FEASIBILITY OF CONCOMITANT BOOST USING CONFORMAL TECHNIQUE IN LOCALLY ADVANCED CARCINOMA UTERINE CERVIX

A dissertation submitted to

the Tamilnadu Dr. M.G.R. Medical University, Chennai,

in partial fulfilment of the requirements for the award of the degree of

DOCTOR OF MEDICINE (M.D.) IN RADIOTHERAPY

April 2017

CERTIFICATE

This is to certify that this dissertation titled "**FEASIBILITY OF CONCOMITANT BOOST USING CONFORMAL TECHNIQUE IN LOCALLY ADVANCED CARCINOMA UTERINE CERVIX"** is a bonafide record of the work done by **DR. Ritesh J.M Santosham**, in the Division of Radiation Oncology, Cancer Institute (W. I. A.), Chennai, during the period of his postgraduate study for the degree of M.D. (Branch IX–Radiotherapy) from 2014-2017 under my direct guidance and supervision.

Date: Sep 30,2016

Place: Chennai

Dr.G.Selvaluxmy

Professor and H.O.D

Division of Radiation Oncology

Cancer Institute (W.I.A)

Adyar, Chennai

ACKNOWLEDGEMENT

First of all I would like to thank GOD for his abundant blessings and grace.

I am ever-grateful to Late. Dr. S. Krishnamurthi, Advisor, Dr. V. Shanta, Chairman, Cancer Institute (WIA), Adyar, for providing me all the facilities for this study

I also thank Dr. A.Vasanthan, Professor and chairman, Division of Radiation Oncology, for his support and inculcating an interest in radiobiology.

I express my gratitude to Dr. G.Selvaluxmy, Professor and H.O.D, Division of Radiation Oncology, for her encouragement, constant support and guidance throughout my postgraduate career and during this study.

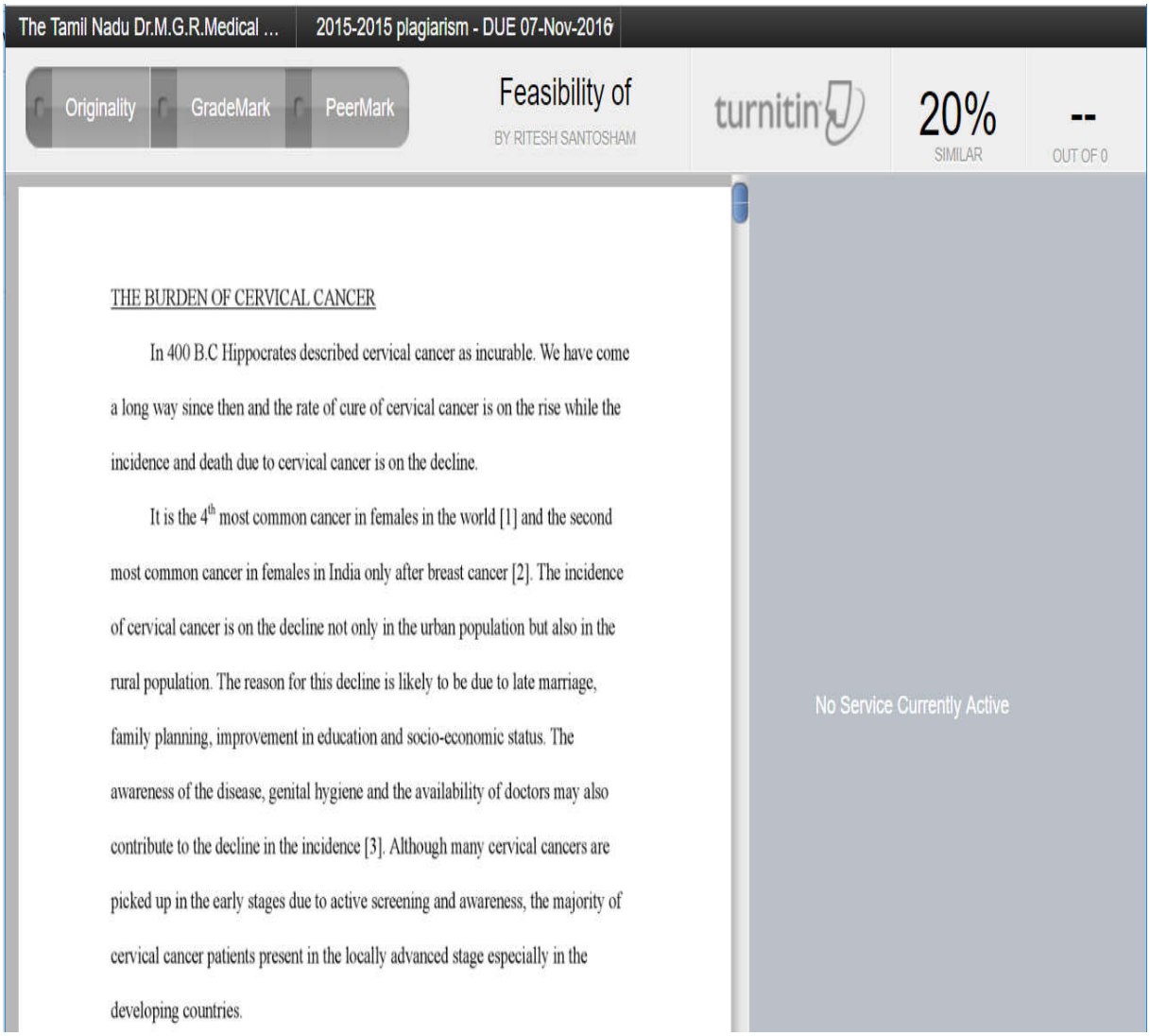
I am also thankful to Dr.C.Vasanth Christopher who has been a source of inspiration, for taking special interest and guided me throughout my thesis.

I thank Dr. N.Vivekanandan, Mr.J.Sam Deva kumar and Mr.Arul Pandian for their innovative ideas and helping me with planning, without whom this study would not have been possible.

I thank all the other faculty members, my colleagues, radiotherapy technologists, physicists and tumour registry staff without whom this study would not have materialised.

I express my gratitude to all the patients who form the most important part of this study

I thank my parents for believing in me and for always being there for me. I also thank my friends and all my family members all of whom have been the greatest sources of motivation and support for me.


The Tamil Nadu Dr.M.G.R.Medical ...
2015-2015 plagiarism - DUE 07-Nov-2016
Originality
GradeMark
PeerMark
Feasibility of
BY RITESH SANTOSHAM
turnitin
20%
SIMILAR
--
OUT OF 0
THE BURDEN OF CERVICAL CANCER
In 400 B.C Hippocrates described cervical cancer as incurable. We have come a long way since then and the rate of cure of cervical cancer is on the rise while the incidence and death due to cervical cancer is on the decline.
It is the 4th most common cancer in females in the world [1] and the second most common cancer in females in India only after breast cancer [2]. The incidence of cervical cancer is on the decline not only in the urban population but also in the rural population. The reason for this decline is likely to be due to late marriage, family planning, improvement in education and socio-economic status. The awareness of the disease, genital hygiene and the availability of doctors may also contribute to the decline in the incidence [3]. Although many cervical cancers are picked up in the early stages due to active screening and awareness, the majority of cervical cancer patients present in the locally advanced stage especially in the developing countries.
No Service Currently Active

THE BURDEN OF CERVICAL CANCER

In 400 B.C Hippocrates described cervical cancer as incurable. We have come a long way since then and the rate of cure of cervical cancer is on the rise while the incidence and death due to cervical cancer is on the decline.

It is the 4th most common cancer in females in the world [1] and the second most common cancer in females in India only after breast cancer [2]. The incidence of cervical cancer is on the decline not only in the urban population but also in the rural population. The reason for this decline is likely to be due to late marriage, family planning, improvement in education and socio-economic status. The awareness of the disease, genital hygiene and the availability of doctors may also contribute to the decline in the incidence [3]. Although many cervical cancers are picked up in the early stages due to active screening and awareness, the majority of cervical cancer patients present in the locally advanced stage especially in the developing countries.

In the modern era, with the advances in the management of cervical cancer, the outcome of early cervical cancer has dramatically improved but the more locally advancer cervical cancers are still a cause for concern.

In developing countries, about 40-45 % cervical cancer patients present in the more locally advanced stage. While concurrent chemoradiation followed by brachytherapy is the treatment of choice for locally advanced cervical cancers, there are several factors that complement treatment and improve the local control.

The pattern of failure in locally advanced cervical cancers is mainly due to

poor local control while only a small number of patients develop distant metastasis. This has led to the need to explore treatment strategies to improve the local control. Several treatment strategies have been evolving in the last few decades from the introduction of chemotherapy and other radiosensitizers to the advancement in brachytherapy, delivery of external beam radiation therapy, introducing hyperthermia and improving patient related factors. Before we investigate the strategies to improve the management of locally advanced cervical cancers, it is essential to understand the magnitude of the disease.

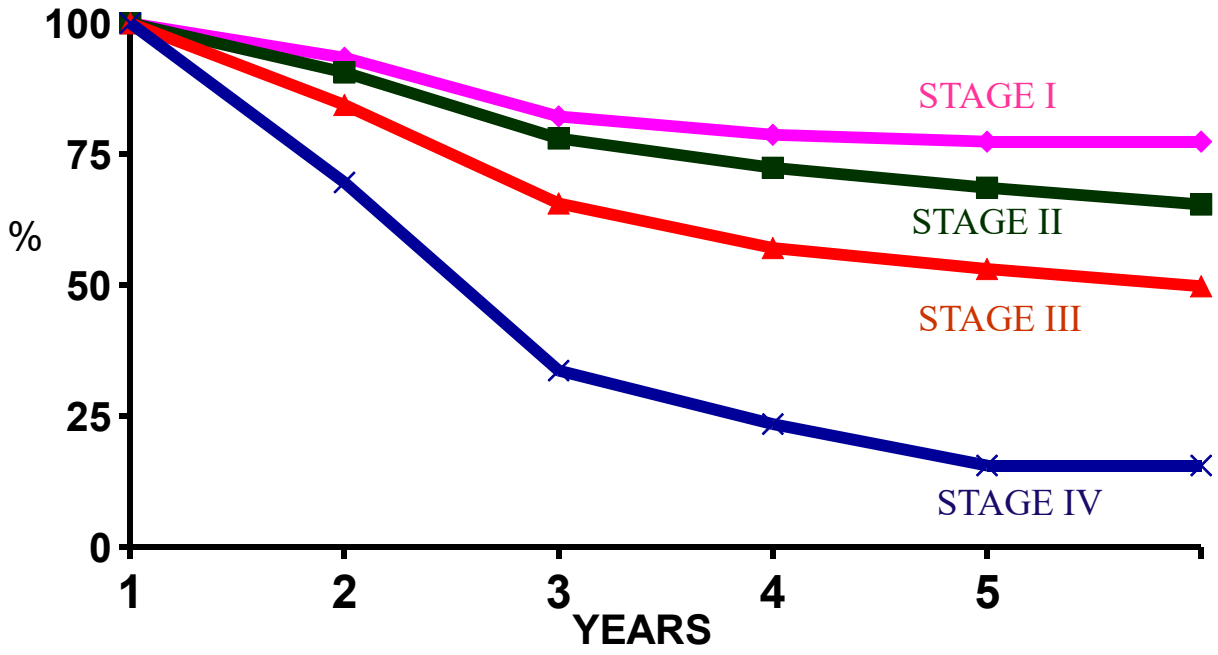
EPIDEMIOLOGY

Cervical cancer is the 4th most common cancer in females worldwide with an annual incidence of 510,000 cases and approximately 288,000 deaths per year. In south asia, India has the highest age standardized incidence of cervical cancer at 22 [4]. In India, cervical cancer is the 2nd most common cancer in females with an annual incidence of 122,844 cases and approximately 288,000 deaths per year.

The recent national cancer registry programme (NCRP) data between 2009 and 2011 showed that the highest incidence at an age adjusted rate was in Aizwal district in the north eastern part of India, followed by Bashi and Bangalore [5].

In Chennai the age adjusted risk has reduced from 41 to 16.7 in 2009 [6]. As per the madras metropolitan tumour registry (MMTR), the majority of the cases present in Stage II and Stage III with a DFS and OS of 67.1 % and 62.3% respectively across all stages.

DFS by Stage between 2006-09 (MMTR)



TREND OF CRUDE INCIDENCE RATE AND AGE STANDARDIZED RATE

MMTR – MADRAS METROPOLITAN TUMOUR REGISTRY

Cervix cancer	1982-1986	1987-1991	1992-1996	1997-2001	2002-2006	2007-2011	2012-2013
CIR / 100,000	33.7	29.6	24.0	24.8	20.4	17.5	16.7
ASR / 100,000	44.5	37.8	29.3	29.0	22.1	17.8	15.9

CRUDE INCIDENCE RATE AND AGE STANDARDIZED RATE

Regions	No. of Cases	CIR	ASR
World	527624	15.1	14.0
More Developed Region	83078	13.0	9.9
Less Developed Region	444546	15.6	15.7
India	122844	20.2	22.0
Chennai(2012-13)	783	16.7	15.9

Number of cases at Cancer Institute over the years

Year	Cases
2006	562
2007	545
2008	385
2009	368
2010	455
2011	474
2012	470
2013	526
2014	505
2015	452

The word cervix is derived from latin which means neck and it has been described anatomically from the time of Hippocrates. The understanding of the anatomy of the cervix, its relation to the pelvic organs, the draining lymph node, its development and staging are fundamental prior to the decision on management.

DEVELOPMENT OF CERVIX

The uterus, fallopian tube, cervix and the upper vagina arise from the paramesonephric or mullerian duct. As it is known, there are three germ layers the ectoderm, endoderm and mesoderm. The intraembryonic mesoderm is subdivided into the para-axial mesoderm, the lateral plate mesoderm and the intermediate mesoderm. The intermediate mesoderm connects the para-axial mesoderm with the lateral plate and differentiates into the urogenital structures [7]. The intermediate mesoderm forms a bulging on the posterior abdominal wall called nephrogenic cord. This gives rise to the Gonads, mesonephros, mesonephric duct and paramesonephric duct [8]. The paramesonephric duct is formed by the invagination of the coelomic epithelium and as the name suggests, it lies lateral to the mesonephric duct. The two paramesonephric ducts cross the mesonephric ducts cross the mesonephric duct and fuse at the midline to form the uterovaginal canal. This is called mullerian organogenesis. The cranial end of the fused ducts will eventually form the uterus and the cervix, the unfused cranial ends will form the fimbrial portion of the fallopian tubes and the caudal end of the fused ducts will form the upper 2/3rd of vagina. In the fetus the cervical part is larger than the body of the uterus [9].

ANATOMY

The uterus is a hollow, muscular organ in the pelvic cavity composing the fundus, body, isthmus and cervix. It is situated between the bladder anteriorly and the rectum posteriorly. The normal position of the uterus is Anteverted and anteflexed. The angle formed by the long axis of the uterus and the long axis of the vagina by the forward bending of the uterus over the vagina of about 90 degrees is called Anteversion.The angle that the uterus flexes on itself is about 120 degrees and is called anteflexion.

The uterus communicates superiorly on either side with the fallopian tube and inferiorly with the vagina through the cervix.

The cervix is the lower fibromuscular portion of the uterus supported by the cardinal ligament or ligament of Mackenrodt laterally and the uterosacral ligaments posteriorly. The shape and size of the cervix vary depending on the woman's age, parity and hormonal status. While the external os is round in nulliparous women, it is slit like in parous ladies.

The cervix is anatomically divided into the supravaginal part and the vaginal part. The vaginal part is also called portio vaginalis which protrudes into the vagina and opens through the external os. The isthmic portion of the uterus meets the cervix at the internal os. Ectocervix is the part of cervix lying exterior to the external os and the endocervix lies proximal to it. The canal between the internal and external os is called Endocervical canal. The part of vagina adjacent to the portio vaginalis is the fornix. The anterior fornix is close to the vesico uterine pouch while the posterior

fornix is deeper and is close to the rectouterine pouch.

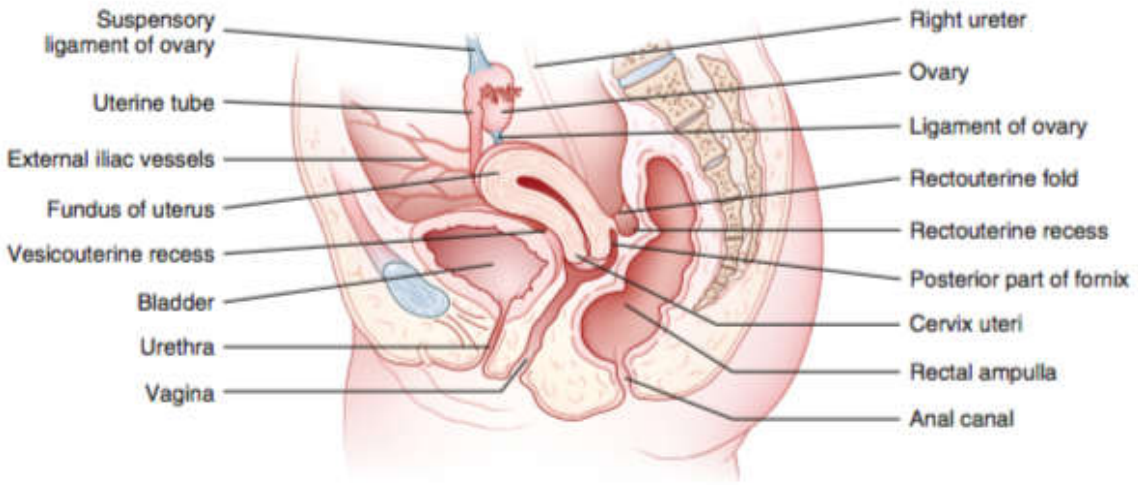
The cervical stroma is composed of dense, fibro-muscular tissue through which vascular, lymphatic and nerve supplies to the cervix pass and form a complex plexus. The arterial supply of the cervix is by the cervical and vaginal branches of the uterine artery which is a branch of the internal iliac artery. The veins run parallel to the arteries and drain into the hypogastric plexus.

The lymphatic drainage of cervix is through three main lymphatic channels. The lateral channel drains into the paracervical lymphnodes and then to the external iliac (of which obturator is the innermost) and hypogastric nodes.The anterior lymphatic channels pass behind the bladder and terminate in external iliac nodes. The posterior channels course through the uterosacrals and terminate in common iliac, subaortic, para-aortic and superior rectal nodes. The pelvic lymphatics drain into the common iliac and para-aortic lymph nodes [11].

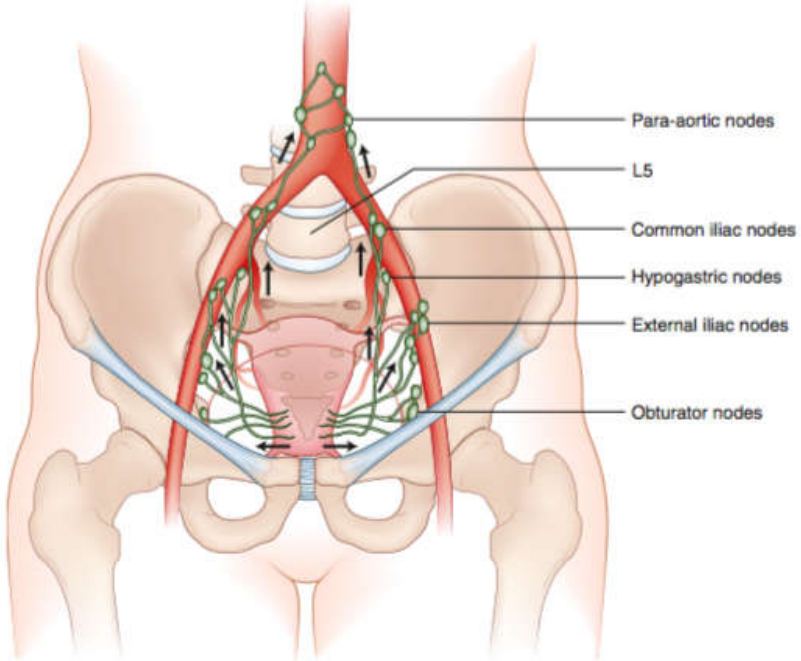
The three main para-aortic chains are the Left aortic chain, the aortocaval and the caval chain. Lymph is then transported cranially to the cisterna chyli , the thoracic duct and eventually the Left supraclavicular node [10]

The nerve supply to the cervix is from the hypogastric plexus. Sensory nerve endings are very few in ectocervix and extensive in endocervix. Hence ectocervix punch biopsy is tolerated in most women even without local anesthesia. Since sympathetic and parasympethetic fibres are abundant in endocervix, dilatation and curettage may lead to vasovagal reaction.

ANATOMY OF CERVIX IN RELATION TO OTHER PELVIC ORGANS



LYMPHATIC DRAINAGE OF CERVIX



Probability of Lymph nodal metastasis

Stage	Pelvic nodal metastasis %	Para-aortic nodal metastasis %
I.A.1	<1	
I.A.2	≤5	
I.B	10	5-8
II.A	15	10
II.B	20	15
III.A	25-30	20
III.B	40-50	30-35
IV	50-60	40-45

The normal epithelium of the ectocervix is the Stratified, non keratinizing squamous epithelium. It is made of 15 to 20 layers of cells. This squamous epithelium is made up of the basal layer, the para basal layer, the intermediate and the superficial layer. The epithelium is separated from the underlying stroma by the basement membrane which is usually straight but occasionally has stromal projections called papillae. The epithelium between the papillae are called rete pegs. The basal layer is a single layer of round cells found just above the basement membrane with a large dark staining nuclei and scanty cytoplasm. The basal cells mature and divide to form the next few layers of cells called the para basal cells which also contain large dark staining nuclei with greenish blue basophilic cytoplasm. This layer of cells further mature and divide to form layers of polygonal cells called intermediate layer with abundant cytoplasm and small round nuclei. These cells mature further to form the

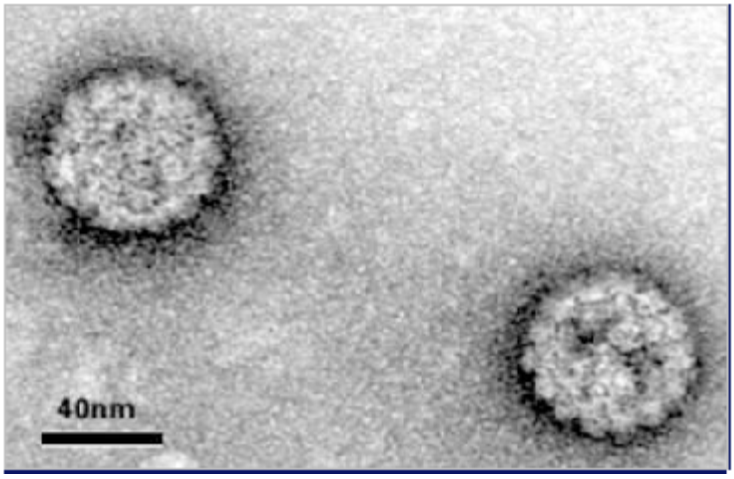
superficial layer composed of large, flattened cells with small dense nuclei and transparent cytoplasm. The superficial and intermediate layer of cells contain abundant glycogen in their cytoplasm which is a normal sign of maturation called glycogenation. The maturation of the squamous epithelium of cervix is estrogen dependent hence, in postmenopausal women the epithelial cells do not mature beyond the parabasal layer. The endocervix is lined by a single layer of columnar epithelium comprising tall cells with dark staining nuclei lying close to the basement membrane.

The junction between the columnar epithelium and the squamous epithelium is called the Squamocolumnar junction (SCJ). With age and puberty, the Squamocolumnar junction everts to expose portions of the columnar epithelium onto the ectocervix. This is referred to as Ectropion. Due to the irritation of the acidic vaginal environment, the ectropion undergoes squamous metaplasia. The area between the original squamocolumnar junction and the new squamocolumnar junction is called the Transformation zone.

HPV IN LOCALLY ADVANCED CERVICAL CANCER

Harald Zur Hausen , a German virologist, first isolated HPV 6 DNA from genital wart by simple centrifugation as early as 1977. This lead to further research and identification of HPV 16 in 1983 and later HPV 18 by southern blot hybridization [91]. He received the Nobel Prize in physiology or medicine in 2008.

STRUCTURE OF HPV:

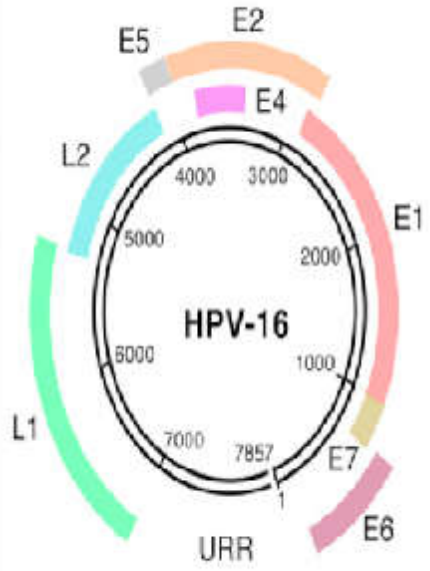


The human papilloma viruses are small, non-enveloped, icosahedral DNA viruses that have a diameter of 50–55 nm. The viral particles contain a single double-stranded DNA molecule of about 8000 base-pairs contained in a capsid composed of 72 pentameric capsomer proteins. The capsid contains two structural proteins –the late L1 and L2 — which are both virally encoded and expressed late in the replication cycle. The genomes of all HPV types contain approximately eight open reading frames (ORFs) that are transcribed from only one DNA strand. The ORF's are classified into three functional parts:

1.The early (E) region that encodes proteins (E1–E7) -For viral replication,

2.The late (L) region encoding the structural proteins (L1–L2)-For virion assembly, and

3.A largely non-coding part that is referred to as the long control region (LCR) which contains cis elements necessary for viral replication and transcription [92] .



Gene	Function
L1	Major capsid protein.
L2	Minor capsid protein.
E1	Transcription factor, helicase activity. Mediates episomal DNA replication.
E2	Transcription factor. Regulates viral copy number.
E4	Facilitates virion release.
E5	Stimulates cell proliferation and prevents differentiation. Downregulates surface MHC class I expression.
E6	Deregulates cell cycle control through p53 inactivation/degradation. Induces malignant transformation together with E7.
E7	Keeps cells active in the cell cycle through Rb inactivation. Induces malignant transformation alone and together with E6.

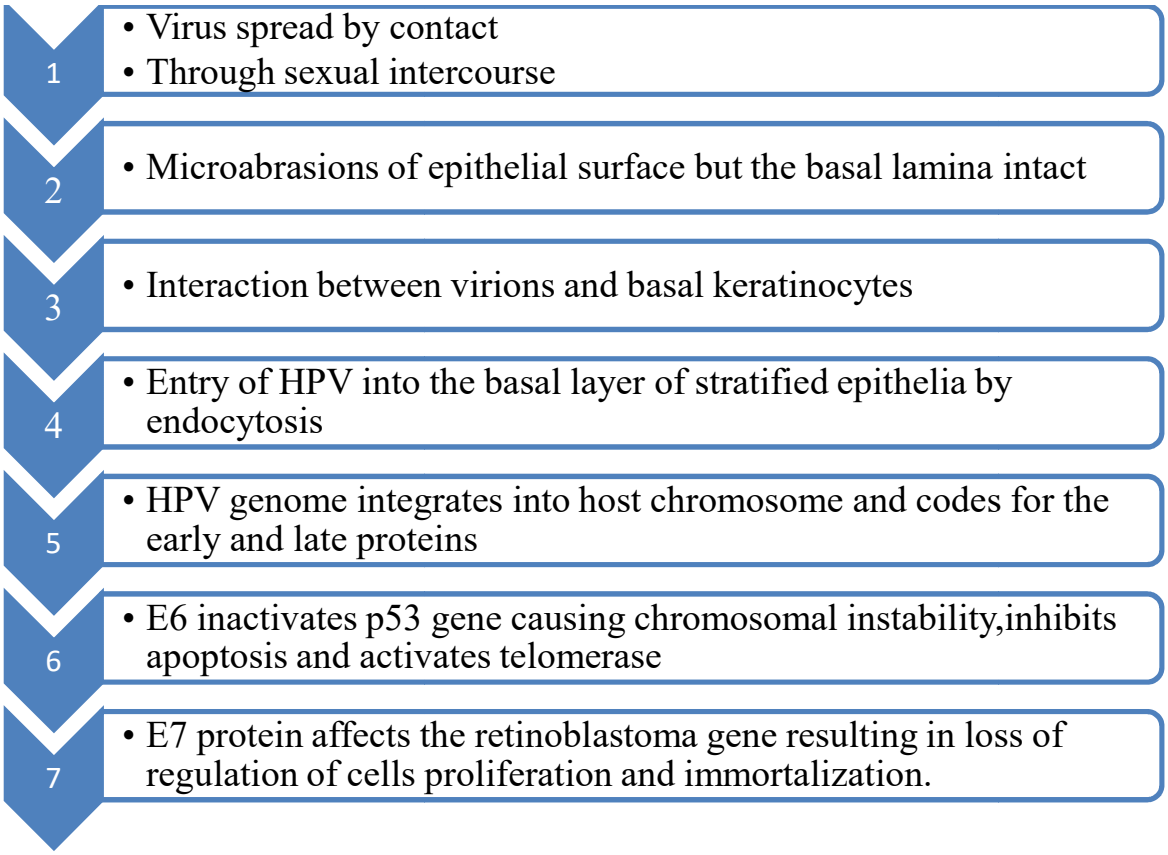
TYPES OF HPV:

There are more than 100 types of HPV, of which at least 13 are oncovirus (high risk type). >90% of cervical cancers are HPV associated and are contracted through sexual intercourse [93].Two HPV types (16 and 18) cause 70% of cervical cancers and precancerous cervical lesions [94] .

RISK GROUPS:

Risk according to clinical sequelae	
High Risk	**16, 18**, 31,33, 35, 39, **45,** 51, 52, 56, 58, 59, 68, 73 & 82
Probable High risk	26, 53, 66
Low risk	**6,11,** 40, 42, 43, 44, 54, 61, 70, 72, 81, CP6108

PATHOGENESIS:



RISK FACTORS FOR HPV INFECTION:

1) Early first sexual intercourse

2) Multiple sexual partners

3) Tobacco use–Smoking

4) Immune suppression-Co existing HIV infection.

5) Male partner sexual behavior

6) Large number of pregnancies

7) History of sexually transmitted diseases-Gonorrhea, Chlamydia or herpes simplex.

NATURAL HISTORY:

HPV prevalence peaks at ages 25 to 35(6).In less than 15% of exposed women, persistent infection develops resulting in dysplasia. Majority, clear the infection within a period of 2 years [93]. Cervical cancer develops 10 to 20 years after the exposure to HPV. Women in whom coexisting immunodeficiency and whose spouses have higher exposure to HPV have higher incidence of persisting infection which later transforms to cervical carcinoma.

Lindel K et al investigated the significance of HPV positivity in 40 patients with advanced cervical cancer treated with radiation therapy. The results of this study revealed that HPV positivity had better disease free survival ($p=0.02$), overall survival ($p<0.02$) and progression free survival (p,0.05) which was significant. Clinical complete remission was seen more in HPV positive tumours (67% vs 33%). A better disease free survival trend was seen with intact E2 gene region.

In a retrospective study of 223 cases of cervical cancer it was found that HPV 16 was found to have an impact on overall survival independently ($p<0.002$).

In 106 patients treated with radical radiotherapy, reduced survival and poor response was seen in the presence of multiple HPV types.

FIGO STAGING OF CERVICAL CANCER

STAGE I	Tumour confined to the uterus
I.A	Microscopic disease
I.A.1	Stromal invasion less than 3 mm in depth and less than 7mm horizontal spread
I.A.2	Stromal invasion between 3 to 5 mm in depth and less than 7mm horizontal spread
I.B	Clinically visible lesion or microscopic lesion greater than I.A
I.B.1	Clinically visible $\leq$ 4 cm
I.B.2	Clinically visible $\geq$ 4 cm
STAGE II	Tumour extends beyond the uterus but not upto lateral pelvic wall or lower third of vagina
II.A	Tumour without parametrial extention
II.A.1	$\leq$ 4 cm in greatest dimension
II.A.2	$\geq$ 4 cm in greatest dimension
II.B	Tumour with parametrial extension
STAGE III	Tumour extends to the pelvic side wall / involves lower third of vagina / Hydroureteronephrosis or non functioning kidney
III.A	Extension into the lower third of vagina
III.B	Tumour extends to the pelvic side wall or causes Hydroureteronephrosis or non functioning kidney
STAGE IV	Spread to pelvic organs or distant metastasis
IV.A	Tumour involves the mucosa of bladder or rectum or extension beyond the true pelvis
IV.B	Distant metastasis

EVALUATION RECOMMENDED BY FIGO

- INSPECTION
- PALPATION
- ENDOCERVICAL CURETTAGE
- HYSTEROSCOPY
- CYSTOSCOPY
- PROCTOSCOPY
- IV UROGRAPHY
- X-RAY CHEST AND SKELETAL X-RAYS.

DRAWBACKS OF FIGO STAGING

- Clinical staging with minimal investigations.
- Optional imaging with MRI/CT/USG/PET does not alter the stage
- Involvement of nodes not taken into account
- Vulval involvement not mentioned in staging
- Inguinal lymph nodes not taken into account
- Involvement of urethra does not alter the stage.

EVOLUTION IN THE MANAGEMENT OF CERVICAL CANCERS

Before the discovery X-rays, all Gynecological malignancies were managed with radical surgery and pelvic exenterations in the 18th century. The discovery of X-rays by Wilhelm Conrad Röntgen in 1985 revolutionized the management of cancers, particularly cervical cancer. Radiotherapy has been used in the management of cervical cancer since the early 1900. Over the years treatment planning techniques have evolved along with the equipment used in therapy and planning. RT techniques have evolved from the single direct field whole pelvic radiation to the 2 opposing AP-PA / 4 field box technique and the more recent Image guided / Adaptive radiotherapy in the management of locally advanced cervical cancer. Based on randomized trials and meta-analysis platinum based Chemotherapy along with radiotherapy has become the standard of care for locally advanced cervical cancers. Earlier Locally advanced FIGO Stage III.B were managed with a palliative intent of treatment but now with the advances in management and multimodality management, more and more cases are being managed with a curative intent. Though the incidence of locally advanced FIGO Stage III.B cervical cancers have drastically declined over the past few decades in the western population, a majority of cases in the developing countries like India present in the locally advanced stage. There are not many advances in the management of locally advanced cervical cancers in the last decade with emphasis on III.B advanced disease. In this article we will attempt to explore the strategies to improve the outcome of Advanced III.B disease.

CHEMOTHERAPY

The use of chemotherapy in the management of cancer came much later than radiotherapy when in World war II it was found that nitrogen mustard reduced the white blood counts. Now based on the results of 5 randomized trials the NCI proposed that cisplatin based chemotherapy concurrent with radiotherapy prolonged survival in patients with locally advanced cervical cancer.

The mechanism of the efficacy of chemotherapy is thought to be due to radiosensitization of tumour cells, direct cytotoxic effect and control of subclinical metastasis [12].

A meta-analysis of 13 trials that compared chemoradiation to only radiotherapy showed a 5 year survival improvement of 6% with chemoradiation (hazard ratio 0.81, $p<0.001$). This resulted in reduction of both local and distant failure.This meta-analysis also suggested that with increasing stage, the benefit of chemotherapy decreased. The 5 year survival benefit reduced by 3% with Stage III.B and IV.A disease [13].

An analysis by Nugent et al showed that the number of cycles of chemotherapy was independently predictive of progression free survival and Overall survival. This study reiterated that advanced stage, longer treatment time to complete radiotherapy and absence of brachytherapy were associaced with decreased overall survival and progression free survival ($p<0.05$) [14].

Chemotherapy has been studied in the Neo adjuvant setting, the concurrent setting and the adjuvant setting.

Adjuvant Chemotherapy in Locally advanced cervical cancer was assessed in a phase III Randomized study comparing concurrent Chemoradiation with cisplatin / gemcitabine followed by adjuvant gemcitabine / Cisplatin versus concurrent chemoradiation. The 3 year progression free survival was 74.4% vs 65% favoring the adjuvant chemotherapy arm (86.5% vs 46.3%) which also included 2 deaths due to treatment related toxicity [15].

Results published by Tseng et al was a randomized trial of advanced cervical cancer patients comparing chemoradiation using cisplatin, vincristine and bleomycin with only radiotherapy which showed that the overall Disease free survival and actuarial survival at 3 years were 51.7% and 61.7% in the chemoradiation group and 53.2 and 64.5% in the only radiotherapy group. Treatment related toxicity was more in the chemoradiation group (36.7% Vs 17.7%). In conclusion, multi agent chemotherapy was not superior to only radiotherapy for patients with advanced cervical cancers [16].

Due to the poor results with chomoradiation in locally advanced cervical cancers, Souhami et al investigated the option of Neo-adjuvant chemotherapy in a randomized trial using BOMP (Bleomycin, vincristine, mitomycin C and Cisplatin) when compared with only radiotherapy. Complete response was seen in 32.5% vs 47% favoring only radiotherapy which translated to 5 year overall survival of 23% with neoadjuvant chemotherapy vs 39% with only radiotherapy. The chemotherapy

related toxicity profile was severe with neoadjuvant chemotherapy and the authors concluded that neoadjuvant chemotherapy adversely affects survival in Stage III.B cervical cancer and is associated with unacceptable toxicity [17].

Another study on Neo-adjuvant chemotherapy by Kumar et al showed contrasting results with bleomycin, ifosfamide-mesna and cisplatin when compared to only radiotherapy showed a 32 month survival of 50 % and 27 % favoring the neoadjuvant chemotherapy arm. While 2 patients died of chemo related toxicity, there was no difference in the radiotherapy related toxicity between the two groups [18].

RADIOSENSITIZERS

Agents that sensitize the tumour cells to radiation are called radio-sensitizers. These agents promote the fixation of free radicals caused by radiation at the molecular level. The damaged molecules undergo biochemical reactions which prevent the repair of radiation induced cell damage. Free radicals are seized by the electron affinity of radio-sensitizers, making the molecules incapable of repair.

- HYPERBARIC OXYGEN

  The radiosensitivity of cells increase when exposed to oxygen. The oxygen interacts with the free radicals produced by ionizing radiation to produce peroxy radicals and hydrogen peroxide which cause structural damage. Hyperbaric oxygen is delivered by placing the patient in a high pressure oxygen tank delivering 100% oxygen during every fraction thus

increasing the oxygen tension of the tumour.

In a randomized trial of 320 patients (Stage III & IV.A) by Watson et al, the 5 year survival was 33% vs 27% in the control group (p=0.08). The rate of local recurrence was 33% in patients treated with hyperbaric oxygen and 53% in patients who received normal air [19].

Advanced cervical cancers treated with radiotherapy and oxygen or radiotherapy alone were reviewed by Dische et al. Analysis of the randomized study showed that the local tumour control without hyperbaric oxygen was poor which was seen in the survival (p=0.042) [20].

Other trials by Fletcher and a review article by Dische et al showed that there was no benefit with hyperbaric oxygen and the toxicity profiles were significantly more in patients treated with hyperbaric oxygen.

Although some of the results of randomized trials are promising, the delivery of hyperbaric oxygen during radiation is very inconvenient with a rise in the toxicity profile. Hence more studies are required with head to head comparison with chemotherapy to come to any definite conclusion.

- CISPLATIN

In 1961, Dr Barnett Rosenberg found that exposing an electric field on bacteria resulted in a change in their morphology which was not because of the electric field but due to the electrolysis products produced by platinum electrodes. Cisplatin a platinum compound interacts preferably at the N7 position of purine analogues forming interstrand and intrastrand cross links

which cause DNA damage and block cell division resulting in apoptotic cell death.

The NCI proposed that Cisplatin based chemotherapy along with radiotherapy prolonged survival in locally advanced cervical cancer based on the findings of 5 randomized trials and meta-analysis.

- CARBOPLATIN

In stage III.B cervical cancers, the disease extends upto the lateral pelvic side walls or may present with Hydro-ureteronephrosis. Such patients have a high chance of renal compromise especially after they are exposed to contrast for spiral CT or pyelogram. These patients may not tolerate cisplatin as it is known to be nephrotoxic. In these situations Carboplatin which is a platinum analog may be used as an alternative to Cisplatin to prevent further damage to the kidneys.

Studies by Katanyou et al and Cetina et al have shown that the use of Carboplatin is better tolerated with less side effects and may have reduced efficacy when compared to weekly Cisplatin [21,22].

- MITOMYCIN – C

It is a naturally occurring antitumour quinone derived from Streptomyces caespitosus (a strain of actinomyces). Most of the studies with Mitomycin C (MMC) have been along with 5 FU which produced a lot of Gastro-intestinal morbidity.

Roberts et al published the results of a randomized trial using MMC alone along with radiotherapy in patients with locally advanced cervical cancer compared with radiotherapy alone. The 4 year disease free survival favored the MMC radiotherapy arm (71% vs 44%) which was not statistically significant. The same results were seen in the local control and systemic control. A subgroup analysis showed that MMC improved the disease free survival in more advanced stages [23]. This sub group analysis is of principle importance as the benefit of Cisplatin reduces with increasing stage and this benefit is less than 5% in locally advanced FIGO Stage III.B cervical cancer. In such cases, MMC may be a good option although randomized head to head trials are required to substantiate this. The use of MMC along with 5 FU produced a lot of toxicity but MMC used as a single agent was well tolerated.

- EPIRUBICIN

It is an analog of anthracyclin. Bulky locally advanced cervical cancer, randomized to receive only radiotherapy and Concurrent Epirubicin followed by adjuvant chemotherapy were analyzed. The disease free survival was statistically significant with Epirubicin although the local control rates were comparable in both arms. The author concludes that the benefit is likely to be due to the adjuvant chemotherapy [24].

- GEMCITABINE

It is one of the main radiosensitizers studied around the world. Studies have shown that gemcitabine compliments both radiation and cisplatin. In a phase II study by pattaranutaporn et al, gemcitabine was delivered at 300 mg/m^2 weekly during radiotherapy for 5 weeks in patients with FIGO Stage III.B cervical cancer. This regiment was tolerated well. At follow up, CR was achieved in all except 2 and at a median follow up of 20 months the DFS and OS were 84% and 100% respectively [95]. Though gemcitabine has shown excellent local control rates, the toxicity when combined with cisplatin is on the higher side as gemcitabine sensitizes both radiation and cisplatin. This was seen in a study by Alvarez et al [96, 97].

In a phase III randomized study comparing cisplatin with gemcitabine and radiotherapy followed by adjuvant cisplatin and gemcitabine versus concurrent cisplatin with radiotherapy in locally advancer cervical cancer showed significantly improved progression free survival (p=0.029) and overall survival (p=0.0224) with the adjuvant chemotherapy arm with manageable toxicities [98].

- BEVACIZUMAB

RTOG 0417 was a phase II study which evaluated the efficacy of bevacizumab in 49 patients with locally advanced cervical cancer. The three year disease free survival and overall survival were 68.7% and 81.3% respectively with no serious adverse events [99].

HYPERTHERMIA

Many randomized trials analyzing the use of hyperthermia combined with radiation and chemotherapy have shown clear and significant clinical benefits. At temperatures >40 degree Celsius direct cytotoxicity occurs as a result of protein denaturation. Radiotherapy and chemotherapy are least effective in hypoxic, acidotic and nutrient deprived areas of the tumour where hyperthermia specially acts.

The Dutch deep hyperthermia trial showed a significant improvement in survival and local control when radiotherapy was combined with hyperthermia in pelvic malignancies. The benefit was more pronounced in locally advanced cervical cancers [25].

In cervical cancers, hyperthermia is administered a maximum of 5 sessions during the course of radiation and delivered 1 to 4 hours after radiotherapy to avoid thermotolerance. Experimental studies have shown that hyperthermia interferes with the repair of DNA damage in cells which potentiates the effect of radiotherapy. Vasodilatation also causes increased blood flow to the tumour which causes better oxygenation of tumour cells and better response to radiotherapy.

The Dutch deep hyperthermia trial compared radiotherapy with hyperthermia to radiotherapy alone in locally advanced cervical cancers. The rate of complete response with hyperthermia was 83% when compared to 57% in the only radiotherapy group. The 5 year pelvic control rate was 61% vs 37% in favor of hyperthermia and the 12 year pelvic control rate was 56% vs 37% which was statistically significant ($p=0.01$). The overall survival was 37% with hyperthermia

when compared to 20% with only radiotherapy. Almost 80% patients in this study were locally advanced stage III.B and IV.A. More importantly hyperthermia did not increase the radiation induced toxicity.

Harima et at compared only radiotherapy to hyperthermia and radiotherapy in Stage III.B cervical cancers. The complete response, 3 year overall survival and disease free survival with only radiotherapy was 50 %, 48.1% and 45% respectively compared with 80%, 58.2% and 63.6% with hyperthermia. The results were not statistically significant and the toxicity profiles of both arms were comparable [26].

The Cochrane database review of 6 randomized trials showed a higher complete response rate, lower rate of local recurrence and improved overall survival with hyperthermia and the toxicity profile was comparable to that of only radiotherapy [27].

In conclusion, hyperthermia has shown promising results in locally advanced cervical cancers where the benefit of chemotherapy is minimal. The toxicity profile in patients receiving hyperthermia is low and it can be used as an alternative to patients who are not fit for chemotherapy due to varied reasons. The drawback of hyperthermia is that it is a tedious process which needs improvements in treatment planning which offers precision and controllability rather than the present empirical approach.

BRACHYTHERAPY

Brachytherapy for cervical cancer was first mentioned in the Journal of American medical association as early as 1902. It describes the use of radium as local application in some cases of internal or quasi internal cancers such as that of cervix uteri [28].

In 1903, James Morton from New York presented various apparatus for radium treatment within the vaginal cavity and reported 3 cases of cervical cancer or recurrent cervical cancer treated with radium which showed better results than treatment with X-rays [29,30].

The advances in equipment, technique and the precision in treatment delivery have been exemplary since then but the underlying message remains the same that 'Brachytherapy is an immortal art' and external beam radiotherapy may never replace brachytherapy.

Brachytherapy plays a vital role in the management of cervical cancer and evidence confirms that the use of brachytherapy for dose escalation after external beam radiotherapy significantly improves survival in locally advanced cervical cancers.

Intracavitary application may be challenging in bulky locally advanced FIGO Stage III.B disease where there may be insufficient tumour regression, persistant parametrial involvement, distal vaginal involvement and vaginal narrowing. In such situations, intracavitary brachytherapy may not adequately cover the residual tumour while maintaining dose constraints to the organs at risk [31]. This has led to the need

to explore other strategies for dose escalation like IMRT and SBRT [32-34]. Although these technological advances have shown to be promising, they have resulted in inferior survival when compared with brachytherapy.

In 2014, B.S.Gill et al published the National cancer data base analysis on the impact of new technological advances in radiotherapy, which reviewed 7000 patients who were treated between 1998 and 2011. The review demonstrated a decline in the use of brachytherapy over the years however the median survival with brachytherapy was 70.9 months while the median survival with IMRT and SBRT boost was only 23.8 months. Also, the IMRT and SBRT boost increased the risk of death more than the lack of chemotherapy [35].

Syed et al demonstrated that at a median follow up of 51 months, the local control rate was 73% with LDR brachytherapy for locally advanced cervical cancers [36].

As brachytherapy has shown to improve local control and survival when compared to EBRT boost, Interstitial brachytherapy may be ideal in certain situation. Interstitial brachytherapy, although feasible is an invasive procedure which requires technical expertise and may cause more treatment related morbidity.

With HDR Interstitial brachytherapy Neeta Kannan et al showed that the 2 year acurial local control, DFS, OS and Grade III toxicities were 61%, 43%, 53% and 10% respectively [37].

Evolution of brachytherapy planning has led to 3D image guided brachytherapy which allows volumetric optimization in improving the coverage of

tumour by sparing critical organs which may potentially reduce toxicities and increase local control.

Studies that compared 2D and 3D image guided brachytherapy showed that 2D radiograph based brachytherapy overestimates the tumour dose. The average volume prescribed dose coverage was Stage I.B.1 – 98.5%, Stage I.B.2 – 89.5%, Stage II.B – 79.5% and 59.95% for Stage III.B. This shows that for advanced stages, 2D brachytherapy becomes less reliable [38]. Similarly other studies showed that 2D based brachytherapy underestimates rectum and bladder dose compared to 3D based brachytherapy by 1 to 5 fold [39-42].

Adequate coverage of large volume disease may be challenging with intracavitary brachytherapy and may require image guided intracavitary/interstitial brachytherapy(vienna applicator) to improve local control by creating an asymmetric dose distribution and dose escalation.

This was reiterated by the vienna group which showed that the 3 year acturial overall survival was 28% for tumours more than 5 cm prior to the era of image based brachytherapy compared to 58% ($p=0.003$) with image based brachytherapy [43,44].

PROPHYLACTIC PARA-AORTIC RADIOTHERAPY

Irradiation of the para-aortic region when there are no significant para-aortic nodes, in patients who are likely to fail or have a high chance to fail in the para-aortic region is called prophylactic para-aortic radiotherapy.

In a randomized trial by Haie et al and EORTC on prophylactic para-aortic

radiotherapy in 441 patients with locally advanced cervical cancer, there was no difference in survival, local control or rate of distant metastasis but the rate of distant failure and failure in the para-aortic region without a pelvic recurrence was significantly more without prophylactic para-aortic radiotherapy. The rate of severe complications was more in the patients who received prophylactic para-aortic radiotherapy (9% vs 4.8%) [100].

In an assessment of 758 patients by Huang et al, dense parametrial infiltration ($p=0.002$), pelvic lymph nodes ($p=0.007$) and SCC-Ag level more than 40 ng/ml($p<0.001$) were factors that independently predicted para-aortic nodal relapse. Serum CEA value more than 10 prior to treatment was also predictive of para-aortic relapse [101]. Thus the decision on prophylactic para-aortic radiotherapy needs to be made based on several factors and the benefits need to be weighed against the side effects and toxicity profile associated with prophylactic para-aortic radiotherapy.

ALTERED FRACTIONATION IN CERVICAL CANCER

In cervical cancer, altered fractionation is known to cause radiotherapy related morbidity due to rapidly renewing cells in the bowel. These are some of the altered fractionation schedules that were tried in locally advanced cervical cancer.

HYPERFRACTIONATION AND ACCELERATED FRACTIONATION

Delivering the same Total dose as conventional regimen in twice as many fractions half the OTT by treating twice a day in the same overall treatment time as

the conventional regimen is defined as 'Pure Hyperfractionation'.

Impure hyperfractionation is the increase in Total dose (TD) and sometimes a longer overall treatment time as well as more fractions, delivered twice a day.

The intent is to achieve better tumour control, reduce late side effects and same or slightly increased early effects. The basic aim of hyperfractionation is to separate early and late effects.

Delivering the same Total dose as conventional regimen in half the OTT by treating two or more fractions per day is called 'Pure accelerated fractionation'. The intent is to reduce the repopulation of rapidly proliferating tumours. In practice it is either necessary to introduce a break in the middle of treatment or reduce the total dose slightly with acute effects as the limiting factor.

In a phase II study by Macleod et al, 61 patients with LACC were treated with accelerated hyperfractionation with 1.25 cGy delivered 2 times a day with atleast 6 hours gap between treatment to a total dose of 57.5 Gy followed by LDR brachytherapy or reduced field boost to a smaller volume. 30 patients developed acute toxicities requiring medication. The 5 year OS was 2 % and the relapse free survival was 36%. 7 patients developed severe late complications requiring surgical intervention and 5 patients had to undergo total hip replacement [45].

In a randomized study of 30 patients by Viswanathan et al, 15 patients received hyperfractionation and 15 patients received conventional fractionation. 2 patients in the study arm and 8 patients in the control arm developed recurrence at 5 years ($p=0.04$). Grade II/III delayed bowel complication was more with hyperfractionation.

(p=0.0006) [46].

In a phase II trial of hyperfractionation by RTOG (8805), 81 patients were treated with 1.2 Gy per fraction, twice daily delivered 6 hours apart followed by brachytherapy in locally advanced cervical cancers. In stage III/IV.A disease, the 5 year cumulative rate of grade 3 or 4 late effects was 12% [47].

CHART – CONTINUOUS HYPERFRACTIONATED ACCELERATED RT

In a pilot study by Biswal et al, 50 patients with locally advanced cervical cancer were treated with 1.4 Gy per fraction deliver 3 times a day with an interval of 6 hours between treatment for 10 days (30 fractions to deliver 42 Gy) without a break, followed by 2 HDR brachytherapy. At the end of treatment 48 % had complete response, 40% had partial response and 8% had stable disease. While the local recurrence rate was 32%, 16% developed metastatic disease. Late morbidity was seen in 4 patients. Thus this regimen was well tolerated with optimal local control rates [48].

The advantages of this schedule is the short treatment time which is preferred by patients, acute reactions develop after the completion of treatment, late effects are minimized and good local control with reduction in overall treatment time. The disadvantage is that it is tedious due to treatment of 3 fractions per day which may be challenging in a high patient load centre.

SIMULTANEOUS INTEGRATED BOOST

Simultaneous integrated boost (SIB) is an IMRT technique that allows the planning and irradiation of different targets at different dose levels in a single treatment session instead of using sequential treatment plans. It is used to increase the dose to the boost volume while keeping the dose to the elective volume at a lower level. This technique was initially used in head and neck cancers and prostate cancer as early as 2000 and has been in use in cervical cancer since 2009 [49-51].

The advantage of SIB is to deliver higher dose to the tumour while reducing the overall treatment time (OTT) which may translate into improvement in local control [52-54]. Reducing the OTT limits the effect of accelerated tumour repopulation.

Due to the non uniform beam intensity and steep dose gradients in IMRT, geographical miss or high dose to organs at risk is a possibility due to organ motion during or between treatments. Studies have shown that interfraction uterine motion can be up to 4.8 cm and interfraction cervical motion can be 1.9 cm [55]. Dosimetrically some studies have shown that SIB-IMRT has advantages over sequential IMRT in dose escalation. These studies state that in SIB IMRT the dose distribution is even more conformal resulting in better coverage of the boost volume while sparing non target tissues [56-58].

OVERALL TREATMENT TIME (OTT)

In cervical cancer, extension of overall treatment time has a negative effect on local control and survival [59-63]. The reason for this may be due to accelerated repopulation of tumour cells during fractionated radiotherapy [64,65]. Hence reduction in the OTT can improve local control. OTT has been stated as one of the most important prognostic factors and pelvic failure rate is approximately 1% per day of extension of treatment time beyond 30 days [66]. The 5 year survival in a study by Girinsky et al with treatment time less than 55 days when compared to more than 55 days was 65% and 54% ($p=0.03$) and the pelvic control rates were 87% and 72% respectively ($p=0.006$). To add to this the survival reduced by 0.6% per day and pelvic control rate by 0.7% per day for all stages [67].

In a study by Mandal Abhijit et al (2007) it was found that patients with Stage III Carcinoma cervix had higher local control rates (100% Vs 76.5 %) which was statistically significant and a 5 year DFS rate of 100% vs 68.6% when the Overall treatment time of less than 50 days was compared with treatment time more than 50 days [68].

Sanjay singh et al's assessment of Stage III patients showed comparable local control rates of 82.6 % and 88.2 % with OTT less than or equal to 50 days when compared to OTT more than 50 days. Across all stages, the local control rate was statistically significant ($p<0.005$) [69].

The aim of accelerated radiotherapy is shortening of OTT by delivering more than 5 fractions per week using standard fractionation (pure accelerated fractionation) or using a larger dose per fraction five times a week (hybrid accelerated fractionation). These studies are ideal for chemical modulation of radiation sensitivity like hypoxic cell sensitizers which require high concentration of the compound in the tumour site at the time of exposure to radiation.

Yang et al reported that Accelerated regimes significantly increase tumour control probability for tumours with clonogenic cell doubling time (T_{pot}) smaller than 3 days [70].

T_k is the lag time defined as the time between the start of treatment and the start of repopulation [70, 71]. It is reported that on the assumption of T_k to be 30 days, to counterbalance tumour repopulation and keep tumour control rates unchanged for OTT's upto 55 days, a dose increment of 0.6 to 0.7 Gy per day is required [72, 73].

Acute responding normal tissues show a proliferative response to radiation induced reproductive cell death as early as the 1st week of treatment [74]. Acute mucosal reaction follow cellular supression and regression.

In a report by Denham et al, the onset of adverse effects (Grade II & III) was higher during accelerated regimens over 3 ½ weeks compared to conventional fractionation schedules over 7 weeks [75].

OTT plays a negligible role in producing late reaction [76, 77]. Late

responding normal tissues have a slow rate of cell renewal, that functional damage and depletion of cells are not apparent until after the end of conventional fractionated radiotherapy eg : onset of repopulation for spinal cord ranges from 120 to 150 days [78, 79]. This is for genuine late effects. On the other hand consequential late effects which are caused due to the severity of acute side effects are affected by OTT [80].

Randomized studies showed that accelerated fractionation is associated with a high rate of severe mucosal sequelae [77] and there was a correlation which was significant between acute mucosal and late effects [81].

FRACTION SIZE

Radiobiologically tumours and acute responding normal tissues are less sensitive to change in fraction size compared to late responding tissues [77]. The effect of change in fraction size for different tissues can be quantified based on the α/β ratio.

The survival curves for acute responding tissues and tumours (high α/β ratio) is more linear while the survival curve for late responding tissues (low α/β ratio) is significantly curved. Hence the effect of fractionation is more in late responding tissues than acute responding tissues or tumour tissue. Bothe the Field size and OTT both determine the response of acutely responding tissues.

Biological Effective Dose (BED)

It is the quantity by which different fractionation regimens are compared.

BED = Total dose x Relative effectiveness.

In the LQ model, α represents the $\log_e$ of cells killed per Gy for the linear portion on the curve and β represents the $\log_e$ of the cells killed per Gy squared. α/β is the dose at which the linear and quadratic components of cell killing are equal.

Biological effect $E = \alpha D + \beta D^2$ (where D is the Total dose)

For a fractionated schedule, where n is the number of fractions and d is the dose per fraction,

Biological effect $E = n(\alpha d + \beta d^2)$

ie. $E = nd(\alpha + \beta d)$

$$E = (\alpha)(nd)\left(1 + \frac{d}{\alpha/\beta}\right)$$

number of fractions *n* multiplied by the daily dose *d* gives the total dose D.

ie. E = α (Total dose) (Relative effectiveness)

where Relative effectiveness $= 1 + \frac{d}{\alpha/\beta}$

If this equation is divided by α throughout,

$\frac{E\ .}{\alpha}$ = Total dose x Relative effectiveness,

and this $\frac{E\ .}{\alpha}$ = is the Biological Effective dose.

Thus, $$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

The use of this equation is justified only if there is complete repair between two successive fractions and no proliferation during treatment. Hence, this formula can be used only for late responding tissues while using SIB-IMRT, whereas for acutely responding tissues and tumour tissues, the cell proliferation should be taken into account to calculate the BED [82].

Fowler formulated that [83],

$$\text{Relative effectiveness} = 1 + \frac{d}{\alpha/\beta} \quad \frac{ln2}{nd\alpha} \quad \frac{T - T_k}{T_{pot}}$$

where

T_{pot} is the potential doubling time

Tk is the time of onset of proliferation and

T is the Overall treatment time (OTT).

$$\text{Relative effectiveness} = nd\left(1 + \frac{d}{\alpha/\beta}\right) \quad \frac{ln2}{nd\alpha} \quad \frac{T - T_k}{T_{pot}}$$

While treating multiple fractions per day, an interfraction interval should be at least 6 hours to ensure a complete repain of sublethal damage after each dose. This time is sufficient for many normal tissues to fully recover between fractions.

DOSE RESPONSE RELATIONSHIP OF EARLY AND LATE RESPONDING TISSUES

The response of early and late responding tissues change with different fractionation. Late reactions are more severe if larger dose per fraction is given over fewer fractions, even though early reactions are matched by adjusting the total dose. This is attributed to the differences in repair capacity or the shape of the shoulder of the underlying dose-response curves. For late responding tissues, the dose response relationship is more curved than early responding tissues. In terms of the LQ model, α/β ratio is the dose at which the linear and quadratic components are equal. The α/β ratio is large for early responding tissues and tumours, as a result α dominates at low doses. The α/β ratio is small for late responding tissues, so that the β term has an influence at low doses.

- If a fractionation is changed from many small doses to a few large doses and the total dose is titrated to produce equal early effects, the treatment involving large doses in few fractions result in more severe side effects.
- In hyperfractionation, where the doses are delivered per day for 6 to 7 weeks, the late effects appear to be greatly reduced if the total dose is titrated to produce equal or slightly more severe acute effects.
- The isoeffect curves are steeper for late effects than acute effects.

ACCELERATED REPOPULATION

Surviving cells or clonogens in a tumour that are triggered by cytotoxic agents like radiotherapy divide faster than before. This is called Accelerated repopulation.

In an analysis by Withers, it was found that clonogen repopulation accelerates at about 28 days after initiation of RT in a fractionated regimen. A dose increment of 0.6 Gy per day is required to compensate for this repopulation. This increment is consistent in a 4 day clonogen doubling doubling rate compared with a median of about 60 days of unperturbed growth.

CONCOMITANT BOOST

Concomitant boost using conformal therapy incorporates the benefits of SIB-IMRT by reducing the overall treatment time and dose escalation to the boost region while sparing the normal tissues using field in field forward planning technique.

Studies have shown that dose escalation to the tumour and reduction in the overall treatment time improves the local control. Dose escalation to the tumour also increases the dose received by the organs at risk like rectum, small bowel and bladder causing acute and late toxicities. A highly conformal IMRT dose distribution allows significant sparing of these organs at risk. In standard fractionation, dose escalation to the tumour can be achieved by increasing the number of fractions which increases the overall treatment time. The increase in overall treatment reduces the local control. Dose escalation to the tumour without increasing the overall treatment time can be achieved by Concomitant boost or Simultaneous integrated boost. There have been

few studies where Simultaneous integrated boost or concomitant boost has been achieved using IMRT technique which showed satisfactory local control with acceptable morbidity by dose escalation to the tumour. SIB – IMRT plans are less likely to cause uncertainties in planning or delivery as it involves the same treatment plan for the entire course of treatment.

In April 2016, Waqar M Haque published and article in the International journal of cancer and oncology on SIB using conformal therapy for cervical cancer. 21 patients were treated with 45 Gy to the pelvis and 50 Gy to the boost volume in 25 fractions. 61 % patients were locally advancer III.B/IV.A. The 2 year local control rate was 95.2% and 2 year disease free survival was 80.9%. 2 patients developed acute Grade III toxicity and 3 patients developed chronic Grade III toxicities. Though the majority of the patients were Stage III.B/IV.A, the local control rates were excellent with acceptable toxicities [84].

In a retrospective feasibility study on the impact of organ motion and tumour regression in patients treated with simultaneous integrated boost by Fernanda G Herrera showed that SIB required frequent re plans or adaptation of treatment plan to prevent increased dose to the organs at risk and reduced dose to the target volume [85].

A prospective phase II study LARA-CC (Large field radiotherapy in advanced cervical cancer) where 40 Gy in 2 Gy per day for 20 days was delivered to the whole

pelvis along with 0.25 Gy boost to the macroscopic disease(2.25 Gy) to a total dose of 45 Gy which was followed by surgery. The local control in terms of pathological complete response was not superior to conventional treatment [86].

Katrien Vandecastele et al published an article on SIB-IMAT in locally advanced cervical cancer. 6 patients were treated with SIB and dose escalation was achieved with acceptable dose to the elective lymph nodes and organs at risk [87].

A study by Kavanagh et al showed that IMRT Concomitant boost can be used as an alternative to brachytherapy in patients who are not fit for the procedure in view of age and co-morbid illness with acceptable toxicity profile [88].

This is a study proposing feasibility of 3D CRT to provide a higher dose simultaneously to the primary tumour area. The role of IMRT to simultaneously boost the primary is unquestionable when small volumes are considered and where more organs are at risk around our target. But in an advanced pelvic malignancy where the target volume is large and where completely avoiding the bladder base or the recto-sigmoid septum are not recommended, 3D CRT may be tried.

AIM OF THE STUDY

To evaluate the feasibility and efficacy of concomitant boost using 3D-CRT in patients with locally advanced cervical cancer.

MATERIALS AND METHODS

After obtaining an informed consent 29 patients with locally advanced FIGO Stage III.B were enrolled with clearance from the ethics committee. All patients included were ECOG performance status 0 or 1 and were investigated as outpatient basis after a detailed history and clinical examination. A cervical punch biopsy was done on the first day of hospital visit.

- INVESTIGATIONS

-Complete blood count

-Biochemical evaluation – RFT, LFT, Sr.Electrolytes, Creatinine clearance and Fasting / post prandial blood sugar.

-Blood grouping and RH typing

-Viral markers – HIV, HbsAg and HCV

-ESR and Urine routine

-Chest X-ray

-ECG and Echocardiogram

-Ultrasound Abdomen and pelvis

-Cystoscopy

After a complete evaluation, patients were admitted for treatment. A complete Gynecological examination (per speculum and per vaginal) was done prior to starting treatment and the clinical stage was confirmed based on FIGO staging (2009).

INCLUSION CRITERIA

- FIGO Stage III.B bulky disease.
- Curative intent of treatment.
- Fit for Brachytherapy under short GA

EXCLUSION CRITERIA

- Presence of distant metastasis
- Prior irradiation to primary site
- Presence of para-aortic nodes
- Presence of bulky pelvic nodes
- > 70 years
- Medical renal disease
- Involvement of lower third of vagina
- Other histologies-neuroendocrine, sarcoma, lymphoma.

Decision on chemotherapy was based on age, general condition of the patient, nutritional status of the patient and associated co-morbid illness.

Prior to the start of treatment, the patients and attenders were extensively counseled regarding the precautions that need to be taken during the course of treatment with an emphasis on dietary habits.

Concurrent Chemoradiation was delivered with External beam radiation to the

pelvis along with weekly cisplatin (40 mg/m^2) for 5 cycles, followed by reassessment for brachytherapy.

CT simulation was done on a flat couch in supine position. Although the ideal method to simulate and treat in pelvic malignancies would be to use a Vac-Lok or in prone position with full bladder, our patients were simulated after complete voiding and consumption of a fixed dose of 200 ml water and CT simulation was done after 20 min and this was carried out every day during the course of treatment. CT simulation was done with a thickness of 5mm without oral or IV contrast extending superiorly from the liver upto mid thigh region.

After CT simulation, the images were acquired into the treatment planing system and after registration, the target volumes and organs at risk were contoured based on the RTOG guidelines.

External beam radiotherapy will be delivered with 49.4 Gy EBRT to whole pelvis(apart from the primary GTV) and concomitant boost to the primary GTV TD 54.6 Gy followed by intracavitary brachytherapy. The target volumes included the GTV(Gross tumour volume), CTV (Clinical target volume) and PTV (Planing target volume).

Treatment planning was done with forward planning conformal therapy using field in field technique based on the recommendations of ICRU 83.

CTV

The clinical target volume (CTV cervix) was defined as the GTV cervix, corpus uteri, bilateral parametrium, involved nodes and upper third of vagina. In

cases with vaginal involvement, the CTV cervix was extended 2 cm below the vaginal involvement. The planning target volume of the CTV cervix (PTV cervix) was obtained using a three dimensional anisotropic expansion of 10, 7, and 7 mm in the antero-posterior, left-right, and superoinferior direction, respectively.

The elective lymph nodal areas included the common, internal and external iliac nodes, the obturator and presacral region. Using a three dimensional expansion of 2 mm and 7 mm around nodes, respectively, the CTV nodes and PTV nodes will was created.

DOSE PRESCRIPTION

PTV 1 (Whole pelvis apart from primary GTV)- 1.9 Gy per day, 5 fractions per week for a total 26 fractions, receiving TD 49.4 Gy.

PTV 2 (Primary GTV)- 2.1 Gy per day, 5 fractions per week for a total of 26 fractions was delivered concomitantly to receive TD 54.6 Gy.

Rectum – $D_{mean} \leq 44$ Gy and $D_{max} \leq 54$ Gy. Rectal volume receiving 40 Gy (≤ 40 %).

Rectal volume receiving 45 Gy (78-85 cm^3)

Small bowel – $D_{max} \leq 50$ Gy and $D_{mean} \leq 33$ Gy. Volume receiving 35 Gy $\leq 35\%$.

Volume receiving 45 Gy $\leq 14\%$ and ≤ 360 cm^3.

Bladder – D_{max} and $D_{50} \leq 50$ Gy.

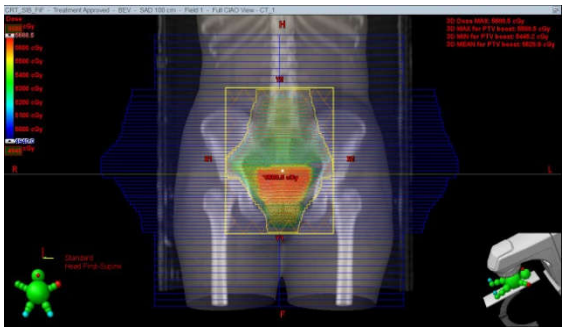
3D-CRT was delivered in 26 fractions over 5 to 6 weeks, 5 fractions per week. An on board image was taken on Day 1 after applying the field shift for confirmation of patient position and this was repeated every week.

BEAM ARRANGEMENT

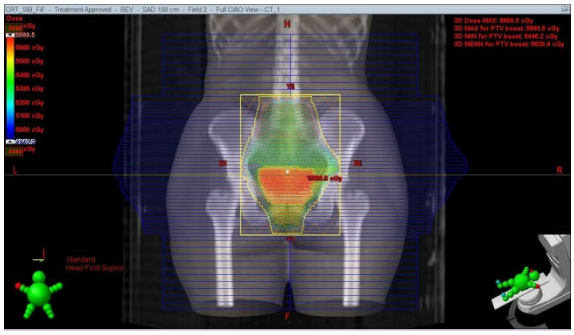
8 main fields were used of which 4 (AP/PA and 2 lateral fields)were used for the whole pelvis and 4(AP/PA and 2 lateral fields) were used for the boost volume.

BEAM EYE VIEW OF THE PELVIC FIELD(4940 cGy)

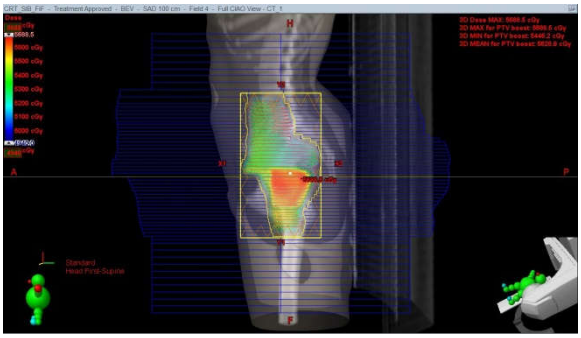
ANTERIOR FIELD



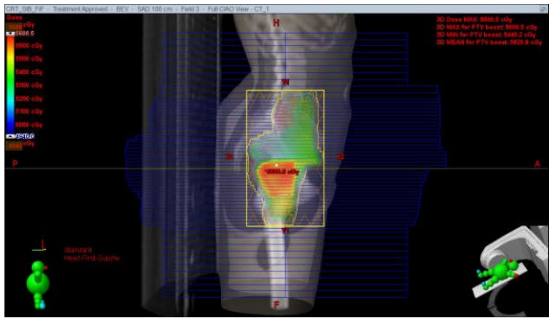
POSTERIOR FIELD



RIGHT LATERAL

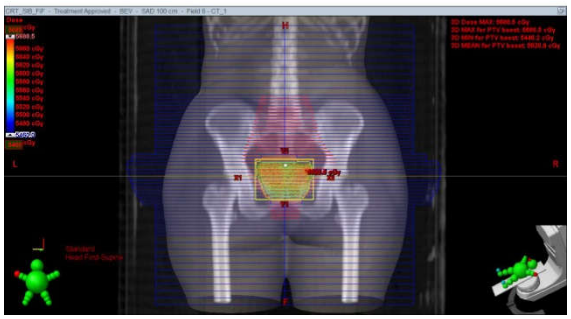


LEFT LATERAL

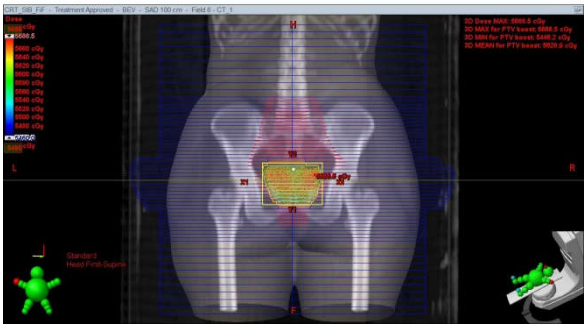


BEAM EYE VIEW OF THE BOOST FIELD 5460cGy

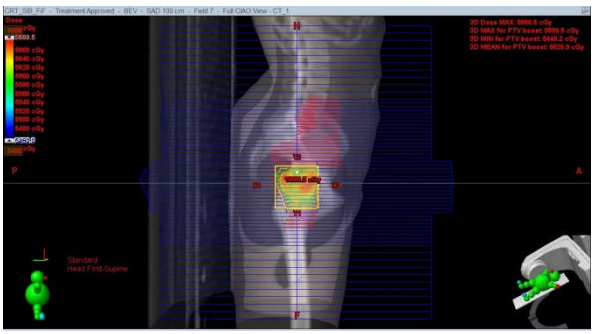
ANTERIOR FIELD



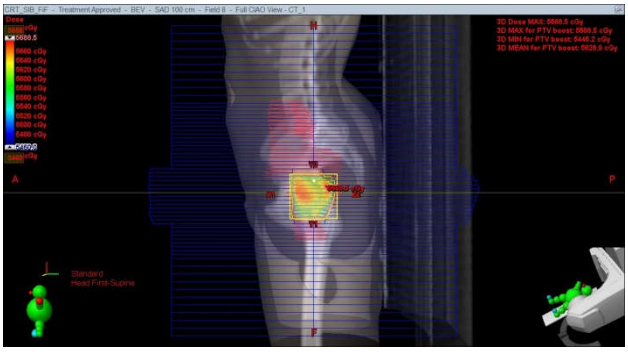
POSTERIOR FIELD



RIGHT LATERAL FIELD



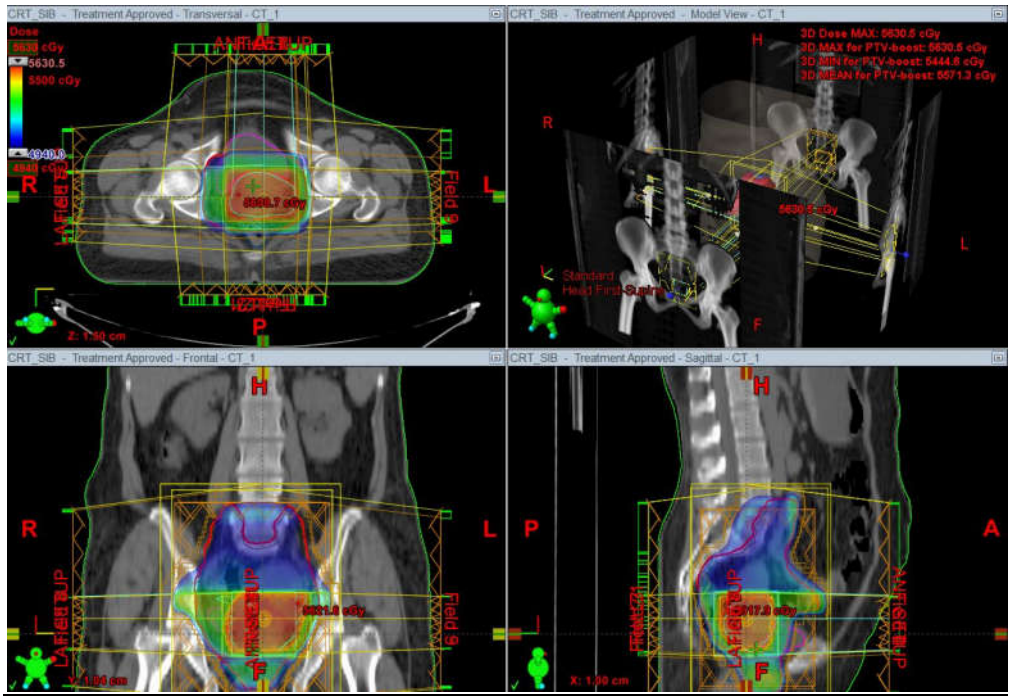
LEFT LATERAL FIELD



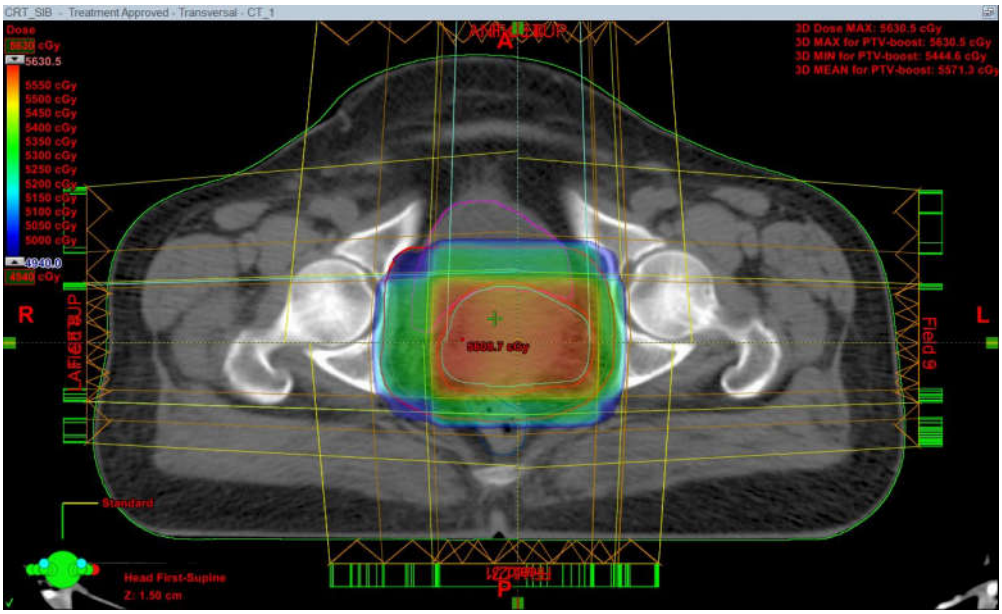
DOSE DISTRIBUTION COLOUR WASH AND BEAM GEOMETRY IN AXIAL,

CORONAL AND SAGITAL PLANE

VOLUME RECEIVING 4940 cGy

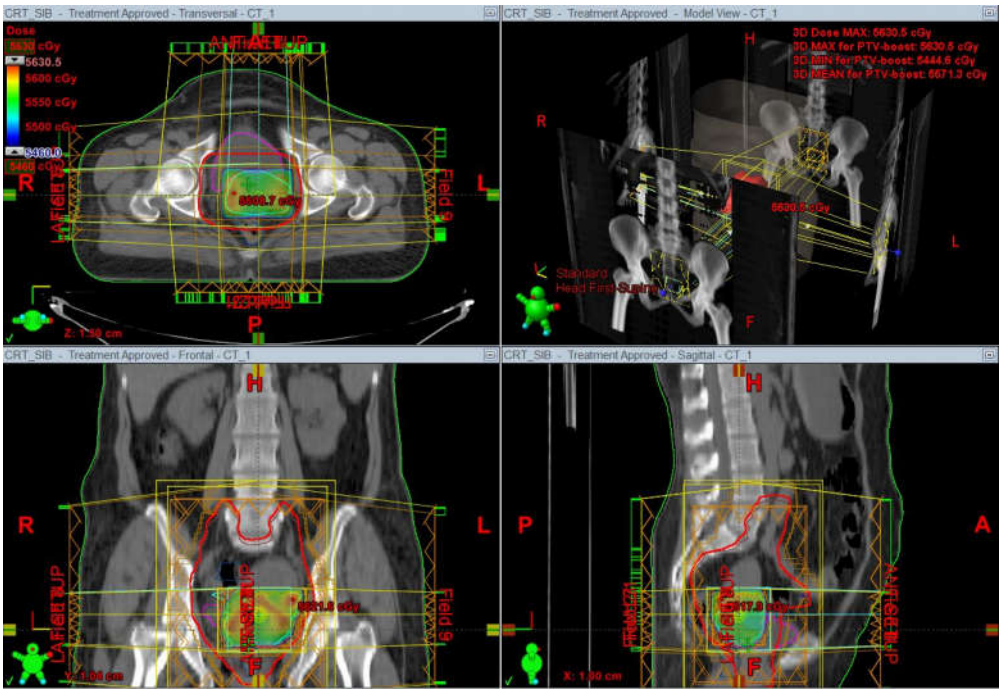


AXIAL SECTION SHOWING VOLUME RECEIVING 4940cGy

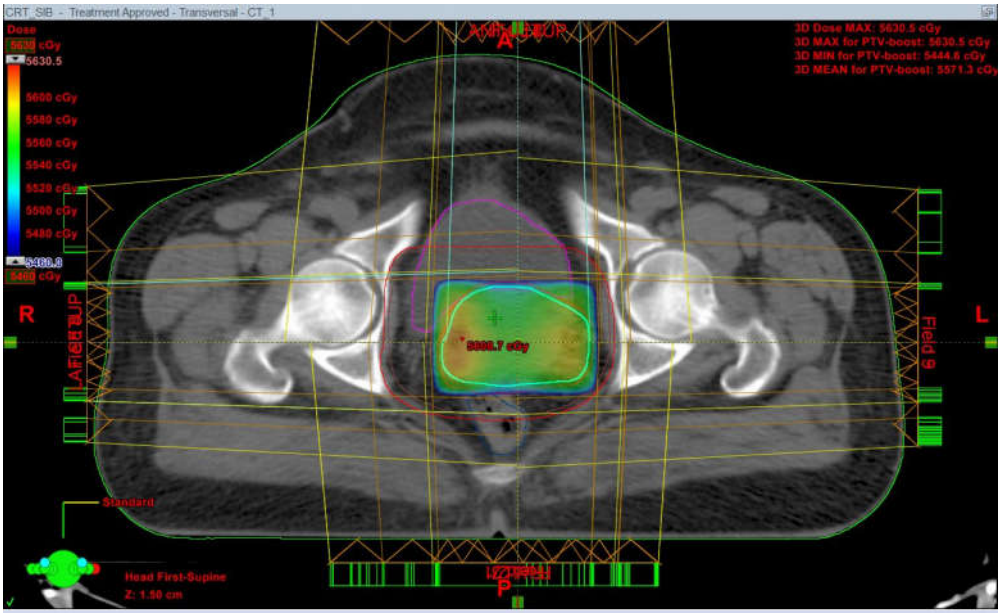


DOSE DISTRIBUTION COLOUR WASH AND BEAM GEOMETRY IN AXIAL, CORONAL AND SAGITAL PLANE

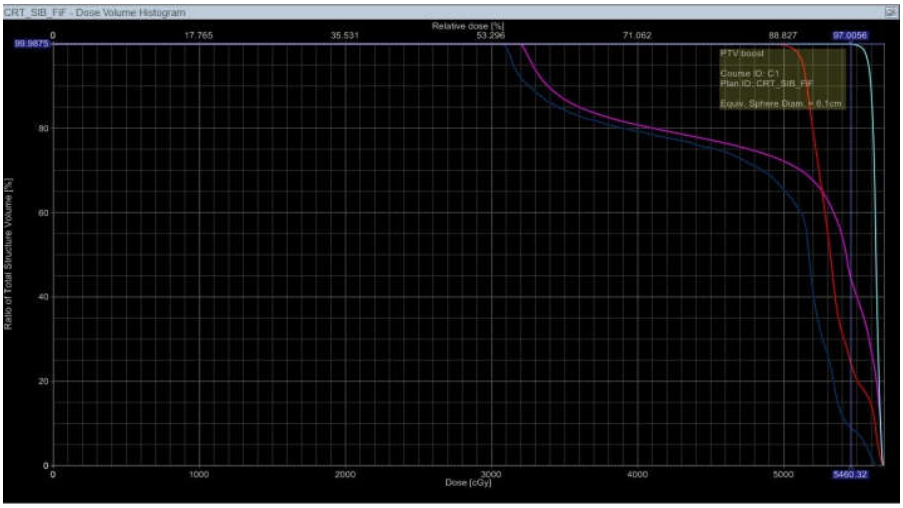
VOLUME RECEIVING 5460 cGy

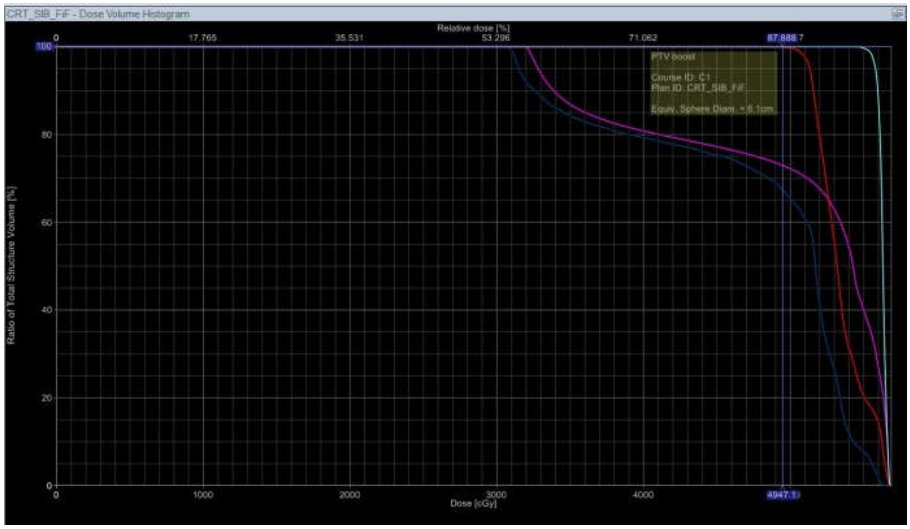


AXIAL SECTION SHOWING VOLUME RECEIVING 5460cGy



DOSE VOLUME HISTOGRAM SHOWING ADEQUATE COVERAGE OF TARGET VOLUMES





All patients were under admission during the entire course of treatment and they were assessed everyday prior to treatment. Treatment related morbidity was assessed based on the CTCAE ver 4.0 and RTOG grading of acute toxicity.

RTOG / CTCAE 4.0 GRADING OF ACUTE TOXICITY [89]

TOXICITY	GRADE I	GRADE II	GRADE III	GRADE IV	GRADE V
SKIN	Faint erythema or dry desquamation	Moderate to brisk erythema. Moist desquamation in skin folds	Moist desquamation inareas other than skin folds	Necrosis or ulceration involving full thickness of dermis. Spont. bleeding	Death
PROCTITIS	Rectal discomfort. No intervention required	Blood or mucus requires intervention.	Urgency and incontinance limiting self ADL	Life threatening consequences. Urgent intervention	Death
DIARRHEA	< 4 episodes per day	4-6 episodes per day	≥ 7 episodes per day requiring hospitalization	Life threatening consequences. Urgent intervention	Death
VOMITING	1-2 episodes separated by 5 minutes	3-5 episodes per day	≥ 6 episodes requiring hospitalization	Life threatening consequences. Urgent intervention	Death
CYSTITIS	Microscopic hematuria. Minimal increase frequency and urgency	Moderate hematuria. Moderate increase in frequency and urgency	Gross hematuria requiring IV medication and transfusion.	Life threatening consequences. Radiology/ operating intervention	Death
HYPO NA	<LLN - 130		130-120	<120 life threatening	Death
HYPO K	<LLN - 3.0	<LLN - 3.0 Symptomatic	3 - 2.5 requiring hospitalizati	<2.5 Life threatening.	Death
HYPO MG	<LLN – 1.2	1.2 – 0.9	0.9 – 0.7	< 0.7	Death
NEUTROPENIA(RTOG)	4000-3000 WBC's	3000-2000 WBC's	2000-1000 WBC's	<1000 WBC's	Death

Radiotherapy was pended in case of Grade III/IV toxicity.

Chemotherapy was suspended/pended in patients with poor compliance or tolerance. The criteria to withhold chemotherapy was persistent myelosupression/ neutropenia Gr II/III/IV, Febrile neutropenia, dyselectrolytemia (Persistent low sodium/ potassium/ magnesium, Sr. sodium <120, Sr. Potassium <3.0, magnesium <1.0), Uncontrolled vomiting, rising renal parameters, Sensory neural hearing loss and Grade II peripheral neuropathy.

A repeat CT and re plan was done at 36 Gy to account for tumour shrinkage. A volumetric assessment of tumour shrinkage was done in comparison with the CT done prior to the start of treatment and response was assessed based on RECIST criteria .

RECIST CRITERIA Version 1.1 [90]

Complete response (CR) is defined as the disappearance of the target lesion and reduction in the short axis of lymph nodes to less than 1 cm.

Partial response (PR) is defined as the reduction in the target volume diameter to least 30 % of the initial volume.

Progressive disease is defined as the increase in the target volume diameter to at least 20 % of the initial volume or appearance of new lesions.

Stable disease (Stable) – When the tumour has not progressed enough to be called progressive disease and has not shrunk enough to be called partial response, it is called stable disease.

A complete clinical and gynecological examination was done at 30 Gy and 50 Gy when the response to treatment, morbidity / tolerance to treatment and feasibility of Intracavitary brachytherapy were assessed.

Intracavitary application was done under aseptic precautions under short General anesthesia following which patients were shifted for orthogonal imaging of the applicator in situ followed by 2D brachytherapy treatment planning.

Brachytherapy planning was done as per the recommendations of ICRU 38 and treatment was delivered with High dose rate After loading technique using Ir 192 (Half life 73.8 days). A minimum interval of 1 week was given between two sittings of brachytherapy.

At the end of treatment, patients were discharged with dietary advice and advice on local care. Oral vitamins and an ointment to be applied in the vagina were prescribed for vaginal dilatation and to keep the vaginal cavity patent and prevent adhesive vaginitis.

GAMMA ANALYSIS

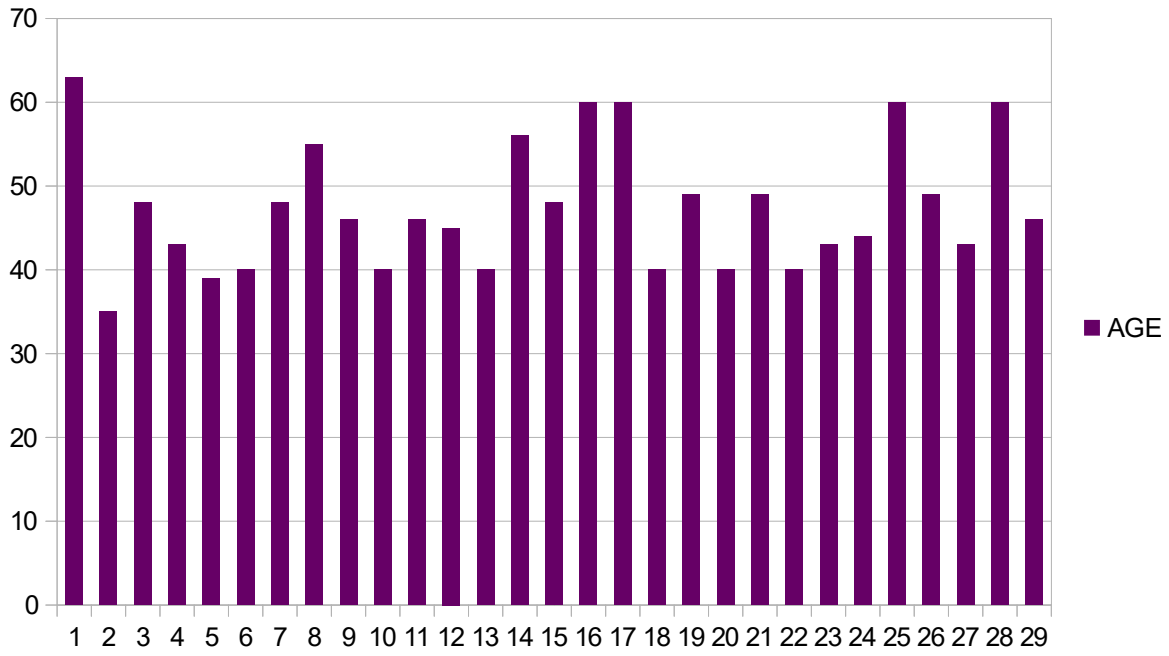
Patient specific QA (Quality assurance) is a fundamental step in treatment planning prior to treatment delivery, to confirm with accuracy that the planned dose is delivered to the patient and to identify errors in beam delivery. The commonly used QA is Gamma analysis which was introduced by Low et al. In this technique, the criteria used for evaluation was pass-fail criteria for both distance to agreement and dose difference. An acceptance criterion of 3 mm for distance to agreement and 3%

for dose difference with respect to maximum dose of the selected size was applied in the gamma analysis. The gamma passing rate is the percentage of the evaluated dose points that pass the above criteria when the passing criteria for gamma is less than or equal to 1. In our study the reference level of the gamma passing rate was between 95% and 100% but all plans had a gamma passing rate between 98% and 100%.

RESULTS

29 patients with FIGO Stage III.B cervical cancer were treated between September 2015 and July 2016 at Cancer Institute Adyar. The median age at diagnosis was 46 years. While 12 patients (41.3%) were below the age of 45, 17 patients (58.7%) were above the age of 45 with the oldest patient being 63 years.

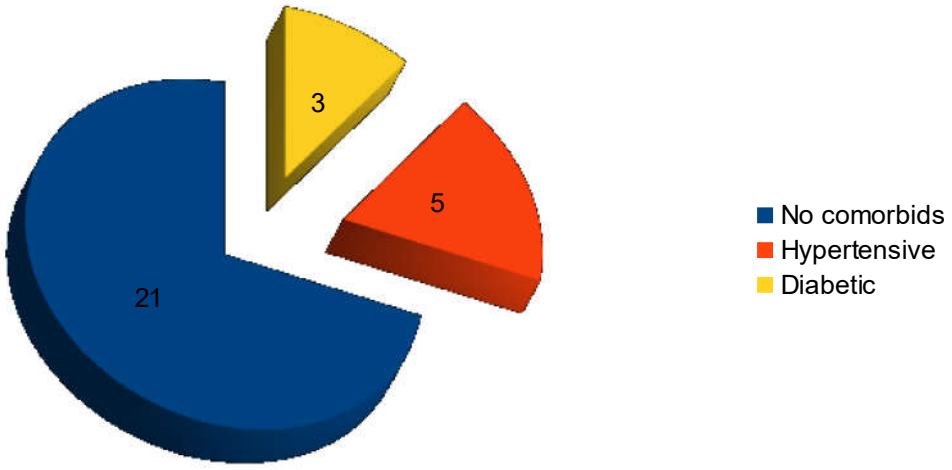
AGE DISTRIBUTION



- Median age – 46 years
- 41.3% ≤ 45 years
- 58.7% ≥ 45 years
- Oldest patient – 63 years

3 patients were diabetics on medication and blood sugars were monitored weekly after initial consultation with a diabetologist. 5 patients were hypertensives on medication and BP was monitored twice daily and was under control.

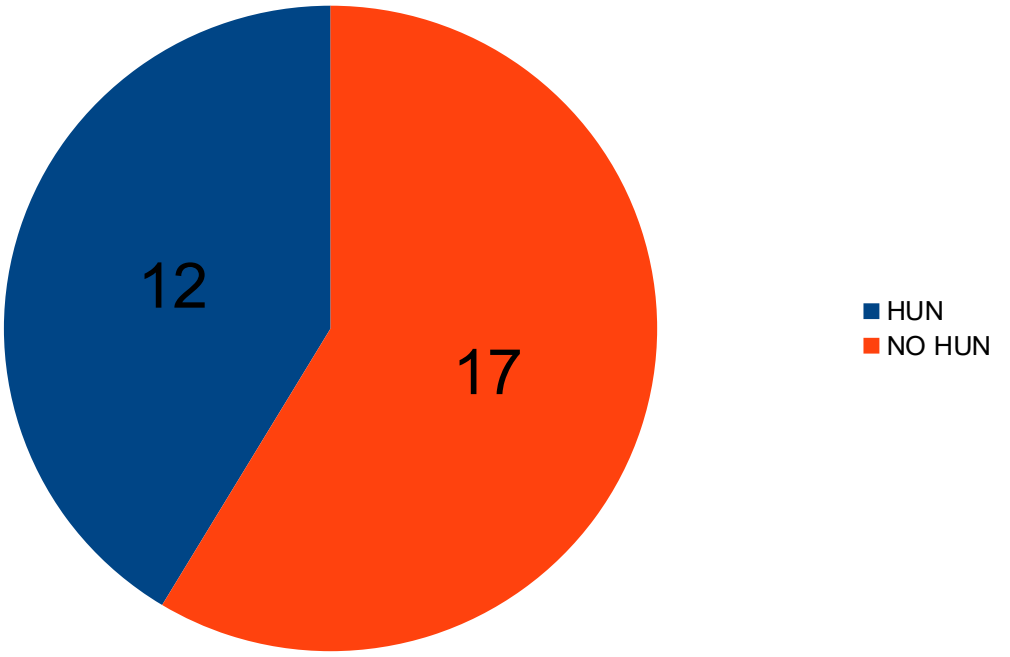
COMORBIDS



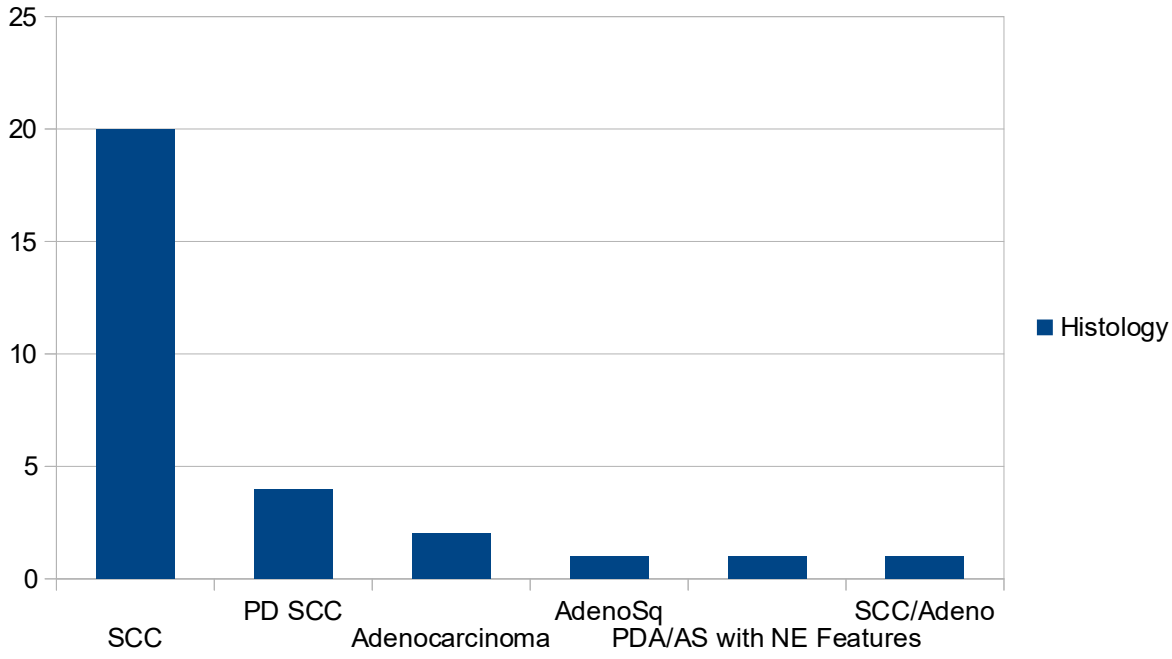
As expected Squamous cell carcinoma was the commonest histology. Other histologies included Poorly differentiated Squamous cell carcinoma (4 patients), Adenocarcinoma (2 patients), Adenosquamous carcinoma (1 patient), Poorly differentiated adenocarcinoma / adenosquamous carcinoma with neuroendocrine features (1 patient) and Squamous cell carcinoma/Adenocarcinoma (1 patient).

Among the 29 patients, 12 patients (41.3 %) had Hydroureteronephrosis and 17 patients had only pelvic side wall involvement.

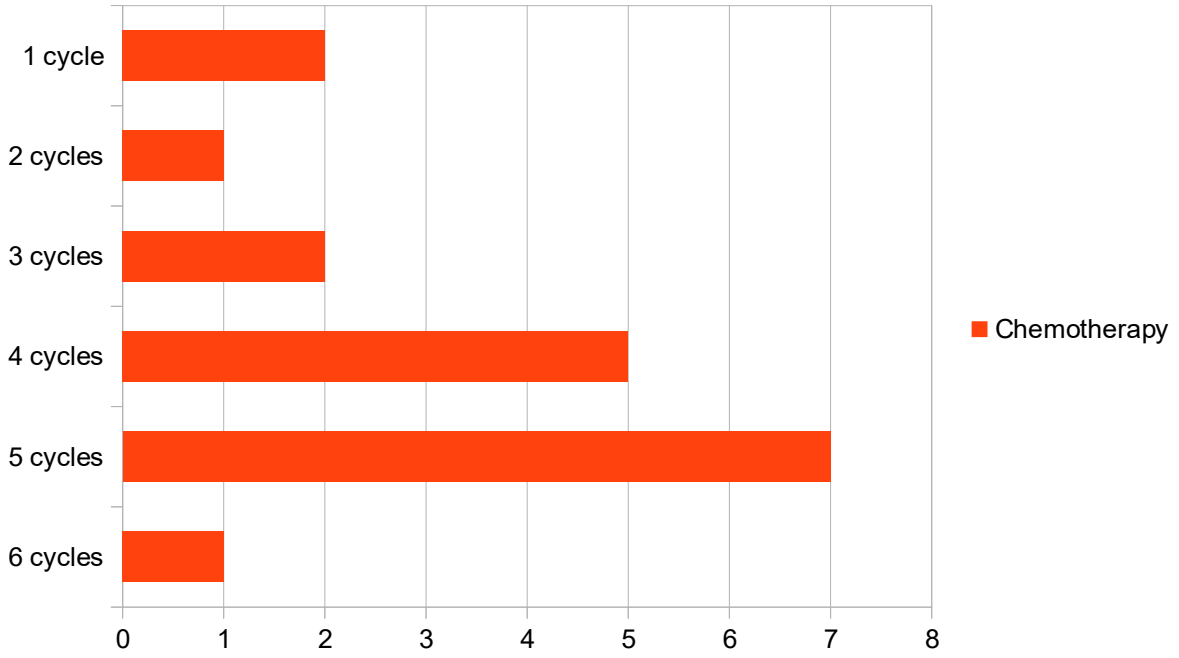
HYDROURETERONEPHROSIS AT PRESENTATION



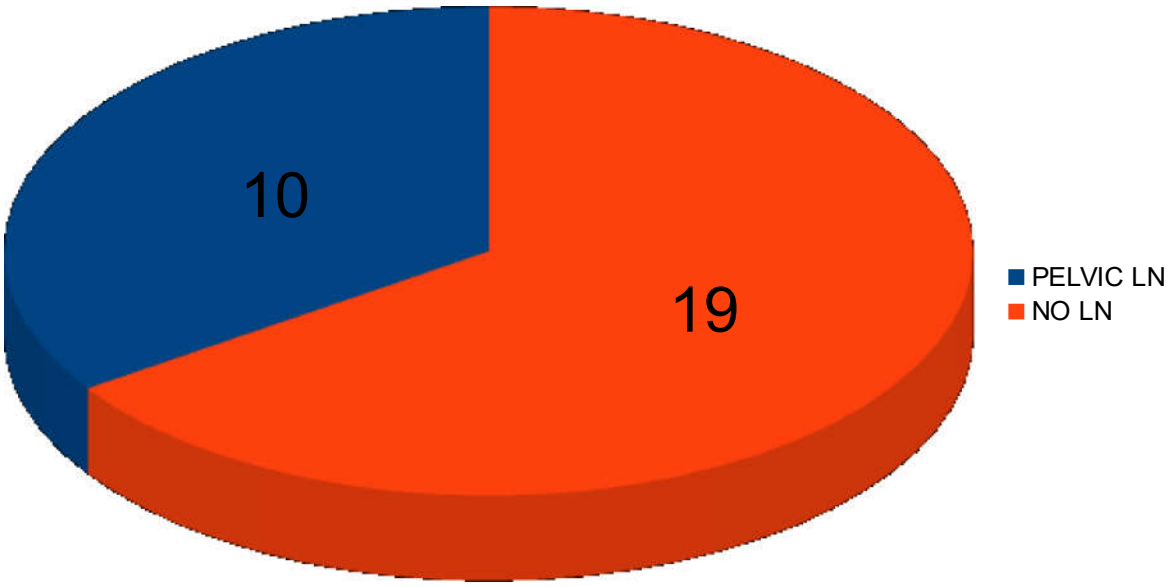
HISTOLOGY



Chemotherapy was delivered to 18 patients of whom only 8 patients (44.4%) completed the complete course of chemotherapy. Among the patients who received chemotherapy, 5 patients (27.7%) tolerated chemo well without any acute morbidity.



INVOLVEMENT OF PELVIC LYMPH NODES



GAMMA ANALYSIS FOR PLAN EVALUATION

All plans were evaluated with gamma analysis. The criteria used for evaluation was pass-fail criteria for both distance to agreement and dose difference with reference to maximum dose of selected slice. The parameters used were 3 mm distance to agreement and 3% dose difference with reference to maximum dose of selected slice. Among all patients the passing rate was between 98% and 100%.

The following table and images are that of a patient's gamma analysis in which 290 dose points were evaluated out of the total 442 dose points. All the 290 dose points passed within the given parameters which is a 100 % passing rate.

Gamma 2D - Parameters

3.0 mm Distance- To- Agreement
3.0 % Dose difference with ref. to max. dose of selected slice
Suppress dose below 10.0 % of max. dose of selected slice
Option "Use 2nd and 3rd pass" selected

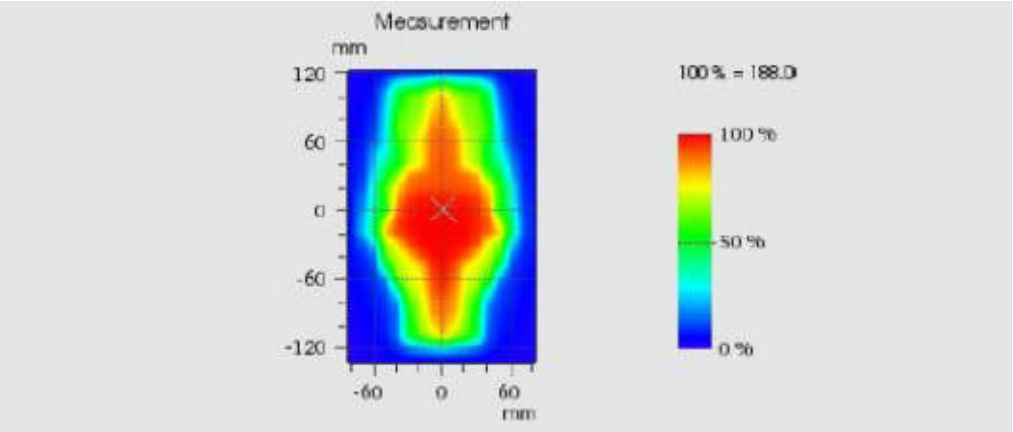
Statistics	
Number of Dose Points	442
Evaluated Dose Points	290 (65.6 %)
Passed	290 (100.0 %)
Failed	0 (0.0 %)
Result	100.0 % (Green)

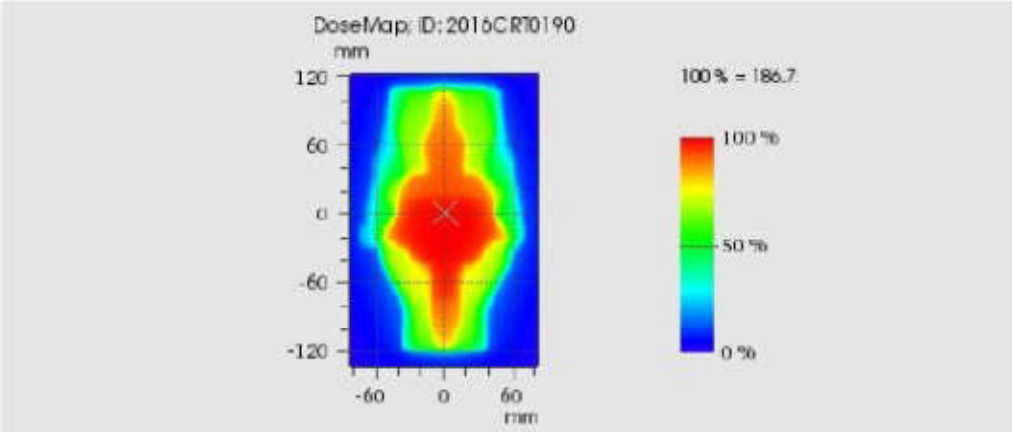
Gamma 2D	
Arithmetic Mean	0.286
Min (LR = 30.0 mm; TG = -10.0 mm)	0.010
Max (LR = 0.0 mm; TG = -120.0 mm)	0.785
Median	0.268

Absolute Difference	
Arithmetic Mean	3.343 cGy
Min (LR = 30.0 mm; TG = -10.0 mm)	0.058 cGy
Max (LR = 0.0 mm; TG = 110.0 mm)	21.581 cGy
Median	2.051 cGy

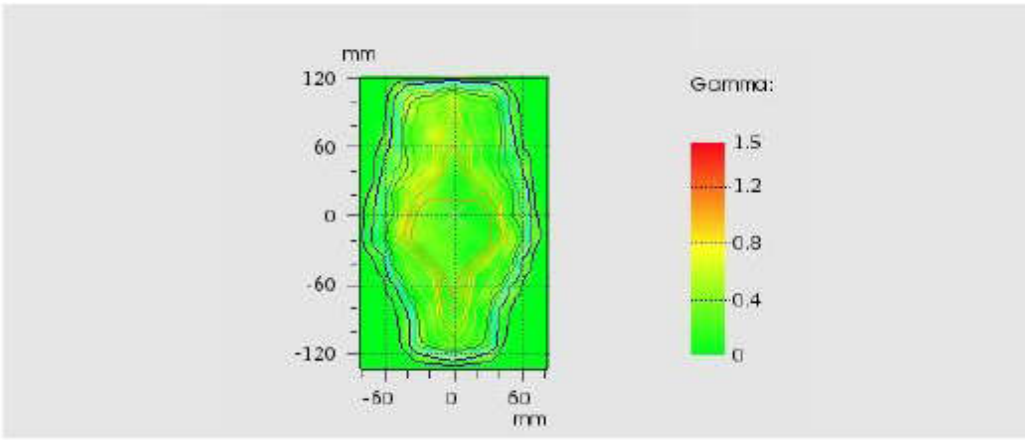
Settings	
Passing criteria	Gamma ≤ 1.0
Green	95.0 % to 100.0 %
Yellow	85.0 % to 95.0 %
Red	0.0 % to 85.0 %

COMPARISSON OF DOSE DISTRIBUTION SHOWING GAMMA ANALYSIS



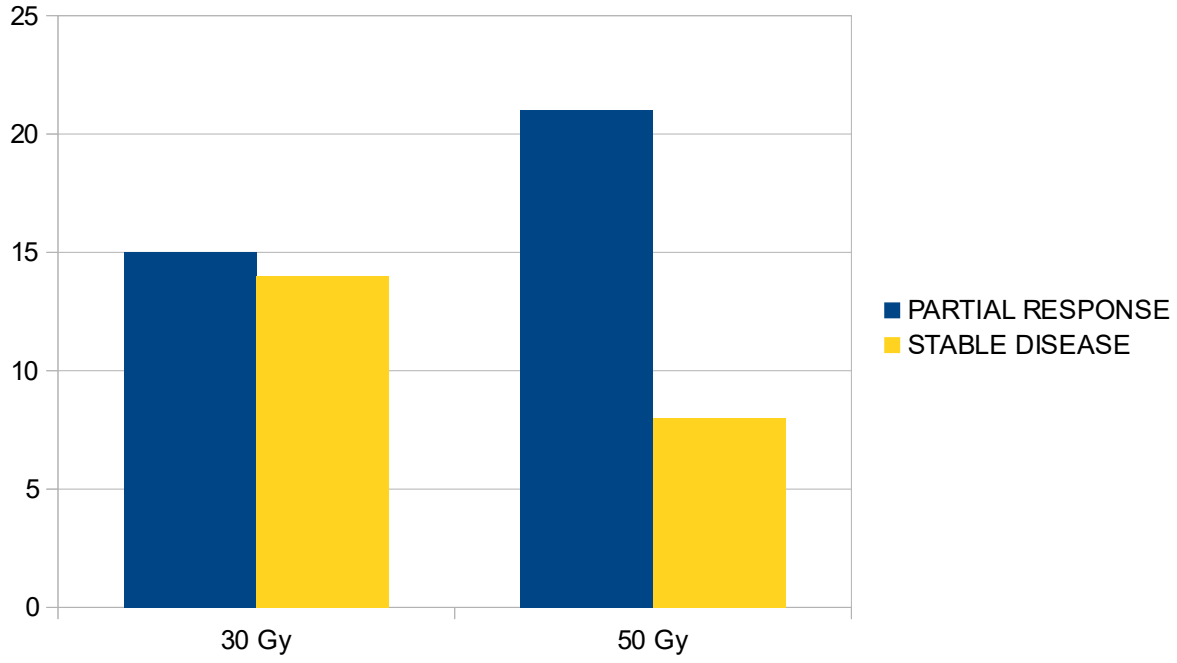


PASSING CRITERIA GAMMA < 1.0



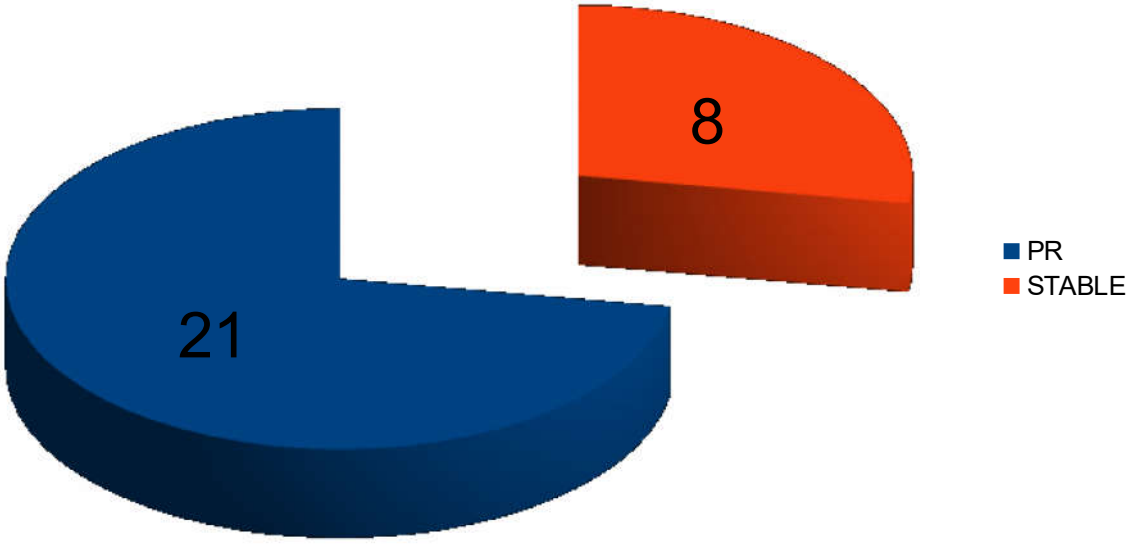
CLINICAL RESPONSE AT 30 Gy AND 50 Gy

At 30 Gy and 50 Gy response was assessed based on gynecological examination using RECIST ver 1.1. 15 patients (51.7%) had partial response (PR) and 14 patients (48.2%) had Stable disease at 30 Gy. At 50 Gy, 21 patients (72.4%) had partial response (PR) and 8 patients (27.5%) had stable disease.



VOLUMETRIC RESPONSE ASSESSMENT AT 36 Gy

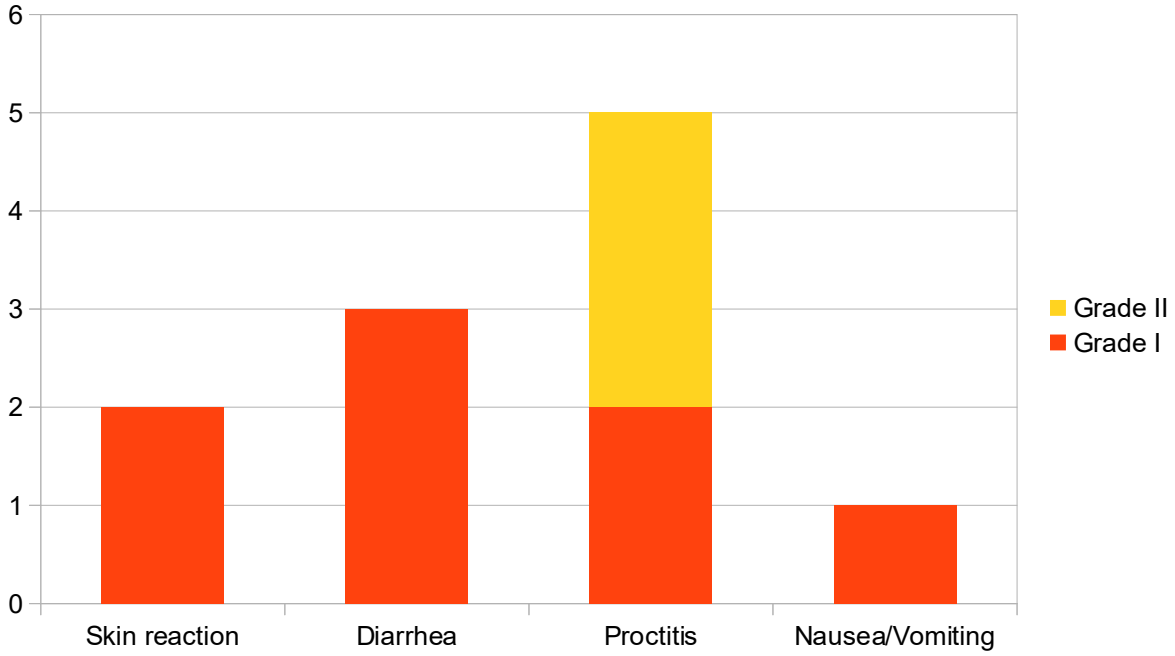
A repeat CT pelvis was done at 36 Gy for all patients. A volumetric assessment of the gross tumour was done in the CT that was done prior to the start of treatment which was compared volumetrically with the assessment at 36 Gy. 21 patients (72.4%) had partial response (PR) and 8 patients (27.5%) had stable disease.



The mean reduction in volume at 36 Gy was 61.79 %. Brachytherapy was performed in 27 patients (93.10%) of whom 26 received Intracavitary brachytherapy and 1 patient received vaginal brachytherapy followed by intracavitary brachytherapy in the next sitting.

RADIATION INDUCED ACUTE TOXICITY

Among 29 patients who received concomitant boost radiotherapy, 18 patients (62.06%) tolerated radiotherapy well without radiation related morbidity. Grade I proctitis was seen in 2 patients and Grade II proctitis in 3 patients. (Grade I/II proctitis 17.2%). 1 patient (3.4%) developed Grade II Nausea and vomiting. 2 patients (6.89%) developed Grade I skin reaction and 3 patients (10.3%) developed Grade I Diarrhea.

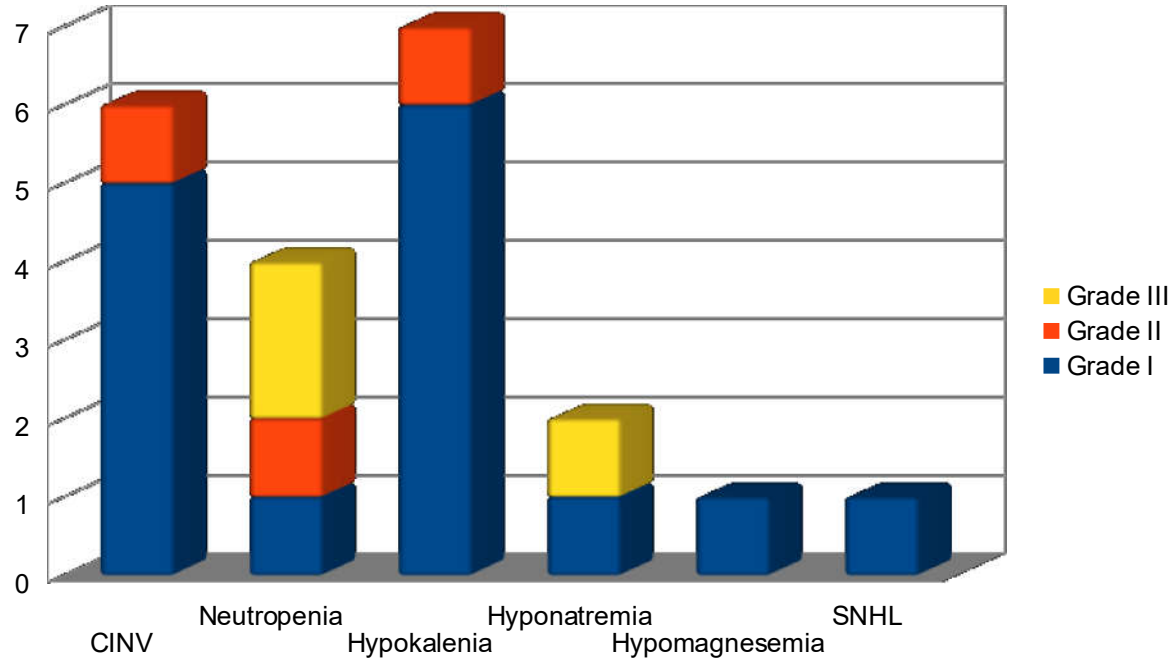


CHEMOTHERAPY INDUCED ACUTE TOXICITY

27.7% patients tolerated chemo well without any acute morbidity. Among the patients who received chemotherapy, 3 patients received Grade III acute morbidity which required radiotherapy to be pended.

5 patients developed Grade I Chemo induced nausea / vomiting(CINV) and 1 patient had Grade II CINV (Grade I/II CINV – 33.3%). Grade III Neutropenia was sees in 2 patients (11.1%) and Grade I/II neutropenia was seen in 2 patients (11.1%). While 5 patients (27.7%) developed Grade I Hypokalemia, 2 patients (11.1%) developed Grade II Hpokalemia. 1 patient (5.5%) developed Grade III Hyponatremia and 1 patient (5.5%) developed Grade 1 Hyponatremia. In this analysis, 1 patient (5.5%) had Cisplatin induced Sensory neural hearing loss and 1 patient (5.5%) had Hypomagnesemia.

CHEMOTHERAPY INDUCED TOXICITY



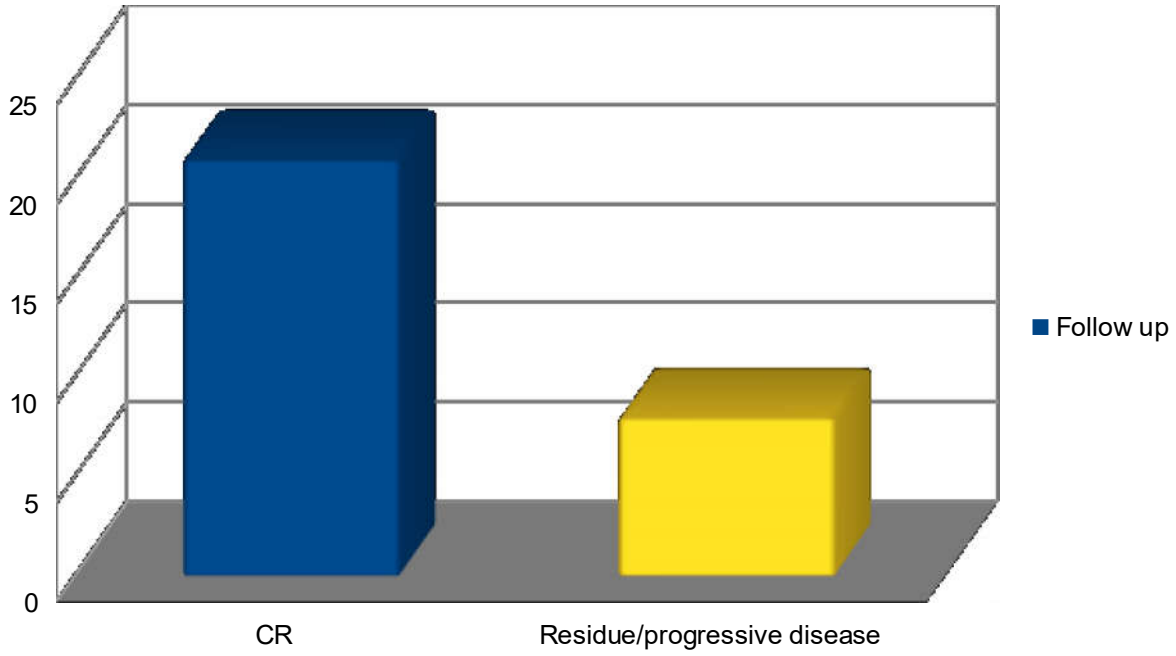
TREATMENT BREAKS:

11 Patients (37.9%) had treatment breaks of more than 10 days of whom 9 patients received chemotherapy but none of the treatment breaks were related to toxicity.

LOCAL CONTROL

After completion of treatment, patients were reassessed after 6 weeks. 21 patients (72.41%) had a complete response and 8 patients (27.5%) had residual or progressive disease. All 8 patients had local failure, among which 2 patients also had distant metastasis (para-aortic node / SCL node).

LOCAL CONTROL RATE



Adverse factors noted among patients who had residual or progressive disease

- 3 patients had histology other than Squamous cell carcinoma,
- 5 patients had HUN at presentation
- 4 patients had stable disease at 50 Gy.
- Brachytherapy not done in 3 patients in view of large volume disease and narrow vagina.
- 5 patients had treatment breaks of more than 10 days.

DISCUSSION

The incidence of locally advanced cervical cancer is on the decline around the globe but it is still a cause for concern as it contributes to the bulk of patients in developing countries. The West and European countries come up with emerging data and guidelines in management of early cervical cancers with advances in prevention and vaccination schedules as the bulk of their patients present in the early stages and only a few present in the locally advanced stage. Hence there is no necessity to improve the outcomes in this category of patients. This is not the case in our part of the world where majority of cases present in the locally advanced stage.

The outcome of early stage cervical is on the rise while the outcome of locally advanced FIGO Stage III.B disease has been static over the past decade with a modest 5 year survival of 45-50%. Thus, it is up to the developing countries like ours to come up with treatment strategies and guidelines to improve the outcome in this group of patients.

Radiotherapy has been a backbone in the management of cervical cancer since the early 1900s prior to which radical surgery and supportive management was the standard of care. Radiotherapy has revolutionized the management of cancer patients especially cervical cancer where Radiotherapy plays a role both in early and locally advanced disease status.

Several treatment strategies have been explored in the past to improve the outcome of locally advanced cervical cancer. This discussion will explore the treatment strategies that have been explored in the past and elaborate on the present

day strategy to improve local control.

The standard of care in managing locally advanced cervical cancer is Concurrent chemoradiation with weekly Cisplatin followed by intracavitary brachytherapy. This is based on the anouncement by NCI taking into account the 5 randomized studies. Various radiosensitizers have been investigated in the past from hydroxyureas to the present day Cisplatin. Hyperbaric oxygen therapy was extensively investigated prior to the advent of Chemotherapy in cervical cancer, which showed good local control rates in locally advanced stages, but the inconvenience in delivering hyperbaric oxygen and its toxicity profile have made it unpopular. Research into more convenient methods of delivering hyperbaric oxygen with randomized trials along side chemotherapy and computer based dose modification to account for increased sensitivity of normal tissue and tumour may be required to establish its role in locally advanced disease.

Mitomycin C was found to be more beneficial in the more advanced stages as opposed to Cisplatin, whose benefit seems to decline with increasing stage.

Hyperthermia has also shown promising results in locally advanced disease where it can be used as an alternative for patients who are not fit for chemotherapy but it needs to be more convenient with improvement in controllability and precision in treatment delivery rather than the present day emperical approach.

The role of brachytherapy in cervical cancer is unquestionable but execution of intracavitary brachytherapy in locally advanced III.B disease especially with residual parametrial invasion and narrow vagina may be challenging. Such cases may benefit

from interstitial brachytherapy. Not many institutes practice Interstitial brachytherapy due to the equipment and the expertise required in application and planning. Studies have shown that the outcome of Intracavitary and Interstitial brachytherapy are comparable in FIGO Stage III.B and IV.A with selection bias favoring intracavitary brachytherapy. There is no randomized trial comparing intracavitary and interstitial brachytherapy. Randomized trials need to substantiate the benefit of interstitial brachytherapy in advanced FIGO Stage III.B cervical cancer not amenable to intracavitary brachytherapy.

The pattern of failure in locally advanced FIGO Stage III.B cervical cancer is predominantly due to local failure. Various dose escalation strategies have been under investigation. Dose escalation may also cause normal tissue toxicity. Grade III toxicities with conventional fractionated radiotherapy has been seen in about 23% of patients. Thus, dose escalation needs to be carried out by reducing the normal tissue toxicity or reducing the dose to organs at risk.

IMRT has revolutionized treatment planing with a better therapeutic ratio even in pelvic tumours. In view of the close proximity of organs at risk like rectum, small bowel and bladder to the target volume, multiple beams are required to ensure adequate PTV coverage while sparing organs at risk.

There have been many studies that have used IMRT-SIB in managing cervical cancer. It is beyond doubt that IMRT and IMAT – SIB provide a superior therapeutic ratio and dose distribution while sparing normal tissues adequately.

This article aims to assess the feasibility of concomitant boost using forward

planned conformal therapy in locally advanced cervical cancer. The rationale behind this treatment is to exploit the benefits of SIB-IMRT by escalating the dose to the gross tumour, optimizing the dose to the elective pelvic field and sparing organs at risk in a lesser treatment time compared to conventional fractionation.

In our study, 1.9 Gy per day for a total of 26 days (TD 49.4 Gy) was delivered to the PTV_1 which included the whole pelvis apart from the boost volume(primary GTV) and 2.1 Gy per day for 26 days was delivered concomitantly to PTV_2 which is the primary GTV (boost volume).

In conventional fractionation 50.4 Gy is delivered in 28 days at 1.8 Gy per day. This produces a homogeneous distribution which delivers higher dose to the elective volume and comparatively lower dose to the primary GTV.

The B.E.D received by the elective volume in conventional fractionated radiotherapy and concomitant boost are 59.4Gy and 58.7 Gy respectively. The B.E.D received by the primary tumour (boost volume) in conventional fractionation and concomitant boost are 64.4 Gy (with parametrial RT) and 66.06 Gy respectively.

The overall treatment time in conventional fractionation in about 6-7 weeks of external beam radiotherapy, followed by weekly intracavitary brachytherapy. Treatment planning was done with forward planning conformal therapy using field in field technique.

While none of the patients developed radiation induced acute Grade III morbidity, 3 patients developed chemotherapy induced Grade III morbidity requiring treatment breaks.

11 patients (37.9%) had treatment breaks of more than 10 days of whom 9 patients received chemotherapy but none of the prolonged breaks were related to treatment. The most common cause was due to the natural calamity that Chennai witnessed.

Between November 9th and December 6th Chennai was affected by rain and witnessed the worst floods in over a century which cost over 500 lives in Tamil nadu damaging property worth up to rupees 100,000 crores. While most of the schools, colleges, offices and hospitals remained closed during this period, our institute stood tall to function on all days with radiotherapy treatment machines not being turned on for only 3 days. Unfortunately, the patients who had treatment breaks had them because they were stranded in their native place with no source of transport into the city.

At presentation 10 patients complained of severe lower abdominal pain or lower backache with a pain score of 5 or more. After completion of treatment only 1 patient persisted to have a pain score of 5 while none of the patients had bleeding / white discharge after completion of treatment.

18 patients did not develop radiation induced morbidity and tolerated treatment extremely well, while 12 patients developed radiation induce morbidity but none of them had Grade III toxicity. The rates of Proctitis, diarrhea and skin reaction were acceptable (17.2%, 10.3% and 6.89% respectively).

27.7% patients tolerated chemotherapy well without any acute morbidity. Grade III toxicity was seen in 3 patients (2 Neutropenia and 1 Hyponatremia)

requiring treatment breaks. The chemotherapy tolerability and the rate to GI morbidity were acceptable.

8 patients had local recurrence of whom 1 patient progressed to develop para-aortic nodes and another patient had progressed in the Left Supraclavicular region. The patients who had local recurrence had poor prognostic factors at presentation. 3 patients had histologies other than Squamous cell carcinoma and 3 patients had pelvic lymph nodes. 5 patients also had hydroureteronephrosis at presentation while 3 patients could not undergo intracavitary brachytherapy in view of large necrotic disease.

Locally advanced cervical cancer continues to be a burden in developing countries. FIGO Stage III.B cervical cancer includes a wide spectrum of characteristics which cannot be managed with the same approach. Individualized treatment approach that is tailor-made for particular characteristics and identification of those high risk characteristics is the need of the hour. Categorizing patients and identifying strategies that may be suitable for them is essential. With the available information it is safe to say that Brachytherapy improves local control which translates to survival but local control strategies like dose escalation are required to achieve parameters to eventually execute brachytherapy. Dose escalation with concomitant boost is feasible with acceptable acute toxicity but long term follow up and randomized trials are required to validate the local control. In cases where the response to external beam radiation is inadequate, Image guided and interstitial brachytherapy should be made available. Chemotherapy with Cisplatin is the standard

of care but benefit of cisplatin reduces with increasing stage and the percentage of patients with Stage III.B disease receiving Cisplatin may also be less due to the renal dysfunction that may be caused due to the disease. Hence other radiosensitizers and advances in Hyperthermia and hyperbaric oxygen therapy may be beneficial in this sub group of patients but further studies are required to substantiate this.

CONCLUSION

Concomitant boost using conformal technique is feasible in locally advanced cervical cancer with acceptable toxicity profile. The patients enrolled in this study were locally advanced Stage III.B with bulky disease. Although the local response rates with concomitant boost appears to be satisfactory, long term follow up and further randomized studies with standard chemoradiation is necessary before coming to any conclusion.

BIBLIOGRAPHY:

1. Ferlay J, Soerjomataram I, Ervik M, et al. GLO-BOCAN 2012 cancer incidence and mortalityworldwide: IARC cancerbase No. 11. Lyon,France: InternationalAgency for Research onCancer, 2013.

2. Three Year Report of the PBCRs (2012-2014). Comparison of Cancer Incidence and Patterns of all Population Based Cancer Registry. Available from: http://www.pbcrindia.org.

3.Cancer Incidence Trends in India Rajendra A. Badwe1,*, Rajesh Dikshit1, M. Laversanne2 and Fredie Bray2 Jpn J Clin Oncol 2014;44(5)401–407 doi:10.1093/jjco/hyu040

4.Sankaranarayanan R, Ferlay J. Worldwide burden of gynecological cancer: The size of the problem. Best Pract Res Clin Obstet Gynaecol. 2006;20:207–25. [PubMed: 16359925]

5.NationalCentreforDiseaseInformaticsandResearch,NationalCancer Registry Programme, ICMR. *Three Year Report of Population Based Reg- istries, 2009–2011*. Bangalore, India: NCDIR-NCRP (ICMR); 2014.

6.NationalCentreforDiseaseInformaticsandResearch,NationalCancer Registry Programme, ICMR. *Time Trends in Cancer Incidence Rates, 1982–2010*. Bangalore, India: NCDIR-NCRP (ICMR); 2013.

7.Kumar, Rani (2008). *Textbook of human embryology*. I.K. International.

8.Inderbir Singh, Pal GP. Human Embryology. 8th ed. India: Mac Millan Publishers Limited; 2007. p. 116.

9.Moore KL, Persaud TVN (1998) The urogenital system. In: Moore KL, Persaud TVN (eds) The developing human. Clinically oriented embryology, ed 6. WB Saunders, Philadelphia, pp 303–347

10.The spread and staging of cervical cancer. Gallup, D, *Glob. libr. women's med.,(ISSN: 1756-2228)* 2008; DOI 10.3843/GLOWM.10231

11. Nelson J, Macaset M, Tea L: The incidence and significance of para-aortic lymph node metastases in late invasive carcinoma of the cervix. Am J Obstet Gynecol 1974; 118:749.

12.Rose PG: Chemoradiotherapy for cervical can- cer. Eur J Cancer 38:270-278, 2002

13. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;26:5802–5812.

14.Nugent EK, Case AS, Hoff JT, et al. Chemoradiation in locally advanced cervical carcinoma: an analysis of cisplatin dosing and other clinical prognostic factors. *Gynecol Oncol* 2010;116:438–441.

15.Duenas-Gonzalez A, Zarba JJ, Patel F, et al. Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in

patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011;29:1678–1685.

16.Tseng CJ, Chang CT, Lai CH, et al. A randomized trial of concurrent chemoradiotherapy versus radiotherapy in advanced carcinoma of the uterine cervix. *Gynecol Oncol* 1997;66:52–58.

17.Souhami L, Gil RA, Allan SE, et al. A randomized trial of chemotherapy followed by pelvic radiation therapy in stage IIIB carcinoma of the cervix. *J Clin Oncol* 1991;9:970–977.

18.Kumar L, Kaushal R, Nandy M, et al. Chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer: a randomized study. *Gynecol Oncol* 1994;54:307–315

19.Watson ER, Halnan KE, Dische S, et al. Hyperbaric oxygen and radiotherapy: a Medical Research Council trial in carcinoma of the cervix. *Br J Radiol* 1978;51:879–587.

20.Dische S, Saunders MI, Sealy R, et al. Carcinoma of the cervix and the use of hyperbaric oxygen with radiotherapy: a report of a randomised controlled trial. *Radiother Oncol* 1999;53:93–98.

21.Duenas-Gonzalez A, Cetina L, Sanchez B, Gomez E, Rivera L, Hino- josa J, Lopez-Graniel C, Gonzalez-Enciso A, de la Garza J: A phase I study of carboplatin concurrent with radiation in FIGO stage IIIB cervix uteri carcinoma. *Int J Radiat Oncol Biol Phys* 2003, 56:1361-1365.

22.Katanyoo K, Tangjitgamol S, Chongthanakorn M, et al. Treatment outcomes of concurrent weekly carboplatin with radiation therapy in locally advanced cervical cancer patients. *Gynecol Oncol* 2011;123:571–576.

23.Roberts KB, Urdaneta N, Vera R, Vera A, Gutierrez E, Aguilar Y, Ott S, Medina I, Sempere P, Rockwell S, Sartorelli AC, Fischer DB, Fischer JJ: Interim results of a randomized trial of mitomycin C as an adjunct to radical radiotherapy in the treatment of locally advanced squamous-cell carcinoma of the cervix. *Int J Cancer* 2000, 90:206-223.

24.Calero F, Rodriguez-Escudero F, Jimeno J, Mendana J, Iglesias J, Murillo F, Ugalde F, Armas A, Rementeria A, Asins J: Single agent epirubicin in squamous cell cervical cancer. A phase II trial. *Acta Oncol* 1991, 30:325-327.

25.Van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Pu en WL, Hart AA. Com- parison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumours: a prospec ve, randomised, mul centre trial. Dutch Deep Hyperthermia Group. Lancet 2000;355:1119-25.

26.Harima Y, Sawada S, Nagata K, et al. Mutation of the PTEN gene in advanced cervical cancer correlated with tumor progression and poor outcome after radiotherapy. *Int J Oncol* 2001;18:493–497.

27.Lutgens L, van der Zee J, Pijls-Johannesma M, et al. Combined use of hyperthermia and radiation therapy for treating locally advanced cervix carcinoma. *Cochrane Database Syst Rev* 2010:CD006377.

28.The radium rays in therapeutics. In: Journal of the American Medical Association 39, 846 (1902).

29. Morton, WJ: Treatment of cancer by the x-ray, with remarks on the use of radium. In: The International Journal of Surgery 16, 295–300 (1903).

30. Abbe, T: Notes on the physiologic and the therapeutic action of radium. In: Washington Medical Annals 2, 363–76 (1904).

31.Tan PW, Koh VY, Tang JI (2015) Outpatient combined intracavitary and interstitial cervical brachytherapy: barriers and solutions to implementation of a successful programme - a single institutional experience. J Contemp Brachytherapy 7: 259-263.

32. Hsieh CH, Tien HJ, Hsiao SM, Wei MC, Wu WY, et al. (2013) Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result. Onco Targets Ther 6: 59-66.

33. Haas JA, Witten MR, Clancey O, Episcopia K, Accordino D, et al. (2012) CyberKnife Boost for Patients with Cervical Cancer Unable to Undergo Brachytherapy. Front Oncol 2: 25.

34. Gielda BT, Shah AP, Marsh JC, Smart JP, Bernard D, et al. (2011) Helical tomotherapy delivery of an IMRT boost in lieu of interstitial brachytherapy in the setting of gynecologic malignancy: feasibility and dosimetric comparison. Med Dosim 36: 206-212.

35. Gill BS, Lin JF, Krivak TC, Sukumvanich P, Laskey RA, et al. (2014) National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. Int J Radiat Oncol Biol Phys 90: 1083-1090.

36. Syed AM, Puthawala AA, Abdelaziz NN, el-Naggar M, Disaia P, et al. (2002) Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol 54: 67-78.

37. Syed AM, Puthawala AA, Abdelaziz NN, el-Naggar M, Disaia P, et al. (2002) Long-term results of low-dose-rate interstitial-intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol 54: 67-78.

38.Kim RY, Pareek P. Radiography-based treatment planning compared with computed tomography (CT)-based treatment planning for intracavitary brachytherapy in cancer of the cervix: analysis of dose-volume histograms. Brachytherapy. 2003;2:200–206. [PubMed]

39.Ling CC, Schell MC, Working KR, Jentzsch K, Harisiadis L, Carabell S, Rogers CC. CT-assisted assessment of bladder and rectum dose in gynecological implants. Int J Radiat Oncol Biol Phys. 1987;13:1577–1582. [PubMed]

40. Schoeppel SL, LaVigne ML, Martel MK, McShan DL, Fraass BA, Roberts JA. Three-dimensional treatment planning of intracavitary gynecologic implants: analysis of ten cases and implications for dose specification. Int J Radiat Oncol Biol Phys. 1994;28:277–283. [PubMed]

41. Stuecklschweiger GF, Arian-Schad KS, Poier E, Poschauko J, Hackl A. Bladder and rectal dose of gynecologic high-dose-rate implants: comparison of orthogonal radiographic measurements with in vivo and CT-assisted measurements. Radiology. 1991;181:889–894. [PubMed]

42. Kapp KS, Stuecklschweiger GF, Kapp DS, Hackl AG. Dosimetry of intracavitary placements for uterine and cervical carcinoma: results of orthogonal film, TLD, and CT-assisted techniques. Radiother Oncol. 1992;24:137–146. [PubMed]

43. Dimopoulos JC, Kirisits C, Petric P, Georg P, Lang S, Berger D, Pötter R. The Vienna applicator for combined intracavitary and interstitial brachytherapy of cervical cancer: clinical feasibility and preliminary results. Int J Radiat Oncol Biol Phys. 2006;66:83–90. [PubMed]

44. Pötter R, Dimopoulos J, Georg P, Lang S, Waldhäusl C, Wachter-Gerstner N, Weitmann H, Reinthaller A, Knocke TH, Wachter S, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. Radiother Oncol. 2007;83:148–155. [PubMed]

45.MacLeod C, Bernshaw D, Leung S, et al. Accelerated hyperfractionated radiotherapy for locally advanced cervix cancer. *Int J Radiat Oncol Biol Phys* 1999;44:519–524.

46.Viswanathan FR, Varghese C, Peedicayil A, et al. Hyperfractionation in carcinoma of the cervix: tumor control and late bowel complications. *Int J Radiat Oncol Biol Phys* 1999;45:653–656.

47.Komaki R, Pajak TF, Marcial VA, et al. Twice-daily fractionation of external irradiation with brachytherapy in bulky carcinoma of the cervix. Phase I/II study of the Radiation Therapy Oncology Group 88-05. Cancer. 1994 May 15;73(10):2619–2625. [PubMed]

48.Biswal BM, Ahmad NM, Hanafia ZA, Zakaria A, Othman NH, et al. (2011) Pilot Study on Continuous Hyperfractionated Accelerated Radiotherapy (CHART) and High Dose Rate Brachytherapy in Locally Advanced Cervical Cancer. J Cancer Sci Ther 3: 125-129. doi:10.4172/1948-5956.1000073.

49.Wu, Q., Manning, M., Schmidt-Ullrich, R., et al. The potential for sparing of parotids and escalation of biologically effective dose with intensity-modulated radiation treatments of head and neck cancers: a treatment design study. (2000) Int J Radiat On- col Biol Phys 46(1): 195-205.

50. Bos, L.J., Damen, E.M., de Boer, R.W., et al. Reduction of rectal dose by integration of the boost in the large- eld treatment plan for prostate irradiation. (2002) Int J Radiat Oncol Biol Phys 52(1): 254-65.

51. Vandecasteele, K., De Neve, W., De Gersem, W., et al. Inten- sity-modulated arc therapy with simultaneous integrated boost in the treatment of primary irresectablecervical cancer. Treatment planning, quality control, and clinical implementation. (2009) Strahlenther Onkol 185(12): 799-807.

52.Choy, D., Wong L.C., Sham, J., et al. Dose-tumor response of carcinoma of cervix: an analysis of 594 patients treated by radiotherapy. (1993) Gynecol Oncol 49(3): 311-17.

53. Lanciano, R.M., Martz, K., Coia, L,R., et al. Tumor and treatment factors improving outcome in stage III-B cervix can- cer. (1991) Int J Radiat Oncol Biol Phys 20(1): 95-100.

54. Niibe, Y., Hayakawa, K., Kanai, T., et al. Optimal dose for stage IIIB adenocarcinoma of the uterine cervix on the basis of biological effective dose. (2006) Eur J Gynaecol Oncol 27(1): 47-9.

55.Krebs, L., Maillard, S., Gaillot-Petit N., et al. Total radiation dose and overall treatment time are predictive for tumor steril- ization in cervical carcinoma treated with chemoradiation and pulsed-dose-rate brachytherapy. (2015) Brachytherapy 14(1): 16-22.

56.Dogan N, King S, Emami B, et al. Assessment of different IMRT boost delivery methods on target coverage and normal tissue sparing. Int J Radiat Oncol Biol Phys 2003;57:1480–91.

57. Fogliata A, Bolsi A, Cozzi L, Bernier J. Comparative dosimetric evaluation of the simultaneous integrated boost with photon inten- sity modulation in head and neck cancer patients. Radiother Oncol 2003;69:267–75.

58. Mohan R, Wu Q, Manning M, Schmidt-Ullrich R. Radiobiological considerations in the design of fractionation strategies for intensity- modulated radiation therapy of head and neck cancers. Int J Radiat Oncol Biol Phys 2000;46:619–30.

59.Girinsky T, Rey A, Roche B, et al. Overall treatment time in advanced cervical carcinomas: a critical parameter in treatment outcome. Int J Radiat Oncol Biol Phys 1993;27:1051-6.

60.Lanciano RM, Pajak TF, Martz K, et al. The influence of treatment time on outcome for squamous cell cancer of the uterine cervix treated with radiation: a patterns-of-care study. Int J Radiat Oncol Biol Phys 1993;25:391-7.

61.Sugawara T, Mizutani Y, Nakazawa M. The effect of treatment time on pelvic recurrence in patients with stage III-IV uterine cervix cancer. J Jpn Soc Ther Radiol Oncol 1993;5:117-123.

62.Perez CA, Grigsby PW, Castro-Vita H, et al. Carcinoma of the uterine cervix. I. Impact of prolongation of overall treatment time and timing of brachytherapy on outcome of radiation therapy. Int J Radiat Oncol Biol Phys 1995;32:1275-88.

63.Nishimura Y, Okajima K, Hiraoka M. Optimal overall treatment time in fractionated radiotherapy for head and neck cancers, esophageal cancer, and uterine cervical cancer. J Jpn Soc Ther Radiol Oncol 1996;8:303-315.

64.Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131-46.

65.Petereit DG, Sarkaria JN, Chappell R, et al. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Oncol Biol Phys 1995;32:1301-1307.

66.Fyles AW, Pintilie M. Prognostic factors in patients treated cervix cancer treated by radiation therapy: results of multiple regression analysis. Radiotherapy Oncol.1995; 35:107-17.

67.Petereit DG, Sarkaria JN, Chappell R, Fowler JF, Hartmann TJ. The adverse effect of treatment prolongation in cervical carcinoma. Int J Radiat Onco Biol Phys 1995; 32:1301-7.

68.Abhijit Mandal, Anupam Kumar Ashtana, Lalit Mohan Aggarwal., Clinical Significance of cumulative biological effective dose and overall treatment time in the treatment of carcinoma cervix. Journal of Medical Physics, Vol. 32 No.2, 2007

69."The effect of treatment prolongation in treatment of cervical cancer patient" – treated patients at rural center in India" Sanjay Singh Chandel1, K K singh2, A K Nigam3, Rajesh Singh Baghel4 IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 9, Issue 2 (Jul.- Aug. 2013), PP 70-75

70.Yang Y, Xing L. Optimization of radiotherapy dose-time frac- tionation with consideration of tumor specific biology. Med Phys 2005;32:3666–77

71. Fowler JF. Biological factors influencing optimum fractionation in radi- ation therapy. Acta Oncol 2001;40:712–7

72.Withers HR, Taylor JMG, Maciejewski B. The hazard of acceler- ated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988;27:131–46.

73. Withers HR, Peters LJ, Taylor JMG, et al. Local control of carcinoma of the tonsil by radiation therapy: an analysis of patterns of fractionation in nine institutions. Int J Radiot Oncol Biol Phys 1995;33:549–62.

74.Fowler J. Dose–responses curves for organ function in cell survival. Br J Radiol 1983;56:497–500.

75.Trans Tasman Radiation Oncology Group (TROG)Denham JW, Walker QJ, Lamb DS, Hamilton CS, O'Brien PC, Spry NA. Mucosal regener- ation during radiotherapy. Radiother Oncol 1996;41:109–18.

76.Tarnawski R, Fowler J, Skladowski K, et al. How fast is repopulation of tumor cells during the treatment gap? J Radiot Oncol Biol Phys 2002;54:229–36.

77.Nguyen LN, Ang KK. Radiotherapy for cancer of the head and neck: altered fractionation regimes. Lancet Oncol 2002;3:693–701.

78.Stewart FA, van der Kogel AJ. Proliferative and cellular organization of normal tissues. In: Steel GG, editor. Basic clinical radiobiology.
London: Arnold; 1997. p. 24–9.

79.Hornsey S, Myers R, Coultas PG, Rogers MA, White A. Turnover of proliferative cells in the spinal cord after X irradiation and its relation to time-dependent repair of radiation damage. Br J Radiol 1981;54:1081–5.

80.Dorr W, Hendry JH. Consequential late effects in normal tissues. Radio- ther Oncol 2001;61:223–31.

81.Robertson AG, Robertson C, Boyle P, Sysmonds RP, Wheldon TE. The effect of differing radiotherapeutic schedules on the glottic carcinoma of the larynx. Eur J Cancer 1993;29:501–10.

82.Hall, Eric J. Radiobiology for the Radiologist. Hagerstown, Md. :Medical Dept., Harper & Row, 1973. Print.

83.Fowler JF, Tomè WA, Fenwick JD, Mehta MP. A challenge to tra- ditional radiation oncology. Int J Radiat Oncol Biol Phys 2004;60: 1241–56.

84.Haque, W.M., et al. Simul- taneous Integrated Boost using Confor- mal Radiation Therapy for Treatment of Cervical Cancer. (2016) Intl J Cancer Oncol 3(1): 1- 7.

85.Herrera et al.: Retrospective feasibility study of simultaneous integrated boost in cervical cancer using tomotherapy: the impact of organ motion and tumor regression. Radiation Oncology 2013 8:5.

86.Concomitant boost plus large-field preoperative chemoradiation in locally advanced uterine cervix carcinoma: Phase II clinical trial final results (LARA-CC-1) Macchia, Gabriella et al.

Gynecologic Oncology , Volume 125 , Issue 3 , 594 - 599

87.Vandecasteele, K., De Neve, W., De Gersem, W. et al. Strahlenther Onkol (2009) 185: 799. doi:10.1007/s00066-009-1986-8

88.Kavanagh BD, Gieschen HL, Schmidt-Ullrich RK, et al. A pilot study of concomitant boost accelerated superfractionated radiotherapy for stage III cancer of the uterine cervix. *Int J Radiat Oncol Biol Phys* 1997;38:561–568.

89.Kluetz PG, Chingos DT, Basch EM, Mitchell SA. Patient-Reported Outcomes in Cancer Clinical Trials: Measuring Symptomatic Adverse Events With the National Cancer Institute's Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

Am Soc Clin Oncol Educ Book 2016; 35:67.

90.Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).
(Eur J Cancer 2009; 45: 228-47)
91.Zur Hausen H, de Villiers EM, Gissmann L. Papillomavirus infections and human genital cancer. Gynecol Oncol. 1981;12:S124-8
92.Zheng ZM,Baker CC.Papillomavirus genome structure,expression and post-transcriptional regulation.Frontiers in Bioscience.2006;11:2286-302.
93.Perez and Brady's,Principles and practice of radiation oncology,sixth edition,Chapter 69,pg 1356.
94.Munoz et al.N Engi J Med 2003;348:518-527
95.McCormack M, Thomas H: A phase Ib study of gemcitabine (GEM) and concurrent radiotherapy (RT) in carcinoma of the cervix. *Ann Oncol* 2000, 11:88-89.
96.Cetina L, Rivera L, Candelaria M, de la Garza J, Duenas-Gonzalez A: Chemoradiation with gemcitabine for cervical cancer in
patients with renal failure. *Anticancer Drugs* 2004, 15:761-766.
97. Alvarez AM, Mickiewicz E, Roth B, Bonomi M, Brosio C, Porcella H, Rodger J, Menendez P, Giglio R, de Dios D, Cinat G, Lizos S: Feasi- bility of accelerated radiotherapy (Rt) concurrent with low dose biweekly gemcitabine (G) and cisplatin (C) in locally advanced cervical carcinoma (LACC) [abstract]. *Procc ASCO* 2001, 20:100a.

98.Zarba JJ, Jaremtchuk AV, Gonzalez Jazey P, Keropian M, Castagnino R, Mina C, Arroyo G: A phase I-II study of weekly cisplatin and gemcitabine with concurrent radiotherapy in locally advanced cervical carcinoma. *Ann Oncol* 2003, 14:1285-1290.

99.Schefter TE, Winter K, Kwon JS, et al. A phase II study of bevacizumab in combination with definitive radiotherapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma: preliminary results of RTOG 0417. *Int J Radiat Oncol Biol Phys* 2012;83:1179–1184.

100.Haie C, Pejovic MH, Gerbaulet A, et al. Is prophylactic para-aortic irradiation worthwhile in the treatment of advanced cervical carcinoma? Results of a controlled clinical trial of the EORTC radiotherapy group. *Radiother Oncol* 1988;11:101–112.

101.Huang EY, Wang CJ, Chen HC, et al. Multivariate analysis of para-aortic lymph node recurrence after definitive radiotherapy for stage IB-IVA squamous cell carcinoma of uterine cervix. *Int J Radiat Oncol Biol Phys* 2008;72:834–42.