"COMPARISON OF V10 AND V20 OF BONE ARROW IN CARCINOMA CERVIX PATIENTS RECEIVING RADIATION WITH BONE MARROW SPARING (BMS) – IMRT, IMRT , 3DCRT, AND 4 FIELD BOX TECHNIQUE "

DISSERTATION

Submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

in partial fulfilment of the requirement

for the award of the degree of

DOCTOR OF MEDICINE

in

RADIOTHERAPY

by

NISHA ELIZA THOMAS

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CHRISTIAN MEDICAL COLLEGE

VELLORE - 632004

APRIL – 2015

Certificate

I Nisha Eliza Thomas, PG Registrar ,Department of Radiation therapy ,Christian Medical College Vellore hereby declare that the dissertation titled **" Comparison of V10 and V20 of bone marrow in carcinoma cervix patients receiving radiation with Bone Marrow Sparing (BMS) –IMRT, IMRT , 3DCRT, and 4 field box technique"** is a bonafide work done by me for partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2015.

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This is to certify that the dissertation entitled **"Comparison of V10 and V20 of bone marrow in carcinoma cervix patients receiving radiation with Bone Marrow Sparing (BMS) –IMRT, IMRT , 3DCRT, and 4 field box technique"** is an original work by Dr. Nisha Eliza Thomas in partial fulfilment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2015.

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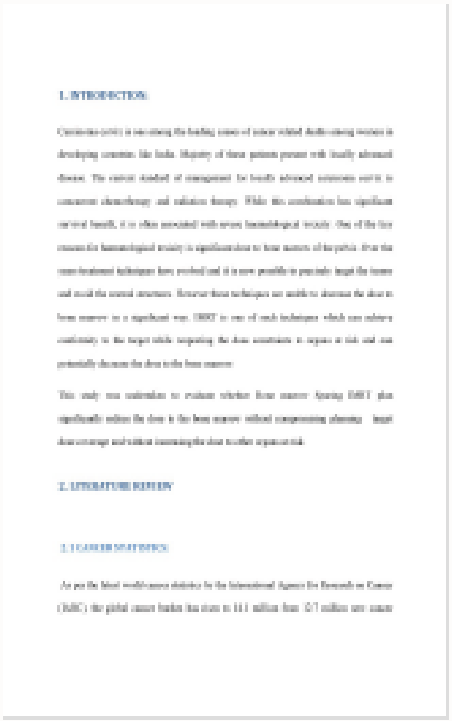

1. INTRODUCTION

2. LITERATURE REVIEW

2.1 CANCER STATISTICS

bone marrow sparing imrt in carcinoma cervix

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Dr. Nisha Eliza Thomas
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Comparison of V10 (the volume of bone marrow receiving >10 Gy0 and V 20 (the volume of bone marrow receiving >20Gy) of bone marrow in carcinoma cervix patients receiving radiation with bone marrow sparing (BMS) IMRT, IMRT and 3 DCRT and 4 field box technique.
Dr. Nisha Eliza Thomas, PG Registrar, Radiotherapy, Dr. Thomas Samuel Ram, Radiotherapy, Dr. Selvamani B, Mrs. Y. Retna Ponmalar, Radiotherapy.

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The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Comparison of V10 (the volume of bone marrow receiving >10 Gy0 and V 20 (the volume of bone marrow receiving >20Gy) of bone marrow in carcinoma cervix patients receiving radiation with bone marrow sparing (BMS) IMRT, IMRT and 3 DCRT and 4 field box technique." on April 16, 2013.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Cvs of Drs. Nisha Eliza Thomas,Thomas Samuel Ram, Selvamani B, Mrs. Y. Retna Ponmalar.
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Dr. Anup Ramachandran	Ph D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences	Internal
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We approve the project to be conducted as presented.

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3 of 3

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ACKNOWLEDGEMENT

I would like to thank Almighty Lord who worked through various people and circumstances ,whose continual goodness never did leave me.

I express my deep gratitude to my guide Dr.Thomas Samuel Ram for his great patience and kindness with which he has guided me in completing this thesis. He is a constant source of inspiration for a high standard in education and continually challenged us to keep up to date with the latest developments in the field of Radiation Oncology.

I thank Dr. Selvamani.B for guiding me in the write up and in designing the study and who was patient with me where I was ignorant. She has always been a source of constant motivation to do excellently, especially in maintaining a high standard of patient care.

I would like to thank Mrs. Ratna Ponmalar, who is my co -guide from the department of Medical Physics for helping me in planning cases . Special thanks to Mr.Sivasakthi.A for his patient and untiring help.

A special mention of all my family members especially my beloved husband Dr.Renjit John Mathew who always prayed and worked with me in completing this work.

Contents

ABSTRACT TITLE :Comparison of V10 and V20 of bone marrow in carcinoma cervix patients receiving radiation with Bone Marrow Sparing (BMS)–IMRT, IMRT , 3DCRT, and 4 field box technique.

DEPARTMENT: Ida B Scudder Cancer Centre, Department of Radiation Oncology

NAME OF THE CANDIDATE: Nisha Eliza Thomas

DEGREE&SUBJECT :MD Radiotherapy

NAME OF THE GUIDE Thomas Samuel Ram

OBJECTIVE:

To assess the feasibility of modelling Bone Marrow Sparing IMRT without compromising the dose to the planning target volume and without increasing the dose to other organs at risk.

METHODS:CT Data set from 16 women with Carcinoma cervix treated in our institution from July 2013 to January 2014 using 3D CRT or IMRT were selected for the study. For all the 16 patients ,4 plans ;four field box,3DCRT, IMRT and Bone Marrow Sparing IMRT were modeled.Bone marrow was contoured using free hand technique in each CT cut including entire L5 vertebral body, sacrum, coccyx, ileum, ischium, pubis and femoral head extending down till the level of ischial tuberosity. Constraints to the organs at risk and the target volume were prescribed as per the standard RTOG guidelines.Bone Marrow constrain was V10< 95% and V 20< 76%.Dose volume histogram,isodose curves, dose colour wash and presence of hot spot were used for plan evaluation. Chi-square test was used for statistical analysis.

RESULTS

Out of the 16 plans with BMS IMRT, 15 plans achieved the desired goals while respecting the bone marrow constrains. This gave a 93.8% chance of achieving this constrain with a p value of .001.The The mean V10 and V20 to bone marrowin our study was 89.58% and 69.99%. In case of femoral head, it was observed that the constrain was attained for 12/16 patients with 4 FIELD BOX, 12/16 patients for 3DCRT, 16/16 patients with IMRT and 16/16 patients with BMS – IMRT.The bowel bag constrain could be achieved for 13/16 patients with 4 FIELD BOX plan, 12/16 patients with 3DCRT plan, 16/16 patients with IMRT plan an 16/16 patients with BMS – IMRT plan .Bladder and rectum constrains could not be achieved in any of the plans.

Bone Marrow Sparing IMRT is a feasible option for the management of locally advanced carcinoma cervix as it helps in reducing the dose received by the bone marrow without compromising the planning target volume coverage and without increasing the dose to other normal organs at risk.

1. INTRODUCTION:

Carcinoma cervix is one among the leading causes of cancer related deaths among women in developing countries like India. Majority of these patients present with locally advanced disease. The current standard of management for locally advanced carcinoma cervix is concurrent chemotherapy and radiation therapy.While this combination has significant survival benefit, it is often associated with severe haematological toxicity.One of the key reasons for haematological toxicity is significant dose to bone marrow of the pelvis .Over the years treatment techniques have evolved and it is now possible to precisely target the tumor and avoid the normal structures.However these techniques are unable to decrease the dose to bone marrow in a significant way.IMRT is one of such techniques which can achieve conformity to the target while respecting the dose constraints to organs at risk and can potentially decrease the dose to the bone marrow.

This study was undertaken to evaluate whether Bone marrow Sparing IMRT plan significantly reduce the dose to the bone marrow without compromising planning target dose coverage and without increasing the dose to other organs at risk.

2.AIM

Dosimetric comparison between Bone marrow sparing Intensity modulated radiotherapy (BMS IMRT) , Intensity modulated radiotherapy (IMRT), Three dimensional conformal

radiation therapy (3D CRT) and Conventional four field box technique in the treatment of carcinoma cervix and evaluate its role in sparing bone marrow .

3.OBJECTIVES

1. Comparison of V10 and V20 of bone marrow in carcinoma cervix patients with BMS IMRT , IMRT , 3D CRT and four field box technique
2. Comparison of dose volume sparing effect on other normal pelvic organs
3. Comparison of dose coverage to the planning target volume

4. LITERATURE REVIEW

4.1 CANCER STATISTICS:

As per the latest world cancer statistics by the International Agency for Research on Cancer (IARC), the global cancer burden has risento 14.1 millionfrom 12.7 million new cancer cases and cancerdeaths rises from 7.6 million to 8.2 million from 2008 to 2012 . With more than 5 lakhincident cases peryear, cervical cancer is currently the fourth most common cancer affecting women worldwide. According to the SEER Data base in US, the incidence rate of cervical cancer was found to be 7.9 per 1 lakh women per year for all the races and 6.6 per 1 lakh women for Asia and Pacific region(1).

In case of carcinoma cervix, approximately 70% of the cases are reported from developing countries(1).Among the developing countries, one fifth of new cases are diagnosed in

India.The reasons for this can be mainly attributed to the etiological factors, low socioeconomic status and lack of screening programs.

In India the most common malignancy that affects women is carcinoma cervix and most of our patients present with advance disease.As per the various cancer registries during the year 1990-1997, the cervical cancer incidence was found to be varying from 10.9 to 65.4(2). According to the ICMR-Population based cancer registry-Chennai, in Chennai the relative proportion of cervical cancer is found to be 18.5 % of all cancers in females, with crude ratio of 20.3 and age adjusted ratio of 22.3 incidence rate per 1 lakh person(3).

4.2 ANATOMY:

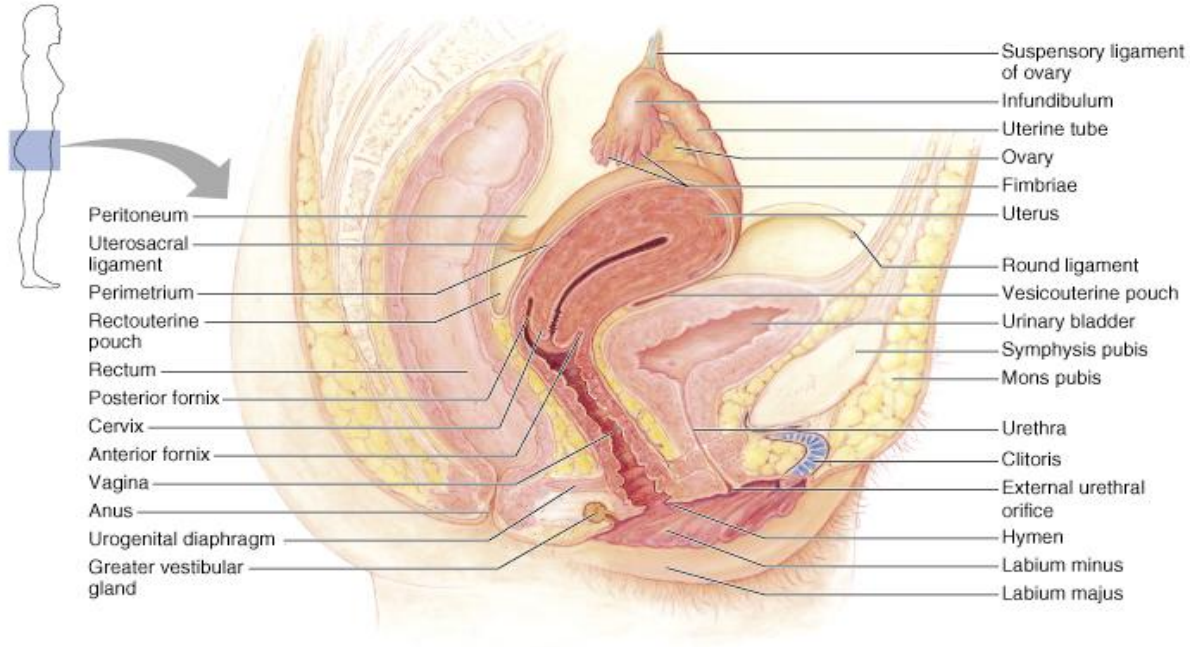


Fig 1.1: Anatomy of the Uterine Cervix

Uterus is a hollow,pear shaped; muscular organ usually in an anteverted position, located in the pelvis. It is bounded anteriorly by the urinary bladder and posteriorly by rectum. It is

covered by the peritoneum partially at the fundus and posterior aspect. The inferior most part of the uterus is called uterine cervix .The cervix measures approximately 3 cm in length and 3 cm in breadth. It is mainly a fibrous organ. The cervix itself is divided into a supravaginal portion which is above the vagina and vaginal portion which protrudes into the vagina.

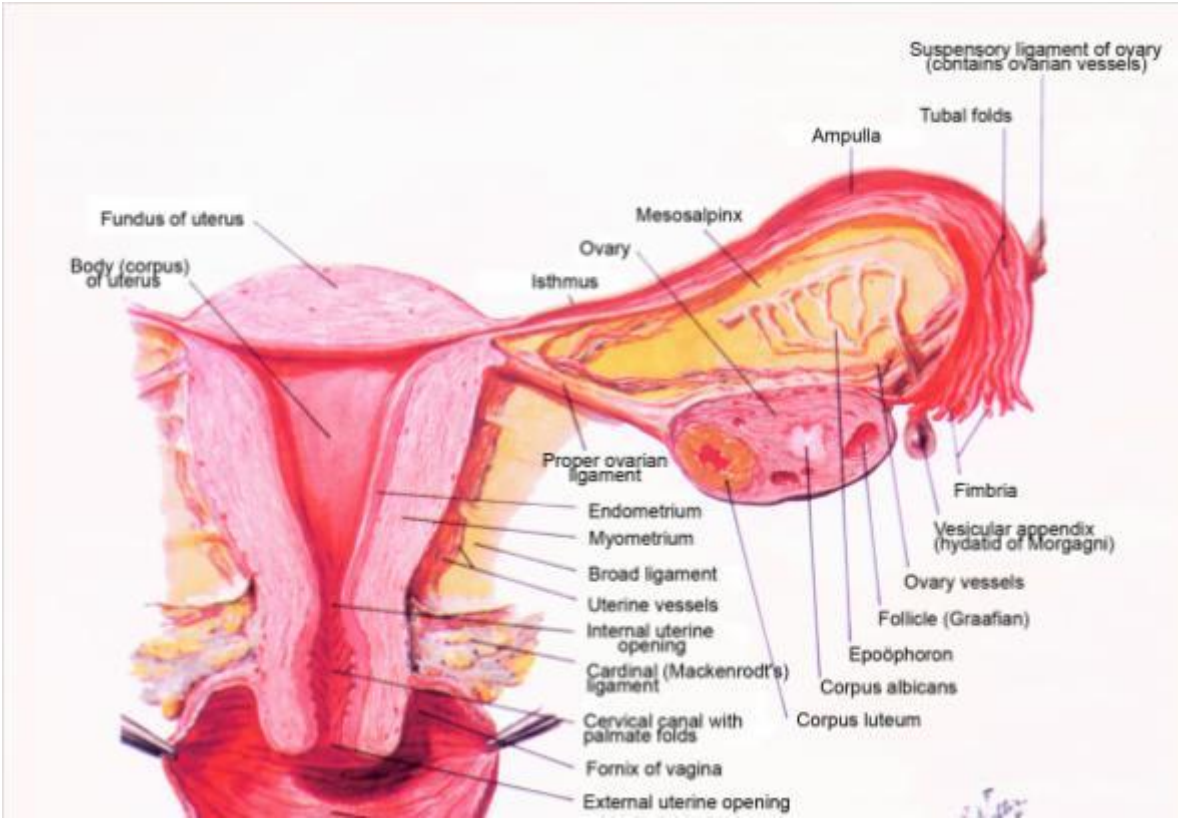


Fig 1.2: Uterus and Adnexa

Uterus is attached to the surrounding structures in the pelvis by means of two ligaments, broad ligament and the round ligament. The broad ligament is composed of two layers of peritoneum.It extends from the lateral pelvic wall to the lateral margin of the uterus.It encloses the parametrium as it reaches the uterus.It contains the fallopian tube. The broad ligament follows the plane of pelvic floor inferiorly and ends in the upper portion of the vagina medially.

The round ligament is a band of smooth muscle and connective tissue .It contains small vessels and nerves. It extends horizontally from its attachment in the Anterolateral aspect of the uterus to the lateral pelvic wall. From there the cord ascends, reaches more laterally to reach the abdominoinguinal ring through which it leaves the abdomen to traverse the inguinal canal and terminates in the superficial fascia.

The utero sacral ligaments are paired supports for the lower uterus. It runs along the recto-uterine-peritoneal fields connecting uterus to the sacrum. The cardinal ligament, otherwise named as the transverse cervical ligament or Mackenrodt`s ligament arises from the upper lateral margins of the cervix and insert into the fascia covering the pelvic diaphragm.

Lymphatic supply: Uterine cervix has a rich lymphatic supply that drains mainly into the paracervical lymphnodes.From there it drains into the external iliac lymphnodes and the hypo gastric lymph nodes.Finally the pelvic lymph nodes drain into the common iliac lymph nodes andthe Paraaortic lymph nodes.

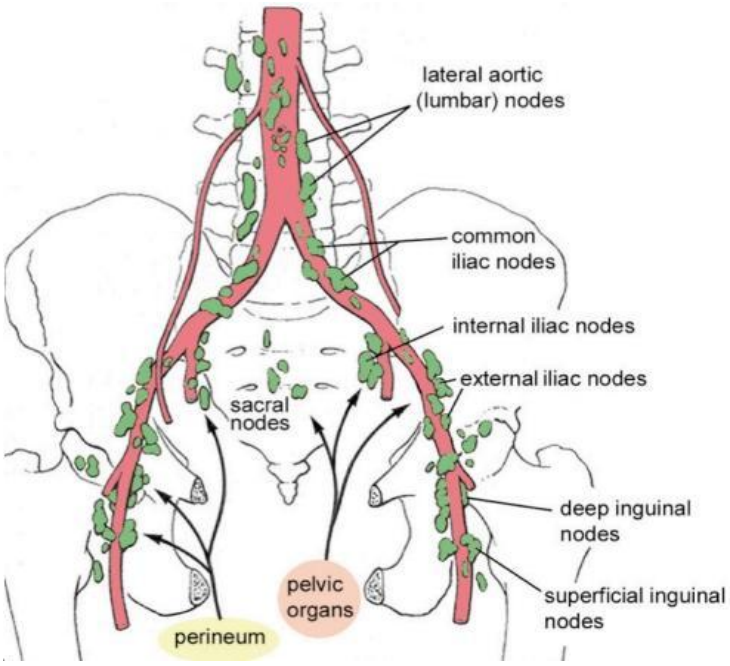


Fig 1.3: Lymphatic drainage

Lymphatics from the uterine fundus crosses laterally across the broad ligament, ascends along the ovarian vessels into the Paraaortic lymphatic nodes. Few other lymphatics from the uterine fundus region drain into the common iliac lymph nodes.

Arterial Supply: The main arterial supply is by the uterine artery which originates from the anterior division of the hypo gastric artery.

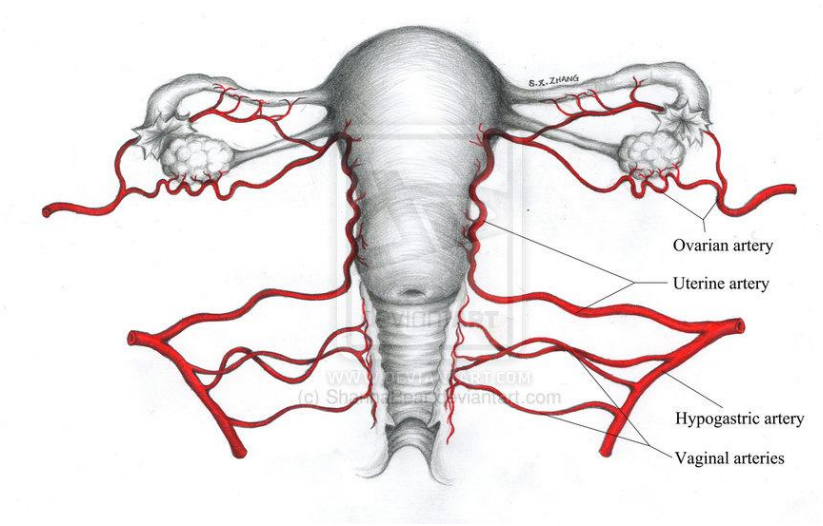


Fig.1.4:Arterial Supply of Uterus and cervix

4.3 EPIDEMIOLOGY:

Cervical cancer is the most common gynaecological cancer. It often affects young women and has a significant socio-economic impact on the society. In developing countries like India carcinoma of the cervix cause is the leading for cancer related death(4).It is more common in area where there is less access to cancer screening programs.

There are many known and unknown factors that leads to cervical cancer and cannot be attributed to lack of cancer screening alone.The various factors includes socio economic status, health care access , parity, smoking , presence of other infections , immune status and other factors affecting host immunity such as nutritional status.

HUMAN PAPILLOMA VIRUS

It is indicated by various estimates that more than 90 % off the cervical cancers are related to human papilloma virus (HPV).It is contracted via sexual intercourse.HPV is a small double stranded DNA virus.HPV 16 and 18 are the most common causative agents for cervical cancer(5) with some with some geographical variation.

Mechanism of action of HPV virus leading to cervical cancer:

Once infected the genome of HPV virus integrates into the host cell chromosome in cervical epithelial cells. This virus genome codes for six early and two late open reading frame proteins. Of these three viral genes, E5, E6 and E7 alter cellular proliferation. In HPV positive cervical cancers two viral genes E6 and E7 are typically expressed.E6 protein inactivates the tumour suppressor gene p53 hence resulting in chromosomal instability(6), inhibition of apoptosis and activation of telomerase.The E7 protein affects the retinoblastoma protein (Rb)(7) .This results in loss of regulation of cellular proliferation and immortalization.

Peak age of prevalence of HPV infection is between 25 to 35 years of age.After getting infected with HPV virus less than 15 % of the exposed women gets persistent infection that results in dysplasia.Majority of the women get cleared of the infection within 2 years.Cervical cancer usually develops 10 to 20 years after the initial exposure of HPV virus.

The major social factors that results in cervical cancer including those associated with HPV transmission are early age of first intercourse, more number of pregnancies , multiple sex partners, a male partner with history of contact with multiple sexual partners , a history of sexually transmitted disease, which may include gonorrhoea, Chlamydia , herpes simplex virus II , and / or Human immunodeficiency virus(HIV).

Other causative factors implicated in cervical cancers include exposure to chemicals, hormones, or other carcinogens. Association of cervical cancers and usage of oral contraceptives is considered controversial. Prenatal exposure to diethylstilbestrol is associated with development of clear cell adenocarcinoma(8). But the overall incidence is very small. Active cigarette smoking may increase the risk of carcinoma cervix. Few reports have shown that the usage of intrauterine contraceptive devices may decrease the potential of carcinoma cervix .The mechanism is said to be increased cellular immunity triggered by the device.

4.4 NATURAL HISTORY AND PATTERN OF SPREAD:

Squamous cell carcinoma of the cervix usually arises from the squamo columnar junction which is other called as the transformation zone between the endocervical canal and the portion ofcervix. Once cellular transformation occurs there will be a stepwise progression from normal to higher levels of dysplasia. In case of the patients who are diagnosed to have cervical intraepithelial neoplasm (CIN) type 1, 60% have regression of lesion and in those with CIN type 2, 40 % will have regression. Higher levels of dysplasia usually progresses to cancer in the presence of other cofactors like smoking and impairedimmunity. The progression of the disease usually takes 10 to 20 years except in some instances where there is rapid progression to carcinomas with aggressive disease.

CIN is said to be progressed to carcinoma when the malignant cells break through the basement membrane of the epithelium and invades the cervical stroma. Further invasion via lymphatic or blood route can lead to spread to lymph nodes as well as distant spread. If the disease is detected at initial stage by Papinicolaou (Pap) smear test, minimally invasive treatment will be sufficient .But if the disease is not detected by screening methods at the

early stage, the lesion may progress.If the disease is not detected and treated even in this stage then it may spread initially locally to the vaginal fornices, paracervical, parametrial tissue or even to neighbouring structures like bladder and rectum.

PAP SMEAR SCREENING:

Pap smear screening should begin at the age of 21 years every two yearly until the age of 30 years(9). If three consecutive Pap smear test result comes negative and if there is no history of CIN 2, CIN3, DESexposure or HIV infection and if the women is not otherwise immunocompromised, screening can be done every three yearly.

Women who had undergone hysterectomy in view of benign reasons who never had history of high grade intraepithelial lesion may discontinue testing. Women who have been treated for CIN2 and CIN 3 need annual screening at least for 20 years. Those who had hysterectomy and had a history of CIN2 or CIN3 should undergo screening with annual pelvic examination.

Category	PAP Screening Recommendation
1st PAP Smear	~ 3 years after 1st sexual intercourse or by age 21, whichever comes first
<30 years old	Annual PAP testing—Also Chlamydia through age 25
>30 years old	Combination PAP & high risk HPV test —If both results negative, then screen with combined tests every 3 years —If only HPV+, then repeat combined tests annually until both negative
≥65 years old	No PAP smear (if most recent PAP normal)
Hysterectomy (w/ Cervix)	No PAP smear (if most recent PAP normal)

Fig 3.2: Recommendation for Pap screening

4.5 CLINICAL PRESENTATION:

Patient usually presents with complaints of post coital bleeding, inter menstrual bleeding, menorrhagia or post menopausal bleeding. In case of chronic bleeding, the patient may present with fatigue or other features related to anaemia. In developed countries cervical cancer is frequently identified during routine clinical examination.

In case of advance disease conditions, patient may present with feature of renal failure, bowel obstruction, foul smelling serosangunious vaginal discharge, pelvic pain, flank or leg pain , rectal bleeding, dysuria , hematuria ,or persistent oedema of lower limbs due to lymphatic or venous blockage by pelvic sidewall disease. There may be associated pain in the pelvis or hypogastrium due to tumour necrosis or pelvic inflammatory disease.If patient is presenting with pain in the lumbosacral area, involvement of Para aortic nodes or hydronephrosis should be considered.

4.6 DIAGNOSTIC WORKUP:

When a patient`s Pap smear shows Abnormal Squamous cells of Undetermined Significance (ASCUS) and if the HPV status is negative, follow up in one year time period is recommended(10). If the second Pap smear also shows positive report, irrespective of the HPV status a colposcopy is recommended. If both ASCUS and HPV results are present (11)or adenocarcinoma in situ or squamous cell intraepithelial lesion is identified, direct biopsies at the time of colposcopy are advised. Endocervical curettage is recommended

except in pregnant women. If the biopsy results are negative, same procedure should be repeated after 6 months. If they are positive, conisation should be performed.

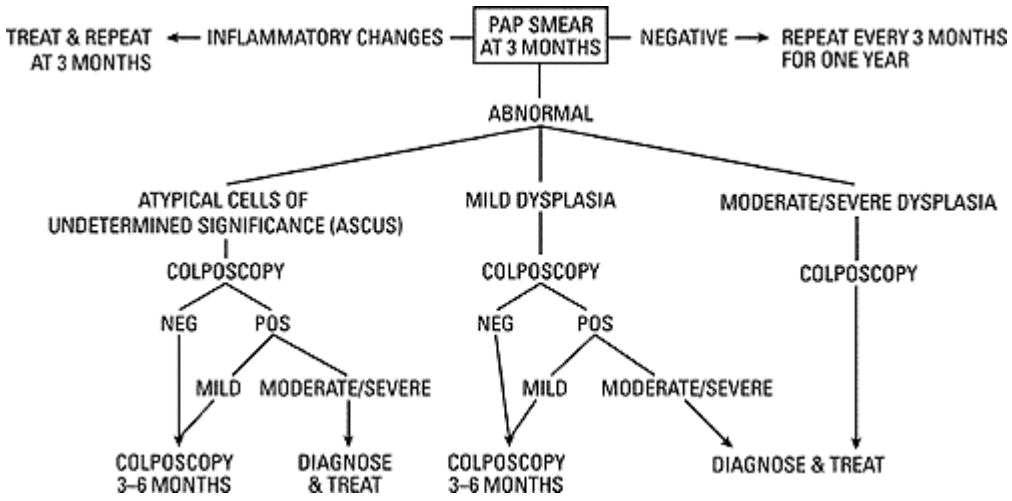


Fig 3.3: Flowchart showing how to proceed with a Pap smear

Patient who presents with a clinically significant cervical lesion should be evaluated by radiation oncologist as well as a gynaecologic oncologist .After getting a careful history, a thorough general examination, systemic examination and pelvic examination should be carried out. Pelvic examination should include inspection of external genitalia, per speculum examination of vagina, cervix, a rectal examination and bimanual palpation of the pelvis.Pelvic examination under anaesthesia is useful and is accepted universally forpain free clinical staging of the disease and assessment of parametrial involvement or pelvic side wall tumour extension.

MRI can be done if it available to estimate the tumour extension beyond the uterine cervix(12). If it is not available then MRI can be replaced by examination under anaesthesia. Cystoscopy or rectosigmoidoscopy should be performed in all the patients who are having

symptoms suggestive of vesicovaginal fistula or rectovaginal fistula .It should be also performed in patients having stage IIB,III,IV A disease who cannot afford an MRI scan or in a patient whose MRI shows features suggestive of bladder or bowel involvement(13).

DIAGNOSTIC WORKUP FOR CARCINOMA CERVIX
General History **General Examination** : Performance status Pallor ,icterus ,lymphadenopathy. **Local Examination**: Inspection of external genitalia Per Speculum Examination Per Vaginal Examination **Systemic Examination**
Diagnostic Procedures Cytological smear Colposcopy Conisation(Subclinical tumour) Punch biopsies

Dilatation and curettage Cystoscopy, rectosigmoidoscopy(14)
Radiographic studies Chest Radiograph Ultrasound of the abdomen and pelvis. MRI/CT Scan(If indicated)
Laboratory Studies Routine blood counts, Blood chemistry, Urine analysis , Blood borne virus screening

4.7 TNM STAGING

Primary Tumour (T)		
TNM Categories	**FIGO Stages**	
TX		Cannot assess primary tumour
T0		No evidence of primary tumour
Tis*	*	Carcinoma in situ (preinvasive carcinoma)
T1	I	Carcinoma confined to uterus (extension to corpus should be disregarded)
T1a[†]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread 7.0 mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest

Primary Tumour (T)		
TNM Categories	**FIGO Stages**	
		dimension
T2	II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour extends to pelvic wall and/or involves lower third of vagina, and/or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina, no extension to pelvic wall
T3b	IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of bladder or rectum, and/or extends beyond, true pelvis (bullous oedema is not sufficient to classify a tumour as T4)

Regional Lymph Nodes (N)		
TNM Categories	**FIGO Stages**	
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1	IIIB	Regional lymph node metastasis

Distant Metastasis (M)		
TNM Categories	**FIGO Stages**	
M0		No distant metastasis
M1	IVB	Distant metastasis (including peritoneal spread, involvement of supraclavicular, mediastinal, or paraaortic lymph nodes, lung, live, or bone)

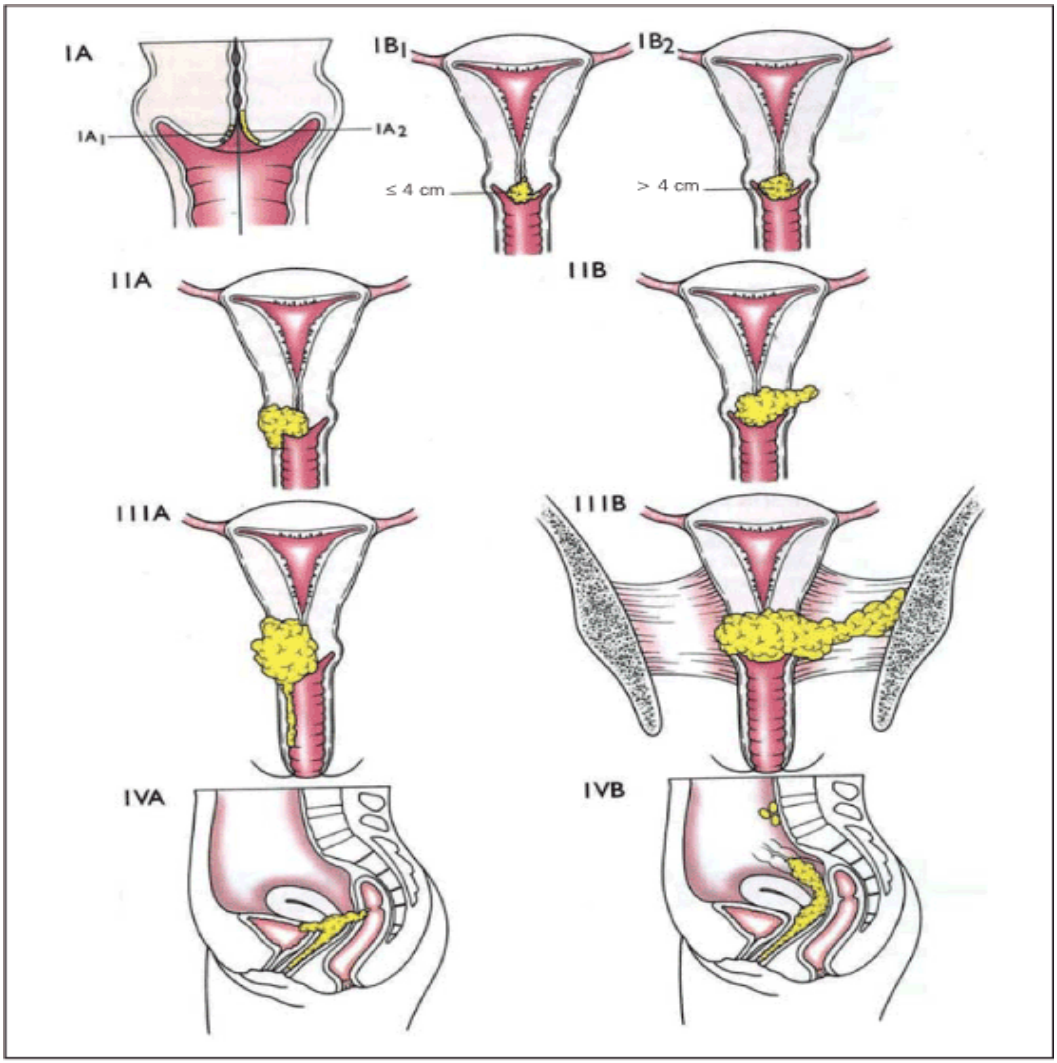


Figure 1. Staging of uterine cervix carcinoma according to FIGO[3].

Fig 4.1: T staging in carcinoma cervix

4.8 PATHOLOGICAL CLASSIFICATION.

Histopathologically , more than 90% of the tumours are squamous cell carcinoma, 7% -10% adenocarcinoma and 1-2% clear cell mesonephric type(15). Squamous cell carcinomas are sub divided into large cell keratinizing, none keratinizing and small cell carcinomas.

According to the degree of differentiation they are subdivided into well, moderately and poorly differentiated.

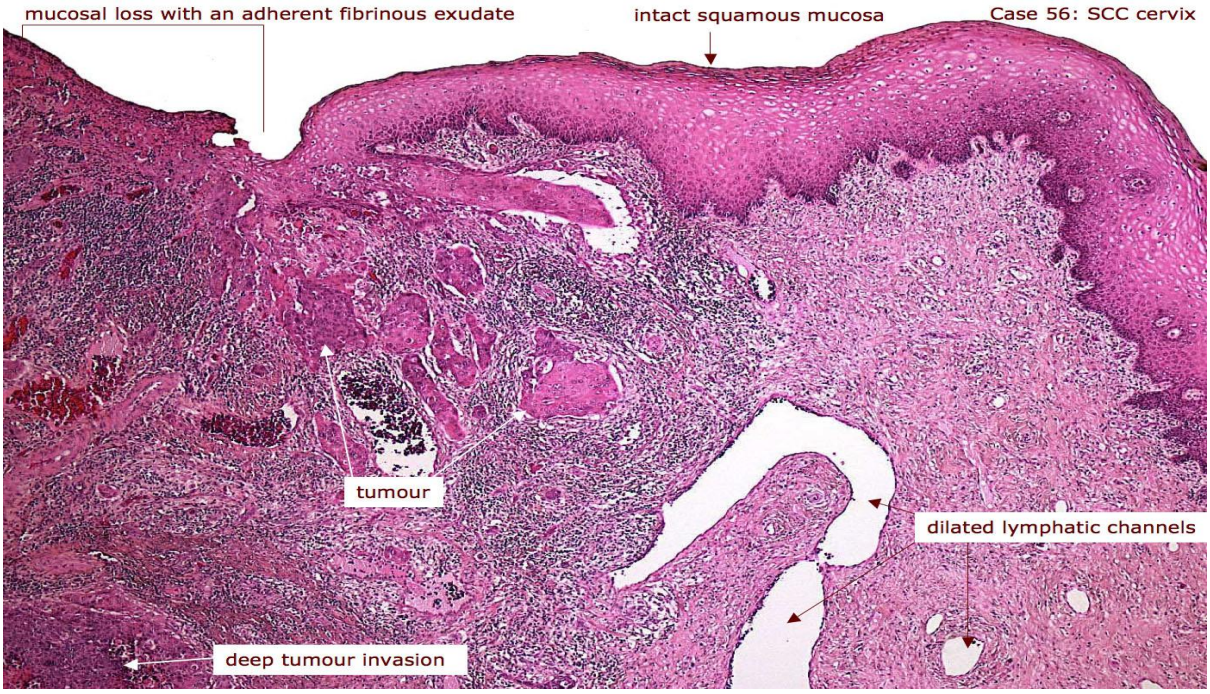


Fig. 4.2: Histopathology of squamous cell carcinoma cervix

Adeno carcinoma arises from the cylindrical mucosa of the endocervix or the mucin secreting endocervical glands.Mucinous is the most common subtype .This type may form mucosal gland lined by high columnar cells. In another type the cells resembles those of intestine. The epithelium tends to be pseudo stratified and may contain goblet cells. The third variant is signet-ring cell adenocarcinoma.

In an analysis of 25 patients by Van Nagell et al., it was noted that 5 year survival rate for all stages of small cell carcinoma was 54%(16) compared with 68% for large cell non keratinizing squamous cell and 74% for keratinizing Squamous cell carcinomas.

4.9 PROGNOSTIC AND PREDICTIVE FACTORS:

Prognostic and predictive factors can be classified into

1.Patient related Factors.

2.General Medical Factors.

3. Tumour Factors.

4. Margin status after Radical Hysterectomy.

5. Histological Grade.

6. Treatment Duration.

7. Biomarkers.

1. PATIENT RELATED FACTORS:

AGE

Age is not a prognostic indicator in carcinoma cervix according to some reports while some other authors noted decrease survival in women with age < 35-40 years who has a greater frequency of poorly differentiated tumours. Two European studies showed improved survival in younger age in contrast to the other studies. Mitchell et al. evaluated 398 women with carcinoma cervix Stage I-III treated with radiotherapy. In this study, patients were divided into twogroups,non elderly from35 to69 years of age and elderly patients with age >70 years of age (n=60).In case of elderly women, co morbidities resulted in diminished ability to do intracavitary brachytherapy. Even if the 5 years cause-specific survival and disease-free

survival and were comparable between the two groups, tumour recurrence rate and death from malignancy were more common in elderly group(17).

RACE AND SOCIOECONOMIC STATUS:

It was noted by several authors that there is a relationship between racial or socioeconomic outcome of the patient and treatment outcome. Mundt et al examined in 316 African American (18)and 94 white patients undergoing RT for carcinoma cervix the factors affecting the outcome. African Americans had a poorer 8 year cause specific survival rates in comparison to the white patients.

Factors resulting in poorer outcomes like low blood Hb was observed in African American group. It was demonstrated in Multivariate analysis that race is not an independent prognostic factor in carcinoma. In another study, 471 patients diagnosed to have squamouscell cervixcarcinoma treated in United States and 215 randomly selected cases from 17 institutions withmore than 40 % of the minority patients were selected. It was observed that African Americans have a poorer initial performance status, higher stage or bulky central tumour and a lower pre treatment blood Haemoglobin level.

GENERAL MEDICAL FACTORS:

ANEMIA AND TUMOUR HYPOXIA

Even if the stage, tumour volume, histopathological type of the lesion and vascular and lymphatic invasion are the major prognostic factorin case of a patient with carcinoma cervix,blood Haemoglobin level also contributes to the treatment outcome.Pre treatment

blood Haemoglobin level has a great impact on radiosensitivity and hence on the treatment prognosis. It is desirable to maintain blood haemoglobin level between 12-12.5 g/dL(19).

Whether surgery or radiation therapy is the primary modality of treatment, hypoxic tumour cells are more likely to recur loco regionally than well oxygenated tumour cells. It was reported by various investigators that there is worse outcomes for patients whose pre treatment tumour tissue oxygen measurement was <10 mm Hg(20).

Usage of recombinant erythropoietin is not an alternative to blood transfusion in order to sustain or raise blood haemoglobin levels. This is not encouraged because it results in thrombotic complications and there is no proven survival benefit.

OTHER MEDICAL FACTORS:

It was observed in various studies that there is high incidence of pelvic recurrences in patient with arterial hypertension, diastolic pressure of >110 mm Hg. Patients who were found to have carcinoma of cervix associated with HIV infection had more advanced tumours.They h higher rdes of tumour recurrence after treatment and death as a consequence of malignant process.

TUMOUR FACTORS

HPV SUBTYPE:

HPV 16 and 18strains are the commonest HPV subtype worldwide. Studies have shown that the incidence of lymph node metastases and distantmetastases is higher with HPV 18 subtype when compared to subtype 16(21).

TUMOR VOLUME:

It has been found that there is a close relationship between the size of the tumour, depth of stromal invasion and the incidence of parametrial and pelvic node metastases and survival.

In a study on women who underwent hysterectomy, 181 patients with Stage 1B1 (<4 cm) had 90% 5 year disease free survival when compared to 48 patients with stage 1B2 disease who had 72.8% disease free survival. Various studies have shown that bulky barrel shaped lesions results in greater incidence of lymphatic metastases, distant metastases, and pelvic recurrence and decreased survival rates.

Perez et al studied on 1,499 carcinoma cervixpatients, stage IA to IV A.All of them were treated with external beam radiation therapy followed by two intra cavitary insertions to deliver 70 to 90 Gy to point A. He found out that there is a close relationship between the tumour size and pelvic tumour control, distant metastases and disease free survival in all stages.

MARGIN STATUS AFTER HYSTERECTOMY:

Positive margin after hysterectomy is one of the high risk factors for local recurrence and distant metastases in carcinoma cervix. It is an indication for combined modality management with concurrent chemotherapy and radiation therapy. But only very small series studies have indicated the significance of close margins.

Viswanathan et al did a study among 284 carcinoma cervix patients(22) ,post radical hysterectomy .The crude rates for recurrence were 38% ,20% and 11% for patient with

positive margins, close(>0 and <1 cm) and negative margins(>1 cm) respectively. Post operative radiation therapy decreases the rate of local recurrence from 50% to 25% for positive margins,17% to 0% for close margin and 10 % to 0% for negative margin. The predictors for decreased relapse free survival on univariate statisticalanalysis were depth of invasion, positive margin, tumour size, lymphovascularinvasion, and margin status.

HISTOLOGIC GRADE

Reports have shown that there is no significant relation between survival or behaviour of the tumour with the degree of differentiation of Squamous cell carcinoma or adenocarcinoma of cervix .Alfsen et al did analysis with 417 cervical cancer patients with adenocarcinoma histology(23) and 88 with other non Squamous cell histology.

On multivariate analysis, it was found that small cell histology, vascular invasion, corpus infiltration and positive lymph nodes were the significant prognostic factors. Even though Reagan et al (24)and Fu et al opined that there was significant value of histopathological differentiation in patients treated with radiation, Crissman et al(25) failed to obtain a correlation between the histopathological grading and survival. In this era of chemo radiation Monk et al showed that there is no significant impact of histology or grade on survival in case of post operative carcinoma cervix patients with other high risk feature.

TREATMENT DURATION

Overall treatment time is an important factor in tumour control in case of carcinoma cervix patients who are receiving radiation therapy. Timely integration of external beam radiation

therapy and intracavitary radiation therapy is necessary. Studies have proved that when the overall time is prolonged for radiation, there are lower pelvic tumour control and survival rates. Chatani et al (26)studied 216 patients diagnosed to have stage IIB to III cervical cancer who were treated with external beam radiation and HDR brachytherapy .It was aLSO noted in multivariate analysis that the overall treatment time is the most significant factor for local tumour control (p=0.0005) .

Fyles et al reported that there was approximately 1% loss of tumour control per day of prolongation of treatment beyond 30 days in 830 patients diagnosed to have carcinoma cervix treated with radiation alone. Lanciano et al analysed 837 patients diagnosed to have carcinoma cervix. It was noted that a four year actuarial in field recurrence increased to20% from 6% with the increase in treatment timeto 10 weeks from 6 weeks (27).

Girinsky et al also noted that 10 year recurrence free survival decreases when the total time of treatment exceeded 52 days. It was also noted that there was loss of a1.1% pelvic tumour control with each day loss of radiation(28).

BIOMARKERS

Several studies were conducted to determine the association between various biological markers and disease prognosis in carcinoma cervix. But there was no multivariate analysis to assess any independent factor. Noordhuis et al did a systematic review of 42 studies with 82 biological tumour markers.34 biomarkers showed association with survival(29).

4.10 MANAGEMENT OF CARCINOMA CERVIX ACCORDING TO STAGE:

4.10.1 CARCINOMA IN SITU:

In case of carcinoma in situ of cervix, the most important factor in the treatment decision is the extent of the disease. The other factors like age, fertility, and other medical co morbidities also influence the treatment decision. For ectocervical lesions, various options like loop electrosurgical excision procedure(LEEP), laser therapy, conisation and cryotherapy are available.

For endocervical canal involvement, in patients to preserve fertility and to avoid radiotherapy or more extensive surgery, options like laser or cold knife conisation are available. For post reproductive age group, Total Abdominal Hysterectomy or vaginal hysterectomy is an established modality of treatment particularly when the malignant process extends to the inner cone margin. If the patient is medically inoperable, a single intracavitary brachytherapy insertion to deliver a dose of 8000cGy to the vaginal surface can be used.

4.10.2 STAGE IA1:

Carcinoma cervix is staged IA1 when there is micro invasive disease which is not greater than 3mm depth and not wider than 7mm. Various options like conisation, Total abdominal or vaginal hysterectomy or intracavitary radiation alone is available in management .

CONIZATION:

It is the preferred modality of management in patients diagnosed with carcinoma cervix IA1 who wishes to preserve fertility if there is no evidence of vascular or lymphatic involvement and if the margins of the cone arenegative.

TOTAL ABDOMINAL AND VAGINAL HYSTRECTOMY:

It can be performed in patients with stage 1A1 who has completed their family. If there is no vascular or lymphatic emboli the occurrence of lymph node involvement is very low, hence lymph node dissection may not be obligatory. In case of young women ovaries can be preserved.

INTRACAVITARY RADIATION:

In 1A1 lesion when there is no lymphovascular invasion the frequency of nodal involvement will be very low. As a result external beam radiation therapy may not be required.In these cases,intracavitary brachytherapy can be considered.

4.10.3 STAGE IA2:

Carcinoma cervix is staged IA2 when the tumour extends 3.1 to 5mm beneath the basement membrane and when the transverse diameter is < 7mm. In this group radical hysterectomy with pelvic node dissection is recommended as the risk of lymph node metastasis is up to 10 %. However few studies suggest that the rate of lymph node involvement may be much lower and they question that conservative therapy may be sufficient in cases of patients who are not having residual disease after conisation. Radical hysterectomy should be also considered in

caseswhere the extent of tumour invasion in doubtful due to the presence of invasive tumour at the margins of the cone.

RADIATION THERAPY:

Intracavitary along with external pelvic irradiation or radical intracavitary radiotherapy can be an option in patients who are poor candidates for surgery

In stage IA,non-bulky IB, and early-stage IIA tumours, primary surgical management with hysterectomy is indicated in. In these stages primary radiation therapy results in similar outcome.

4.10.4 STAGE IB- II A

The management of stage I B –II A of carcinoma cervix whether to go ahead with definitive Irradiation or radical surgery is still controversial .The preference for one procedure over the other depends upon the need to preserve fertility , patient`s general condition and preference, characteristics of the lesion , and the resources and expertise available in the institution. In some young patients surgery is preferred over RT in attempt in preserving ovarian function and not attaining post menopausal state early .However studies have shown that in 50- 60% cases only ovarian function is retained even after surgery with no radiation therapy.

In post menopausal women it has been shown that there is survival benefit in radical treatment with chemo radiation therapy over surgery. By this approach the complications of surgery can be avoided as well.

Though surgery gives an opportunity to examine abdomen and pelvis thoroughly it has not shown any added benefit to improve patient`s overall survival.

The contribution of external beam radiation therapy to improve tumour control in larger lesion is documented. Hamberger et al (30)showed that out of 151 patients with stage IA or stage IB < 1 cm treated with intracavitary RT alone, there was no failure in 41 patients with stage IA disease, only 4 out of 93 patients with stage IB, small volume disease,3 out of 17 with more extensive stage IB lesion had regional failure. It was concluded that intracavitary brachytherapy is inadequate for larger primary tumour, including stage IB1.

If external beam RT and brachytherapy is delivered without chemotherapy, the usual 5 year survival for stage Ibis 86% to 92%and for stage II A it is 75 %.Concurrent chemotherapy improves survival significantly in stage IB-IIA. RTOG 90-01, among 272 stage IB- IIA % patients, 8 year over all survival was 55 % with radiation therapy alone versus 78% with concurrent chemotherapy and radiation therapy.

In patients diagnosed with carcinoma cervix stage IB to II A, there are few studies which compared the results of radical surgery to definitive radiation therapy. There are no studies which compared surgery to chemo radiationtherapy. These studies have shown that there is equivalent survival and pelvic recurrence rates in both the arms in those with Stage IB to IIA carcinoma cervix.

STAGE IB1:

It can be treated with external beam radiation therapy combined with intracavitary radiation together delivering an equivalent dose of 80 Gy to point A or with radical hysterectomy and bilateral pelvic lymphadenectomy.

STAGE IB2AND IIA

The management options comprise

1. Radical radiation therapy(external beam RT with intracavitary radiation)
2. Radical hysterectomy and bilateral lymphadenectomy
3. Radiation therapy with chemotherapy

ADJUVANT THERAPY AFTER RADICAL SURGERY:

To decide the need for post operative radiation therapy , based on the post operative histopathology report the patients are categorized as high risk, intermediate risk and low risk

HIGH RISK-

When the post operative HPE reveals lymph node metastasis, positive surgical margin and parametrial extension the patients are classified as having high risk features.. In this case adjuvant chemo irradiation with external pelvic irradiation and concurrent weekly cisplatin chemotherapy is recommended.

INTERMEDIATE RISK-

When there is deep invasion of cervical stroma,lymph vascularinvasion,tumour size>4cms ,the patient is classified as intermediate risk.. In this case, adjuvant radiation therapy alone is recommended if at least two of the above are present.

LOW RISK-

When none fo the above factors are present in the Post operative HPE, the patients are considered as low risk. In these patients , no further adjuvant treatment is recommended.

4.10.5 STAGE IB2 to IV A

Before 1999,<30% of patients treated with radiotherapy for local advanced carcinoma cervix were receiving concurrent chemotherapy. In 1999-2000, it was shown by 5 randomised trials that there is a survival benefit in patients with carcinoma cervix treated with radiotherapy and concurrent cisplatin based chemotherapy. In 1999, The National Cancer Institute issued an alert indicating that concurrent chemo radiotherapy should be considered as the standard of care for patients with locally advanced carcinoma cervix.

Patients diagnosed with carcinoma cervix stage II B to IV A are treated with radiation therapy including external beam radiation combined with concurrent chemotherapy and brachytherapy. The usageof concurrent cytotoxic agents along with radiation therapy provides a radio sensitizingeffect. One of the most commonly used cytotoxic agents in squamous cell carcinoma cervix is Cisplatin.

4.11 RANDOMIZED TRIALS ON CONCURRENT CHEMOTHERAPY AND RADIATION THERAPY

There are results from several cooperative oncology groups which demonstrated that concurrent chemotherapy with cisplatin along the radiation therapy prolongs survival in women with locally advanced carcinoma cervix and women with stage I to IIA disease who was found to have positive node, positive parametrium or positive margin during primary surgery.

DETAILS OF THE TREATMENT PROTOCOLS OF THE FIVE RANDOMIZED TRIALS THAT FORMED THE BASIS OF THE NATIONAL CANCER INSTITUTE ANNOUNCEMENT.

Trial	FIGO stage	Number of patients	Comparison	Follow-up	HR	Increase in survival (%)
GOG 85	IIB–IVA	368	PF versus HU	8.7 years	0.7	10%
RTOG 9001	IB (>5 cm)–IVA	388	PF versus none	43 months	0.59	15%
GOG 120	IIB–IVA IIB–IVA	526 526	P versus HU PFHU versus HU	35 months 35 months	0.61 0.58	18% 18%
GOG 123	IB_2 (>4 cm)	369	P versus none	36 months	0.54	9%
NCI/Canada	IB (>5 cm)–IVA	253	P versus none	64 months	0.91	3%
Meta-analysis	IB–IVA	3,452	Chemo-therapy versus none	62 months	0.78	3496

HR: hazard ratio, P: cisplatin, F: 5-fluorouracil, HU: hydroxyurea

Source: Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (2008) 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 26:5802–5812

Fig. 5.1: Trials favouring chemoradiation therapy in carcinoma cervix

4.12 BONE MARROW

Bone marrow is a supple tissue found in the inside of bones.In human beings the red blood cells are formed from the core of bone marrow located in the head of long bones. This blood cell production is called hematopoiesis. Bone marrow makes up 4% of the total body mass in humans. In an adult of weight 65 kilograms, bone marrow isroughly 2.6 kilograms. The hematopoietic constituent of bone marrow produces in the order of 500 billion blood cells per day. Bone marrow also produces the lymphocytes that support the body's immune system(31).

4.12.1 MARROW TYPES

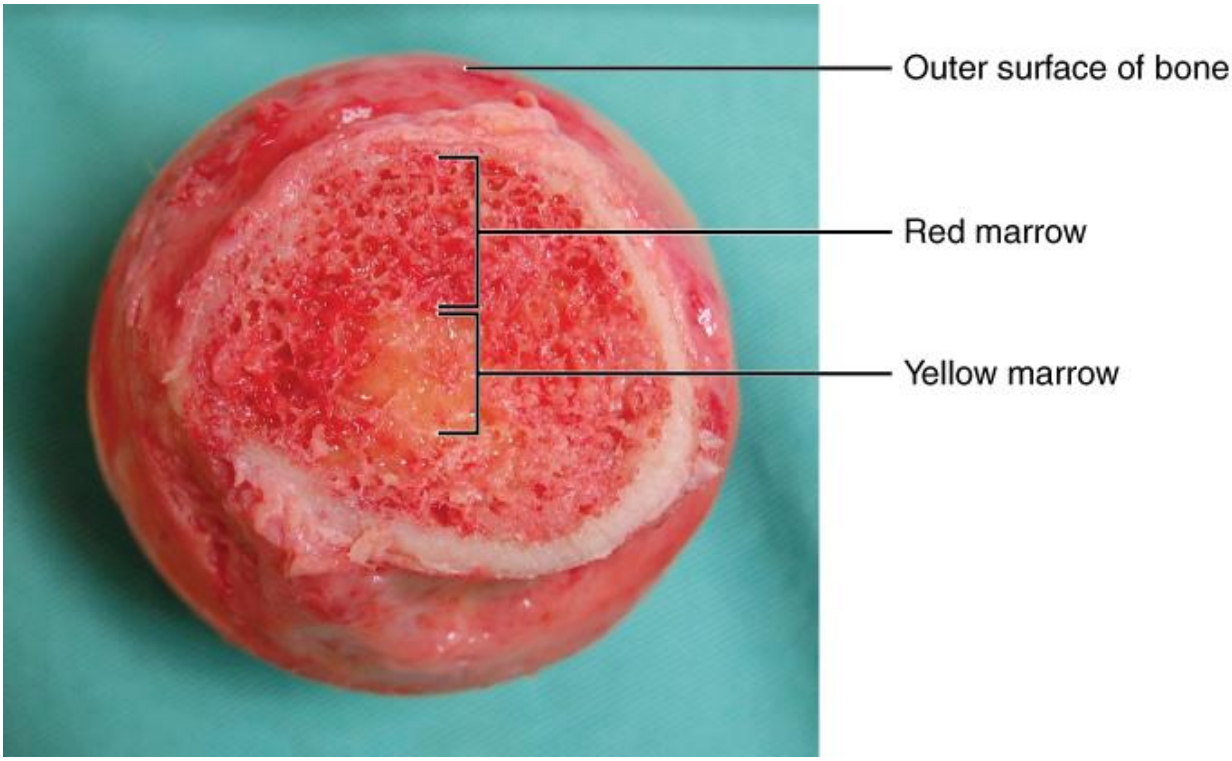


Fig.6.1:A femoral head with an outer cortex of cortical bone, medulla of trabecular bone with red bone marrow and yellow bone marrow.

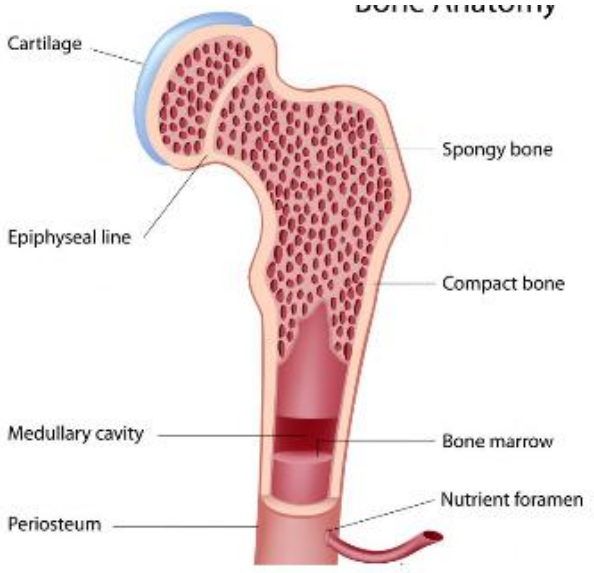


Fig.6.2: Anatomy of bone including the marrow

There are mainly two main types of bone marrow , red and yellow marrow.Themedulla ossiumrubra or the red marrow comprisechiefly of hematopoietic tissue, and medulla ossiumflava or the yellow marrow mostly consist of fat cells.The Red blood cells, platelets, and most white blood cells come up from the red marrow.At birth all the bone marrow is red. As the person grows old, moreof the red marrow is transformed to the yellow type. Finally only about half of adult bone marrow remains red.

Red marrow is mainly found in the flat bones likepelvis, sternum, ribs, vertebrae, cranium, and scapulae.It is as well found in thecancellousmaterial at the epiphyseal ends of long bones like the femur and humerus. Yellow marrow is mainly found in the medullary cavityof long bones. In situations where there is severe blood loss, yellow marrow is converted back to red marrow to boost blood cell production.

Apart from the hematopoietic stem cells the other major part of the bone marrow is constituted by stromal cells. These tissue do not involve directly in the process of hematopoiesis.Majority of these tissue is found in the yellow marrow and smaller concentration in the red bone marrow. But it play a major role in haematopoiesis indirectly by providing an appropriate microenvironment for the parenchymalcells.They release colony stimulating factors that has a significant role in hematopoiesis.Thestromal cells comprises of fibroblasts, macrophages, adiposities, osteoblasts, osteoclasts, endothelial cells .Among these, macrophages is having a significant role in the production of the red blood cells as they deliver iron for the production of hemoglobin.

4.12.2 FUNTIONS OF BONE MARROW

Red blood cells deliver oxygen to the tissues.

Platelets or thrombocytes (derived from megakaryocytes) help thwart bleeding and assist in clotting of blood.

Granulocytes (neutrophils, basophils and eosinophils) and macrophages (jointly known as myeloid cells) battle infections from bacteria, fungi, and other parasites. They also get rid of dead cells and remodel tissue and bones.

B-lymphocytes produces antibodies, while T-lymphocytes can directly destroy or isolate invading cells.RBC live for just about 170 days and rest have shorter life spans and have to be replenished constantly. An average human requires roughly one hundred billion new hematopoietic cells each day. This is performed by the Hematopoietic Stem Cells (HSCs).

Red marrow parenchyma

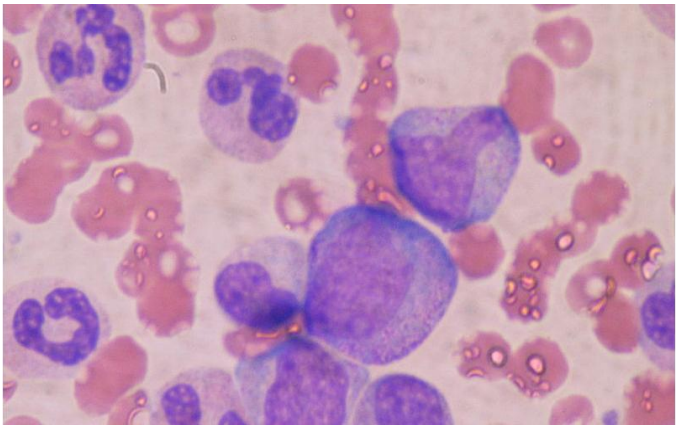


Fig .6.3: Hematopoietic precursor cells: pro myelocyte in the center, two metamyelocytes adjacent to it and band cells from a bone marrow aspirate.

Group	Cell type	Average fraction	Reference range
Myelopoietic cells	Myeloblasts	0.9%	0.2-1.5
	Promyelocytes	3.3%	2.1-4.1
	Neutrophilic myelocytes	12.7%	8.2-15.7
	Eosinophilic myelocytes	0.8%	0.2-1.3
	Neutrophilic metamyelocytes	15.9%	9.6-24.6
	Eosinophilic metamyelocytes	1.2%	0.4-2.2
	Neutrophilic band cells	12.4%	9.5-15.3
	Eosinophilic band cells	0.9%	0.2-2.4
	Segmented neutrophils	7.4%	6.0-12.0
	Segmented eosinophils	0.5%	0.0-1.3
	Segmented basophils and mast cells	0.1%	0.0-0.2
Erythropoietic cells	Pronormoblasts	0.6%	0.2-1.3
	Basophilic normoblasts	1.4%	0.5-2.4
	Polychromatic normoblasts	21.6%	17.9-29.2
	Orthochromatic normoblast	2.0%	0.4-4.6
Other cell types	Megakaryocytes	< 0.1%	0.0-0.4
	Plasma cells	1.3%	0.4-3.9
	Reticular cells	0.3%	0.0-0.9
	Lymphocytes	16.2%	11.1-23.2
	Monocytes	0.3%	0.0-0.8

Fig.6.4: Cellular constitution of the red bone marrow parenchyma

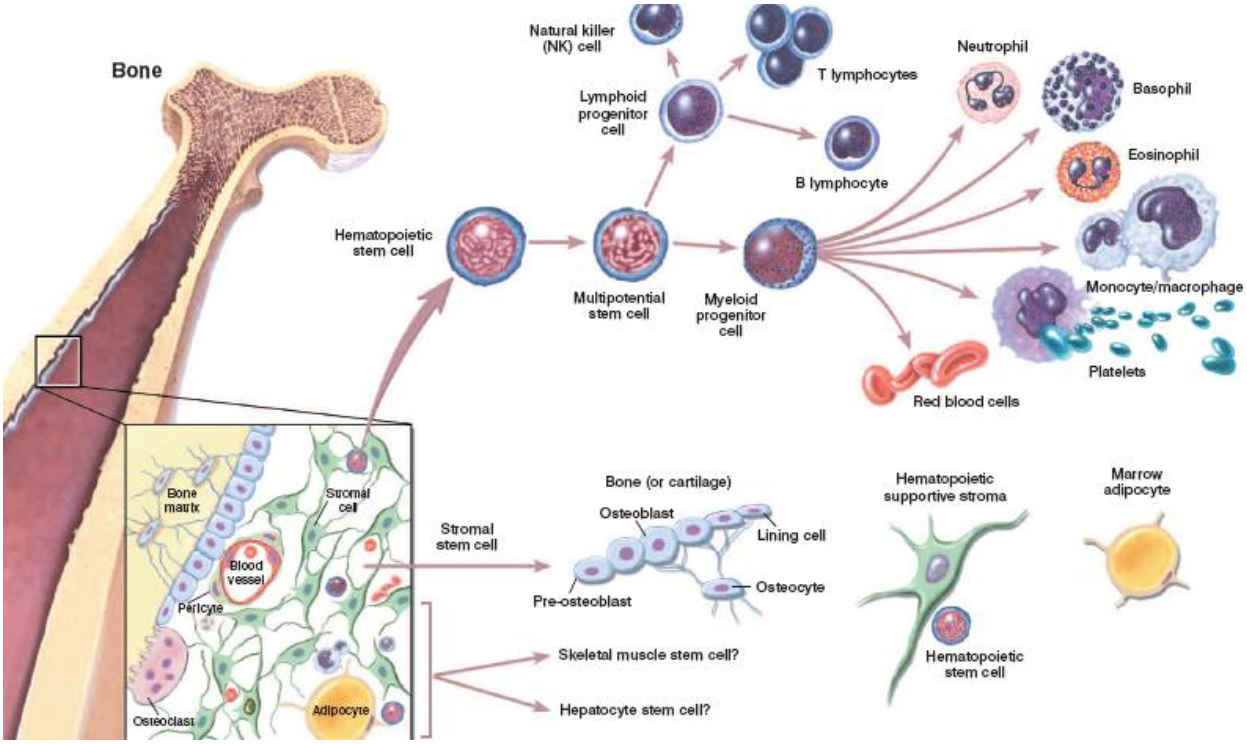


Fig.6.5: Steps of hematopoesis

4.12.3 AVERAGE LIFE SPAN OF BLOOD CELLS

The average life span of RBC s is about 4 months, WBC s is 18 -36 hrs and that of platelet is 9-10 days.If we consider WBC s the life span differ with each type.Neutrophil-5.4 days, B lymphocytes 3-4days up to 5 weeks, T lymphocytes last for several months.

Subsequent tothe discovery of X-rays and radium in 1895 and 1898, scientists found out that there can be effects like hair loss and skin damage from their rays. Both theseagents were tried experimentally in the treatment of superficial skin diseases and for removing unwanted hair. X-rays wasquickly found useful by physicians for diagnostic purpose. Radium wasnot found to be useful during this time. By 1913, America started mining radium. At that time radium was scarce and expensive .It was kept in small tubes and was inserted directly into

cancers or body cavities containing cancer. Inoperable cervical cancer was made curable with radium.

Scientist started their studies on stem cells following the repercussion of the bombings in Hiroshima and Nagasaki in 1945. Those patients who died after a prolonged period from lower dose of radiation had affected hematopoietic system that could not regenerate adequate white blood cells for immunity and sufficient platelet for blood clotting.These changes were detected by blood tests after receiving a whole-body acute dose as low as 0.25 Gy. Later, from various laboratory studiesit was established that mice that were subjected to whole body irradiation developed the same type of radiation syndromes. The mice died two weeks after radiation from hematopoietic failure weeks after radiation exposure. It was noticed that shielding of a bone or the spleen from radiation helped in preventing irradiation syndrome.

In 1950 s it was demonstrated by scientists that those mice which had received whole body irradiation that developed hematopoietic failure could be rescued by injection of suspensions of cells from blood forming organs such as bone marrow.

In 1956, studies from three laboratories established that direct injection of bone marrow cells helps in regenerating blood forming system rather than releasing factors. Till date the only acknowledged treatment for hematopoietic failure following whole body irradiation is transplantation of bone marrow cells or stem cells to renew the blood-forming system.

From all these historical experiences it was clear that radiation therapy as a treatment modality is a double edge sword and accurate technique to deliver it precisely to the target without affecting normal structure remains a never ending quest.

The same quest paved way to the evolution of radiation therapy delivery techniques in carcinoma cervix from conventional techniques like AP-PA , Cross fire technique , 4 field box technique , 3 dimensional conformal radiation therapy towards Intensity Modulated radiation therapy.

In patients with carcinoma cervix pelvic radiation therapy causes significant haematological toxicity. This can be attributed to the fact that more than half of the body's bone marrow is located in the lower lumbar spine , sacrum , os cocci and proximal femora which are included in the treatment volume of conventional pelvic irradiation therapy for patients with carcinoma cervix(32)

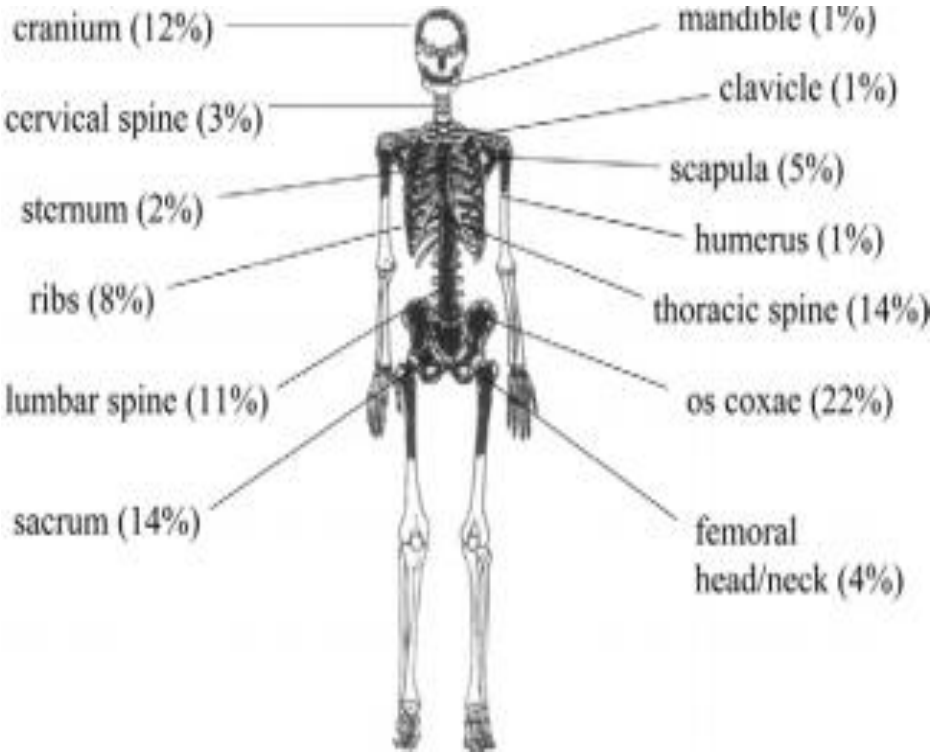


Fig. 6.6: Distribution of bone marrow in human body

Blomlie V et al(33) conducted an imaging based study on 31 women with locally advanced carcinoma cervix. 161 MRI examinations were carried out before during and seven weeks after radiation therapy. They found significant changes in the irradiated marrow on T1 weighted images in all 31 patients. A complete fatty bone marrow was observed on T1 weighted images after 6-8 weeks of starting radiation therapy in 28 (90 %) of the 31 patients.

4.13 STUDIES IN CARCINOMA CERVIX PATIENTS WHICH SHOWED THAT CONCURRENT CHEMOTHERAPY INCREASES THE HEMATOLOGICAL TOXICITY WHEN COMPARED TO RADIATION THERAPY

Keys et al (34)conducted a trial on patients with large stage 1b cervical cancer to determine whether weekly infusion of cisplatin during radiation therapy improves progression free survival and overall survival. 183 women were randomised into radiotherapy chemotherapy arm and 186 were assigned to receive radiotherapy alone, the rates of overall survival (p value =0.008) and progression free survival (p value < 0.001) were appreciably higher in combined modality group at the end of four years. In combined therapy group they found that there were elevated frequencies of transient grade 3 (moderate) and grade 4(severe) adverse haematological toxicity (21 % in combined group vs. 2 % in radiotherapy group).

Rose et al in(35) 1999 analysed 526 women with locally advanced cervical cancer. patients were randomised into 3 groups , radiotherapy with cisplatin alone ; radiotherapy in combination with cisplatin , fluorouracil and hydroxyurea ; radiotherapy with hydroxyurea alone .He found that both the groups who received cisplatin had higher rate of progression

free survival when compared to the group that received hydroxyurea alone , but at the same time it was analysed that the groups who received cisplatin based combination chemo regimen were having increased frequencies of grade 3 grade 4 haematological toxicity.

From these studies it was observed that Concurrent chemo radiotherapyis leading to increased haematological toxicity. This predisposed the patient to infection,hospitalisation,blood transfusion and usage of growth factors. There resulted in delayed or missed chemotherapy cycles and even break in treatment.

This brought the question in mind of many that whether this delay in treatment can compromise disease control. It was found that treatment with any cytotoxic agent including radiation is triggering clonogens in the tumour to divide faster than before which led to accelerated repopulation .Even if the tumour was found to be shrinking and regressing; the surviving clonogens were dividing and increasing in a more rapid fashion than ever. Various analyses suggest that this clonogenic repopulation in human cancers accelerates at about 28 days after the initiation of radiation therapy in a fractionated regimen. This ascertainedthat treatment should be completed as soon after it has begun as is practical.

In their study on the effect of treatment duration in the local control of carcinoma cervix Fyles et al showed a significant effect of treatment duration in 830 patients with carcinoma cervix treated with chemo radiation therapy. They found that the loss of control consistently declined approximately 1% per day of treatment prolongation beyond 30 days(36). This is consistent with the occurrence of accelerated repopulation which alarms at timely completion of treatment.

Rachelle et al analysed the effect of total treatment time on outcome in 837 patients with locally advanced carcinoma cervix. A statistically significant decrease in survival (p= 0.0001) and pelvic control (p=0.0001) was demonstrated with increase in total treatment time from less than 6 , 6 to 7.9 , 8 to 9.9 and 10+ weeks .This was significant in patients with carcinoma cervix stage III and above .

Patient should receive ideally 5-6 doses of concurrent weekly cisplatin along with radiation to achieve the beneficial radio sensitising effect of chemotherapy. Therefore any modality that may help in preventing haematological toxicity which results in delay in delivery of chemotherapy will help in increased local control and disease free survival.

4.14 RADIATION THERAPY IN CARCINOMA CERVIX

External beam radiation therapy is routinely administered in patients with carcinoma cervix stages IB2 to IV A along with concurrent chemotherapy in a curative fashion. It may be administered in stages IA to IB1 if those patients are inoperable or if they prefer avoiding surgery. In stage IVB, palliative radiation to pelvis is offered for selected indications such as to stop vaginal bleeding, alleviate urethral obstruction from extrinsic compression or to relieve pain

External beam radiation should cover the primary cervical tumour, bilateral parametrium, uterosacral, uterine or vaginal extension and most importantly the microscopic disease present in the pelvic lymph nodes. The primary drainage lymph nodes from the cervix include all the pelvic lymph nodes including the lower common iliac nodes, the external iliac

nodes, the presacral nodes and the obturator nodes. These nodes are usually covered using a whole pelvic field with the superior border of the field at L4 –L5 junction.

4.14.1 ORGAN AT RISK

The main aim of radiation therapy is to deliver adequate dose to the target volume and to avoid dose deliverance to the surrounding normal structures as much as possible. While considering radiation to uterine cervix, the main organs at risk include small/large bowel, rectum,bladder, and bilateral femoral head. Dose constrains required for an optimal IMRT plan have not been standardised .According to RTOG0921(37), the normal tissue constrains are given as follows

ORGAN AT RISK	DOSE CONSTRAIN
Small / large bowel(bowel bag)	V45< 25%
Bladder	V45 < 35%
Femoral Head	V45< 25%
Rectum	V50 <50%

Table1.1: Constrains of organs at risk

The application of these OAR constrains is practical only in conformal radiation therapy and not in conventional techniques.In RTOG0921 study, bone marrow was not considered as an OAR and constrains for the same are not known.

4.14.2 TARGET

The target volume in any radiation therapy plan should include Gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV)(38) . GTV accounts for clinical or radiological gross tumour volume. CTV= GTV +potential regions at risk for microscopic spread. PTV = CTV + margin for patient and organ movement and daily setup reproducibility.

4.15 DIFFERENT TYPES OF RADIATION THERAPY TECHNIQUES

External beam radiotherapy is delivered using either conventional techniques like four field box; AP-PA technique or by conformal techniques like 3D CRT and IMRT.

4.15.1 FOUR FIELD BOX TECHNIQUE

In four field box technique radiation is delivered using four fields, AP, PA, and 2 lateral fields .Patient is first positioned supine .Midline is checked with the help of plain x-raysimulation. In the AP –PA field the upper extent is set at the L4-L5 interspace in order to cover the lower common iliac nodes. The lateral borders are kept 1.5 to 2 cms from the pelvic brim in order to cover the iliac nodes. The inferior border is kept below the obturator foramen if vagina is not involved or 2 cm below the lower extent of the tumor. When there is vaginal involvement the entire length of the organ is treated up to the introitus. For the lateral field, the superior and inferior border is kept the same as that of AP-PA field. The posterior border is set in such a way that the entire sacrum is included within the field as the uterosacral ligaments are at high risk of microscopic extension. The anterior border of the lateral field is set at a vertical line anterior to the pubic symphysis or 3 cm anterior to the anterior border of forth lumbar vertebrae, in order to cover the external iliac lymph nodes.

4.15.2 3 DIMENSIONAL CONVENTIONAL RADIATION THERAPY

The most common acute side effects experienced by carcinoma cervix patients on radiotherapy includes nausea , vomiting , diarrhoea , irritation of urinary tract and bone marrow suppression . These side effects are worsened when administered along with concurrent chemotherapy. Late side effects of pelvic irradiation in carcinoma cervix include anatomical and physiological alterations which include strictures, fistula formation, soft tissue fibrosis, lymphedema, increased chance of fractures all of which lead to severe morbidity. Even if these late side effects are less well documented,with the recent emphasis on long term quality of life, experts have recommended that these late toxicities can be prevalent.

In the past two decades the external radiotherapy techniques have evolved dramatically. With modern imaging techniques it is easy to differentiate target volume from the normal tissue structures in the pelvis. Traditional methods of radiation delivery like four field box technique based on bony landmarks delivers unnecessary radiation to normal structures like bladder, rectum, small intestine and bone marrow. The widespread usage of cross sectional imaging like CT scan and MRI has resulted in use of 3 dimensional treatment planning.

CT simulation helps in direct assessment of extent of tumour, pelvic vessels and location of pelvic nodes. Oral contrast helps to identify the small bowel as well .During treatment delivery multi leaf collimator is used in each field to block unnecessary radiation to skin, soft tissue,muscle, small bowel and portions of the anus and lower rectum.

Various studies have shown that better dose delivery to target volume with decreased dose to OARs is achievable with 3D CRT technique when compared to conventional four field box technique. While planning the superior border is set based on the CT visualised bifurcation of

common iliac nodes into external and internal iliac nodes. The inferior border is kept 2 cm below the lowermost extent of the tumour. The lateral border of the anterior field is based upon the iliac node location as per CT.

Bonin et al did detailed anatomic mapping of pelvic lymph nodes using lymphangiography in 22 patients with carcinoma cervix. They concluded that with the margin of 1.5 cm on the pelvic brim used in the AP portal of conventional four field box technique and lateral field anterior edge as a vertical line anterior to the pubic symphysis, 10 patients (45%) had inadequate nodal coverage in the lowest lateral external iliac group(39). The omissions of these nodes can be prevented with CT simulation based contouring used in 3D CRT technique.

Zunino et al conducted similar lymphangiographic study to analyse the appropriateness of posterior coverage of the target volume in conventional box technique for carcinoma cervix(40). After defining the PTV with a 3 D planning system, they compared the field configuration of the simulator planning with a second one based on defined PTV. It was found that planning by simulation resulted in one geographic miss and the coverage of PTV was inadequate in 10 cases.

Yamazaki et al compared 34 patients with cervical cancer treated with CT simulation based planning and 40 patients who received external beam RT with conventional technique. With a follow up of 60 months, the 5 year tumour control was 94% with conventional technique and 100% with CT based technique. The incidence of grade II or III bowel complications was significantly lower in conformal technique when compared to conventional technique(41).

These studies emphasized that 3D CRT is superior to conventional technique in target coverage and reduced dose to organs at risk.

4.15.3 INTENSITY MODULATED RADIATION THERAPY

IMRT was developed using techniques that are required for inverse planning whereby the necessary dose to the target volume and dose constrain to the organs at risk are prescribed and then the programming system works backward to develop the requisite beam intensities. In IMRT, the intensity of the beam is spatially modulated using the motion of multi leaf collimators. IMRT requires delineation of the target volume and organs at risk .Dose to the tumour is prescribed in terms of gross tumour volume (GTV), clinical target volume (CTV) and planning target volume(PTV).

Dose is prescribed after making a best plan based on dose volume histograms. The prescription is optimised based on dose volume constrains specified for both target volume and organs at risk .More time and resources by physicians and technologist are required for IMRT planning and treatment delivery when compared to 3D CRT .The tumour volumes for the treatment are delineated with the help of clinical findings, imaging and clear understanding about loco regional pathway of spread of the tumourand anatomical barriers of tumourextension.

Organs at risk coming within the irradiated volume such as bowel,bladder, rectum and femoral heads must be contoured individually and appropriate dose constrains are prescribed. To maximise the therapeutic ratio, an IMRT plan appropriately optimises the dose distribution to the target volume and OARs using a computer inverse algorithm and through multistep physician feedback after the review of isodose plans and dose- volume histograms generated by the computer. Adhering to the dosimetric plans developed the linear accelerator sets up specifications by which the target volume receives the ultimate intended dose with the integration of multiple segments of radiation exposure using multileaf collimators.

Dosimetric studies have shown that IMRT can reduce normal tissue irradiation significantly in gynaecologic patients especially bowel, bladder and rectum.

Roeske et al selected 10 women with gynaecological malignancies to assess the ability of IMRT to lessen the volume of small bowel irradiated in comparison to normal conventional planning(42) .A planning CT scan was obtained for each patient target volume and OARs likerectum, bladder and small bowel were delineated for each patient . 2 plans were created, a standard four field box plan and an IMRT plan for each patient. Both plans were normalised to deliver 45 gray to the PTV , dose- volume histograms and isodose distributions were compared .In all the 10 patients IMRT plan reduced the volume of irradiated small bowel at doses above 30 gray . The average volume of irradiated small bowel was reduced by a factor of two at the prescription dose (17.4 versus 33.8%, p=0.0005) .In addition at the prescription dose the average volume of rectum and bladder irradiated was reduced by 23%. The average PTV dose delivered by IMRT and conventional plans were 47.4 Gy and 47.8 Gy respectively. It was concluded that IMRT is auseful means of reducing the volume of irradiated small bowel in patients with gynaecological malignancies in patients who received whole pelvic radiation therapy.

In a study was conducted by Mundt et al , 40 patients with gynaecological malignancy were selected after making customised immobilisation(43). All patients were evaluated with contrast enhanced CT and target volume was contoured. Using available software, 7 or 9 fields, 6 MV, coplanar IMRT plans were drawn up for all the patients. The acute gastrointestinal and genitourinary toxicity during treatment was scored on a 4 point scale :0, none; 1, mild , no medication required ;2, moderate , medication required ;3 , severe, treatment break or cessation, hospitalisation.

The results were analysed and it was found that IMRT plans are providing excellent PTV coverage with substantial sparing of adjacent normal structures. On an average 98.1% of the PTV received the prescription dose. The proportion of PTV receiving 110% and 115% of the prescribed dose were 9.8 % and 0.2 % respectively. IMRT was well tolerated by all the patients, no patients developed grade 3 gastrointestinal toxicity. When compared to conventional group grade 2 acute gastrointestinal toxicity was less common in IMRT group (60 versus 91 %, p=0.002). Grade 2 genitourinary toxicity was seen less in the IMRT group.

Selvaraj et al studied 10 patients with gynaecological malignancy at the University of Pittsburgh. The aim of the study was to evaluate the feasibility of IMRT plan in these patients and to determine the acute and long term toxicity with IMRT plan when compared to 3D CRT plan. A seven field technique using 6MV photon was used for IMRT. Restrains on small bowel for IMRT was set as 23.0 Gy +/- 5% and 35.0Gy +/- 5% for the rectum and 37.5 Gy +/- 5% for bladder while delivering 45 Gy to the target volume in 1.8 Gy per daily fraction. The volume of small bowel receiving doses more than 30 Gy was reduced by 52 % in IMRT plans when compared to 3DCRT. Similarly in rectum, there was reduction of 66% and bladder 36% without compromising dose to the target volume.

A similar study was conducted by Portelance et al (44)to prove that intensity modulated radiotherapy reduces small bowel , rectal , and bladder doses in patient with cervical cancer receiving pelvic radiotherapy. It was concluded that with comparable target coverage, normal tissue sparing was superior with IMRT in the treatment of cervical cancer when compared to other techniques

While the above studies were conducted in order to show the superiority of IMRT over other conventional or 3D techniques in the management of gynaecological malignancies in

reducing bowel and bladder toxicities, it was also noted that there was an additional benefit of reduced incidence and severity of acute haematological toxicity.

This benefit in haematological toxicity was seen without considering bone marrow as constrain in the treatment planning. The reduction in volume of bone marrow irradiated especially the iliac crest was a natural result of IMRT planning.

These observations paved the way to the concept that contouring bone marrow as a separate organ at risk and giving a constrain for the same in IMRT treatment planningmay help in better sparing of bone marrow which can result in decreasing haematological toxicity without compromising the coverage to the target.

Mundt et al reported the first clinical series of 40 patients treated with whole pelvic IMRT in 2001, most of whom were post hysterectomy patients. They compared the results of this study with 35 historic controls treated with conventional fields. They focussed on reduction of the volume of OARs irradiated to decrease toxicity. He noticed that IMRT patients showed a decrease in hematopoietictoxicity. There was significant drop in the volume of bone marrow receiving more than 30% of the treatment dose. On average the IMRT planning resulted in a 50% reduction in the bone marrow volume irradiated to doses more than 22.5Gy m. Acute hematologic toxicity in patients treated concurrently with chemotherapy was significantly less when treated with IMRT(40% versus 12.5%, p=0.06), attributed to less iliac crest bone marrow volume being irradiated(45) .

Lujan AE et al selected 10 patients with cervical or endometrial cancer formerly treated with IMRT for analysis. 3 plans were formed for each patient: a standard 4 field plan, IMRT treatment plan excluding bone marrow and a bonemarrow sparing IMRT (BMS IMRT) plan in which bone marrow is included as an additional treatment planning constrain(46)I. For

each of the 10 patients, BMS-IMRT treatment plans confirmed a significant reduction of the volume of bone marrow which received more than 40% (18 Gy) of the prescription dose '(45 Gy) in comparison with both IMRT and 4 fields box treatment technique. BMS IMRT resulted in just 60% of the bone marrow volume irradiated to > 50% of the dose compare with 87.4% ($p<0.001$) of the bone marrow volume in a four field plan and 75.7% ($p<0.003$) of the volume in an IMRT plan . The BMS IMRT plan resulted in considerable sparing of all other normal tissue that was comparable to the IMRT plan. In all 10 cases, the BMS IMRT plan did not produce any significant differences in the PTV and small bowel dose volume histograms, compared with the IMRT treatment plan.

Brixey et al conducted a study to assess the impact of intensity modulated pelvic radiation therapy on acute haematological toxicity in gynaecological patients. 36 patients diagnosed to have gynaecological malignancy who received IMRT between February 2000 and June 2001 was recruited in the study, target volume consisted of uterus,parametrium,and uppervagina, presacral and pelvic lymph nodes. Using 7 or 9 coplanar beams IMRT plans were generated, their aim was to acquire adequate coverage to the target while minimising the dose to bladder, rectum and small bowel. Bone marrow was not used as a constrain in the planning method. The variable used to analyse acute haematological toxicities included white blood count, absolute neutrophil count, platelet count and haemoglobin. These variables were analysed before RT and weekly during RT. As a comparison, 88 patients treated to attain the same target volume and same total dose (45 Gy) with conventional four field radiation was analysed. It was found that there was no differences in the baseline white blood cell count, absolute neutrophil count, platelet or haemoglobin levels between the two groups. It was observed that significant haematological toxicity was uncommon in women treated with RT alone and it was similar in both the groups. However, patients who received whole pelvic

radiation therapy with concurrent chemotherapy experienced more grade 2 or greater white blood cell toxicity (60% versus 31.2 %, p=0.08) and absolute neutrophil count (1874 versus2669, p=0.04) nadirs than intensity modulated whole pelvic radiotherapy. It was also found that chemotherapy was withheld more often in conventional RT group due to acute haematological toxicity (40% versus 12.5%, p=0.06). Therefore, it was concluded that IMRT is having a favourable impact on acute haematological toxicity in gynaecological patients especially in those who are receiving concurrent chemotherapy(47).

Loren et al did a comparative study between bone marrow sparing IMRT with four field box technique and AP-PA technique in 7 patients with carcinoma cervix(48). Uterus, cervix, upper vagina,and parametrium, presacral and other pelvic lymph nodes were included in CTV.Bladder, bowel, rectum and pelvic bone marrow were considered as normal tissues which are organs at risk.Comparison was made between the DVH curves for the planning target volume and normal tissues in BoneMarrow Sparing - IMRT versusother conventional techniques. It was found that Bone Marrow Sparing IMRT is superior over conventional techniques in reducing the total dose received by the bonemarrow,bladder, small bowel and rectum. BMS IMRT reduced bone marrow dose to less than 16.4 Gy . It was concluded that Bone Marrow Sparing IMRT can reduce irradiation of pelvic bone marrow when compared to either conventional techniques.

In view of various study results it was concluded that with an IMRT plan in which bone marrow is contoured as an OAR , adequate dose coverage to the target with reduced dose to other normal structures including bone marrow is achievable . However the clinical importance and best possible technique of bone marrow sparing IMRT in patients with gynaecological is still under evalaution.

Various bone marrow sparing studies have mainly focussed on iliac crest bone marrow sparing .However information from various imaging,histopathologic and clinical studies have pointed out that regions of pelvic bone which are exposed to radiation such as lumbosacral spine, ischium, pubis and proximal femur are also major contributing factor in haematological toxicity.

Differentstudies were performed to determine factors predictive for haematological toxicity in patients receiving concurrent chemo radiation.

Kevin et al did retrospective study on 40 women who received concurrent chemo radiation for cervical cancer(49). A common terminology criterion for adverse events (version 3.0) wasconsidered to define haematological toxicity. Various predicting factors for haematological toxicity such as age ,BMI, transfusions and volume of irradiated bone marrow were incorporated in the data scrutiny .Out of the 40 patients, 13 patients had grade 0 or grade1Haematological Toxicity,27 patients had grade 2 to 4 Haematological toxicity. Multiple logistic regression analysis was done which showed that volume of bone marrow receiving 20 Gy (V20) for whole pelvic bone showed significance towards grade 2to grade 4 haematologicaltoxicity. A partitioning analysis to predict grade 2 and more Haematological toxicity showed value of around 80% for V20 of whole pelvic bone implying that if the volume of bone marrow receiving 20 Gy exceeds above 80%, the risk of developing grade 2 and more haematological toxicityexceeds by a factor of 4.5.

Mundt et al analysed 37 cervical patients receiving chemo radiation , for each patient bone marrow contoured , was divided into 3 sub sites ; lumbosacral spine , ilium and lower pelvis . The volume of each region receiving 10,20,30,>/= 40 Gy was calculated. It was found that increased pelvic bone marrow V10 was associated with increased grade 2 leukopenia and

neutropenia. It was found that there was no association between haematological toxicity and V30 and V40. It was concluded from his study that volume of pelvic bone marrow receiving low dose radiation is the predictor for haematological toxicity(48).

In order to put the hypothesis to the test that increased pelvic bone marrow irradiation can lead to increased haematological toxicity in patients receiving chemoRT and to develop a normal tissue complication chance for haematological toxicity, Rose et al conducted a study on 44 cervical patients. The volume of bone marrow receiving more than 10 and 20 Gy and its association with hematologic nadirs were tested using linear regression model. It was observed that there was significant negative correlation between WBC nadir and V10 (regression coefficient = -o.06, p=0.009) and V20 (regression coefficient = -0.044, p=0.010). Patients with V10 > 95% were highly likely to experience more than or equal to grade 3 leukopenia than were patients with V20 > 76(50). It was concluded that as the irradiated pelvic bone marrow volume increases, haematological toxicity increases. Efforts to restrict V10 < 95% and V20 < 76% may reduce haematological toxicity.

At present as there are no standard guidelines for contouring bone marrow, various methods are practiced. Among them Whole bone contouring and freehand contouring of inner cavity of bone are the commonly used techniques.

Loren et al, in their study to analyse dosimetric predictors of acute haematological toxicity in carcinoma cervix patients treated with concurrent chemoRT contoured bone marrow by delineating the external outline of the bone from L4-L5 junction to the inferior border of ischial tuberosities.

PET CT technique is the optimal technique in delineating bone marrow as it helps in delineating the active bone marrowbased upon the SUV value's based technique is asurrogate

for the volume of bone marrow and is considered as arepresentative of the actual marrow delineated using PET CT.Two contouring methods are available for bone marrow contouring on CT scans, free hand contouring and auto contouring.Free hand bone marrow contouring,is considered better than auto contouring in order to create an acceptable bone marrow volume for radiation planning.

In free hand contouring, two methods are used to contour marrow worldwide, either contouring the entire bone marrow outside the cortex which will represent the bone marrow or just contouring the inner hypodense area in the bone adjusting the bone window in CT scan which will also represent the marrow.

Various pilot studies are have compared these two methods to see which is more accurate in contouring the bone marrow. Nomulti institutional studies has been done so far on the same and there is no universally accepted guidelines for bone marrow contouring.

Recent advances in the radiation therapy delivery in the management of carcinoma cervix include tomotherapy and proton therapy. Tomotherapy is a combination of IMRT with the precision of inbuilt CT technology in the same .Using tomotherapy we can deliver the radiation even more precisely to the tumor than IMRT technique. With the help of inbuilt CT scan, it is possible to confirm the position of the tumor each day during treatment with which the advantage of adaptiveradiation. All these helps in increasing dose conformity to the tumor there by decreasing the dose to the normal structures like bowel , bladder and bone marrow(51).Recent studies on proton therapy and carbon ion therapy in carcinoma cervixhave shown that the tumor control , morbidity and survival are similar to that seen in conventional techniques (52).

5.METHODS AND MATERIALS

Data set from 16 women with Carcinoma cervix treated in our institution from July 2013 to January 2014 using 3D CRT or IMRT were selected for the study.

5.1 INCLUSION CRITERIA:

CT scans of

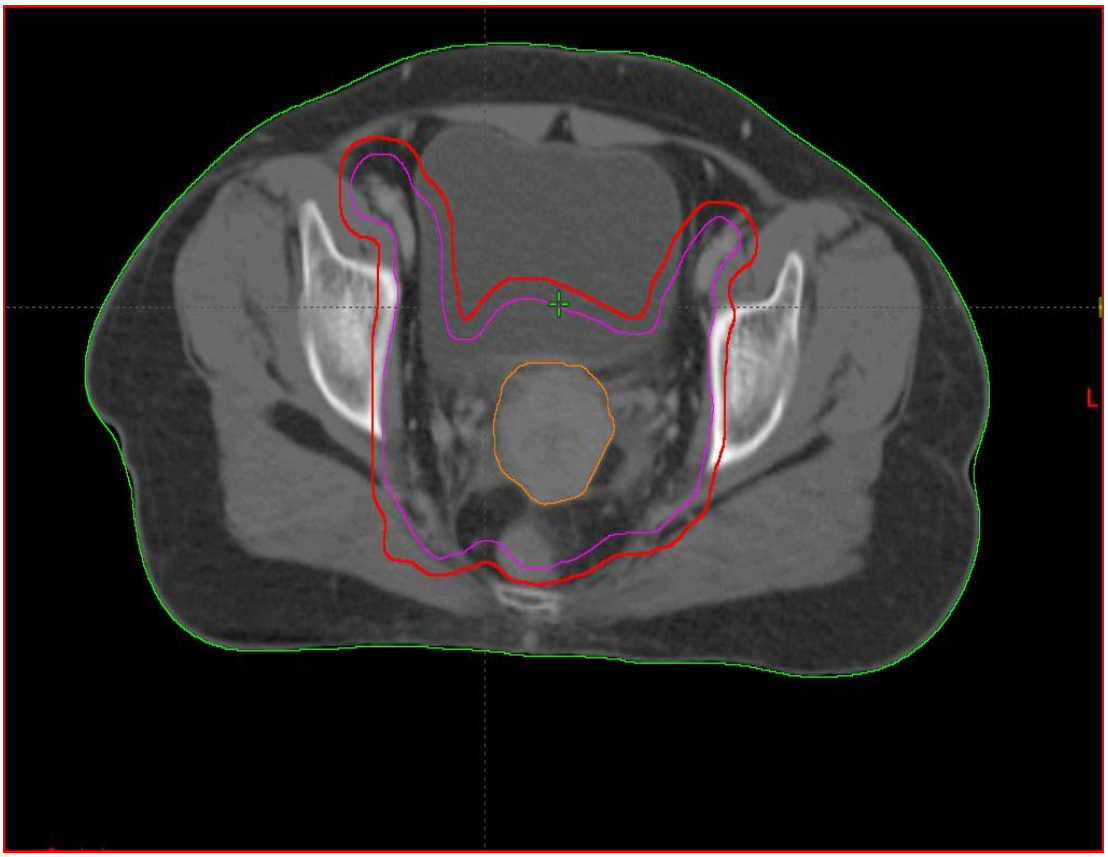
1. Female patients of more than 18 years of age
2. ECOG 0-1
3. With squamous cell carcinoma cervix
4. Diagnosed to have carcinoma cervix IIA to IVA (FIGO staging)
5. Patients who were planned and treated with radical chemo irradiation with or without brachytherapy and , treated with conformal techniques.dile
6. Patients who already had CT scan in our institution.

5.2 EXCLUSION CRITERIA

1. Female patients less than 18 years of age
2. ECOG >1
3. Patient diagnosed to have Carcinoma cervix with histology other than squamous cell.
4. Patients with FIGO stage IA, IB and IVB
5. Patients who did not receive radical chemo irradiation
6. Patients who were treated with conventional technique , and did not have CT scan in our institution

All the 16 patients who were selected in the study had CT scan with 5mm slice thickness from the diaphragm to midthigh. These images were imported to Eclipse Treatment Planning version 10.0.39. Following this, after discussing with radiologist and with clinical correlation Gross Tumour Volume was drawn. The Gross Tumour Volume (GTV) was defined as the gross disease determined from clinical information and imaging .CTV or the clinical target volume was the area considered to have potential microscopic spread. This was contoured separately as primary CTV and nodal CTV.Primary CTV included the entire GTV,uterus,cervix, parametrium,bilateral adnexa including ovaries and upper half of the vagina if there was minimal or no vaginal involvement ,upper two third of the vagina if upper vagina was involved and entire vagina if there was extensive vaginal involvement.Nodal CTV included all the regional lymph nodes like the internal (hypo gastric and obturator), external, and common iliac lymph nodes and pre sacral nodes. For contouring the nodal CTV, initially the vessels were contoured and a 7 mm margin to this vesselproduced the nodal CTV.Psoas muscle, piriformis, bone,and intraperitoneal small bowel were excluded from the CTV.About 1-2 cm of tissueanterior to the S1, S2 and S3 sacral segments was added to the CTV in order to include the presacral lymph nodes and uterosacral ligaments.Antero-lateral external iliac lymph nodes that lie just before the inguinal canal were excluded from the CTV .Nodal CTV was stopped at the level of the femoralhead. The CTV of the nodes were also stopped 7 mm from L4/L5 junction to account for the PTV.The final CTV was created fusing the primary CTV and the nodal CTV.A margin of 7mm all around the final CTV was used to generate the PTV.PTV or the planning target volume was given to account for the daily set up error and organ motion and was limited at L4/L5 junction.

FIGURE SHOWING DELINEATED GTV, CTV AND PTV ON CT SCAN:



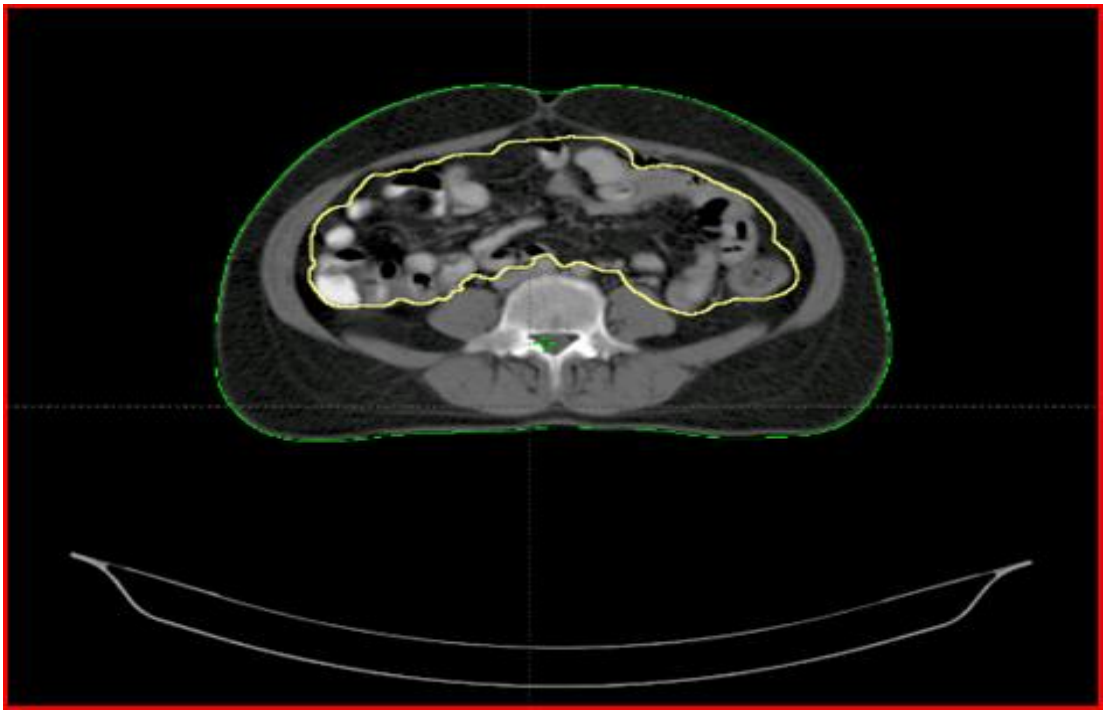
-PTV - CTV - GTV -BODY

Fig 7.1: Delineation of GTV, CTV and PTV

The normal Organs at risk contoured included the bladder,small bowel,rectum, femoral heads and bone marrow.

Bladder was outlined on all slices,together with the portion lower to the planning target volume.Rectum was contoured on all slices, including the portion inferior to the planning targetvolume.Superiorly rectum was contoured till it leaves the posterior pelvis around the region of therecto sigmoid.Bowel bag was contoured at least 2 cm above the planning targetvolume.The femur was contoured including the femoral head , the neck and upto the lesser trochanter or upto the level of last cut of ischial tuberosity.

FIGURE SHOWING DILENIATED ORGANS AT RISK IN CARCINOMA CERVIX IMRT PLANNING CT:



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BODY -BOWEL

Fig.7.2: Delineation of bowel bag on CT scan

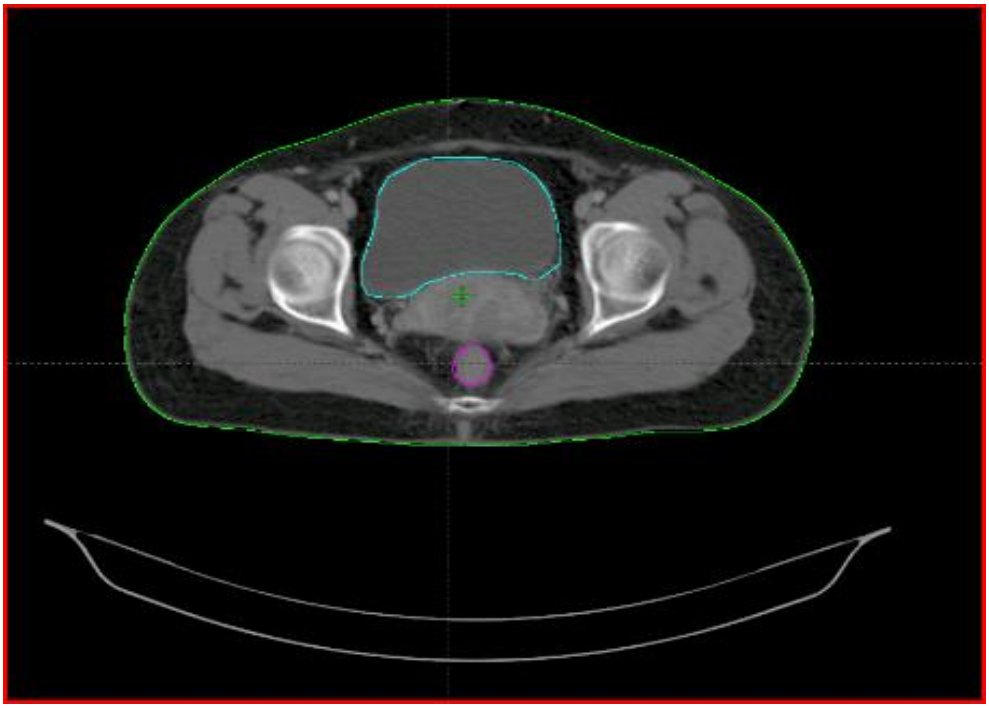

Fig.7.3: Delineation of bladder and rectum

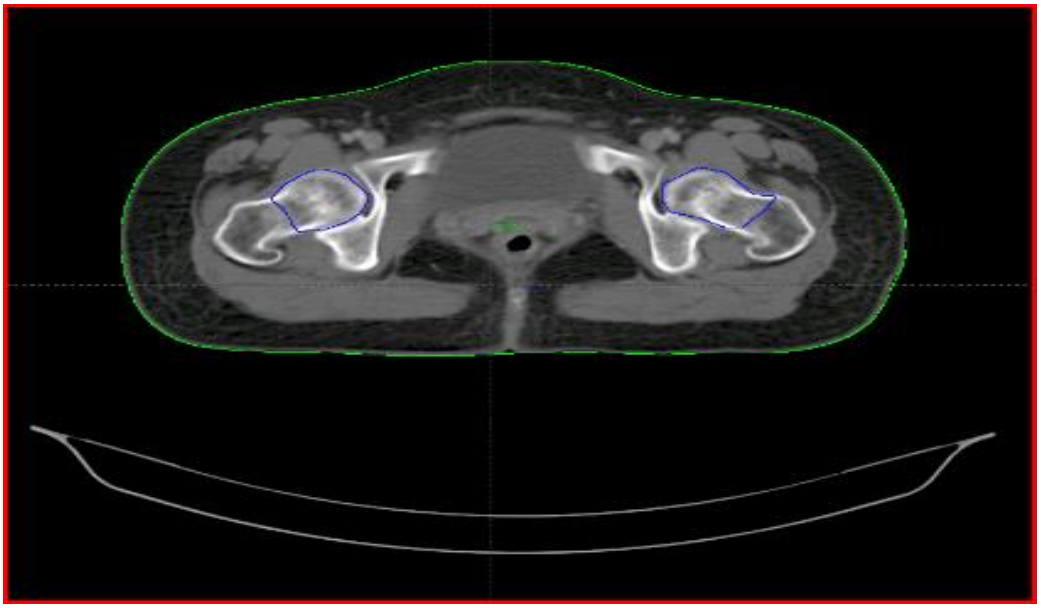

Fig 7.4: Delineation of femoral head

In bone marrow sparing IMRT plans alone (BMS-IMRT), bone marrow was drawn as a separate organ at risk.Bone marrow was contoured using free hand technique in each CT cut including entire L5 vertebral body, sacrum,coccyx, ileum,ischium, pubis and femoral head extending down till the last cut of ischial tuberosity on the CT.2 cm 3D brush was the tool used in contouring the bone marrow in all the patients.

5.3 DELINEATION OF BONE MARROW

FIGURE SHOWING BONE MARROW DILENIATED ON CT SCAN:

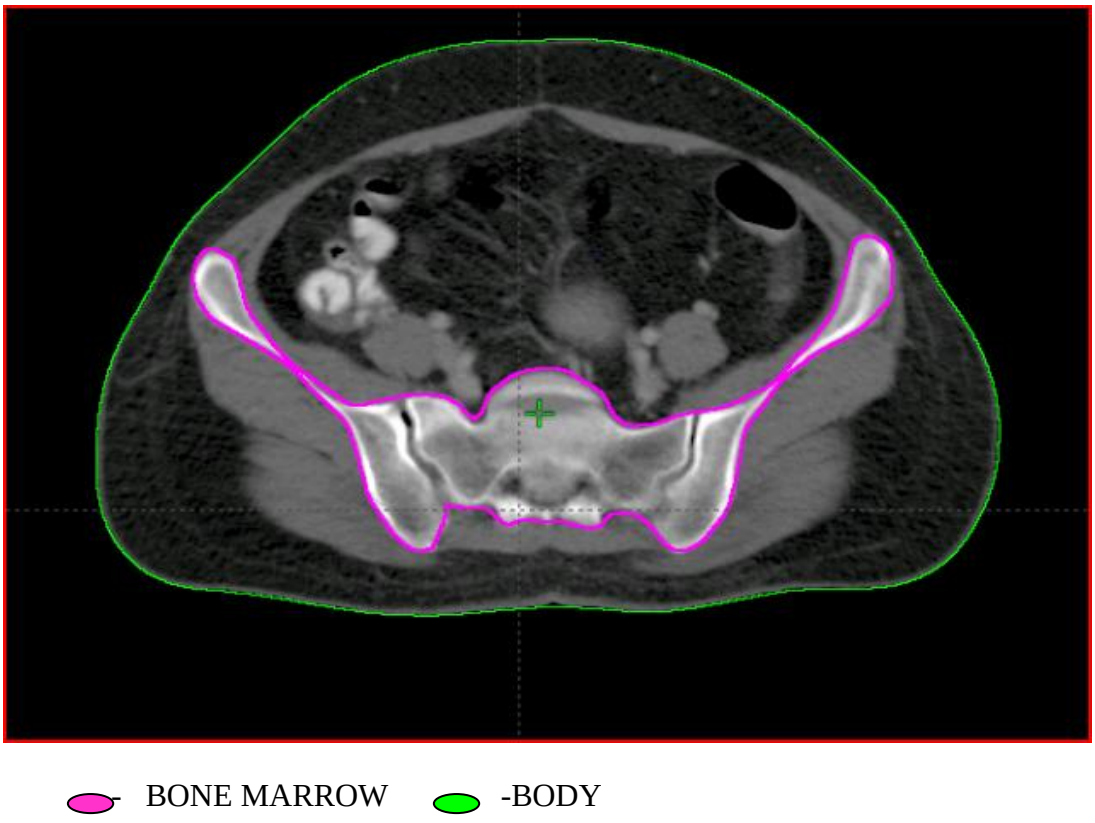

Fig.7.5: Delineation of bone marrow on CT scan

Constraints to the organs at risk and the target volume were prescribed as per the standard RTOG guidelines given below.

PTV (Planning Target Volume):

Prescription Dose: 5040 cGy in 28 fractions.

Desirable D 98 = 50.4Gy, Acceptable D98= 47.88Gy ,D 2cc < 55.44Gy

47.88Gy D 98- Dose received by 98 % of the target volume.

CONSTRAINTS TO ORGANS AT RISK(RTOG-0921)

Small Bowel – V 45 < 25%

V 45- Volume of the OAR receiving 45 Gy.

Femoral Head- V 45 < 25%

V 35< 15%

Bowel - V 45 < 25%

Bladder- V 45 < 35%

Rectum - V 50 < 50%.

5.4 CONSTRAIN TO BONE MARROW:

Currently there is no universally accepted bone marrow constrain for treatment planning .Rose et al, proposed **V 10 <95%** **and** **V 20 < 76%**(V 10 and V 20 represented the volume of

bone marrow getting 10 Gy and 20 Gy respectively) as bone marrow constrain after correlating with grade 3 bone marrow toxicity(53).

Following this four treatment plans were developed for all of the patients.

1. Conventional Four field box plan.
2. ThreeDimensional Conformal Radiation Therapy (3DCRT)
3. Intensity modulated radiation therapy (IMRT)
4.Bone Marrow Sparing Intensity Modulated Radiation Therapy (BMS- IMRT).

CONVENTIONAL FOUR FIELD BOX PLANNING

Four field box technique was modelled same as conventional 4 field planning except the fact that instead of putting shields manually, multi leaf collimators were used for shielding the upper corners in anteroposterior and posterior upper corner in lateral fields .In this technique Organs at risk were not subjected to any shielding. Planning was done using 2 anteroposterior and 2 lateral 6 MV beams with equal weightage .

3 DIMENSIONAL CONFORMAL RADIATION THERAPY (3DCRT)

In three dimensional conformal radiation therapy (3DCRT) planning, beams were added in different gantry angles or sometimes with same gantry angle according to the tumour shape and coverage.The main difference from 4 FIELD BOX shaping in this planning was, along with shaping of target with multi leaf collimators the organs at risk were also

shielded.3DCRT planningconsidered as forward planning was modelled such that it provided an optimal coverage of PTV and respected the dose constraints of the organs at risk in the best possible way.

INTENSITY MODULATED RADIATION THRAPY (IMRT)

Intensity modulated radiation therapy planning is otherwise named as inverse planning. In this first the dose to the tumour along with the tolerance dose constraints to the organs at risk were initially fed in the planning system. The organs at risk considered in the plan included bowel, bladder, rectum and femoral head. Using AAA planning algorithm, plans were created with 7 to 9 non coplanar beams using, 6MV energyto get adequate tumour coverage and dose to the organs at risk within the tolerance limits as per the guidelines.

BONE MARROW SPARING INTENSITY MODULATED RADIATION THERAPY (BMS- IMRT).

Bone marrow sparing IMRT plans were also similar to IMRT plans. The addition in this plan above IMRT plan was, bone marrow was contoured as an extra organ at risk with dose constrain. This dose constrain was also incorporated with other OAR s dose constrain to the planning system and the plans were modelled.

6.DATA COLLECTION:

Once all four plans were modelled ,plan evaluation was done.Dose volume histogram (DVH curves), isodose curves, dose colour wash and presence of hot spot were used for plan evaluation. It was analysed that whether the values are fulfilling the requirement as per RTOG guidelines. As the objective of the study, theparameters looked into were

1. Volume of bone marrow receiving 10 Gy (V 10) and Volume of bone marrow receiving 20 Gy (V 20) in various plans.

2. Whether there is adequate dose coverage to PTV with bone marrow sparing IMRT plan in comparison to other planning techniques?

3. Whether the doses to the organs at risk are within the acceptable limits of RTOG guidelines with BMS- IMRT plan?

   The end point of the study was to assess whether it is feasible to create an IMRT plan in which bone marrow is contoured as an organ at risk with a given dose constrain and to see whether it is possible to decrease the dose to bone marrow when compared to other plans in which bone marrow is not considered as an organ at risk without compromising the dose to the target volume and increasing dose to other organs at risk.

Volume of bone marrow receiving 10 Gy (V 10) and Volume of bone marrow receiving 20 Gy (V 20) in various plans.

This data was analyzed from the Dose Volume histograms of bone marrow in all the four plans for all 15 patients. For each patient, for all four plans from the DVH curves, the volume of bone marrow receiving 10 Gy and 20 Gy was documented.

Whether there is adequate tumour coverage with Bone marrow sparing IMRT plan in comparison to other planning techniques?

The assessment of adequate tumour coverage was made by observing the dose received by 98% of the planning target volume (D98) and the maximum dose received by 2cc volume of the PTV (D 2cc).The data was collected for all the four plans for all patients.

Whether the doses to the organs at risk are within the acceptable limits of RTOG guidelines with BMS- IMRT plan in comparison with other techniques?

The organs at risk considered in all the four plans were femoral head, bowel, bladder , rectum and bone marrow .As per the RTOG guidelines normal OAR s dose constraints, for femoral head volume receiving 35 Gy and 45 Gy (V 35 and V 45)was measured from the dose volume Histograms (DVH). For bowel, the volume receiving 45 Gy was measured (V45).For bladder and rectum, the volume receiving 45 Gy and 50 Gy was measured (V 45 and V 50).

7.OBSERVATIONS:

7.1 DOSE TO BONE MARROW

VOLUME OF BONE MARROW RECEIVING 10 Gy (V 10) AND VOLUME OF BONE MARROW RECEIVING 20 Gy (V 20) IN VARIOUS PLANS.

SL NO	4FB-V10	4FB-V20	3DCRT-V10	3DCRT-V20	IMRT-V10	IMRT-V20	BMSIMRT-V10	BMS1MRT-V20
1	95.59	91.59	97.05	92.06	98.49	83.46	87.93	67.32
2	99.47	97.07	99.49	96.91	96.19	87.97	87.74	69.11
3	95.97	91.31	95.88	90.94	95.6	81.92	83.12	54.71
4	98.5	94.89	97.95	94.62	99.36	92.03	91.29	70.95
5	100	99.7	99.99	99.63	100	93.95	92.05	72.91
6	99.34	97.25	99.32	97.07	99.65	87.59	91.49	71.65
7	99.19	96.33	99.36	95.93	96.5	87.83	92.14	70.08
8	98.57	95.52	98.31	95.21	99.4	94.9	91.78	71.84
9	96.1	92.07	96.06	92.09	99.55	83.48	86.39	69.17
10	98.42	95.52	98.01	95.68	97.5	89.57	85.68	66.27
11	99.66	98.52	99.56	98.5	99.04	96.95	94.91	74.44
12	96.24	91.35	95.48	89.76	96.58	85.96	86.88	71.94
13	98.08	94.99	98.15	95.27	98.36	89.97	91.75	75.45
14	100	99.3	99.99	99.22	99.53	93.25	94.04	77.62
15	98.98	96.32	98.88	96.26	97.57	82.16	86.63	66.92
16	96.42	93.11	96.71	92.79	97.67	88.66	89.51	68.59
MEAN	**98.15**	**95.30**	**98.13**	**95.12**	**98.18**	**88.72**	**89.58**	**69.99**

Mean V10 in BMS-IMRT = 89.58% Mean V 20 in BMS-IMRT = 69.99%

Table 2.1: V 10 and V 20 of bone marrow in various plans

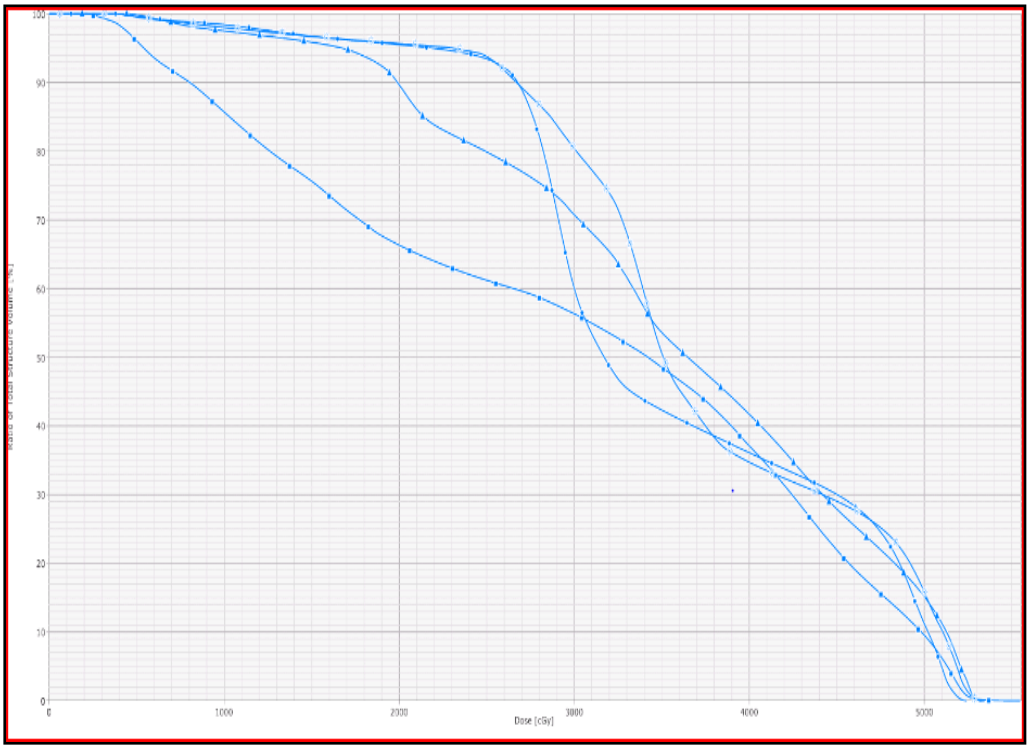

Fig .8.1: DVH curves of bone marrow in 4 FIELD BOX plan, 3DCRT, IMRT and BMS-IMRT for comparison of V10 AND V20

-WITH PELVIC BONE -WITHOUT PELVIC BONE

- 4 FIELD BOX - 3DCRT

AXIAL SECTIONS OF THE CT SCAN OF A REPRESENTATIVE PATIENT SHOWING 100% ,70%,50% AND 40% ISODOSE LINES FOR BMS-IMRT,IMRT ,3DCRT AND 4FIELD BOX 4 FIELD BOX TECHNIQUE

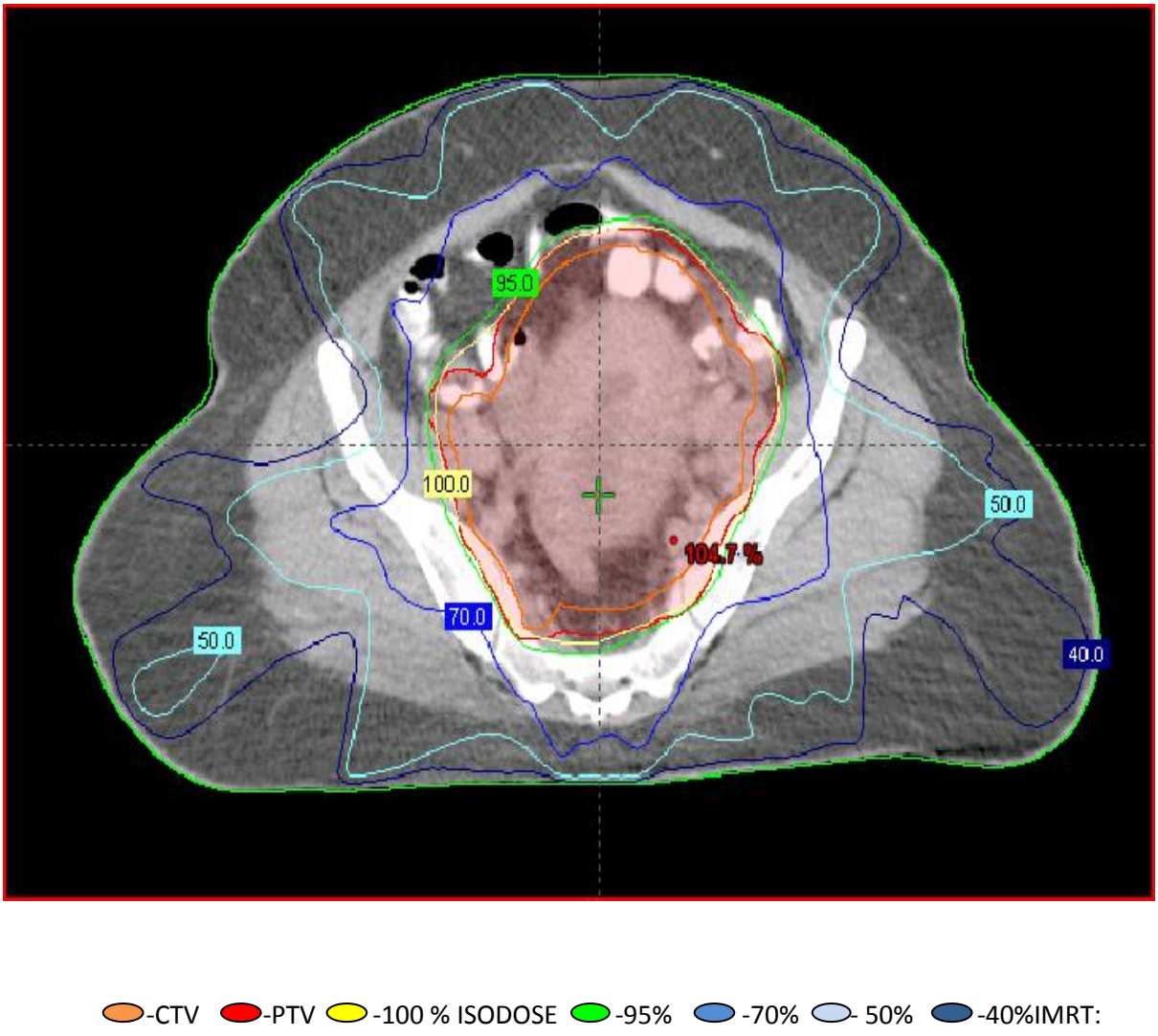

Fig.9.1: Bone marrow sparing IMRT, 100%, 70%, 50% AND 40% isodose lines.

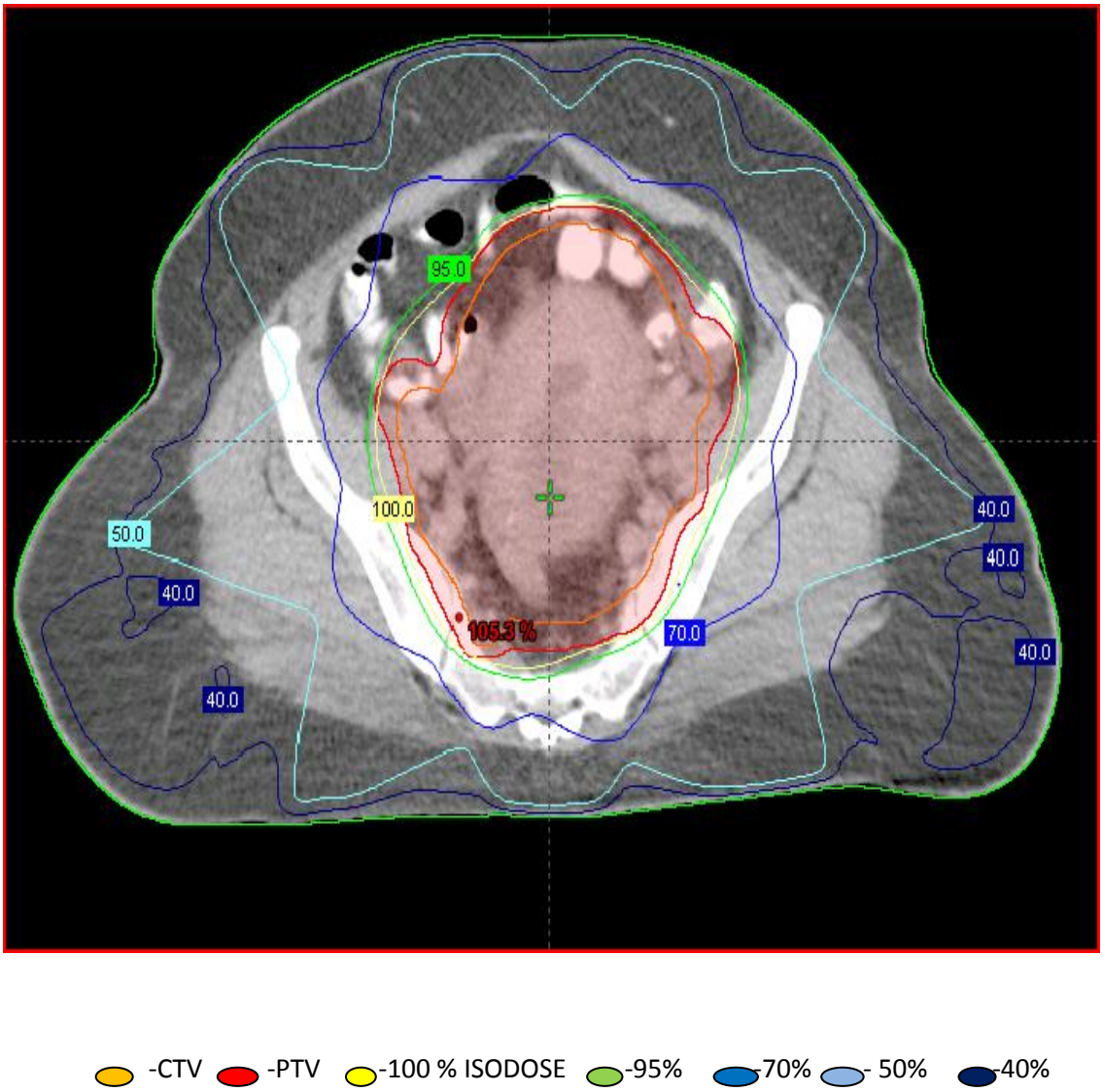

Fig.9.2: IMRT plan showing 100%, 70%, 50% and 40% isodose lines.

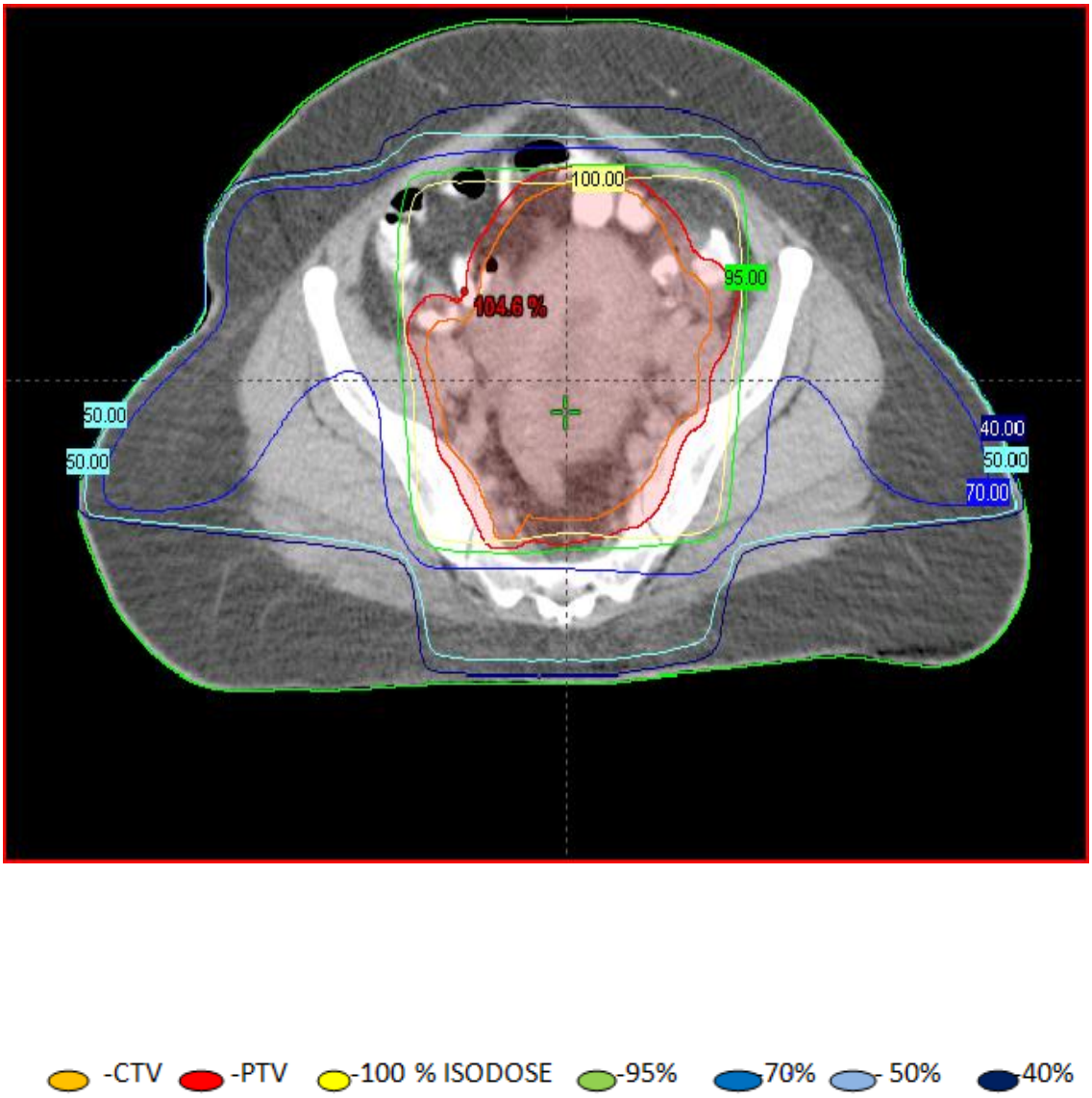

Fig.9.3: 3DCRT plan showing 100%, 70%, 50% and 40% isodose lines.

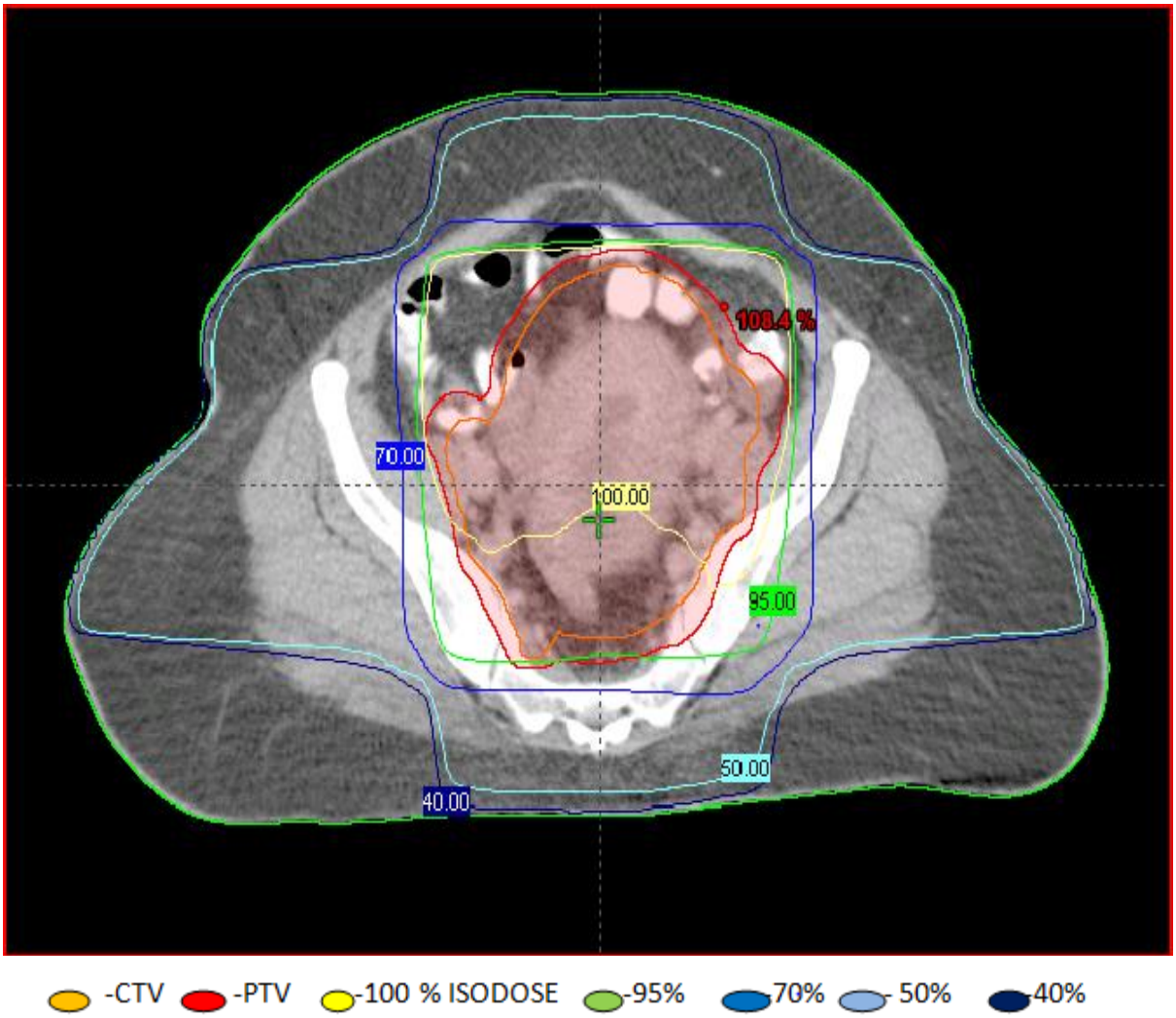

Fig.9.4:4 FIELD BOXplan showing 100%, 70%, 50% and 40% isodose lines.

It was observed by visual inspection of the isodose curves that in BMS-IMRT plan ,there was a greater bending of the isodose curves away from the bone marrow, conforming the dose more closely to the PTV in the regions were bone marrow was contoured when compared to the same isodose lines in IMRT,3DCRT and 4 field box 4 FIELD BOXtechnique. It was observed that IMRT plans were showing better sparing of the bone marrow when compared to 3DCRT and 4 field box 4 FIELD BOXtechniques. The observation noted for this lone patient was also seen in the average DVHs for all the 15 patients.

DOSE COLOUR WASH IN A REPRESENTATIVE PATIENT FOR ALL FOUR PLANS WITH BMS-IMRT, IMRT, 3DCRT AND 4 FIELD 4 FIELD BOX TECHNIQUES

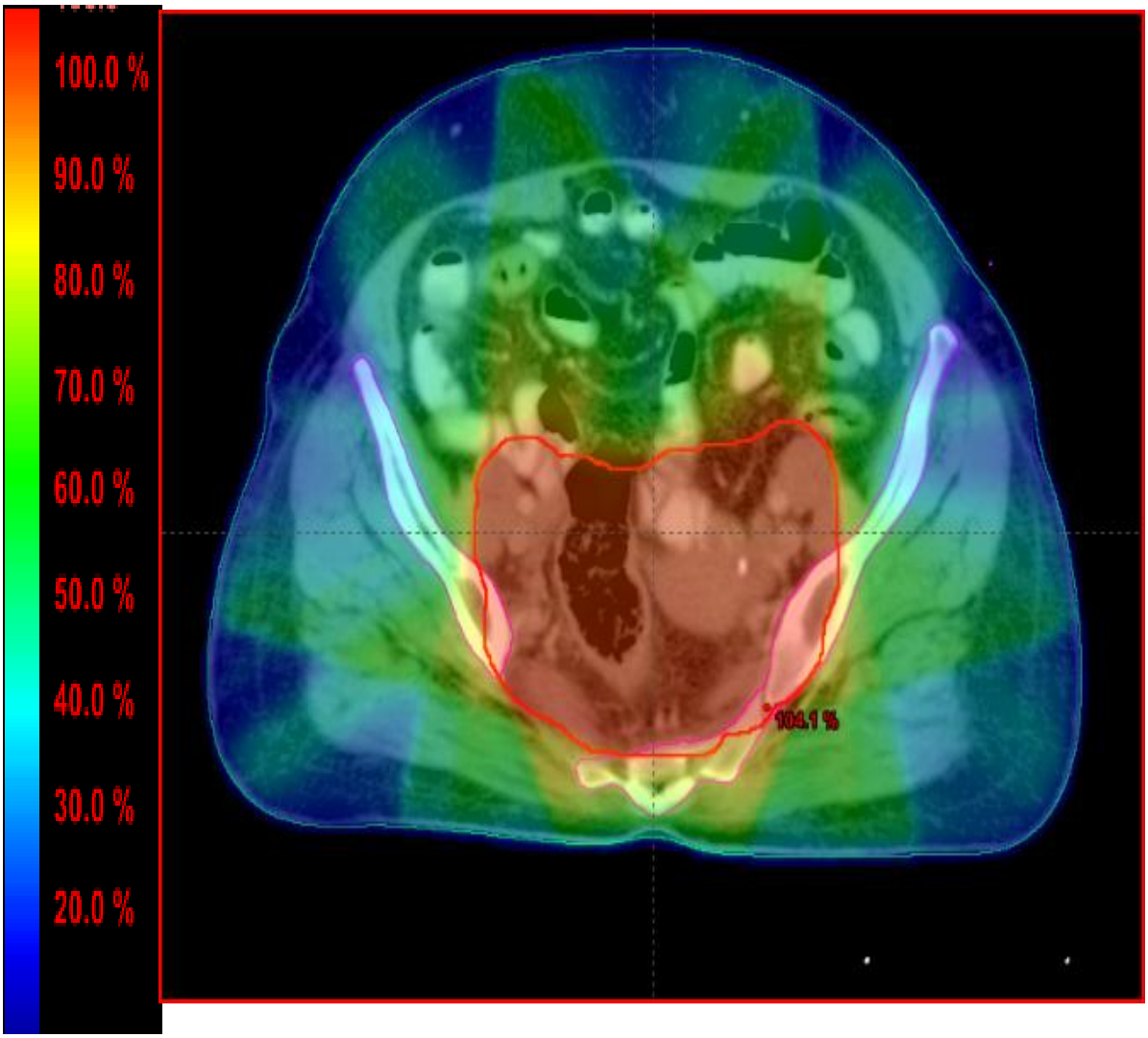

Fig.10.1: Dose colour wash in BMS –IMRT plan

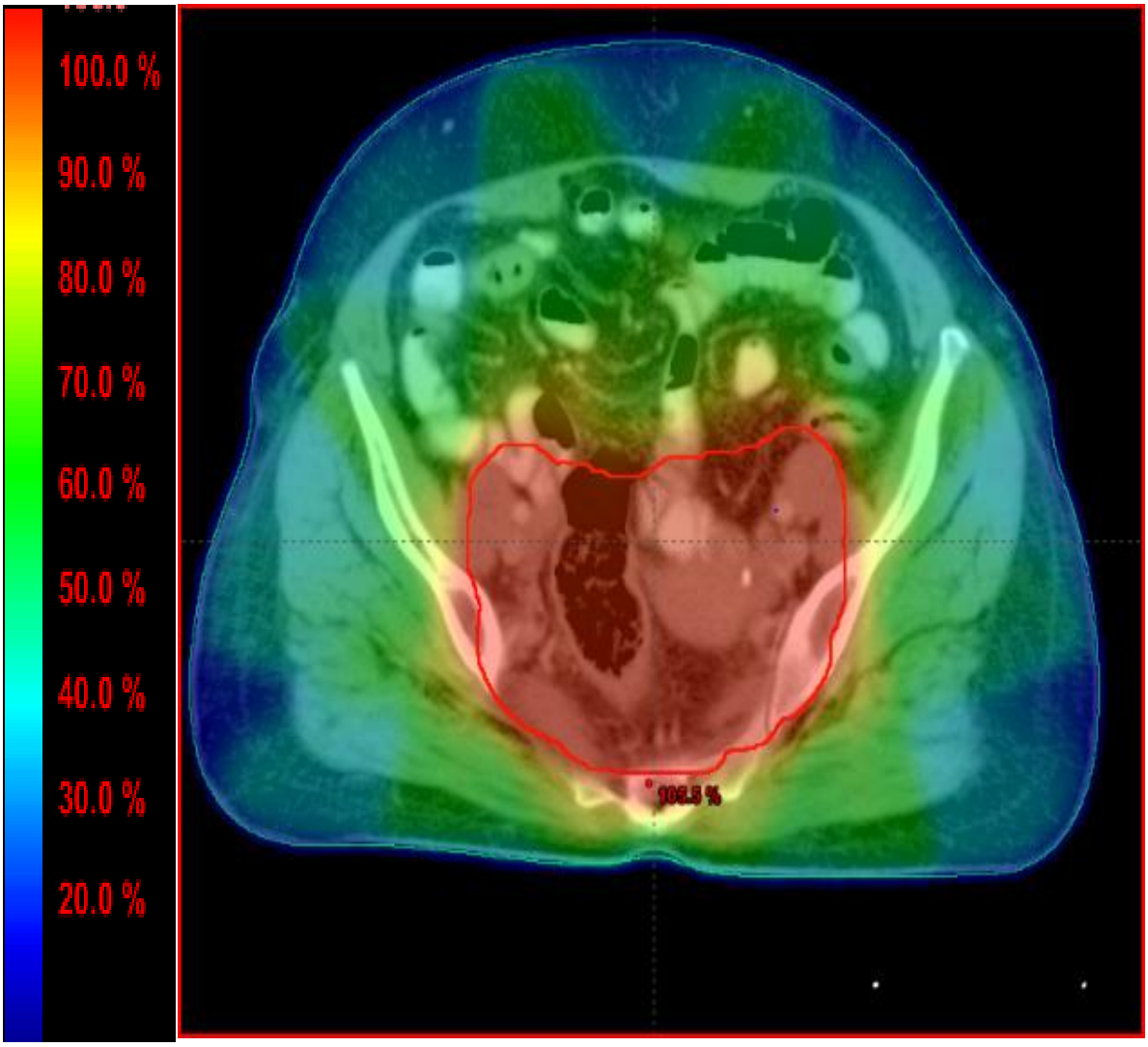

Fig.10.2: Dose colour wash in IMRT plan

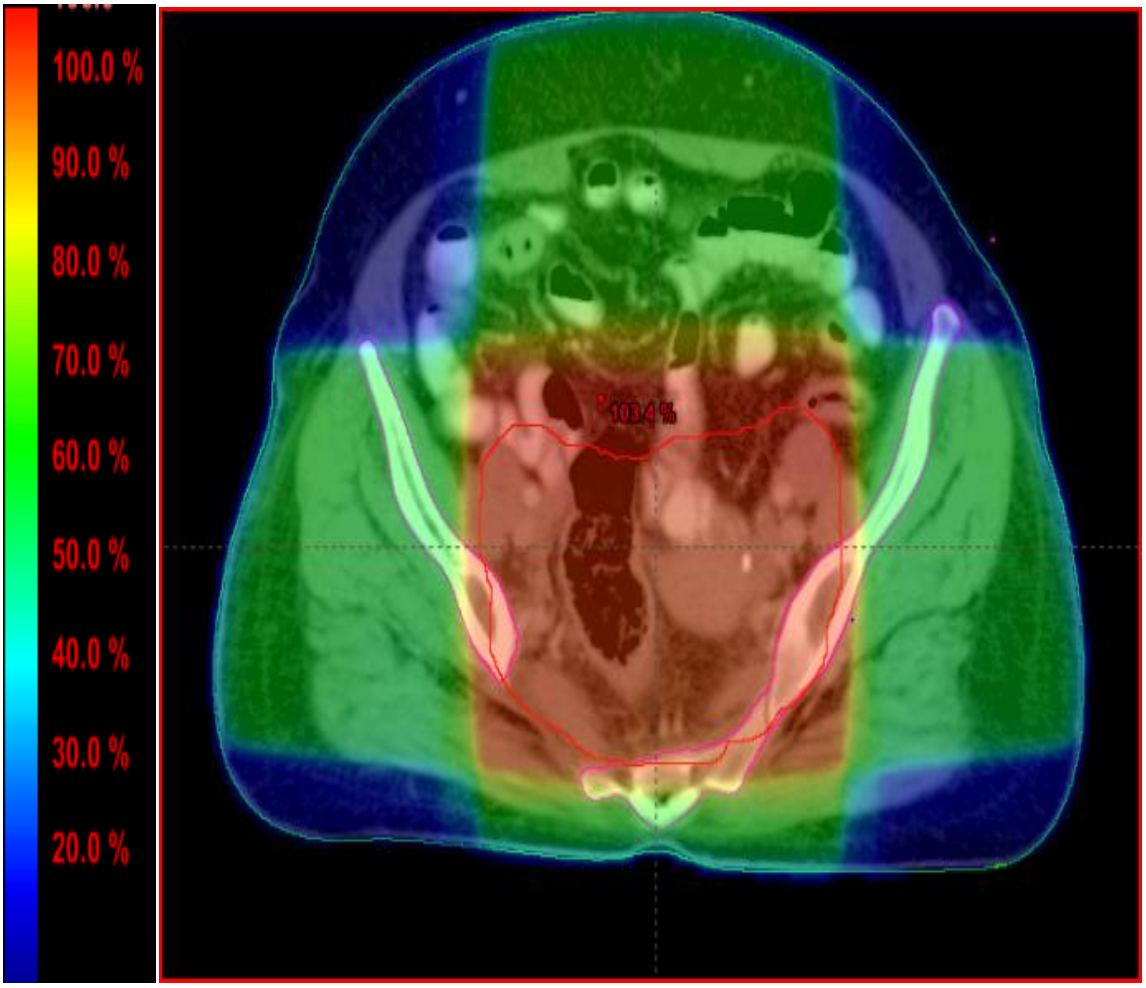

Fig.10.3: Dose colour wash in 3DCRT plan

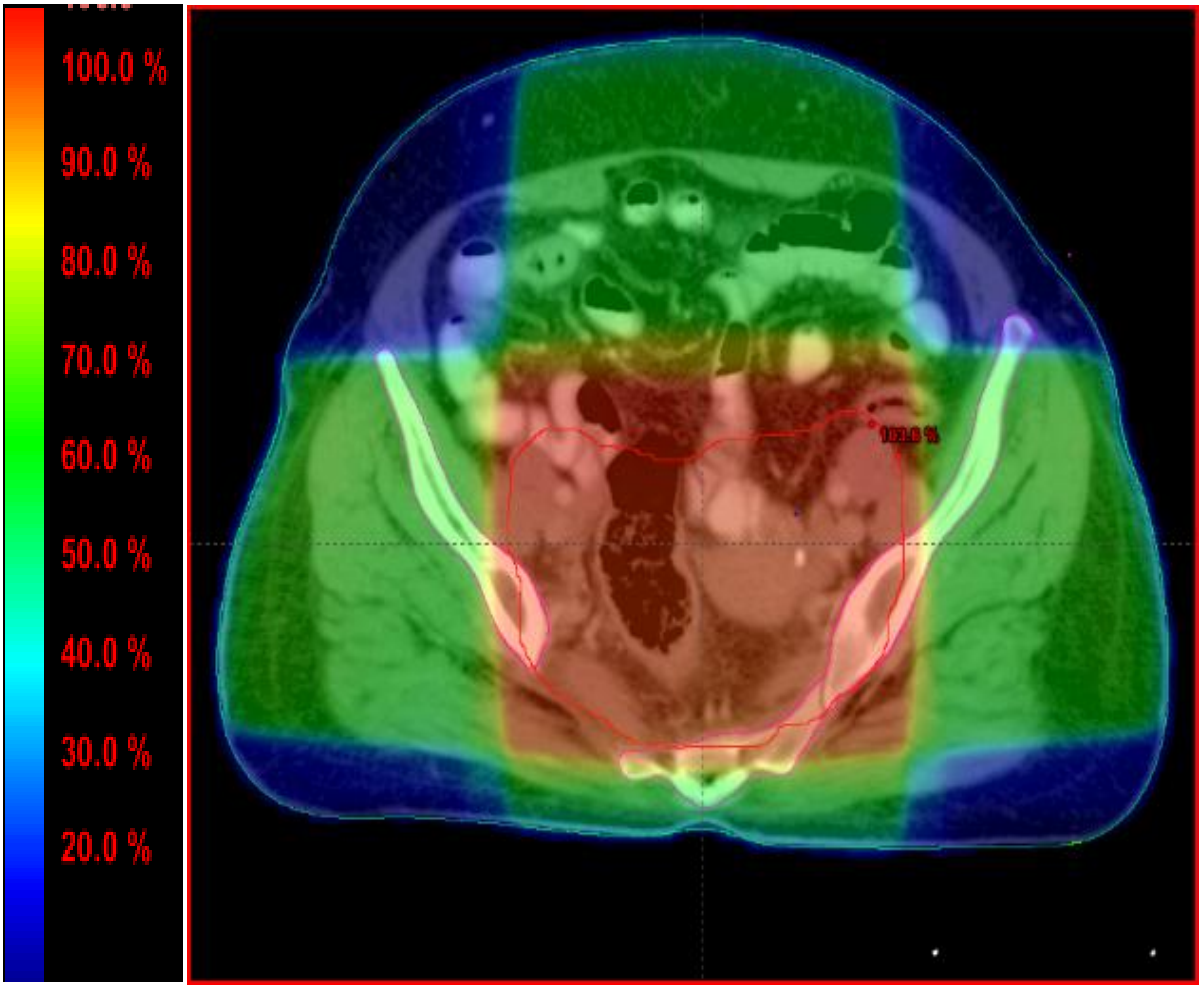

Fig.10.4: Dose colour wash in 4 FIELD BOX plan

Dose colour wash also gave similar representation of less doses to the bone marrow in BMS-IMRT technique when compared to other techniques. But it was more appreciable in comparison between IMRT technique with 3DCRT and 4 field 4 FIELD BOX techniques.

7.2 TARGET DOSE COVERAGE

This was analyzed with the help of DVH curves, isodose lines and dose colour wash. ThePTV adequacy was evaluated by noting the corresponding D98 on the isodose curves .

DOSE VOLUME HISTOGRAM OF PLANNING TARGET VOLUME FOR THE AVERAGE DISTRIBUTION OF A REPRESENTATIVE PATIENT COMPARING BMS-IMRT, IMRT,3DCRT AND MILC PLANNING.

Fig.11.1: DVH curves of PTV for the average distribution of a representative patient in 4 FIELD BOX plan, 3DCRT, IMRT and BMS-IMRT plan.

▲ -4 FIELD BOX ● -IMRT ■ -3DCRT ✸ - BMS-IMRT

Sl no	4 field box	3D CRT	IMRT	BMS IMRT
1	96.48	96.47	102.36	98.53
2	95.37	97.50	99.89	96.60
3	94.72	95.24	99.21	98.04
4	95.27	95.20	98.90	98.50
5	97.30	98.50	100	97.14
6	98.20	97.23	98.80	97.67
7	97.65	97.17	97.31	97.49
8	97.38	96.06	98.95	96.70
9	95.51	95.85	98.19	96.71
10	95.78	95.33	101.10	99.20
11	94.99	97.07	95.27	97.58
12	97.58	98.75	95.59	99.79
13	97.05	96.85	96.51	97.62
14	95.78	95.63	99.63	96.69
15	95.79	96.01	99.90	96.19
16	93.63	95.51	99.34	98.64

Table2. 3: Data set of PTV dose coverage(D 98 – in %) for 16 patients with 4 field box , 3D CRT, IMRT and BMS IMRT plan

7.3 DOSE TO ORGANS AT RISK

DOSE RECEIVED BY ORGANS AT RISK IN BMS-IMRT, IMRT, 3DCRT AND 4 FIELD BOX PLAN

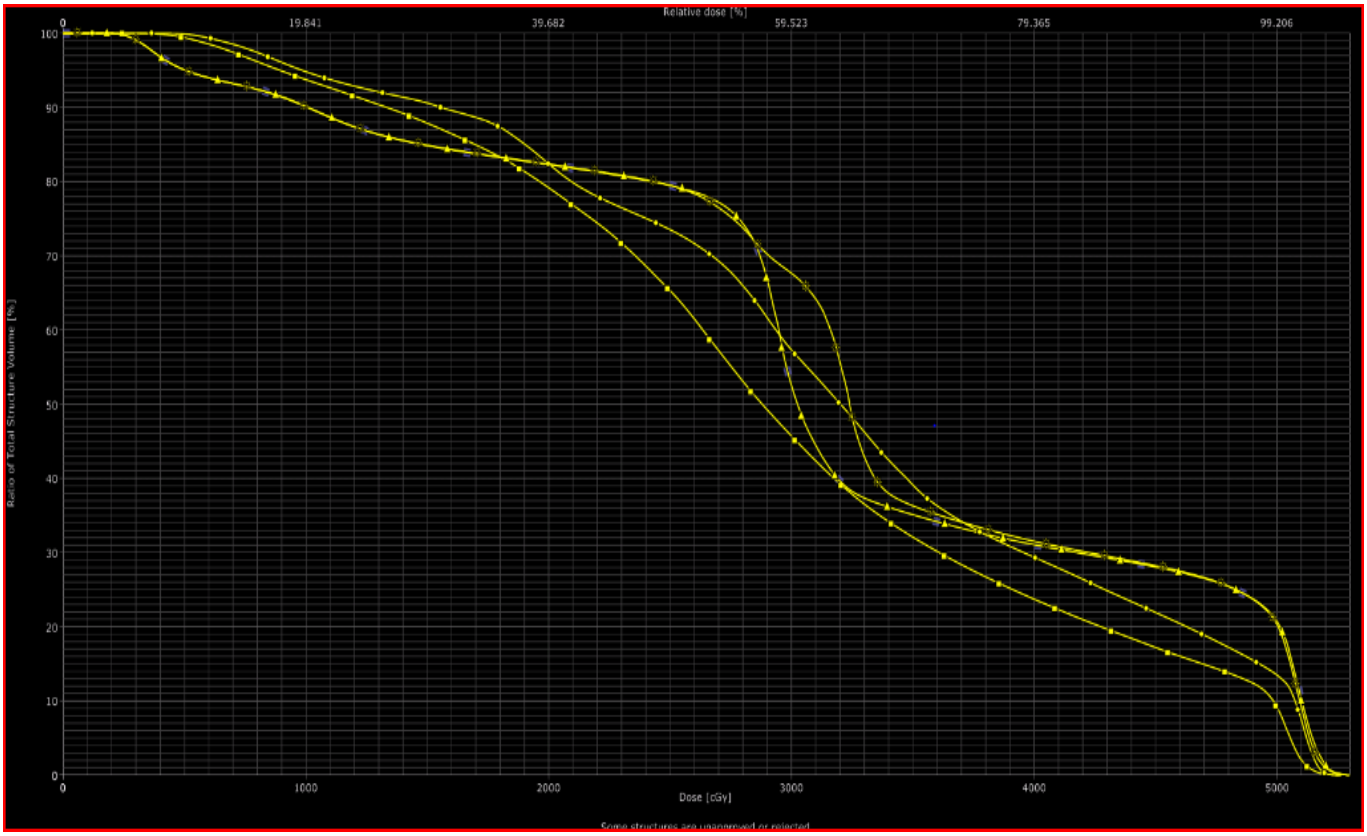

Fig.11.2: DVH curves for bowel of a representative patient in BMS-IMRT, IMRT, 3DCRTand 4 field boxplans.

○IMRT △4 FIELD BOX □BMS IMRT ☼3DCRT

SL NO	4 field box	3D CRT	IMRT	BMS IMRT
1	23.98	28.07	23.14	19.19
2	16.18	15.99	15.29	14.49
3	18.01	18.50	13.67	11.84
4	18.29	18.46	14.84	17.62
5	20.34	19.25	14.31	13.70
6	17.39	16.61	9.05	10.79
7	7.27	6.64	5.32	4.45
8	22.27	21.30	16.58	16.73
9	15.48	16.43	10.69	9.85
10	18.09	17.73	14.68	14.29
11	35.92	35.03	21.34	23.56
12	29.90	29.21	16.80	20.38
13	6.77	7.38	5.05	3.89
14	24.10	22.89	16.18	12.57
15	28.03	28.21	21.91	17.18
16	8.80	8.24	5.37	5.42

Table 2.4: V45 (in %) of bowel bag in 4 field box plan, 3D CRT , IMRT and BMS IMRT .

From the isodose curves itself it was evident that in IMRT and BMS-IMRT, as the prescription isodose curve and 95% isodose lines were conforming to the shape of the PTV, there was significant dose reduction to the bowelbag. According to the RTOG 0921 , volume of bowel bag receiving 45 Gy (V45)was documented for all the four plans for 15 patients. It was observed that there was significant reduction in volume of bowel bag receiving 45 Gy in BMS-IMRT and IMRT plans when compared to 3DCRT and 4 field box 4 FIELD BOX plans.3DCRT plans were superior over 4 field Box 4 FIELD BOX plans in sparing the bowel.

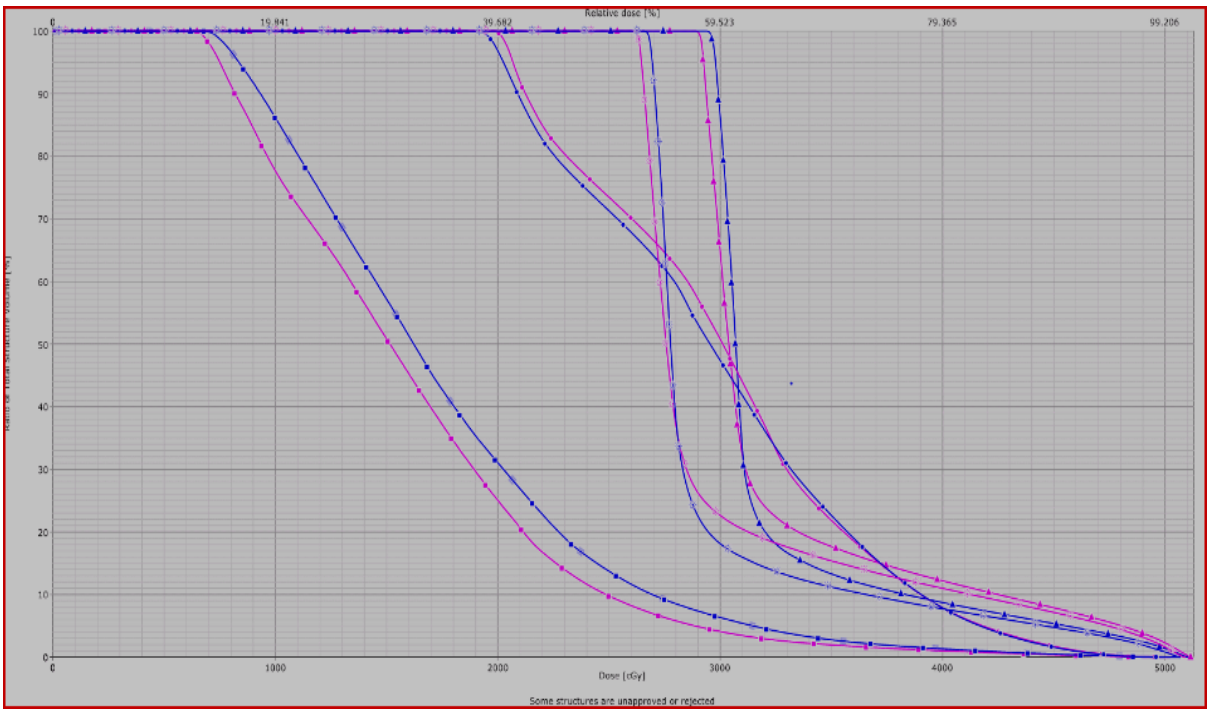

Fig.11.3: DVH curve for femoral head of a representative patient in BMS-IMRT, IMRT, 3DCRT and 4 field box plan.

SL NO	4 field box		3D CRT		IMRT		BMS IMRT	
	Rt	Lt	Rt	Lt	Rt	Lt	Rt	Lt
1	17.05	19.85	12.88	13.72	29.15	27.17	9.43	7.81
2	16.87	23.26	16.57	23.01	19.40	3.66	5.24	5.29
3	3.06	3.21	1.31	1.85	0.01	0.001	0.08	0.001
4	6.73	6.91	6.20	6.34	5.05	6.16	3.37	4.38
5	35.79	42.19	34.16	40.89	27.72	22.04	8.94	5.33
6	9.62	8.82	9.02	8.19	7.51	6.21	0.80	2.33
7	22.98	20.03	10.59	8.40	0.56	1.30	0.10	0.04
8	97.51	92.30	97.55	91.71	7.37	7.40	12.71	16.95
9	16.94	16.28	2.95	6.11	8.63	6.60	4.66	1.55
10	4.62	2.55	0.24	0.04	2.27	2.50	0.08	0.009
11	8.75	40.81	8.28	38.39	0.52	8.36	0.04	11.79
12	25.53	28.88	28.06	31.69	2.02	2.21	7.68	8.69
13	17.92	17.82	17.54	17.38	14.89	12.43	3.48	4.71
14	20.45	20.67	19.79	20.59	16.53	13.36	0.66	1.28
15	5.34	7.87	4.72	7.11	1.54	1.68	0.48	0.38
16	10.22	11.84	10.03	12.07	1.23	2.21	1.61	2.93

Table 2.5: V45(in %) of right and left femoral head with 4 field box plan, 3D CRT, IMRT and BMS IMRT plan

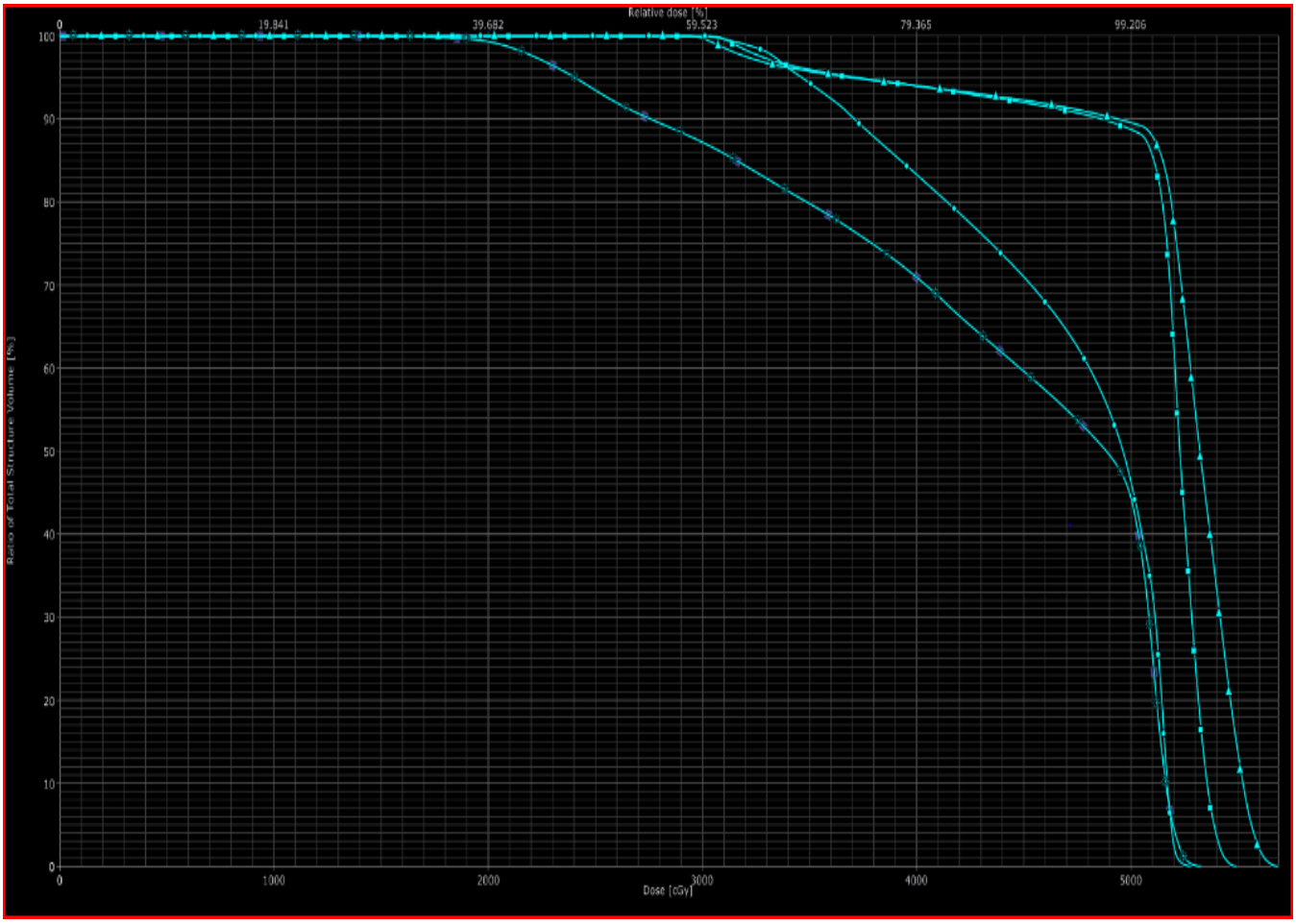

Fig.11.4: DVH curve for bladder for a representative patient for BMS-IMRT, IMRT, 3DCRT and 4field box technique.

SL NO	4 field box	3D CRT	IMRT	BMS IMRT
1	88.94	90.16	73.13	66.99
2	90.47	90.00	84.93	82.96
3	99.74	100	99.12	95.07
4	100	100	100	100
5	98.80	99.02	86.80	75.18
6	85.69	87.21	50.45	47.19
7	95.55	90.62	88.20	88.72
8	100	100	87.80	79.97
9	81.10	87.60	79.64	89.08
10	89.25	73.83	89.06	91.01
11	90.73	90.78	78.99	82.31
12	91.09	91.35	70.53	91.38
13	92.25	91.95	70.85	59.50
14	78.89	77.78	72.33	54.12
15	81.57	82.25	78.01	63.76
16	87.27	85.82	73.02	66.44

Table2. 6: V45 (in %) of bladder in 4 field box plan , 3D CRT , IMRT and BMS IMRT plan

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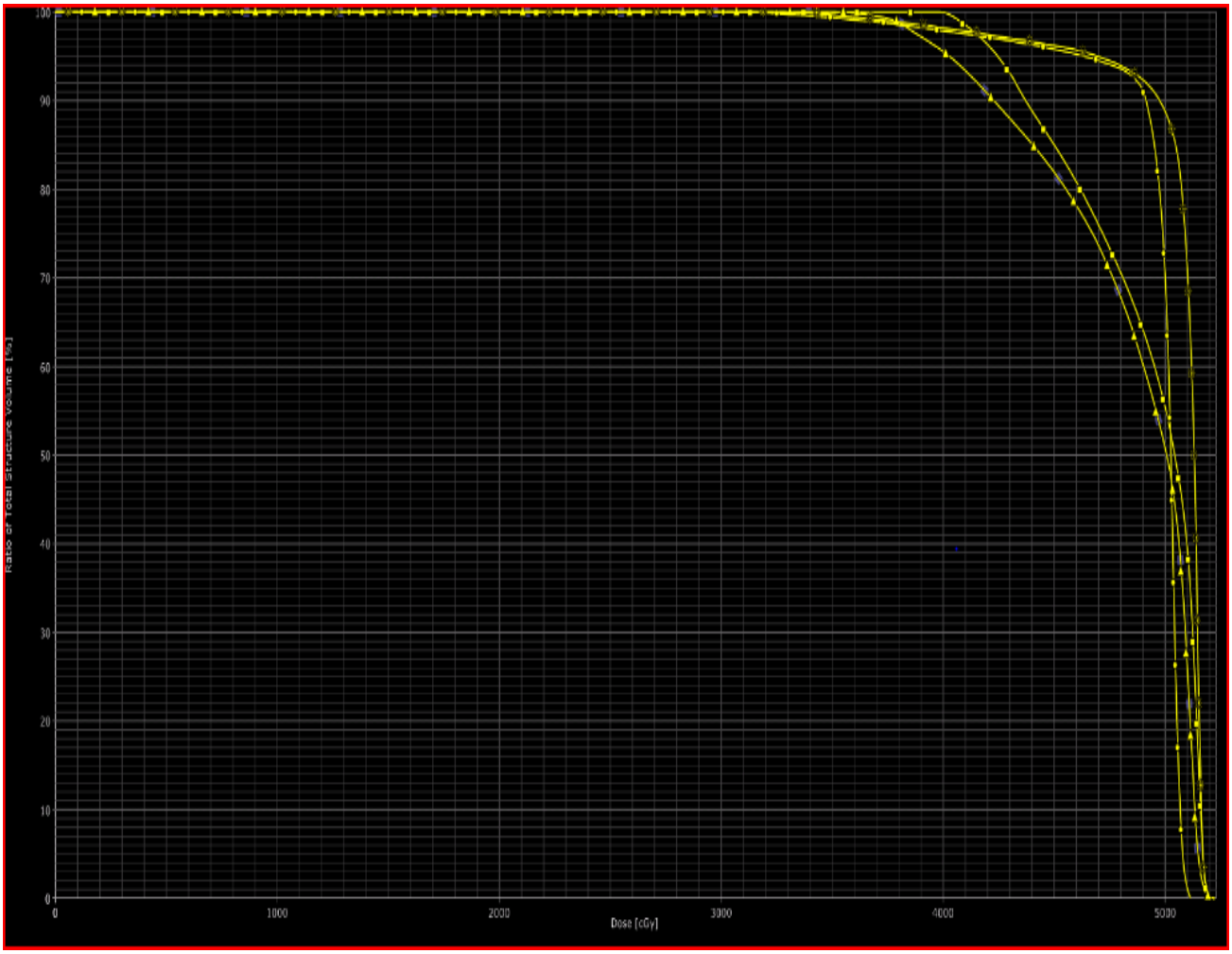

- 4 FIELD BOX ○BMS-IMRT -IMRT △ -3DCRT □ ☼

Fig.11.5: DVH curve for rectum for a representative patient for BMS-IMRT, IMRT, 3DCRT and 4 field box technique.

Sl no	4 field box	3D CRT	IMRT	BMS IMRT
1	69.24	67.38	88.55	77.50
2	72.68	72.80	80.27	78.29
3	64.18	77.49	80.59	74.70
4	89.75	90.40	91.70	89.45
5	100	100	100	100
6	98.52	99.24	100	98.37
7	100	100	100	96.52
8	97.10	98.58	67.02	55.99
9	69.60	88.40	55.16	50.66
10	41.33	99.91	100	99.95
11	74.17	99.79	100	99.85
12	97.53	98.63	70.84	97.13
13	92.60	95.24	55.75	62.38
14	60.33	92.85	99.20	77.54
15	98.01	99.67	99	75.41
16	58.31	74.22	92.46	90.45

Table2.7: V50 (in %) of rectum in 4 field box , 3D CRT , IMRT and BMS IMRT plans

As per the RTOG guidelines the bladder constrain is V 45 < 35% and constrain to rectum is V 50 < 50%.It was observed in all the patients all four plans that these constrains are never achievable and these structures are getting almost 100 % of the prescribed dose. This can be attributed to the fact that major portion of these structures were coming within the planning target volume to which the dose of 5040 cGy is prescribed. But since the maximum bladder tolerance dose is 80 Gy and that of rectum is 70 Gy the maximum point dose received by these structures during each plans can be documented and it can be considered during brachytherapy plan optimization later.

8.STATISTICAL ANALYSIS:

BONE MARROW

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL	P Value
4 FIELD BOX	0	16	16	.001
3DCRT	0	16	16	
IMRT	0	16	16	
BMS IMRT	15 (93.8%)	1 (6.3%)	16 (100%)	

Table 3.1: Tabularcolumn showing the number of cases andpercentage in which bone marrow sparing could be achieved by different planning techniques

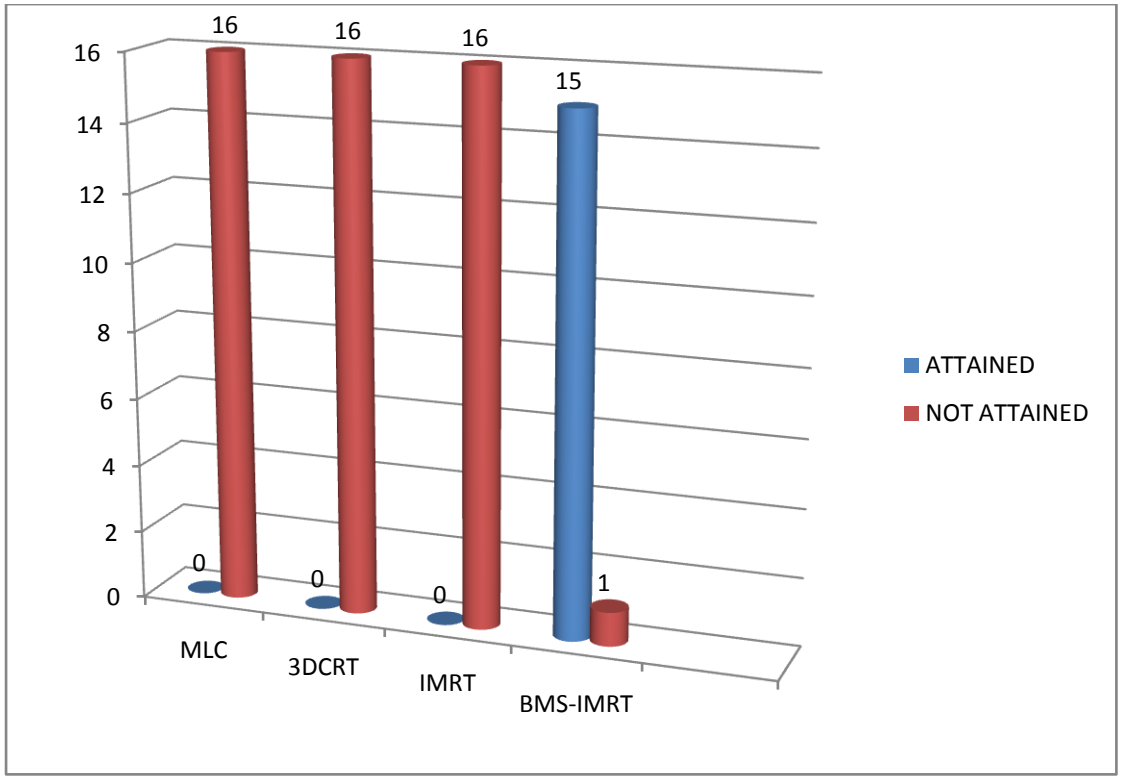

Fig 12.1: Bar diagram showing the number of cases in which bone marrow sparing could be achieved by different planning techniques.

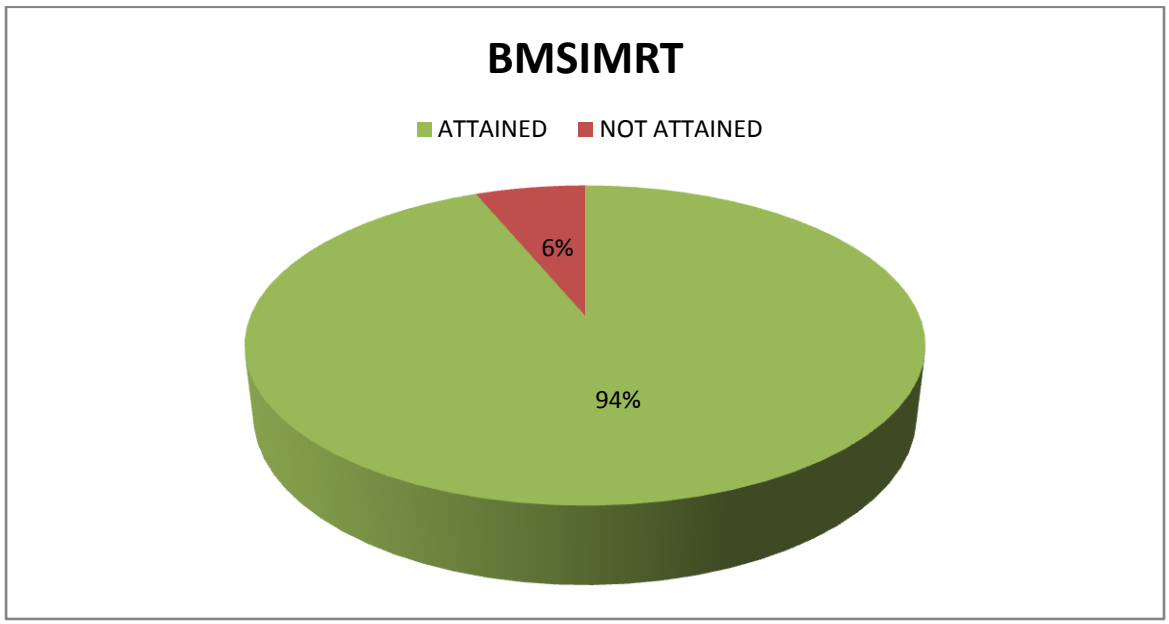

Fig 12.2:Pie diagram showing the % of patients for which BMS-IMRT could attain the constrain of V 10< 95% and V 20 < 76%

TARGET COVERAGE:

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL	P VALUE
4 FIELD BOX	13 (81.3%)	3 (18.8%)	16 (100%)	**0.094**
3DCRT	16	0	16	
IMRT	16	0	16	
BMS IMRT	16	0	16	

Tabel 3.2: Tabular column showing the number of cases and percentage in which PTV constrains could be achieved by different planning techniques

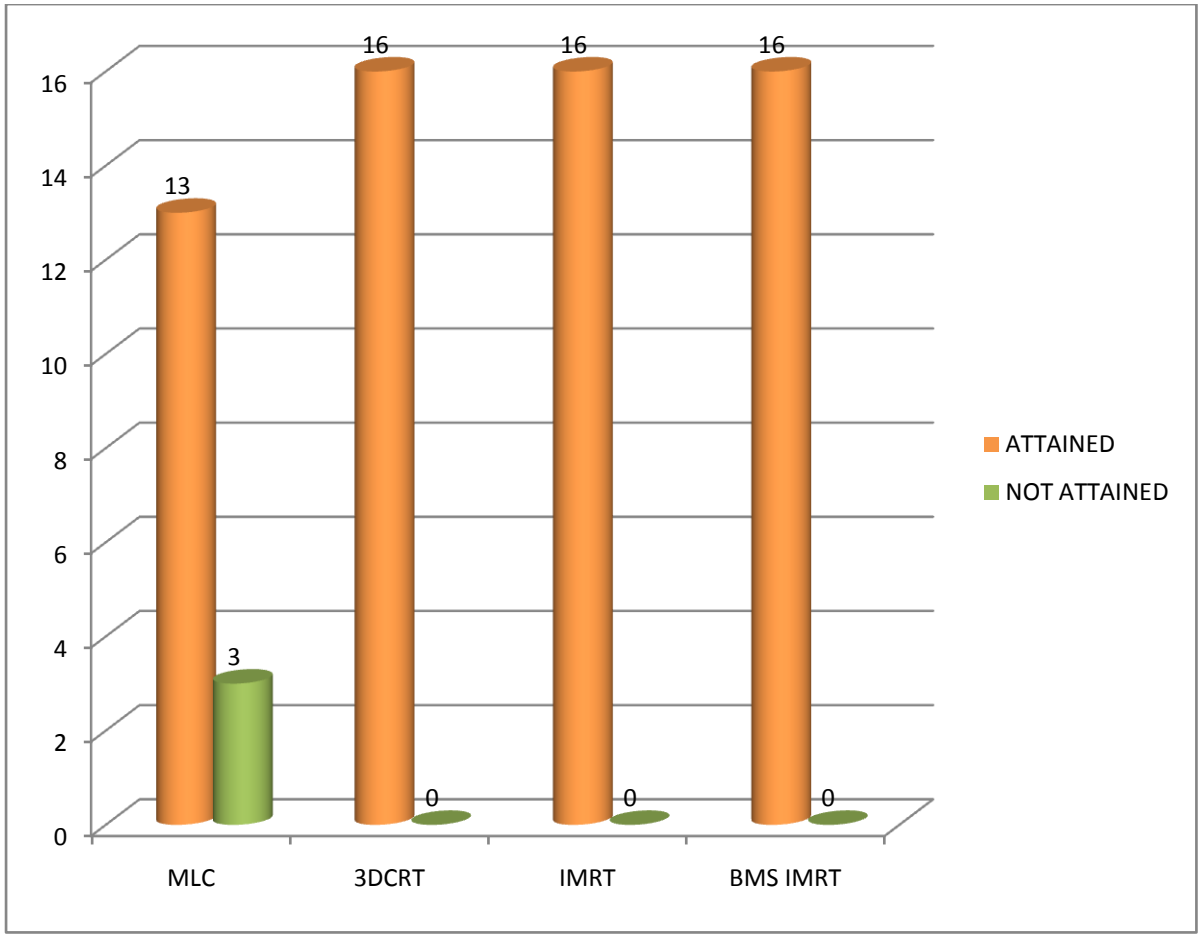

Fig 12.3: Bar diagram showing the number of cases in which adequate PTV coverage (V 98> 95%, D 2 cc < 110%) could be achieved by different planning techniques.

OTHER ORGANS AT RISK:

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL	P VALUE
4 FIELD BOX	13 (81.3%)	3 (18.8%)	16 (100%)	0.228
3DCRT	13 (81.3%)	3 (18.8%)	16 (100%)	
IMRT	15 (93.8%)	1 (6.3%)	16 (100%)	
BMS IMRT	16	0	16	

Table 3.3: Tabularcolumn showing the number of cases and percentage in which the left femoral head constrains could be achieved by different planning techniques

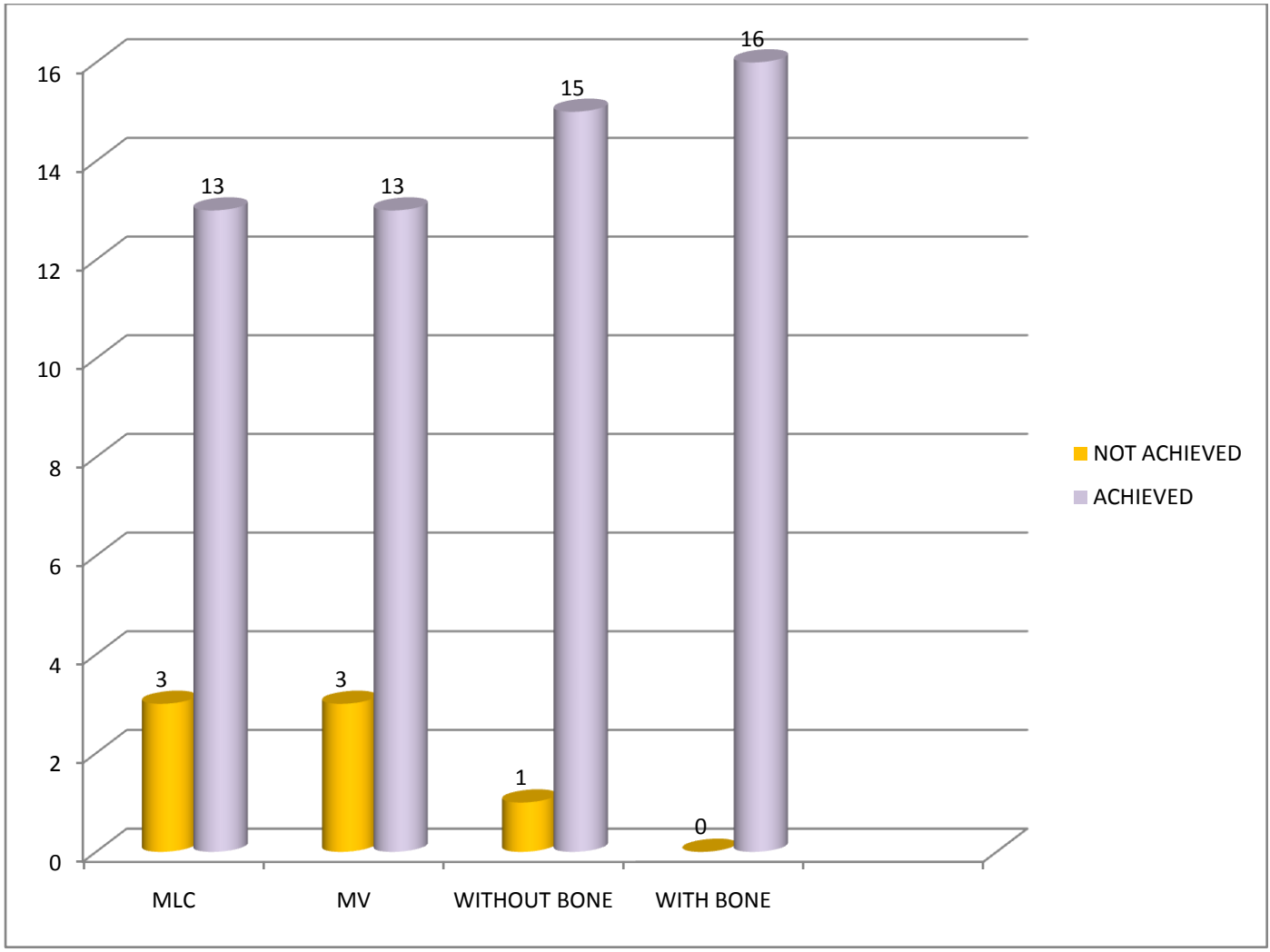

Fig 12.4: Bar diagram showing the number of cases in which left femoral head constrain could be achieved by different planning techniques.

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL	P VALUE
4 FIELD BOX	12 (75%)	4 (25%)	16 (100%)	0.027
3DCRT	12 (75%)	4 (25%)	100%	
IMRT	100%	0%	100%	
BMS IMRT	100%	0%	100%	

Table3.4: Tabularcolumn showing the number of cases and percentage in which the right femoral head constrains could be achieved by different planning techniques

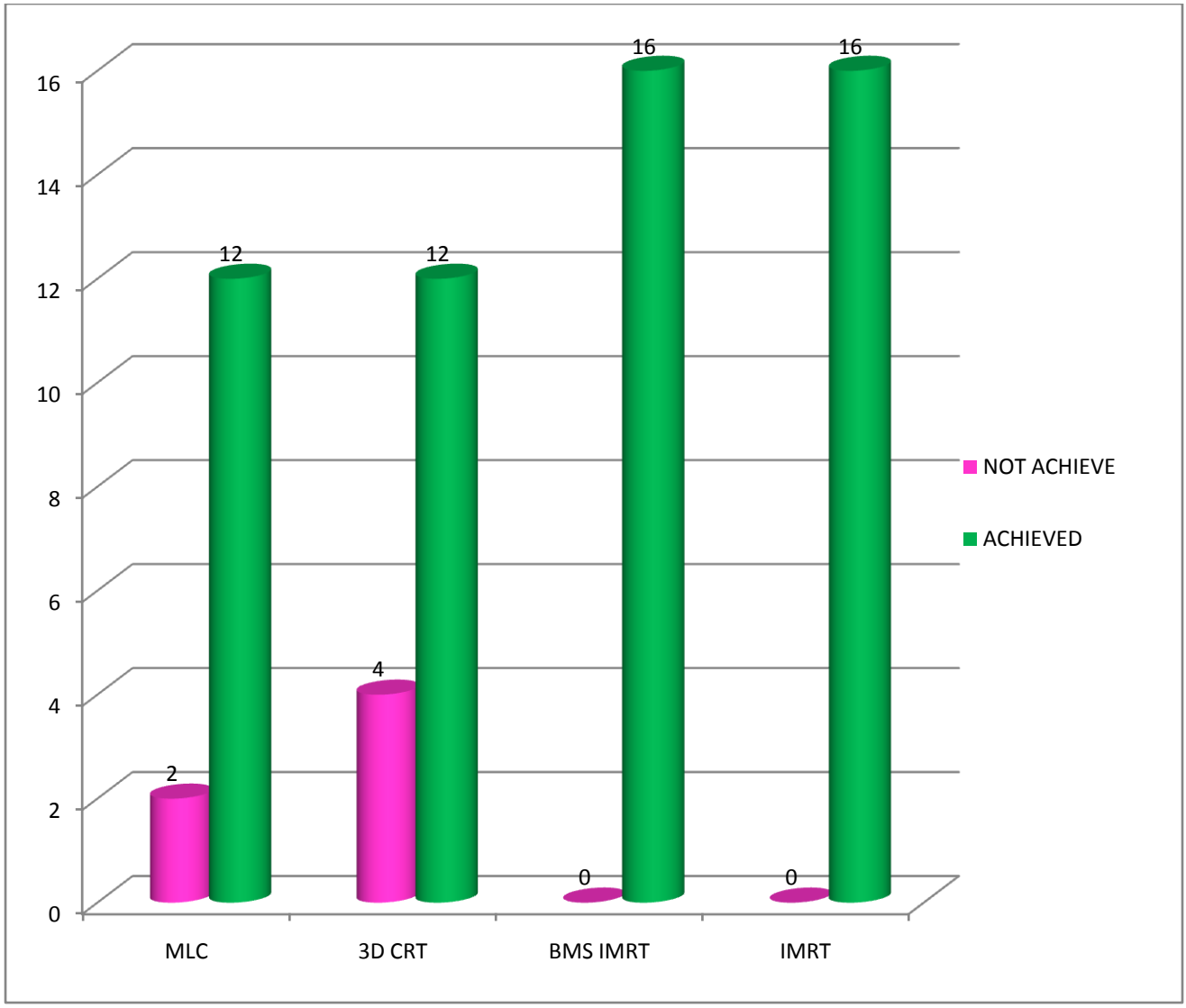

Fig 12.5: Bar diagram showing the number of cases in which right femoral head constrain could be achieved by different planning techniques

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL
4 FIELD BOX	**0**	**16**	**16**
3DCRT	**0**	**16**	**16**
IMRT	**0**	**16**	**16**
BMS IMRT	**0**	**16**	**16**

Table3.5: Tabularcolumn showing the number of cases and percentage in which the bladder constrains could be achieved by different planning techniques

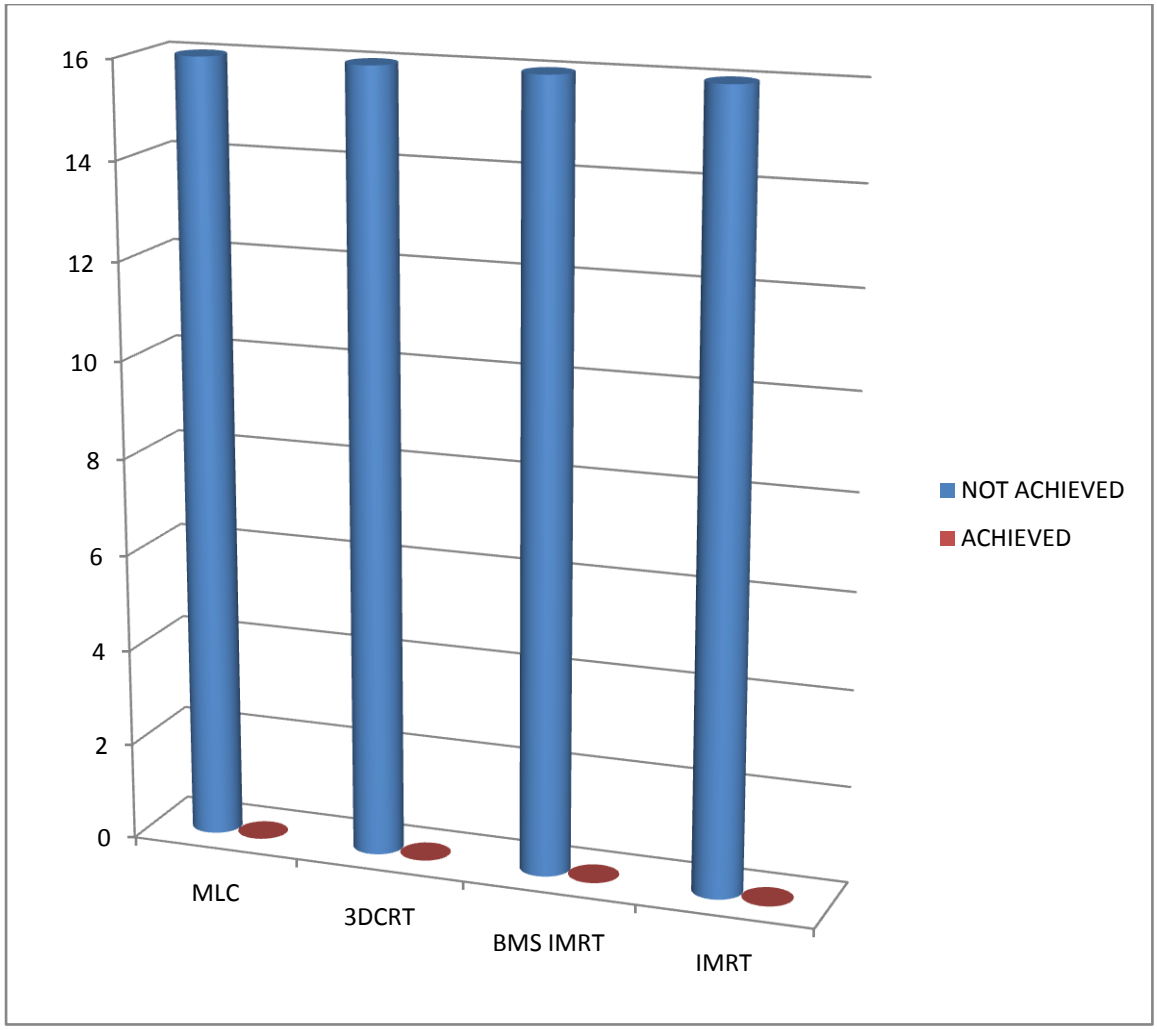

Fig 12.6: Bar diagram showing the number of cases in which the bladder constrain could be achieved by different planning techniques

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL
4 FIELD BOX	0	16	16
3DCRT	0	16	16
IMRT	0	16	16
BMS IMRT	0	16	16

Table 3.6: Tabularcolumn showing the number of cases and percentage in which the rectum constrains could be achieved by different planning techniques

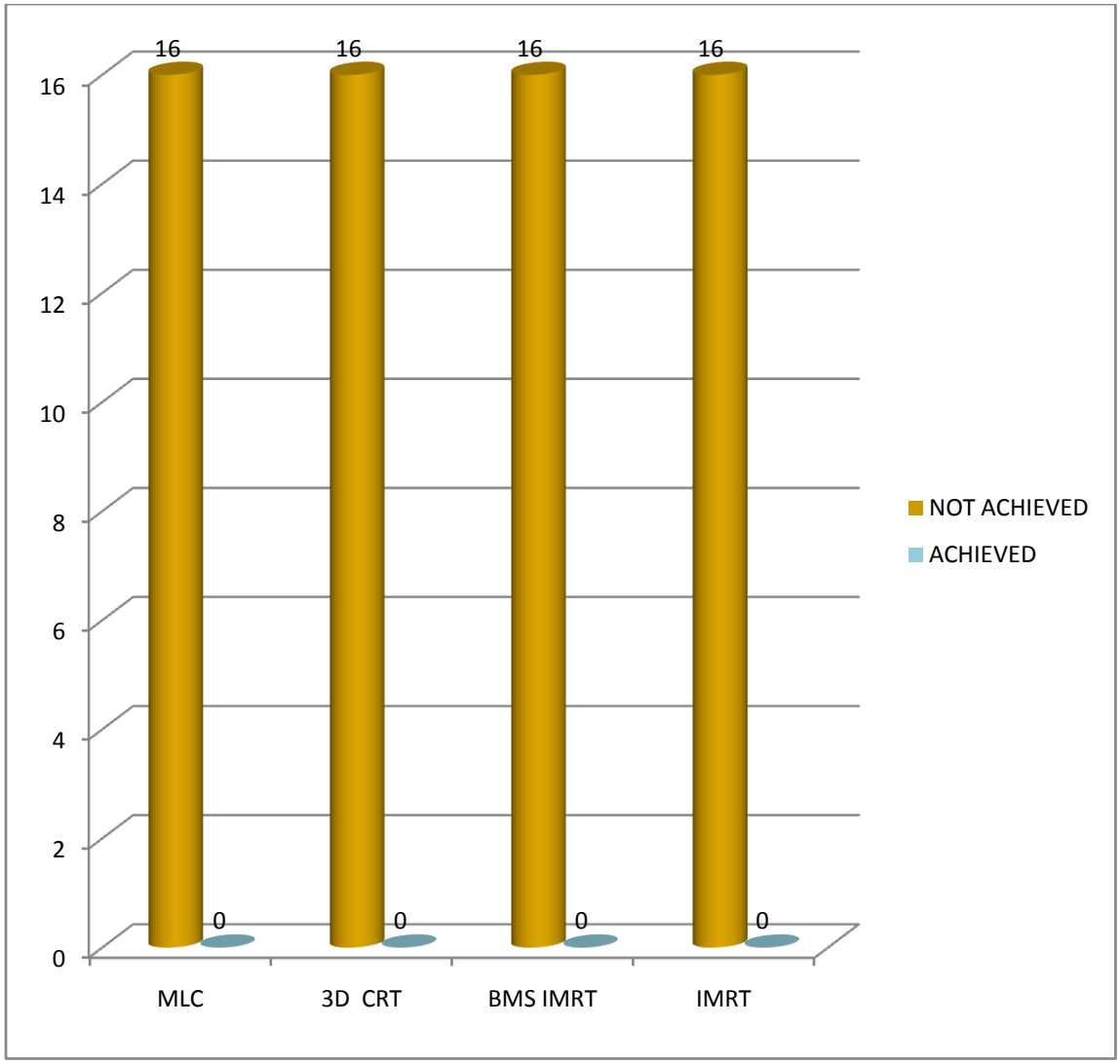

Fig 12.7: Bar diagram showing the number of cases in which the rectum constrain could be achieved by different planning techniques

PLANS	ACHIEVED	NOT ACHIEVED	TOTAL	P VALUE
4 FIELD BOX	13 (81.3%)	3 (18.8%)	16	
3DCRT	12 (75%)	4 (25%)	16	
IMRT	16 (100%)	0 (0%)	16	0.027
BMS IMRT	16 (100%)	0 (0%)	16	

Table 3.7: Tabularcolumn showing the number of cases and percentage in which the bowel constrains could be achieved by different planning techniques

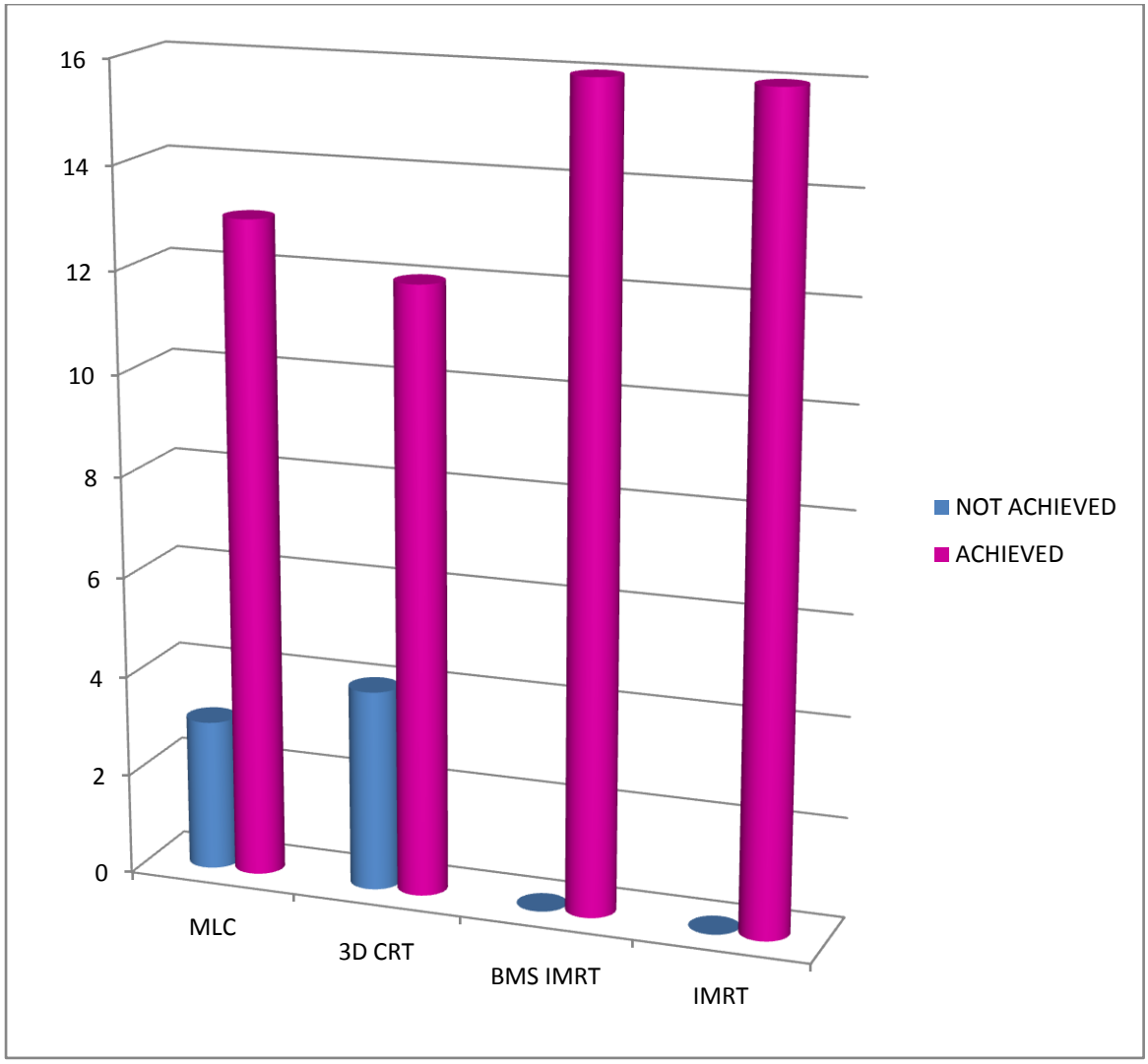

Fig 12.8: Bar diagram showing the number of cases in which the bowel bag constrain could be achieved by different planning techniques

STATISTICAL ANALYSIS

As per the aim of the study statistical analysis was done to analyse whether a bone marrow sparing IMRT plan can be made without compromising coverage to the target volume and without increasing dose to other organs at risk which are normally considered in ordinary plans. Analysis was made between 4 different treatment plans;4 FIELD BOX plan, 3DCRT, IMRT and BMS –IMRT plans for all 16 patients. Chi-square test was used for statistical analysis.

Statistical analysis for bone marrow.

As per the earlier discussions the constrains for bone marrow were considered as V 10 < 95% and V 20 < 76% as a value below these ranges have shown to significantly reduce haematological toxicities. Out of the 16 plans with BMS IMRT, 15 plans were achieved with bone marrow dose well below the above constrains. This gave a 93.8% chance of achieving this constrain with a p value of .001.None of the remaining plans , even with ordinary IMRT plans could achieve the prescribed constrain. The case of BMS –IMRT which could not achieve the constrain had V10=94.04% (within normal limit) and V 20= 77.62%. This value of 77.62% for V20 with BMS-IMRT was well below and near normal to the constrain(V 20< 76%) when compared to other three plans(4 FIELD BOX V20= 99.30%, 3DCRT V 20=99.22%and IMRT V20=93.25%) .

Statistical analysis of target volume coverage

As per the protocol, the adequate target coverage was analysed by evaluating whether D 98> 95% and D 2cc < 110% of the prescribed dose. These parameters were considered in all 4 plans for all the 16 patients. Out of 16 patients all of these constrains were achieved together in 13/ 16 patients with 4 FIELD BOX plan, 16/16 patients with 3DCRT, 16/16 patients with IMRT and 16/16 patients with BMS-IMRT.

Statistical analysis of other organs at risk

Femoral head

The femoral head was drawn as two separate structure, right and left femoral head . The constrain considered for femoral head was V 45 < 25%.V 45 was measured for all the plans for all 16 patients. In case of right femoral head, the constrains could be achieved for 13/16 patients with 4 FIELD BOX plan, 13/16 patients with 3DCRT plan, 15/16 patients with IMRT plan a 16/16 patients with BMS –IMRT plan. Hence BMS-IMRT was found to be superior over other plans in achieving the femoral head dose constrain.

In case of left femoral head, it was observed that the constrain was attained for 12/16 patients with 4 FIELD BOX, 12/16 patients for 3DCRT, 16/16 patients with IMRT and 16/16 patients with BMS –IMRT. From these observations it can be concluded that BMS –IMRT is equally beneficial as IMRT over decreasing dose to the femoral head well below the dose constrains.

Bowel bag

The constrain given to the entire bowel bag was V45< 25%.It was measured for all the plans for all 16 patients.Theconstrains could be achieved for 13/16 patients with 4 FIELD BOX plan, 12/16 patients with 3DCRT plan, 16/16 patients with IMRT plan an 16/16 patients with BMS –IMRT plan.

Bladder

The dose constrain considered for bladder was V 45< 35%.As mentioned earlier , as most of the portion of the bladder was within the planning target volume in carcinoma cervix treatment planning this constrain was never achievable. In order to show that BMS –IMRT is not inferior to other plans when the bladder dose is considered, V 45 for all the 16 patients in all the 4 plans was noted. It was observed that 0/16 patients achieved the dose constrain for bladder in 4 FIELD BOX, 3DCRT, IMRT and BMS-IMRT plan.

Statistical analysis for Rectum

The dose constrain to the rectum was V 50 <50%.Similar to the observation for bladder ,as most of the portion of the rectum is involved within the planning target volume , this constrain was never achievable. V 50 for all the 16 patients in all the 4 plans was noted. It was observed that 0/16 patients achieved the dose constrain for bladder in 4 FIELD BOX, 3DCRT, IMRT and BMS-IMRT plan.BMS –IMRT was hence proved non inferior to other plans in toxicity to rectum.

Maximum dose to the rectum was measured. No hot spots were noted within the rectal volume.

9.DISCUSSION

The current standard of care in patients diagnosed with locally advanced carcinoma cervix is concurrent chemo irradiation. Over the past many decades, the radiation delivery technique evolved with an aim to reduce the toxicity to the normal structures without compromising the dose to the target volume .Majority of the earlier studies emphasised decreasing the dose to bowel , bladder and rectal toxicities. Later, clinicians started observing that haematological toxicity is also a matter of concern in patients undergoing chemo irradiation which resulted in delayed treatment and subsequently decreased survival . This paved way to various studies in which bone marrow was considered as a separate organ at risk with a dose constrain. Rose et al came up with the observation that V10 and V20 of the bone marrow (volume of bone marrow receiving 10 Gy and 20 Gy respectively) influences grade 3 and grade 4 hematological toxicity (54).

This wasa dosimetric study on data set from 16 women diagnosed with carcinoma cervix and treated in our institution from July 2013 to January 2014 using 3D CRT or IMRT. For all of the 16 patients 4 plans, BMS- IMRT, IMRT , 3D CRT and four field box technique were modelled. The aim of this study was to analyse whether a bone marrow sparing IMRT plan could be achieved without compromising coverage to the target volume and without increasing dose to other organs at risk. BMS - IMRT planningalgorithm was similar to IMRT plans,except that in BMS-IMRT the bone marrow was contoured and given dose constrain.It was observed that it is feasible to achieve a BMS-IMRT plan without compromising the target coverage and without increasing the dose to other organs at risk.The mean V10 and

V20 to bone marrowin our study was 89.58% and 69.99%and was comparable to the mean doses of 95% and 76% as reported by Rose et al (50)

Eventhough this dosimetric study focused on carcinoma cervix patients, this modality can be beneficial in reducing marrow toxicity in pelvic malignancies like rectum and anal canal where adjuvant treatment also plays a significant role(55).It may be of significant benefit as these patient are subjected to further insult to their marrow by undergoing systemic chemotherapy Another group who may benefit from this study are the patients who are diagnosed to have lymphomas on combined modality treatment with consolidation pelvic radiation therapy following chemotherapy and stem cell rescue(56).

The main drawback of this study was,that it was a dosimetric study with no clinical correlation between the percentage reduction of dose to the bone marrow and its effect on blood parameters which helps in quantifying haematological toxicity.Another drawback of this study was the non availability of a universally accepted contouring consensus guidelines for bone marrow and imaging technique which can be used for the same. In the light of various studies done by the pioneers in BMS-IMRT(54) , the entire medullary cavity was contoured as a surrogate of the active bone marrow. As the red bone marrow is involved in active haematopoiesis and yellow marrow is predominantly fat, this method of contouring the entire bone outside the cortex can be quite inaccurate.

Inorder to overcome this ,various studies have come up now incorporating functional scan like PET CT or MRI which gives a better representation of bone marrow than CT into the

IMRT planning(53).These studies are still under way and no robust data is available .The accurate SUV value which represent the active part of bone marrow is also under evaluation.

In theIndian scenario where majority of the patients are of low socio economic status and even the access to state basic health care is limited , incorporating PET CT or even MRI to the treatment planning for bone marrow sparing in routine practice may not be a feasible option . In such a situation CT scan may be a better surrogate option over PET CT or MRI in a limited resource setting. While the optimal way to dilineate bone marrow is still evolving , there is strong evidence which is emerging that Bone marrow sparing IMRT significantlyreduces the dose to Bone marrow and hence reduce haematological toxicity. Though not yet ready to be considered as a standard of care Bone Marrow sparing IMRT should be considered in appropriate patients.

10.CONCLUSION

Bone Marrow Sparing IMRT is a feasible option for the management of locally advanced carcinoma cervix as it helps in reducing the dose received by the bone marrow without compromising the planning target volume coverage and without increasing the dose to other normalorgans at risk.However the clinical benefit needs to be evaluated in a prospective clinical trial

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12.ANNEXURES

CHRISTIAN MEDICAL COLLEGE, VELLORE
Gynecological Cancer Study Group

Comparison of V10 and V20 of bone marrow in carcinoma cervix patients receiving radiation with Bone Marrow Sparing (BMS)–IMRT, IMRT, 3DCRT, and 4 field box technique.

Case Record Form

CMCCXRT1 01-13 ID NO | Date of Birth (dd mm yyyy) | Hospital Number

RT No | Telephone No | Email

rt no yy unit

PTV	D 98				
	D 2 cc				
BONE MARROW	V 10				
	V 20				
FEMORAL HEAD (LEFT)	V 45				
FEMORAL HEAD(RIGHT)	V 45				
BLADDER	V 45				
RECTUM	V 50				
BOWEL	V 45				

Date: __/__/____ Investigator's Signature:_____