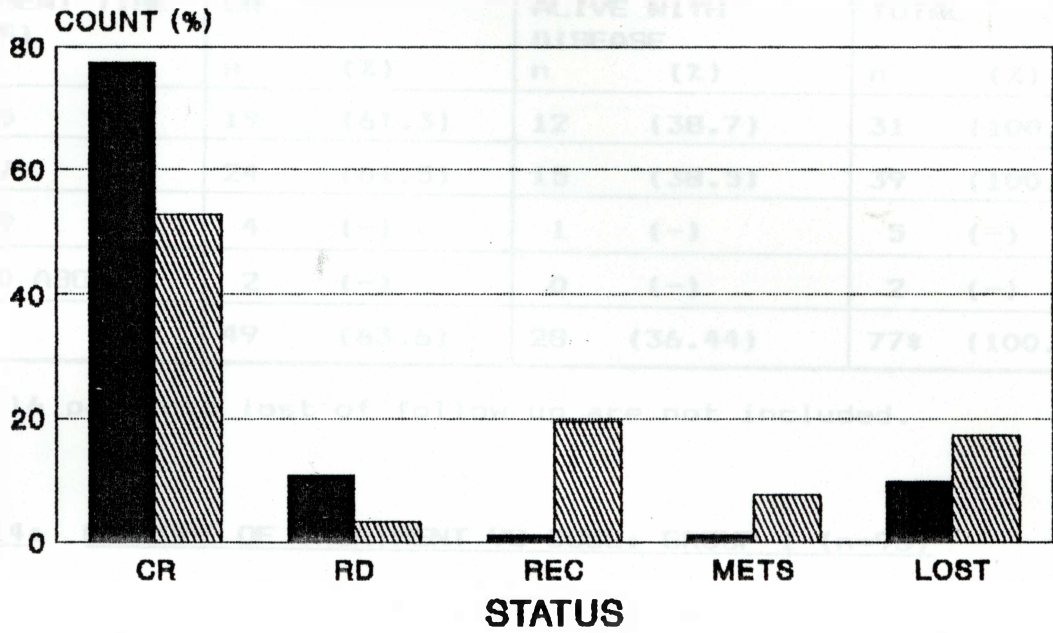
Fig. 4 DISEASE STATUS (GROUP 1)

OUTCOME	1st FOLLOW UP		2nd FOLLOW UP	
	FREQ	%	FREQ	%
CR	72	77.4	49	52.7
RD	10	10.7	3	3.2
REC	1	1.1	18	19.4
METS	1	1.1	7	7.5
LOST	9	9.7	16	17.2
TOTAL	93	100.0	93	100.0

TABLE 12: DISEASE STATUS AT LAST FOLLOW-UP: GROUP 2

CONDITION	FREQUENCY	PERCENT
CR	24	18.8
RD	47	36.7
REC	6	4.7
METS	7	5.4
LOST	44	34.4
TOTAL	128	100.0

Fig. 4 DISEASE STATUS GROUP-1



■ Series 1=1st F/UP ▨ Series 2=2nd F/UP

F/UP= FOLLOW UP

TABLE 13: OUTCOME VS DURATION OF TREATMENT: GROUP 1

TREATMENT TIME (WEEKS)	CR		ALIVE WITH DISEASE		TOTAL	
	n	(%)	n	(%)	n	(%)
4 - 5	19	(61.3)	12	(38.7)	31	(100.0)
6 - 7	24	(61.5)	15	(38.5)	39	(100.0)
8 - 9	4	(-)	1	(-)	5	(-)
10 AND ABOVE	2	(-)	0	(-)	2	(-)
TOTAL	49	(63.6)	28	(36.44)	77*	(100.0)

* The 16 patients lost of follow up are not included.

TABLE 14: OUTCOME OF TREATMENT VS DOSE: GROUP 1 (n=93)

OUTCOME	DOSE (Gy)					
	55-59 n (%)	60-64 n (%)	65-69 n (%)	70-74 n (%)	75-79 n (%)	80 + n (%)
CR	0 (-)	1 (-)	0 (-)	15 (60)	30 (51)	3 (-)
RD	0 (-)	0 (-)	0 (-)	1 (4)	2 (3)	0 (-)
REC	0 (-)	0 (-)	1 (-)	4 (16)	12 (20)	1 (-)
METS	0 (-)	0 (-)	0 (-)	2 (8)	5 (9)	0 (-)
LOST	1 (-)	0 (-)	0 (-)	3 (12)	10 (17)	2 (-)
TOTAL	1 (-)	1 (-)	1 (-)	25(100)	59	6

Fig. 5 OUTCOME VS DURATION OF TREATMENT: GROUP-1

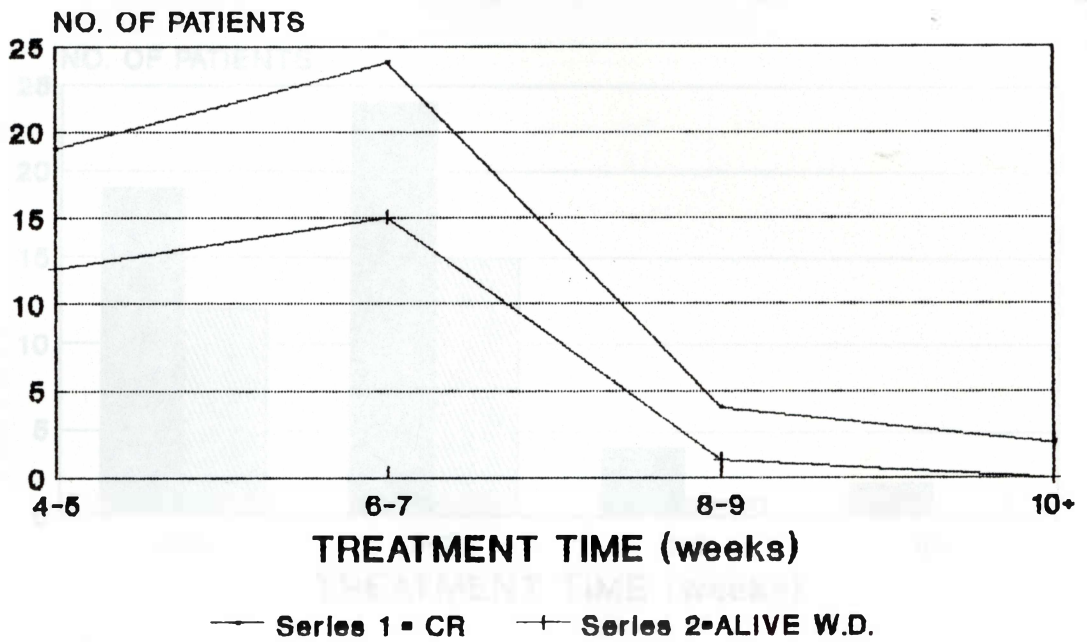


Fig. 6 OUTCOME VS DURATION OF TREATMENT: GROUP-1

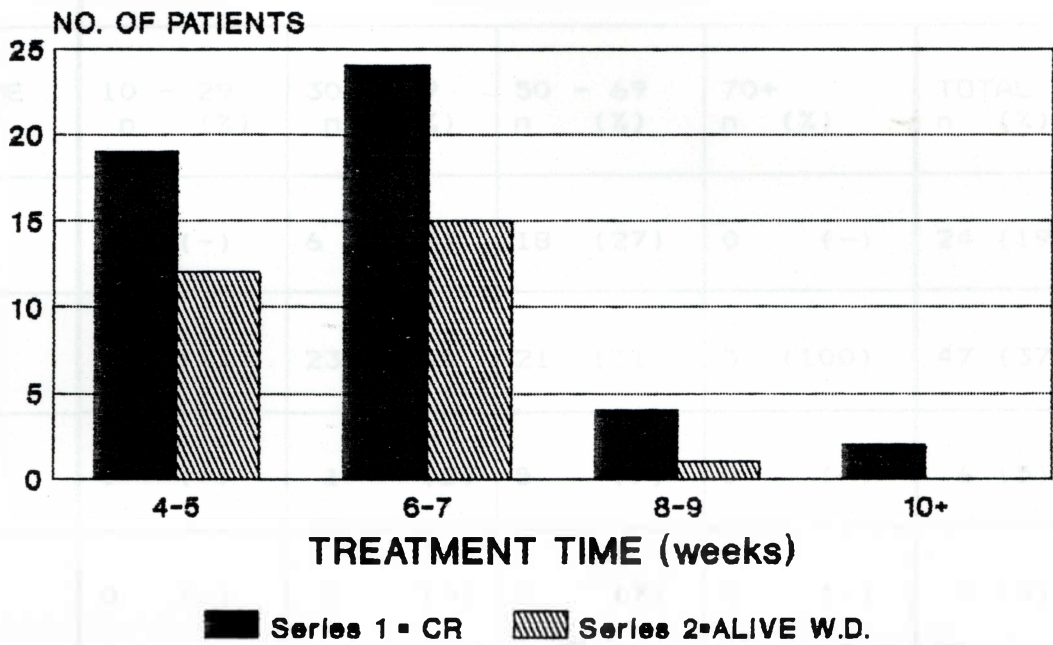


TABLE 15: OUTCOME OF TREATMENT VS DOSE: GROUP 2

OUTCOME	DOSE (GY)				TOTAL n (%)
	10 - 29 n (%)	30 - 49 n (%)	50 - 69 n (%)	70+ n (%)	
CR	0 (-)	6 (12)	18 (27)	0 (-)	24 (19)
RD	0 (-)	23 (46)	21 (31)	3 (100)	47 (37)
REC	0 (-)	1 (2)	5 (7)	0 (-)	6 (5)
METS	0 (-)	2 (4)	5 (7)	0 (-)	7 (5)
LOST	8 (100)	18 (36)	18 (27)	0 (-)	44 (34)
TOTAL	8 (100)	50 (100)	67 (100)	3 (100)	128(100)

DOSE RANGE = 10 - 92 Gy

TABLE 16: OUTCOME AT SECOND FOLLOW-UP VS STAGE: GROUP 1

OUTCOME	STAGE						
	I	IIA	IIB	IIIA	IIIB	III A+B	TOTAL
CR	n 6	5	27	2	8	1	49
	(%) (86)	(56)	(60)	(40)	(89)	(50)	(64)
ALIVE WITH DISEASE	n 1	4	18	3	1	1	28
	(%) (14)	(44)	(40)	(60)	(11)	(50)	(36)
TOTAL	7	9	45	5	9	2	77*

* 16 patients were lost to follow up

TABLE 17: OUTCOME VS STAGE: GROUP 2

OUTCOME	STAGE						
	I	IIA	IIB	IIIA	IIIB	III A+B	IV
CR	n 1	2	6	2	10	3	0
	(%) (50)	(67)	(55)	(50)	(19)	(9)	(-)
ALIVE WITH DISEASE	n 1	1	5	2	44	31	20
	(%) (50)	(33)	(45)	(50)	(81)	(91)	(100)
TOTAL	2	3	11	4	54	34	20

TABLE 18: OUTCOME VS FOLLOW UP TIME IN MONTHS: GROUP 1

FOLLOW UP TIME (MONTHS)	OUTCOME					
	CR	RD	REC	METS	LOST	TOTAL
0 - 2	0	0	0	0	11	11
3 - 5	1	0	1	0	5	7
6 - 8	6	1	6	2	0	15
9 - 11	6	0	4	2	0	12
12 - 14	5	0	2	2	0	9
15 - 17	10	1	2	1	0	14
18 - 20	12	0	3	0	0	15
21 - 23	5	1	0	0	0	6
24 +	4	0	0	0	0	4
TOTAL	49	3	18	7	16	93

TABLE 19: OUTCOME VS FOLLOW UP TIME IN MONTHS: GROUP 2

TIME	CR	RD	REC	METS	LOST	TOTAL
0 - 2	2	5	0	2	44	53
3 - 5	7	17	2	4	0	30
6 - 8	5	11	1	0	0	17
9 - 11	4	7	2	0	0	13
12 - 14	3	4	1	0	0	8
15 +	3	3	0	1	0	7
TOTAL	24	47	6	7	44	128

TABLE 20: ACUTE COMPLICATIONS: GROUP 1

COMPLICATION	FREQUENCY	PERCENT
NO COMPLICATIONS	49	52.7
MILD	24	25.8
MODERATE	18	19.4
SEVERE	2	2.1
TOTAL	93	100.0

**TABLE 21: NATURE AND FREQUENCY OF ACUTE COMPLICATIONS:
GROUP 1 (n=93)**

NATURE	FREQUENCY	PERCENT
DIARRHOEA	24	25.8
NAUSEA & VOMITING	4	4.3
SKIN REACTION	6	6.5
DYSURIA	7	7.5
OTHER	3	3.2
TOTAL	44/93	47.3

Fig. 7 NATURE AND FREQUENCY OF ACUTE COMPLICATIONS

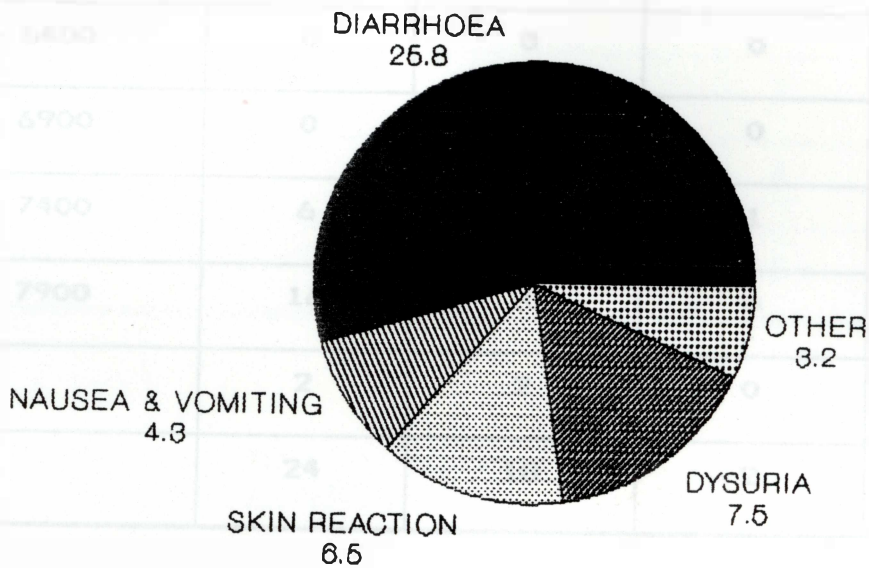


TABLE XI: RISK OF ACUTE COMPLICATIONS

DOSE (mg)	NO. OF PATIENTS	NO. OF COMPLICATIONS	PERCENTAGE
500 - 1000	10	1	10%
1000 - 1500	10	2	20%
1500 - 2000	10	3	30%
2000 - 2500	10	4	40%
2500 - 3000	10	5	50%
3000 - 3500	10	6	60%
3500 - 4000	10	7	70%
4000 - 4500	10	8	80%
4500 - 5000	10	9	90%
TOTAL	100	40	40%

TABLE 22: ACUTE COMPLICATIONS VS DOSE IN cGy: GROUP 1

DOSE TO POINT A	MILD	MODERATE	SEVERE	TOTAL	
				n	(%)
5500 - 5900	0	0	1	1	(2.3)
6000 - 6400	0	0	0	0	(0)
6500 - 6900	0	0	0	0	(0)
7000 - 7400	6	6	1	13	(29.5)
7500 - 7900	16	10	0	26	(59.1)
8000 +	2	2	0	4	(9.1)
TOTAL	24	18	2	44	(100.0)

TABLE 23: RISK OF ACUTE COMPLICATIONS VS DOSE: GROUP 1

DOSE (cGy) TO POINT A	NO. OF PATIENTS	NO OF COMPS	%
5500 - 5900	1	1	-
6000 - 6400	1	0	0
6500 - 6900	1	0	0
7000 - 7400	25	13	52
7500 - 7900	59	26	44
8000+	6	4	67
TOTAL	93	44	47

TABLE 24: ACUTE COMPLICATIONS VS DURATION OF RADIOTHERAPY IN WEEKS: GROUP 1

GROUP 1

DURATION OF RT	COMPLICATIONS			
	MILD	MODERATE	SEVERE	TOTAL n (%)
4 - 5	8	9	1	18 (40.9)
6 - 7	14	9	1	24 (54.5)
8 - 9	1	0	0	1 (2.3)
10 +	1	0	0	1 (2.3)
TOTAL	24	18	2	44 (100.0)

TABLE 25: RISK OF ACUTE COMPLICATIONS VS DURATION OF RADIOTHERAPY IN WEEKS: GROUP 1

DURATION OF RT	NO. OF PTS	NO OF COMPS	%
4 - 5	39	18	46
6 - 7	46	24	52
8 - 9	6	1	17
10+	2	1	-
TOTAL	93	44	47

TABLE 26: TDF DISTRIBUTION IN THE 24 CR PATIENTS: GROUP 2

TDF	NO. OF PTS.	%
60 - 79	3	12.5
80 - 99	17	70.8
100 - 120	3	12.5
120 +	1	4.2
TOTAL	24	100

* TDF 99 \equiv 60Gy in 30 fractions in 6 weeks

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