A PROSPECTIVE STUDY TO COMPARE T2 WEIGHTED MRI TO CT IMAGING IN VOLUME DELINEATION FOR RADIOTHERAPY PLANNING IN CARCINOMA CERVIX

DISSERTATION

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Certificate

This is to certify that the dissertation entitled " **A prospective study to compare T2W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix**" is an original work by Dr Aparna.M.P in partial fulfillment towards MD Radiotherapy (Branch IX) Degree examination of the Tamil Nadu Dr M G R Medical University to be held in April 2014.

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Contents

ABSTRACT

TITLE OF THE ABSTRACT;–

A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix

DEPARTMENT : RADIOTHERAPY

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OBJECTIVES - To compare magnetic resonance imaging (MRI), computed tomography (CT), and clinical examination to evaluate the impact of MRI on target volume delineation as compared to the volumes obtained on a CT scan and also to see the effect on staging and prognosis.

METHODS- Twenty patients diagnosed with locally advanced carcinoma cervix underwent planning CT abdomen and pelvis which was fused with T2 weighted MRI images to evaluate the impact of MRI on target volume delineaton , to see if CT scan along with clinical findings can be a good alternate to MRI scan.A descriptive analysis and frequency distribution of the patient characteristics was done. Fisher's exact test was done to find out relationship between prognostic factors and image findings. PABAK was done to compare different imaging modalities (CT versus MRI).Paired T test was used for tumor volume comparison.

RESULTS -MRI was better in tumor delineation as compared to CT scan. Additional imaging gave information regarding local extent of the disease, nodal involvement . Upstaging of disease helped in selecting appropriate treatment modality. Conclusion-

Though the findings on CT, MRI, or PET examinations are not mandatory for FIGO staging it could be of additional benefit and provide extra information that would result in stage migration, help appropriate selection of treatment modality,result in more accurate radiotherapy treatment planning and also provide prognostic information that would impact on the outcome of treatment and survival. CT with good clinical examination could be used as an alternate to MRI where MRI is not feasible.

Key words- MRI, CT, carcinoma cervix, staging and Radiotherapy planning.

1. AIM OF THE STUDY

Primary objectives:

The investigational imaging MRI will be compared with CT imaging to

- -Compare the target volume delineation and evaluate the impact of MRI on target volume as compared to the volumes obtained on a CT scan -

  GTV Primary (Cervical tumour, involvement of uterus, vagina and parametrium)

  GTV Lymph nodes
- To determine whether there is any change in the staging of the disease
- To determine any change in management or prognosis depending on the extra information.

Secondary objective:

- To see if CT scan along with clinical findings can be a good alternate to MRI scan
- To look at the possibility of reduction in treatment volume
- To evaluate the possibility of avoiding invasive procedures like cystoscopy based on MRI/CT findings

2. INTRODUCTION

Cervical cancer is a major health problem in developing countries like India .Appropriate evaluation of disease extent and staging is important as this has an impact on the management, prognosis and outcome.

The International Federation of Gynecology and Obstetrics is the most commonly used staging system for carcinoma cervix. Since the staging system should be uniform and feasible at all centres and also allow for comparison of results from different centres, FIGO has recommended staging to be based on clinical findings which includes assessment of the tumour extent (ie, extent of local disease, tumor size, involvement of cervix, vagina, parametrium and extent into adjacent normal tissue like rectum and bladder)along withlimited radiological investigations which does not include MRI and CT scans for staging in carcinoma cervix. Clinical staging may be adequate forevaluating local disease extent, but does not take in to account involvement of the uterus, lymph nodesor distant metastasis.It has been reported in literature that MRI is superior to CT scan and clinical examination for assessing the tumor and involvement of the uterine body.

As patients with carcinoma cervix belong to the lower socioeconomic strata where MRI/CT is not feasible and also as MRI/CT may not available in all centers it is not possible to do these routinely for staging and management.Hence evaluation in the form ofless expensive imaging and thorough clinical examination would be a good alternatethat could be carried out.Though the findings on CT, MRI, or PET examinations are not mandatory for FIGO staging itcould be of additional benefit and provide extra

information that would result in stage migration, help appropriate selection of treatment modality (surgery/chemo-irradiation/chemotherapy), and will result in more accurate radiotherapy treatment planning and also provide prognostic information that would impact on the outcome of treatment and survival. Prognostic factors likestage at presentation , tumor diameter, tumor volume,lymph node metastasis,lymphatic vascular space invasion,deep stromal invasion, microscopic evidence of parametrial invasion , cell type and haemoglobin level, have an impact on survival .Therefore the revised FIGO staging 2009 has included imaging with MRI in addition to clinical staging where resources permit.

In patients with carcinoma cervix,CT scan is primarily used to evaluate the size of the tumor to detect enlarged lymph nodes, obstruction of the ureter, and any distant metastases to lung or liver.MRI has got better soft tissue contrast resolutionthan CT scan and has the capability of acquiring images in multi planar dimension. It is useful in determining the size of the tumor and in detecting parametrial invasion, bladder and rectal invasion .It also helps in assessing the presence of enlarged lymph nodes, obstruction of the ureter, and to detect lung or liver metastases.

The aim of radiotherapyis to get adequate tumor control with minimum acceptable amount of toxicity. The factors like tumor size, tumor extension and radiotherapy technique used significantly affect radiation treatment in carcinoma cervix

Conventional radiation therapy with four field box techniquehas been used for treating patients with locally advanced carcinoma cervix. This technique was designed according to bony land marks and better compared to AP-PA technique,with lateral portals designed to shield the rectum and small bowel in order to reduce the dose to these organs at risk. Despite

its proven efficacy and safety this technique has some shortcomings. Many studies has showninadequate coverage and chance of geographical miss in conventional methods when this was assessedwith cross sectional imaging modalities like computed tomography (CT) or magnetic resonance imaging (MRI).The aim of this study is to evaluate the impact of MRI on target volume delineation as compared to the volumes obtained on a CT scan and to see if CT scan along with clinical findings can be a good alternate to MRI scan. To look at the possibility of reduction in treatment volume and to evaluate the possibility of avoiding invasive procedures like cystoscopy based on MRI/CT findings

3. REVIEW OF THE LITERATURE

3.1 Epidemiology

World wide, uterine cervical neoplasm is the third most common malignancy in women after breast and colorectal cancers (2). According to the SEER data in US , an estimated incidence of 12,340 women and mortality of 4,030 women with cancer of the cervix uteri is predicted in 2013 . The age-adjusted incidence rate was found to be 7.9 per one lakh women per year for all races and 6.6 per one lakh women for Asian /Pacific region .(3)

Compared to western countries there is increase in cervical cancer incidence in Asian countries including India .Low socioeconomic status and lack of screening programs may attribute to this.

In India ,cervical cancer is the most common malignancy in women. The age-adjusted incidence rates for cervical cancer was found to be varied from 10.9 to 65.4 amongst various registries during the year 1990-1997. Most of our patients present with advanced stage of disease .(4)

In Chennai 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 rates per 100,000 person (ICMR- population based cancer registry-Chennai)

3.2 Anatomy

The uterus is a muscular hollow organ located in the mid plane of the true pelvis. It is situated behind the bladder and in front of the rectum ,usually in an anteverted position.

Uterus is partially covered by peritoneum in its fundal portion and posterior aspect. The anterior surface is related to the bladder and lateral surfaces are related to the broad ligaments. The corpus is separated from the cervix by a subtle constriction which is called the isthmus. Cervix is further divided into two regions based on the ring containing the endocervical canal, into supravaginal portion which is above and the vaginal portion, which is projecting in to the vaginal vault. (Fig.1)

The uterus is attached to the surrounding structures by means of 2 pairs of ligaments, called the broad and the round ligaments . Broad ligament extends from the lateral margin of the uterus to the lateral wall of the pelvis and it is made of double layer of peritoneum. It enclose the parametrium as it reaches the uterus and it also contains the fallopian tubes. The broad ligament follows the plane of the pelvic floor inferiorlyand ends in the upper portion of the vagina, medially.

The round ligament is a band of smooth muscle and connective tissue , which extends forward horizontally from its attachment in the anterolateral portion of the uterus to the lateral pelvic wall ,later it crosses the pelvic brim and extends laterally to reach the abdominoinguinal ring, finally terminates in the superficial fascia. It contains small vessels and nerves.

The uterosacral ligaments traverse along the recto-uterine-peritoneal fields and gives support mainly for the lower uterus . The cardinal ligaments, other wise known as Mackenrodt's ligaments are thickened connective tissue and fascia arising at the upper lateral margins of the cervix and which inserts into the fascial covering of the pelvic diaphragm.

The rich lymphatic network of uterine cervix , drains mainly into the adjacent paracervical lymph nodes and later to the external iliac which includes obturator nodes and the hypogastric lymph nodes. These pelvic lymph nodes mainly drain into the common iliac and from there to the para-aortic lymph nodes (Fig.2). Some of the lymphatic channels from the funduspass laterally across the broad ligament along the ovarian vessels into the para-aortic lymph nodes and some of them drain into the common iliac lymph nodesthrough the external and internal lymphnodes.

3.3 Histology

Most common histology seen in uterine cervical malignancies are squamous cell carcinomas (80-90%). Adenocarcinomas are increasing in incidence and are commonly of endocervical type . Anaplastic small cell tumors are aggressive tumors and they have a bad prognosis with less than 50 per cent survival rate for stage I disease. Lymphomas and melanomas are rare presentations. Metastases from colon and breast and direct spread from uterine malignancies are also seen.

3.4 Risk factors

Infection with human papillomavirus (HPV), is postulated as the main etiologic agent for the main histological subtype of cervical carcinoma, the squamous cell carcinoma and its preinvasive disease (5). The factors associated with an increased risk of acquiring or having compromised immune response to HPV infection includes

Early onset of sexual activity – The risk is approximately 1.5 times more for those who are 18 to 20 years old and it is two times more for whom those are younger than 18 years when compared to those who had first intercourse after 21 yrs or old.

Multiple sexual partners –risk is approximately two times more with two partners and three times more with 6 or more partners when compared with one partner.

A partner withacquired human papillomavirus infection and other sexually transmitted infections like Chlamydia trachomatis and genital herpes or with multiple sexual partners is also high risk for developing carcinoma cervix.

Past history of vulvar and vaginal squamous intraepithelial neoplasia or cancer is high risk factor as the etiology is same in all these conditions

Any form of immunosuppression is associated with an increased risk (eg, human immunodeficiency virus infection)

It has been shown that cervical cancer is less common in sexual partners of circumcised males .

Younger age at the time of first birth (younger than 20 years old) and multiparity (3 or more full term births) are also associated with an increased risk of cervical cancer, as these are associated with increased risk of exposure to HPV through sexual intercourse .

Studies has shown that low socioeconomic status is also contributing to an increasedincidence of cervical cancer.

Increased risk of cervical cancer has been reported with usage of oral contraceptive pills .

3.5Natural history and patterns of spread

Squamous-cell carcinoma of the uterine cervix usually originates at the squamous columnar junction. In majority of patients the lesion begins with severe cervical dysplasia and carcinoma in situ, later progressing to invasive carcinoma over 10 to 20 years . As the lesion advances it breaks through the basement membrane and invades the cervical stroma. The chance of lymphatic spread to pelvic and paraaortic nodes increases with increase in the the depth of stromal invasion . The malignant process later manifests as either superficial ulceration or exophytic growth in the ectocervix and in the endocervix it often presents as diffuse infiltration of endocervical region . If left untreated, the lesion has the potential to spread to the adjacent vaginal fornices, paracervical and parametrial tissues and direct invasion of the adjacent structures like bladder and the rectum.Multiple studies has shown thatlocal l extension is often associated with the depth of stromal invasionand presence of lymphatic invasion, which in turn leads to lymph node metastasis

The lower uterine segment and the endometrial cavity involvement by uterine cervical cancer can occur in 10% to 30% of patients ,and these patients have more chance of distant metastases . Regional lymphatic or hematogenous spread occurs, depending on the stage of the tumor, but dissemination does not always follow an orderly sequence.

In a study conducted by Girardi et al, incidence of parametrial nodes were found high 78% patients out of 359 specimens of radical hysterectomies. Sub analysis showed ,only 26% of patients had positive iliac lymph nodes in the absence of parametrial nodes. All these data supports the need for a complete bilateral pelvic lymphadenectomy in patients with invasive cervical carcinoma or irradiation of parametrial tissues in patients undergoing radical radiotherapy.Regional lymph nodes includes, the nodes in the parametrium, external iliac nodes including obturator nodes, internal iliac nodes and common iliac nodes were commonly involved in patients with locally advanced carcinoma cervix . Para-aortic lymph nodes were found to be involved in3/91 (3.3%) patients with stage IB and IIA tumors and in 5/38 patients (13.1%) with stage IIB and III disease.

Increased depth of stromal invasion is associated with increased risk of pelvic lymph node metastasis, according to the International Federation of Gynecology and Obstetrics (FIGO) staging system. It is estimated to be around 0.2 -0.6 % for stage IA1 disease and 7 % for stage IA2 disease.

There is an increased risk of paraaortic nodal involvement in addition to pelvic nodal disease as the extend of local disease increases,, 8 %,12 %,29 % 17 % and 27 % respectively for stage IB,stageIIA, stage IIB, stage IIIA and stage IIIB disease.

3.7 FIGO staging for carcinoma cervix

Staging of cervical cancer is one of the oldest staging in the literature, dating back to 1928. Classification of Carcinoma of the Uterine Cervix is done by International Federation of Gynecology and Obstetrics (Appendix I). Since the initial staging was introduced by them, 2 revisions has done in 1988 and 2009. The controversies surrounding cervical cancer staging has contributed to revision in 2009 and published in International journal of gynecology and obstetrics which is the official organ of the FIGO.Since the staging system should be uniform and feasible at all centres and also allow for comparison of results from different centres, FIGO has recommended staging to be based on clinical findings which includes assessment of the tumour extent (ie, extent of local disease, tumor size, involvement of cervix, vagina, parametrium and extent into adjacent normal tissue like rectum and bladder)along with limited radiological investigations which does not include MRI and CT scans for staging in carcinoma cervix. Clinical staging may be adequate forevaluating local disease extent, but does not take in to account involvement of the uterus, lymph nodesor distant metastasis.

3.8 Prognostic factors

A retrospective analysis undertaken by Kapp et al, in an attempt to identify prognostic pretreatment factors showed that FIGO stage is an important prognostic factor (6,7) .Other factors like patient ,s age at diagnosis, , histology, pretreatment haemoglobin level and neutrophil count , co morbid illness like diabetes mellitus and history of

multiple number of pregnancies are found to be associated with prognosis. It was found that increased tumor size (8) was associated with decrease disease-free survival and local-regional control rates, when all other factors including stage was controlled for. The diagnosis of pelvic lymph node metastasis is an important prognostic factor in patients with uterine cervical cancer (9,10) as it adversely effects out come. Some of the studies which have reported prognostic factors and is suggested to be included in the staging system are depth of stromal invasion (11-16), tumor size, presence or absence of lymphatic vascular space invasion (17-24), pelvic lymph node status (25,26), tumor volume, endometrial extension of cervical carcinoma, and parametrial involvement. Other patient factors which have been extensively studied are the age and the socioeconomic factor. Medical factors include anemia, tumor hypoxia , arterial hypertension, fever and HIV infection.

When we consider lymphatic spread and the various types of histology, positive lymph nodes are found in adenocarcinoma more than in squamous cell carcinoma, showing the difference in their behavior. It was found by Korhonen et al that there is no significant difference in survival rate between pure adenocarcinoma with other subtypes like adenosquamous carcinoma and clear cell adenocarcinoma (27) . Histologic type and grade of thetumour also has an impact on survival to a lesser extent.

Prognostic factors based on imaging -There are data showing that the size of the cervix evaluated in CT scans is directly proportional to local control and overall survival (28,29). In a retrospective study of CT scans done on cervical cancer patients by Shepherd et al showed that tumor depth was correlated with lymph node involvement(30)

Based on MRI volume Kodaira et al showed that 5 year DFS of patients treated with radiotherapy with tumor diameter more than 5 cm was significantly lower (46.2%) than that for patients with size less than 5cm.(88%) (31) .MRI dynamic enhancement during the first 2 weeks of radiation therapyhas shown early prediction of tumor regression rate(32).MRI studiesconducted by Hantano et al at 30 Gy of external radiation and 3 months after radiation therapy were predictive of local tumor control.(33)

Tumor with cranio -caudal diameter,(which was obtained by measuring the length of the tumor parallel to the long axis of uterine body) lessthan or equal to4 cm was associated with better five-year disease-free survival (70%) compared to patients with tumor diameter more than 4 cm.(34)

Study by Toita showed that antero posterior diameter (AP) of tumor more than4 cm was associated with increased incidence of lymph node metastasis and distant metastasis(35)

In another study by Kodaira et al, showed large tumor size (volume more than 50 cm3)and positive lymph node enlargement showed a significantly unfavorable influence on survival and local and distant failure ($p < 0.05$) (36)

Recently, Kim et al(37) showed lower ADC in metastatic lymphnodes ($0.7651 \times 10{-}3$ mm2/sec) than in non metastatic lymph nodes ($1.0021 \times 10{-}3$ mm2/sec).

MRS study has shown that lactate level in cervical cancer tissue correlated with more chance of metastatic spread . There was higher levels of cholines and amino acid residues and lower levels of glucose in malignant tissue of the cervix when compared to nonmalignant tissue ..(38)

Another biomarker is ADC histogram analysis which has proven its efficacy in predicting tumor recurrence in patients treated with chemoradiation. (39)

3.9 Staging and workup

It is advisable that all patients with carcinoma cervix should be jointly evaluated by the radiation and gynecologic oncologist. Detailed history and physical examination of the patient including a pelvic examination should be done. Special attention to the supra clavicular nodal areas ,per abdomen findings for hepatomegaly, tenderness in hypogastrium or renal angle tenderness and inguinal area examination for any palpable lymph nodes should be carried out. Pelvic examination should include inspection and of external genitalia, vagina and uterine cervix and rectal examination and bimanual palpation of the uterus and adnexa with special emphasis on parametrial involvement. In all patients with stage IIB and more advanced disease and in those patients who gives a history of urinary or lower gastrointestinal tract complaints cystoscopy or rigid rectosigmoidoscopy is recommended to rule out local infiltration.

Staging of Carcinoma of the uterine cervix is managed by means of the International Federation of Gynecology and Obstetrics (FIGO) staging system. The FIGO staging system is determined mainly by the clinical assessment. This was seen to be quite sufficient for early stage disease, but it has limitations in assessing advanced stage disease. It does not take into account the nodal involvement. Though not routinely used in the developing countries, CT and MR imaging are widely used elsewhere to evaluate tumor size and extent, and nodal involvement. In this it was found that MR imaging is

excellent for depicting invasive cervical carcinoma with objective measurement of tumor volume. It rules out conclusively parametrial invasion and stage IVA disease.

The following investigations are recommended for the work up of carcinoma of cervix, by FIGO.

Diagnostic work-up for carcinoma of the cervix

General	*History *Physical examination, including bimanual pelvic and rectal examinations
Diagnostic procedures	*Cytological smears(Papanicolaou) if not bleeding *Colposcopy *Conization (subclinical tumor) *Punch biopsies (edge of gross tumor, four quadrants) *Dilatation and curettage *Cystoscopy, rigid rectosigmoidoscopy(stages IIB, III, and IVA

Radiographic Studies	Standard *Chest radiography *Intravenous pyelography *Barium enema (stages III and IVA and earlier stages if there are symptoms referable to colon or rectum) Complementary *Lymphangiography *Computed tomography (CT) or magnetic resonance imaging (MRI) *Positron emission tomography (PET) scan(optional)
Lab tests	*Complete blood count including manual platelets *Biochemical evaluation including LFT and RFT *Urine analysis *blood born virus screening

3.9 Role of imaging in the management of carcinoma cervix

Imaging used in oncological setting should be capable of differentiating between malignant and non malignant tissues at all stages . These imaging techniques helps in staging of disease accurately and also have a role in the delineation of the target volumesfor planning radiation therapy. The idea about extent of the tumor influence therapeutic decisions, therapy outcomes and thus patient prognosis.

Chest Xray

Standard chest radiographs are recommended to evaluate the lungs for metastases

Intravenous pyelograms

Intravenous pyelograms are used to evaluate the kidneys for ureteral obstruction.

Barium enemas

Barium enemas and and X-rays are allowed in staging ,but are more helpful in patients with bulky tumors as part of staging and treatment planning.

Lymphangiography.

1961, Wallace et al demonstrated that Lipiodol a dye can demonstrate the structure of metastastic nodes . People then started doing lymphangiography to detect lymph node metastases in patients with cervical cancer.It is performed by direct cannulation and injection of contrast agents into the lymphatic ducts. It will penetrate lymph nodes and normal lymph nodes appear opaque on film. The lymph nodes which contains metastatic cellswill not become opaque after the injection of contrast material. The size of a lymph node as well as the internal architecture can be demonstrated by lymphangiography and it can also detect abnormalities within a normal-sized lymph node on other imaging. Its specificity is more than sensitivity ,which was found to be ranging from 47% to 100%

False-negative results may occur in the presence of microscopic metastases and false-positive results can occur in case of fatty infiltration and inflammatory processes.

Following bipedal lymphangiography in carcinoma cervix patients , the external iliac, common iliac, and retroperitoneal lymph nodes are seen as opaque. The contrast material remains in the lymph nodes for several months, will be useful for the localization of nodes at the time of radiation treatmentplanning.

However, the procedure is invasive and difficult to perform.

Ultrasonography

Ultrasound generated by piezoelectric materials is a form of non radiation exposure imaging modality. In gynaecological practice , both trans abdominal and trans vaginal ultrasonography are commonly used . Ultrasonographic evaluation in carcinoma cervix patients helps in assessing cervical size, enlarged pelvic or para aortic lymph nodes and hydrouretero nephrosis or liver metastasis. .Many of the studies using TransRectal UltraSonography (TRUS) has shown benefit in the evaluation of tumor size and also in parametrial involvement. Innocenti et al.(39) reported for 83 % staging accuracy with TRUS, compared to physical examination

Magee et al.(40)evaluated correlations between tumor size measured by TRUS and overall survival. Gitsch et al.(41) reported that stromal reaction detected in TRUS have high specificity for diagnosing parametrial invasion . Cobby et al.(42) reported when compared to clinical examination and MRI ,accuracy rates of 95% for Transrectal ultrasound (TRUS),which is relatively a cheap investigation . It has shown efficacy in

the evaluation of early parametrial infiltration ,tumor volume , and even of identification of residual tumor in early-stage cervical cancer as compared to MRI(43).

Imaging modalities like computed tomography and magnetic resonance imaging detects cancer by identifying anatomical distortion or altered tissue appearance. Administration of intravenous contrast medium enhances delineation. With the emergence of functional imaging like diffusion weighted imaging and PET CT it is possible to more accurately define the tumor , monitoring treatment response and to make out relapsed disease when compared to conventional imaging techniques.

MRI and CT SCAN:

1.Tumor size and local spread - If imaging is considered, MRI is the modality of choice.In a prospective study included 208 women, most with stage IB disease, who underwent MRI and CT prior to surgery [44]. MRI correlated more closely with surgicopathologic findings than CT or physical examination. An important observation from this study is that , overestimation of tumor size in all imaging modalities.Over estimation of findings in surgical candidates may not change treatment or prognosis, while underestimation of size can potentially triage a patient to surgical excision where chemoradiation is the treatment.

MRI is more helpful in the assessment of extra cervical tumor extension(45).It is a useful imaging modality in patients allergic to iodinated contrast or impaired renal function. Any way it is contraindicated in patients with pacemakers, cochlear implants ,metallic prosthesis or large vascular clips .On T2 weighted images a cervical cancer may be seen

as a mass usually of greater intensity than fibro cervical stroma . Parametrial invasion is easily identified on T2 –weighted images from low intensity cervix and uterine ligaments. MRI was superior to CT scan in localizing the primary site. MRI is shown superiority ove CT scan in detection of parametrial extension and invasion of surrounding structures .It has limitation in detecting lymphnodes .and false positive results can occur because of volume averaging with bowel (46).

Estimating the presence of parametrial spread is also of critical importance for deciding whether patients are candidates for surgical treatment.Results from multiple studies are controversial, whether imaging studies are better able to detect parametrial spread than clinical staging [47-50]. Imaging studies performed better than clinical staging in one study, a prospective multicenter study of 172 women with cervical cancer who were clinically staged as IB or higher underwent CT and MRI prior to surgery [47]. Detection of stage IIB or higher was poor for all approaches, but imaging studies performed better than clinical staging: clinical staging (sensitivity: 29 percent and specificity: 99 percent); CT (42 and 82 percent); and MRI (53 and 74 percent). In contrast, a retrospective study byHancke K et al found clinical staging to be superior to CT and MRI [50]. In that study, the sensitivity and specificity for detection of parametrial involvement (stage IIB) was: clinical staging (sensitivity: 66 percent and specificity: 81 percent); CT (43 and 71 percent); and MRI (52 and 63 percent).

MRI was found to be superior to CT for evaluation of parametrial involvement in a meta-analysis of 57 studies ,byBalleyguier C et al (51,52)

There are limited data regarding the use of PET/CT for the evaluation of tumor size or local spread in cervical cancer (53)

The scope of MR spectroscopy in cancer cervix has gained attention in the recent years to establish their role as predictive biomarkers. MRS Studies have shown that ADC and total cholinelevel was different between different histological types of cervical cancer.(54)

2.Lymph node metastases — Cervical cancer may spread to the pelvic or Paraaortic lymph nodes, as well as more distal nodes. The presence of lymph node involvement is associated with a worse prognosis and impacts decisions regarding the radiotherapy field (55) . Parameters like short axis diameter, roundness index , irregular outline and extra capsular spread are used for evaluation of enlarged lymphnodes based on different imaging modalities. Ultrasonography can make out presence or absence of hilar structures ,any alteration in cortical structures and presence of microcalcification or necrotic areas. Where as CT scan detects presence of necrosis as hypodense areas and metastatic nodes show nonhomogenous enhancement following intravenous contrast administration.

Metastatic nodes also show inhomogenous enhancement following Gadolinium administration in MRI . Nodes are seen as inhomogenous signal in T2 weighted images, intensity will be unchanged after USPIO administration in T2 weighted sequences and hyper intense areas in T2 weighted sequence shows the presence of necrosis.

The overall accuracy of CT scan in staging cervical cancer ranges from 63% to 88%.(56).The accuracy of CT scan in detection of lymphnode is found to be 77%

to85%. With a sensitivity of 44% and specificity of 93%.(57). In his study by Camelion, it was shown that CT scan is more useful in the detection of Para-aortic nodes with a sensitivity of 67% and specificity of 100%.

Initial evaluation of lymph nodes is commonly performed with CT to minimize expense, but PET and PET/CT are the imaging modalities used to provide information for treatment decisions. These studies have largely replaced MRI and lymphangiography .

Integrated PET/CT imaging is a technique in which both PET and CT are performed and images are fused using software.This gives additional information of physiologic activity seen on PET along with the anatomic localization on CT images.

Studies has shown the superiority of PET to other imaging modalities.In a meta-analysis of 72 studies including 5042 women with cervical cancer,imaging modalities were compared for the detection of lymph node metastases sensitivity and specificity of PET was 75 % 98 % ,when compared to MRIand CT [58]. Integrated PET/CT may be more sensitive than PET alone for detection of nodal metastases, particularly for pelvic lymph nodes [59-61].

However,in locally advanced cervical cancer, PET/CT may have a higher false-negative rate for detecting Paraaortic lymph node spread . In a study of 60 patients with stage IB2 to IVA disease found that 12 percent of those with no finding of positive Paraaortic nodes on PET/CT findings had pathologically positive Paraaortic nodes [62]. A subset of patients with PET/CT findings of positive pelvic and negative Paraaortic negative nodes had an even higher rate of pathologically positive Paraaortic disease (22 percent). In a separate study of PET/CT and pathologic analysis of Paraaortic nodes, patients with PET positive pelvic and

negative Paraaortic negative nodes had a similarly high unrecognized disease to Para aortic nodes (24 percent) [63].

Recent studies done for comparison of imaging and histology in the diagnosis of metastatic lymph nodes imaging showed poor sensitivity of CT (24%;), MR (29%), and even PET (58%;). This was postulated to be due to inaccuracy in detecting lymph nodes which harbor cancer cells.Routine crieteria used for detecting metastatic lymphadenopathy by measuring short axis diameter (SAD)which is said to be significant if SAD greater than 1 cm. Recently, Kim et al(64) showed that the apparent diffusion coefficient was lower in the metastatic lymph nodes. Diffusion weighted images gives additional information regarding ADC .It has advantages over other routine imaging modalities in the detection of metastatic lymph nodes as it is independent of size of the node.

3.Bladder and rectal infiltration by uterine cervicalcarcinomas — Tumor extension to the bladder and ureter may result in hydronephrosis and, ultimately, in nonfunctioning kidney in women with cervical cancer. The urinary tract is imaged in all patients with more than a microscopic tumor. While intravenous pyelography (IVP) is the examination included in the guidelines for clinical staging, MRI and CT are typically used where available .IVP still has a role in low resource settings.

Trans vaginal ultrasound is another investigation of choice for ruling out bladder infiltration, where echogenic boundary between the cervix and posterior bladder wall is intact.

In a retrospective study by Krestin GP, Hauser M et al, where they compared 6 different imaging signs of focal bladder infiltration in 129 patients who underwent 92 CT and/or 64 MRI examinations. These findings were later correlated with cystoscopy, rectoscopy ,intraoperative findings and histological examination of surgical sections (65).In 27 patients submitted to both imaging examinations it was found that MRI provided similar results as endoscopic procedures like cystoscopy and rectoscopy .Subset analysis showed that MRI was superior to CT scan. This study showed that Imaging can predict bladder or rectalwall infiltrationin carcinoma of the uterine cervix and can avoid endoscopic procedures.

In another study MRI 5 point scoring system was done to rule out bladder and rectal infiltration and score of 3 or above were used to identify patients with bladder and rectal infiltration (66). This study showed that MRI scoring system predicts local infiltration of bladder and can safely avoid the need for invasive cystoscopic or endoscopic procedures in the majority of patients with cervical cancer. This leads to a reduction in morbidity associated with these procedures.

4.Response assessment to treatment –To assess disease status on follow up evaluation . Recommendation mentioned earlier under ABS guidelines.

5. Diffusion –weighted MRI imaging in pelvic malignancies

Stejskal and Tanner in 1965 described diffusion –weighted sequence as an advanced methodof T2 – weighed sequence. Itprovides bothqualitative and quantitative information about structural tissue changes at cellular level.

Diffusion weighted imaging uses the principle of exploitation of water movement in the intracellular as well as extracellular spaces . The movement of water molecule in an unrestricted environment is random and is known as a phenomenon called Brownian motion. Within the organ ,the impedence of water molecule diffusion depends upon the the extend of tissue cellularity and presence of intact cell membranes .

Hence those tissue types which are associated with tumor, cytotoxic edema, abscess and fibrosis will show impeded diffusion .

Mechanism of diffusion –weighted sequence (Kindly refer Fig .1 on annexure)

The T2- weightedMRI sequence consists of a 90 degree followed by a 180 degree radiofrequency (RF) pulse and is associated with T2 decay due to transverse relaxation. In diffusion weighted sequence , a diffusion sensitizing gradient otherwise called a dephasing gradient is applied prior to the 180 degree RF pulse followed by a symmetric rephasing gradient after 180 degree pulse.Water molecules movement with in a restricted environment cannot move long distance and the shift obtained within it during the application of dephasing gradient will be cancelled by the application of rephrasing gradient.This results in no net loss in signal intensity. But if the cellularity of the tissue is low,water molecule move long distance and will not get rephrase with second gradient and often result in net loss of signal intensity.

b value –

b value is the strength of diffusion sensitizing gradient .It is measured in seconds per square millimeter. It is directly proportional to the amplitude of gradient ,its duration and time interval between the gradients.

At a b value of 0 sec/mm2 (i.e. if there is no diffusion sensitizing gradient) ,the signal intensity of the imaged organ will be same as T2 weighted imaging. At high b values (500 – 1000 sec/mm2) water movement in those tissues which has highly cellular tissues such as tumor, neurological tissue, normal lymphatic tissue, bowel mucosa and normal endometrium will appear bright on diffusion weighted images. As the b values are organ specific, diffusion weighted images should be tailored accordingly.

Qualitative assessment by means of Diffusion-weighted imaging-

Depending on the region or organ which has to be imaged ,diffusion –weighted imaging is performed using at least 2 b values ,0 sec/mm2 and 500-1000 sec/mm2. The signal loss in different water molecules helps in characterization of the lesion as increased signal intensity at high b value suggests restricted diffusion consisted with highly cellular tissue. This interpretation is always compared with other sequences of MRI for final conclusion.

Quantitative assessment of Diffusion weighted imaging

It is based on ADC value. When we plot logarithm of signal intensity versus b values ,there will be exponential decay of signal with increasing b values. The slope of this line gives ADC value. The ADC values of tumors are usually low as the decay in signal is reduced in tissues with restricted diffusion. Thus quantitative measurement of ADC

value helps to differentiate malignant lesion from benign lesion based on the low signal intensity of malignant lesion on ADC mapping.

Normal cervical stroma shows low signal intensity on T2-weighted images and delayed enhancement on gadolinium-enhanced images as it contains large amounts of fibrous tissue .But as cervical cancer tissue has greater cellularity , it shows higher signal intensity on T2-weighted images and greater enhancement on gadolinium –enhanced T1-weighted images.

Cervical carcinomashows significantly lower ADC as it demonstrates impeded diffusion relative to normal cervical stroma.Many of the studies has shown ADC value of 1.09 +/-0.2x10-3 mm2/sec for cervical carcinoma compared to normal cervix 1.79 +/-0.24x10-3 mm2/sec. The usage of diffusion weightedimaging for the characterization of pelvic lymph node in gynaecological cancers is not recommended as it has lots of pitfalls.

2. Radiotherapy treatment planningand imaging

Radiotherapy is the mainstay of treatment in locally advanced carcinoma of cervix. Radiotherapy is delivered by a combination of external beam photon therapy and brachytherapy. External irradiation is used to treat the whole pelvis and parametrium including the common iliac nodes whereas the central disease- cervix, vagina and the medial pat of the parametrium is primarily irradiated with the intra cavitary sources.

External beam irradiation

It is delivered before intracavitary insertions in patients with a) bulky cervical lesions or tumors beyond stage IIA to improve the geometry of the intracavitary application; b) exophytic easily bleeding tumors, c) tumors with necrosis or infection, d) parametrial involvement

It is important to deliver the adequate doses of irradiation not only to the primary tumor and to the pelvic lymph nodes. The common iliac bifurcation being cephalad to the lumbosacral prominence, the superior border of the pelvic portal should be at the L4/L5 inter space to include all of the external iliac and the hypogastric lymph nodes. This margin is extended to the L3/L4 interspace if common iliac nodes are to be covered. A 2 cm margin lateral to the bony pelvis is adequate. If there is no vaginal extension, the lower border of the portal is at the inferior border of the obturator foramen. If the vagina is involved, the entire length upto the introitus should be treated. In patients with tumor involving the distal half of the vagina, the portal fields should include the inguinal lymph nodes. The anterior border of the lateral field is kept 3 cm in front of the anterior surface of the L4 vertebral body or at the pubic symphysis and posteriorly at the S2/S3 junction. In locally advanced tumors the posterior border maybe extended to include the entire sacral hollow.

Previously the most common technique recommended for irradiation of the whole pelvis was the two-field approach using an A-P/P-A technique . The four-field box technique which is commonly used now for conventional planning was introduced in the early

1980s .The aim of of this method was to reduce the volume of normal tissue being treated and to increase the dose to the tumor volume. This technique has two lateral portals and one anterior and posterior portals each.The lateral ports were recommended to shield posterior wall of the rectum, anterior wall of the bladder and some of the small bowel, in order to reduce the dose administered to these critical organs.

In 1993, based on the lymphangiography examinations, Pendlebury *et al*reported that at least 2.5 cm margin from the pelvic side wall would be required for adequate coverage of pelvic lymph nodes in 90% of patients (67) . Guidelines for the lateral pelvic ports were based on the bony landmarks that can be identified radiographically. The commonly used field borders for the lateral fields wasanteriorly 3 cm anterior to anterior border of L5 vertebral body and posteriorly S2/S3 interspace . Ports defined by these guidelines is not always suitable for the individual patient's anatomy. Based on intra-operative measurements, Greer *et al.* opined that the entire anterior sacral silhouette should be included in the lateral fieldin patients with locally advanced carcinoma cervix ,due to posterior extension of the parametria (68)

Several methods have been made periodically attempted to improve treatment planning taking into account the individual anatomy of the patients .Initially conventional radiographic treatment planning using contrast medium in the bladder and rectum were tried .The information obtained from this method was limited regarding the localization of tumor and uterus.

There after comes the era of computed tomography which enabledthe visualization of the pelvic organs, structures including in the clinical target volume and organs at risk. In a prospective study conducted on 34 patients with cervix carcinoma Kim *et al* ,(69) simulated all patients with conventional four-fieldpelvic portals .Customized blocks were used to shield the posterior wall of therectum and a part of small bowel using the barium silhouette of those organs. Following this CT scan was done to identify the tumor volume on each slice.It was found that posterior margin coverage was ranging from 39% to 50% only in the conventional as compared to CT based planning. There were inadequate coverage at the customized rectal block, and in the posterior border on the lateral fields. With a median follow-up of 36 months, it was found that pelvic control for inadequate margins was 100% and 71% for stage IB, 88% and 50% for stage IIB.

In 1992Russell *et al.*,reported the value of pelvic MRI indetermining the lateral fields of the four field box technique (70).It is proven that MRI has the additional advantage in the visualization the anatomy of the pelvis in all the planes .It also provides a better soft tissue delineation and tumor depiction than CT scan[71-76].From their study, Russell and colleagues found that using the conventional lateral portals , the tumor volume wasadequately covered in only 44% of patients . There was incomplete coverage of the uterine fundus in 62.5% and marginal miss in more than 50% of patients. In their study Zunino *et al.* found that due to uterusflexion and associated pathology like myoma, endometriosis and pyometra ,the lateral portals failed to involve PTV in 50% of cases(77).

Thomas *et al* conducted a study in which the MRI images were acquired in the treatment position using flat table and MR detectable tubing for marking radiation ports, concluded that MRI in treatment position alone could assess the simulated fields .

All these studies showed that the potential benefit of the lateral fields to shield the rectum and small bowel is outweighed most of the time by the loss of tumor margins.

Multiple studies has shown that the most common pattern of regional recurrence (66-97%) in patients treated with conventional radiotherapy was at the margin of the radiation field. Cross sectional images (CT/MRI) helps radiation oncologists to customize the external radiation treatment fields based on the findings. Nowadays, the CT based simulation has been widely established. The CT simulation helps to include the tumor volume inside the treatment fields either treated with conventional technique (AP/PA), or advanced techniques such as 3 dimensional conformal radiation therapy (3DCRT), or intensity modulated radiation therapy (IMRT)

3D conformal radiotherapy is the standard of choice for irradiation of gynaecological malignancies at present. CT-based 3D planning and mainly the use of the beam's eye view (BEV) helps the physician delineating the target volumes and organs at risk .It helps in the optimal design of individually shaped fields .Thus helps to avoid geographical misses and to reduce the dose to organs at risk .

Recently, the concept of pelvic radiotherapy using IMRT has emerged with its increased usage for external radiation treatment. Rationale for IMRT in cervical cancer is based on multiple studies .It has shown improved delivery of conventional doses, simultaneously achieved with decreased dose to normal tissue like small bowel,bladder,rectum and bone marrow (78-80).The concept of bone marrow sparing IMRT has come with benefit of

reduced haematological toxicity with concurrent chemotherapy(81).It allows dose escalation in high risk patients like node positive disease and gross residual disease. Simultaneous integrated boost to node positive patients has shown benefits(78) .It has also shown reduced dose to normal tissues in extended field radiotherapy (82).The role of IMRT to an alternative for brachytherapy was considered in patients with for locally advanced gynecological cancers that may not be amenable to brachytherapy for anatomic or medical reasons. IMRT with simultaneous integrated boost has shown benefit to conventional two-phase treatments (whole pelvic irradiation followed by brachytherapy or EBRT boost) due to shorter treatment time, significant sparing to normal structures and capability of potential for dose escalation (83).

Additionally, cervical cancer patients receiving IMRT treatment showed superior cause specific and overall survivals compared to patients who were treated with conventional radiation therapy (Kidd et al., 2010).

The target delineation is very important for complicated radiation treatments. Radiation doses would be delivered to only the designated targets and avoid the non-designated areas. Likewise, the normal tissues may not be spared if these structures are not assigned.

The implementation of MRI into radiation planning has its limitations mainly due to reasons such as distortions and lack of electron density for radiotherapy dose calculation (84).MRI can be used in the planning system after integrating tools for CT/MR image registration. These registered images from each modality are preferably taken with the patient in the treatment position .The MR image helps in delineation and the calculation is often made on CT. Perez *et al (85).*Showed that when compared to CT alone

automatic rigid fusion followed by a deformable soft tissue fusion improves high degree of anatomical correlation .

MRI vs CT in tumor volume delineation

In a study by . Subak LL, showed that tumor volume was evaluated accurately by MRI, when compared to CT and later confirmed by pathological evaluation . Magnetic resonance was 88% accurate evaluating the presence of stromal invasion and 78% accurate for depth of stromal invasion. Computed tomography could not evaluate tumor size or stromal invasion because it could not distinguish cancer from the surrounding normal cervical tissue (86).

A number of publications from The American College of Radiology Imaging Network (ACRIN) and The Gynecologic Oncology Group (GOG) have demonstrated that traditionalT2-weighted MR imaging is superior to CT for tumor delineation in cervical cancer (44).

Recent recommendations from GEC-ESTRO have emphasized the role of MRI in target delineation for brachytherapy in cervical cancer (87).

Brachytherapy

Like external radiotherapy, brachytherapy also has progressed from two dimensional (2D) planning to three dimensional (3D) planning with the help of new imaging modalities. Conventionally, brachytherapy has been planned with the knowledge of clinical examination in conjunction with orthogonal radiographs .Treatment was based on arbitrary 2D prescription points and normal adjacent organs for dose prescription. In

individual patients this 2D method can cause inadequate dose delivery to the tumor and may lead to underestimate the doses to organ at risk. Recently, 3D brachytherapy planning using CT/MRI images has become popular, where there is provision to make out the residual tumor related to adjacent organs .This in turn provides adequate dose coverage to the primary tumor and surrounding microscopic diseases while reducing the dose to the adjacent critical structures

During the last 10 years, MRI is being used in conformal brachytherapy treatment planning as it provides superior soft tissue resolution compared to CT post external beam radiotherapy and and because electron density does not play a role in dose calculation in brachytherapy. The GECESTRO Working Group and the American Image-Guided Brachytherapy Working Group have proposed the use of T2- weighted MRI in image guided brachytherapy. This images are preferably done using a pelvic surface coil and image-compatible brachytherapy applicators. According to the GYN ESTRO Group the GTV for BT (GTVB) includes macroscopic tumor extension at the time of BT as detected by clinical examination and as visualized on MRI (high signal intensity mass .High-risk CTV for BT (HR CTV) includes GTVB, the whole cervix, and the extra cervical tumor extension at the time of BT defined by means of clinical examination and residual grey zones on MRI. No safety margins are recommended. Intermediate-risk CTV for BT (IR CTV) carrying a significant microscopic tumor load encompasses HR CTV with a safety margin of 5–15 mm depending on the pretreatment tumor location, tumor size , potential areas of microscopic spread, extend of tumor regression during treatment and the treatment plan(87)

Adaptive radiation therapy

The concept of adaptive radiation therapy was generated to take account of target changes such as tumor shrinkage and internal organ motions during radiation therapy . Image guided radiation therapy (IGRT) make use of reconstructed cross-sectional images taken during treatment .It enables the delivery of radiation doses to the actual targets, to monitor the tumor changes, both intrafraction and interfraction, during the external radiation courses. Tumor shrinkage during treatment is a concern and action should be taken to monitor changes during the radiation treatment.

Following table shows comparison of three different modalities frequently used for disease assessment in carcinoma cervix patients(ref;Advanced Imaging Applications for Locally Advanced Cervical Cancer ,Janjira Petsuksiri et al)

	CT	MRI	PETCT
Primary tumor visualization	Feasible	Recommended	Feasible
Parametrial invasion	Feasible	Recommended	-
Vaginal invasion	-	-	-
Rectal invasion	Feasible	Recommended	-
Bladder invasion	Feasible	Recommended	
Pelvic	Feasible	Feasible	Recommended

lymph node metastasis			
Para aortic lymph node metastasis	Feasible	Possible	Recommended
Distant metastasis	-	-	Recommended
Radiation treatment planning	Use for simulation, radiation field designation and radiation dose calculation	Better for primary tumor delineation	Treatment aim changes in patients with metastatic disease Assess the metabolic activity of the equivocal lymph node whether or not to include in the radiation fields Adaptive radiation therapy based on the metabolic activity
Tumor response after definitive treatment	Feasible	Feasible	Recommended

Overall advantage	Easily accessible Acceptable for l o c o r e g i o n a l disease assessment	Better for tumor delineation due to higher soft tissue contrast	Assess the metabolic activity of the tumor Detect distant metastasis
Overall disadvantage	Poor soft tissue contrast	Relatively inaccessible in endemic areas of cervical cancer	High cost and barely accessible in the endemic areas of cervical cancer

3. 9 Clinical Presentation

Early invasive carcinoma of the cervix can be detected before it becomes symptomatic by cytological smears. Sero sanguienous or whitish, foul-smelling vaginal discharge may be noted in patients with invasive carcinoma, particularly with more advanced necrotic lesions. If chronic bleeding occurs, the patient may -complain of fatigue or other symptoms related to anemia.

Pain, usually in the pelvis or hypogastrium, may be noted and could be caused by tumor necrosis ,pyometra or associated pelvic inflammatory disease or urinary tract infection. Low back ache is another common presentation. In these cases the possibility of par

aortic lymph node involvement with extension in to the lumbosacral roots or hydronephrosis should be considered. Occasionally epigastric pain may be caused by metastasis to high Para-aortic lymph nodes.

Urinary and rectal symptoms (hematuria , dysuria and rectal bleeding) may appear in advanced stages as a consequence of invasion of the bladder or rectum by the neoplasm.
Diagnostic work-up for carcinoma of the cervix

General	*History *Physical examination, including bimanual pelvic and rectal examinations
Diagnostic procedures	*Cytological smears(Papanicolaou) if not bleeding *Colposcopy *Conization (subclinical tumor) *Punch biopsies (edge of gross tumor, four quadrants) *Dilatation and curettage *Cystoscopy, rigid recto sigmoidoscopy(stages IIB, III, and IVA
Radiographic Studies	Standard *Chest radiography *Intravenous pyelography *Barium enema (stages III and IVA and earlier stages if there are symptoms referable to colon or rectum) Complementary *Lymphangiography *Computed tomography (CT) or magnetic resonance imaging (MRI)

	*Positron emission tomography (PET) scan(optional)
Lab tests	*Complete blood count including manual platelets *Biochemical evaluation including LFT and RFT *Urine analysis *blood born virus screening

Laboratory studies

Blood tests included serum for Biochemistry – creatinine and liver function tests, blood for Pathology-hemoglobin, total count with differentials, platelets, and Virology sample for Blood Borne Viruses, and urine analysis.

Radiological tests- Chest X-ray *(PA),* and intravenous pyelogram is recommended for all patients. A colon barium enema is advised for all patients with stage IIB and more advanced disease and in those patients who gives a history of urinary or lower

gastrointestinal tract complaints.Those who afford can do USG abdomen and pelvis or CT or MRI evaluation instead of the same.

3.10 Prognosis

According to statistics from the American Cancer Society, the five-year survival rate by stage is [88]:

Stage IB – 80 percent

Stage IIA – 63 percent

Stage IIB – 58 percent

Stage III – 30 percent

Stage IVA – 16 percent

3.11 TREATMENT

Intraepithelial disease (cervical intraepithelial neoplasia[CIN]) is treated with superficial ablative techniques.

3.8A. Early stage disease

Stage Ia2 (tumor with deep stromal invasion 3-5 mm and no greater than 7 mm diameter) and Ib1 (4 cm or less in size) are treated with radical hysterectomy and bilateral pelvic lymphadenectomy.

In selected patients with tumors less than 2 cm who are keen to preserve fertility, radical vaginal trachelectomy (removal of cervix, the upper part of the vagina, and parametrial tissue) and laparoscopic pelvic lymphadenectomymay be carried out.

Stage Ib1 and IIA (tumor 4 cm or less) are treated equally effectively with radical surgery or combined radical EBRT and brachytherapy with both treatments giving 80–90 per cent 5-year survival rates.

Stage Ib2 or IIa tumors (>4 cm tumor size) have deep stromal invasion and an increased risk of parametrial and lymph node involvement. Surgery is performed in selected patients with large tumors, lymphovascular space invasion (LVSI) and adenosquamous or high grade histology, followed by postoperative radiotherapy.

Ovarian transposition may minimize the chances of radiation-induced menopause.

Primary radical radiotherapy is preferable for other stage Ib2 and IIA patients.

This avoids the increased morbidity seen when surgery is followed by postoperative radiotherapy.

Lymph node dissection

As the risk of lymph node metastases with stage IA1 squamous cell cervical carcinoma is low (<1 percent) lymphadenectomy is not recommended unless there is lymphovascular space invasion .

For stage IA2 disease or microscopic IB1 disease (nonvisible, >5 mm in depth and ≤4 cm in greatest dimension), the risk of nodal metastasis is 2 to 8 percent and pelvic lymphadenectomy alone is generally sufficient since the risk for Para aortic nodal metastases is quite small. However, if pretreatment imaging shows positive Para aortic nodes or if pelvic nodes that are enlarged or fixed are encountered at surgery, frozen

section should be performed. If metastases are confirmed, par aortic lymphadenectomy should be performed as well.

For macroscopic stage IB1 and IIA1 tumors, a complete pelvic lymphadenectomy should be performed at time of hysterectomy. Paraaortic lymphadenectomy is performed at the surgeon's discretion and when pelvic lymph nodes are enlarged or fixed.

Adjuvant therapy indications — For women with early stage cervical cancer treated with a primary surgical approach, adjuvant therapy should be administered if final pathologic findings suggest they are at risk for disease recurrence.

Intermediate-risk disease — Final pathologic criteria (sometimes referred to as Sedlis' criteria) used to define women at intermediate risk includes the following

- Presence of lymphovascular space invasion (LVSI) plus deep one-third cervical stromal invasion and tumor of any size
- Presence of LVSI plus middle one-third stromal invasion and tumor size ≥2 cm
- Presence of LVSI plus superficial one-third stromal invasion and tumor size ≥5 cm
- No LVSI but deep or middle one-third stromal invasion and tumor size ≥4 cm

The risks of recurrence and death in the presence of these factors are up to 30 percent following surgery alone

Treatment of intermediate-risk disease — adjuvant radiotherapy to decrease the risk of recurrence.

The benefit of adjuvant RT was shown in a 2012 meta-analysis that compared adjuvant RT to no further treatment after hysterectomy in 397 women with early-stage cervical cancer (stage IB to IIA) [89]. Adjuvant RT resulted in:

- A reduction in the risk of disease progression (RR 0.58, 95% CI 0.37-0.91).
- No difference in the risk of death at five years (RR 0.84, 95% CI 0.3-2.36), although the wide confidence interval suggests the study was underpowered to assess survival.

More toxicity, including serious (grade 3/4) hematologic toxicity (RR 2.38, 95% CI 0.63-9.05) and gastrointestinal toxicity (RR 7.32, 95% CI 0.91-58.8) was noted in this study.

Although limited data suggest that chemoradiation may improve the risk of recurrence, it remains unclear whether this will translate into an overall survival. A retrospective analysis of 129 patients with intermediate-risk disease treated over a 13-year period compared outcomes following treatment with platinum-based chemoradiation (n=89) or RT alone (n=40) . Compared to RT alone, chemoradiation resulted in a lower recurrence rate (9 versus 23 percent, p=0.049) and a trend towards improved PFS at five years (90 versus 78 percent, HR 2.82, 95% CI 0.99-8.02). However, the authors reported there was

no difference in OS between the treatment groups (though the median duration or the OS rate at five years was not reported).

In the absence of supporting data to inform both the benefits and the risks of chemoradiation following hysterectomy in these patients, adjuvant radiotherapy is the line of management recommended at present.Results of ongoing clinical trials, such as GOG 263, which is a prospective evaluation of RT versus chemoradiation as adjuvant treatment in women with stage I or II cervical cancer is awaited.

High-risk disease — Women are considered to be at high-risk if any of the following features (sometimes referred to as Peters' criteria) are present at final pathologic review .

- Positive surgical margins
- Pathologically confirmed involvement of the pelvic lymph nodes
- involvement of the parametrium

For women with high-risk factors, the recurrence risk is approximately 40 percent and the risk of death is up to 50 percent following surgery alone [90-92].

Treatment of high-risk disease — Adjuvant chemoradiation is recommended for women at high-risk of recurrence. The benefits of adjuvant chemoradiation were shown in GOG 109, in which 268 women who underwent a hysterectomy for early cervical cancer and were found to have high-risk disease [91,92]. These patients were randomly assigned

treatment with RT (49.3 Gy in 29 fractions to a standard pelvic field) with or without chemotherapy (four cycles of cisplatin 70 mg/m2 on day 1, plus 5-fluorouracil [5-FU] 1000 mg/m2 per day by continuous infusion for four days, every three weeks). With a median follow-up of 42 months, compared to chemoradiation with cisplatin and 5-FU, RT resulted in [90]:

- Lower progression-free survival at four-years (63 versus 80 percent, respectively; hazard ratio [HR] 2.01, p=.003)
- Lower overall survival at four years (71 versus 81 percent, respectively; HR 1.96, p=.007)
- Less serious (grade 3/4) toxicity, including neutropenia , leucopenia, nausea , and vomiting.

Given the toxicity associated with cisplatin and 5-FU in combination with RT, later administration of single agent cisplatin with RT instead was followed because it is used most frequently as primary treatment of locally advanced cervical cancer and is associated with less morbidity than cisplatin plus 5-FU. In addition, a retrospective analysis of 187 patients confirmed that single agent platinum-based chemoradiation resulted in significant improvements in the recurrence rate, progression-free, and overall survival compared to primary RT [93].

Preliminary data suggest that more contemporary RT techniques administered postoperatively, such as intensity-modulated RT (IMRT), may achieve similar survival

outcomes with an improved toxicity profile [94,95]. However, the results of clinical trials, such as the RT Oncology Group 0418 trial (RTOG 0418), is awaited to inform the role of postoperative pelvic IMRT as a treatment modality in early stage cervical cancer.

3.8B Locally advanced disease

Primary radiotherapy is the treatment of choice for locoregionally advanced disease with a careful balance of EBRT and brachytherapy to maximize dose to tumor and avoid normal tissues.

Five-year survival rates with radiotherapy alone for stage IIB, IIIB and IVA disease are 65–75 per cent, 35–50 per cent and 15–20 per cent,

respectively. Studies of combined chemoradiation with cisplatin _ 5FU have

shown a 30–50 per cent decrease in risk of death from cervical cancer compared with extended field radiotherapy alone. However, the main draw back of this study was that patients with poor PS, impairedrenal function and Para-aortic node disease were excluded, which means these results are applicable to a selected population only. Similar good results have been shown with concurrent mitomycin and 5FU, but neoadjuvant chemotherapy shows no benefit when given before radiotherapy. Data from randomized trials show that cisplatin-based chemotherapy improves survival, and locoregional control mainly in stage II disease. It is commonly delivered as a single agent, weekly during EBRT.

The benefit of chemoradiation for women with locally advanced cervical cancer rather than RT alone was demonstrated in a 2010 meta-analysis [96]. Compared with primary RT, the use of chemoradiation resulted in:

- A reduction in the risk of death (hazard ratio [HR] 0.69, 95% CI 0.61-0.77), which translated into a 10 percent absolute improvement in survival. The survival benefit associated with chemoradiation significantly decreased with increasing stage. For women with stage IB to IIA, IIB, and III to IVA cervical cancer, the five-year survival benefit was 10, 7, and 3 percent, respectively ($p = 0.017$).
- A reduction in the risk of recurrence (HR 0.66, 95% CI 0.59-0.73), which translated into a 13 percent absolute improvement in progression free survival. There was no association between stage and disease free survival reported.
- A reduction in the risk of local recurrence (odds ratio [OR] 0.59, 95% CI 0.50-0.69) and a trend towards a reduction in distant metastases (OR 0.81, 95% CI 0.65-1.01). This reduction was seen in trials using both platinum-based and non-platinum based regimens.
- Higher rates of serious (grade 3/4) adverse events including gastrointestinal toxicity (OR 1.98, 95% CI 1.49-2.63).

Chemotherapy regimen — RT is usually administered with either single-agent cisplatin or the combination of cisplatin plus 5-fluorouracil (5-FU) for the treatment of cervical cancer.Weekly cisplatin (40 mg/m2) during RT [96-98] achieves similar

outcomes to cisplatin plus 5-FU and has a better toxicity profile. This was demonstrated in a randomized trial of 155 women with stage IIB to IVA cervical cancer (without Para-aortic node involvement) who were randomly assigned treatment with RT plus either cisplatin or cisplatin plus 5-FU [97]. When compared to cisplatin plus 5-FU, treatment with cisplatin ,at a median follow-up of 39 months, resulted in :

- A higher rate of completion of chemoradiation (71 versus 60 percent, respectively)
- Less serious (grade 3/4) hematologic toxicity (26 versus 43 percent)
- Similar complete response rate (91 percent in both arms) and overall survival rate at four years (67 and 70 percent)

Whether cisplatin in combination with an alternative agent to 5-FU would improve survival outcomes is not clear.

A phase III trial that enrolled 515 women compared cisplatin alone to cisplatin plus gemcitabine during concurrent RT [99]. Women randomized to combination chemotherapy also received two additional 21-day cycles of cisplatin plus gemcitabine after completion of RT. With a median follow-up of three years, the use of cisplatin plus gemcitabine resulted in:

- An improvement in progression free survival (PFS) compared to cisplatin alone (HR for progression 0.68, 95% CI 0.49 to 0.95; three-year PFS 74 versus 65 percent)
- An improvement in overall survival (OS, HR for death 0.68, 95% CI 0.49 to 0.95)
- But was associated with significantly more serious (grade 3/4) toxicities (87 versus 46 percent) and rate of hospitalizations (30 versus 11)

It is not clear whether the benefits of the investigational treatment were due to the use of cisplatin plus gemcitabine during RT or following chemoradiation.

Treatment of Para-aortic nodes — Women with evidence of Para-aortic node involvement have a poor prognosis with a five-year survival rate of approximately 40 percent .It is routine practice to treat these patients with extended field RT. There are no trials that compare chemoradiation using extended field RT (to cover the Para-aortic region) versus pelvic RT

In the largest study, the Gynecologic Oncology Group enrolled 95 women with histologically confirmed Para-aortic node metastases and treated them with concomitant chemoradiation using extended field RT and reported the following results [104]:

- The three-year overall and PFS rates were found to be 39 and 34 percent, respectively.

- Comparatively low degree of grade 3 or higher gastrointestinal toxicity (19 %), likely due to a lower dose to the Para-aortic region used in this study compared to the RTOG study.
- The rate of late morbidity at four years was 14 percent.

These data suggest that disease control can be attained in some women with locally advanced cervical cancer. However, treatment is associated with a high rate of acute and late toxicity.

The role of elective para-aortic node irradiation is controversial with no survival advantage shown by the EORTC trial, but another study has reported 25–50 per cent long term survival after treatment for microscopic disease but with increased morbidity

Importance of time to completion of chemoradiation — For all women undergoing chemoradiation, treatment should be completed within eight weeks. Although older studies demonstrated the importance of the timely completion of RT [100-102], there are limited data on the importance of time to completion for women undergoing chemoradiation [103]. In one series of 113 women with stage IB to IIIB disease, with a median follow-up of 26 months, time to completion of brachytherapy >56 days was associated with a higher rate of disease progression within the pelvis (26 versus 9 percent, HR 2.8, 95% CI 1.2-16) [104]. However, the time to completion of

chemoradiation was not a significant factor for distant disease progression or disease-specific mortality.

Any urinary tract obstruction should be corrected prior to cancer treatment, especially in patients who are otherwise candidates for primary chemoradiation. In a retrospective study performed by the Gynecologic Oncology Group involving 539 women with stage III cervical cancer (44 percent of whom presented with hydronephrosis) treated with chemoradiation, women who received treatment for ureteral obstruction had a significantly longer progression-free survival (PFS) and median overall survival (OS) than those in whom obstruction was not treated (PFS: median 18 versus 10 months; OS median 34 versus 17 months) [105].

Where a vesico- or recto-vaginal fistula is present, a urinary diversion procedure or defunctioning colostomy should be performed prior to radiotherapy

3.8c Stage IVB metastatic disease

Short course pelvic radiotherapy is successful in relieving bleeding and pelvic pain in patients with metastatic disease.

Palliative radiotherapy is used to relieve pain from bone secondaries and symptoms from brain and nodal metastases.

4.METHODS AND MATERIALS

4.1Methodology

Data was collected from May 2012 to May 2013.During this period,20 women with locally advanced biopsy proven squamous cell carcinoma cervix underwent,T2-weighted MRI in addition to planning CT scan were enrolled in this study.

Approval from institutional research and ethics committeewas obtained.

All suitable subjects were explained about the study, and were provided with the informed consent with details of the study. After reading it and the clarification of any doubts, they were enrolled into the study after obtaining their written informed consent .

4.2Inclusion criteria

The patients were screened for the following inclusion criteria and then enrolled.

- Female patients of more than 18 years of age
- Diagnosed to have squamous cell carcinoma cervix IIA- IIIB[FIGO staging]
- Being planned for treatment with radical chemo-irradiation
- ECOG0-1
- Willing to participate in the trial

4.3Exclusion criteria-

- previous irradiation to pelvis

- other malignant disease

4.4Patient workup

The patients who fulfilled the inclusion and the exclusion criteria were selected for the study.

The history and clinical examination findings was carried out

4.5 Pre Treatment investigations:

A cervical punch biopsy was done to confirm the diagnosis.

Blood tests—

Renal Function Tests and Liver Function Tests

Complete Blood Counts

Blood Borne Virus screen

Urine analysis--Microscopy / Culture

Cystoscopy and Proctoscopy

Radiological tests--Chest X-ray *(PA),* Ultrasonogram abdomen and pelvis

Baseline ECG

4.6 Treatment simulation

All patients underwent treatment simulation, prior to initiation of radiotherapy. Patients either underwent conventional radiotherapy planning with conventional technique or conformal radiotherapy technique (3DCRT, IMRT) . Immobilization with Vacloc was done in patients who were undergoing conformal radiotherapy. Patients are simulated supine with arms on the chest, knees and lower legs immobilized, and anterior and lateral tattoos marked with radio-opaque material,aligned with lasers to prevent lateral rotation. .Planning CT scans were taken from the level of diaphragm to 5 cm beyond the vaginal introitus.

4.7 Imaging

Imaging was performed in these 20 patients to assess tumor size, locoregional extent, and pelvic nodal status and these Images were used for radiotherapy planning. Intravenous contrast is used to outline pelvic blood vessels to be used as surrogates for pelvic nodes in CTV delineation. It may also enhance the GTV primary.Oral contrast was given to all patients to outline the bowel.

MRI scans were performed on a 3-T MR scanner (Intera Achieva) according to Radiology department protocol for pelvic malignancies , CMC Vellore. Axial T2 weighted HR images were primarily assessed. Imaging parameters for the T2W HR images were given below .Repetition time (TR) 3625 ms, echo time (TE)100 ms, echo

train length 12, band width 21.78kHZ, field of view 32 cm, slice thickness 3 mm ,gap 0mm,number of excitations 3,no phase wrap, matrix 352x293.

4.8 Image registration

T2 Weighted MRI images were later fused to the planning CT scan for contouring .The image registration method used for fusion of planning CT scan with T2W MRI series is by Automatic image registration using DICOM coordinate system.This registration is done by aligning the origins of the DICOM coordinate system saved to the images by the imaging device.

The images will be used to delineate the tumor volumes and OAR s on the treatment planning system[ECLIPSE_ ARIA].

4.9 Contouring

Contouring of tumor volume and organs at risk were done as per RTOG guidelines .The volumes generated GTV –gross tumor volume delineated on CT and MRI werer compared . Accurate delineation of GTV , CTV and organs at risk is an important advantage of image based planning.

- GTV - Entire GTV; intermediate/high signal seen on T2-weighted MR images/enhanced lesion in cervix on CT imaging

Comparison was done between tumor volume (GTV primary) delineated by these imaging modalities(MRI GTV p vs CT GTV p).

4.10.Comparison between imaging modalities

The investigational imaging MRI was compared with CT imaging to compare the target volume delineation and evaluate the impact of MRI on target volume as compared to the volumes obtained on a CT scan in terms of assessment of GTV Primary (Cervical tumour, involvement of uterus, vagina and parametrium) and GTV Lymph nodes.

Study also looked at any change in the staging of the disease based on additional information form image modalities which will automatically change the management and prognosis in these patients.

Attempt was done to see if CT scan along with clinical findings can be a good alternate to MRI scan .Another objective was to look at the possibility of reduction in treatment volume based on MRI when compared to CT based planning.

Evaluation was also done to check the possibility of avoiding invasive procedures like cystoscopy based on MRI/CT findings.

4.10 Treatment

Patients either underwent treatment with radical chemoradiation or neoadjuvant chemotherapy followed by radical chemoradiation.

4.11 First follow up evaluation

The first follow up was done after 6 weeks. History of all the complaints and a thorough clinical examination is done. The clinical evaluation was done to assess the tumor response as well as any toxicity.

4.12 Statistical Analysis

A descriptive analysis and frequency distribution of the patient characteristics was done.

Fisher's Exact test was done to find out relationship between prognostic factors and image findings.PABAK was done to compare different imaging modalities (CT versus MRI).

Paired T test was used for tumor volume comparison

5.Results

Twenty patients, diagnosed with locally advanced carcinoma cervix underwent planning CT scan of abdomen pelvis and T2 Weighted MRI pelvis . Data were collected and analyzed.

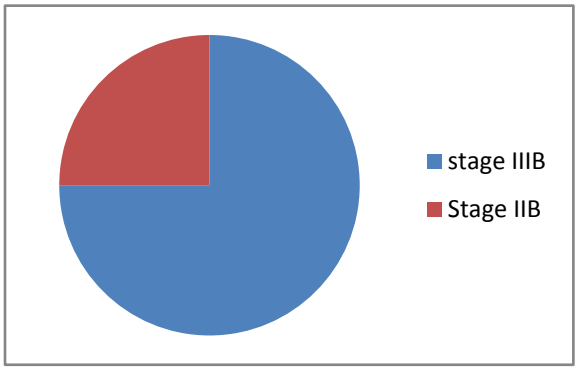
5.1Demographics

Most of the patients belonged to the age group between 40 to 50 years (12 out of 20 patients). Among them 2 patients were below the age of 40 and 4 patients were in the age group of 50 to 60 years and 2 patients were above 60 years.

5.2.Symptoms of primary disease

The main presenting complaint was white discharge per vaginum (13 out of 20 patients) and bleeding per vaginum (11 out of 20 patients) and low backache (10 out of 20 patients)

5.3 FIGO staging



Among 20 patients , 15 were clinically staged as FIGO stage IIIB and 5 patients belonged to FIGO stage IIB.

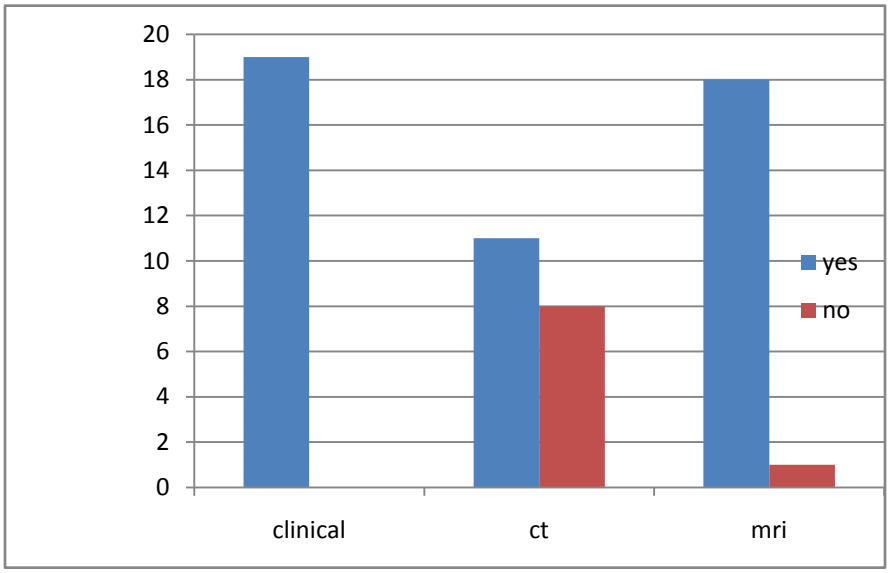
Comparison between clinical and image findings based on USG abdomen pelvis, CT abdomen pelvis and MRI pelvis

5.4 Primary tumor assessment

Primary tumor assessment was done by clinical examination and different modalities of imaging like ultrasonography, CT abdomen pelvis and MRI pelvis.

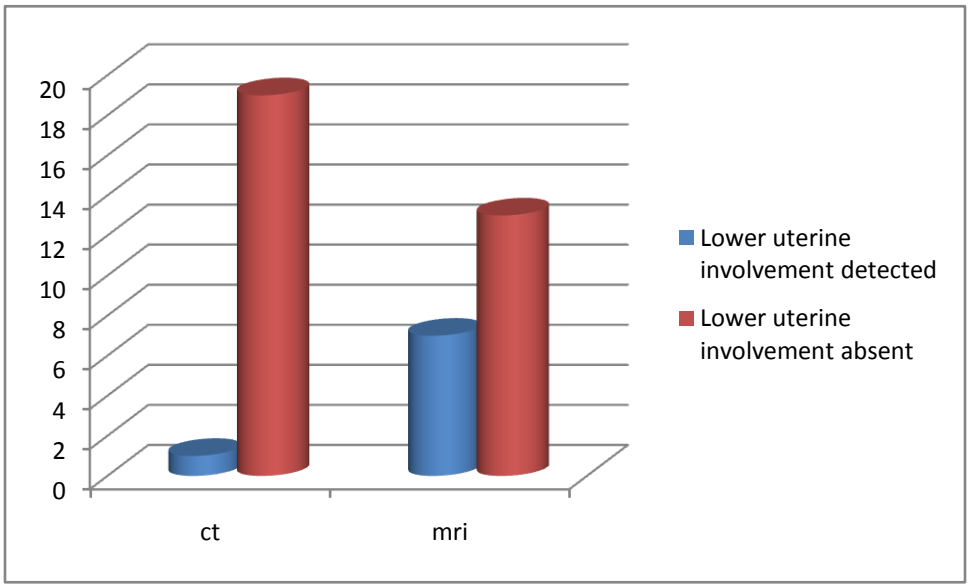
A**ssessment of local extent of tumor based on clinical and imaging findings**

5.5.Vaginal involvement assessment



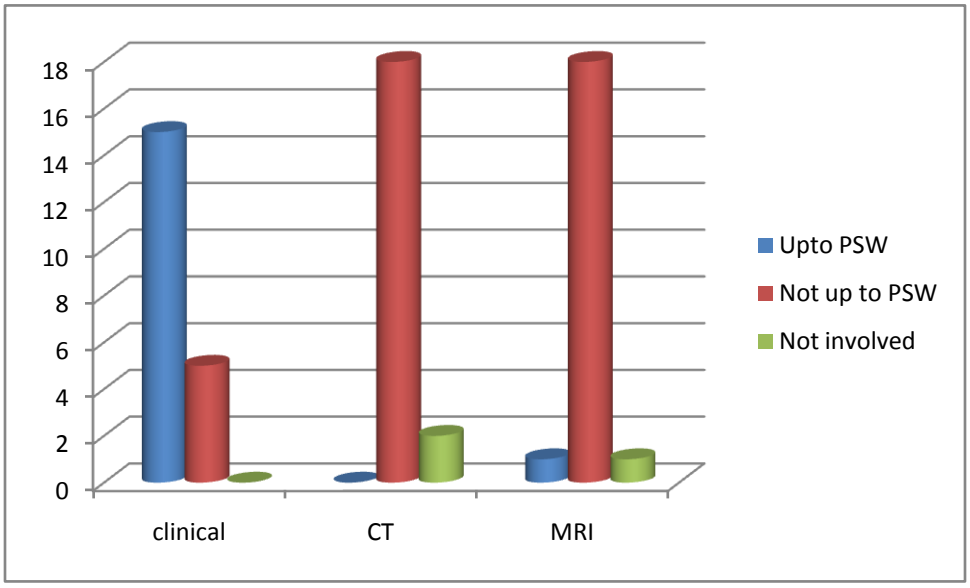
Clinical examination showed vaginal involvement in 19 out of 20 patients. Of these 19 patients,MRI showed vaginal involvement in 18 patients and CT scan showed vaginal involvement in only 11 patients. There is good correlation between clinical examination finding and MRI.

5.6Lower uterine segment involvement assessment



MRI showed lower uterine segment involvement in 6 out of 20 patients and CT scan showed uterine involvement in only in one patient

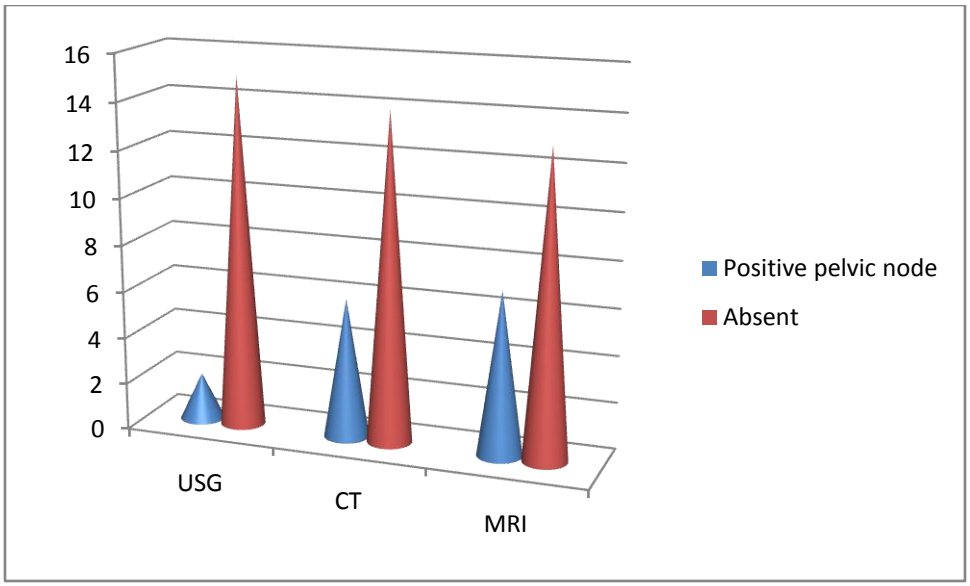
5.7 Assessment of parametrial extension



All 20 patients showed parametrial involvement on clinical examination, while MRI showed involvement in 18 patients.Clinically parametrial involvement was up to pelvic side wall in 15 out of 20 patients while this wasseen only in1 patient on MRI.The remaining 14 patients with clinical 3B disease there was bulky parametrial disease on MRI but this was not upto pelvic sidewall.

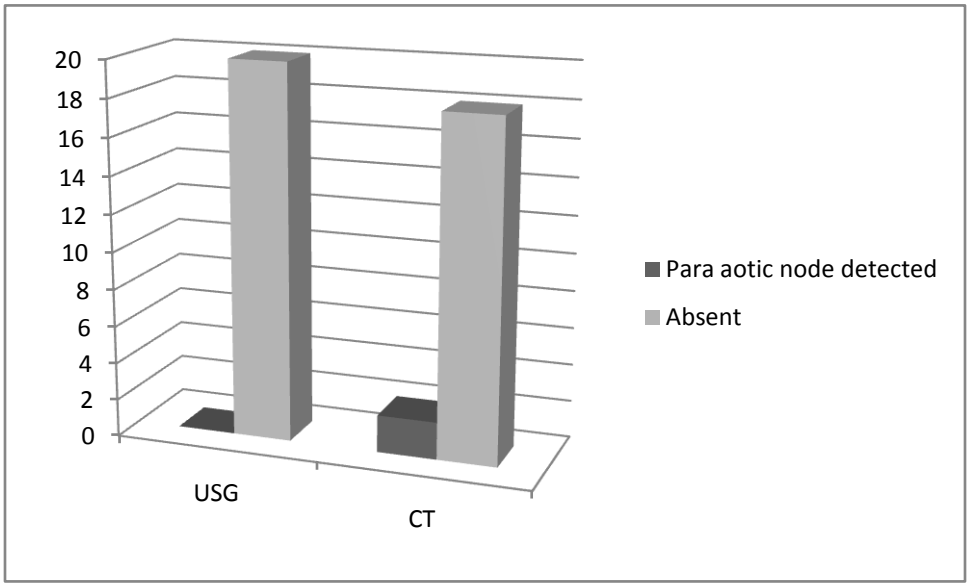
CT scan showed parametrial involvement in 18 of the 20 patients, not extending up to pelvic side wall,but it was difficult to makeout the extent of parametrial involvement on CT scan.

5.8Assessment of pelvic lymphadenopathy



Detection of pelvic lymphaedenopathy was assessed by these imaging modalities and comparison was done between USG abdomen ,CT and MRI was done in only 17 patients as only 17 patients had undergone USG abdomen in our study. Comparison was done between CT, abdomen and MRI pelvis in detecting pelvic nodes in 20 patients. CT and MRI had similar findings and Ultrasonography under estimated pelvic lymphaedenopathy.

5.9 Assessment of para aortic nodes

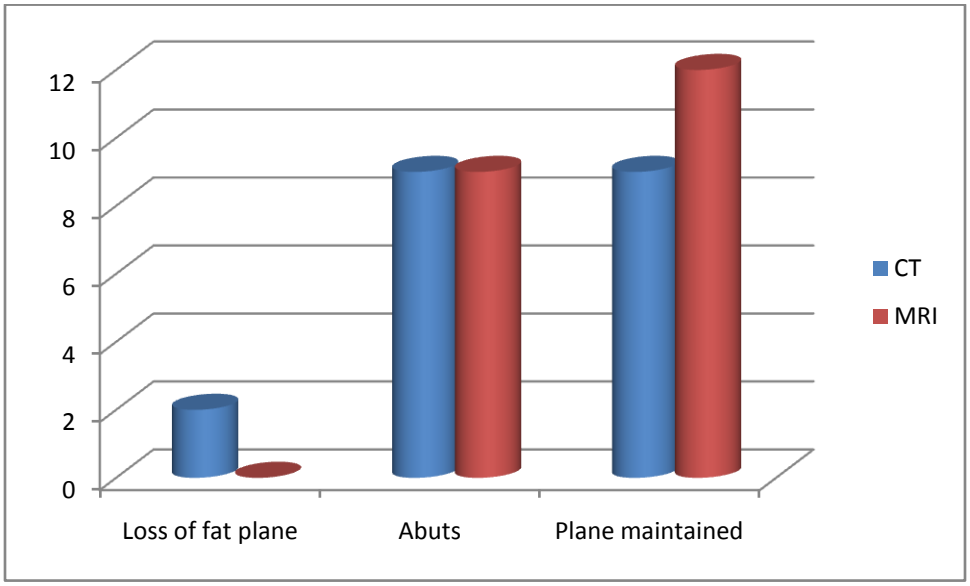


Comparison between CT scan and Ultrasonography of the abdomen only was done for the detection of paraaortic nodes as the patients had MRI of the pelvis only done.Among 17 patients, who underwent CT and USG abdomen, CT scan detected para aortic nodes in 2 which was not picked up on USG.

5.10Assessment of metastatic disease

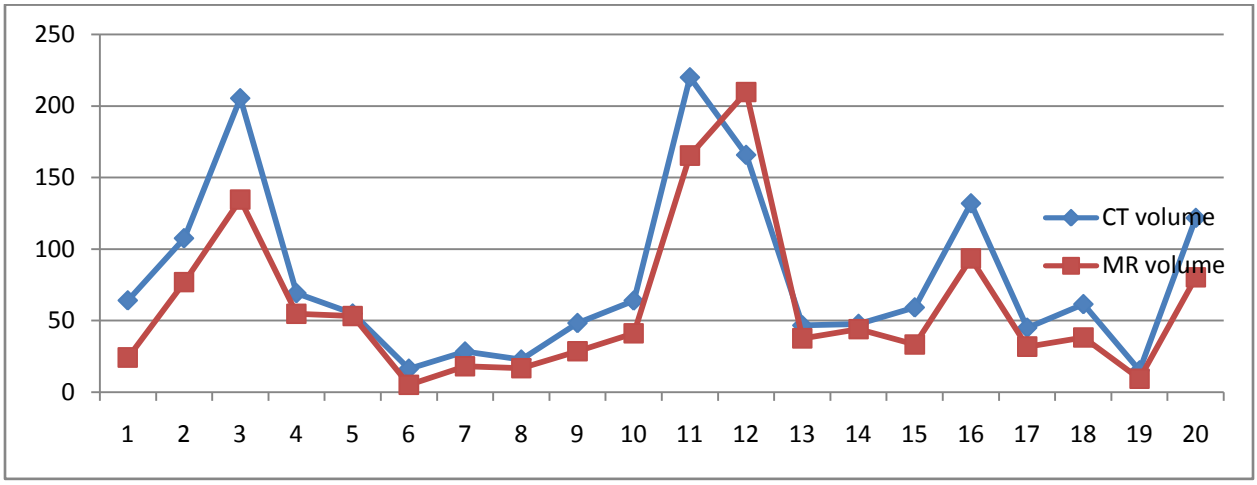
Among the 17 patients who had USG abdomen pelvis and CT abdomen there no evidence of visceral metastasis.

5.11 In assessing bladder involvement



CT scan showed loss of fat plane with bladder in 2 patients and one of these patients had tumor abutting the bladder on MRI. Tumor abutting bladder was seen in 6 patients on both CT scan and MRI, 3 patients on CT scan only and 2 others on MRI only. Cystoscopy was normal in all these patients. There were 2 patients, one with bladder mucosal irregularity and another one with trigonal edema on cystoscopy,biopsy from the lesion was negative for malignancy. Imaging did not picked up these 2 changes.The patient with bladder mucosal irregularity had findings of tumor abutting bladder on MRI but normal findings on CT.

5.12 Target volume delineation based on CT and MRI



Volume of cervical growth based on CT and MRI

	Mean volume
Tumor volume on CT scan	79.8
Tumor volume on MRI scan	59.7
Difference	20.02

Mean volume of primary growth measured by CT scan was 79.8 cm3 and MRI was 59.7 cm3 with a difference of 20.02 cm3, which was statistically significant by Paired t test

5.13Posterior extent of the primary lesion

Posterior extent of the primary lesion was upto the level of S2 and beyond in a total of 18patients with 11 patients having tumour upto the level of S2,6 patients up to the level

of S3 and 1 patient beyond S3. The position of the uterus was retroverted in one patient and was beyond the posterior border of the conventional four field box technique which was kept at S2/S3 junction. Therefore the conventional field would have resulted in gross tumour being beyond the target volume in 12 patients,having inadequate tumour volume margin in 7 patients and therefore would have been inadequate in 19 out of 20 patients.

5.14 Prognostic factors

1.Significance of AP diameter more than 4 cm and disease status.

It was found that in disease progression in 6 out of 9 patients ,who had anteroposterior (AP) tumor diameter more than 4 cm . There was only 1 patient,who had disease progression out of 8 patients,with AP diameter less than 4 cm.Statistical analysis with Fisher,s exact- showed significant p value (0.05).This showed significant association between anteroposterior diameter > 4cm with disease progression.

2.Significance of tumor volume more than 50 mm3 and disease progression

In 6 out of 12 patients with tumor volume more than 50 cm3 had disease progression,compared to only one out of 5 patints with tumor diameter less than 50 cm3 had disease progression. This Appears to be significant but was not statistically significant due to less number of patients.

3.Relation ship between tumor volume and nodal status.

In 8 out of 15 patients with tumor volume more than 50 cm3 had pelvic lymphaedenopathy,compared to only one out of 5 patints with tumor diameter less than 50 cm3 . This Appears to be significant but was not statistically significant due to less number of patients.

6.DISCUSSION

Uterine cervical neoplasm is a major health problem in developing countries like India. Appropriate evaluation of disease extent and staging is important as this has an impact on the management, prognosis and outcome.

The International Federation of Gynecology and Obstetrics is the most commonly used staging system for carcinoma cervix. Since the staging system should be uniform and feasible at all centres and also allow for comparison of results from different centres, FIGO has recommended staging to be based on clinical findings which includes assessment of the tumour extent (ie, extent of local disease, tumor size, involvement of cervix, vagina, parametrium and extent into adjacent normal tissue like rectum and bladder)along with limited radiological investigations which does not include MRI and CT scans for staging in carcinoma cervix. Clinical staging may be adequate for evaluating local disease extent, but does not take in to account involvement of the uterus, lymph nodesor distant metastasis. It has been reported in literature that MRI is superior to CT scan and clinical examination for assessing the tumor size and involvement of the uterine body.

As patients with carcinoma cervix belong to the lower socioeconomic strata where MRI/CT is not feasible and also as MRI/CT may not available in all centers it is not possible to do these routinely for staging and management. Hence evaluation in the form of less expensive imaging and thorough clinical examination would be a good alternate that could be carried out. Though the findings on CT, MRI, or PET examinations are not mandatory for FIGO staging it could be of additional benefit and provide extra information that would result in stage migration, help appropriate selection of treatment

modality (surgery/chemo-irradiation),essential for (result in) more accurate radiotherapy treatment planning and also provide prognostic information that would impact on the outcome of treatment and survival. Prognostic factors like stage at presentation , tumor diameter, tumor volume,lymph node metastasis,lymphatic vascular space invasion,deep stromal invasion, microscopic evidence of parametrial invasion , cell type and haemoglobin level, have an impact on survival .Therefore therevisedFIGO staging 2009 has included imaging with MRI in addition to clinical stagingwhere resources permit.

Primary tumor assessment

It is advisable that all patients with carcinoma cervix should be jointly evaluated with detailed history and physical examination by the Radiation and Gynecologic oncologist. Examination under anesthesia provides better assessment of primary tumor in early stage disease. In all patients with stage IIB and more advanced disease and in those patients who give a history of urinary or lower gastrointestinal tract complaints ,cystoscopy or rigid rectosigmoidoscopy is recommended to rule out local infiltration.

In cervical cancer, tumor is visualized as a soft tissue mass on CT imaging,which often results in enlargement of the cervix. Generally there will be non-homogenous enhancement around the tumor following contrast administration with areas of necrosis and ulceration seen as hypodense areas within it. Evidence of parametrial soft tissue mass, any irregularity of the lateral margins of the cervix and obliteration of periureteral fat planes are indicators that suggest parametrial invasion, but these are not definitive indicators. Therefore it is difficult to make out parametrial infiltration on CT imaging.

The ability of CT scan in assessing the tumor size is limited by poor soft tissue discrimination. Yang et al reported 85 %accuracy for CT scan in assessing tumor size .

T2 –Weighted MRI provides better description of cervical anatomy. The normal cervical stroma has low signal intensity on T2 weighted images , and cervical tumors appears as high signal intensity compared to cervical stroma and can be easily differentiated from surrounding normal structures. In his study, Subak et al reported that, estimation of tumor size by MRI was with in o.5 cm of the surgical sample in 93 % of patients (76).

Donald et al(ACRIN6651 /GOG intergroup study) , in his study comparing MRI, CT and clinical examination for delineating early cervical cancer,reported that MRI was superior to CT and clinical examination in assessing tumor size (109) .

In a prospective study by Mitchell DG et al, which included 208 women, most with stage IB diseasewho underwent pretreatment MRI and CT [44],It was found that MRI correlated more closely with surgicopathologic findings than CT or physical examination. This study also showed that there was an overestimation of tumor size in both imaging modalities.Hricak H showed in his study that MRI wasmore helpful in the assessment of extra cervical tumor extension than CT scan (45).

Study done by Hancke K, Heilmann, and Bipat S (50,51) shown superiority of MRI over CT scan in detecting parametrial involvement .MRI was found to be superior to CT for evaluation of parametrial involvement in a meta-analysis of 57 studies, done byBalleyguier C et al (52) .

All 20 patientsshowed parametrial involvement on clinical examination, while MRI showed involvement in 18 patients.Clinically parametrial involvement was up to pelvic side wall in 15 out of 20 patients while this wasseen only in 1 patient on MRI.The

remaining 14 patients with clinical 3B disease there was bulky parametrial disease on MRI but this was not upto pelvic sidewall.

CT scan showed parametrial involvement in 18 of the 20 patients, not extending up to pelvic side wall, but it was difficult to make out the extent of parametrial involvement on CT scan.

Thereforein our study thelocal tumor extent into parametrium was more on clinical assessment than what was detected on both imaging modalities. Between CT and MRI findings, the tumour was better seen on MRI and the findings correlated betterwith clinical findings than CT scan.

Vaginal involvement

Choi *et al*. (106) in his study among 23 patients ,pretreatment evaluation with MRI reported a sensitivity of 87.0% and a specificity of 79.0% with 3 false negative reports for detecting vaginal involvement. In his study Sheu *et al*., (107)reported that, MRI identified vaginal involvement in 9 patients, with 2 false negative reports and and 6 false positive reportswith histological comparison. The sensitivity of MRI was found to be 82.0% and specificity 84.0% with histological comparison in this study..

In our study among the 19 patientswho had vaginal involvement clinically,MRI showed vaginal involvement in 18 patients and CT scan showed vaginal involvement in only 11 patients. So detection of vaginal involvement with CT scan along with clinical examination would result in similar findings as MRI.

Lower uterine involvement

In a study by Sahdev*et al.,* (108) the efficacy of MRI in detecting lower uterine segment involvement was found to be superiorwith a specificity of 99.0%.. In a comparative study by Donald et al(ACRIN6651 /GOG intergroup study) showed MRI is superior to CT scan for evaluationg uterine body involvement (109).

In our study, MRI was found superior to CT in detecting lower uterine involvement. MRI showed lower uterine segment involvement in 6 out of 20 patients and CT scan showed uterine involvement in only 1 patient. Detection of lower uterine segment involvement is important as this is associated with a bad prognosis and this cannot be made out on clinical examination.

Pelvic Lymph node detection

The rate of detection of pelvic lymphadenopathy was compared across all three modalities in 17 patients. Comparison was done between CTand MRI in 20 patients.

CT and MRI had similar findings and Ultrasonography under estimated pelvic lymphaedenopathy.

Stage migration based on imaging only in para aortic node detection

In a comparative study by Heller et al (Gynecologic Oncology Group (GOG) protocol), Pre operative CT scan,Lymphangiography and ultrasonography was performed to assess para aortic adenopathy and later it was compared with a histological reports of Para-aortic node dissection in patients whom had negative staging studies (110). False

negative results for pelvic node evaluation was more with ultrasonography (30%) and less for lymphangiography (14%).. The sensitivity and sensitivity was high for for lymphangiography, and less for for ultrasonography .This study recommended that ultrasonography,, is not a reliable imaging in preoperative detection of lymph node metastases.

Multiple studies has shown that the accuracy of CT scan in staging cervical cancer ranges from 63% to 88%.(27). In the detection of lymph node the accuracy is found to be 77% to85%. y of 93%(28).The CT scan is more valuable in evaluation of para aortic nodes and Camilien et al in his study where pre operative CT scans were correlated with histopathological report collected by exploratory laparotomy showed , 67 % sensitivity and 100 % specificity for CT scan in detecting para aortic nodes (111) .

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In his study ,Hawnaur et al. compared pretreatment examination under anesthesia (EUA), transrectal ultrasonography (TRUS), and MRI in assessing tumor volume and staging in 60 patients with invasive carcinoma of the cervix. It was found that MRI was superior in assessing the tumor extent and lymph node enlargement when compared to TRUS and EUA. (112)

According to Chung*et al*., [113] introduction of MRI has improved staging in cervical cancer patients. American College of Radiology Imaging Network (ACRIN) study (44)], reported that staging accuracy improvedfrom 30% - 40% to about 70% with the introduction of MRI.

Target volume delineation based on CT and MRI

Accurate delineation of GTV and CTV is an important advantage of image based planning. Thus addition of MRI is likely to give a better and more accurate tumor volume delineation which would in turn translate into appropriate dose to the tumor with more sparing of the normal tissues. It was also shown to reduce geographical miss during treatment planning.

A number of publications from the American College of Radiology Imaging Network and the Gynecologic Oncology Group have demonstrated that traditional *T*2-weighted MRI is superior to CT for tumor delineation in cervical cancer, mainly due to its high soft-tissue contrast for the evaluation of local tumor extension (44).

In a study by Subak LL, showed that tumor volume was evaluated accurately by MRI,when compared to CT and which was later confirmed by pathological evaluation . Computed tomography could not distinguish cancer from the surrounding normal cervical tissue (116).

In our study,mean volume of primary growth measured by CT scan was 79.8 cm3 and MRI was 59.7 cm3 with a difference of 20.02 cm3, which was statistically significant by Paired t test. The tumour was better seen and it was easy to delineate on MRI.Most of the time, it was difficult to make out tumor from surrounding normal cervical stroma with CT scan and therefore could have been overestimated. 3D Conformal radiotherapy uses a set of fixed radiation beams that are shaped using the projection of target volume and have a uniform intensity across the field. The use of intensity modulated radiotherapy provides to confine the high dose portions of the radiation field to nontraditional shapes. IMRT has been shown to reduce normal tissue irradiation and has been associated with reduced acute and chronic toxicity compared with 3DCRT. Accurate delineation of GTV and CTV is an important

advantage of image based planning.Thus addition of MRI is likely to give a better and accurate tumor volume delineation which would in turn translate into appropriate dose to the tumor with more sparing of the normal tissues

Posterior extent of the primary lesion and change in conventional field borders based on imaging findings.

The commonly used field borders for the lateral fields were the anterior aspect of the symphysis and the S2/S3 interspace. Ports defined by these guidelines will not always besuitable for the patients presenting with different stage and local extent of disease.Based on intra-operative measurements, Greer *et al*.opined that the entire anterior sacral silhouette should be included in the lateral field in patients with locally advanced carcinoma cervix,due to posterior extension of the tumor. (68)

In a prospective study conducted on 34 patients with cervix carcinoma Kim *et al* ,(69) simulated all patients with conventional four-fieldpelvic portals .Customized blocks were used to shield the posterior wall of therectum and a part of small bowel using the barium silhouette of those organs. Following this CT scan was done to identify the tumor volume on each slice. It was found that posterior margin coverage was ranging from 39% to 50% only in the conventional as compared to CT based planning. There were inadequate coverage at the customized rectal block, and in the posterior border on the lateral fields. With a median follow-up of 36 months, it was found that pelvic control for inadequate margins was 100% and 71% for stage IB, 88% and 50% for stage IIB.

In 1992 Russell *et al.*,reported the value of pelvic MRI in determining the lateral fields of the four field box technique (70).It is proven that MRI has the additional advantage in the visualization the anatomy of the pelvis in all the planes .It also provides a better soft tissue delineation and tumor depiction than CT scan[71-76].From their study, Russell and colleagues found that using the conventional lateral portals , the tumor volume wasadequately covered in only 44% of patients . There was incomplete coverage of the uterine fundus in 62.5% and marginal miss in more than 50% of patients. In their study Zunino *et al.* found that due to uterusflexion and associated pathology like myoma, endometriosis and pyometra ,the lateral portals failed to involve PTV in 50% of cases (77).

Posterior extent of the primary lesion was up to the level of S2 and beyond in a total of 18 patients with 11 patients having tumour up to the level of S2, 6 patients up to the level of S3 and 1 patient beyond S3. The position of the uterus was retroverted in one patient and was beyond the posterior border of the conventional four field box technique which was kept at S2/S3 junction. Therefore the conventional field would have resulted in gross tumour being beyond the target volume in 12 patients,having inadequate tumour volume margin in 7 patientsand therefore would have been inadequate in 19 out of 20 patients.

Target volume delineation was superior with MRI than CT scan. With CT scanthe pick up of nodal disease, evaluation ofbladder involvement, rectalinvolvement and metastatic disease was similar to MRI and superior to ultrasound examination and the volumes

obtained were larger than on MRI and so could be used along with good clinical examination as alternate to MRI where MRI is not feasible.

Bladder infiltration

In a retrospective study by Krestin GP, Hauser M et al, they compared 6 different imaging signs of focal bladder infiltration in 129 patients who underwent CT and MRI examinations. These findings were later correlated with cystoscopy, rectoscopy,intraoperative findings and histological examination of surgical sections (65).In 27 patients submitted to both imaging examinations it was found that MRI provided similar results as endoscopic procedures like cystoscopy and rectoscopy .Subset analysis showed that MRI was superior to CT scan. This study showed that Imaging can predict bladder or rectalwall infiltrationin carcinoma of the uterine cervix and can avoid endoscopic procedures.

In another study by Rockall AG, 5 point scoring system was done based on MRI findings to rule out bladder and rectal infiltration and score of 3 or above were used to identify patients with bladder and rectal infiltration (66). This study showed that MRI scoring system can predict local infiltration of bladder and can avoid the need for invasive procedures like cystoscopy in majority of patients with cervical cancer. This leads to a reduction in morbidity associated with these procedures.

In our study, cystoscopy was normal in 18 out of 20 patients. Among these 18 patients, CT scan reported loss of fat plane with bladder in 2 patients andtumor abutting bladder was seen in 6 patients on both CT scan and MRI, 3 patients on CT scan only and 2 others on MRI only.

There were 2 patients, one with bladder mucosal irregularity and another one with trigonal edema on cystoscopy, biopsy from these lesions was negative for malignancy. Both these patients had dysuria and increased frequency of urination and also urine microscopy showed increased number of RBC,s. The patient with bladder mucosal irregularity had findings of tumor abutting bladder on MRI but normal findings on CT and the patient with trigonal edema on cystoscopy, the imaging was not contributory.

So MRI and CT may be adequate for evaluation of bladder involvement and could be an alternate method for majority of patients, with an invasive procedure like cystoscopy reserved for patients with urinary symptoms and who have findings of involvement or probable involvement on imaging.

Prognostic factors based on Imaging

Size of the cervical lesion evaluated in CT scans were correlating with local control and overall survival .(25,26). In a retrospective study of CT scans done on cervical cancer patients by Shepherd et al showed that tumor depth was correlated with lymph node involvement(29).

Based on MRI volume Kodaira et al showed that 5 year DFS of patients treated with radiotherapy with tumor diameter more than 5 cm was significantly lower (46.2%) than that for patients with size less than 5cm(88%) (32) .

Study done by Nihon Igaku showed that tumor with craniocaudal diameter,(which was obtained by measuring the length of the tumor parallel to the long axis of uterine body) was less than or equal to 4 cm was associated with better five-year disease-free survival (70%) compared to patients with tumor diameter more than 4 cm(35).

Study by Toita showed that antero posterior diameter (AP) of tumor more than4 cm was associated with increased incidence of lymph node metastasis and distant metastasis.(36).

In our study there was significant association between antero-posterior diameterof tumour of more than 4cm with disease progression.

In another study by Kodaira et al, large tumor size (volume more than 50 cm3) was associated with positive lymph node enlargement which inturn results in unfavorable influence on survival ($p < 0.05$) (37). In our study, mean volume of primary growth measured by CT scan was 79.8 cm3 and MRI was 59.7 cm3 . In 6 out of 12 patients with tumor volume more than 50 cm3 had disease progression,compared to only one out of 5 patints with tumor diameter less than 50 cm3 had disease progression. This appears to be significant but was not statistically significant due to less number of patients.

7. Limitations of my study

1.Sample size was small

2.It was difficult to fuse CT axial images with T2W MRI images due to the following reasons

- MRI was done in a different date where the bowel and bladder filling status were different
- planning CT scan images were obtained with immobilization and CT markers in flat couch,where MRI was done by conventional method.
- MRI images were with 6 mm thickness and has been obtained in an angle perpendicular to the axis of the uterus ,which was the departmental protocol for obtaining pelvic images ,where CT images were axial images with 5 mm thickness

3.MRI imaging was confined to pelvis due to economic reasons in these patient where, MRI was done additional to CT abdomen pelvis .

4.Biased sample collection.

5.Tumor volume delineation -can have interpersonal variation.

8. CONCLUSIONS AND RECOMMENDATIONS

In this pilot project done to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix,showed that imaging modalities have a role in accurate delineation of gross tumor volume (GTV).

Though the findings on CT, MRI, or PET examinations are not mandatory for FIGO staging it could be of additional benefit and provide extra information that would result in stage migration, help appropriate selection of treatment modality, result in more accurate radiotherapy treatment planning and also provide prognostic information that would impact on the outcome of treatment and survival.

Image based planning would in turn translate into appropriate dose to the tumor with more sparing of the normal tissues. It would also reduce geographical miss during treatment planning.

MRI appears to be better than CT for locoregional disease assessment especially for primary tumor and adjacent soft tissue extension.

CT with good clinical examination could be used as an alternate to MRI where MRI is not feasible.

Bowel and bladder preparation are required before CT and MRI for better fusion with more accurate delineation of target and OAR.

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APPENDIX 1 : Proforma

Comparison of T2 W MRI to CT imaging in volume delineation for radiotherapy planning in locally advanced carcinoma cervix patients

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Name: Age:

Hospital No: RT no:

Adress:

Phone number:

Presenting complaints

- White discharge PV Yes (1)/ No (2)
- Bleeding PV Yes (1)/ No (2)
- Post Coital Bleeding Yes (1)/ No (2)
- ow Backache Yes (1)/ No (2)
- Abdominal pain Yes (1)/ No (2)
- Bowel symptoms Yes (1)/ No (2)
- Bladder Symptoms Yes (1)/ No (2)

Medical comorbidities

Diabetis mellitus Yes (1)/ No (2)

Hypertension Yes (1)/ No (2)

Pulmonary tuberculosis Yes (1)/ No (2)

Cardiac comorbidities Yes (1)/ No (2)

Renal dysfunction Yes (1)/ No (2)

Any chronic illness Yes (1)/ No (2)

Past history of abdominal surgery Yes (1)/ No (2)

Examination findings

Height : cm. Weight: Kg

BSA: Estimated creatinine clearance:

- Pallor- Yes (1)/ No (2)
- Pedal edema Yes (1)/ No (2)

- Nodes- inguinal Yes (1)/ No (2)
- Neck nodes Yes (1)/ No (2)

Per abdominal

- Scar of previous surgery Yes (1)/ No (2)
- Liver Yes (1)/ No (2)
- Free fluid Yes (1)/ No (2)

PV/PS/PR

Cervix

clinical volume -AP xCC xRL

cervix - 1)Anterior 2)posterior3)both lips of cervix

Growth 1) exophytic 2) Ulcerative

3)Infiltrative

Fornices-1)Left lateral 2)right lateral

3)anterior 4)posterior 5)all

Vagina 1)Upper 1/3rd 2) Upper 2/3rd

3) Lower1/3 rd

RV septum 1)yes 2)no

Parametrium

Right- 1)Not up to pelvic side wall 2)Upto

pelvic side wall 3)not involved

Left- 1)Not up to pelvic side wall 2)Upto

pelvic side wall 3)not involved

Cystoscopy 1)bladder infiltration 2)trigonal edema 3)normal

Proctoscopy 1)Rectal mucosal infiltration 2)Normal

Final diagnosis-

Carcinoma cervix stage 1) I 2)IIA 3)IIB 4)IIIA 5)IIIB 6)IVA 7)IVB

USG abdomen

tumor volume - APxCCxRL

Nodes- 1)yes 2)no

Hydroureteronephrosis 1)yes 2)no

Liver metastasis 1)yes 2)no

CT ABDOMEN PELVIS

Tumor size APxCCxRL

Extension to parametrium 1)yes 2)no

Parametrial involvement 1)Not up to pelvic side wall

2)Upto pelvic side wall 3)not involved

Extension to vagina 1)yes 2)no

Bladder infiltration 1)yes 2)no

Infiltration of rectum 1)yes 2)no

Mesorectal infiltration 1)yes 2)no

Uterine involvement 1)yes 2)no

Distal metastasis 1)yes 2)no

Superior extend 1)L4 2)L5 3) S1 4) S2 5) S3 6) Below S3

Posterior extend 1)S1 2)S2 3)S2p 4)S3 5)S3p

Position-1)Anteverted 2)retroverted

MRI PELVIS

Extension to parametrium 1)yes 2)no

Parametrial involvement 1)Not up to pelvic side wall

2)Upto pelvic side wall 3)not involved

Extension to vagina 1)yes 2)no

Bladder infiltration 1)yes 2)no

Infiltration of rectum 1)yes 2)no

Mesorectal infiltration 1)yes 2)no

Uterine involvement 1)yes 2)no

Distal metastasis 1)yes 2)no

Superior extend 1)L4 2)L5 3) S1 4) S2 5) S3 6) Below S3

Posterior extend 1)S1 2)S2 3)S2p 4)S3 5)S3p

Position-1)Anteverted 2)retroverted

Nodal status

CT abdomen plevis

Para aortic 1)yes 2)no

Common iliac 1)yes 2)no

External ilac 1)yes 2)no

Internal iliac 1)yes 2)no

inguinal 1)yes 2)no

pre sacral 1)yes 2)no

MRI pelvis

External ilac 1)yes 2)no

Internal iliac 1)yes 2)no

inguinal 1)yes 2)no

pre sacral 1)yes 2)no

Others

Hydroureteronephrosis 1)yes 2)no

Distant metastasis 1)yes 2)no

Tumor volume delineation

CT

GTV Primary -Volume in cm3

CTV primary -Volume in cm3

MRI

GTV Primary -Volume in cm3

CTV primary -Volume in cm3

Disease status on follow up

1)Disease free

2)Residual disease

3)Local recurrence

4)Nodal recurrence

5)distant metastasis

6)lost follow up

Comparative volume between CT and MRI

CT-GTV vs MR-GTV

CT-CTV vs MR-CTV

APPENDIX II : Protocols

FiGO staging (Fig.3)

Stage 0-The carcinoma is confined to the surface layer (cells lining) of the cervix. Also called carcinoma in situ (CIS).

Stage I -The carcinoma has grown deeper into the cervix,

IA Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion <5 mm and the largest extension <7 mm

- IA-1 Measured stromal invasion of <3.0 mm in depth and extension of <7.0 mm
- IA-2 Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm

- IB Macroscopic lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA
  - IB-1 Clinically visible lesion <4.0 cm in greatest dimension
  - IB-2 Clinically visible lesion >4.0 cm in greatest dimension
- Stage II-Cervical carcinoma that infiltrates beyond the uterus, but involving pelvic wall or to the lower third of the vagina
  - IIA Without parametrial invasion

- IIA-1 Clinically visible lesion <4.0 cm in greatest dimension
- IIA-2 Clinically visible lesion >4.0 cm in greatest dimension

- IIB With obvious parametrial invasion

- Stage III-The tumour spread to the pelvic side wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney

    - IIIA Tumour infiltrates lower third of the vagina, without extension to the pelvicside wall
    - IIIB Tumor extension to the pelvic sidewall and/or hydronephrosis or non-functioning kidney

Stage IV-The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous oedema, as such, is not considered as Stage IV

IVA Infiltrating adjacent organs

IVB distant metastases

APPENDIX III : FIGURES

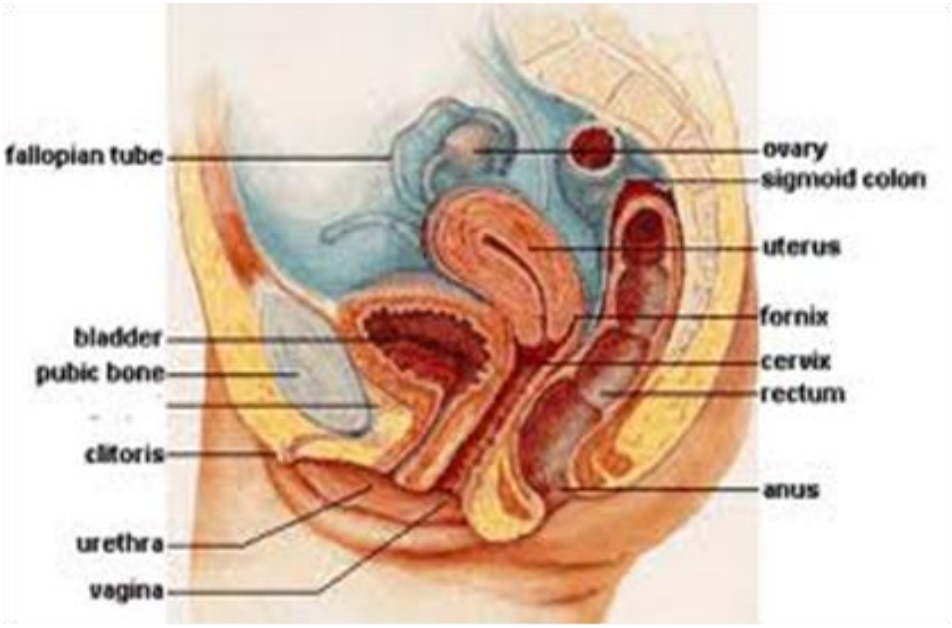

Figure .1 Anatomy of female pelvis -Sagittal view

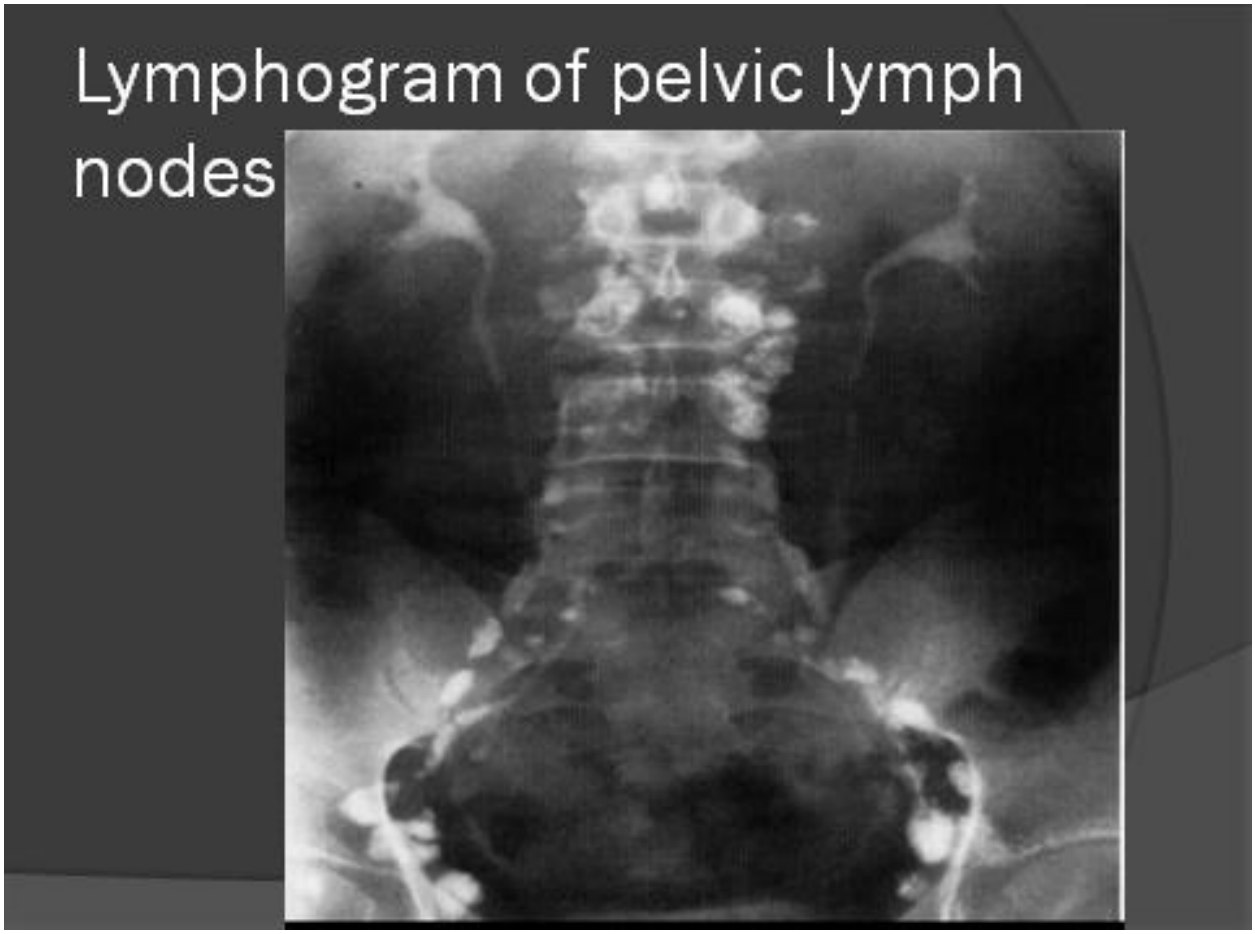

Figure 2.Lymphangiogram for pelvic lymphnodes

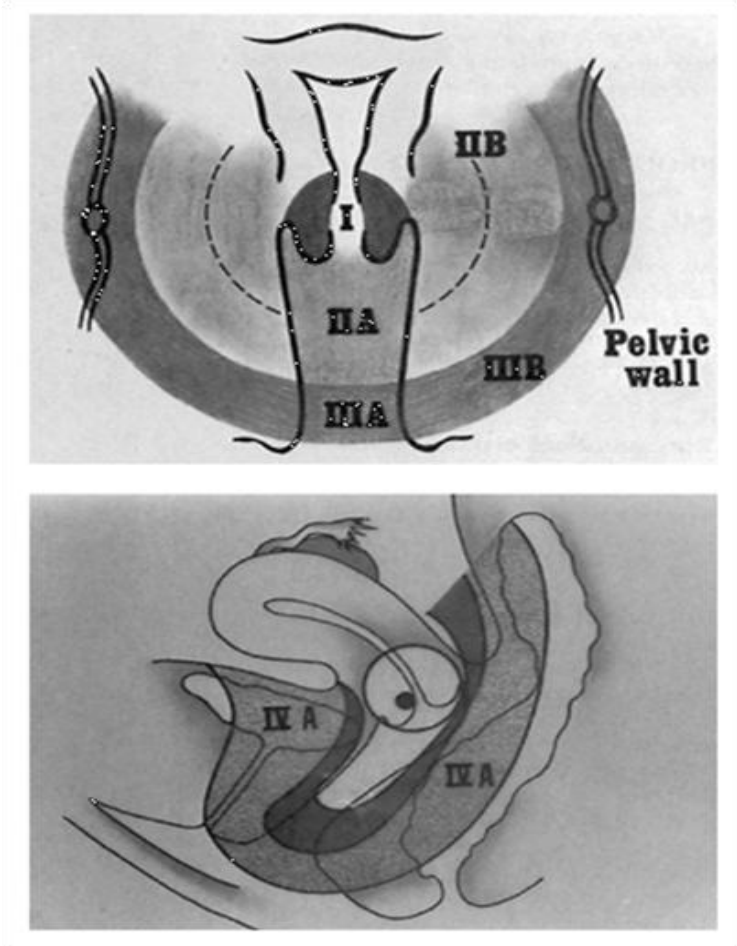

Figure 3 .Diagrammatic representation of various anatomic stages of carcinoma of the uterine cervix, according to the Federation of Gynecologists and Obstetricians classification.

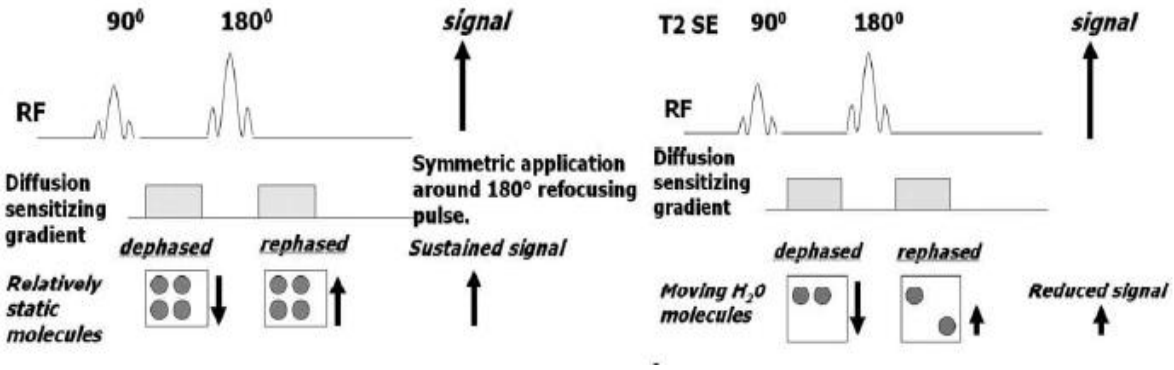

Fig.4
Diffusion- weighted imaging in the abdomen and pelvis; concepts and applications
RadioGraphics 2009; 29:1797–1810 • **Published online**
10.1148/rg.296095521

APPENDIX IV : Information sheet for participants

Study title:- A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix

Name-_____

It is for the information that you have been diagnosed to have Cancer of the cervix stage_____ (FIGO). The current recommended therapy is concurrent chemo radiation with weekly administered Cisplatin followed by brachytherapy.

We are inviting you to participate in the study conducted in the Dept. of Radiation Oncology Unit II, Christian Medical College, Vellore in patients with carcinoma of the cervix.

You are hereby being requested to participate in the above mentioned study.

1.What is the study all about- The standard followed in our institution for the image based external beam radiotherapy for carcinoma cervix is CT scan based. However RTOG and other professional bodies use and recommend the use of MRI in addition of CT scan for the same.

However, this is costly and all patients are unable to afford the same. The study attempts to determine if MRI do significantly change the treatment

2. What will be done? –Patients recruited in this study will undergo additional MRI evaluation based on the additional information the treatment plan may get modified. The MRI images will be fused with CT images which will give more soft tissue delineation. The fused MRI with CT will be used for treatment plan to be generated for the plan to be used for treating the patient. This is the standard of care as prescribed by RTOG.

3.Description of any reasonably foreseeable risks or discomforts to the Subject-

All contrast studies are associated with a small risk of drug reaction. If patient is asthmatic or have allergies, steroids and antihistamines will be given prior to the procedure. If patient had a previous contrast reaction ,contrast study will be avoided.

MRI –Patients with pace makers, cochlear implants, some type of aneurysm clips and implanted drug infusion devices or with suspected metallic injury anywhere in the body cannot undergo MRI evaluation.

4 Is there any benefit in getting enrolled in the study?

Additional imaging helps in better tumor volume delineation, which in turn helps in maximum dose delivery to the target volume with minimal toxicity to the normal tissues and reduced chance of geographical miss. Depending on additional information, The plan of management may change, which is expected to benefit the patient.

1. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.

   Patient can be treated with information based on CT scan alone in case of CT based planning.

6. What about the data security-

   The data so collected will only be used for research purpose and not any other purpose and will not be supplied to any person or body except those authorised (investigators, institutional review board, ethics committee, professional bodies or any legal authorities whenever required). However, in any matter, your identity will be protected and will not be revealed.

7. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)

   There is no provision of any randomisation.

8. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury

   We are not adding or removing any component of your treatment, therefore the possibility of treatment for trial related injury does not arise.

9. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury

For any trail related querries the principal investigator Dr.Aparna can be contacted at 0416 228 2046 or 9176950471

10. Monetary considerations-

No money or compensation in any form will be given for participating in this study

11. Subject's responsibilities on participation in the trial-

The subject's responsibility in this trial is limited to undergo the treatment as per medical advice and undergo tests as required and answer the questionnaire at scheduled time. The patient is also expected not to delay inordinately in his/her follow up. If the patient refuses to undergo any of the diagnostic tests , after clearing any doubts about the tests or regarding the study , she will deemed to have expressed her desire to be excluded form the study and will be regarded as been withdrawn from the study

12. Participation-

The participation is purely voluntarily. No monetary compensation or otherwise will be provided

Can I leave the study-?

In this study your treatment will be the same as the recommended practice . You are free to withdraw from this study at any point of time. We assure that withdrawal from the study will not affect the rest of your treatment in any way and it will be continued as per the recommended treatment.

1.2 Additional elements, which may be required

a. Foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.

If you are found to have any condition that prevents you from undergoing any of the required tests, [CT / MRI] your participation in the study will be deemed to be terminated. However in any such situation, you will continue to have appropriate standardised care at per with all other trial and non-trial patients.

b. Additional costs to the Subject that may result from participation in the study:

As a participant of the study you will be asked to undergo some additional tests. The tests are expected to cost Rs-5610 INR. Extra cost incurred due to the study will not be bound to the patient.

c. The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.

As mentioned earlier, you can withdraw, from the study any moment you wish to. You would not be asked to furnish any reason neither your treatment nor follow up would get affected. However, we would like to hear from you the reasons if you please, and clear any doubts that may have risen.

d. <u>Can I know about my results</u>-?

Surely, you will be provided with the results. Under no circumstances any information of your problem will be concealed from you.

e. Any treatment with radiotherapy or chemotherapy involves risks to fetus or embryo, and therefore we would ask you to confirm that you are not pregnant at time of the treatment and take appropriate contraceptive measures to prevent pregnancy during the treatment and till at least for the next follow up, if you were on chemotherapy.

Nursing mothers are advised not to wet nurse the baby till all chemotherapy is over and till 1st follow up.

This is applicable to all patients undergoing radiotherapy or chemotherapy irrespective of the fact that you are a part of the trial or not. Even if you wish to withdraw from the trial, these precautions are to be taken.

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:

_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date: _____/_____/_____

Name of the Witness: _____

Informed consent form

Study Title: A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix

Study Number:

Subject's Initials _____ Subject's Name: _____

Date of Birth____/____/_____(DD/MM/YYYY) / Age: _____yrs

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: ___________________________

Date:_____/_____/_______

Name of the Witness: _______________________________

APPENDIX V-DATA SHEET

sno	name	age	hno	cervix	growth	forni	vagina	rvsep	rtpara	ltpara	cystosco	proctos	findiag	nodes1	hydrour	livermet	ctextparam	mrextpara	ctinvolv	mrinvolv	ctvagina	mrvagina	ctbladin	mrbladin	ctrectal	mrrectal
1	Gajalakshn	42	210992F	3	1	5	2	2	2	2	3	2	5	4	2	2	1	1	2	2	2	1	2	2	2	2
2	Settuamm	49	242244F	3	1	5	1	2	2	2	3	2	5	4	2	2	1	2	2	2	2	1	2	2	2	2
3	SUSILA	45	245484F	3	1	5	2	2	1	2	3	2	5	4	2	2	1	1	2	2	1	1	2	2	2	2
4	GAYATRI D	65	250616F	3	3	1	1	2	1	1	3	2	3	4	2	2	1	1	2	2	1	1	2	2	2	2
5	ZOTHANSA	43	215453F	3	2	5		1	2	2	3	2	5	4	2	2	1	1	2	2	1	1	2	2	1	1
6	THARA	47	171163F	3	2	1	1	2	1	1	3	2	3	4	2	2	1	2	2	2	1	1	2	2	2	2
7	SUNAY DEV	51	312082F	3	3	5	2	2	2	2	3	2	5	4	2	2	1	1	2	2	1	1	2	2	2	2
8	SHANTHA	46	330536F	3	2	5	1	2	1	2	3	2	5	4	2	2	2	1	2	2	2	2	2	2	2	2
9	EASWARI	48	309560F	3	2	5	2	2	2	2	3	2	2	2	2	2	1	1	2	2	2	1	2	2	1	2
10	KALA	36	339870F	3	2	5	2	2	1	2	3	2	5	4	2	2	1	1	2	2	1	1	2	2	2	2
21	PODDUTU	46	295500F	3	1	5	1	2	2	2	3	2	5	2	1	2	1	1	2	2	1	1	2	2	1	2
22	AMBIKA D	41	471165F	3	1	5	3	2	2	2	3	2	5	4	2	2	2	1	3	2	1	1	2	2	2	2
23	KASTHURI	57	785577C	3	1	5	1	2	2	1	3	2	5	4	2	2	1	1	2	2	1	1	2	2	2	2
24	JYOTHI	42	233999F	3	3	5	1	2	1	2	3	2	5	4	2	2	1	1	2	2	2	1	2	2	1	2
25	BHARATHI	41	329328F	3	3	5	2	2	2	2	3	2	5	4	2	2	2	1	2	2	2	1	2	2	2	2
26	SELVI R	34	531107B	3	2	5	1	2	2	2	3	2	5	4	2	2	1	1	2	2	2	1	2	2	2	2
27	SABITRI SH	61	410416F	3	1	5	1	2	1	2	3	2	7	4	2	2	1	1	2	2	2	1	2	2	2	2
28	DHANAM	53	619071F	3	1	5	1	2	2	1	3	2	5	4	2	2	1	1	2	1	1	1	2	2	2	2
29	DEIVANI	51	370860A	3	1	5		2	1	1	3	2	3	4	2	2	1	1	2	2	1	1	2	2	2	2
30	RAMANI	44	171946F	3	3	5	1	2	3	1	3	2	3	4	2	2	2	2	3	3	1	1	2	2	2	1
31																										

sno	ctmesrec	mrmesrec	ctuter	mruter	ctdismet	mrdismet	ctparaaor	mrparaaor	ctcomili	mrcomili	ctextili	mrextili	ctintili	mrintili	ctinguin	mringuin	ct	mrpresac	cthydrou	mrhydrou	ctpyomet	mrpyomet	ctgtvp	mrgtv
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30	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	121.76	8
31																								

APPENDIX VI

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
Director, Christian Counseling Centre
Editor, Indian Journal of Psychological Counseling
Chairperson, Ethics Committee, IRB

Dr. Alfred Job Daniel, MS Ortho
Chairperson, Research Committee &
Principal

Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

10th May, 2012

Dr. Aparna
PG Registrar
Department of Radiotherapy
Christian Medical College
Vellore 632 002

Sub: **FLUID Research grant project NEW PROPOSAL:**
A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix
Dr. Aparna, PG Registrar, Radiotherapy, Dr. Subhashini John, Dr. Saikat Das, Dr. Rajesh Isiah, Radiotherapy.

Ref: IRB Min. No. 7802 dated 18.04.2012

Dear Dr. Aparna,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix"

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English, Tamil and Hindi)
3. Cvs of Drs. Saikat Das, Aparna , Subahshini John, Rajesh I
4. A CD containing documents 1- 3

The following Institutional Review Board (Ethics Committee) members were present at the meeting held on April 18, 2012 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore- 632002.

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

INSTITUTIONAL REVIEW BOARD (IRB)
CHRISTIAN MEDICAL COLLEGE
VELLORE 632 002, INDIA

Dr.B.J.Prashantham, M.A.,M.A.,Dr.Min(Clinical)
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Dr. Nihal Thomas
MD, MNAMS, DNB(Endo), FRACP(Endo), FRCP(Edin)
Secretary, Ethics Committee, IRB
Additional Vice Principal (Research)

Name	Qualification	Designation	Other Affiliations
Dr. B.J.Prashantham	MA (Counseling), MA (Theology), Dr Min(Clinical)	Chairperson(IRB)& Director, Christian Counselling Centre	Non-CMC
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC
Mrs. Ellen Ebenezer Benjamin	M.Sc. (Nursing), Ph.D.	Deputy Nursing Superintendent, CMC.	
Dr. Vathsala Sadan	M.Sc, Ph.D	Addl. Deputy Dean, College Nursing, CMC.	
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M.Phil, BL.	Legal Advisor, CMC.	
Mr. Joseph Devaraj	BSc, BD	Chaplain, CMC	
Dr. Nihal Thomas	MD MNAMS DNB(Endo) FRACP(Endo) FRCP(Edin)	Secretary IRB (EC)& Dy. Chairperson (IRB), Professor of Endocrinology & Addl. Vice Principal (Research), CMC.	

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any serious adverse events occurring in the course of the project, any changes in the protocol and the patient information/informed consent and requires a copy of the final report.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

TEL : 0416 - 2284284, 2284282 FAX : 0416 - 2262788, 2284481 E-mail : research@cmcvellore.ac.in

APPENDIX VII

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Turnitin Originality Report

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- Word Count: 15821
- Submitted: 2

A prospective study to compare T2 W MRI to CT imaging in volume delineation for radiotherapy planning in carcinoma cervix By 20113751 . M.d. Radio Therapy APARNA M P . PRAKASAN

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Michele Follen. "Imaging in cervical cancer", Cancer, 11/01/2003

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Submitted to Mahidol University on 2012-07-25

1% match (publications)

&NA;. . "Abstract :", International Journal of Gynecological Cancer, 2012.

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Assignment title	Medical
Author	20113751 . M.d. Radio Therapy APARNA M P . PRAKASAN
E-mail	aparnasannu@gmail.com
Submission time	18-Dec-2013 03:52PM
Total words	15821

First 100 words of your submission

AIM OF THE STUDY Primary objectives: The investigational imaging MRI will be compared with CT imaging to • -Compare the target volume delineation and evaluate the impact of MRI on target volume as compared to the volumes obtained on a CT scan - GTV Primary (Cervical tumour, involvement of uterus, vagina and parametrium) GTV Lymph nodes • To determine whether there is any change in the staging of the disease • To determine any change in management or prognosis depending on the extra information. Secondary objective: • To see if CT scan along with clinical findings can be a good alternate to MRI scan • To look at the possibility of reduction in treatment volume • To evaluate the possibility of...