IMPACT OF TREATMENT BREAKS DURING RADIATION THERAPY IN THE SURVIVAL OF CERVICAL CANCER PATIENTS

in partial fulfillment of the requirements for the award.

The degree of

DOCTOR OF MEDICINE (M.D.)
IN RADIOTHERAPY

A DISSERTATION SUBMITTED TO
THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI

April 2018

CERTIFICATE

This is to certify that this dissertation titled, "IMPACT OF TREATMENT BREAKS DURING RADIATION THERAPY IN SURVIVAL OF CERVICAL CANCER PATIENTS" is a bonafide record of the work done by **Dr.Bharathi Srilatha.G**, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of her postgraduate study for the degree of M.D. (Branch IX – Radiotherapy) from 2015-2018 under my direct guidance and supervision.

Date:
Place: Chennai

Dr.G.Selvaluxmy,
Professor and Head of Department,
Division of Radiation Oncology,
Cancer Institute, (WIA), Chennai

ACKNOWLEDGMENT

At the first instance i thank Dr V.Shantha,Executive chairman,Cancer Institute , Adyar,for being a source of inspiration and providing me the opportunity to do my study.

I would like to thank my professor and HOD Dr.G.Selvaluxmy ,Additional Director Cancer institute ,for providing me with all the necessary support and encourgement to undertake this study,impact of treatment breaks during radiotherapy in survival of cervical cancer patients.I am grateful to her for the opportunity

I would like to thank my Assistant Professor Dr.Vasanth Christopher Jayapal who has provided me with suggestions and guidance at every phase ,and who's constant encouragement helped me complete this study.

My deep thanks to our Tumour registry staffs who helped with in collecting case records for data collection.

I thank the almighty God and my family for standing by my side and helping me to complete the study.

Preface

I.Introduction

1)Cervical cancer epidemiology

2)Anatomy of cervix

3)Etiology of cervical cancer

4)Natural history of cervical carcinoma

5)Pathology and prognostic factors

6)Staging of cervical cancer

7)Treatment modalities for cervical cancer

8)Concurrent chemoration and acute toxicities

9)Ideal treatment period and how often treatment gaps occur during radiotherapy

10)Impact of length and timing of treatment gaps

11)Factors to determine treatment breaks

12)Management of treatment gaps

13)Prevention of treatment gaps

II.Objectives and methodology

1)Aim of the study

2)Background

3)Objective

4)Study design

III.Results and analysis

IV.Discussion

V.Conclusion

VI.References

INTRODUCTION

Radiotherapy is a important modality in management of patients with cervical cancer.Discovery of Xrays by Wilhelm Conrad Roentgen on December 28,1895,marked the dawn of radiation oncology. In 1902 Xrays were used to treat cervical cancer,which was the first documented evidence.In early years they had limited knowledge about the radiobiology and dose distribution in the tumour and surrounding normal tissue.Hence the dose was entirely empirical so complications and failures are common

To achieve cure of a patient with any cancer ,radiotherapy,must eradicate every stem cell associated with the tumour and also those that are generated during course of treatment.The larger the course of treatment more the stem cells can repopulate,increasing the number of stem cells that have to be killed.As overall treatment time increases the probability of local tumour control decreases.In cervical cancer Overall treatment time includes combined external beam radiation with or without chemotherapy and brachytherapy.Studies have shown that overall treatment time in carcinoma cervix should be as short as possible and should not exceed 56 days

Both surgery and radiotherapy can be offered as primary treatment in stage I-IIA disease as both treatment options showed similar cure rates in this population .Standard treatment for patients with more advanced disease is concurrent chemoradiation and external beam RT followed by brachytherapy

CERVICAL CANCER EPIDEMIOLOGY

Cervical cancer is the 4th most common cancer among females all over the world and is one of the most common causes of cancer related mortality globally.World wide there were 5,27,600 new cases with 265,700 deaths in 2012.The incidence in age group 15-39 years old is16 per 1,00,000 women .In India which is the second most populated country cervical cancer is the second most common cancer in females with annual incidence of 1,22,844 cases.Globally cervical cancer incidence varies with variation in cultural outlook towards sexual practices and differences in the mass screening programs.The incidence of cervical carcinoma is more in populations with poor rates of screenings and high HPV infection.

The first screening test used for cervical cancer is the pap smear test which was developed by George papanicolaou,a greek cytopathologist in1923. He incidentally found cancer cells in cervical smears of patients in whom in was observing various cellular changes during menstruration.

The high incidence of advanced cervical cancer in developing countries due to lack of screening which help in detection of precancerous and early lesion. Effective methods of screening that can be used in countries that are still developing and under developed includes visual inspection with Using acetic acid or lugols iodine and testing for HPV DNA in cervical cell samples.HPV Types(16 and 18)cause 70% of cervical cancers and precancerous lesions in the cervix. Fact is cervical cancer is most common HPV related malignancy with almost all cases of cervical cancer linked to HPV infection.Varies risk factors of Various trials have been performed in low economy countries like India to find the effectiveness of HPV testing and in one such trial it was found that there a 50% reduction in risk of developing advanced cervical cancer due to HPV testing.

The first HPV vaccine-Gardisil quadrivalent HPV recombinant vaccine was approved and came to use in the month of june in 2006 .The following year 2007 the bivalent HPV vaccine cervarix was approved by the FDA.The vaccine showed 100% efficacy in vaccinated women and vaccine must be administered before sexual exposure.

HPV Vaccine is recommended for all boys and girls ages 9-16 years ,two doses 6 months apart.

TYPES - Cervarix- Only females – 16,18

Gardasil- Males and females – 6,11,16,18

Nanovalent - Males and females – 6,11,16,18,31,33,45,52,58

DOSE –0,1,6 months

Herpes simplex virus 2 has been implicated as a cofactor for development of cancer cervix.Many studies have implicated that herpes simplex virus 2 showes higher incidence in cervical cancer patient but no definitive evidence was proved.

Association between HIV and cervical cancer is proven ,since AIDS will cause immunosuppression.

Recently smoking and tobacco on causation of cervical cancer has been seen in new light.Women who smoke keep cervical HPV infection longer and so have more chance of developing cervical cancer than non smokers. In Indian scenario passive smoking is usally more common than active smoking.

Diethylstilbestrol which was used in 1940 s for prevention of recurrent and threatened miscarriages was found to be associated with the development of clear cell carcinoma of cervix and vagina.So it was banned by FDA in the year 1971.

In India screening programs are available only at tertiary care centre and women are not motivated enough for screening.Usually women who are symptomatic only end up in screening program resulting in detection only at advanced stages of disease.

Guidelines for screening

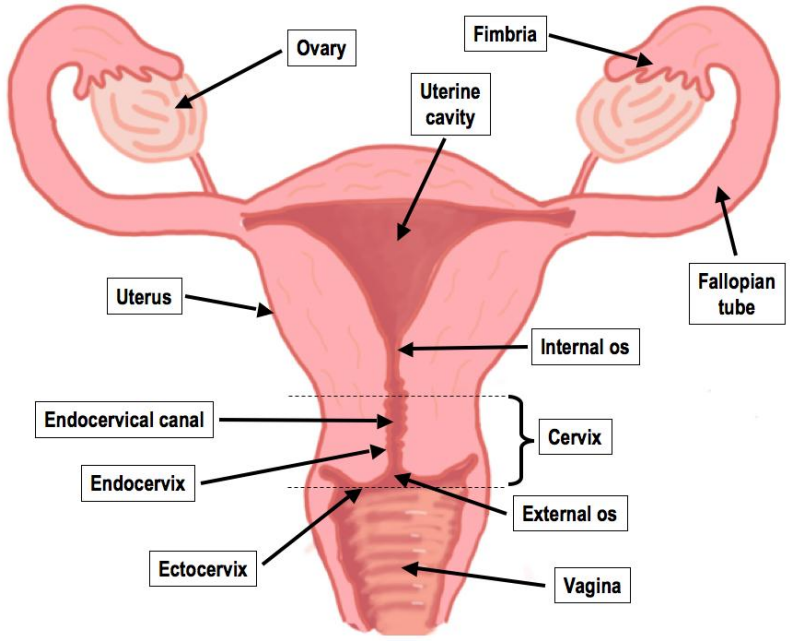
i)Women under 21 years should not be screened

ii)Women aged 21 to 29 years-Pap smear test every 3 years

iii)Women starting 30 years –preferred screening is Pap smear test with HPV test every 5 years until age 65 or Pap smear only ever 3 years until 65 years

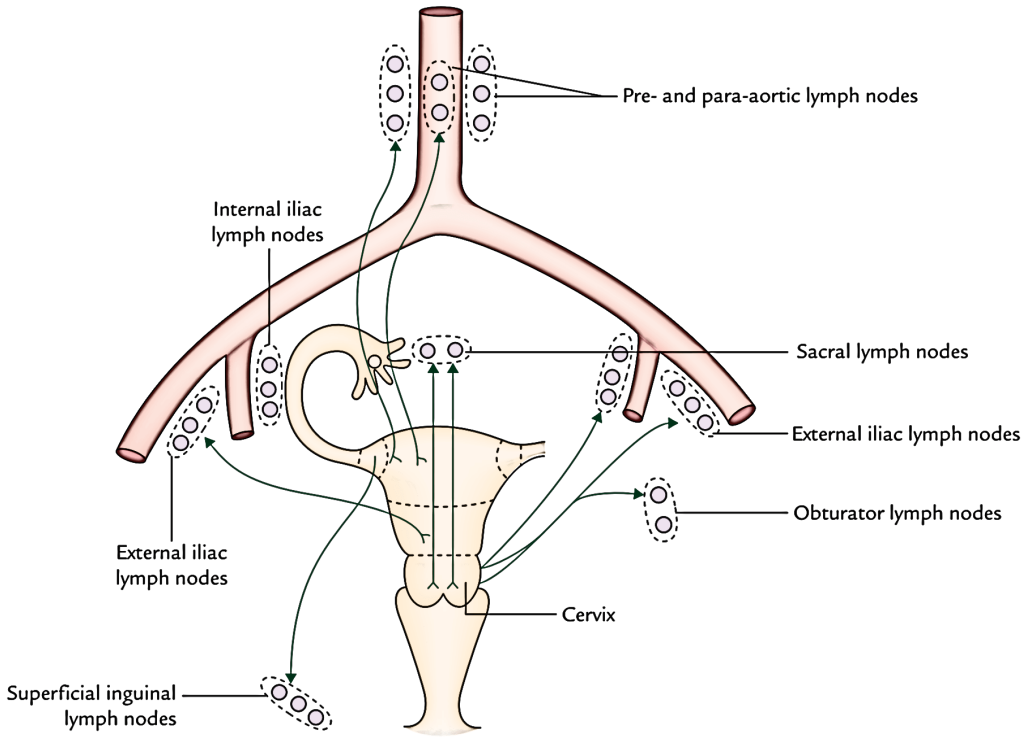
ANATOMY OF CERVIX

The uterus is a pear organ situated in the true pelvis above the vagina but posterior to the bladder and anterior to the rectum. The uterus is made up of the corpus superiorly and cervix inferiorly. The uterus measures 7x8cm in lengh ,5-6cm wide and 2-3cm thick.Cervix measures 3x3cm and is divided into a superior supravaginal portion above the ring containing the endocervical canal and the vaginal portion protruding into the vaginal vault. Central in the rounded vaginal region is the external os bounded by the anterior and posterior lips of the cervix, extending inward to the internal os ,the endocervical canal and endometrial canal



Lymphatic drainage is through the external iliac (of which the obturator nodes are the innermost) and the hypogastric nodes. The pelvic lymphatics drain into the common iliac and the paraaortic lymphnodes

Lymphatic drainage of cervix



PERCENTAGE OF LYMPH NODAL METASTASIS CA CERVIX

STA	PELVIC NODAL METASTASIS%	PARA AORTIC NODAL METASTASIS %
IA1	1	<1
IA2	2	<=5
IB	10	10
IIA	15	15
IIB	20	15
IIIA	25-30	20
IIIB	40-50	30-35
IV	50-60	40-45

ETIOLOGY OF CANCER CERVIX

- Socioeconomic status
- Access to health care
- Parity
- Smoking
- Presence of other infections
- Immune status
- Nutritional status

HPV

Studies suggest than more than 90 percentage of cervcal cancer is related to HPV infection.HPV is a sexual transmitted infection. HPV is small double stranded DNA.

Types - 16,18,31,33,35,39,45,51,52,56,58

HPV genome causes alteration in the chromosomes of the cells in the host by integrating with the host cell chromosomes. It encodes for E5,E6,E7 proteins which alter cellular proliferation. E6 inactivates p53 which results in chromosomal instability which inhibits apoptosis and activates telomerase. Incidence is between 25 – 35 years.It can take as long as 10-20 years after initial exposure for cancer to occur

Other factors associated with carcinoma cervix-

- Early age at first sexual intercourse.
- History of multiple sexual partners.
- A male partner with a history of multiple partners.
- Large number of pregnancies.
- History of sexually transmitted diseases/HIV

NATURAL HISTORY OF CARCINOMA CERVIX

Squamous cell carcinoma of uterine cervix usually originates at the squamocolumnar junction (transformational zone) of the endocervical canal and the exocervix. There is a structural progression from normal to higher levels of dysplasia.60% of CIN I and 40 % of CIN II will regress. Higher levels of dysplasia are more likely to transform into cancer. More so in the presence of cofactors like smoking ,impaired immunity. The transformation may be slow (10 – 20 years) or a rapid development in an aggressive disease.

Malignancy occurs when cells break the basement membrane and invades into the stroma of the cervix. This might result in spread to pelvic lymph nodes or distant organs.

Early detection at this point by a Pap smear will result in using minimally invasive therapy. However if the tumour progresses, it will become a superficial ulceration or exophytic tumour in the ectocervix or endocervix. If the cancer is not treated at this point it will spread further to the adjacent vaginal fornices, paracervical or parametrial or surrounding organs like urinary bladder or rectum or both. Paracervical extension is related to the depth of stromal invasion, tumour size, lymphatic invasion and the presence of lymph node metastasis.10 – 30 % of patients with carcinoma of the uterine cervix have extension to the lower uterine segment and the endometrial cavity. Regional lymphatic or hematogenous spread may occur and increases with stage although it does not occur in a definite order. Spread can progress to the obturator lymph nodes

(medial group of external iliac chain),other external iliac nodes to the hypogastric nodes, common iliac or paraaortic lymph nodes. The incidence of metastasis to pelvic or paraaortic lymph nodes depends on the stage of the disease. Spread through the venous plexus and paracervical veins resulting in hematogenous dissemination though rare in early stages is quite common in advanced stages. Spinal epidural compression from metastatic tumour often involving lumbar segments can occur rarely and spread to brain, lung and heart has also been reported.

Site of metastasis	**Incidence%**
Lung	21
Bone	10
SCL Node	7
Liver	4
Peritoneal/abdomen	4
Inguinal Lymph nodes	3

PATHOLOGY

Squamous cell carcinoma – 90% - Squamous-cell carcinomas are divided intothree types: large-cell keratinizing and nonkeratinizing and small-cell type, and they are subdivided according to the degree of differentiation into well, moderately, or poorly differentiated

Adenocarcinoma -7 – 10 %

Clear cell mesonephric type – 1- 2 %.

PROGNOSTIC FACTORS

I) PATIENT FACTORS

1. Age
2. Race
3. Socioeconomic status
4. General medical factors like anemia and hypoxia

II) TUMOR FACTORS

1. HPV subtypes
2. Tumor volume
3. Grade of the tumor
4. Treatment duration
5. Biomarkers like VEGF,BAX,BcL2

FIGO STAGING-CARCINOMA CERVIX

The FIGO staging system is based on clinical evaluation (inspection, palpation, colposcopy); roentgenographic examination of the chest, kidneys, and skeleton and endocervical curettage and biopsies. Lymphangiograms, arteriograms, imaging findings, and laparoscopy or laparotomy findings should not be used for clinical staging. Suspected invasion of the bladder or rectum should be confirmed by biopsy. Bullous edema of the bladder and swelling of the mucosa of the rectum are not accepted as definitive criteria for staging

I-Carcinoma confined to the uterus-extension in corpus should be disregarde

IA-Preclinical invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0mm measured from the base of the epithelium and a horizontal spread of 7.0mm or less. Vascular space involvement, venous or lymphatic does not affect classification.

IA1 –Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread.

IA2 – Measured stromal invasion more than 3.0 mm and non 5.0mm with 7.0 mm or less in horizontal spread.

IB – Clinically visible lesion confined to the cervix or microscopic lesion greater than IA2.

I B1 – Clinically visible lesion 4.0 cm or less in greatest dimension

I B2 – Clinically visible lesion more than 4.0 cm in greatest dimension.

II –Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina.

II A – Tumour without parametrial invasion

II A 1 – Clinically visible lesion 4.0 cm or less in greatest dimension

II A 2 - Clinically visible lesion more than 4.0 cm in greatest dimension.

II B – Tumour with parametrial invasion

III – Tumour extends to pelvic wall and / involves lower third of vagina, and / or causes hydronephrosis or non functioning kidney.

III A-Tumour involves lower third of vagina ,no extension to pelvic wall.

III B – Tumour extends to pelvic wall and /or causes hydronephrosis or nonfunctioning kidney.

IV A – Tumour invades mucosa of bladder or rectum,and/or extends beyond true pelvis (bullous edema is not sufficient to classify as IV A)

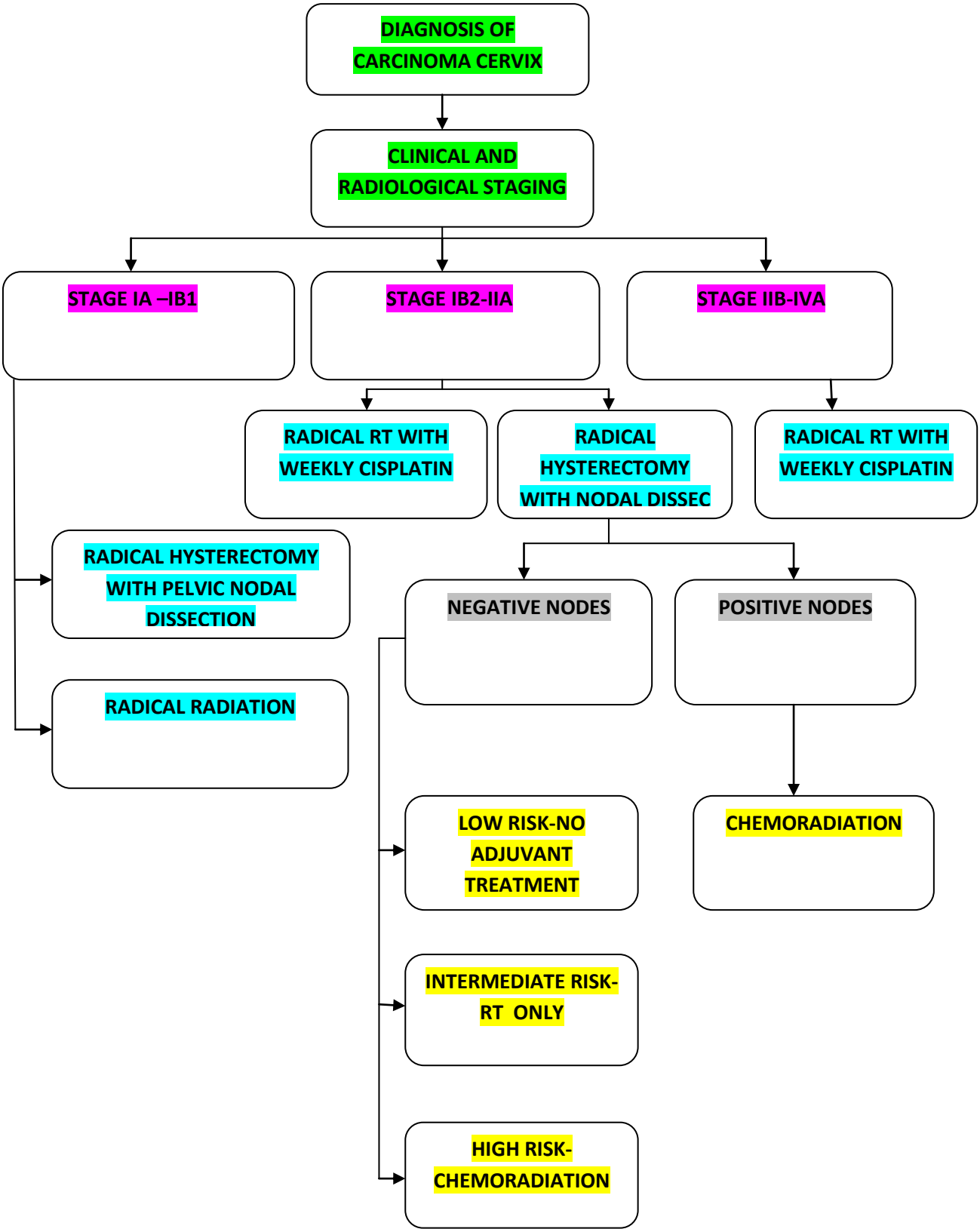
IV B – Distant metastasis including peritoneal spread, involvement of supraclavicular mediastinal or paraaortic lymphnodes, lung, liver or bone

DEMOGRAPHIC DATA

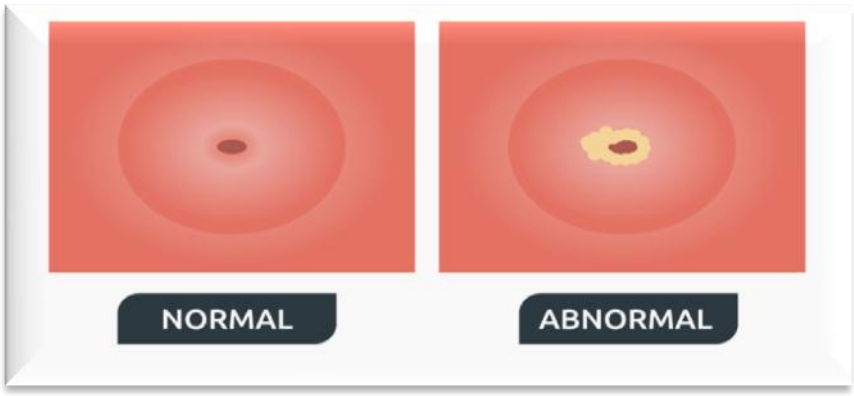
MMTR DATA

Cervix cancer	**1982-1986**	**1987-1991**	**1992-1996**	**1997-2001**	**2002-2006**	**2007-2011**	**2012-2013**
Annual No. of cases: Women	563	535	465	516	445	400	193
% to total cancers	37.7	31.5	26.1	24.6	18.5	14.3	12.8
Women: CIR / 100,000	33.7	29.6	24.0	24.8	20.4	17.5	16.5
ASR / 100,000	44.5	37.8	29.3	29.0	22.1	17.8	15.7
Cumulative Risk % - One in	21	25	31	31	39	47	53

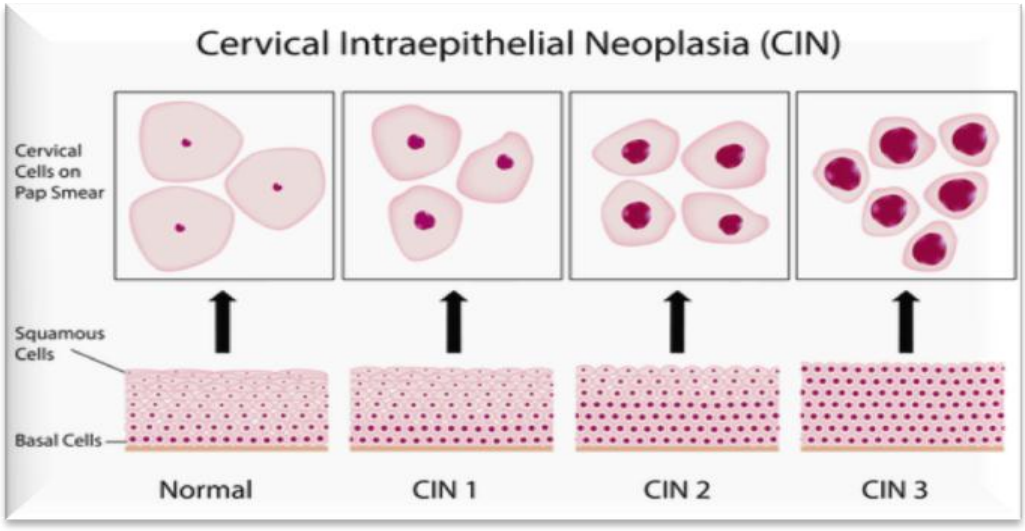
TREATMENT MODALITIES FOR CERVICAL CANCER



Premalignant squamous lesions of the cervix were earlier named with terms like mild,moderate,severe.Rubin in the year 1910 first introduced the term carcinoma in situ for invasive carcinoma.In the year 1967 Richard introduced the concept CIN with varying degree of atypia.



WHO in 1975 classified CIN into three categories CIN1,CIN2,CIN3.CIN1 is mild dysplasia confined to the basal 1/3 of the epithelium.CIN2 is moderate dysplasia confined to the basal 2/3 of the epithelium.CIN3 is severe dysplasia involves more than 2/3 of epithelium.



GENERAL PRESENTATION:

Low back pain and pain in gluteal region may be present due to advanced aggressive disease or due to enlarged pelvoc adenopathy which causes pressure effect on the lumbosacral nerves or hypogastric nerves .

Patients can also present with bleeding per vaginum to massive tumour bleeding which can be life threatening.Prongled history of minimal bleeding may be associated with anaemia and generalised tiredness.

Locally aggressive disease an cause invasion of organs surronding Hematuria and dysuria can occur because of invasion of the bladder and blood in stools or frank blood in rectum and rectal pain can occur due to rectal involvement or hydronephrosis and uremia secondary to ureteral obstruction by tumor may occur.

In very advanced and neglected cases, fistula formation may be present with fecal or urinary diversion into the vagina. Fever secondary to local infection of the cervix, vagina, and vulva, or urinary tract infections with the possibility of pyelonephritis may be seen.

MANAGEMENT OF CARCINOMA CERVIX AND OVERVIEW

Carcinoma In Situ :Patients with carcinoma in situ, which may include severe dysplasia, usually are treated with a total abdominal hysterectomy, with or without a small vaginal cuff. The decision to remove the ovaries depends on patient age and the status of the ovaries. Intracavitary irradiation (tandem and ovoids) may be useful for the treatment of in situ carcinoma, particularly in patients with strong medical contraindications for surgery or when there is multifocal carcinoma in situ in both the cervix and vagina

FIGO Stage IA:

Early invasive carcinoma of the cervix (stage IA2) usually is treated with a total abdominal or modified radical hysterectomy, but it can be treated with intracavitary radioactive sources alone.

FIGO Stages IB and IIA:

The choice of definitive chemoradiation or radical surgery for stage IB and IIA carcinoma of the cervix remains highly controversial, and the preference of one procedure over the other depends on the general condition of the patient and the characteristics of the lesion. Tumor control and survival are equivalent with either modality.

FIGO Stages IIB, III, and IVA:

Patients with stage IIB and III tumors are treated with chemoradiation alone.

Patients with stage IVA disease (bladder or rectal invasion) can be treated either with pelvic exenteration, or with high doses of external irradiation to the whole pelvis, intracavitary insertions, and additional parametrial irradiation.

Concomitant use of irradiation and cisplatin, has been administered to obtain a radiosensitizing effect. Several randomized trials have shown improved outcome with concomitant irradiation and chemotherapy compared with irradiation alone.

Adjuvant postoperative therapy:

The decision on adjuvant therapy following hysterectomy depends on the prognostic factors like status of the lymph nodes, size of the primary tumor, depth of stromal invasion, presence or absence of lymph-vascular space invasion, presence or absence of parametrial extension, histologic cell type and status of the vaginal margins. There were three independent prognostic factors:

- The clinical size of the tumor.
- The presence or absence of lymph-vascular space invasion.
- The depth of tumor invasion.

The risk stratification is done by calculating the GOG score. The GOG score is calculated by multiplying the relative-risk for depth X tumour size X lympho vascular space involvement.

- Low risk (GOG score less than 40) – No adjuvant therapy.
- Intermediate risk (GOG score 40-120) – only radiation.
- High risk (GOG score more than 120) – concurrent chemoradiation.

CONCURRENT CHEMORADIATION IN CARCINOMA CERVIX

Use chemotherapy along with radiation, has been proven to increase either mutual or simultaneous sensitization. Like more than 100 years ago there is a example when radiation treatment and systemic benzene treatment were combined for the treatment of leukemia. In the late 1970 s Steel and Peckham developed a conceptual framework for analyzing drug-radiation interactions . In this seminal work, four mechanisms were described in which combined modality therapy could

improve therapeutic outcome they are spatial cooperation.toxicity independence,protection of normal tissue.and enhancement of tumour response

Now for more than 20 years , these mechanisms provided the backbone for evaluating chemoradiation combinations clinically. Based on these clinical investigations, combined with the rapid emergence of molecularly targeted agents, Bentzen and colleagues proposed an updated conceptual framework to evaluate drug-radiation combination.One of the clearest clinical examples demonstrating improved outcomes of combined chemoradiation is in locally advanced cervical cancer.

In earlier days radiation therapy was the most effective modality for treatment of carcinoma cervix, when either surgical resection is not possible or when surgical resection is not medically feasible. Many cases fail in the scenario of bulky local disease or regional metastatic disease. For the past 45 years many studoies and trials have been conducted to explore the pontential agents which are likely to increase the possible cure in these patients. Initial studies evaluated the potentcy of hydroxyurea to increase the cure with radiation. Many studies found to have benefit, but a Cochrane review in 2004 proved that there is no evidence to support the use of hydroxyurea combined with radiation in the treatment of carcinoma cervix. Another cause for selective radio resistance, in large tumours was tissue hypoxia. Many studies combined radiation with hypoxic- cell radiosensitizers like misonidazole, pimonidazole, but none proved the benefit of these agents in carcinoma cervix. Observation from all these earlier trials were taken together,and in 1996 the National Institutes of Health Consensus Statement on Cervical Cancer stated that there was no proven benefit on combining chemotherapy with radiation in locally advanced cervical cancer.

For the next 4 years (1996 to 1999)a series of five phase three randomised clinical trials combining radiation with cisplatin revolutionized treatment of carcinoma cervix. Based on the results of these trials, in the 2nd month of 1999, the National Cancer Institute(NCI) issued a clinical announcement stating

that strong consideration should be given in the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.

VARIOUS TRIALS FOR CONCURRENT CHEMORADIATION

GOG 85 & SWOG 8695 Study- Charles W.Whitney et al:

Patients with stage IIB- IVA(368) were randomised based on eligibility to receive either hydroxyurea or cisplatin /5 flurouracil. The median follow up for 8.7 years.There was a significant changes in 5-year progression free survival with cisplatin/5-Flurouracil (57% versus 47%) and overall survival at 5 years(62% versus 50%). Thus proving that cisplatin based regimen is superior compared to hydroxyurea

GOG 120 study- Peter.G. Rose et al:

Patient with stage IIB–IVA were randomised either to weekly cisplatin alone or hydroxyurea alone or combination with cisplatin, 5-flurouracil and hydroxyurea. This study concluded that there is a significant survival benefit with cisplatin containing regimens.3 year overall survival was 65% for platinum based arms versus 47% in non platinum based arm. This study also concluded that weekly cisplatin is effective and less toxic.

RTOG 90-01 protocol- Mitchell Morris et al:

Patients with stage IB–IVA were randomised to either pelviradiation with cisplatin and 5-flurouracil versus pelvic with para aortic radiation. There was a significant difference in the 8 years disease free survival (61% with chemotherapy versus 46%) and overall survival (67% with chemotherapy versus 41%). Interestingly there was no change inthe para aortic failure rates

GOG 123 study- Henry M.Keys et al:

Women with bulky stage IB cervical cancers were randomly assigned to receive radiotherapy alone or in combination with cisplatin, followed in all patients by adjuvant hysterectomy. There was a significant change in 3-year progression free survival(79% with cisplatin versus 67%); 3- year overall survival(83% with cisplatin versus 74%). The pathogical complete response rates were also higher with cisplatin. This study concluded that weekly cisplatin is superior to radiation alone in bulky stage IB2

Intergroup 0107 (SWOG 8797/GOG 109/RTOG 91-12)- Pearcey et al:

Patients eligible for this intergroup study were those with stage IA2, IB, or IIA carcinoma of the cervix who was initially treated with radical hysterectomy and pelvic lymphadenectomy and who was found to have positive pelvic lymph nodes, positive margins, and/or positive parametrial infiltration on microscopic evaluation. They were randomised to either concurrent chemoradiation with

cisplatin and 5-fluro uracil or radiation alone. There was a significant difference in 4 year over all survival (81% with concurrent chemoradiation versus 71%).

Overview of concurrent chemoradiation trials:

The five studies had different eligibility criteria, but in total included a broad spectrum of clinical presentations:

- locally advanced tumors for which chemoradiation represented primary therapy,
- bulky early-stage cancers in which chemoradiation was delivered prior to adjuvant hysterectomy, and
- postradical hysterectomy cases with high-risk pathologic factors for whom adjuvant chemoradiation was given.

There was a consistent statistically significant survival advantage favoring the RT arm that included a concurrent cisplatin-based regimen, as compared with RT alone or RT combined with hydroxyurea, with a dramatic 30% to 50% decrease in the risk of death from cervical cancer. Several of these studies, have been updated and confirm that the statistically significant survival advantage of cisplatin based chemoradiation is maintained over the long term, and they validate the 1999 NCI clinical alert.

In 2010, Cochrane gynaecological oncology group evaluated all concurrent chemoradiation trials. It is a review of twenty four trials (21 published, 3 unpublished) and 4921 patients and concluded, ‖Concomitant chemoradiation appears to improve overall survival and progression-free survival in locally advanced cervical cancer. It also appears to reduce local and distant recurrence suggesting concomitant chemotherapy may afford radiosensitisation and systemic cytotoxic effects. Some acute toxicity is increased, but the long-term side effects are still not clear.

The other chemotherapeutic agents which have been tried along with irradiation to the pelvis are carboplatin, 5-Fluoro uracil, epirubicin, gemcitabine and mitomycin C, either alone or in combinations. Balanced against the indeterminate individual trial results described above, a recent comprehensive meta-analysis has suggested that nonplatinum agents may also improve outcome when combined with RT and deserve further evaluation.

ACUTE TOXICITIES IN CONCURRENT CHEMORADIATION

Concurrent chemoradiation with cisplatin based chemotherapy, marked its success through a series of trials in improving not only the local control rate, but also the overall survival. In the late 1970s Soloway and colleagues demonstrated radiosensitization in a murine model of transitional cell carcinoma. In a study of 19 human cervical-cancer cell lines, Britten et al. found that radiotherapy and concomitant treatment with cisplatin increased the rates of death of these tumor cells. However, radiosensitivity was increased in only four cell lines, suggesting that the effect of this combined therapy is primarily caused by direct cytotoxicity.Cisplatin is Cis-diamminedichloroplatinum, a water soluble coplanar complex, which is converted to its active form by replacement of its chloride ions with hydroxyl groups[30]. The cytotoxicity of cisplatin is primarily ascribed to its interaction with nucleophilic N_7-sites of purine bases in DNA to form both DNA–protein and DNA–DNA interstrand and intrastrand crosslinks[32]. The basis for interaction between cisplatin and radiation may be appreciated at multiple levels,like by increased formation of toxic platinum intermediates in the presence of radiation-induced free radicals,or the capacity of cisplatin to scavenge free electrons formed by the interaction between radiation and DNA that may fixate otherwise reparable damage to DNA,

- a radiation-induced increase in cellular cisplatin uptake,
- a synergistic effect because of cell cycle disruption, and
- the inhibition of repair of radiation-induced DNA lesions.

The toxicity of concurrent chemoradiation in carcinoma cervix can be attributed to

Cytotoxic effects of chemotherapy.

Toxicity due to pelvic radiation.

Enhanced toxicity due to synergistic

Cytotoxic effects of chemotherapy:

Edward Chu in his ―Cancer Chemotherapy Drug Manual‖ describes 13 toxicities due to cisplatin. The notable ones are nephrotoxicity, nausea & vomiting, myelosupression, neurotoxicity and ototoxicity. The other likely side effects are hypersensitivity, optic neuritis, papilloedema, cerebral blindness, transient elevation of liver function tests, metallic taste of food & loss of appetite, vascular events like myocardial infarction, cerebral infarction, Raynaud's phenomena, azoospermia, alopecia and syndrome of inappropriate secretion of anti diuretic hormone. Toxicity due to pelvic radiation:

Acute symptoms of the rectum can be seen early in the course of radiation therapy for cancers in the pelvic region. Symptoms usually begin following 20 Gy of standard fractionation. Early symptoms may include tenesmus, bleeding,

and diarrhea. O'Brien et al. found that the presence of acute proctitis was the only factor to predict any of the late rectal symptoms of urgency, frequency, and diarrhea. Similarly Acute sequelae during radiation commonly include frequency and dysuria. These symptoms typically occur following more than 20 Gy to the bladder with conventional fractionation.

Regarding treatment related lymphoedema there is a report of patients treated with surgery and radiation for cervical cancer. 41% had unilateral lymphoedema. Of these patients, 28% had a slight swelling, 6% had moderate swelling and 7% had severe swelling, which was interpreted as treatment-induced lymphedema. 22% of the patients had lymphoedema that was severe enough to cause symptoms.

Insufficiency fractures in the pelvic bones and femoral neck fractures do occur do to the effect of radiation on bone. The bone marrow is one of the most radiosensitive organs in the pelvis. Approximately 40% of the total body bone marrow reserve lies within pelvic bone. Hematologic toxicity can be seen acutely during radiation and exposure to radiation can result in long-term myelotoxicity. The radiation dose, dose rate, and volume all affect the acute response of the bone marrow to therapy. When small bone marrow volumes are irradiated, bone marrow in unexposed areas of the body responds by increasing its population of progenitor cells meeting the demands for haematopoiesis.

Therefore, acute effects are not seen unless a substantial portion of the marrow is exposed. With exposure to large bone marrow volumes, neutropenia occurs in 2–3 weeks followed by thrombocytopenia and then anemia in 2–3 months.

Enhanced toxicity in concurrent chemoradiation:

Similar to the enhanced tumour killing effect by combined chemoradiation, there is also increased incidence of toxicity in these patient. In the GOG 123 study by Keys et al, it is observed that the incidence of grade 3&4 toxicity between the radiation only arm and concurrent chemoradiation (with cisplatin) arm was comparable for genitourinary, cutaneous and neurological toxicity. But for haematological toxicity, the incidence was 21% in the chemoradiation arm versus 1.6% in the radiation arm. Similarly for gastrointestinal toxicity, the incidence was 14.2% in the chemoradiation arm versus 4.8% in the radiation arm. These data clearly proves that there is enhance myelotoxicity, when cisplatin is combined with radiation. The myelotoxicity is more profound when radiation is combined with other chemotherapeutic agents other than cisplatin.

PATHOPHYSIOLOGY OF CONCURRENT CHEMORADIATION

Chemotherapy given along with radiation has a great influence on cancer treatment. The use of chemotherapy along with radiation has been proven to be far better than radiation alone in many clinical trials though there associated toxicities

Rationale behind concurrent chemoradiation

a)Causes reduction in the number of cells in tumors undergoing radiotherapy. This occurs by its separate cytotoxic action and by making tumor cells more suseptable to be killed by the ionizing rays.

b)It also acts on metastatic disease .There must be a positive Therapeutic Index (>1) for concurrent chemoradiation to be useful therapeutically.

Steel and Peckham – classification

Spatial cooperation

Independent toxicity

Enhancement of tumor response

Protection of normal tissues

Strategy	Advantages	Disadvantages
Sequential chemoradiation	• Least toxic • Maximizes systemic therapy • Smaller radiation fields if induction shrinks tumor	• Increased treatment time • Lack of local synergy
Concurrent chemoradiation	• Shorter treatment time • Radiation enhancement	• Compromised systemic therapy • Increased toxicity • No cytoreduction of tumor
Concurrent chemoradiation and adjuvant chemotherapy	• Maximizes systemic therapy • Radiation enhancement • Both local and distant therapy delivered upfront	• Increased toxicity • Increased treatment time • Difficult to complete chemotherapy after chemoradiation
Induction chemotherapy and concurrent chemoradiation	• Maximizes systemic therapy • Radiation enhancement	• Increased toxicity • Increased treatment time • Difficult to complete chemoradiation after induction therapy

How cisplatin acts along with radiation?

- ❖ It inhibits DNA synthesis
- ❖ Causes inhibition of DNA interstand cross link elongation during transcription
- ❖ Inhibition of repair occurring during radiation – induced DNA damage

Emerging strategies for implementation of chemo radiation therapy

1. Increasing antitumour efficacy of chemotherapeutic drugs by the following methods :
   a. Chemical modifications of the drug.
   b. Making chemotherapeutic drugs more toxic to the tumour and at the same time less toxic to normal tissues by conjugating it with water soluble polymeric drugs such as polyglutamic acid.
   c. Radiation modification of vasculature thereby enabling drugs to accumulate specifically in tissues
   d. Radioprotective and chemoprotective drugs –eg.Amifostine WR – 2721 (prodrug) is converted to WR – 10665 (active metabolite).It protects cisplatin induced nephrologic, ototoxicity and neurotoxicity. By the following mechanism of action – Free radical scavenging, Donation of hydrogen atoms to facilitate direct

chemical repair of DNA damage and Transcriptional regulation of genes involved in apoptosis,cell cycle regulation and repair.

2. Normal tissue protection.

3. Strategies to improve delivery of radiation therapy.

RADIOBIOLOGY-ACCERATED REPOPULATION OF TUMOUR CELLS

When ever we are treating a tumour with any form of cyto toxic agent which includes radiation,cytotoxic agents ,that is chemotherapy the surviving tumour cells (the clonogens) tend to divide faster than before .This phenomenon is called as accelerated repopulation.

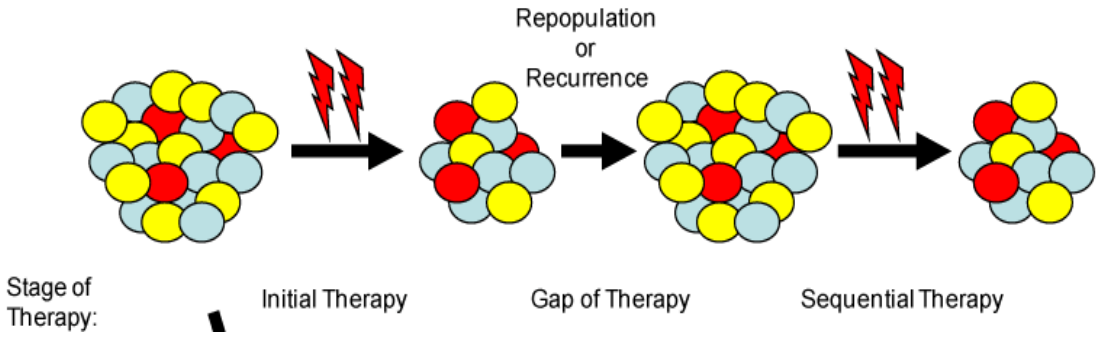
This phenomenon is illustrated in transplanted rat tumour.Which shows initial shrinkage of the tumour followed by regrowth occurs after a single dose of 20Gy of photons.The individual tumour cells that are surviving after treatment were dividing with a cycle time of 12 hours.The important thing is that during the perid that the tumour is overtly shrinking and regressing ,the \ cells that are surviving are dividing and increasing in number more rapidly than before treatment.

There is evidence of similsr phenomenon in humar tumours also.Withers and his colleagues surveyed the literature on radiotherapy and estimated the dose to achieve local control in 50% of cases as a function of the overall duration of fractioned treatment.This analysis proved that clonogens repopulation in rapidly growing human cancer accelerates at about 28 days after radiotherapy initiation in fractioned regimen.A dose increment of about 0.6Gy per day is required to comensate for this repopulation.Such a dose increment is consistant with a 4 day clonogen doubling rate.compared with median of 60 days for unperturded growth.The conclusion is that radiotherapy for fast growing tumours should be completed as soon after it has beganand also it may be better to delay inititation of treatment than to introduce delays during treatment which

will adversely affect outcome.The overall treatment time if is too long ,the effectiveness of later dose fractions is compromised because the surviving clonogens present in the tumour can be triggered into rapid repopulation. This data is referred for radiotherapy.It might be anticipated however that similar phenomenon would apply to chemotherapy and to combination of chemotharpy with radiothaerapy.But there is no evidence for that.

Ideal treatment period and how often treatment gaps occur during radiotherapy

Radiotherapy is a important modality in management of patients with cervical cancer.To achieve cure of a patient with any cancer ,radiotherapy,must eradicate every stem cell associated with the tumour and also those that are generated during course of treatment.The larger the course of treatment more the stem cells can repopulate,increasing the number of stem cells that have to be killed.As overall treatment time increases the probability of local tumour control decreases.



The impact of the prolongation of treatment time in cervical cancer radiation therapy has already been studied. The increase in overall treatment time will decrease the survival at the rate of 0.3-1.6% per day. This impact is more in stage III.B disease and also been demonstrated in patients who were treated with HDR brachytherapy. But still there are grey zones because brachytherapy is the integral part of cervical cancer treatment. The effect of chemotherapy and the duration between external radiation and brachytherapy need to be assessed.

In cervical cancer Overall treatment time includes combined external beam radiation and brachytherapy.Studies have shown that overall treatment time in carcinoma cervix should be as short as possible and should not exceed 56 days

The total radiation dose should be given within a specific time.In daily clinical practice treatment breaks due to radiation reactions,patients unwilling or unspecified reasons results in prolongation of overall treatment time.In many studies which includes planned interruptions (Split course)schedules,and also retrospective analysis suggest :the role of overall treatment time on outcome.This suggests the deleterious effect of accelerated repopulation of tumour clonogens.

Evidence suggest that treatment gaps in radical radiation results in prolongation of overall treatment time affect local control rates and survival in certain cancer types.This is for different modalities of radiotherapy like

a)Radical radiation therapy

b)External beam radiotherapy followed by brachytherapy(Treatment time overall includes time taken for combined therapy)

c)Radiotherapy combined with chemotherapy(Treatment time overall includes time taken for combined therapy)

d)Post op radiation therapy

Patients are categorised under three group to manage treatment gaps

Group 1-Rapidly growing tumours like squamous cell carcinoma where treatment is given with radical intent.Many studies has been done on this group.Treatment duration overall should not be prolonged even by two days more than the prescribed.

Group 2-Slower growing tumours like adenocarcinoma where treatment is given with radical intent.Treatment break of five days also have not been significant.Treatment duration overall still should not be prolonged by more than five days

Group 3-This group belongs to patients that are treated with palliative intent.Here overall treatment time has no effect on achieving desired palliation.Only gaps more than 7 days needs to compensated.

It is so assumed that fast growing tumour will be more affected by treatment breaks but it is not always true.there are exceptions,example is glioblastomas there has been no evidence of effect of treatment breaks on outcome since repair mechanism in brain tissue is different.Similarly certain slow growing tumours like carcinoma anus does not significant change in outcome if the treatment gap is less than 5 days.When it comes to cancer cervix,head and neck malignancies ,lung cancer ,oesophageal cancer ,medulloblastoma and primitive neuroectodermal tumors are greatly affected by gaps in treatment.

In palliative scenario for reducing pain and bleeding,preventing ulceration,managing cord compression and superior vena caval

obstruction,reducing tumour burden overall treatment time prolongation does not matter that much ,but still for good palliation prolongation must not be more than 7 days.

Question is how frequently treatment gaps occur during radical radiation therapy?

This is a difficult question since it varies with different tumour types and location and also when given concurrently with chemotherapy.Since acute morbidity due to radiation is different for different tumour types and location and also chemo can add up to the acute morbidity individually. In a study conducted in 80s and 90s on head and malignancies more than 30 percent treatment breaks were reported.With present guidelines such interruptions can be corrected.

Impact of length and timing of treatment gaps

The length of gap which results in significant effect on tumour control locally as discussed varies with different tumour type and site and also on standard department treatment times and protocols.On analysing data from split course regimens, studies show that fourteen to sixteen day interruptions definitely affect treatment outcome.Also prolongation of treatment by a week can result in 3 to 16% loss of local tumour control. Uncompensated gap of 1 day in a patient with cervical cancer can lead to reduction of local control of tumour by 1-1.4%.For locally advanced carcinoma cervix total treatment duration combining both external beam radiotherapy and brachytherapy should not be more than 56 days.

The timing of breaks that occur during long course radiation does not seem to be significant .Recently studies done suggests that gaps arising in short course of treatment and during initial 28 days in long course RT are different from those appearing in later part of long course radiation.Also correction of breaks arising in the later part of long course radiation is always difficult to corrected since it requires large fractions over short time and can may cause increase in late morbidity.Studies have also shown that break on Monday and Friday increases weekend gap by 33% so it is worser than break that occur in the middle of the week.

Factors to determine treatment breaks

Treatment associated factors

I.Radiation related

a)Diarrhoea-Proctitis

b)Reactions to radiation

II.Chemo related factors

a)Nausea and vomiting

b)Neutropenia

Department associated factors

a)Machine failure/service

Patient associated factors

a)Did not report to treatment due to personal reasons

b)Natural disasters interrupting treatment

Intercurrent illness associated factors

a)Fever

b)Respiratory infection

c)Other non cancer related infections

MANAGEMENT OF TREATMENT GAPS

Prioritising patients on treatment when treatment interruption is inevitable

Group-1 Patients with rapidly growing tumour which have short volume doubling time, who are treated with curative intent,since overall treatment time should not be prolonged by more than 2 days they should be given first priority.Squamous cell carcinoma of cervix falls under this group

Group-2 Patients with slowly growing tumour who are treated with curative intent.Overall treatment time prolongation of 5 days may not affect survival.Next priority must be given to this group

Group-3 Patients treated with palliative intent must be given least priority

There should be no treatment gap in delivery of any radiotherapy treatment.Unless it is absolutely essential treatment breaks should be avoided.Every patients treatment schedule needs auditing.In case of unforeseen situation such as machine failure occurs atleast group 1 patients must be shifted to other machines if possible

Prevention of potential treatment gaps

Department associated factors

Machine related-

Machine breakdown can cause treatment breaks to many patients simultaneously.Radiation oncology centres should formulate plan to transfer patients to other machines when ever possible or fix the problem as early as possible so that patient can be treated the same day.When a longer prolongation of machine failure is anticipated all measures must be taken to transfer patient to other machine or other centres,which is a complex issue since it requires temporary transfer of staff,doctors and physicist.Also in such cases replanning might be required if the other linear accelerator is not compatable.In case of machine service ,all patients should be transferred to alternate matched linac or service day must be a week end.

Brachytherapy list for every week should have a extra slot for emergency.

Public holidays-

Treating patients on a public holiday is very difficult. At least group1 patients must be treated.Centres should have policies to manage staff and transport to work on public holidays whenever possible

Patient associated factors

Cancer patients are generally immunpcompromised so there is high chance that they can develop chest infection,chicken pox,Herpes on the course of treatment.So necessary advice should be given to them to take

adequate nutrition and hygiene.When ever they develop any infection necessary care must be given for speedy recovery and restarting radiation as erly as possible

Treatment associated factors

Treatment breaks can occur due to acute radiation reactions and chemo related morbidity.Efforts must be taken to minimise radiation related morbility by adequately educating patient regarding personal hygiene,nutrition and care of radiated area.Any reactions that occur must be treated early.Chemo related morbidity must be kept in check by monitoring blood parameters and intervening at the earliest.

Patient associated factors

For any treatment patient cooperation is very important.For radiotherapy patients cooperation is even more important since they require to come every day.So patient must be taught the importance of everyday treatment and advice them to avoid absenting to treatment.Psychological and social support must be given to patient and family whenever possible.

II.Objectives and methodology

Aim of the study-

To study the impact of treatment breaks during radiation therapy in the survival of cervical cancer patients also study other factors associated with survival of cervical cancer patient.

Specific objectives:

To assess the impact of treatment breaks during radiation therapy in the survival of cervical cancer patients

To study the pattern of treatment break and association between overall treatment time and outcome in cervical cancer patients treated with external beam radiation with or without chemotherapy.

To study various factors that contribute to treatment breaks and management of treatment breaks

Study design-

It is a retrospective survival study

Patients treated as case of carcinoma cervix International Federation of Gynaecology and Obstetrics Stage I-IV,who were treated with external beam radiation to pelvis with or without chemotherapy registered from 2010-2012 were studied.

Patients' age, weight, comorbidity, stage, treatment details and time trend are collected from the records

Statistical analysis:

The data will be entered using Epi Data 3.0 and statistical analysis will be done using SPSS software.Survival analysis will be done by generating the Kaplan Meir survival curve.Cox propostional hazard model will be employed to estimate incidence of survival factors

Inclusion criteria:

i)Histologically proven carcinoma of the uterine cervix,treated with curative intent with initial EBRT of 45-50Gy using conventional/conformal technique,with or without concurrent chemotherapy followed by HDR ICA

ii)No evidence of metastasis, in Chest x - ray, USG abdomen normal, no palpable lymphadenopathy

Exclusion criteria:

i. Metastatic disease

ii.Palliative intent

iii.Recurrent disease

iv.H/O Treatment for other malignancies

Institute Data:

In a retrospective study where local tumour control in 102 patients with carcinoma cervix has been examined in relation to occurrence of gaps during radio therapy during the months of September to December 2015 in Cancer institute Adyar Chennai. This time period was chosen since there was historical floods in Chennai during the month of December 2015. This study includes stage II, III diseases with time gap exceeding 15 days taken as significant. All patients had change in brachytherapy schedule of 650cGy at point A twice a weeks in 2 weeks instead of weekly 800cGy per fraction thrice a week. Main outcomes measures were local recurrence in the irradiated volume.

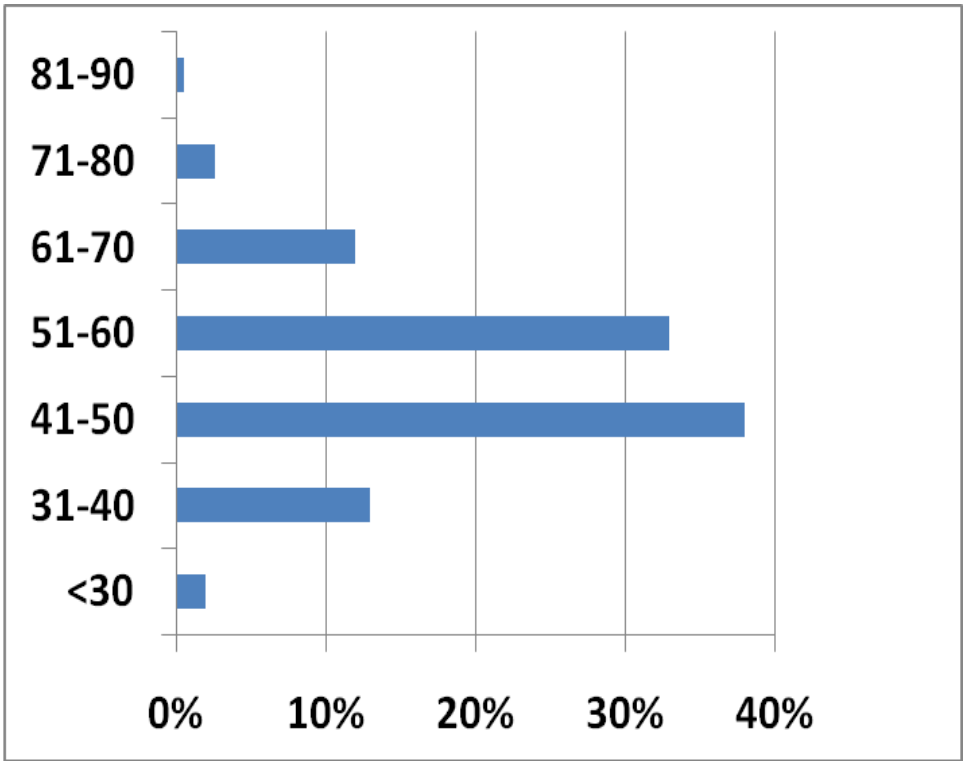
Results:

Radiotherapy was completed without any unplanned interruption in 90/102 patients. The 12 patients who had interruption were due to floods. 8 patients left to their home before intracavitary application and were not able to report on time,among them 4 had progressive diseas 4 patients had breaks during the course of external radiation,among them 1 had progressive disease

This small analysis states that the gap during external radiation and the brachytherapy plays a vital role in causing local failure. Significant gaps in treatment should be avoided.

RESULTS

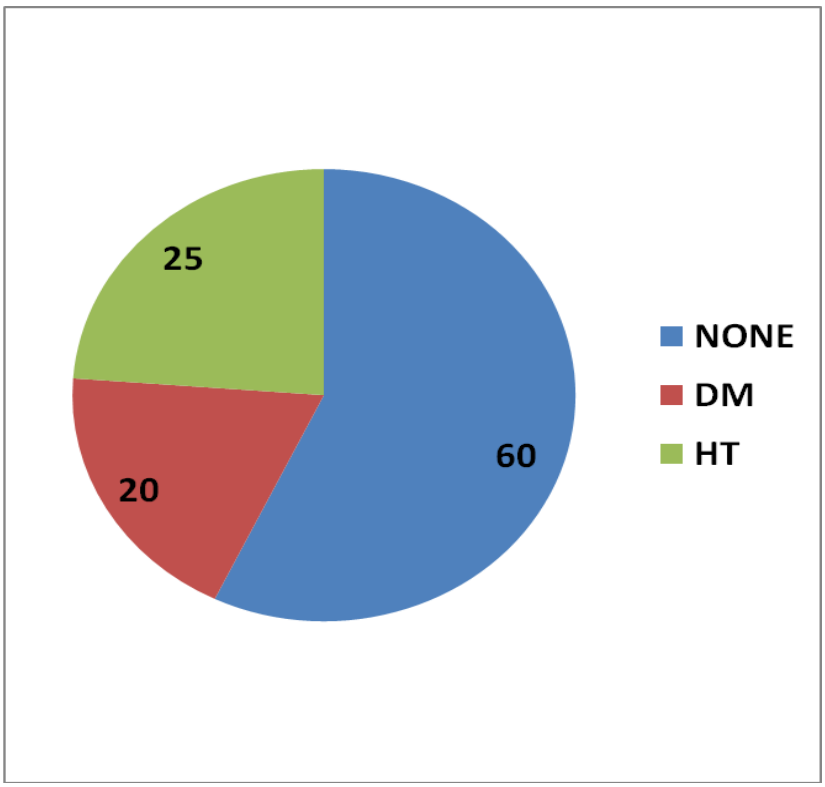
AGE DISTRIBUTION



The most common age group world wide for cervical cancer is 55-59 Years.It is less common in women lesser than 20 years or more than 80 years.Younger the age at presentation worser the prognosis.

In our study also incidence is more in women 51-60 years with peak Incidence in women 41-50 years of age.Incidence in less than 30 years is only around 3% and incidence above 80 years is around 2%.Geriatic patients need special care .

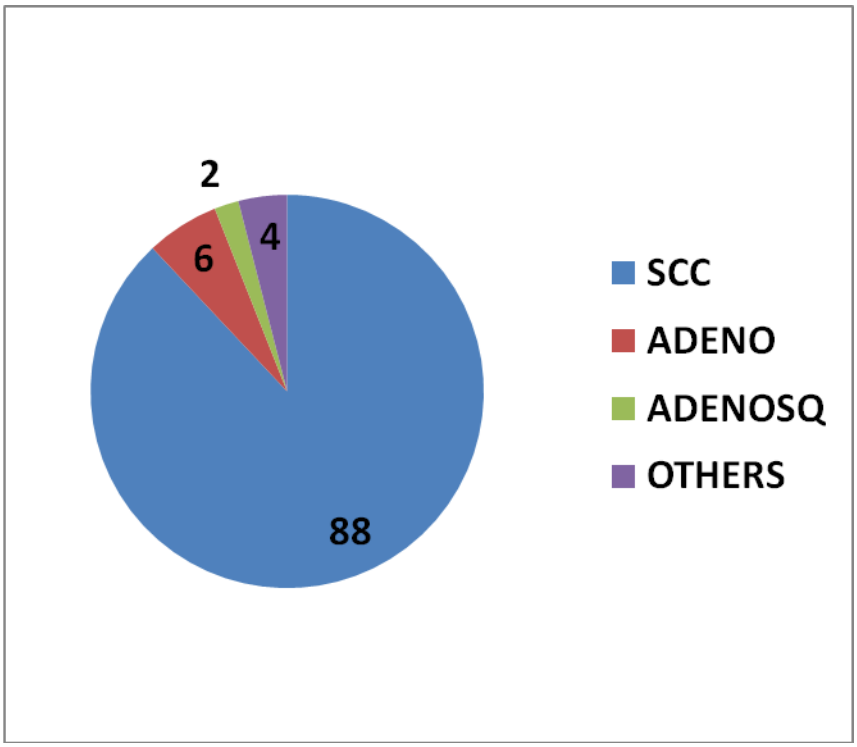
COMORBIDS



Diabetis and hypertension are the most common comorbids in Indian population where as comorbids like hypothyroidism,bronchial asthma,auto immune diseases are less common.Uncontrolled comorbids like hypertension and diabetis can adversely affect outcome in patients with cancer since it makes then easily vulnerable to chemo related toxicity.

In our study population most common comorbid illness was diabetis which is around 25% followed by systemic hypertension which is around 20%.Aroung 60% of the study population did not have any significant comorbid illness

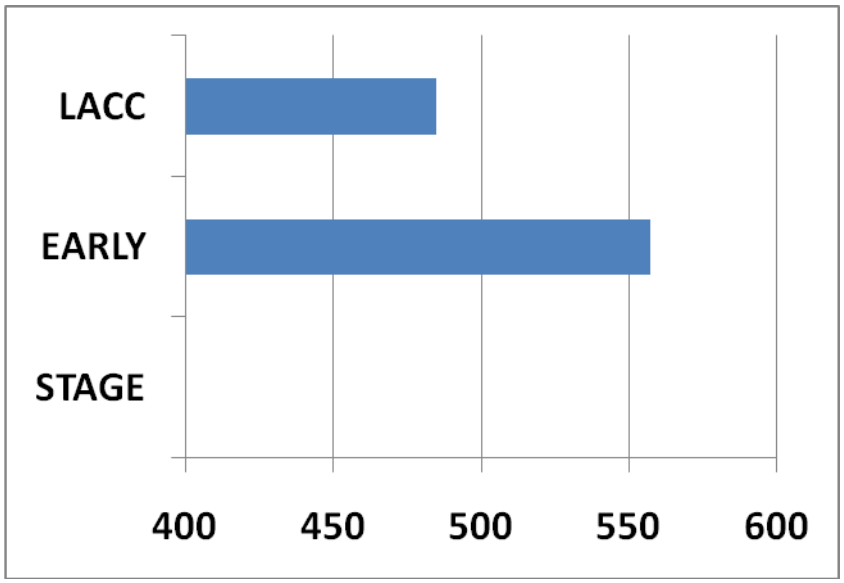
HISTOLOGICAL DISTRIBUTION



The most common histology globally is squamous cell carcinoma which accounts for around 90% of total cases followed by adenocarcinoma which is around 7-10%.Followed by other minor histologies like clear cell carcinoma,neuroendocrine carcinoma ,small carcinoma ,adenosquamous carcinomawhich accounts for nearly 3% of the cervical carcinoma patients .

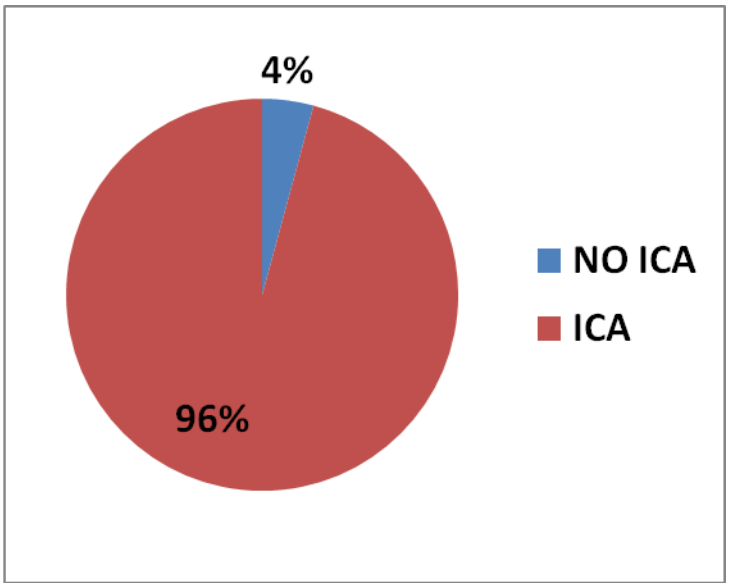
In our study the most common histology is squamous cell carcinoma which accounts for 88%of the population.Followed by adenocarcinoma which accounts for 6% the study population. Adenosquamous carcinoma accounts for 2% and other less common Types like neuroendocrine clear cell carcinoma accounts for 4%

STAGE DISTRIBUTION



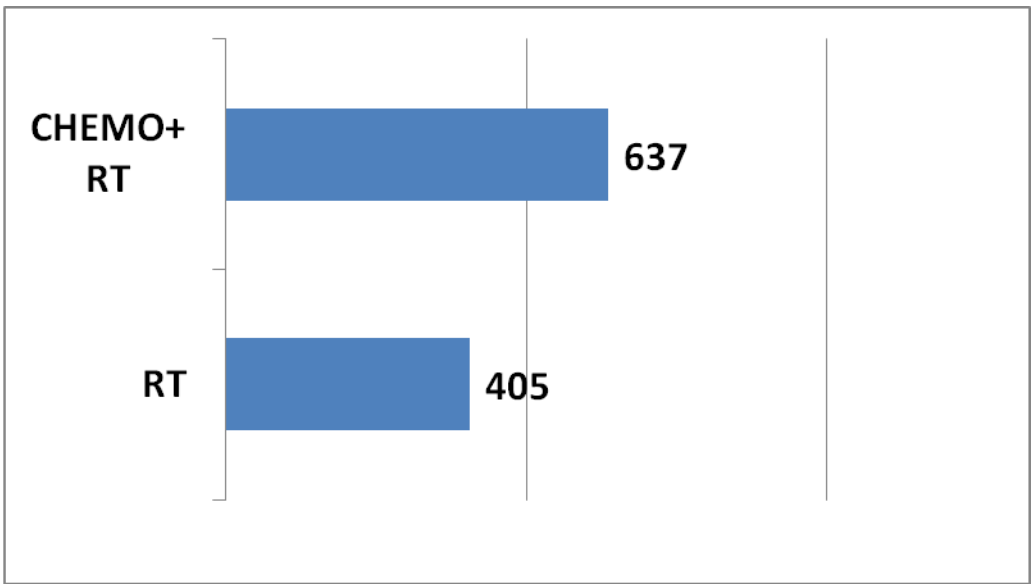
Early stage cervical cancer includes patients with stage I B –IIA2 and locally advanced cervical cancer is stage IIB-IVA. In general early stage cervical cancers are more common than Locally advanced.In our study also out of the total population of 1054 early cervical cancer includes 557 and locally advanced 485,

ICA DISTRIBUTION



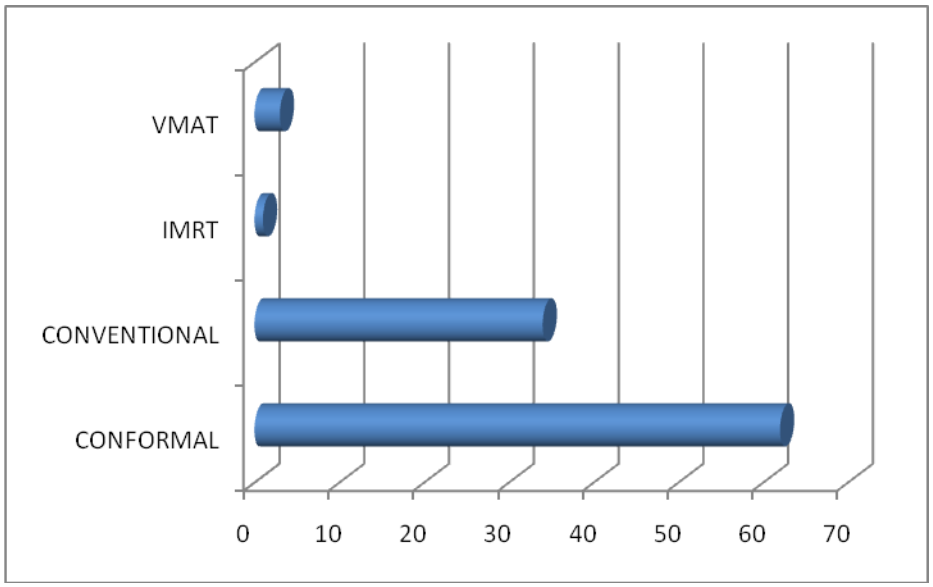
In our study population most patients around 96% received ICA and 4% has not received ICA probable becaue of patient being medically unfit or Ica not feasible due to nature of the disease

CHEMORADIATION/RADIATION



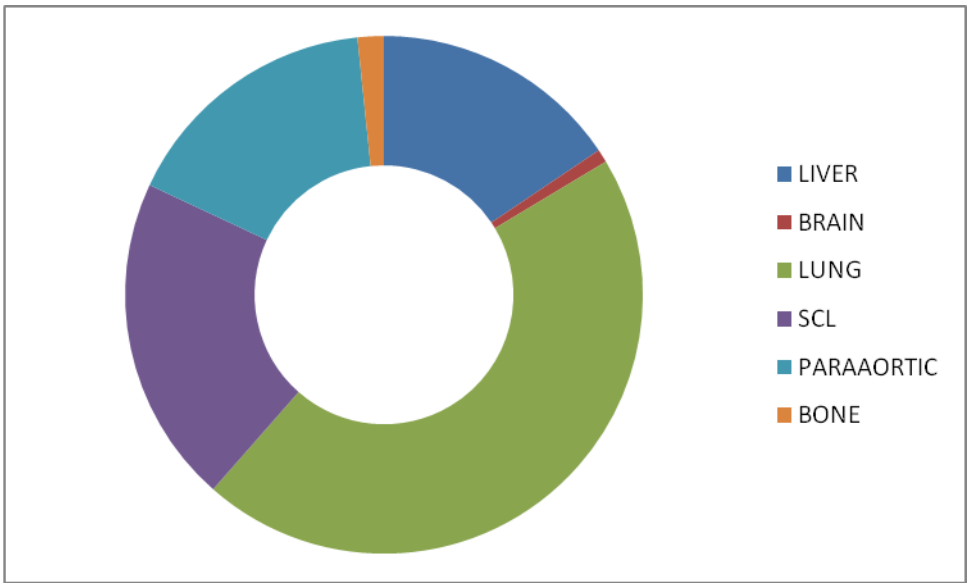
Treatment of choice when ever patient is fit is concurrent chemoradiation.Total of 637 patients have received concurrent chemoradition out of 1054 and 405 patients have received only radical radiation probable because of patient being unfit for chemotherapy or because of unwilling ness to chemotherapy

DISTRIBUTION ACCORDING TO TECHNIQUE



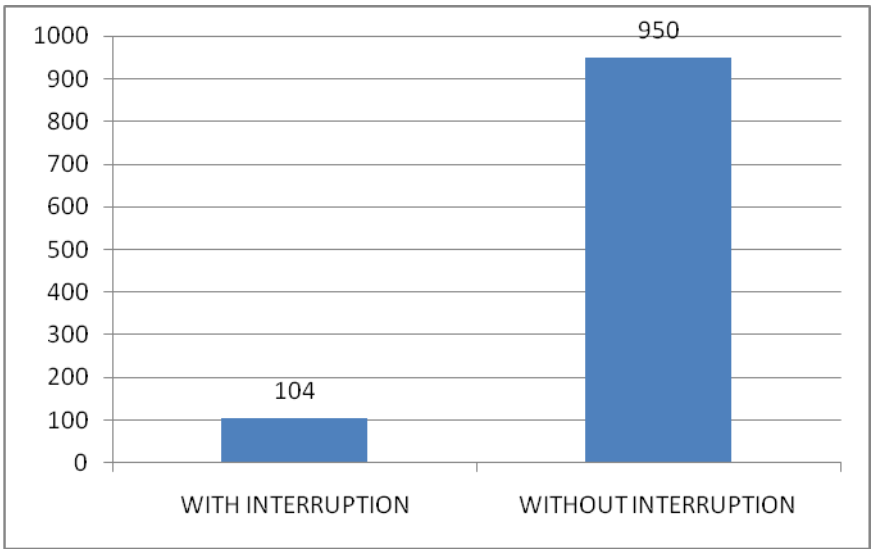
Various RT techniques are used while treating patients with cervical cancer.In our study the most common technique used is 3D conformal treatment planning around 62% and conventional 2D planning used in 34% patients ,IMRT used in 1% and VMAT in 3% of the total study population.

DISTRIBUTION OF DISTANT METASTASIS



The distribution of distant metastasis in our study population is almost similar to the seen in the general population.Of the patients who developed distant metastasis 50% developed in the lungs , 25% developed in liver metastasis, 20% developed in paraaortic nodal metastasis and 18% developed in supraclavicular nodes .

TREATMENT INTERRUPTION

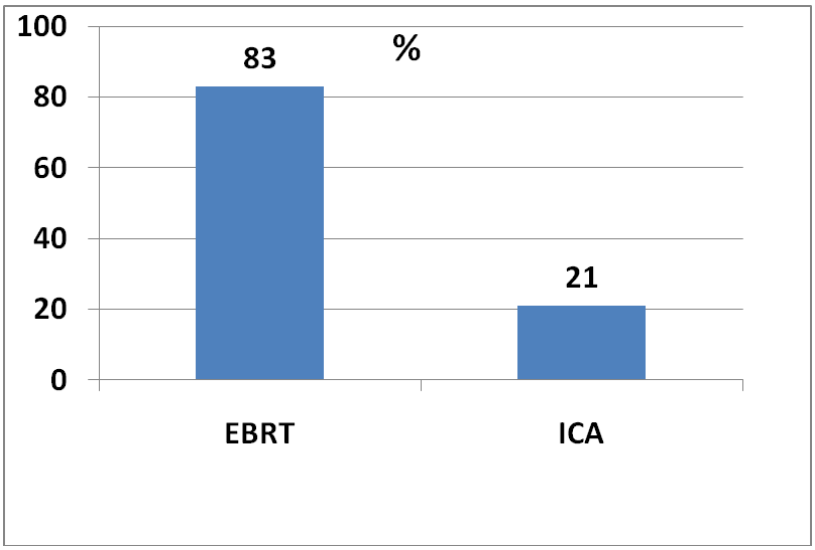


DEFINING OVERALL TREATMENT TIME:

An overall treatment time of 55+/- 3days is taken as treatment without interruption

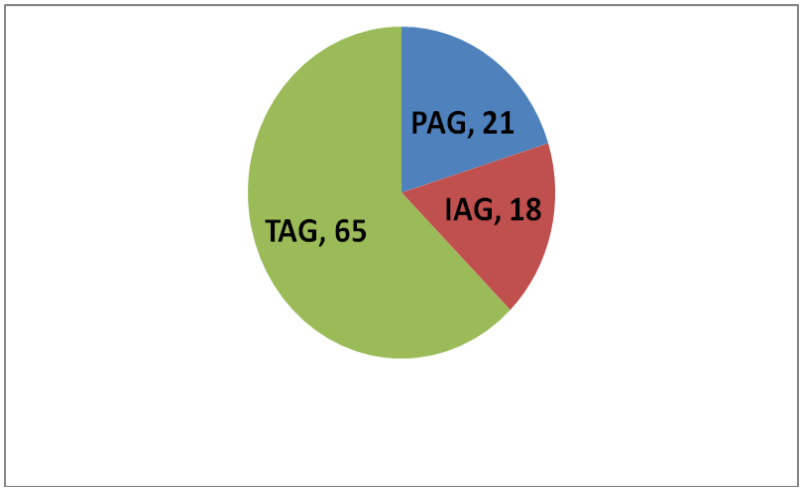
Out of the total 1054 patients 950 completed treatment without significant interruptions 104 patients completed treatment with significant treatment interruption with an increase in overall treatment period.

TIMING OF INTERRUPTION



Of the 104 patients who had treatment interruption 83 had it during EBRT 21 patients during ICA

CAUSE OF INTERRUPTION



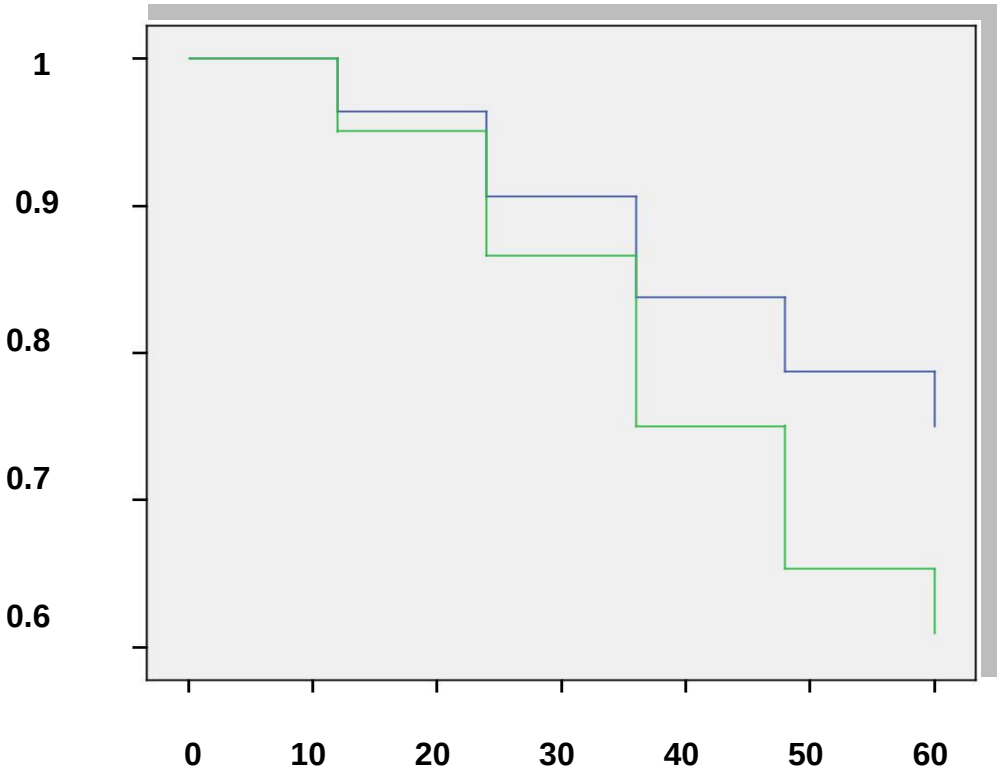
Treatment associated interruption for 65 patients.Patient associated interruption for 21 patients and intercurrent infection associated interruption for 18 patients

COMPARING PATIENTS WHO HAD TREATMENT INTERRUPTION WITH THOSE WHO HAD NO INTERRUPTION

	INTERRUPTION	NO INTERRUPTION	P VALUE
LOCAL FAILURE	28%	19%	0.01*
DISTANT FAILURE	14%	12%	0.8
5 YR DFS	61%	70%	0.04*
5 YR OS	60%	70%	0.03*

The local failure rate was 28% in the treatment interruption arm compared to 19% in the uninterrupted arm which is quiet significant The 5 year disease free survival and 5 year overall survival was also significantly better in patients who had their treatment completed without interruptions.However the distant failure rate is almost same.

SURVIVAL CURVE FOR TREATMENT INTERRUPTION WITH THOSE WHO HAD NO INTERRUPTION

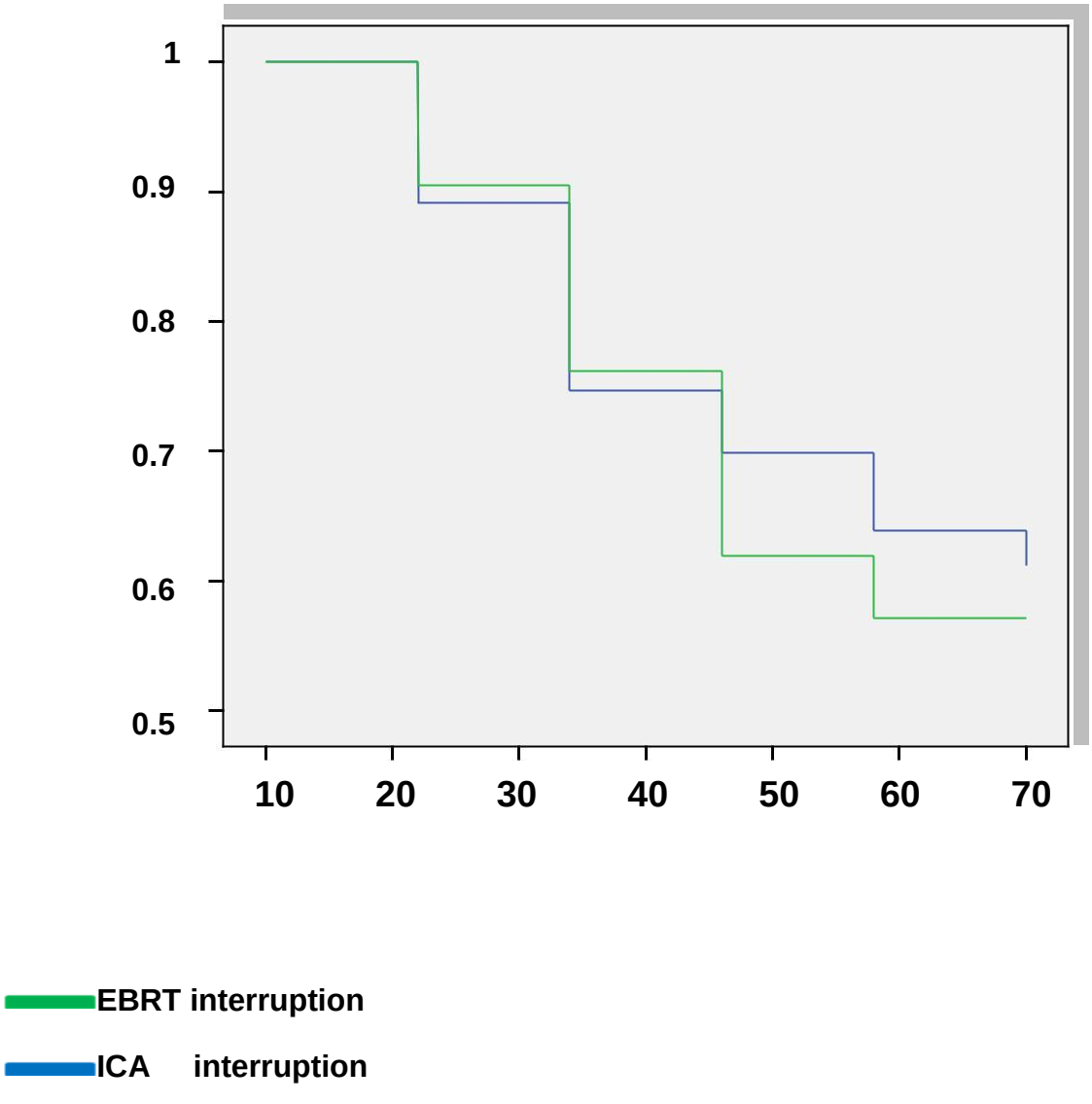


COMPARING PATIENTS WHO HAD TREATMENT INTERRUPTION DURING EXTERNAL BEAM RADIATION WITH THOSE WHO HAD INTERRUPTION DURING ICA

	ICA INTERRUPTION	EBRT INTERRUPTION	P VALUE
LOCAL FAILURE	38%	28%	0.3
DISTANT	9.5%	17%	0.4
5 YEAR DFS	62%	67%	0.6
5 YEAR OS	61%	66%	0.8

The local failure rate was 38% in patient who had interruption during External beam radiation and 28% in patients who had interruption during ICA.Though this is not statistically significant there is a slight difference favouring Increasing local failure in ICA arm on comparing with ICA arm.Whereas surprisinglydistant failure is more in EBRT arm.There was no big difference in 5 year overall survival and 5 year disease free survival in both arms.

SURVIVAL CURVE FOR TREATMENT INTERRUPTION DURING EXTERNAL BEAM RADIATION WITH THOSE WHO HAD INTERRUPTION DURING ICA



COMPARING PATIENTS WHO HAD TREATMENT INTERRUPTION MORE THAN 10 DAYS WITH THOSE WHO HAD INTERRUPTION FOR LESS THAN 10 DAYS

	EBRT INTERRUPTION > 10 DAYS	EBRT INTERRUPTION <10 DAYS	P VALUE
LOCAL FAILURE	30%	23%	0.27
DISTANT FAILURE	15%	15%	0.09
5 YEAR DFS	55%	62%	0.07
5 YEAR OS	55%	62%	0.07

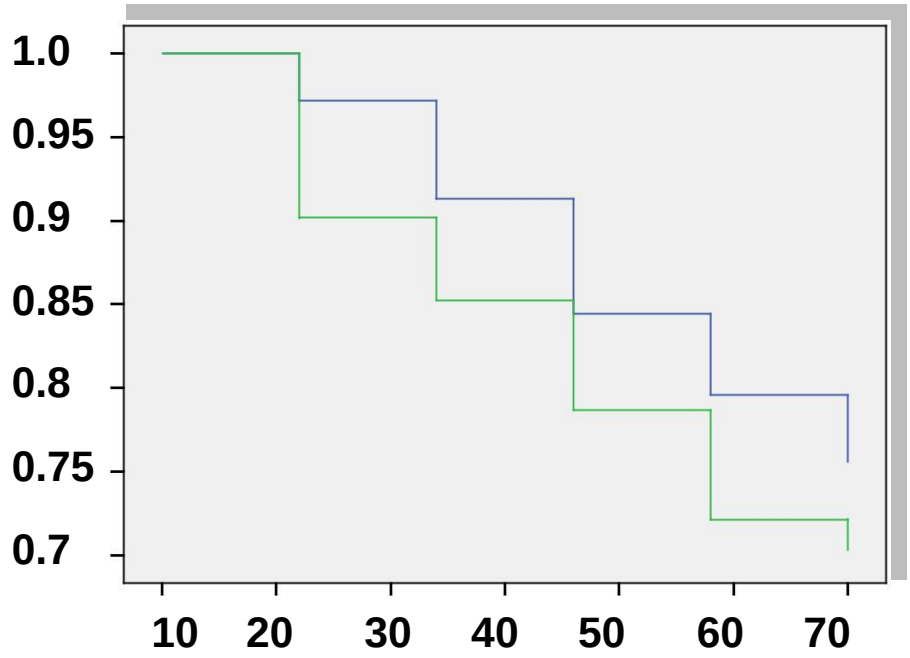
The patients who had treatment interruption for greater than 10 days had local failure of 30% compared to 23% local failure in patients who had interruption for less than 10 days,which is not a significant difference.Earlier studies done also shows similar results when 2 weeks interruptions where compared with less than 2 weeks interruption. But there was no difference in distant failure ,5 year overall survival and disease free survival

COMPARING PATIENTS WITH EARLY CERVICAL CARCINOMA WITH INTERRUPTION AND WITHOUT INTERRUPTION

	EARLY STAGE WITH INTERRUPTION	EARLY STAGE WITHOUT INTERRUPTION	P VALUE
LOCAL FAILURE	24%	13%	0.02*
DISTANT FAILURE	8.6%	11%	0.47
5 YR DFS	68%	76%	0.18
5 YEAR OS	68%	76%	0.18

Patients who were treated for early stage cervical cancer when there was treatment interruption the local failure was 24% which was very high when compared to patients to patients without interruption early cervical carcinoma.This difference is very significant.There was no chance in distant failure rate However.5 year overall survival and disease free survival was slightly better in early stage no interruptions patients

SURVIVAL CURVE FOR EARLY CERVICAL CARCINOMA WITH INTERRUPTION AND WITHOUT INTERRUPTION



Early disease with interruption

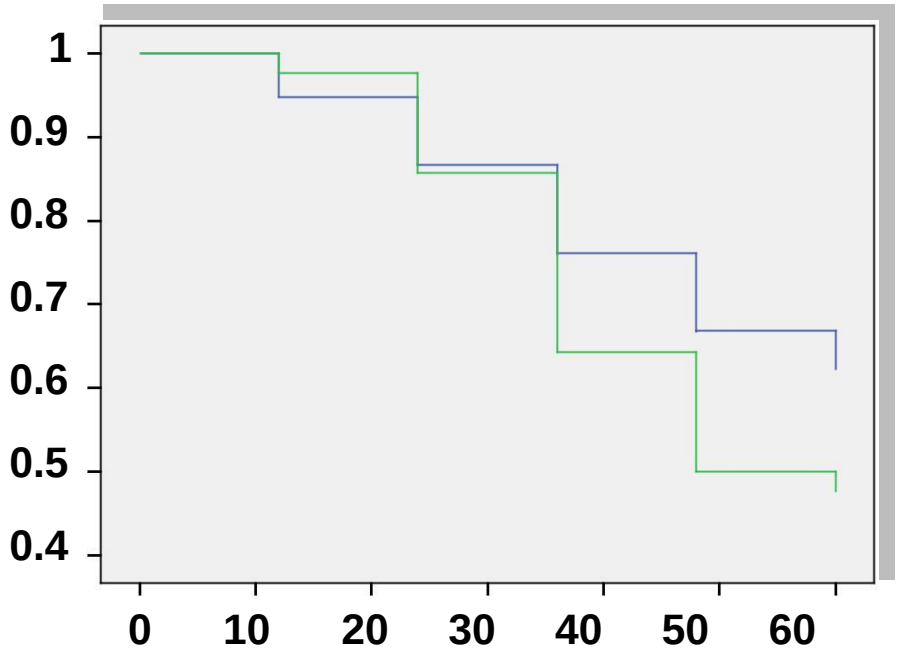
Early disease without interruption

COMPARING PATIENTS WITH LOCALLY ADVANCED CERVICAL CARCINOMA WITH INTERRUPTION AND WITHOUT INTERRUPTION

	LACC WITH INTERRUPTION	LACC WITHOUT INTERRUPTION	P VALUE
LOCAL FAILURE	33%	25%	0.27
DISTANT FAILURE	21%	12%	0.09
5 YEAR DFS	50%	63%	0.07
5 YEAR OS	50%	63%	0.07

Patients who were treated for locally advanced cervical cancer when there was treatment interruption the local failure was 33% when compared to 25% patients to patients without interruption in locally advanced cervical carcinoma.This difference is not very significant.The distance failure was 50% in interruption arm compared to 12% in no interruption arm chance in distant failure rate However there was no difference in 5 year overall survival and disease free survival

SURVIVAL CURVE LOCALLY ADVANCED CERVICAL CARCINOMA WITH INTERRUPTION AND WITHOUT INTERRUPTION



COMPARING PATIENTS WHO RECEIVED CONCURRENT CHEMORADIATION WITH INTERRUPTION AND WITHOUT INTERRUPTION

	CHEMO WTH INTERRUPTION	CHEMO WITHOUT INTERRUPTION	P VALUE
LOCAL FAILURE	30%	15%	0.002*
DISTANT FAILURE	10%	9%	0.7
5 YEAR DFS	63%	74%	0.04*
5 YEAR OS	64%	74%	0.07

Patients who received chemoradiation when treatment interrupted has local failure of 30% compared to chemo radiation patients who had 15% local failure in treatment interruption arm this does not imply that patient despite receiving chemoradiation have failed locally,it means that in spite of receiving chemotherapy when there is a treatment break patient can still fail locally.There was no difference in distant failure 5 year overall survival and disease free survival

COMPARING PATIENTS WHO RECEIVED RADICAL RADIATION WITH INTERRUPTION AND WITHOUT INTERRUPTION

	NO CHEMO WITH INTERRUPTION	NO CHEMO WITHOUT INTERRUPTION	P VALUE
LOCAL FAILURE	23%	29%	0.4
DISTANT FAILURE	20%	18%	0.8
5 YEAR DFS	57%	70%	0.12
5 YEAR OS	57%	70%	0.12

Patients who received only radical radiation had no significant change in local failure.distant failure .But there was patients who had treatment without interruption had better 5 year overall survival and disease free survival

MANAGEMENT OF INTERRUPTION

METHODS	BENIFITS	POTENTIAL DIFFICULTY
1)Overall time and dose per fraction is maintained by treating on weekend days as necessary.	Overall time, fraction size, interfraction interval and therapeutic index maintained	May not be feasible for interrupions occurring near the end of a schedule.
2)Overall time and dose per fraction is maintained by treating twice daily as necessary.	Overall time and fraction size maintained.	Possible increase in late-normal tissue damage
3) Overall time is maintained by increasing dose per fraction for same number of post-interruption days as there were interrupions days	Overall time maintained by accepting reduced number of fractions. Still utilises one fraction on each treatment day.	Therapeutic index adversely affected
4)Accept that treatment extension is unavoidable and deliver extra fractions, using increased dose per fraction to minimise the extension duration.	Allows at least partial restoration of the prescribed schedule	Therapeutic index adversely affected. Might require acceptance of both reduced tumour control and increased late effects

How to manage interruptions during combined EBRT and Brachytherapy

- The corrections for treatment interruption in case of EBRT and BT are similar to those described for EBRT alone.
- However in case of an inevitable interruption during external beam radiation,brachytherapy can be started early if patient disease is suitable
- In breaks happening during High dose rate brachytherapy the fractions that are remaining and intervals between each fractions in the remaining treatment time should be adjusted properly

CONCLUSION-

This analysis states

- Interruption during radiotherapy overall affect local tumour control and survival in all stages of cervical carcinoma
- Interrruption during radiotherapy for early stage cervical cancer can also affect local control
- Despite combining chemotherapy with radiation treatment interruptions during radiation can significantly affect local control.
- Though there is a difference in local control between patients who had interruptions for less than or more than 10 days but still it has no major significance on survival and local control

Review of literature:

1)Carcinoma uterine cervix –Impact of prolongation of overall treatment time and timing of brachytherapy outcome of radiation therapy by Carlos.A.Perez et al ,they analysed records of 1224 patients (Stage IB to III) with definitive irradiation (combination of external beam and two intracavitary insertions to deliver doses of 70 to 90 Gy to point A) were reviewed. Follow-up was obtained in 97% of the patients (median, 12 years; minimum, 3 years; maximum, 28 years).And found that prolongation of treatment time in patients with Stage IB, IIA, IIB, and III carcinoma of the uterine cervix has a significant impact on pelvic tumor control and CSS. The effect of OTT was present regardless of tumor size except in Stage IB tumors ≤3 cm. This may be related to biologic factors such as cell repopulation and increased proliferation resulting from treatment interruptions, in addition to initial clonogenic cells burden. Irradiation for patients with invasive carcinoma of the cervix should be delivered in the shortest possible overall time

2) Effect of total treatment time on event free survival in carcinoma of cervix by Delaloye et al analysed 360 with stage IB-IIIB carcinoma of the cervix were treated with external radiation and brachytherapy as first line therapy. Therapy duration was 45 days. Patients were classified according to whether they had rather long therapies, taking 60 cutoff. Cumulative incidences of local recurrence, metastasis, and death were estimated. The 5-year event-free survival rate was better in patients who had treatment time of less than 60 days .In terms of univariate hazard ratio (HR), the relative difference between the two groups corresponds to an increase in hazard of any of the three events considered more than the double (HR = 1.756, P = 0.003) for the longer therapy duration group. A multivariate analysis, which included selected prognostic factors, confirmed these results (HR = 1.76, P = 0.017). A short radiation therapy duration is a highly significant prognostic factor associated with longer event-free survival in carcinoma of the cervix.

3) The adverse effect of treatment prolongation in cervical carcinoma by Shang wen chen et al analysed 257 treated cases of carcinoma uterine cervix (IB,IIA,II B,IIIA,IIIB,IV A) patients , who underwent external radiotherapy with HDR ICA and a minimum of 3 years of follow-up Median treatment time was 63 days found that For all stages of disease, the 5-year CSS and PCR were significantly different comparing treatment times of less than and greater than or equal to 63 days [83% and 65% (*P*=0.004], 93% and 83% (*P*=0.02), respectively]. Multivariate analysis identified three prognostic factors for CSS, stage (*P*<0.001), tumor response to external RT (*P*=0.001), and overall treatment time (OTT; *P*=0.006).

Prognostic factors for pelvic failure were stage (*P*<0.001), tumor response to external RT (*P*=0.001), and OTT (*P*=0.03).

References:

1) Carlos.A.Perez,Perry.W.Grigby,Hermam Castro Vita,Mary Ann Lockett, July 1995 Int J Radiat Oncol Biol Phys Pages 1275-1288-Carcinoma uterine cervix –Impact of prolongation of overall treatment time and timing of brachytherapy outcome of radiation therapy

2)Dale RG Jones B,British J of Radiol 1996 Pg 830-838.Reduction of tumour control with imcrease in overall time

3)Delaloye JF,Coucke PA,Pampallona S,De Grandi P 1996 GyN Oncology 1996 Pg 42-48.Effect of total treatment time on event free survival in carcinoma of cervix

4).Eifel PJ, Thames HD. Has the influence of treatment duration on local control of carcinoma of the cervix been defined? Int J Radiat Oncol Biol Phys 1995,32:1527

5)Nuran Senel Bese,Jolyon Hendry,Branislav Jeremic(July 2007,)Int J Radiat Oncol Biol Phys 68,654-661-Effects of prolongation of overall treatment time due to unplanned interruption during radiotherapy of different tumour sites and practical methods of copensatrion

6) Petereit, D.G., Sarkaria, J.N., Chappell, R., Fowler, J.F., Hartmann, T.J., Kinsella, T.J., Stitt, J.A., Thomadsen, B.R., Buchler, D.A. Int J Radiat Oncol Biol Phys 1995;32:1301–130 The adverse effect of treatment prolongation in cervical carcinoma

7)Shang wen chen,Ji –An Lian,Shin-Neng Yang,Hui Ling Ko,Fang Jen Lin, . Int J Radiat Oncol Biol Phys,April 2003;67, 69-76 The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy

CANCER INSTITUTE (W.I.A)

(REGIONAL CANCER CENTRE)
INSTITUTIONAL ETHICS COMMITTEE
Reg. No. ECR/235/Inst/TN/2013
Adyar, Chennai - 600 020.
Phone : 044-22209150 Extn : 129, Fax : 044-22354508
E-mail : iec@cancerinstitutewia.org

Date :

Ethics Committee Re-Registration No.ECR/235/Inst/TN/2013/RR-16

17 August 2017

To,
Dr. Bharathi Srilatha. G
Resident
Dept. of Radiation Oncology
Cancer Institute (W.I.A)
38, Sardar Patel Road
Chennai 600 036

Subject: Ethics Committee Approval Letter
Reference: Study Protocol titled "Impact of Treatment Breaks during Radiation Therapy in the Survival of Cervical Cancer Patients".

Dear Dr. Bharathi Srilatha,

This is with reference to the letter dated 14 July 2017 for review of the above referenced study Protocol. The ethics committee reviewed the following documents,

1) Study Protocol
2) Patient Information Sheet in English
3) Patient Informed Consent Form in English

The following members of the ethics committee were present at the ethics committee meeting held on 22.07.2017 at 2.00 pm at auditorium, 1st Floor, Bhagwan Adinath Jain Complex, Dr. Krishna Murthy Campus, Cancer Institute (W.I.A), Chennai 600 036.

S. No	Name	Role/ Designation in ethics committee	Affiliation of the member with Institution	Attendance to the meeting 22.07.2017
1	Dr. V.I. Mathan	Chairman	Not affiliated with Cancer Institute	Present
2	Dr. T.G. Sagar	Member Secretary	Affiliated with Cancer Institute	Present
3	Dr.G.Selva Luxmy	Clinician	Affiliated with Cancer Institute	Present
4	Dr.K.Kalai Chelvi	Clinician	Not affiliated with Cancer Institute	Present
5	Dr.V. Sridevi	Clinician	Affiliated with Cancer Institute	Present
6	Dr.V.K. Ramadesikan	Basic Medical Scientist	Not affiliated with Cancer Institute	Present
7	Mrs. Ranganayaki Kumar	Lay Person	Not affiliated with Cancer Institute	Present
8	Mr. M. Suresh	Legal Expert	Not affiliated with Cancer Institute	Present
9	Dr. S. Padma	Legal Expert	Not affiliated with Cancer Institute	Present
10	Mr. Chaganti V. K. Maitreya	Social Scientist	Not affiliated with Cancer Institute	Present
11	Dr.Niranjali Devaraj	Scientific Member	Not affiliated with Cancer Institute	Present

The Institutional Ethics Committee, Cancer Institute (W.I.A) functions in accordance with Ethical Guidelines for Bio-Medical Research on Human Participants issued by ICMR, Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 and Indian Good Clinical Practice Guidelines.

CANCER INSTITUTE (W.I.A)

(REGIONAL CANCER CENTRE)
INSTITUTIONAL ETHICS COMMITTEE
Reg. No. ECR/235/Inst/TN/2013
Adyar, Chennai - 600 020.
Phone : 044-22209150 Extn : 129, Fax : 044-22354508
E-mail : iec@cancerinstitutewia.org

Date :

The above documents were reviewed and the study was approved by the ethics committee to be conducted in its presented form in accordance with applicable regulations.

Yours Sincerely,

Dr. T.G. Sagar
Member Secretary
Institutional Ethics Committee

Institutional Ethics Committee
Chennai
600 020
Cancer Institute (WIA)

URKUND

Urkund Analysis Result

Analysed Document: thesis final.doc (D31368240)
Submitted: 10/16/2017 2:52:00 PM
Submitted By: sribhavi@gmail.com
Significance: 5 %

Sources included in the report:

amutha thesis.docx (D30979644)
THESIS 15.10.17 word.pdf (D31345752)
THESIS 15.10.17 word.doc (D31345055)
http://www.sciencedirect.com/science/article/pii/S0360301607005044

Instances where selected sources appear:

10