AIM OF THE WORK

The aim of this study was to compare the intensity modulated whole pelvis radiotherapy (IM-WPRT) to 3D-conformal radiotherapy in the treatment of female patients with locally advanced cervical cancer. This study was designed to investigate if the significant reductions in normal tissue volume irradiated could lead to decrease in the incidences of toxicities.

Primary end-point:

- Assessment of acute toxicity resulting from both IMRT and conformal whole pelvis radiotherapy by common toxicity criteria (CTC) which will include weakly assessment of gastrointestinal toxicities and genitourinary toxicities.[119]

Secondary end-points:

1. Determining the impact of replacing magnetic resonance imaging (MRI) completely by computed tomography (CT) as imaging tool of Image Guided Brachytherapy (IGBT) for guiding contouring of clinical target volume and organs at risk and dose volume histogram parameters (DVH) as defined by GEC–ESTRO Working Group I and II.[117, 118] The proposed parameter for measuring this impact was minimum dose to the 90% of the clinical target volume (D90 HRCTV) which was recently being proven to be a stable and reliable predictor of local control.[120]
2. Late side effects were assessed according to Late Effects Normal Tissue Task Force (LENT) score.[121]
3. Assessment of local pelvic control.

PATIENTS

This study included 45 patients with locally advanced (stage IB-IIIB) non metastatic cervical cancer. The patients in the study were divided into two groups.

Group A (Therapeutic group):

This group included 30 female patients were selected prospectively on basis of availability of inclusion criteria. They were subdivided two subgroups according to type of EBRT modality; where

Group A1: Including 15 patients with locally advanced cervical cancer were treated with 3D-conformal whole pelvis radiotherapy then image guided high dose rate (HDR) brachytherapy.

Group A2: Including 15 patients with locally advanced cervical cancer were treated with intensity modulated whole pelvis radiotherapy then image guided HDR brachytherapy.

Group B (Imaging group):

This group included 15 female patients with locally advanced cervical cancer. Fifteen cervix cancer patients were retrospectively selected out of the overall patient cohort on the basis of availability of both CT and MRI with applicator in place and full 3D documentation (cartoon drawings) representing the clinical gynaecological examination. These patients belong to a larger cohort of cervical cancer patients planned, treated and followed up in a prospective manner based on a protocol used at the Radiotherapy Department of the Medical University of Vienna.[122]

Patients selection

1. Inclusion criteria:

1. Positive biopsy showing squamous-cell carcinoma, adenocarcinoma or adeno-squamous cell carcinoma of the uterine cervix.
2. Patient informed consent.
3. Karnofsky performance status more than 80%. [123]
4. Age more than 18 years.
5. Patients with FIGO stage IB-IIIB.
6. No previous or concurrent cancer except basal cell carcinoma.
7. No prior treatment for pelvic malignancy.
8. Adequate renal and liver functions.
9. No contraindications to MRI such as patients with pacemakers.

10. No contraindication of pelvic radiotherapy, e.g. inflammatory bowel disease.

2. Exclusion criteria

- Karnofsky performance status less than 80%.
- Patients with metastatic cervical cancer.
- Previous or concurrent cancer except basal cell carcinoma.
- Prior treatment for pelvic malignancy, previous pelvic or abdominal radiotherapy
- Contraindication to cisplatin as impaired renal or liver functions.
- Contraindication to pelvic radiotherapy, e.g. inflammatory bowel disease.
- Contra indications to MRI

METHODS

Group A (Therapeutic group)
Staging and patient work-up

All examinations had completed before starting of treatment.

For the purpose of this study thirteen patients underwent the following:-

1. History:
   - Gynecological History included the age of patient, history of presenting complaint (such as site pain, radiation, character onset, aggravating & relieving factors), Menstrual History (Menarche and menopause, bleeding between periods, bleeding after intercourse, any post menopausal bleeding), use of contraception.
   - Past Gynecological and obstetric history and gynecological surgery
   - Past Medical and drug history
   - Family History
2. General physical examination, assessing also performance status.
3. Gynaecological examination was performed by radiation oncologist and examination under anesthesia by the gynecologist with topographic documentation on a specific cartoon.
4. Biopsy of primary tumour was done to confirm the histopathological diagnosis.
5. Blood tests including hemoglobin level, Complete blood count (CBC), Liver function (SGOT, SGPT, Alkaline phosphates, albumin, bilirubin, prothrombine activity), Renal Function (blood urea, serum creatinine and creatinine clearance) and Fasting blood sugar.
6. Laparoscopic Lymph node staging for all patients
7. Imaging;

   CT scan of chest to confirm the absence of lung metastases.

   CT scan abdomen and pelvis to detect liver and high para-aortic lymphadenopathy.

   pelvic magnetic resonance imaging (MRI) scan before initiation of treatment and before Brachytherapy application at end of EBRT. ± PET-CT.
8. Morbidity scoring (CTC v3.0) were done for all patients at baseline, then weekly during the course of definitive treatment then every 3 month during the first year of follow up then at 18 month from the end of treatment.

9. ± Cystoscopy and or Rectoscopy if organ involvement was suspected and after taking patient approval.

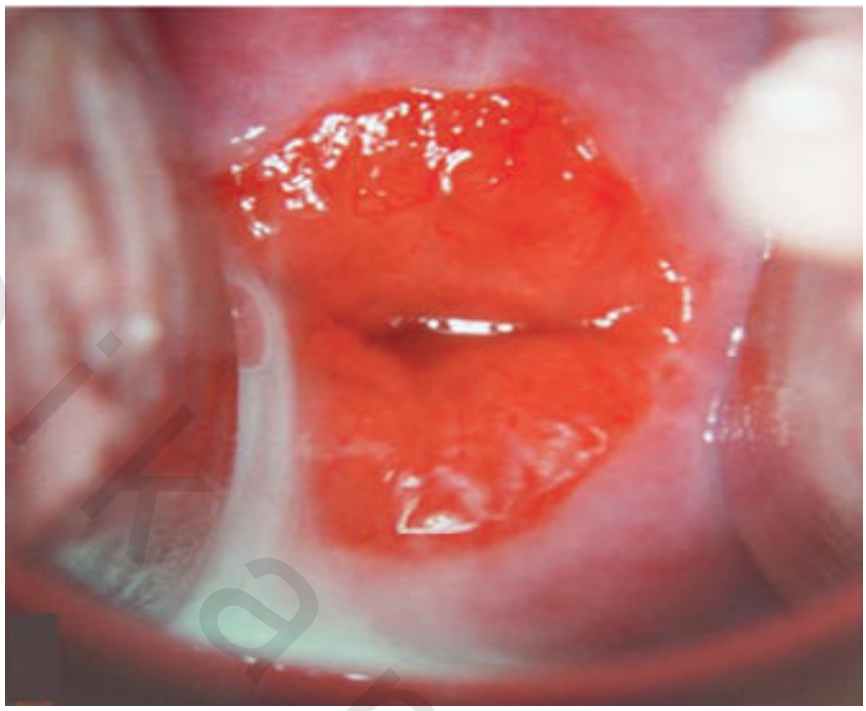


Figure (12): Example of Speculum View for patient showing eroded cervical mass by inspection.

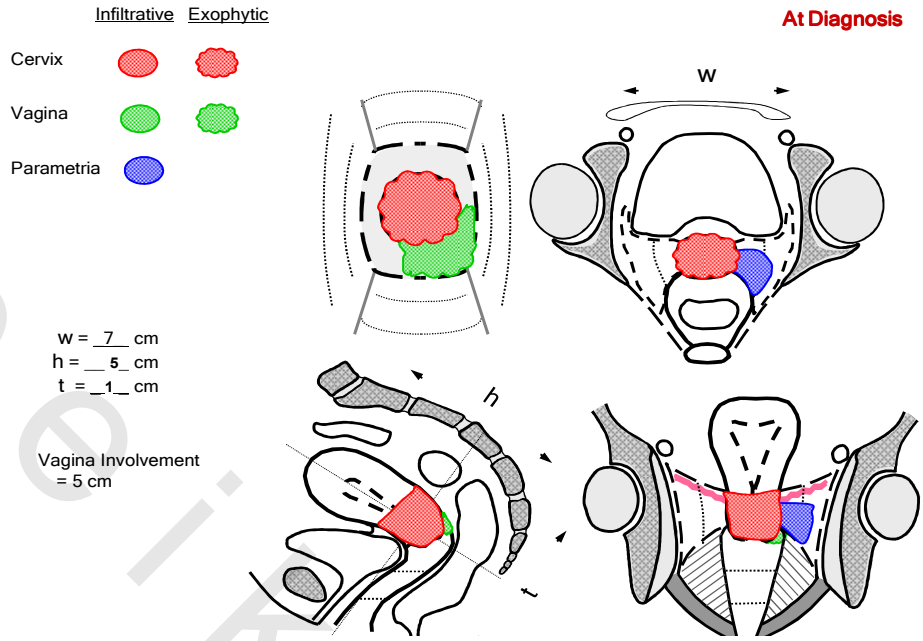


Figure (13): Clinical Drawing documented on special carton indicating the clinical findings at time of diagnosis for patient with stage IIB cervical cancer where endocervical tumor infiltrated the proximal part of left parametrium with invasion of left and posterior fornix.

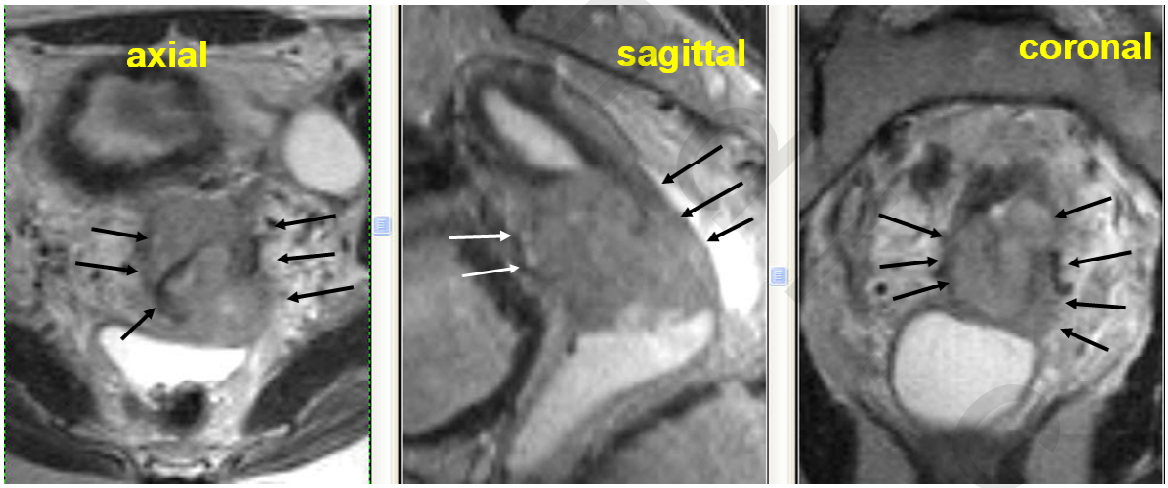


Figure (14): MRI Findings at diagnosis for the same patient with FIGO Stage IIB, SCC, G2, cervical cancer showing; proximal involvement of left parametrium, Invasion of left and posterior fornix.

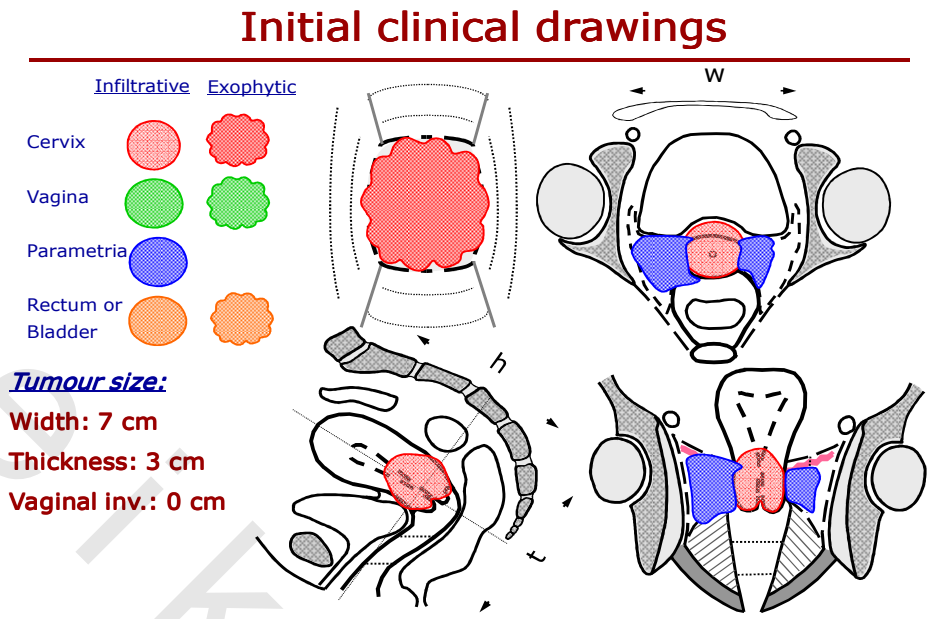


Figure (15): Clinical Drawing documented on special carton indicating the clinical findings at time of diagnosis for patient with stage IIIB cervical cancer, where endophytic tumor infiltrated the outer half of right parametrium till pelvic wall and the inner half of left parametrium.

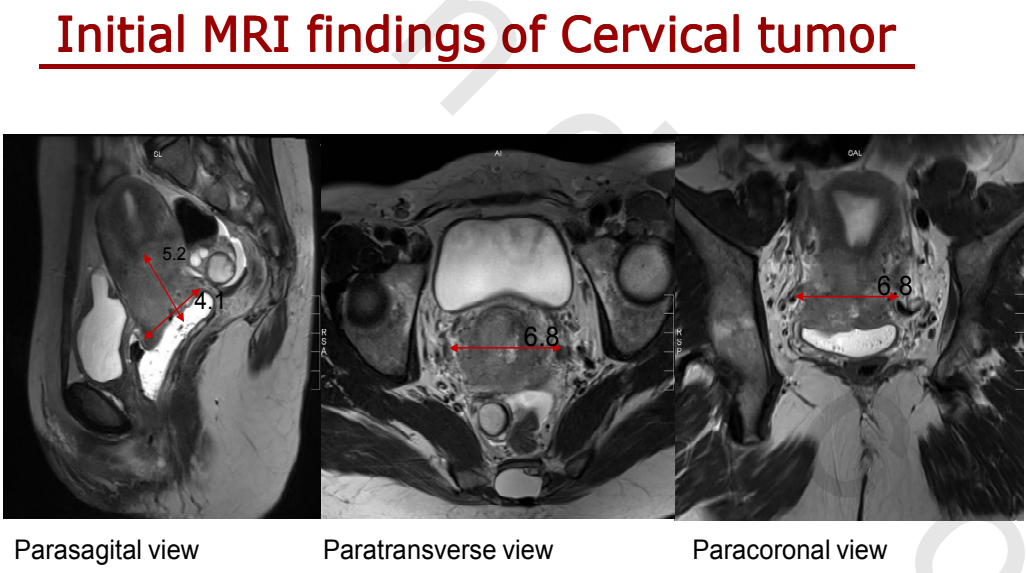


Figure (16): MRI Findings at diagnosis for the same patient with FIGO Stage IIIB, SCC, G2, cervical cancer.

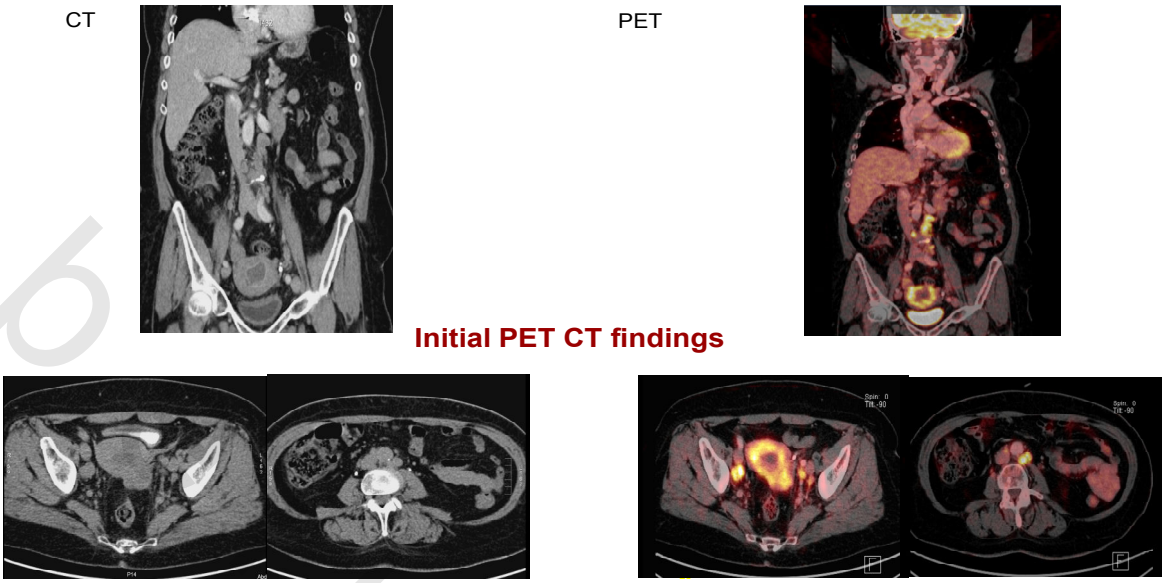


Figure (17): PET CT findings for patient with FIGO stage IIB cervical cancer and PET-CT positive common iliac and internal iliac LN.

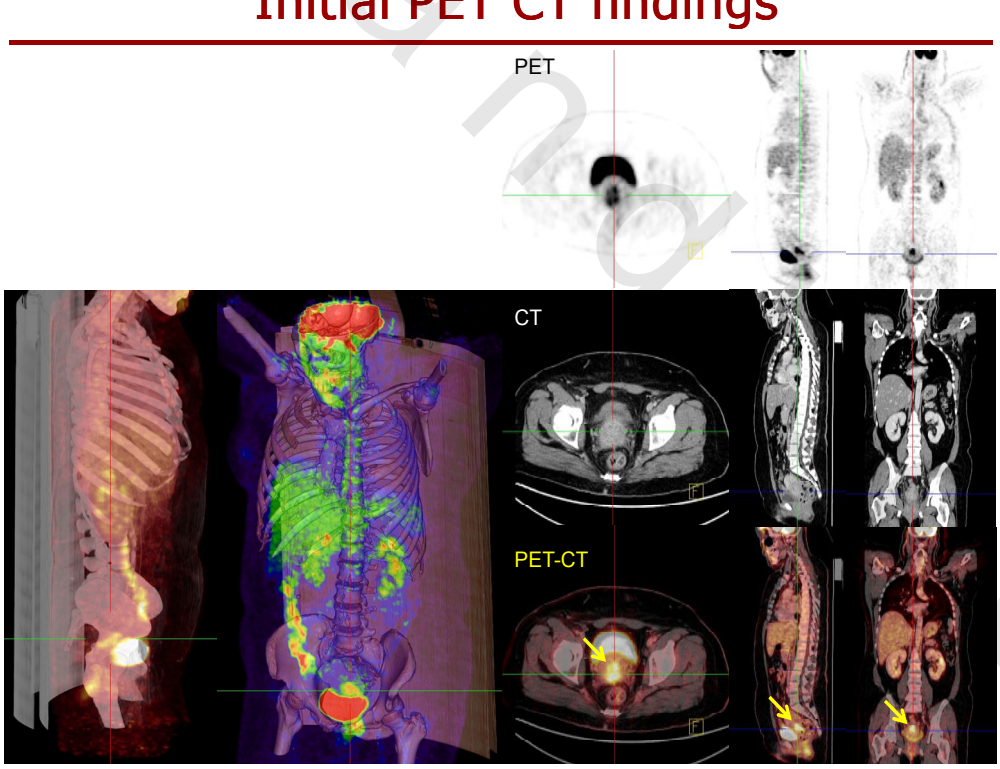


Figure (18): PET CT for patient with FIGO stage IIB showing increase activity over cervical tumor only and no activity over LN.

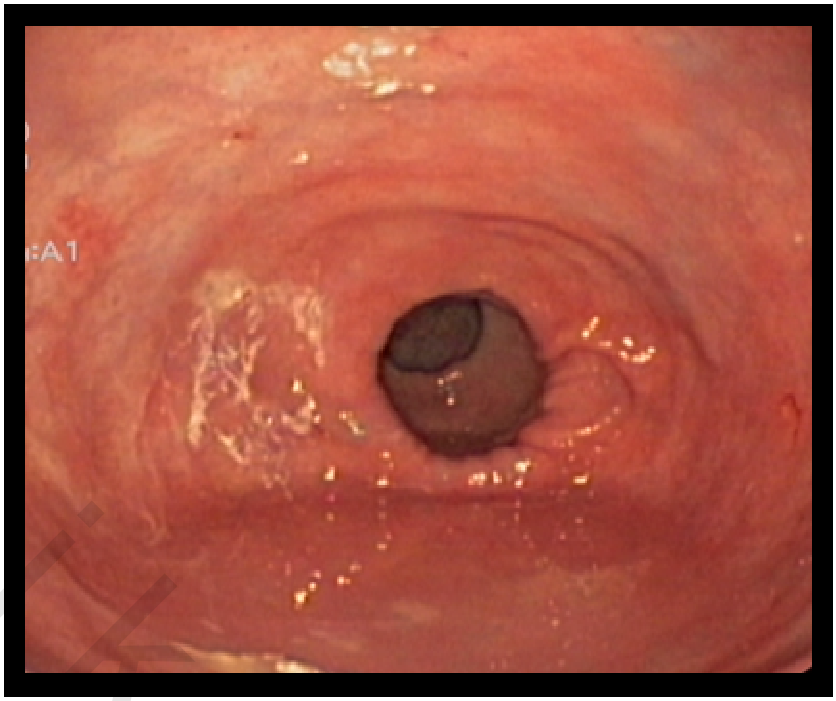


Figure (19): Rectoscopic picture for patient with FIGO stage IIB cervical cancer showing no involvement of rectal mucosa at time of diagnosis before initiation of treatment.

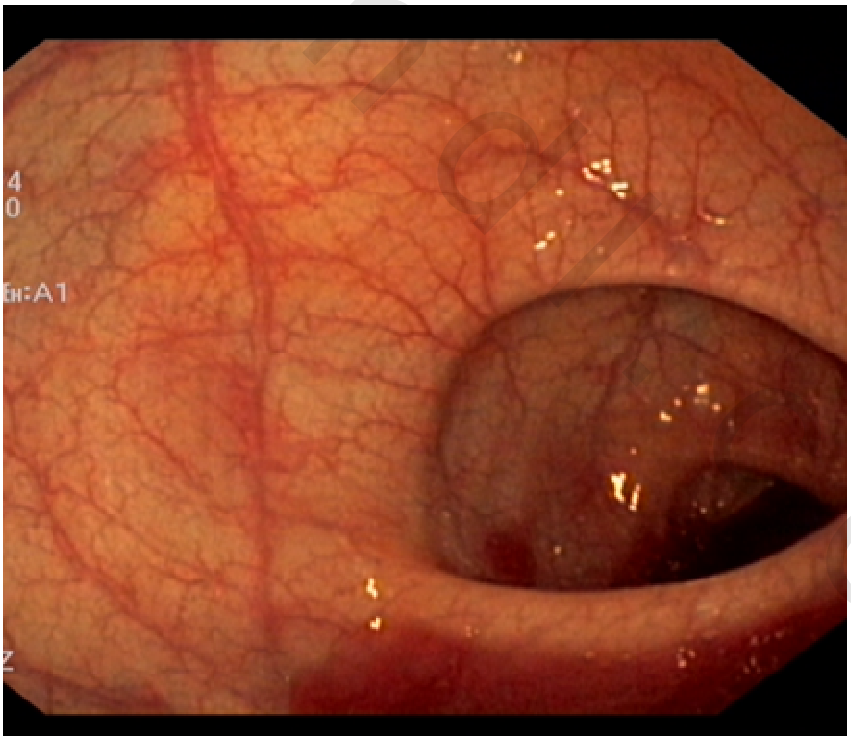


Figure (20): Rectoscopic picture for patient with FIGO stage IIIB cervical cancer showing Grade I telengectasia of rectal mucosa at time of diagnosis before initiation of treatment.

External Beam Radiotherapy

After thirty patients had finished the initial evaluation and assessed for exclusion and inclusion criteria, they underwent the definitive concurrent chemoradiotherapy in the department of Radiotherapy, Medical university, Vienna (AKH, Wien). The eligible 30 patients were divided into two group according to type of EBRT modality. Each group had 15 patients with biopsy confirmed cervical cancer.

Group A1: including 15 patients with locally advanced cervical cancer were treated with 3D-conformal whole pelvis radiotherapy.

Group A2: including 15 patients with locally advanced cervical cancer were treated with intensity modulated whole pelvis radiotherapy.

Both patients groups after external beam component of definitive chemoradiotherapy was finished, received MRI guided HDR BT.

Localization, Simulation, and Immobilization

- Patients were **immobilized** in the supine position in an immobilization device (Vacuum Pillow) that was also used during the course of radiation therapy. In case of IMRT, patients were immobilized using Vacuum Pillow with localizer (blue bag of Elekta).
- The patient was instructed to drink fluid 30-60 minutes before simulation in order to have a full bladder. CT scan simulation was performed with the full bladder because full bladder pushed the small bowel up and out of the field.
- During simulation, small radiopaque marker was inserted into the vaginal apex to identify the vaginal apex on the CT scan or just below the vaginal extension of disease.
- I.V. contrast was used during simulation to better define the vessels and oral contrast medium was used for better visualization of bowel.
- For each patient, Treatment planning CT scans was done from diaphragm to perineum with 4 mm slice thickness to define tumour, clinical and planning target volumes. The treatment planning CT scan should be acquired with the patient in the same position and immobilization device as for treatment.
- CT slice images with a layer thickness of 4 mm were imported to treatment planning system Oncentra-Masterplan (OMP) in case of conformal radiotherapy while to Monaco version_3 in case of IMRT where the Radiation therapy planning was done.

Target volume definition:-

Clinical Target Volume (CTV).-

- Following the recommendations of the ICRU Reports 50 (International Commission on Radiation Units and Measurements) target volumes and the organs at risk were contoured on axial CT slices of all patients. [124]

- The clinical target volume in definitive treated patients (CTV) included the Entire cervix; entire uterus, entire parametrium including; entire mesorectum and uterosacral ligament, part or whole vagina and lymph regions along the iliac vessels, up level of common iliac arterial bifurcation.

- The inferior limit of CTV could be individualized based on inferior spread of tumour on physical examination. If there was no vaginal extension: upper half of the vagina should be treated. If there was upper vaginal involvement: upper two-thirds of the vagina should be included in the treatment volume. If there was extensive or lower third of vaginal involvement:, CTV included the entire vagina.

- Nodal CTV included the internal, obturator, external, and common iliac lymph nodes, presacral lymph node down to the level of S3. The inclusion of paraortic lymph nodes depended on the extent of disease. If there is positive common iliac or par-aortic LN on laparoscopic staging, the paraortic LN was included in treatment field. If there was involvement of lower vagina, inguinal LN bilateral was included in the CTV.

- Identification of the nodal CTV usually begins with the identification of the iliac vessels from level of common iliac arterial bifurcation. A 7-mm margin was added in all directions to the "vessels" contour. Approximately 1-2 cm of tissue anterior to the S1, S2 and S3 sacral segments was added to the CTV for patients with cervical carcinoma in order to include the pre-sacral lymph nodes and utero-sacral ligaments.

- The Planning Target Volume (PTV) will provide a 10 mm margin (anteriorly, posteriorly, laterally, as well as in the superior and inferior directions) around the CTV.[125]

- **Normal structures will be contoured**

- Bladder – will be outlined on every slice, including the portion inferior to the planning target volume.

- Rectum – will be outlined on every slice, including the portion inferior to the planning target volume and superior to the level of recto-sigmoid junction.

- Intestine (defined as peritoneal cavity including bowel) were contoured as single structures on every slice, including at least 2 cm above the planning target volume.

- Also sigmoid, femoral heads and patient outline were contoured.

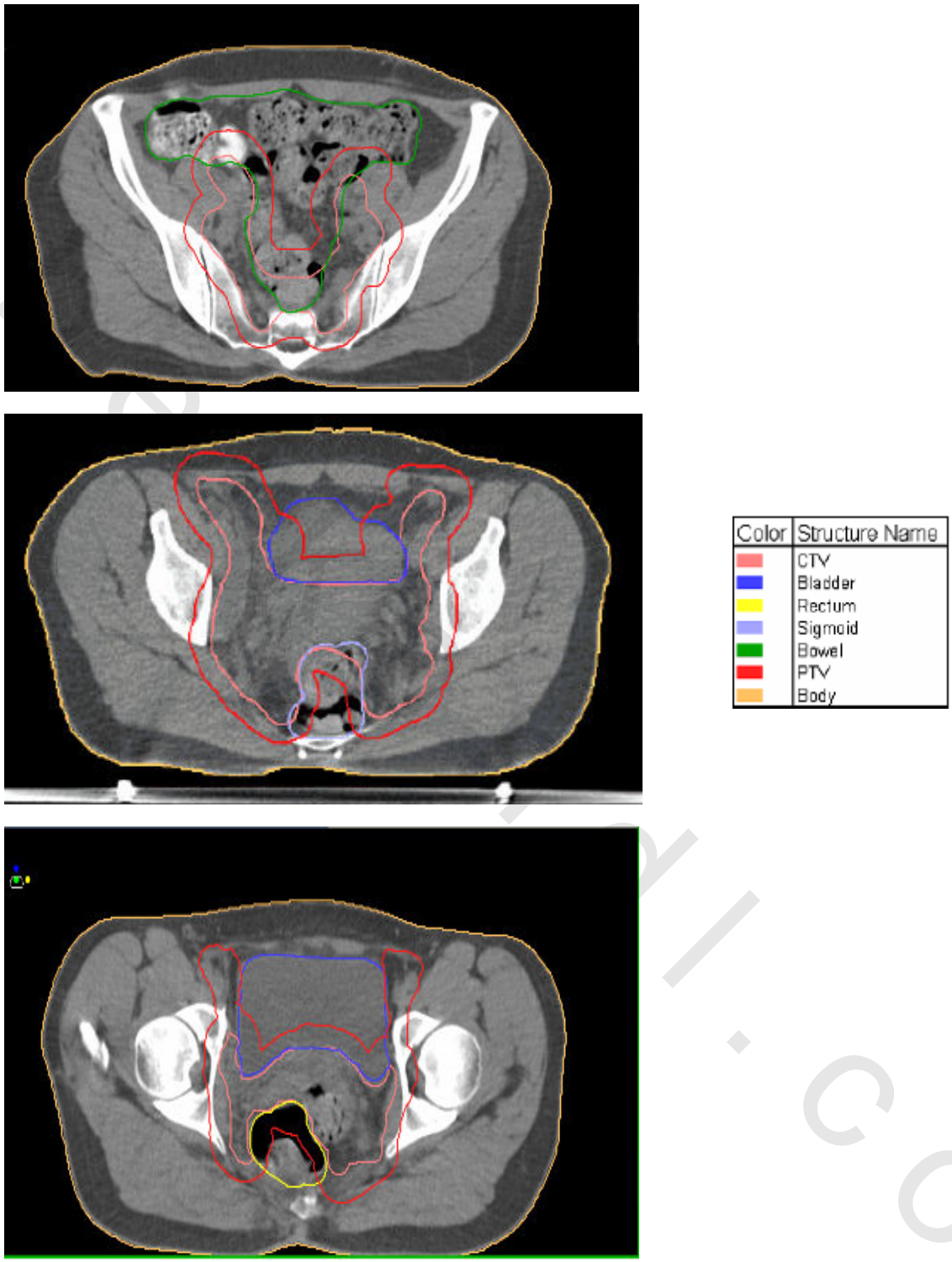


Figure (21): Transverse CT slices showing CTV; PTV; Bladder, Bowel, sigmoid and rectum contours for EBRT.

Treatment planning for conformal technique:

- All treatment plans and DVH analysis were made with the treatment planning Oncenter_Masterplane.

- For all 15 patients, conformal plan were based on a four field box technique (0°, 90°, 180°, and 270°).
- All treatment plans were based on a 10 MV high energy photon beam.
- The plans were normalized to deliver 45 Gy in 1.8 Gy per fraction to the ICRU reference point located in the centre of the PTV.
- The primary acceptance criterion for treatment planning was that at least 95% of the PTV was covered by the 95% isodose volume.
- Irregular beam portals of the 4F plans were shaped with a multi-leaf collimator and manually optimized using the beam's eye view technique.

Treatment planning for IMRT technique:

- For inverse planning; PTV, bladder (B), rectal wall (RW), sigmoid, femoral heads, patient outline, kidney and intestine were contoured to drive the IMRT optimization. Additionally, around two artificial OARs per patient, so-called 'help' structures, were defined for IMRT treatment planning. These structures were located in the anterior and posterior concave parts of the PTV. A minimum distance of 1–1.5 cm was respected between PTV and these help-structures, because steeper dose gradients cannot be achieved with high energy photon beams.
- All treatment plans and DVH analysis were made with the treatment planning system Monaco version 3. This planning system produces optimal intensity-modulation profiles using a Mont Carlo algorithm (Biological optimization using the equivalent uniform dose (EUD)).
- For all patients the IMRT plans based on a nine beam arrangement with equidistant gantry angles. Fields were equally spaced at 40° intervals starting from gantry angle 180. The couch and collimator angel were zero. The delivery mode is step and shoots IMRT.
- All treatment plans were based on a 10 MV high energy photon beam. The 9-field, 10-MV, coplanar, IMRT plan was generated for each patient using an identical set of dose–volume constraints.
- The IMRT treatment plan was based on computerized treatment plan optimization and segmental MLC delivery.
- The plan categories were normalized to deliver 45 Gy in 1.8 Gy per fraction to the ICRU reference point located in the centre of the PTV.
- The primary acceptance criterion for treatment planning was that at least 95% of the PTV was covered by the 95% isodose volume.

- The IMRT plans were optimized to deliver 95% of the prescription dose to 100% of the volume of PTV while max dose did not exceed 107% of prescription dose. Dose–volume constraints for normal tissues in general included the following:

  <40% of bowel to receive 30 Gy,
  <40% of rectum to receive 40 Gy,
  and <40% of femoral heads to receive 30 Gy.

Table (2): Summary of the input planning parameters for an IMRT planning in patients with cervix carcinoma.

Structure	Cost function	Threshold dose	ISO CONSTRAINTS	Relative impact
PTV	Target EUD		45	
	Quadratic overdose	46.5	0.7	++++
	Max dose: 46.50 Gy (107% of prescription dose)…..Excess 0.70Gy			
	Treatment dose: 45 Gy			
Bowel	serial		32	++++
	Equivalent uniform dose (EUD): 32Gy…shrink margin 0.4cm			
	Quadratic overdose	46		++
Sigmoid				
Rectal wall	serial		40	++++
	Equivalent uniform dose (EUD): 40Gy…shrink margin 0.3cm			
	Quadratic overdose	46	0.1	
Bladder	serial		39	++++
	Equivalent uniform dose (EUD): 39Gy…shrink margin 0.5cm			
	Quadratic overdose	46		++
Patient outline	Quadratic overdose	45	0.5	0.14

(EUD) = Equivalent Uniform Dose

Treatment plan analysis

- Average and maximum doses to the PTV were calculated for the conformal four field box technique and for IMRT plans for both patients groups.

- Target conformity was evaluated. The ratio of the target volume and the volume encompassed by the 50% isodose volume (TV/V50) was derived for each plan, which is an indicator of the overall dose gradient.
- Additionally, for all treatment plan categories and patient groups the average volume in [cm3] of bladder and rectal wall and the average volumes of small and large bowel in [cm3] were determined at six dose levels between 10 and 50.4 Gy.
- The parameter D1%, the highest dose delivered to 1% of the respective OAR, was used as a surrogate for maximum OAR doses in order to exclude calculation artifacts.

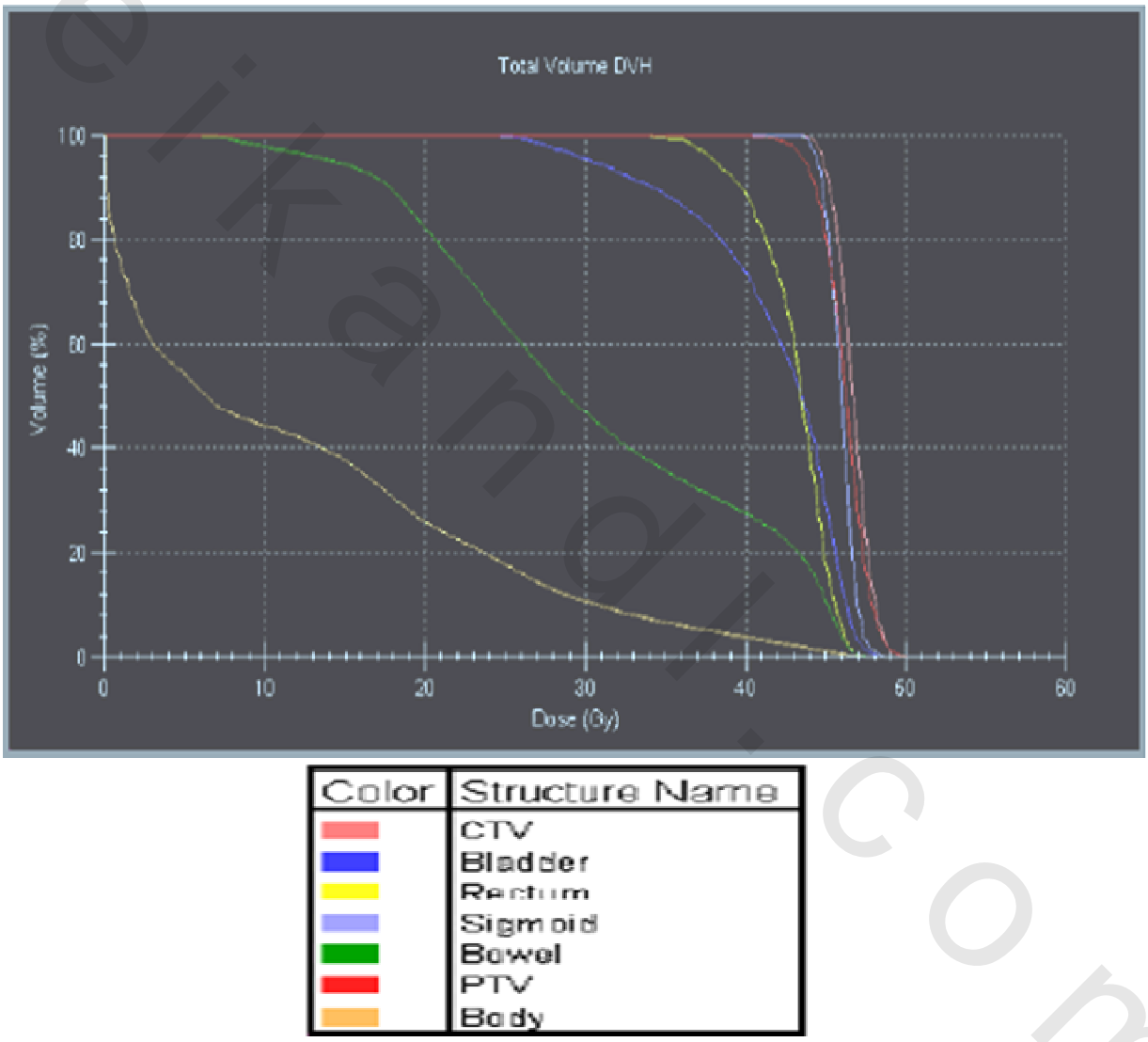
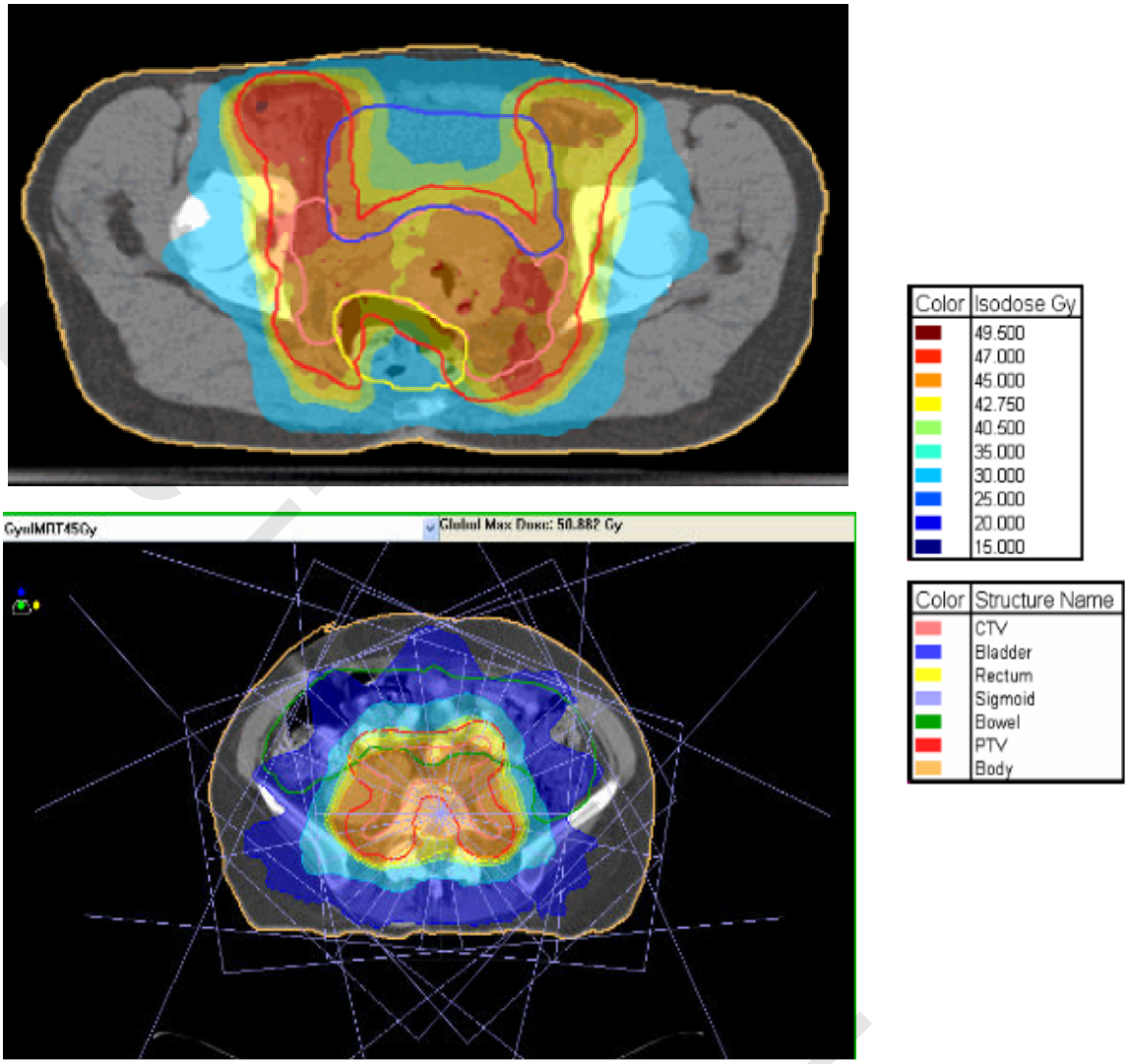


Figure (22): Resulting Dose Volume Histogram of IMRT whole pelvis planning of patient with locally advanced cervical cancer.



Figure(23): Transverse CT slices with isodose distribution of IMRT plane, where the anterior rectal wall and posterior bladder wall were completely spared from high dose (45 Gy) region.

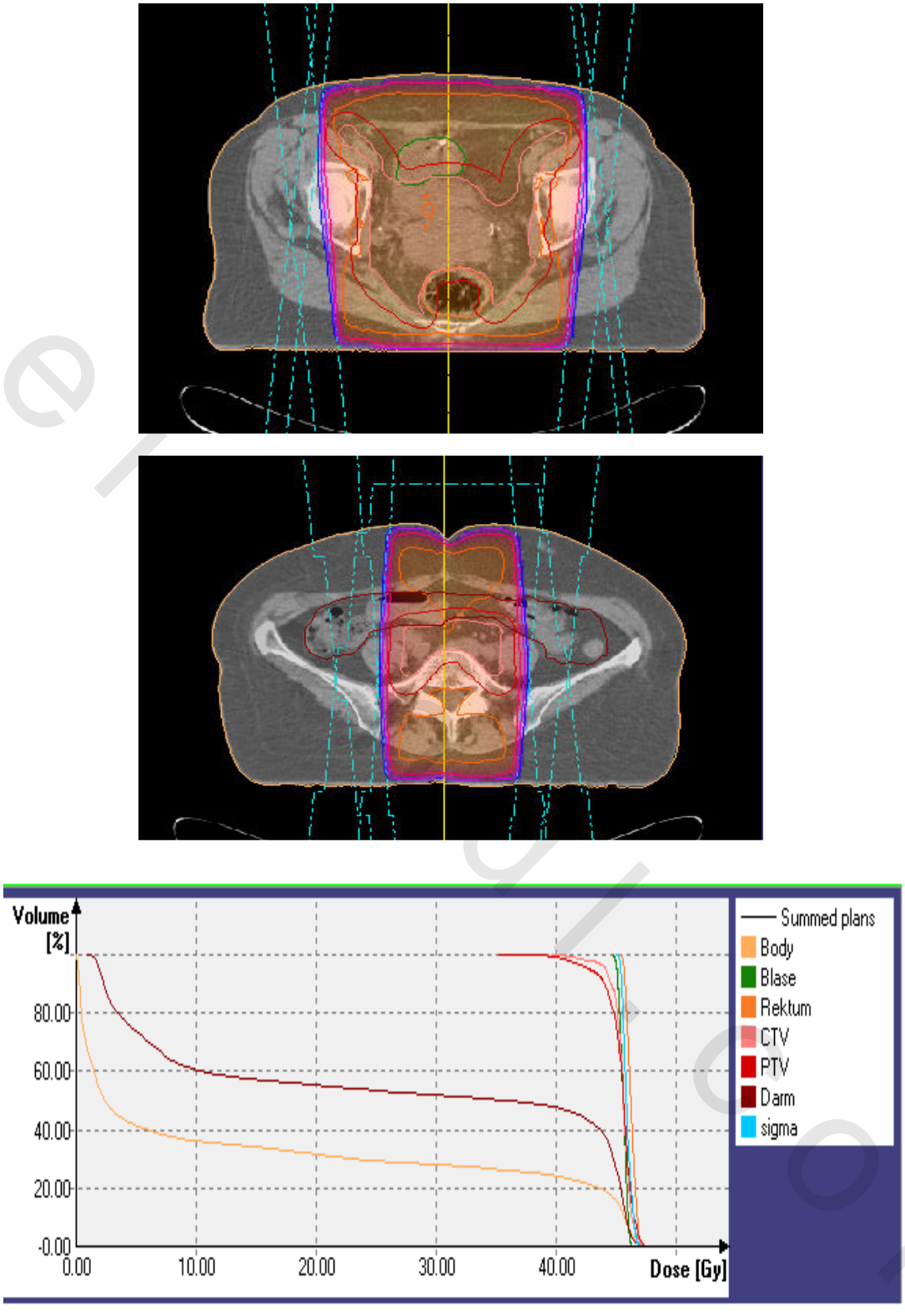


Figure 24:- Transverse CT slices with isodose distribution of 3DCRT plane, where whole rectal wall and bladder wall covered by 95% isodose and resulting DVH.

Concurrent Chemotherapy:

All patients in both groups received concurrent 40 mg/m2 (per square meter of body-surface area) cisplatin weekly for five weeks. pre-treatment hydration with 1 L of fluid infused 1 hour prior to a cisplatin dose. The hydration with Normal saline and mannitol, or furosemide-induced diuresis to effectively decrease cisplatin-induced nephrotoxicity. The normal saline contained KCl 10 mEq and MgSO4 0.5.

Also pre-treatment with a 5-HT3 antagonist (e.g., granisetron, ondansetron) plus a corticosteroid was used to prevent vomiting and was continued for the first 24 hours following chemotherapy.

The image guided Brachytherapy component of the treatment

The Brachytherapy (BT) for cervical cancer patients were performed through two applications for 4 fractions in 2 applications (7Gy/F) of MRI- Guided intracavitry +/- interstitial needles brachytherapy (if there was large residual parametrial disease or unfavorable anatomical position of organ at risk). The tandem and ring were CT/MRI-compatible applicator. The BT was done using Ir-192 high dose rate (HDR) brachytherapy with a stepping source after loading machine (Microselectron HDR classic, Nucletron, Veenendaal, the Netherlands).[126, 127]

The standard brachytherapy included delivery of 2 fractions of HDR-brachytherapy for each application, at least 6 hours apart, at the end or immediately after EBRT.

Brachytherapy application

1- Bowel Preparation:

One the day before the procedure, patient was admitted to department, where the blood laboratory tests (CBC; RFT; LFT; PT) and a chest x-ray were performed. The bowel preparation was performed 24 hours prior to the intervention to achieve an empty sigmoid and rectum.

The bowel Preparation included the following:

- Eating a light breakfast.
- Starting a clear liquid diet (soups, flavored ices, water, juice, coffee or tea) after breakfast and continue it all day and evening up until 12 midnight.
- Do not have anything to eat or drink, after 12 midnight.
- Some patients needed enema before the procedure.

2- Patients' position and details of BT application:-

The patients were brought into operating theatre. all received spinal or epidural anesthesia, then were placed in lithotomy position, and patients were draped.

A urinary Foley catheter was inserted and fixed against the bladder neck after the bladder balloon was filled with 7 mL of diluted gadolinium (ProHance, dilution 1:1). the bladder was emptied and then filled with 50 ml of saline. The clinical gynecologic examination was performed and included;

A- Inspection for external genitalia and speculum examination to assess vaginal wall infiltration and cervical tumor,

B- Palpation to assess the residual tumor topography (dimensions, tumor spread) and transrectal palpation to assess the parametrium infiltration.

The uterus was sounded and the length of the uterine cavity is measured by a semiflexible hysterometer. Serial dilation of the cervical os with Hegars dilators was done. Depending on the length of the uterine cavity and the topography of vagina and cervix as clinically evaluated, the appropriate size, length, and curvature of the uterine applicator was chosen. The tandem was inserted first then the ring was introduced and fixed to Tandem.

MRI-compatible tandem-ring applicators (Nucletron, Veenendal, The Netherlands) were available for nominal dimensions (dimensions of possible source loading) of 20, 40, and 60 mm in length for the tandem (diameter 6 mm) and 26, 30, and 34 mm in diameter for the ring in different curvatures (45°, 60°). The outer applicator dimensions are larger at 40, 60, and 80 mm for the tandem length and 38, 42, and 47 mm for the ring diameter.

This type of applicators(Vienna ring) allowed the placement of interstitial needles to cover the persistent of disease in parametrium if detected clinically and by pre-BT MRI. The depth and position of insertion of interstitial needles were determined mainly by the extent and dimensions of residual disease after EBRT on Pre-BT MRI. The tips of Titanium needles (Acrostak Corp., Winterthur, Switzerland) that were currently in use were made blunt to avoid organ or vessel injuries during BT.

After implantation of the BT applicator, the vagina was packed tightly with gauze to push the rectum and bladder away and to fix the applicator. This gauze was filled with diluted gadolinium (ProHance, dilution 1:10). Rectum probes was inserted for in vivo dosimetry (PTW AM6 diodes, PTW Freiburg, Germany).

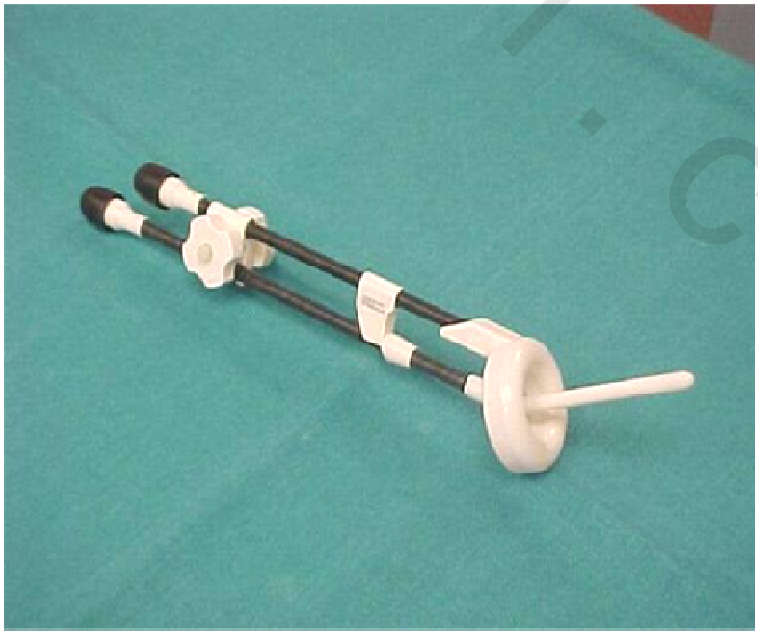


Figure (25): MRI-compatible tandem-ring applicators (Nucletron, Veenendal, The Netherlands)

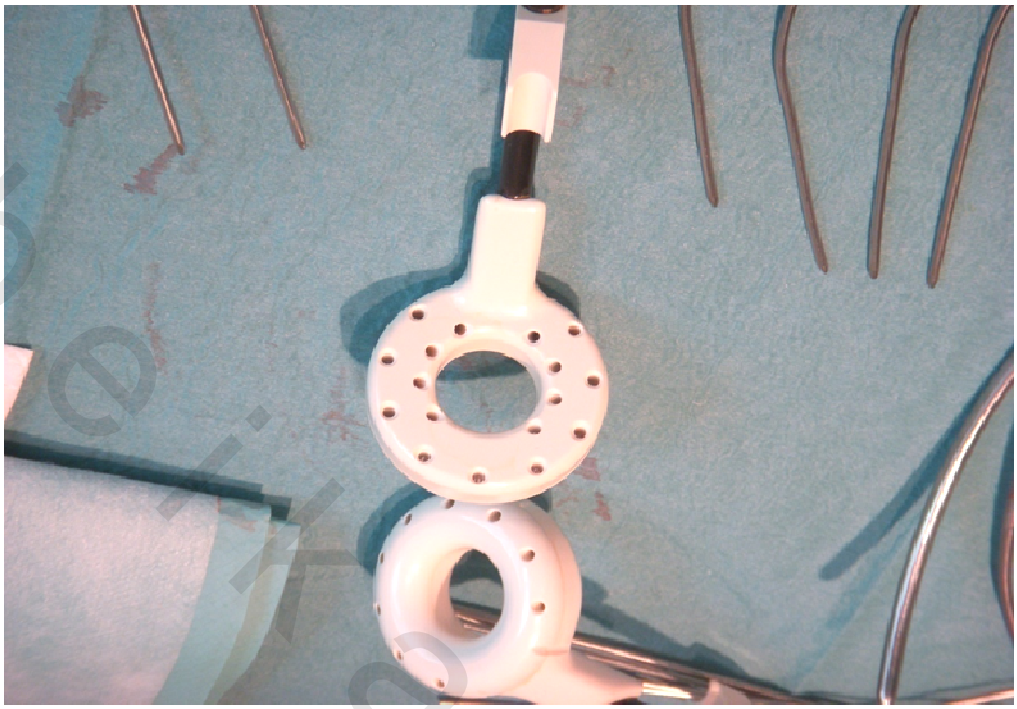


Figure (26): MRI-compatible Vienna I and II applicators (Nucletron, Veenendal, The Netherlands) with holes for interstitial needles.

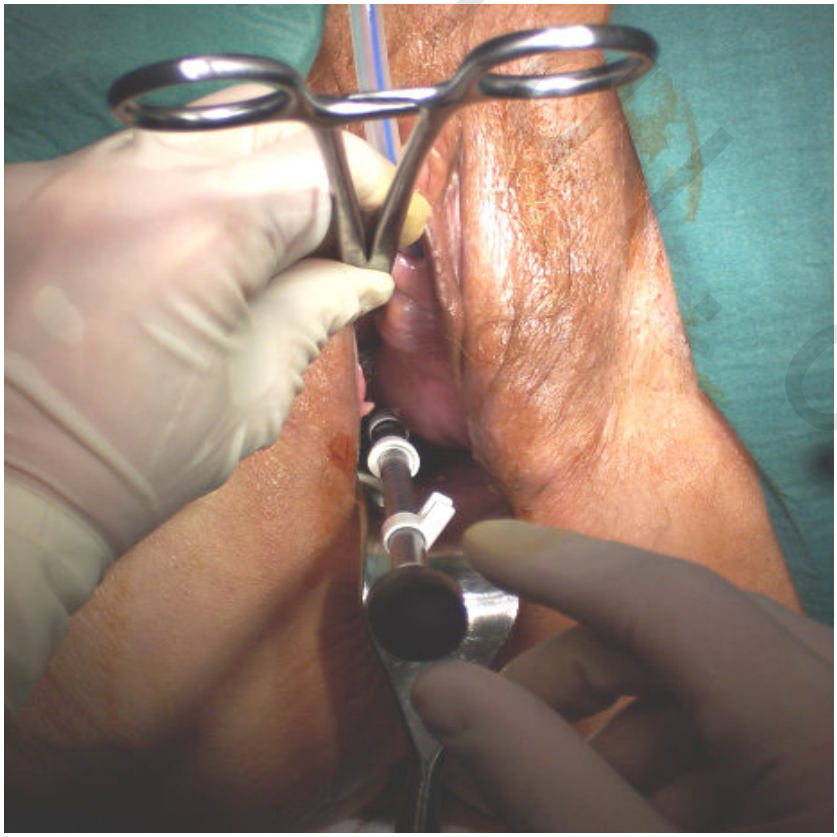


Figure (27): MRI-compatible tandem inserted inside patient.

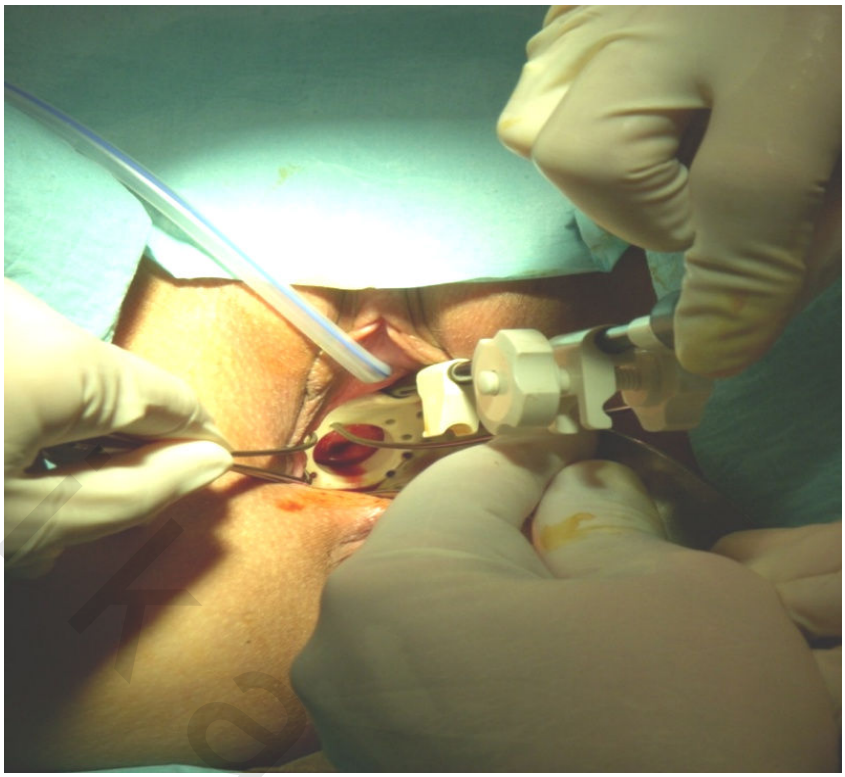


Figure (28): MRI-compatible Vienna II rings with 3 needles inserted inside patient.

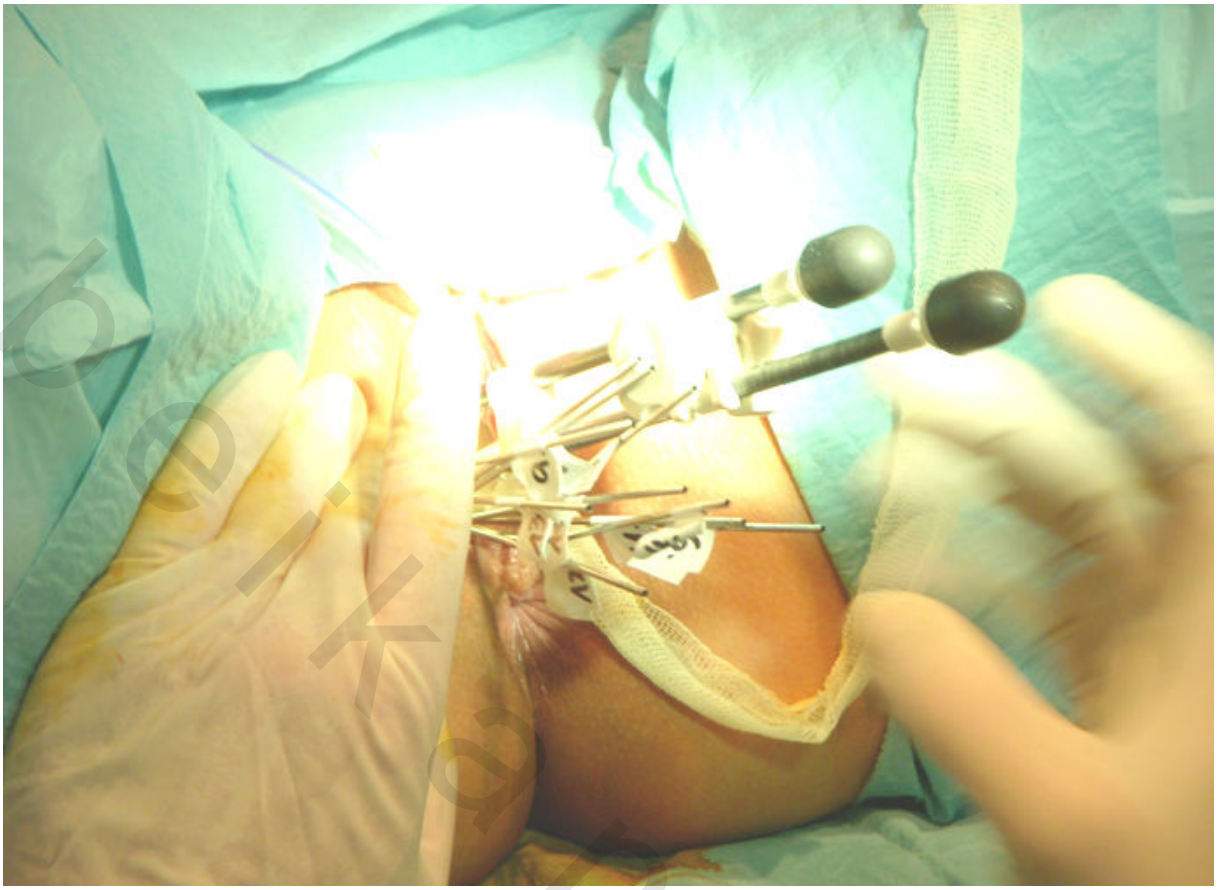


Figure (29): MRI-compatible Vienna II rings with 9 needles inserted inside patient.

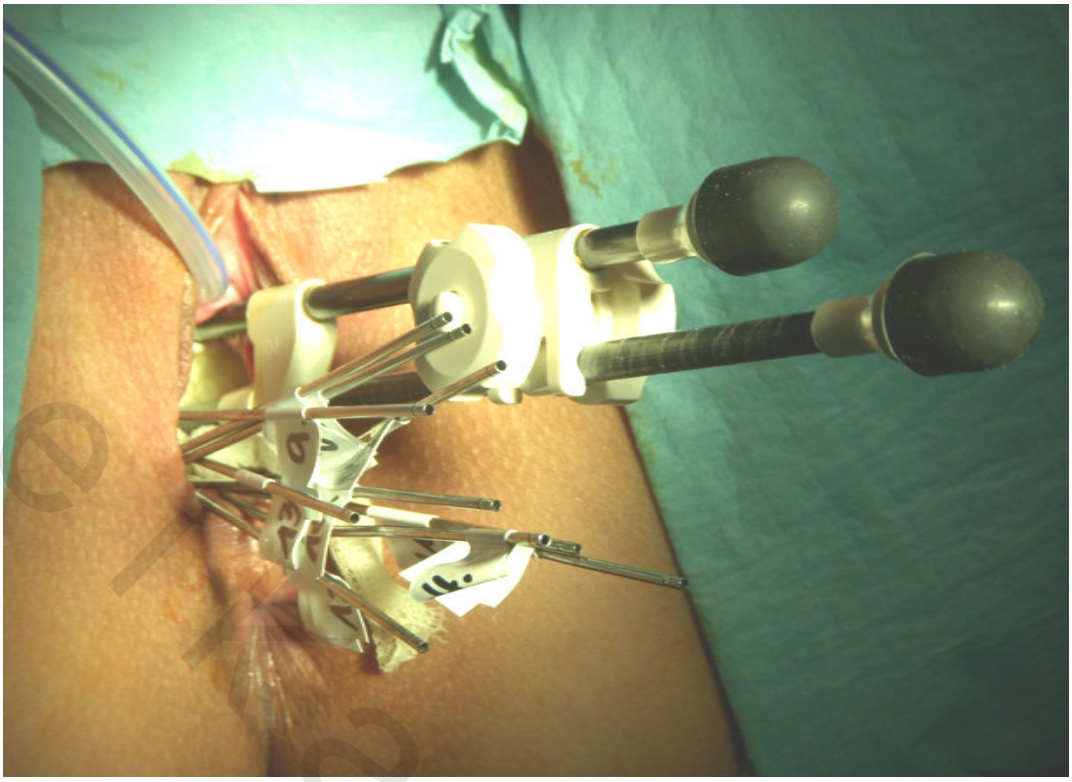


Figure (30): The same patient with MRI-compatible Vienna II rings with 9 needles after complete packing of vagina.

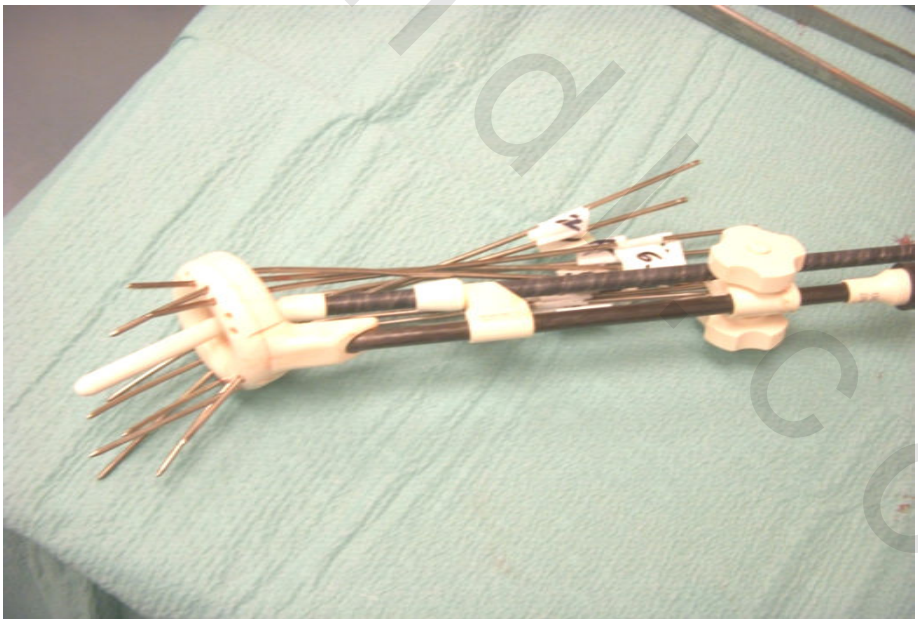


Figure (31): MRI-compatible Vienna II rings with 9 needles after removal from patient.

3- Imaging (X-ray imaging, MRI):-

After application was performed, the X-ray images were taken with the patient in the supine position in the AP and lateral directions with a reconstruction jig. The patient was then transferred from the operating room to the MRI scanner that is located in the proximity of operating room.

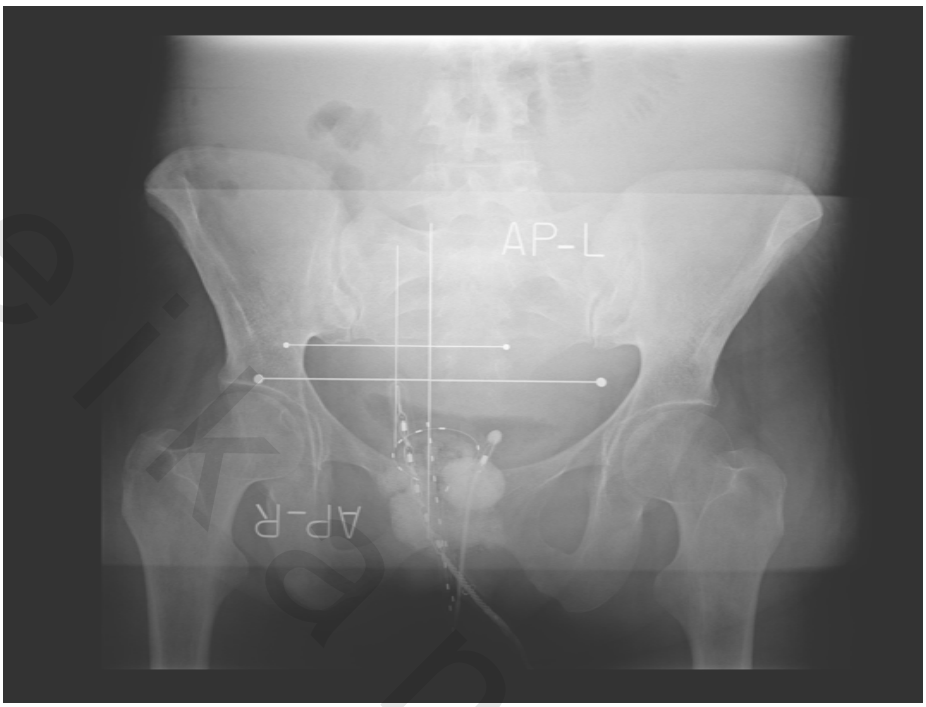


Figure (32): AP- X-ray image for patient with BT applicator in place

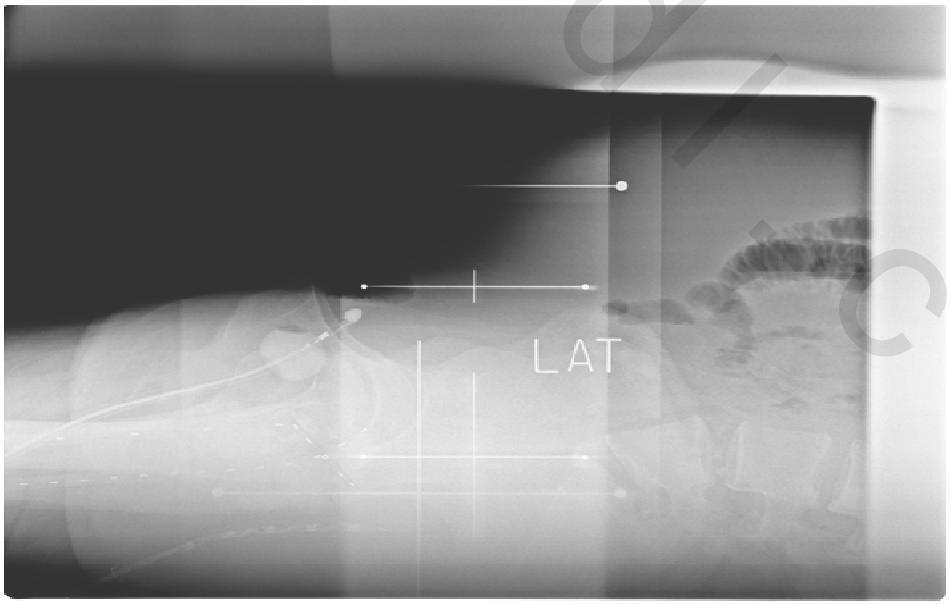


Figure (33): Lat view of X-ray image for patient with BT applicator in place

MRI technique

Magnetic resonance imaging was obtained for every patient, at the time of first (1 fraction) and second (3 fraction) brachytherapy application in every patient, and before 2 and 4 fractions. All patients underwent MR Imaging with a 0.2 tesla low field system (open MRI Magnetom OpenViva 0.2T, Siemens AG, Erlangen, Germany) with applicator in place by use of a pelvic surface coil. Fast spin echo T2-weighted images (TE 96 s, TR 4500 s) were generated with patient in the supine position in a transverse orientation (perpendicular to the body axis) and in parasagittal, paracoronal (parallel to the intrauterine applicator tube), and par-transverse orientation (parallel to the ring). The slice thickness was 5 mm without an intersection gap.

Brachytherapy was performed with a MRI-compatible (Stockholm based) tandem-ring applicator (Nucletron) and, in locally advanced disease, with additional interstitial needles. A foley catheter was inserted and the balloon filled with 7 cm3 of diluted gadoteridol (dilution, 1:1). Vaginal packing impregnated with diluted gadoteridol (dilution, 1:10) to fix the applicator and to displace the rectum and bladder from the ring was used. A plastic rectal probe (diameter, 10 mm) was inserted. Applicator, vaginal packing, bladder balloon, and rectal probe were displayed with low signal intensity on T2-weighted images.

Axial images were obtained from the level above the uterine fundus to the inferior border of the symphysis pubis below any vaginal tumor extension; sagittal images were obtained between internal obturator muscles. Coronal, paracoronal and para-axial images included the tumor, entire cervix, corpus uteri, parametria, and vagina.

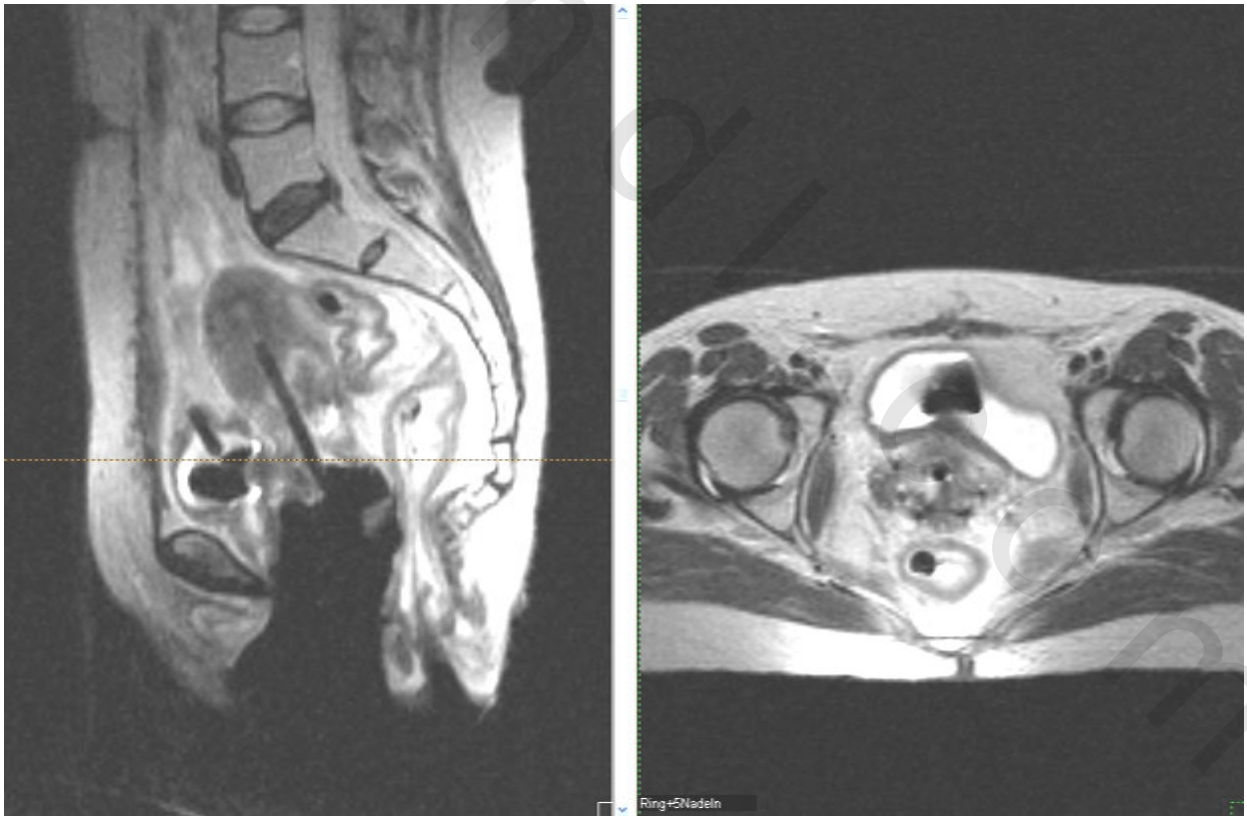


Figure (34): MRI image (sagital and transverse view) for patient with stage IIIB at time of BT application with Vienna I applicator with 5 interstitial needles.

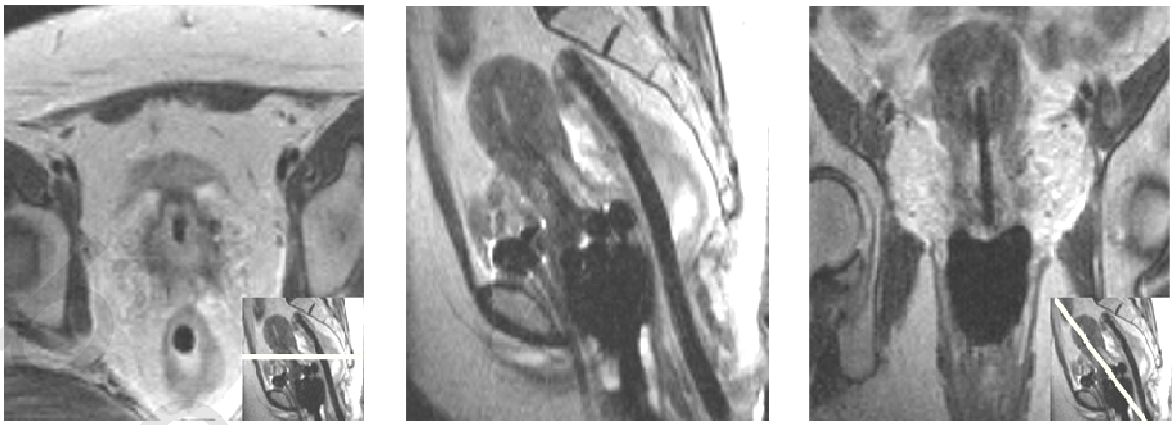


Figure (35): Transverse, sagital and Coronal MRI Views for patient with stage IIB at time of BT application with tandem (60) and ring (30).

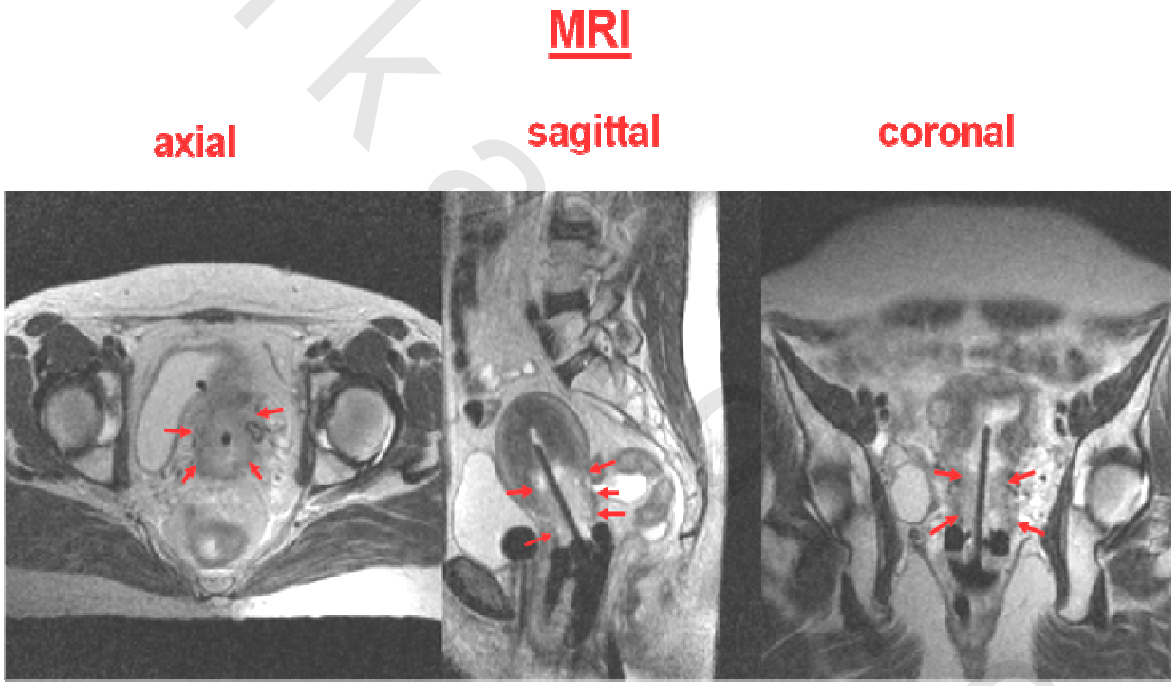


Figure (36): MRI image (sagital and transverse view) at time of brachytherapy with residual invasion of Left parametrium.

4- 3D reconstruction:

Applicator surface reconstruction on MRI images was performed using the 3D library applicator implemented in planning system, OncentraGYN (version 0.9.15 Nucletron, Veenendaal, The Netherlands), as the outer dimensions in relation to the source path of all Vienna ring types were implemented in the system configuration (SoftIntgrDirect) and displayed on each image orientation. As a first step, the location of the applicator was defined using registration points: tip of tandem and centre of ring in the original images (slice mode).

By defining the tip of tandem and the center of the ring, the model was placed on 3D MRI dataset. fine turning was done manually by shifting and rotating the whole applicator. In the ring part of applicator holes for the interstitisl needles could be used as additional markers to define the correct applicator rotation on MRI, as they produce high intensity signals on the MRI due to their filling with blood or fluids. For accurate representation of the actual source path in the ring, a modified circular source path in the treatment planning software was implemented, which fits best for the dwell positions which are most relevant for clinical standard loading pattern. Also verification of this source with radiographs was done. The tandem tip, ring center, tip of the rectal probe, and tip of the bladder probe, which have to be identified on X-ray images and MRI, were always used as marking points for image fusion.

In addition, bony reference points (e.g., most cranial point of acetabulum) were taken. The ICRU points for the bladder, rectum, pelvic wall, and the lymphatic trapezoid were digitized using the ICRU Report 38 recommendations when defining them on AP and lateral radiographs.

MRI based reconstruction of needles was done by selecting the position of the guiding hole built into applicator model and marking the corresponding position of needle tip on the image. small manual adjustments had to be made in case if a needle was bent, so its source path clearly deviated from a straight line.

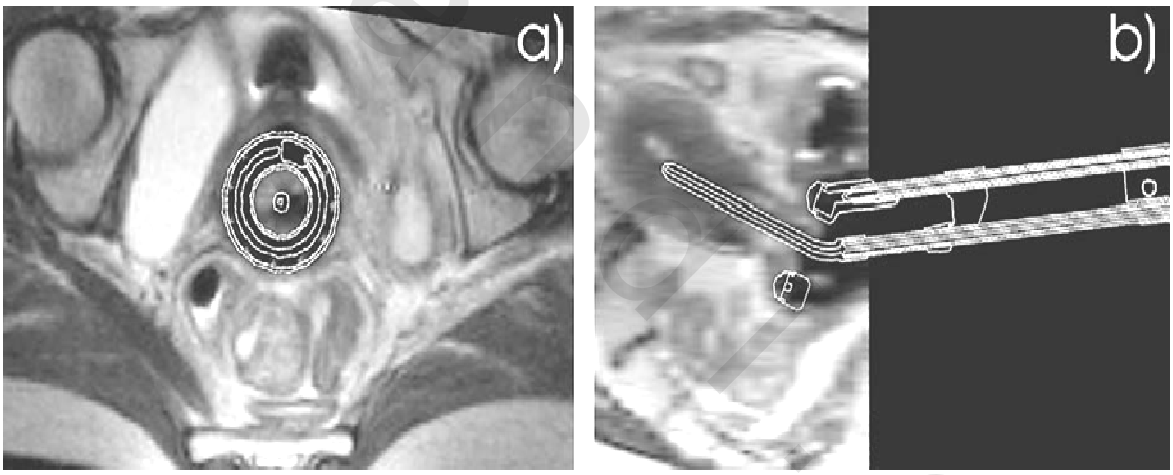


Figure (37): Screen capture taken from the treatment planning system OncentraGYN depicting the software-integrated applied applicator reconstruction on a) paratransverse and b) para-sagittal view.

5- Contouring of OARs and CTV:-

Transverse MRI data were directly transferred to the treatment planning system, OncentraGYN (version 0.9.15 Nucletron, Veenendaal, The Netherlands) via a network connection. Bowel preparation was performed to achieve an empty sigmoid and rectum. The bladder was emptied by opening the urinary catheter and was then filled with 50 mL of saline for both MRI and BT. The limited filling status (50–100 mL) led to a significant distance between the anterior and posterior bladder wall (several centimeters) and usually did not expand the laterodorsal bladder recesses (high-dose parametrial region). The outer organ contours were delineated.

For the rectum, the delineation included all parts from the anorectal junction to the recto-sigmoid flexure. For the sigmoid, it started from this flexure and ended when sigma was far from the uterus or parametria (much greater, but at least 2 cm). The small bowel was only delineated if visible within 2 cm from the uterus. The outer contour of the bladder was delineated if visible. The bladder, rectum, sigma, GTV, IR-CTV and high-risk CTV were delineated directly after image data import.

For contouring, the high-risk CTV, all MRI information was available as hard copy (at diagnosis and BT) and soft copy also, and all clinical information was available as schematic drawings with tumor topography and dimensions and written reports. The CTV was defined as high-risk CTV in accordance with what has been proposed by the Gynecologic GEC ESTRO working group.[117,118]

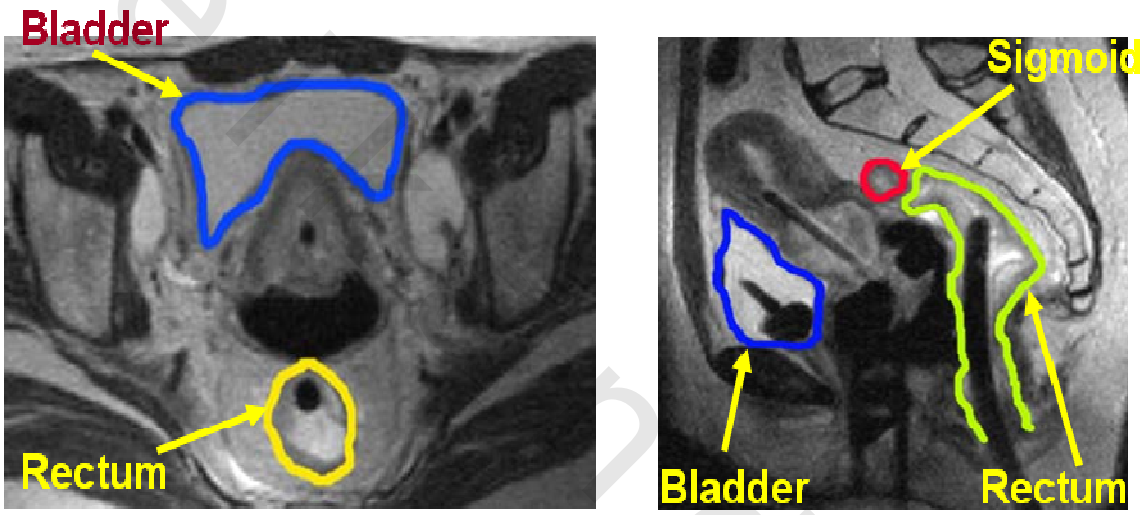


Figure (38): MRI image (Transverse and Sagital views) for patient with cancer cervix at time of BT illustrated the contour of OAR (bladder, rectum and sigmoid).

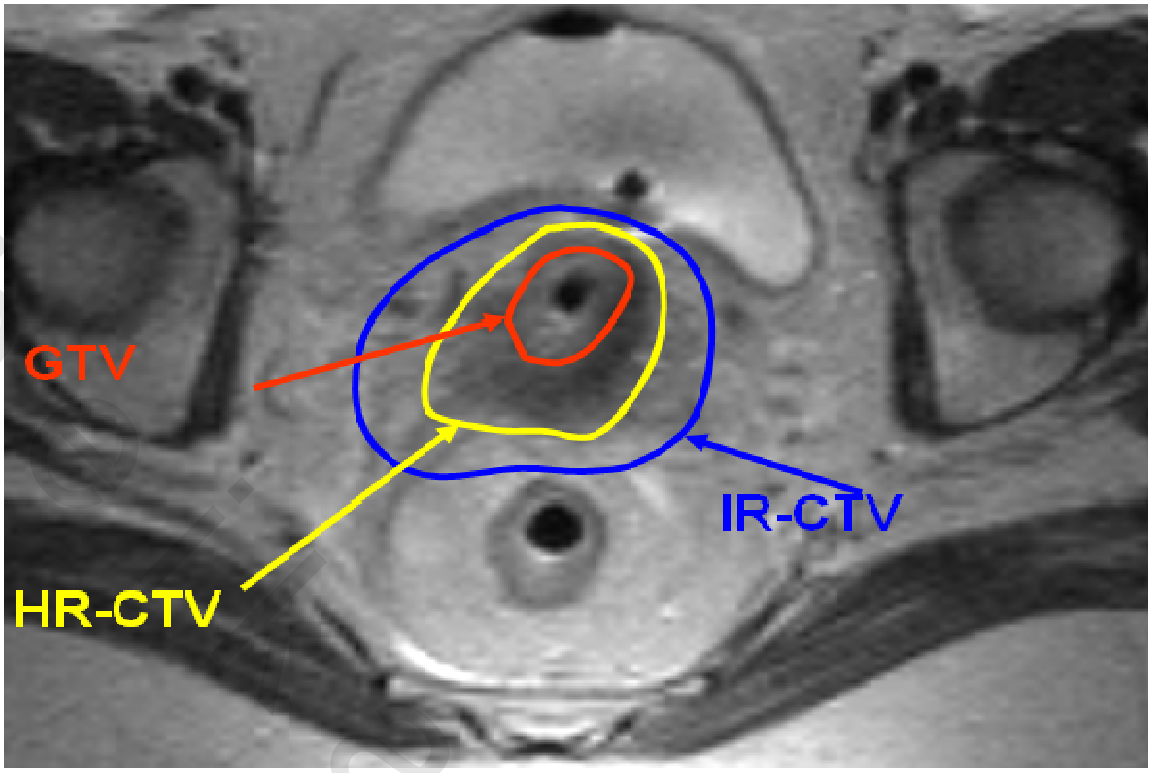


Figure (39): Transverse MRI image at time of BT for patients with stage II cervical cancer illustrated the contour of GTV; HR CTV and IR CTV.

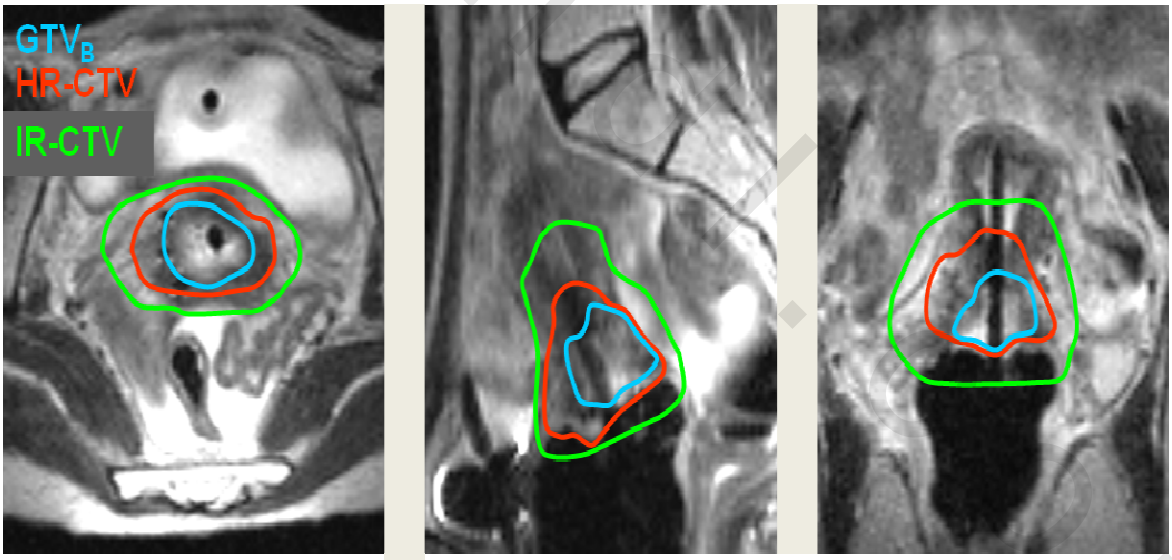


Figure (40): MRI image(Transverse; coronal and Sagital views) for patient with cancer cervix at time of BT illustrated the contour of GTV; HR CTV and IR CTV.

6- Treatment planning

After the reconstruction of the applicator, all treatment plans were computed with oncenter GYN (Nucleatron, veenendael, V1.2.1 -1.2.3) tretment planing system (TPS). A standard loading pattern was automatically defined with 2, 7 (or 6), and 8 dwell positions for the 20, 40, and 60-mm tandem and four dwell positions on each lateral side of the ring (Table 3).

Table (3): Standard loading pattern for mostly used applicator combinations.

Applicator	Active dwell positions (2.5-mm stepsize)
Ring nominal diameter (mm)	
26	4, 6, 8, 10 & 21, 23, 25, 27
30	5, 7, 9, 11 & 24, 26, 28, 30
34	7, 9, 11, 13 & 28, 30, 32, 34
Tandem nominal length (mm)	
20*	1, 4
40	1, 3, 5, 7, 10, 13, 16†
60	1, 3, 5, 7, 10, 13, 16, 20

* If using this tandem length, the ring dwell weights should be decreased to 30%.
† Not used with ring diameter 26 mm.

Point A was defined by relating the applicator at 20 mm from the ring surface parallel to the tandem and 20 mm from the center of the tandem. The dose distribution resulting from the standard plan was evaluated by visual inspection of the isodoses with respect to the OARs and HR-CTV.

The manual dwell times optimization was performed taking into account the protocol based dose constraints. Depending on the tumor and organ anatomy, the adjustments were repeated until the dose and volume constraints were fulfilled as closely as possible. The following adjustments were applied regularly:

1- Shift of specification point/change of point A dose: Points at the level of point A were used to normalize the dose to a distance different from 20 mm (range, 14–24 mm) to the tandem to increase or decrease the total treated volume. In some rare cases, these normalization points were set in planes more caudal to the plane of point A. The change of the specification point was directly related to a change of the dose to point A (range, 4.5–10 Gy). This modification resulted in a symmetrically modified pear-shaped isodose.

2- Asymmetric pear shape: The dose was normalized to points in different distances on both lateral sides (different point A dose) and dwell time weighting was different between ring positions on left and right side.

3- Change of loading pattern: To account for asymmetric ring orientation, asymmetric tumor extension, or unfavorable topography of the bladder or rectum, the dwell positions were shifted, added, or skipped within the ring. If sparing of a sigma loop cranially to the tandem was necessary, dwell positions were skipped at the tip of the tandem.

4- Individual dwell time weighting: The fine tuning of dose optimization was performed by changing the dwell time weighting for individual dwell positions. In the case of an asymmetric pear shape, dwell time weighting between the ring positions on both lateral sides was necessary. In most cases, the dwell time was changed for the ring positions and positions at the tandem tip. However, sometimes it was necessary to weight dwell positions in the middle of the active tandem positions to shape the isodoses according to the specific topography.

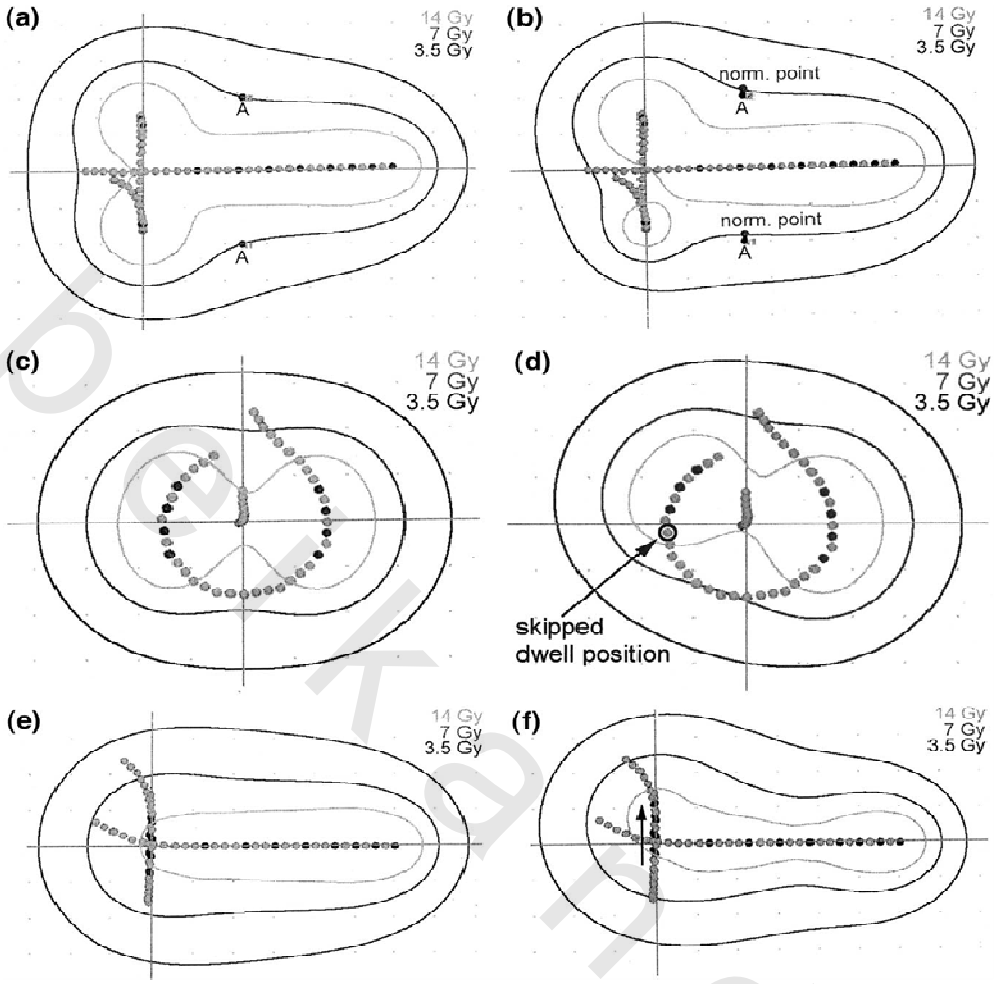


Figure (41): Dose distributions for standard and optimized loading patterns (ring diameter 30 mm, tandem length 60 mm) showing 14 Gy (light gray), 7 Gy, and 3.5 Gy (dark gray) isodose. In the case of the standard regimen of 45 Gy external beam radiotherapy plus 47 Gy brachytherapy, 7-Gy isodose encompasses the 85-Gy reference volume and the 3.5-Gy isodose, 60-Gy reference volume. The active dwell positions are dark colored. **(a)** Coronal view of the standard loading pattern and dose distribution with 7 Gy symmetrically to point A. **(b)** Asymmetric dose distribution with normalization point at level of point A 22 mm to right, 18 mm to left, and 30% dwell time weighting for the left dwell positions in ring. Dose to point A right was 7.6 Gy and left Point A dose was decreased to 6.3 Gy. **(c)** Axial view of standard loading pattern with four active dwell positions on each lateral side of ring. **(d)** Typical loading pattern modification for rectum sparing. Active dwell position on left shifted to the ventral part, skipping most of the dorsal position. **(e)** Sagittal view of standard loading pattern. **(f)** Optimized dose distribution with active dwell positions in ring shifted to ventral part (black arrow). Dwell weights for positions in tandem starting from tip were 100%, 100%, 65%, 40%, 30%, 30%, 65%, and 100%.

EBRT combined with BT

External beam radiotherapy was performed from the start of treatment with a linear accelerator with a 3D conformal four-field box technique or IMRT technique. A total dose of 45 Gy (40–60 Gy) at the ICRU 50 point was given in five fractions of 1.8 Gy (range, 1.6–2 Gy) weekly for advanced disease with simultaneous cisplatin (40 mg/m2) on Days 1, 8, 15, 22, and 29.

To calculate the dose from combined EBRT and BT, it was assumed that the entire high-risk CTV of BT and regions of interest in the OARs received 100% of the prescribed EBRT dose. The dose per fraction and total dose: physical dose and biologically weighted dose The dose per fraction from BT is given in terms of the physical dose. The total dose, combining EBRT and BT, was always normalized to the conventional 2 Gy/fraction using the linear quadratic model for incomplete sublethal damage repair and was sometimes also called the "isoeffective dose." For the GTV, high-risk CTV, prescribed dose (PD), and point A dose, an α/β ratio of 10 Gy was used (3 Gy for OARs).

Dose and volume parameters and constraints

The brachytherapy alone was characterized by the total reference air kerma for each application and as the sum of all fractions for 1 patient. The treated volume should be encompassed by the prescribed dose (PD), independent of any anatomic information and the volume. The dose to point A left, right, and on average was given for each fraction and combined with EBRT. For the GTV and high-risk CTV, the minimal target dose , dose received by at least 90% of volume (D90), and volume treated with at least the PD (V100) was evaluated using the DVH function of the EVAL module with 100,000 points.

Dose to HR CTV was evaluated in terms of dose covering 90% of the HR CTV (D90). Prescribed dose was 4 fractions of 7 Gy at high dose rate (HDR) in advanced disease corresponding to a prescribed dose of 80–85 Gy EQD2.

For the bladder, rectum, and sigma contours, the minimal dose values received by the most irradiated 0.1 cm3, 1 cm3, and 2 cm3 were determined from the cumulative DVHs. Volumes are reported as the average values based on each fraction of 1 patient.

Dose volume constraints for OAR were 75 Gy EQD2 as minimum dose in the most exposed tissue (2 cm3) of rectum and sigmoid and 90 Gy EQD2 in 2 cm3 of the bladder. No dose volume constraints were applied for the vagina. (118) The dose and target coverage were adapted according to dose volume constraints for OAR. If appropriate and feasible, dose was escalated, in particular in advanced disease.

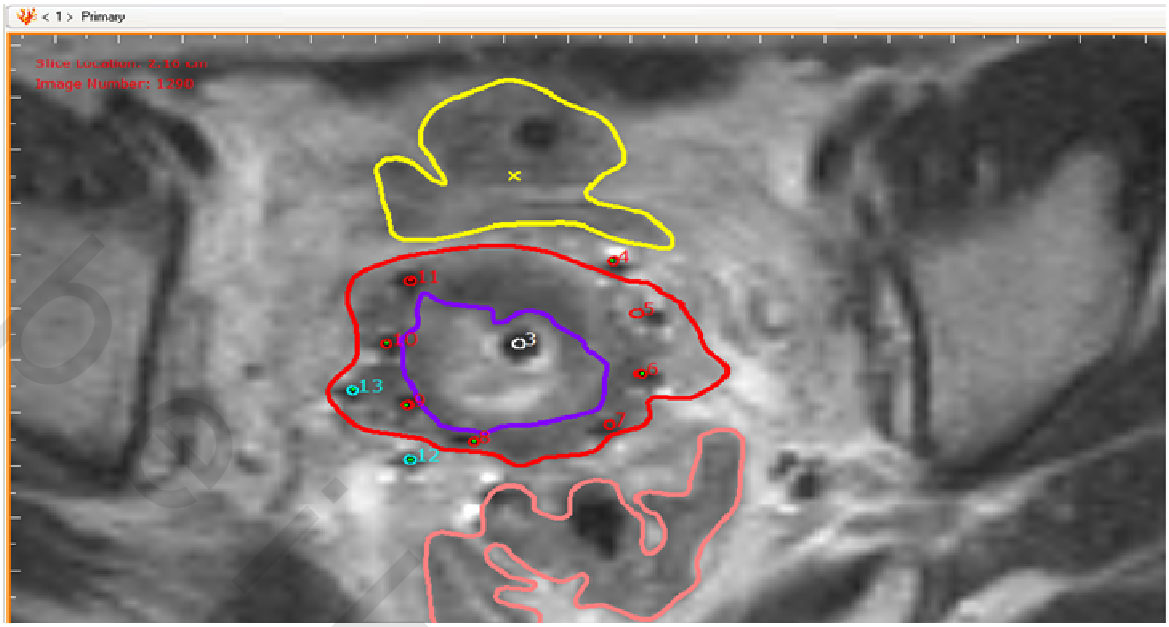


Figure (42): Transverse MRI image at time of BT for patients with stage IIIB cervical cancer illustrated the contour of GTV; HR CTV, Bladder and Sigmoid.

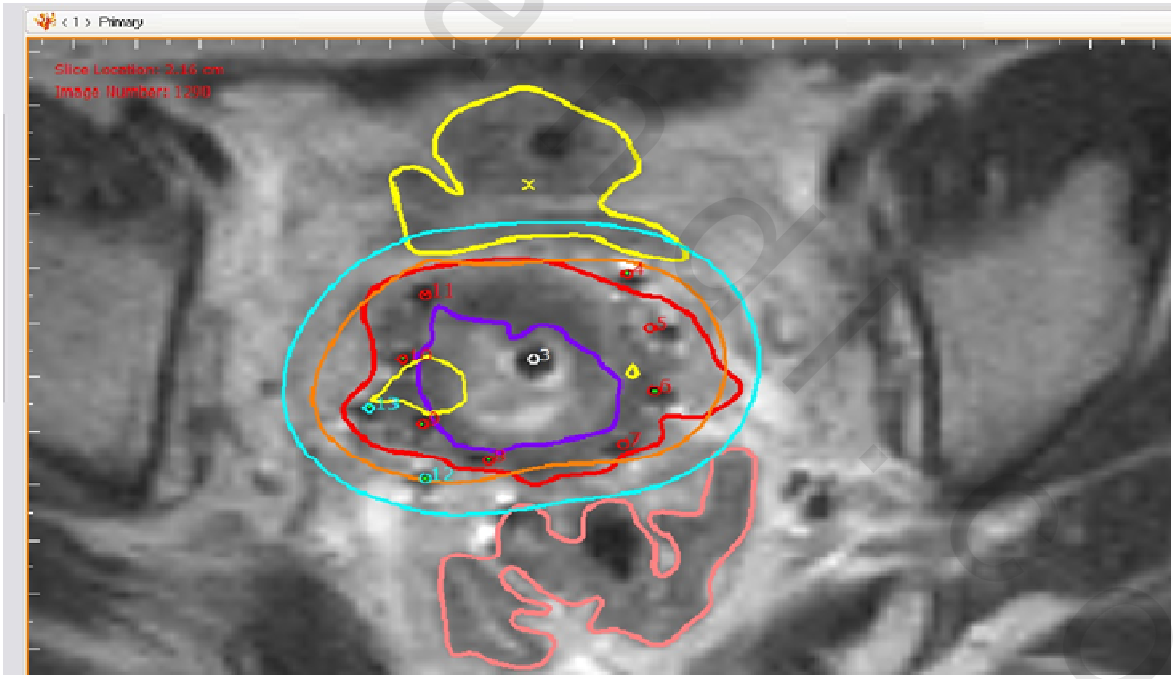


Figure (43): Transverse MRI image at time of BT for patients with stage IIIB cervical cancer illustrated isodose of 7 Gy covered HR CTV.

Group B (imaging group)

This group included 15 female patients with locally advanced cervical cancer. Fifteen cervix cancer patients were retrospectively selected out of the overall patient cohort on the basis of availability of both CT and MRI with applicator in place and full 3D documentation (cartoon drawings) representing the clinical gynaecological examination. These patients belong to a larger cohort of cervical cancer patients planned, treated and followed up in a prospective manner based on a protocol used at the Radiotherapy Department of the Medical University of Vienna. [122]

All patients underwent pelvic EBRT using a four-field box technique with CT-based treatment planning. Concurrent weekly cisplatin chemotherapy at 40 mg/m2 was administered. After completing EBRT, patients underwent HDR brachytherapy with a CT/MRI-compatible applicator (Nucletron Systems, Veenendaal, The Netherlands) with a tandem length of 40 or 60 mm, curvature of 45° or 60°, and a ring diameter of 24, 30, or 36 mm. Patients receiving HDR 192Ir brachytherapy were treated with a Nucletron HDR microSelectron in the brachytherapy suite.

CT and MRI technique

All patients underwent both CT and MRI at brachytherapy with the tandem and ring applicator in place. The MRI unit at the Medical University of Vienna was a 0.2-Tesla Magnetom Open (Siemens, Open-Viva, Erlangen, Germany). MRI was performed with a pelvic surface coil. The applicator, vaginal packing, bladder balloon, and rectal probe were displayed with low-signal intensity on T2-weighted images.

The CT scanner at the Medical University of Vienna was a conventional scanner, the Somatom Plus S (Siemens, Erlangen, Germany). The CT images at brachytherapy were generated in 4-mm slice intervals from the iliac crest to the ischial tuberosities without intravenous contrast. The axial images were obtained from the level above the uterine fundus to the inferior border of the symphysis pubis below any vaginal tumor extension; sagittal images were obtained between the internal obturator muscles.

Contouring and brachytherapy treatment planning

Axial T2-weighted MRI studies taken after brachytherapy applicator placement were contoured in accordance with the GEC-ESTRO recommendations. [117] The GTV was determined as the macroscopic extent of the tumor at brachytherapy, as represented by high-signal-intensity masses on MRI.

The MRI defined HR-CTV (HR-CTVMRI) included the entire cervix and the macroscopic extent of the tumor at brachytherapy plus any pathologic residual tissue in the parametria, uterine corpus, rectum, bladder, and/or vagina. The MRI-defined IR-CTVMRI encompassed the tumor extension at diagnosis or a 1-cm margin around the HR-CTVMRI.

Delineation of the outer wall of the OARs was according to the GEC-ESTRO protocol. The target tissue (HR-CTVCT, IR-CTVCT), bladder, sigmoid, and rectum were contoured on MRI and CT separately.

CT contours of the HR-CTVCT and IR-CTVCT were contoured. The GTV could not be defined on CT, because tumor tissue has the same signal intensity as normal cervical tissue. CT HR CTV volumes were contoured on CT with integration of information from 3D-documentation of precise clinical gynecological examination (CGE) at the time of BT. For stage IB the entire cervix seen on CT with dimensions comparable to CGE was contoured. In IIB, CT HR CTV encompassed cervix and residual parametrial extension according to dimensions and location identified by CGE. For IIIA , HR CTV included cervix, involved parametria and vagina at the time of BT. In IIIB, HR CTV included the entire cervix, and residual parametrial disease as described in the clinical drawings.

The CT contours of the tumor and bladder, rectum, and sigmoid were delineated using Oncentra Masterplan (Nucletron). No contrast was used in this study. Contours of the rectum began 1 cm above the anus, ended at the sigmoid flexure, and covered the outer wall of the organ. The sigmoid was considered to begin at the level of the rectosigmoid flexure and ended at the anterior crossing of the sigmoid by the pubic symphysis. The bladder contour included the outer wall of the bladder and ended at the beginning of the urethra.

The CT and MRI volumes were fused using the anatomy modeling tool of Oncentra Masterplan (Nucletron). Two fusion protocols available in this software system were applied: automatic fusion using mutual registration, and manual fusion using landmarks. The landmarks included the tip of the tandem, center of the ring, tip of bladder, and rectal probes. This fusion method was assessed qualitatively by comparing the location of the applicator. The fusion with the best agreement between data sets was chosen for additional analysis.

After reconstruction of the applicator, an optimized treatment plan was created for the MRI and CT data sets. Dose– volume histograms (DVHs) were evaluated for the bladder, rectum, sigmoid, and tumor. The dose received by at least 90% of the volume (D90) was calculated from the cumulative DVHs. The dose values are reported in the dose/HDR fraction.

The volume, width, and thickness of HR CTV of the CT and MRI contours were analyzed. For comparison between the different contouring modalities, a two-sided paired t test was performed. P values 0.05 were considered significant.

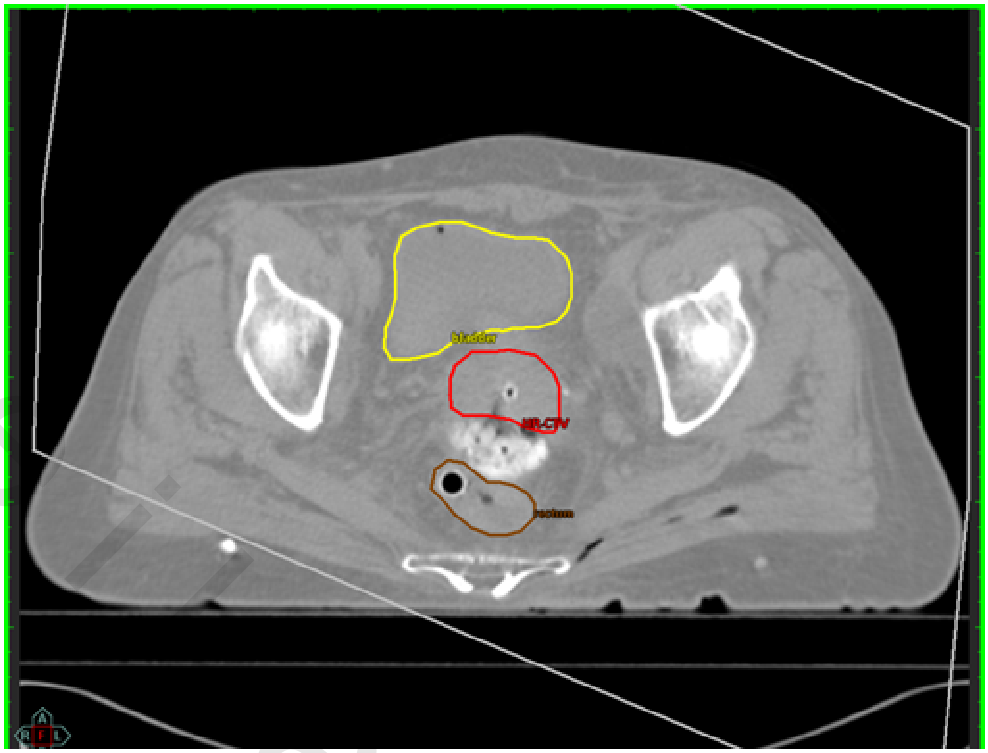


Figure (44): Transverse CT images with ring and tandem in place illustrated contouring of CT HRCTV, bladder and rectum.

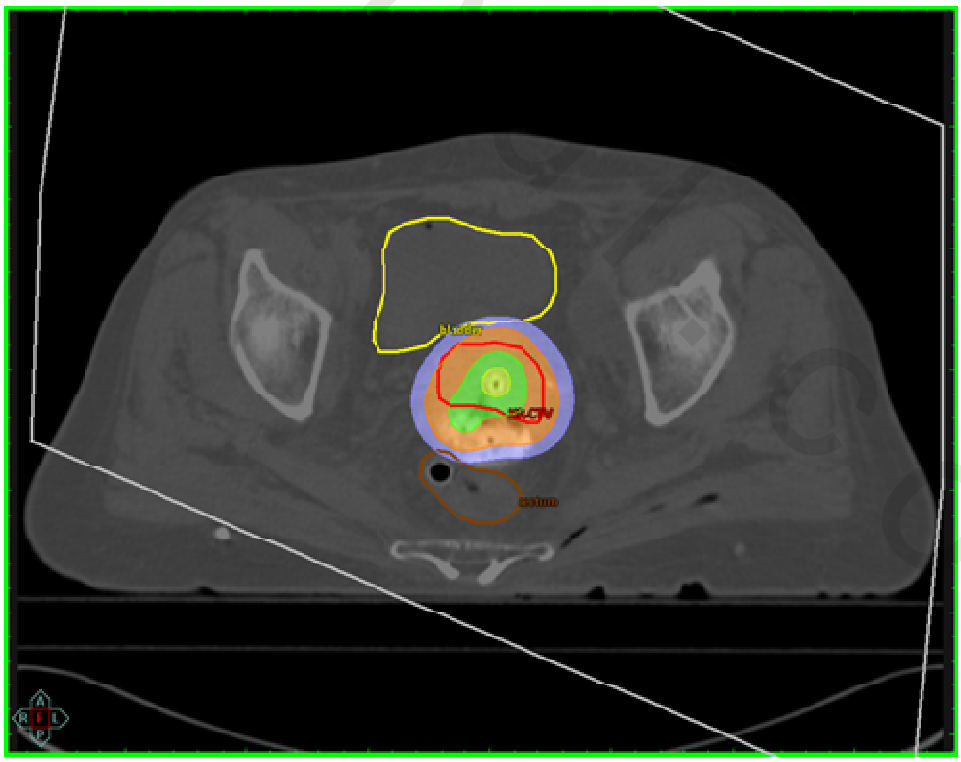


Figure (45): Transverse CT images with ring and tandem in place demonstrated isodose converge of HR CTVCT.

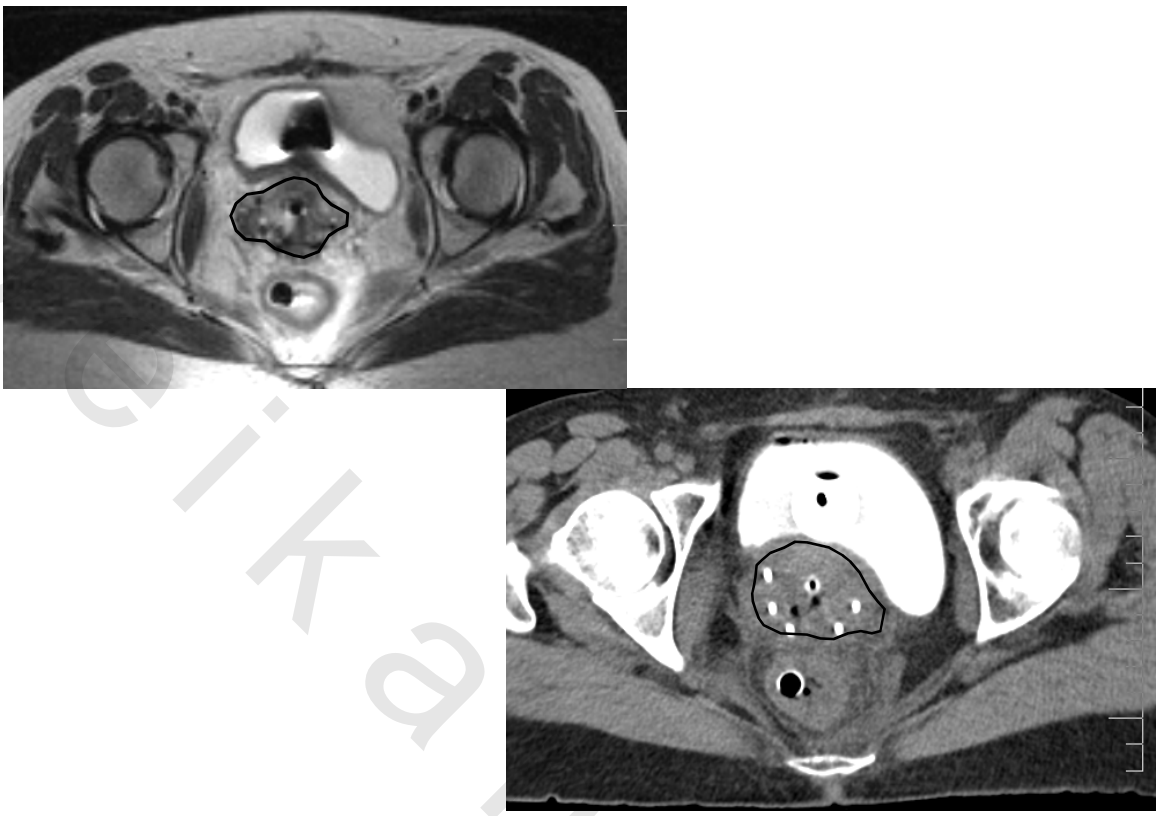


Figure (46): Comparison between HR CTVMRI and HR CTVCT for the same patient.

Statistical analysis

The patient and tumor characteristics for the IMRT and conformal groups were compared using a Chi-square test. The recurrence and survival risk, as well as acute and late GIT and GU toxicity for the IMRT and conformal groups were evaluated using Chi-square analysis. SPSS software (SPSS, Chicago, IL) for all statistical analyses was used and adopted 5% as a significance level for the statistical test. A value of $p < 0.05$ was set as the threshold for significance for all study outcomes. The Kaplan-Meier (product–limit) method was used to derive estimates of survival based on total sample size.

RESULTS

The present study included 45 patients with locally advanced (stage IB-IIIB) non metastatic cervical cancer presented to the department of Radiotherapy, Vienna Medical University. The patients in the study were divided into two groups.

Group A (Therapeutic group):

This group included 30 female patients selected prospectively during the period starting from January 2011till March 2012. on basis of availability of inclusion criteria. They were subdivided into two subgroups according to the type of EBRT modality:

Group A1: included 15 patients with locally advanced cervical cancer and were treated with 3D-conformal whole pelvis radiotherapy then image guided high dose rate (HDR) brachytherapy.

Group A2: included 15 patients with locally advanced cervical cancer and were treated with intensity modulated whole pelvis radiotherapy then image guided HDR brachytherapy.

Group B (Imaging group):

This group included 15 female patients with locally advanced cervical cancer.
Fifteen cervix cancer patients were retrospectively selected out of the overall patient cohort on the basis of availability of both CT and MRI with applicator in place and full 3D documentation.

Group A (Therapeutic group)

A- Patient Characteristics:-

1- Age:

Table (4) shows age distribution in the two groups. In the whole series, the age ranged from 35 to 84 years. The mean age was 57.67 , and 54.20 in group A1 and group A2 respectively.

The two groups were comparable as regards the age without any statistical significant difference (P value = 0.11).

Table (4): Comparison between the two studied groups regarding age.

	Conformal (n = 15)	IMRT (n = 15)	t	P
Age				
Min. – Max.	35.0 – 74.0	36.0 -84.0		
Mean ± SD	57.67 ± 13.68	54.20 ± 14.53	0.673	0.507
Median	63.0	51.0		

t: Student t-test

2 - Marital status:

Regarding the marital status, the two groups were comparable without any statistical significant difference between group A1 and A2 (P value = 0.304).

3 - Parity:

In this study, the gravidity ranged in group A1 from 0-3, and in group A2 from 0-4, while the parity ranged in group A1 from 0-5 and in group A2 from 0-5. There was no statistical significant difference between the two studied groups as regards to the gravidity (P value=0.40) and parity (P value = 0.45).

4- Karnofsky performance state:-

The patients in two groups had good Karnofsky performance state ranged from 90-100% except two patient in group A1 and one in group A2 had Karnofsky performance state 80%.

B- Disease characteristics:

1. FIGO Staging:

Most of the patients included in group A had tumor stage IIB; ten patients in each group A1 and A2 had tumor stage IIB. There was no statistical significant difference between the two treated groups regarding the FIGO stage of primary tumor (P value= 0.59).

Table (5): Comparison between the two studied groups regarding the FIGO staging:

	Conformal (n = 15)		IMRT (n = 15)		Test of sig.	P
	No.	%	No.	%		
FIGO Staging						
Ib	1	6.7	1	6.7		
IIa	1	6.7	2	13.3		
IIb	10	66.7	10	66.7	Z = 0.544	0.586
IIIa	1	6.7	0	0.0		
IIIb	2	13.4	2	13.4		

X2: Chi square test
FE: Fisher Exact test
Z: Z for Mann Whitney test

2. lymph node (LN) status:

In group A1 five patients had positive lymph node while in group A2; 6 patients had positive lymph node. There was no statistical significant difference between the two groups. The assessment of lymph node status was done by laparoscopic staging for all patients and LN sampling (figure 47).

Table (6): Comparison between the studied groups according to LN status

	Conformal (n = 15)		IMRT (n = 15)		Test of sig.	P
	No.	%	No.	%		
LN status						
Negative	10	66.7	9	60.0	$\chi^2 = 0.144$	0.705
Positive	5	33.3	6	40.0		
Lymph node site						
No	10	66.7	9	60.0		
Pelvic LN	4	33.3	4	33.3		
Paraortic LN	1	6.7	2	13.3		

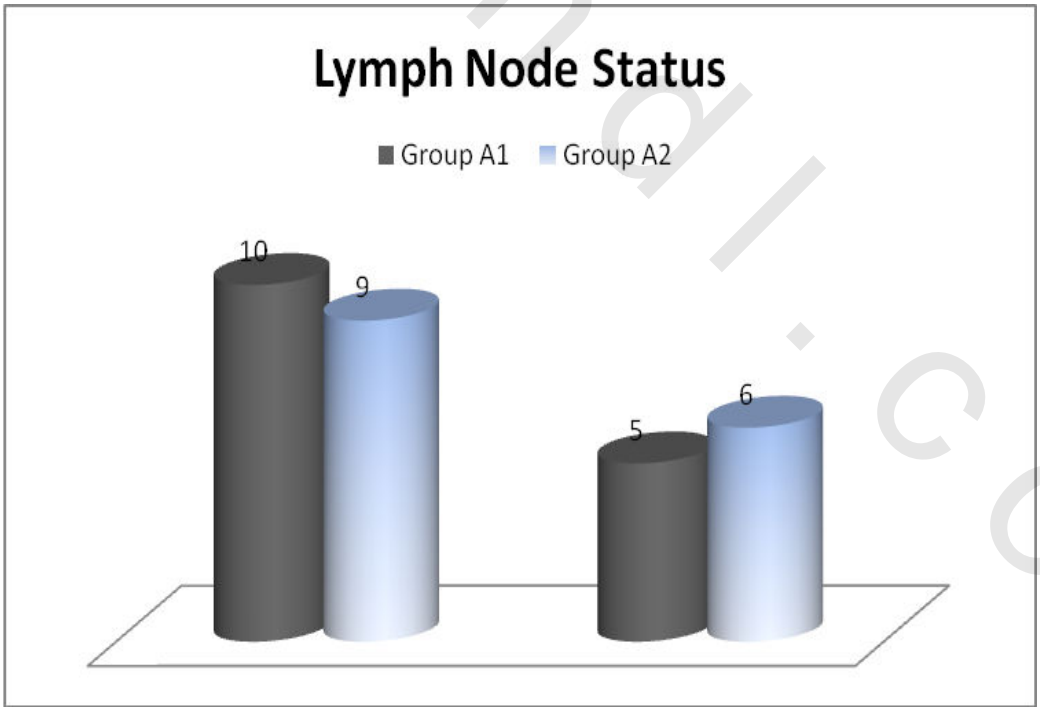


Figure (47): Comparison between groupA1 and GroupA2 regarding LN status.

3. The Site of parametrium infiltration:

The groups were comparable as regards the site of parametrium infiltration (P value = 0.88). The distal parts of parametrium were infiltrated in most of patients in group A1 (10 patients) and group A2 (9 patients) (table 7).

Table (7): Comparison between the studied groups according to tumor location

	Conformal (n = 15)		**IMRT (n = 15)**		**Test of sig**	**p**
	No.	**%**	**No.**	**%**		
Site of Parametrium infiltration						
No Infiltration	1	6.7	1	6.7	χ^2 = 0.690	^{MC}p= 1.000
Proximal	2	13.3	2	13.3		
Middle	2	13.3	3	20.0		
Distal	10	66.7	9	60.0		
Infiltration of Vagina						
No	6	40.0	8	53.3	χ^2 = 1.068	^{MC}p= 0.876
Upper 1/3	8	46.7	7	33.3		
Middle 1/3	0	0	0	0		
Lower 1/3	1	6.7	0	0		

4. Histopathological type

Squamous cell carcinoma was the most frequent type in both groups, where it was detected in 73% and 80% of the pathological specimens in group A1 and group A2 respectively. Three patients from group A1 and one patient from group A2 had adenocarcinoma. No statistical significant difference was found between both groups regarding the histopatholgical type of tumor.

5. Grade:

Regarding the histological grade, group I and II were comparable without any statistical significant difference (P value = 0.26), where in group A1 and A2 eleven patients had grade II tumor.

6. Lymphovascular invasion:

Both groups (group I and II) were comparable without any statistical significant difference (P value = 0.068) as regards the presence or absence of lymphovascular invasion. (Table 8)

Table (8): Comparison between the studied groups according to pathological features

	Conformal (n = 15)		IMRT (n = 15)		Test of sig	p
	No.	%	No.	%		
Histology						
SCC (squamous-cell carcinoma)	11	73.3	12	80.0	$\chi^2 = 1.393$	$^{MC}p = 0.689$
ACC (adenocarcinoma)	3	20.0	1	6.7		
Adenosquamös	1	6.7	2	13.3		
Grading						
G1	1	6.7	2	13.3		
G2	11	73.3	11	73.3	Z = 0.696	0.487
G3	3	20.0	2	13.3		

C- Treatment Results

1-Resulting Dose Volume Histogram in each group:-

The mean radiotherapy dose received by PTV during the whole pelvis radiotherapy were comparable without statistical significant difference between patients in both group A1 and group A2 (P value=0.62).

Regarding the organ at risk, the median of mean bladder radiotherapy dose were significantly higher in group A1 compared to group A2 (p value = <0.001) figure 2. While the median of dose that was received by 10% of bladder, was significantly higher in group A2 compared to A1 (p = 0.049) table 9.

Table (9): Comparison between the two studied groups according to bladder DVH

Bladder DVH	Conformal (n=15)	IMRT (n=15)	t	P
Dose 10				
Min – Max	43.85 – 51.63	44.30 – 49.72		
Mean ± SD	46.79 ± 1.94	48.05 ± 1.37	2.058*	0.049*
Median	46.72	48.37		
Mean dose				
Min - Max	43.0 – 47.0	39.90 – 44.0		
Mean ± SD	45.20 ± 1.26	41.40 ± 1.35	7.940*	<0.001*
Median	45.0	41.0		

t: Student t-test
*: Statistically significant at $p \leq 0.05$

Analysis of rectal dose-volume histogram showed that there was no significant difference between two groups (group A1 and A2) regarding the dose received by 10% of volume during the whole pelvis radiotherapy (table 10).

While the median of the mean rectum radiotherapy dose were significantly higher in group A1 compared to group A2 (p value = 0.003) (figure 48).

Table (10): Comparison between the two studied groups according to rectum DVH parameters.

Rectum DVH	Conformal (n=15)	IMRT (n=15)	t	P
Dose 10				
Min – Max	44.96 – 49.37	44.0 – 48.46		
Mean ± SD	46.77 ± 1.41	46.30 ± 1.33	0.928	0.361
Median	46.90	46.0		
Mean Dose				
Min - Max	44.51 – 74.86	39.90 – 43.0		
Mean ± SD	47.93 ± 7.51	41.46 ± 0.93	3.313*	0.003*
Median	46.32	41.0		

t: Student t-test
*: Statistically significant at $p \leq 0.05$

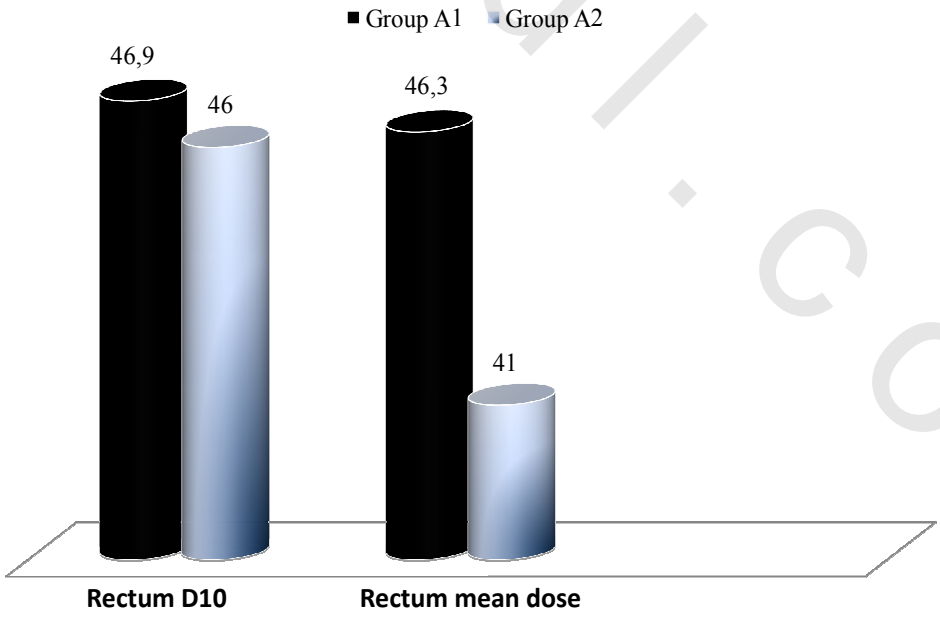


Figure 48: Comparison between two studied groups regarding rectal dose volume histogram parameters

Analysis of bowel dose-volume histogram showed that there was no statistical significant difference between two groups (group A1 and A2) regarding the dose received by 10% of volume during the whole pelvis radiotherapy (table 11).

However the median of the mean bowel radiotherapy dose were significantly higher in group A1 compared to group A2 (p value =<0.001).

Table (11): Comparison between the two studied groups according to bowel DVH

Bowel DVH	Conformal (n=15)	IMRT (n=15)	t	p
Dose (10ccm)				
Min – Max	45.01 – 51.40	45.10 – 48.98		
Mean ± SD	46.80 ± 1.56	47.74 ± 0.94	2.007	0.055
Median	46.72	47.94		
Mean Dose				
Min - Max	39.0 – 44.0	24.0 – 28.80		
Mean ± SD	41.07 ± 1.33	27.16 ± 1.43	27.493*	<0.001*
Median	41.0	27.60		

t: Student t-test
*: Statistically significant at $p \leq 0.05$

DVH Statistics Report

Hospital/Clinic: AKH Wien, Univ.-Klink f. Strahlentherapie
Patient Name
Patient ID: 05ZNFFBKK
Plan Name: GynIMRT45Gy
Comment:

DocNumber: 01020101223.135910.000 Monaco 2.04.00
Save Plan Date/Time: Plan modified since last Save
Print Date/Time: Jan 13, 2011 14:31:38
Workstation ID: MTSTRCWS01 10.122.13.23

Structure	Volume (cm³)	Plan Name	Min Dose Gy	Max Dose Gy	Mean Dose Gy	Cold Ref Gy	% Vol < Cold Ref	Hot Ref Gy	% Vol > Hot Ref	% Inside Calc Vol	Inside StudySet
Bladder	294.592	GynIMRT45Gy	23.963	48.707	41.689			47.000	3.19	100.00	no
Body(Unsp.Tiss.)	20686.816	GynIMRT45Gy	0.000	49.930	11.002					100.00	no
Bowel	1585.856	GynIMRT45Gy	3.809	48.220	30.374			47.000	0.41	100.00	no
CTV	945.472	GynIMRT45Gy	42.699	50.882	46.614					100.00	no
PTV	2313.728	GynIMRT45Gy	33.828	50.882	46.095			42.750	98.11	100.00	no
Rectum	91.776	GynIMRT45Gy	33.428	47.095	42.965			47.000	0.24	100.00	no
Sigmoid	45.632	GynIMRT45Gy	43.559	48.434	45.872					100.00	no

Resolution: 0.40 cm **Bin Width:** 0.100 Gy

All DVH data is based on DVH resolution and bin width.

Figure (49): Resulting dose volume histogram parameters of patient treated with IMRT

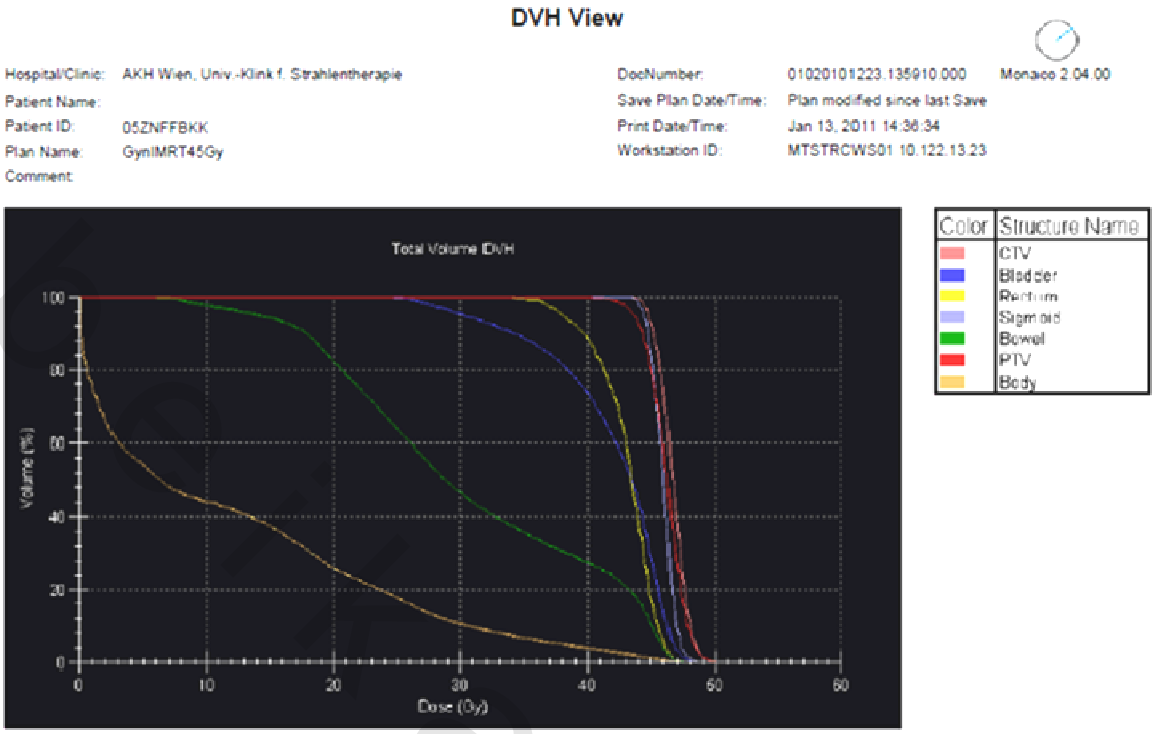


Figure (50): Dose volume histogram of patient treated with IMRT

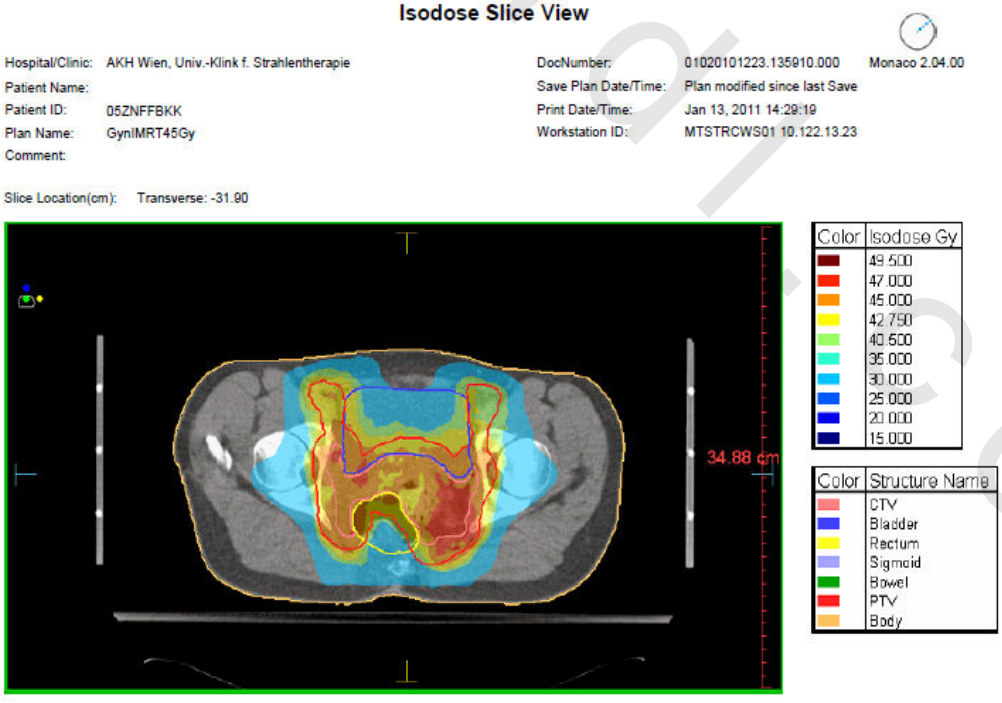


Figure (51): Transverse CT slice for patient treated with IMRT with isodose lines-

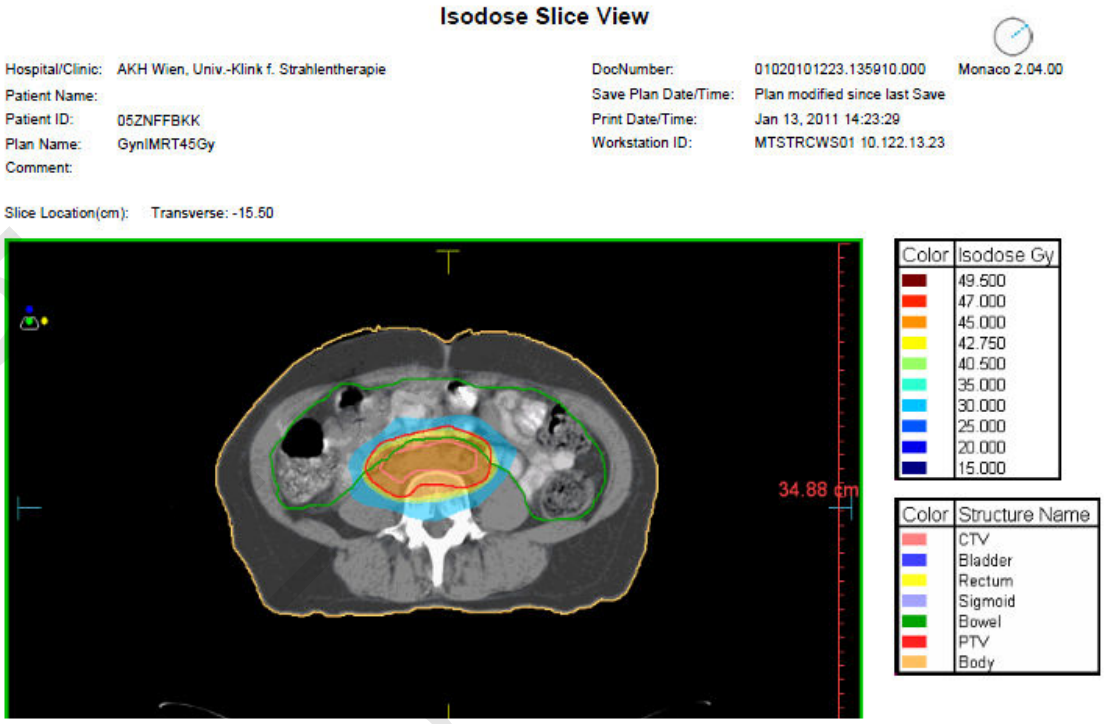


Figure (52): Transverse CT slice for patient treated with IMRT with isodose lines.

Name	Min [Gy]	Max [Gy]	Median [Gy]	Average [Gy]	Std. Dev. [Gy]	Calculated Points	Dose volume [ccm]
Body	0.00	47.89	2.30	14.96	18.93	471025	29854.681
Blase	44.85	46.35	45.66	45.62	0.32	1319	82.810
Rektum	45.45	47.14	46.26	46.28	0.38	1343	84.612
CTV	39.97	47.55	45.67	45.56	0.87	19272	1227.304
PTV	37.66	47.77	45.67	45.44	1.27	42952	2741.834
Darm	0.90	47.56	34.76	26.09	19.41	12850	808.612
sigma	45.22	47.02	45.89	45.93	0.38	766	46.842

Figure (53): Dose Volume Histogram parameters of patient treated with 3D CRT.

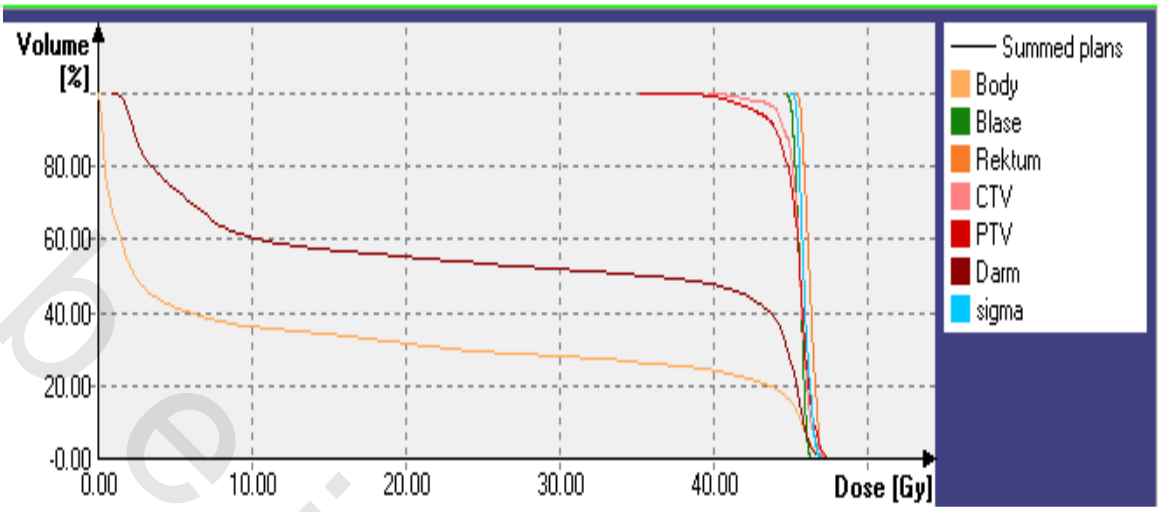


Figure (54): Resulting dose volume histogram of patient treated with 3D CRT.

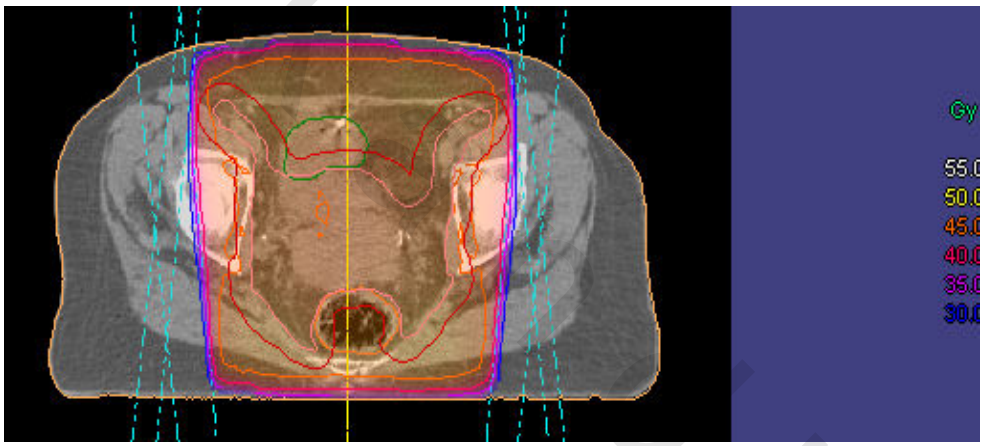


Figure (55): Transverse CT slice for patient treated with 3D CRT and CTV and OAR contouring and surrounding isodose.

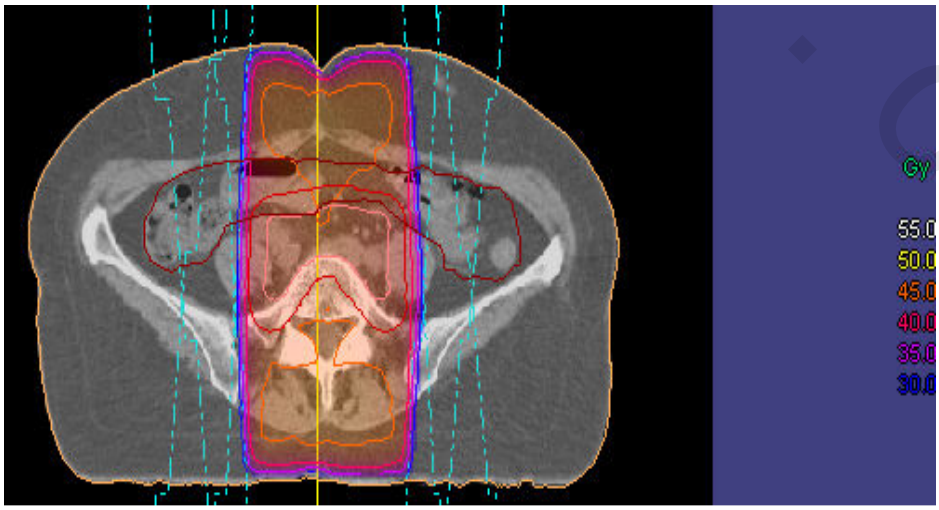


Figure (56): Transverse CT slice for patient treated with 3D CRT with isodose and CTV and OAR contouring

2- Acute toxicity during external beam radiotherapy (EBRT) and 6 weeks after end of treatment:

All patients in group A1 and A2 who received whole pelvis radiotherapy ± paraortic field radiotherapy with or without concomitant cisplatin followed by Brachytherapy (BT) were assessed for acute toxicity according to Common Toxicity Criteria (CTC). The overall therapy in both treated groups was tolerated

Genitourinary:-

Regarding the incontinence, five patient (33.3%) developed grade I incontinence in group A1 (3D conformal radiotherapy) while only two patients (13.3) in group A2 (IMRT group) suffered from Grade I incontinence.

Six weeks after the end of treatment, four and one patients in group A1 and group A2 respectively still had grade I incontinence. There was statistical significant difference between two groups (p = 0.14) (Table 12).

Table (12): Comparison between the two studied groups according to urinary incontinence

Urinary incontinence	Conformal (n = 15)		IMRT (n = 15)		Z_1	P
	No.	%	No.	%		
During radiotherapy						
0	10	66.7	13	86.7		
I	5	33.3	2	13.3		
II	0	0.0	0	0.0	1.273	0.203
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	11	73.3	14	93.3		
I	4	26.7	1	6.7		
II	0	0.0	0	0.0	1.445	0.148
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	0.577 (0.564)		1.000 (0.317)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and after 6weeks
Z_2: Z for Wilcoxon signed ranks test for comparing between during and after 6weeks radiotherapy in each group
*: Statistically significant at $p \leq 0.05$

The most frequently encountered symptom was frequency of urination seen in 13 and 8 patients of groups A1 and A2 respectively. Ten patients (66.6%) of group A1 experienced grade I frequency and 3 patients (20%) developed grade II. In group A2 only 46% developed grade I and 6% developed grade II. Both groups were comparable without any statistical significance difference (p value = 0.45) (Table 13).

Within two groups, there was no grade II urinary frequency 6 weeks after end of treatment. Eight and four patients in group A1 and A2 respectively suffered from Grade I urinary frequency without statistical significance between both groups (Figure 57, 58).

However in group A 1, the acute urinary frequency was statistical higher during EBRT than 6 weeks after with p value = 00.005 (Table 13).

Table (13):- Comparison between the two studied groups according to CTC side effect Urinary frequency:-

Urinary Frequency	Conformal (n = 15)		IMRT (n = 15)		Z_1	p
	No.	%	No.	%		
During radiotherapy						
0	2	13.3	7	46.7		
I	10	66.7	7	46.7		
II	3	20.0	1	6.7	2.007	0.45
III	0.	0.0	0	0.0		
IV	0.	0.0	0	0.0		
6 Weeks after radiotherapy						
0	7	46.7	11	73.3		
I	8	53.3	4	26.7		
II	0.	0.0	0	0.0		
III	0.	0.0	0	0.0		
IV	0.	0.0	0	0.0		
Z_2 (p)	2.828* (0.005*)		1.890 (0.059)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and 6 w after treatment
Z_2: Z for Wilcoxon signed ranks test for comparing between during and 6 w after radiotherapy in each group
*: Statistically significant at $p \leq 0.05$

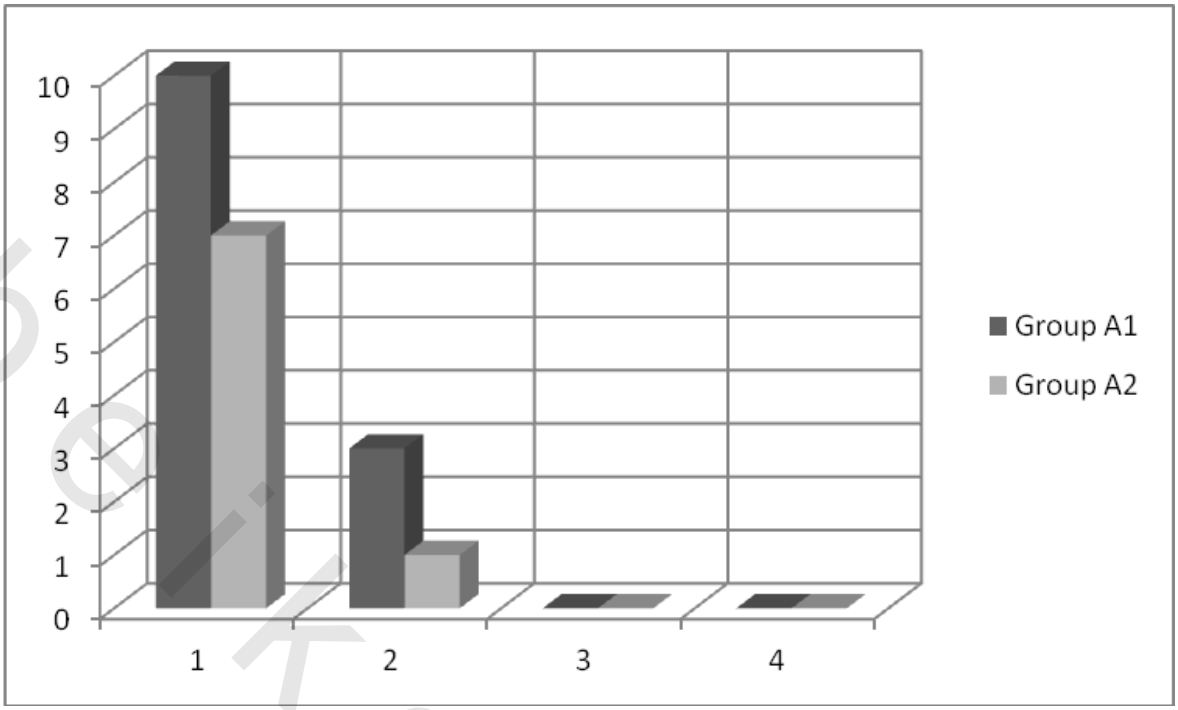


Figure (57): Comparison between group A1 and A2 regarding the frequency during the external beam radiotherapy treatment.

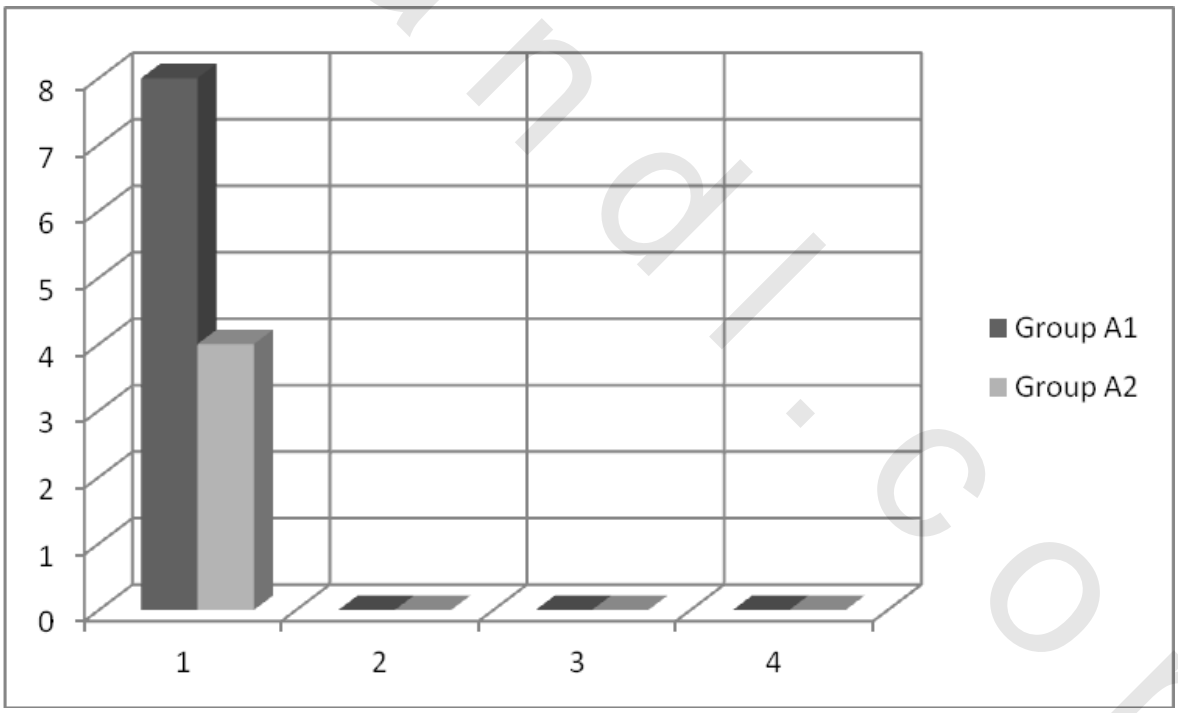


Figure (58): Comparison between group A1 and A2 regarding the frequency 6 weeks after end of treatment.

Sixty percent of patients in group A1 and forty percent of patient of group A2 developed grade 1 dysurea during External beam radiotherapy. Non of studied patients developed grade 2 or higher dysurea. There was no statistical significant difference between 2 groups regarding dysurea during and also 6 weeks after end of treatment (Table 14 and figure 59).

Table (14): Comparison between the two studied groups regarding acute Dysurea during EBRT and 6 weeks after end of treatment:

Dysurea	Group A1 (n = 15)		Group A2 (n = 15)		Z_1	P
	No.	%	No.	%		
During radiotherapy						
0	6	40.0	9	60.0		
I	9	60.0	6	40.0		
II	0	0.0	0	0.0	1.077	0.281
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	9	60.0	13	86.7		
I	6	40.0	2	13.3		
II	0	0.0	0	0.0	1.624	0.104
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	1.732 (0.083)		1.633 (0.102)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and 6 w after treatment
Z_2: Z for Wilcoxon signed ranks test for comparing between during and 6 w after radiotherapy in each group
*: Statistically significant at $p \leq 0.05$.

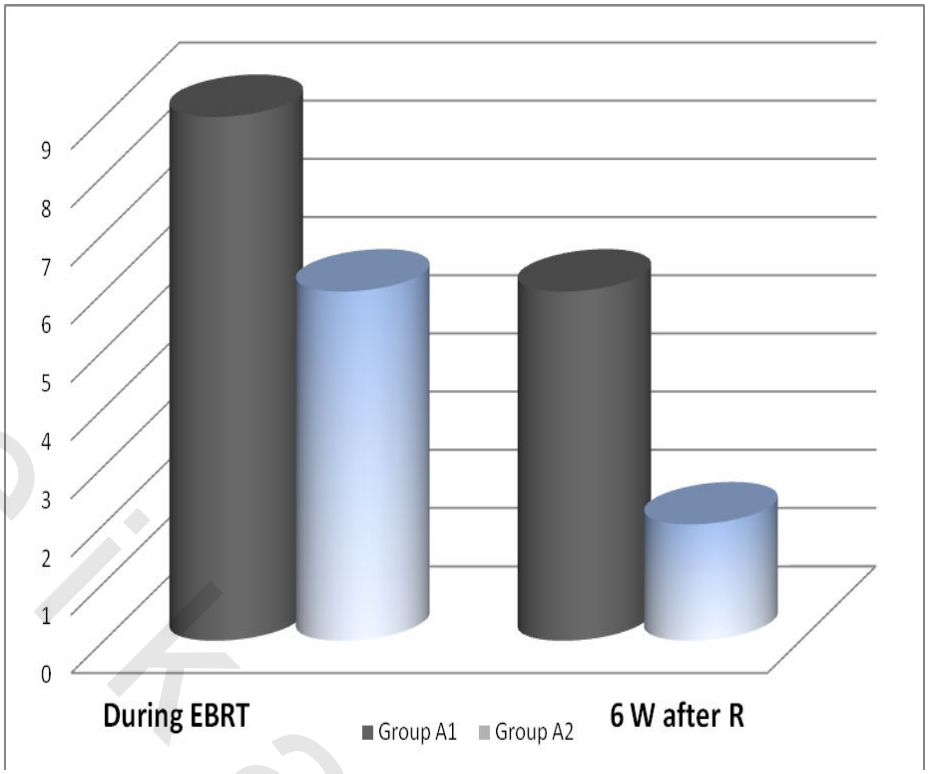


Figure (59): Comparison between group A1 and A2 regarding the grade I Dysurea during EBRT and 6 weeks after end of treatment.

Acute grade I haematuria was seen in 26.7% of patients in group A1 and only 6.7% of patients in group A2. All acute genitourinary symptoms were frequently higher in group A1 compared to group A2 patients during EBRT. Three patients and one patient in group A1 and A2 respectively still suffered from grade I haematuria 6 weeks after end of treatment (table 15).

Table (15): Comparison between the two studied groups according to CTC side effect Haematuria during EBRT and 6 W after end of treatment.

Hematuria	Conformal (n = 15)		IMRT (n = 15)		Z_1	P
	No.	%	No.	%		
During radiotherapy						
0	10	66.7	14	93.3		
I	4	26.7	1	6.7		
II	0	0.0	0	0.0	1.819	0.069
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	12	80.0	14	93.3		
I	3	20.0	1	6.7		
II	0	0.0	0	0.0	1.056	0.921
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	1.342 (0.180)		0.0 (1.000)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and after 6weeks
Z_2: Z for Wilcoxon signed ranks test for comparing between during and after 6weeks radiotherapy in each group
*: Statistically significant at $p \leq 0.05$.

Acute Gastrointestinal toxicity during external beam radiotherapy (EBRT) and 6 weeks after end of treatment:-

Diarrhea was the most frequent acute GIT toxicity seen in both groups. Acute grade I diarrhea was seen in 53.3 % and 46.7% of patients in group A1 and A2 respectively during EBRT. Three patients in group A1 developed grade II diarrhea compared to two patients in group A2. Both groups are comparable without any statistical significant difference (p value = 0.18) (table 16 and figure 60).

Grade II diarrhea was not seen in patients of group A1 and A2 6 weeks after end of treatment. Sixty percent of patients of group A1 suffered from grade I diarrhea compared to 33% of patients of group A2 (figure 61).

Table (16): Comparison between the two studied groups according to acute diarrhea during EBRT and 6 Weeks after end of treatment.

Diarrhea	Group A1 (n = 15)		Group A2 (n = 15)		Z_1	P
	No.	%	No.	%		
During radiotherapy						
0	3	20.0	6	40.0		
I	8	53.3	7	46.7		
II	3	20.0	2	13.3	1.332	0.183
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	6	40.0	10	66.7		
I	9	60.0	5	33.3		
II	0	0.0	0	0.0	1.439	0.150
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	2.530* (0.001*)		2.449* (0.014*)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and after 6weeks
Z_2: Z for Wilcoxon signed ranks test for comparing between during and after 6weeks radiotherapy in each group
*: Statistically significant at $p \leq 0.05$

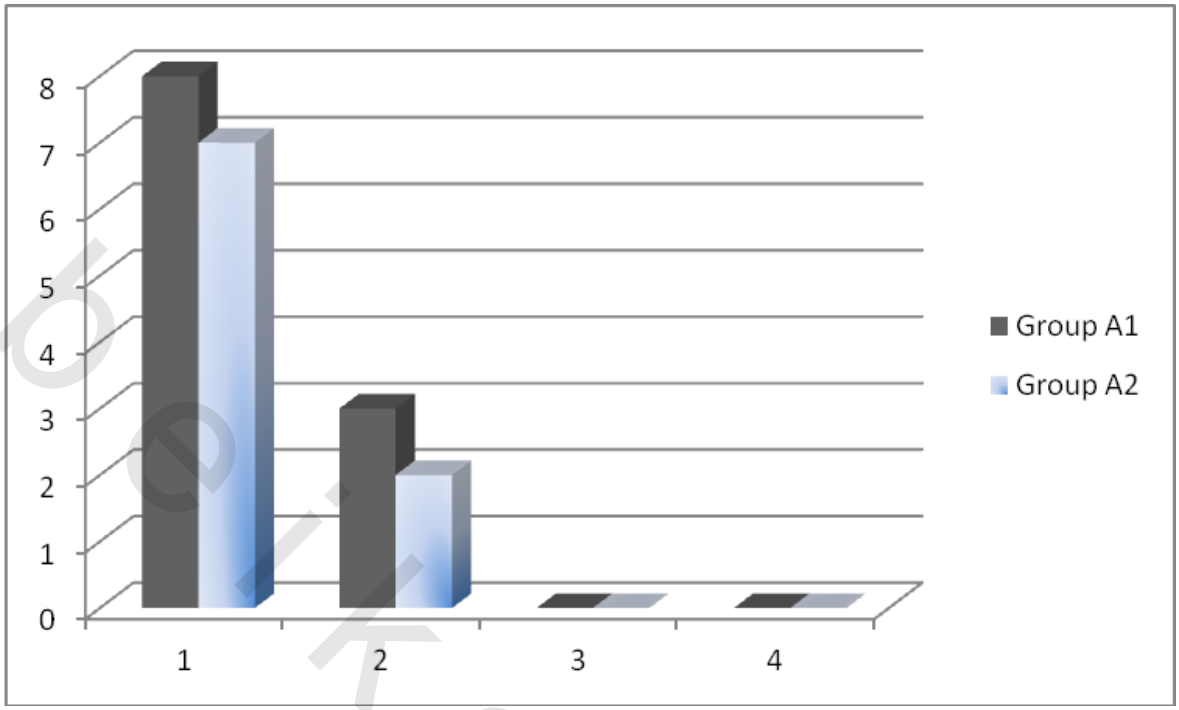


Figure (60): Comparison between the two studied groups according to diarrhea grades during EBRT.

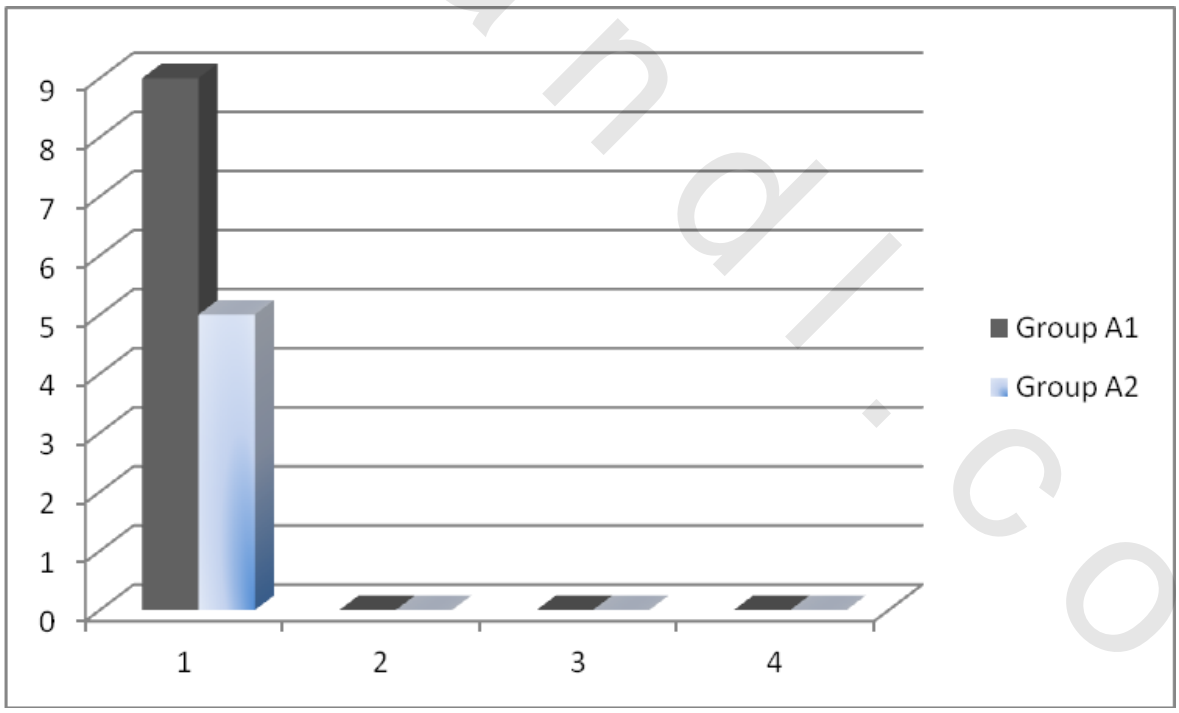


Figure (61): Comparison between the two studied groups according to diarrhea grades 6 weeks after end of treatment.

During EBRT; four patients (26%) in group A1 and two patients (13.3%) in group A2 developed grade I vomiting while only one patient in group A1 developed grade II vomiting. Both groups are comparable with p value of 0.15 (figure 62).

Non of patients in group A2 has any grade of vomiting 6 weeks after end of treatment while 2 patients of group A1 suffered from grade I vomiting. Two groups are comparable without any statistical significant difference (table 17).

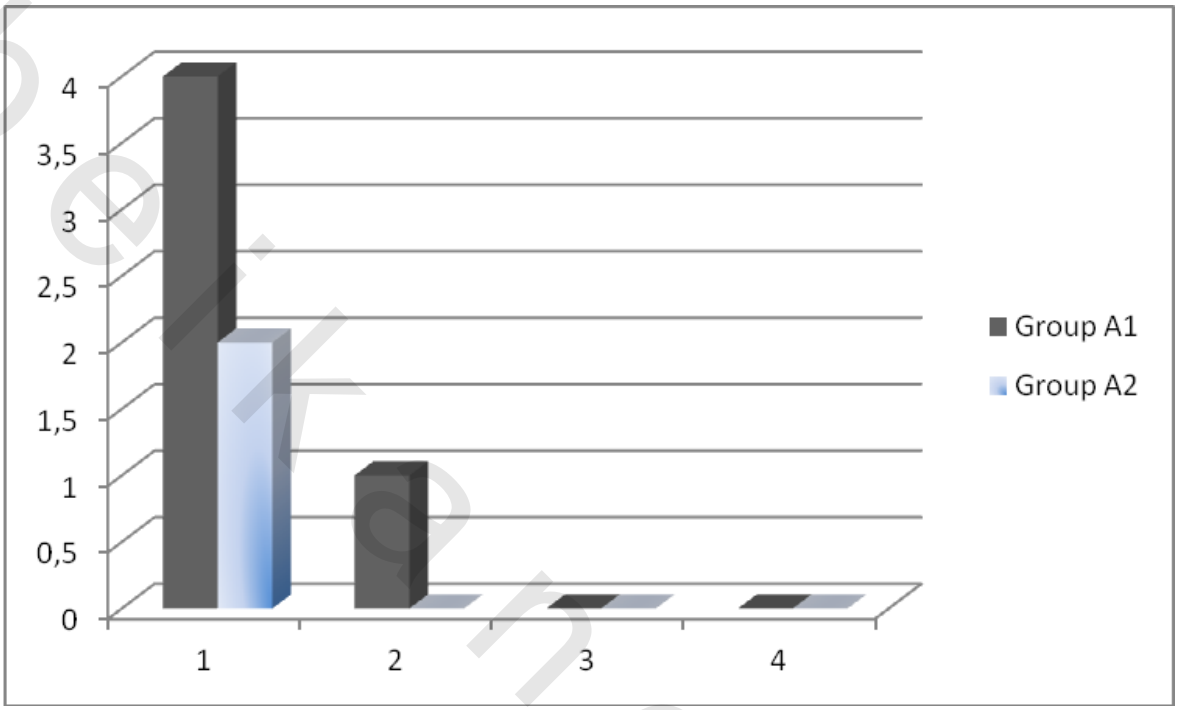


Figure (62): Comparison between the two studied groups according grading of vomiting during EBRT

Table (17): Comparison between the two studied groups according the grade of vomiting during EBRT and 6 weeks after end of treatment.

Vomiting	Conformal (n = 15)		IMRT (n = 15)		Z_1	p
	No.	%	No.	%		
During radiotherapy						
0	10	66.7	13	86.7		
I	4	26.7	2	13.3		
II	1	6.7	0	0.0	1.324	0.185
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	13	86.7	15	100.0		
I	2	13.3	0	0.0		
II	0	0.0	0	0.0	1.439	0.150
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	1.414 (0.157)		1414 (0.157)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and after 6weeks
Z_2: Z for Wilcoxon signed ranks test for comparing between during and after 6weeks radiotherapy in each group
*: Statistically significant at $p \leq 0.05$

Forty percent of patients in group A1 and 13.3% of patients in group A2 developed acute abdominal pain during the external beam radiation therapy. The incidence of acute abdominal pain was higher among group A1 patients compared to group A2 patients, however this was not statistically significant (p= 0.10) (table 18).

The abdominal pain was slightly improved after end of treatment where four and two patients of group A1 and A2 respectively suffered from Grade I abdominal pain6 weeks after end of treatment. (Figure 63)

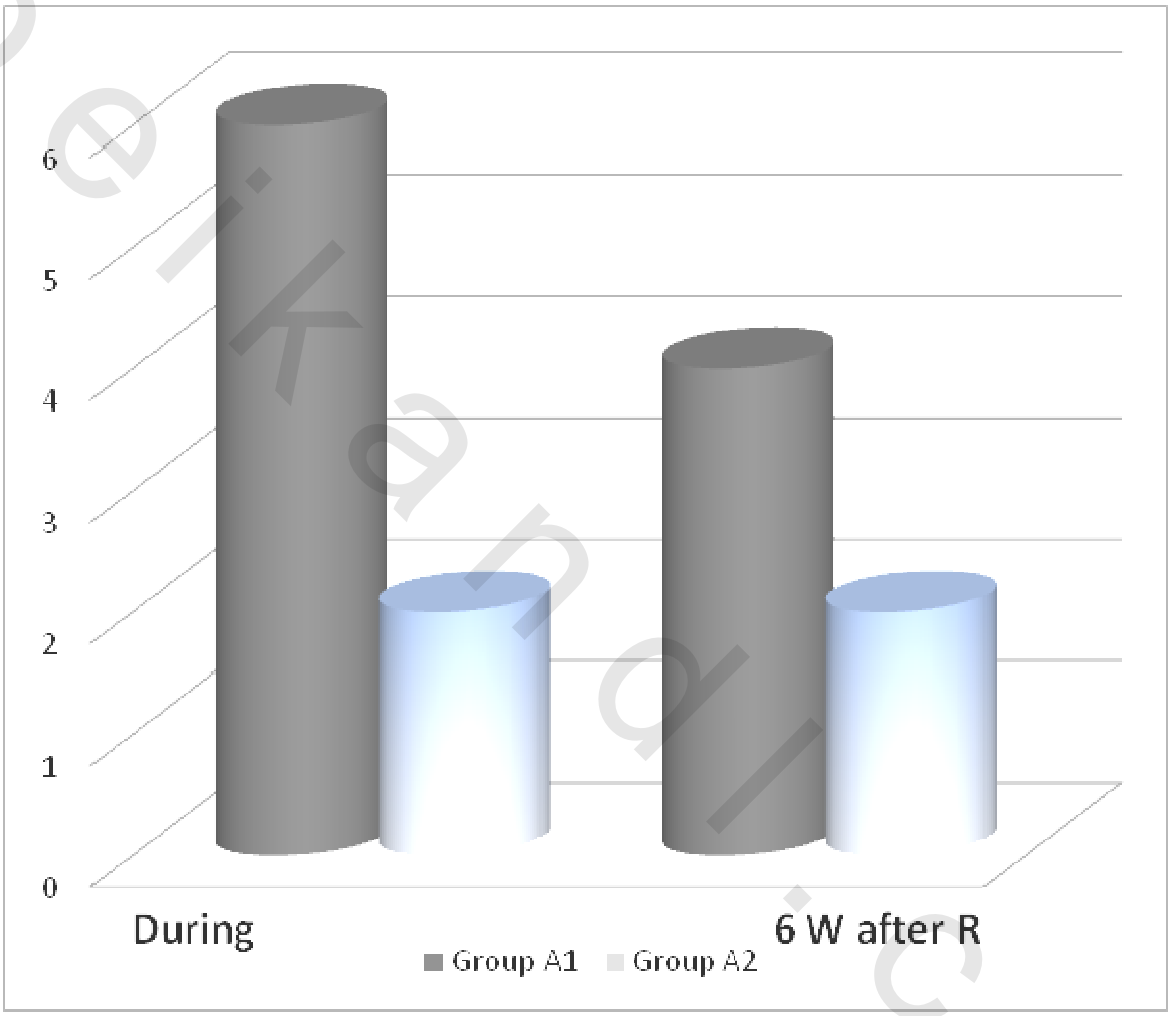


Figure (63): Comparison between the two studied groups according grade I vomiting during EBRT and 6 weeks after end of treatment.

Table (18): Comparison between the two studied groups according to CTC side effect Abdominal pain

Abdominal pain	Conformal (n = 15)		IMRT (n = 15)		Z_1	p
	No.	%	No.	%		
During radiotherapy						
0	9	60.0	13	86.7		
I	6	40.0	2	13.3		
II	0	0.0	0	0.0	1.624	0.104
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
6 Weeks after radiotherapy						
0	11	73.3	13	86.7		
I	4	26.7	2	13.3		
II	0	0.0	0	0.0	0.898	0.369
III	0	0.0	0	0.0		
IV	0	0.0	0	0.0		
Z_2 (p)	1.414 (0.157)		0.0 (1.000)			

Z_1: Z for Mann Whitney test for comparing IMRT and conformal group during and after 6weeks
Z_2: Z for Wilcoxon signed ranks test for comparing between during and after 6weeks radiotherapy in each group
*: Statistically significant at $p \leq 0.05$

Other toxicities:

The patients of studied group are subjected to laboratory investigations including hemoglobin level, white blood cell count, platelet count, creatinine level and liver function test in radiation therapy department before start of radiation therapy and at end of EBRT and before each brachytherapy application then during follow up visits.

As regards to Creatinine level patients in both treated group had normal creatinine level. After the end of external beam radiotherapy with or without concomitant cisplatin, 20% and 13% of patients of group A1 and group A2 respectively had creatinine level between 1.5-3 mg/dL. Both groups are comparable without any statistical significant difference (table 19).

Table (19): Comparison between the two studied groups according to CTC side effect serum creatinine level

Serum creatinine level (mg/dL)	Conformal (n = 15)		IMRT (n = 15)		χ^2	p_1
	No.	%	No.	%		
Before radiotherapy						
0- < 1.5	0	0.0	1	6.7		
1.5	15	100.0	14	93.3		
>1.5 – 3	0	0.0	0	0.0	1.034	^{FE}p =1.000
>3 – 6	0	0.0	0	0.0		
>6	0	0.0	0	0.0		
End of EBRT						
0- < 1.5	0	0.0	1	6.7		
1.5	12	80.0	12	80.0		
>1.5 – 3	3	20.0	2	13.3	1.204	^{MC}p =1.000
>3 – 6	0	0.0	0	0.0		
>6	0	0.0	0	0.0		
χ^2 ($^{MC}p_2$)	3.333 (0.224)		2.020 (0.731)			

p_1: p value for comparing IMRT and conformal group during and after 6weeks
p_2: p value for comparing between during and after 6weeks radiotherapy in each group
χ^2: Chi square test
MC: Monte Carlo test
FE: Fisher Exact test
*: Statistically significant at $p \leq 0.05$

Most of patients in two groups (10 patients in group A1 and 12 patients in group A2) had hemoglobin level (Hb) more than 11 g/dl. Four and three patients in group A1 and group A" respectively had Hb level between 10-11 g/dl and only one patient in group A1 had Hb level more than 8 g/dl but less than or equal 10 g/dl.

After end of EBRT 27% and 20% of patients of groupA1 and A2 developed anemia with hemoglobin level more than 8 g/dl but less than or equal 10 g/dl. Both groups were comparable without any statistical significant difference (p value= 0.07) (table 20). However 80% of patients in group A1 who received 3D conformal radiotherapy has anemia by end of radiotherapy compared to 33% of patient at baseline (P= 0.04) (Figure 64)..

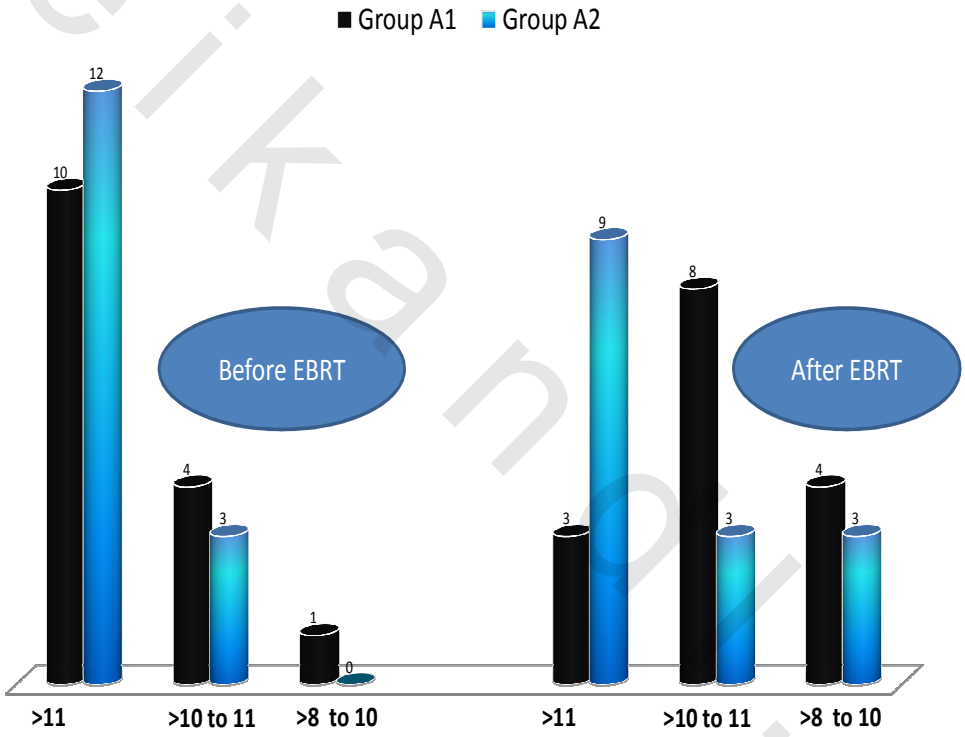


Figure (64): Comparison between the two studied groups regarding Hemoglobin level before and after radiotherapy.

Table (20): Comparison between the two studied groups according to CTC side effect blood hemoglobin level

Blood hemoglobin level (g/dl)	Conformal (n = 15)		IMRT (n = 15)		χ^2	$^{MC}p_1$
	No.	%	No.	%		
Before radiotherapy						
>11	10	66.7	12	80.0		
>10 to 11	4	26.7	3	20.0		
>8 to 10	1	6.7	0	0.0	1.311	0.687
>6,5 to 8	0	0.0	0	0.0		
to 6,5	0	0.0	0	0.0		
Death related to toxicity	0	0.0	0	0.0		
End of EBRT						
>11	3	20.0	9	60.0		
>10 to 11	8	53.3	3	20.0		
>8 to 10	4	26.7	3	20.0	5.279	0.072
>6,5 to 8	0	0.0	0	0.0		
to 6,5	0	0.0	0	0.0		
Death related to toxicity	0	0.0	0	0.0		
χ^2 ($^{MC}p_2$)	6.618* (0.042*)		3.109 (0.349)			

p_1: p value for comparing IMRT and conformal group during and after 6weeks
p_2: p value for comparing between during and after 6weeks radiotherapy in each group
χ^2: Chi square test
MC: Monte Carlo test

Before patients started, 14 patients in each group (A1 and A2) has normal WBCs counts (table 21). After patients finished EBRT, 60% and 26 % of patients in group A1 and A2 respectively developed Leucopenia. Moreover, there was statistical significant difference between degree of leucopenia before and after EBRT in group A1 (P= 0.015) (Figure 65).

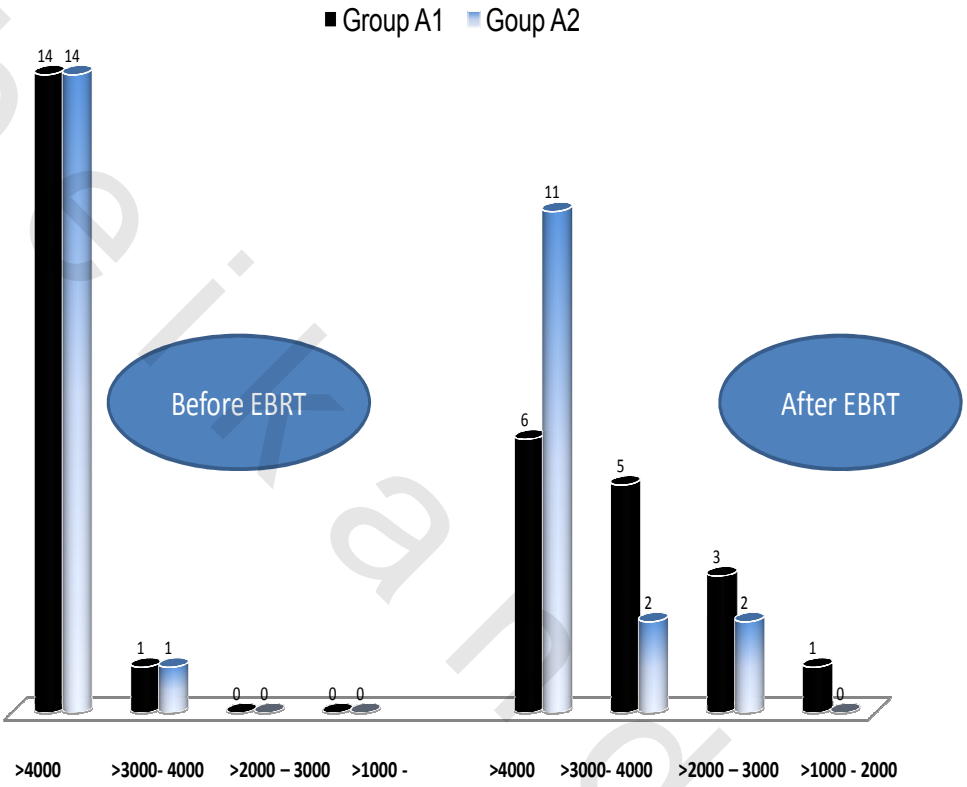


Figure (65): Comparison between the two studied groups according to WBCs counts before and after.

Table (21): Comparison between the two studied groups according to CTC side effect on WBCs counts

WBCs counts	Conformal (n = 15)		IMRT (n = 15)		χ^2	p_1
	No.	%	No.	%		
Before radiotherapy						
>4000	14	93.3	14	93.3		
>3000- 4000	1	6.7	1	6.7		
>2000 - 3000	0	0.0	0	0.0	0.0	^{FE}p =1.000
>1000 - 2000	0	0.0	0	0.0		
Less than 1000	0	0.0	0	0.0		
End of EBRT						
>4	6	40.0	11	73.3		
>3 - 4	5	33.3	2	13.3		
>2 - 3	3	20.0	2	13.3	3.836	^{MC}p =0.266
>1 - 2	1	6.7	0	0.0		
1	0	0.0	0	0.0		
χ^2 ($^{MC}p_2$)	9.166* (0.015*)		2.389 (0.395)			

p_1: p value for comparing IMRT and conformal group during and after 6weeks
p_2: p value for comparing between during and after 6weeks radiotherapy in each group
χ^2: Chi square test
MC: Monte Carlo test
FE: Fisher Exact test

Also fourteen patients in each group (A1 and A2) has normal platelet counts (table 19). After patients finished EBRT, 27% and 13 % of patients in group A1 and A2 respectively developed thrombocytopenia. There was no statistical significant difference between degree of thrombocytopenia between 2 groups (P= 0.79).

Table (22): Comparison between the two studied groups according to platelets counts

Platelets counts	Conformal (n = 15)		IMRT (n = 15)		χ^2	p_1
	No.	%	No.	%		
Before radiotherapy						
>150	14	93.3	14	93.3		
>75 -150	1	6.7	1	6.7		
>50 - 75	0	0.0	0	0.0	0.0	^{FE}p = 1.000
>10 - 50	0	0.0	0	0.0		
Till 10	0	0.0	0	0.0		
End of EBRT						
>150	11	73.3	13	86.7		
>75 -150	3	20.0	1	6.7		
>50 - 75	1	6.7	1	6.7	1.341	^{MC}p =0.789
>10 - 50	0	0.0	0	0.0		
Till 10	0	0.0	0	0.0		
χ^2 ($^{MC}p_2$)	2.220 (0.334)		1.214 (1.000)			

p_1: p value for comparing IMRT and conformal group during and after 6weeks
p_2: p value for comparing between during and after 6weeks radiotherapy in each group
χ^2: Chi square test
MC: Monte Carlo test
FE: Fisher Exact test

3- Late Toxicity:

Late side effects were assessed according to Late Effects Normal Tissue Task Force (LENT) score.

Late Gastrointestinal Toxicity:

According to LENT score, 60% of patients in group A1 developed late GIT toxicities compared to 46.7% of patients of group A2. Both groups were comparable without statistical significant difference (p = 0.39) (figure 66). One patients in group A2 had Grade IV toxicity where she suffered from recto-vaginal fistula. This patient had underwent surgical excision followed by anastomosis.

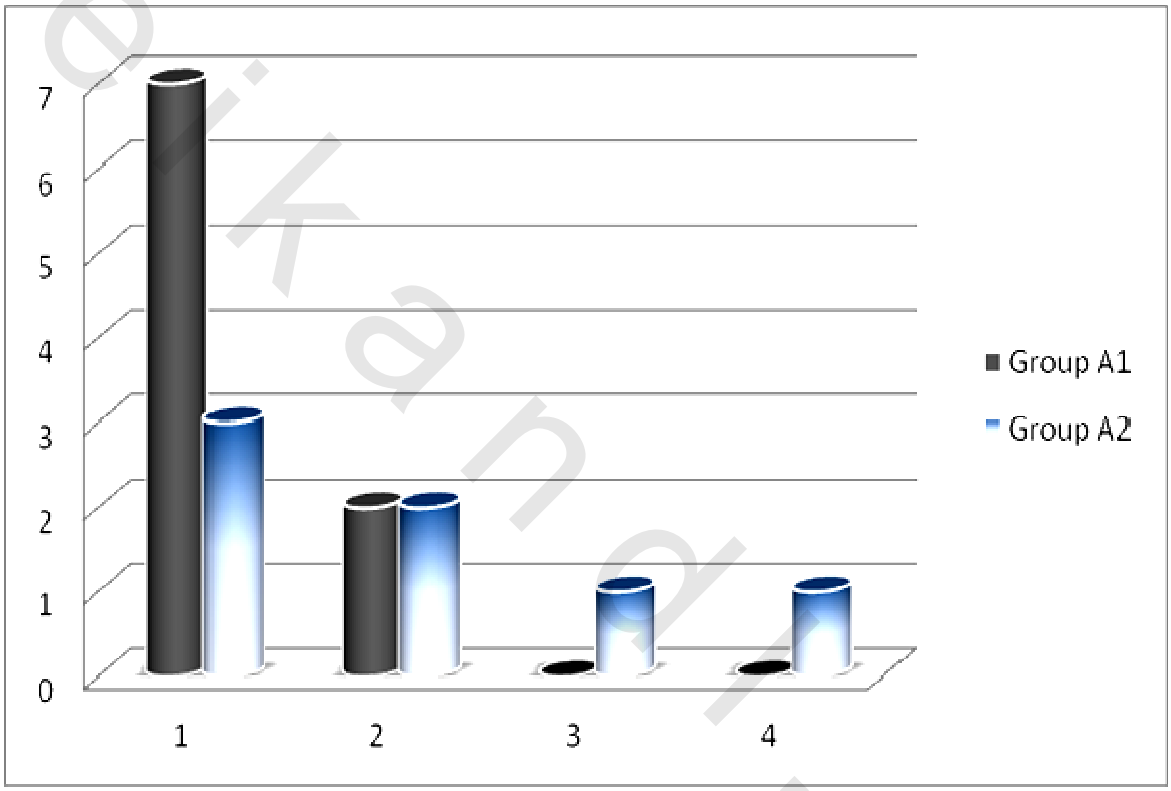


Figure (66): Different grade of late GIT toxicities between 2 groups.

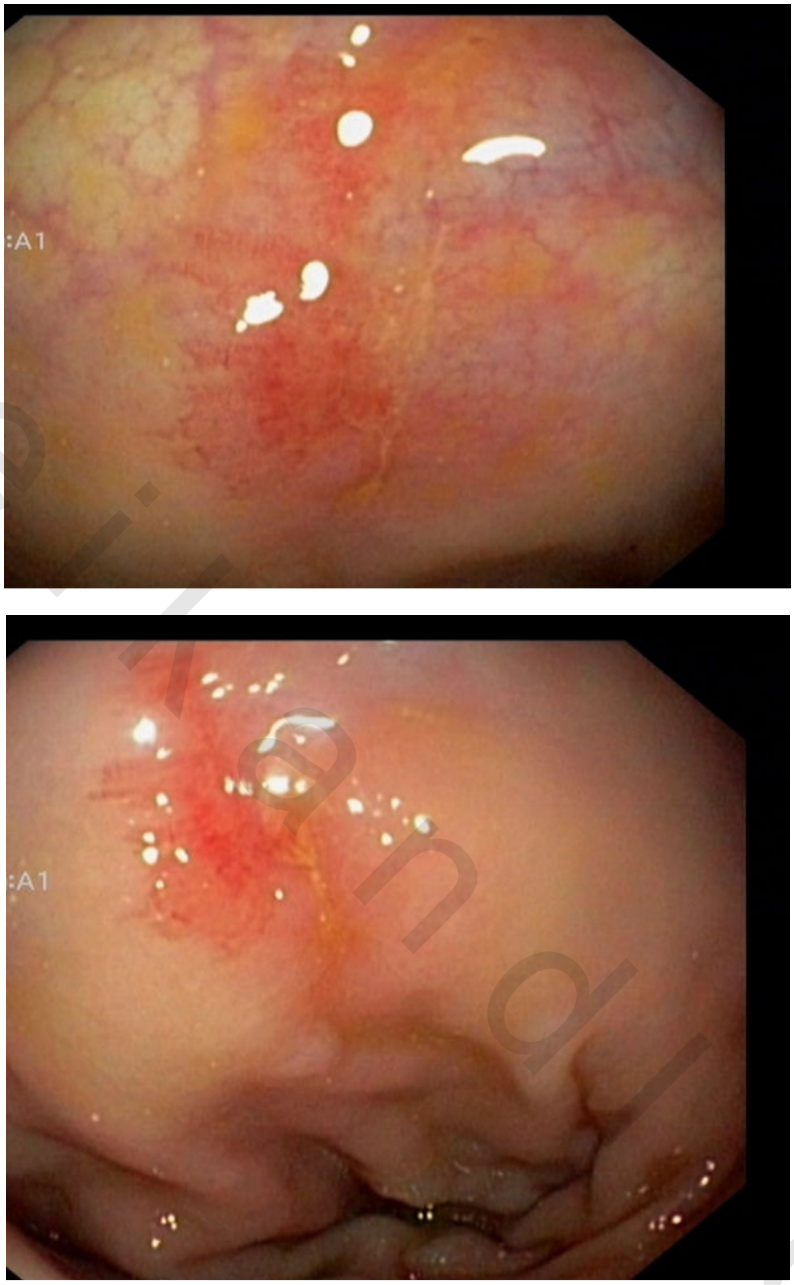


Figure (67): Endoscopic view showing Grade II telangectesia of rectum

Late Genitourinary Toxicity:

According to LENT score, 53.3% of patients in group A1 developed late genitourinary toxicities compared to 46.7% of patients of group A2. Both groups were comparable without statistical significant difference (p = 0.45). Two patients in group A1 had Grade IV toxicity where patients developed vesico-vaginal fistula.

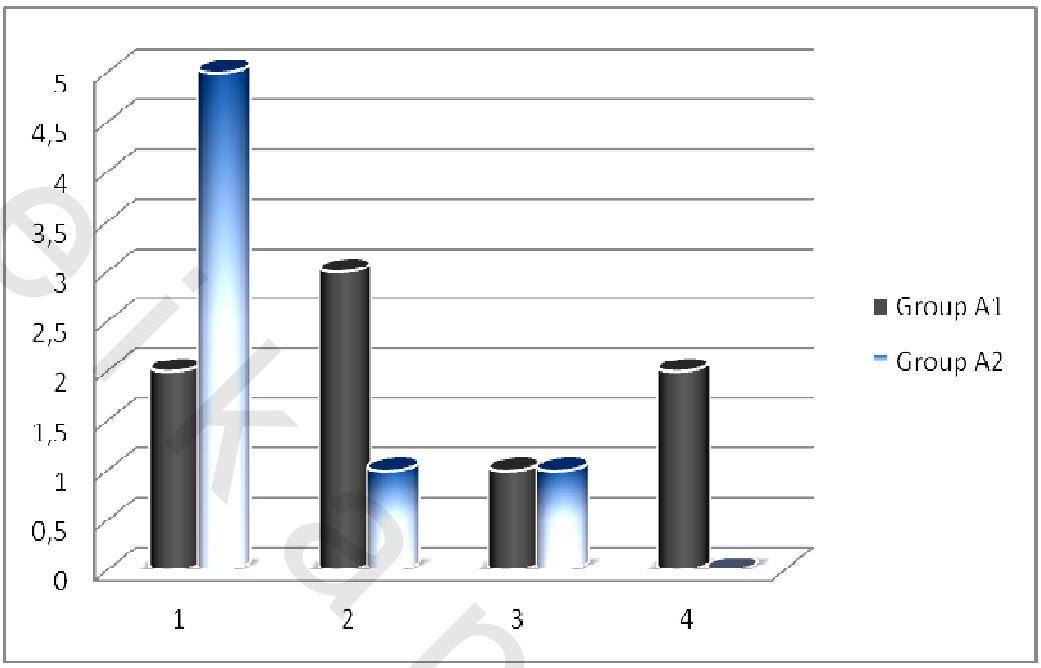


Figure (68): Different grade of late GU toxicities between 2 groups.

Table (23): Comparison between the studied groups according to late toxicities:

Late Side effect	Conformal (n = 15)		IMRT (n = 15)		Test of sig.	p
	No.	%	No.	%		
Fistule						
Yes	2	13.3	1	6.7	χ^2 =0.70	1.000
No	13	86.7	14	93.3		
Fistule localization	**(n = 1)**		**(n = 2)**			
Rectum	0	0.0	1	100.0	-	-
Vesico- vaginal	2	100.0	0	0.0		
Fistule therapy	**(n = 1)**		**(n = 2)**			
With conservative therapy	2	100.0	0	0.0	-	-
With surgical treatment	0	0.0	1	100.0		
Lent Soma late side effect						
Genitourinary						
No	7	46.7	8	53.3		
I	2	13.3	5	33.3		
II	3	20.0	1	6.7	Z =4.101	0.457
III	1	6.7	1	6.7		
IV	2	13.3	0	0.0		
GIT						
No	6	40.0	8	53.3		
I	7	46.7	3	20.0		
II	2	13.3	2	13.3	Z =3.813	0.396
III	0	0.0	1	6.7		
IV	0	0.0	1	6.7		
Vagina						
No	2	13.3	2	13.3		
I	7	46.7	9	60.0	Z =0.788	0.874
II	6	40.0	4	26.7		

χ^2: Chi square test Z: Z for Mann Whitney test

Effect of para-aortic field radiotherapy and acute GIT toxicities:

Two patients from group A1 and four patients from group A2 received paraortic field radiotherapy with whole pelvis radiotherapy. There was statistical significant positive correlation between paraortic field RT and acute vomiting (p= 0.007), abdominal pain grades (p=0.029) and acute diarrhea (p=0.01)

Table (24): Relation between para-aortic field radiotherapy and vomiting during radiotherapy (n = 30)

	para-aortic field radiotherapy				χ^2	^{MC}p
	No		Yes			
	No.	%	No.	%		
CTC vomiting during radiotherapy						
G0	21	87.5	2	33.3		
G1	2	8.3	4	66.7	8.569*	0.007*
G3	1	4.2	0	0.0		

χ2: Chi square test
MC: Monte Carlo test
*: Statistically significant at $p \leq 0.05$

Table (25): Relation between para-aortic field radiotherapy and diarrhea during radiotherapy (n = 30)

	para-aortic field radiotherapy				χ^2	^{MC}p
	No		Yes			
	No.	%	No.	%		
CTC side effect Diarrhea During radiotherapy						
G0	9	37.5	0	0.0		
G1	13	54.2	2	33.3		
G2	2	8.3	3	50.0	9.546*	0.010*
G3	0	0.0	1	16.7		

χ2: Chi square test
MC: Monte Carlo test
*: Statistically significant at $p \leq 0.05$

Table (26): Relation between para-aortic field radiotherapy and abdominal pain during radiotherapy (n = 30)

	para-aortic field radiotherapy				χ^2	^{FE}p
	No		Yes			
	No.	%	No.	%		
CTC side effect Abdominal pain During radiotherapy						
G0	20	83.3	2	33.3		
G1	4	16.7	4	66.7	6.136*	0.029*

χ^2: Chi square test
FE: Fisher Exact test
*: Statistically significant at $p \leq 0.0$

Follow up:-

After 6 weeks of the end of definitive chemoradiotherapy for patients, 13 patients in group A1 and 14 patients in groups A2 had complete clinical and radiological response (table 27). At end of follow up 80% of patients in both group survived. One patients in group A2 and two patients in group A2 died due to causes related to disease progression (Figure 70).

Three patients of group A1 (3D CRT) developed local recurrence while non of patients of group A2 developed local recurrence. The site of recurrence was at lateral pelvic wall in 2 patients while one patients has central recurrence at primary tumor site (Figure 69).

Table (27): Comparison between the studied groups according to follow up

	Conformal (n = 15)		**IMRT (n = 15)**		**χ^2**	**p**
	No.	**%**	**No.**	**%**		
Remission 6 Weeks after end of treatment						
Complete remission	13	86.7	14	93.3	0.730	$^{FE}p = 1.000$
Incomplete Remission	2	13.3	1	6.7		
Survival at end of 18 months						
Live	12	80.0	12	80.0	0.0	$^{FE}p = 1.000$
Died	3	20.0	3	20.0		
State of patient at end of 18 months						
Live healthy	10	66.7	12	80.0	3.442	$^{MC}p =0.393$
Live with disease recurrence	3	20.0	0	0.0		
Died due to disease	2	13.3	1	6.7		
Died due to another cause	1	6.7	2	13.3		

χ^2: Chi square test
MC: Monte Carlo test
FE: Fisher Exact test.

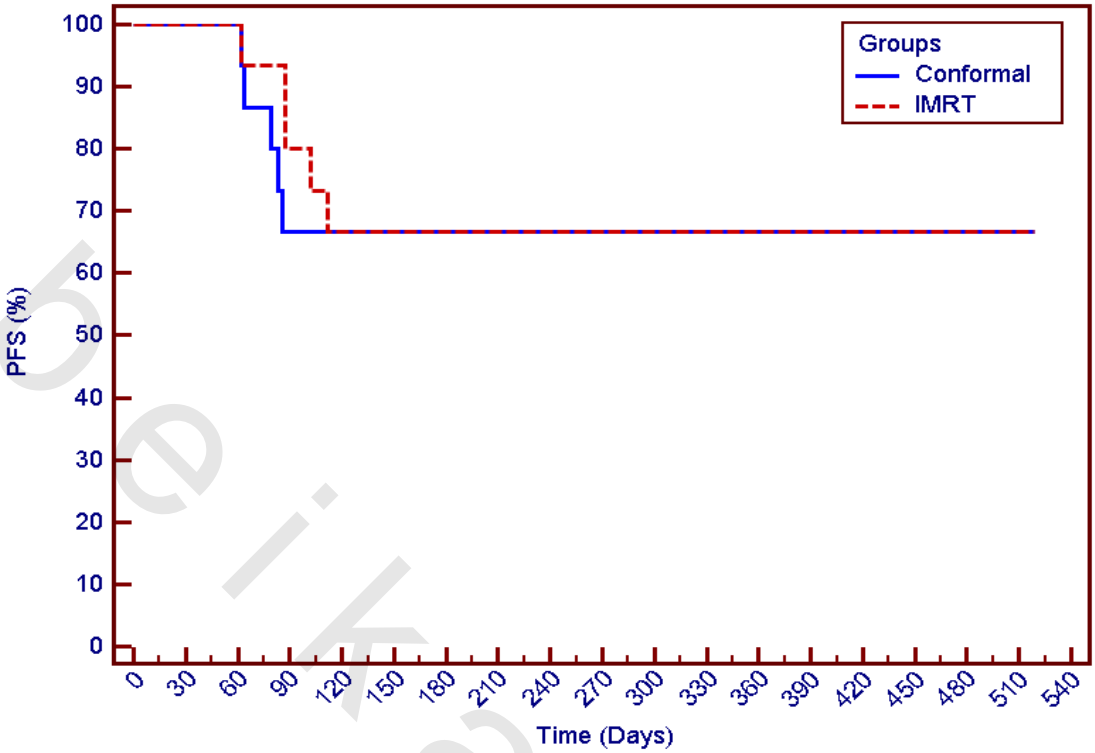


Figure (69): Progression free survival of both treated groups.

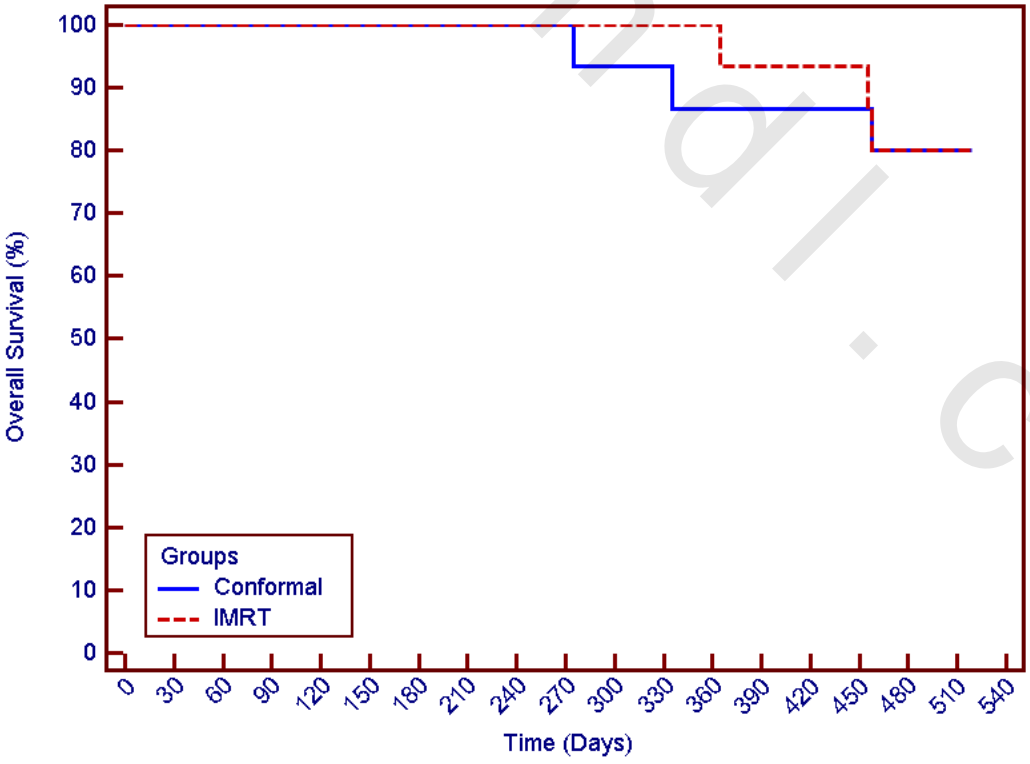


Figure (70): Overall survival for both treated groups.

Group B (Imaging Group):

Ten patients with cervix cancer were retrospectively selected on the basis of availability of both CT and MRI with applicator in place and full 3D-documentation (diagram drawings) representing clinical examination at time of diagnosis and time of BT. T2-weighted MRI studies after BT applicator placement were generated in 5 mm slice intervals. The HR CTV_{MRI} was contoured according to the Gyn GEC-ESTRO recommendations using PLATO/Oncentra Masterplan (OMP) workstations (Nucletron, Veenendaal, The Netherlands) .

The CT images at time of BT with applicator in place were generated in 4 mm slice intervals. Contouring was done findings on an OMP workstation (Nucletron, Veenendaal, The Netherlands). HR CTV_{CT} was delineated using information on FIGO stage, and 3D-documentation of CGE, as depicted on the clinical diagrams.

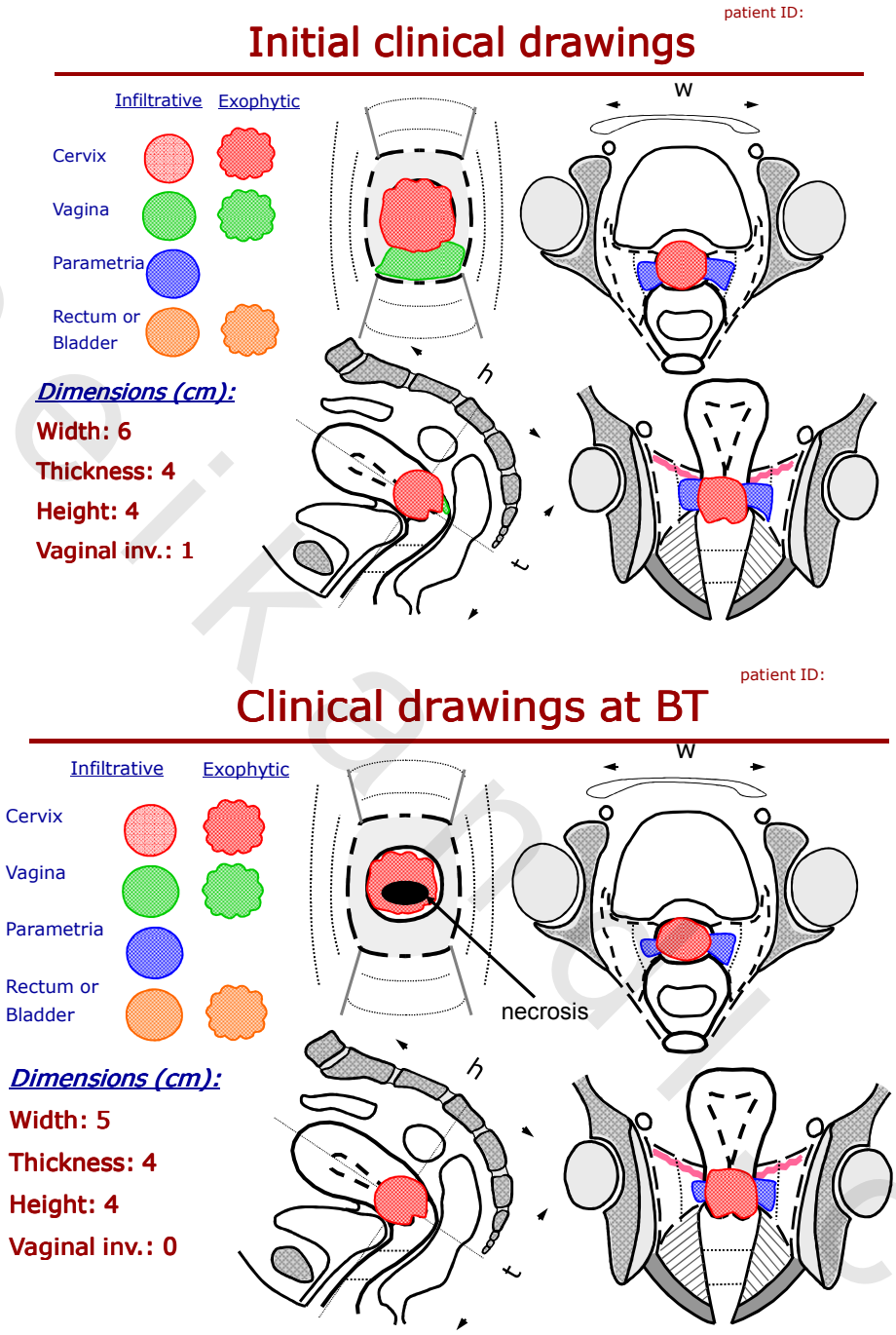


Figure (71): Example of clinical drawing at time of diagnosis and Brachytherapy.

Three-dimensional parameters, i.e., maximum height, thickness, and width, were measured for each HR CTV. The height of CT-based HR CTV indicates the cranio-caudal diameter assessable on mid-sagittal view along the uterine axis. The thickness was measured as the largest anteroposterior diameter on axial view. The width is the largest transverse diameter, measured on axial view. The volumes of all HR CTVs calculated by the treatment planning system were recorded for each patient.

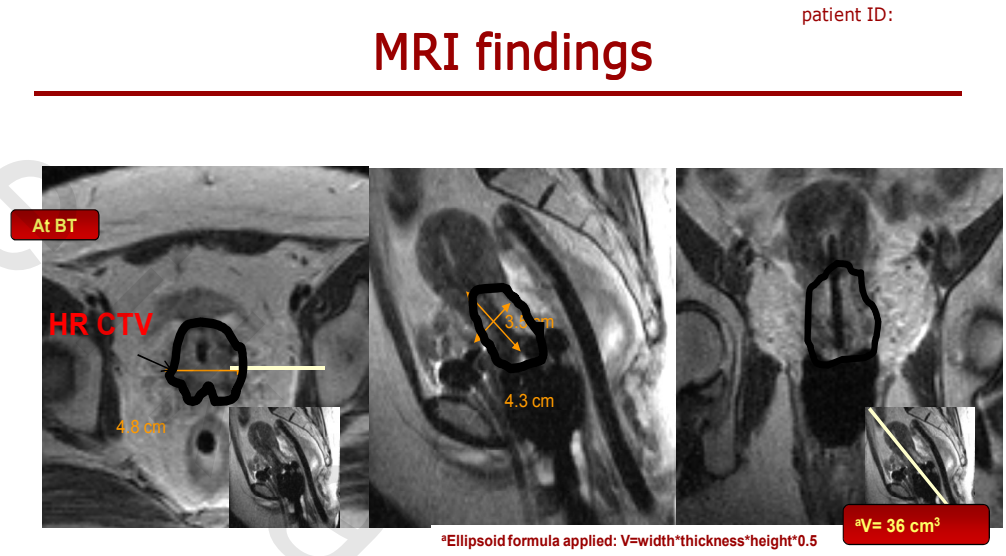


Figure (72): Evaluation of 3D dimensions (Width, Height, Thickness) of HR CTV MRI

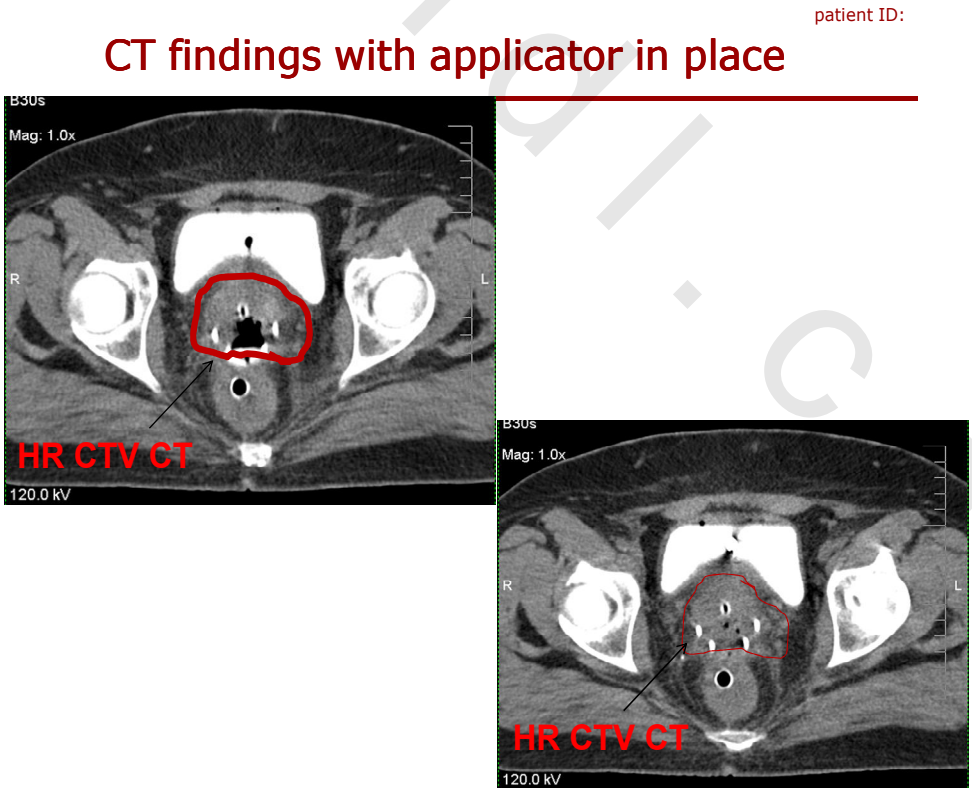


Figure (73): Transverse CT slice with contouring of HR CTV CT

The resulting 3D parameters of HR CTVCT and HR CTVMRI were compared with each other. For comparison between the different HR CTV volume parameters a paired Wilcoxon–rank test was performed. P values < 0.05 were considered significant.

The mean values and standard deviations of height, width, thickness and volume of HR CTVCT and HR CTVMRI are listed in table 28. All parameters are reported as mean ± standard deviation (SD).

Table (28): Mean and standard deviations of volume, height, width, and thickness of HR CTV_{CT}, and HR CTV_{MRI}.

Parameters (mean ± SD)	Volume [cm^3]	Height [cm]	Width [cm]	Thickness [cm]
HR CTVCT	56 ± 20	5.1 ± 1.3	5.4 ± 0.6	3.7 ± 0.5
HR CTVMRI	34 ± 15	4.1 ± 1.5	4.4 ± 0.7	3.2 ± 0.6

Statistically significant differences between the volume of HR CTVCT and volume of HR CTVMRI were found ($p < 0.05$). The volume of HR CTVCT were significantly larger ($p < 0.05$) than the volumes of HR CTVMRI (Figure 74).

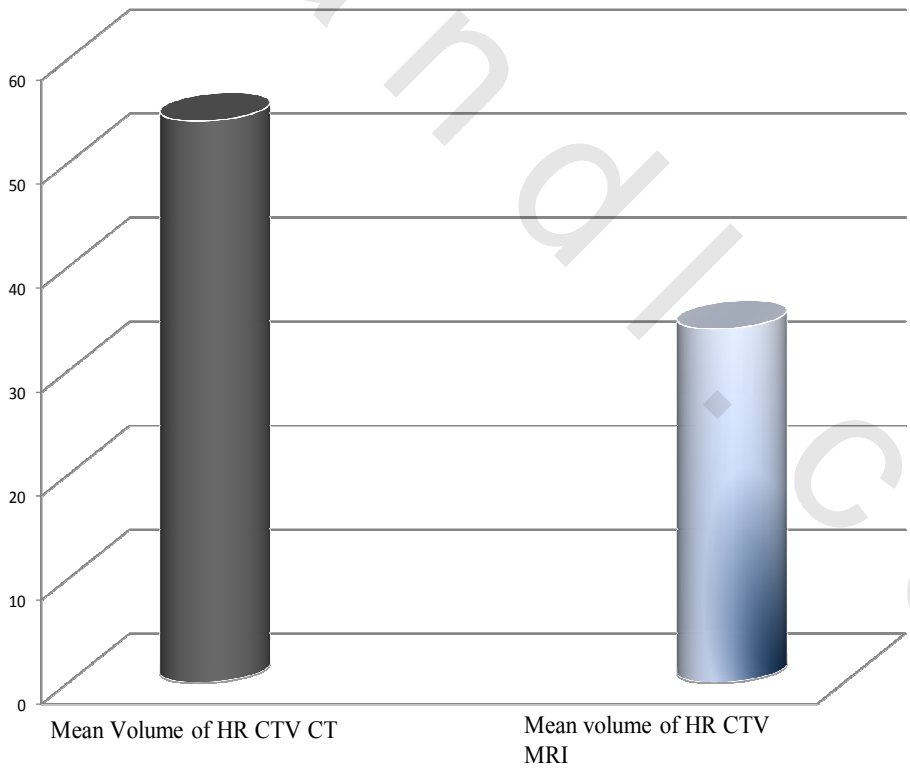


Figure (74): Comparison between Mean volumes of HRCTV CT and HRCTV MRI

The widths of the CT-based HR CTV were larger than the widths of HR CTVMRI. The differences between the mean widths of HR CTVCT and HR CTVMRI was statistical significant (Figure 75) . No statistically significant differences were noticed in regard to thickness (table 28).

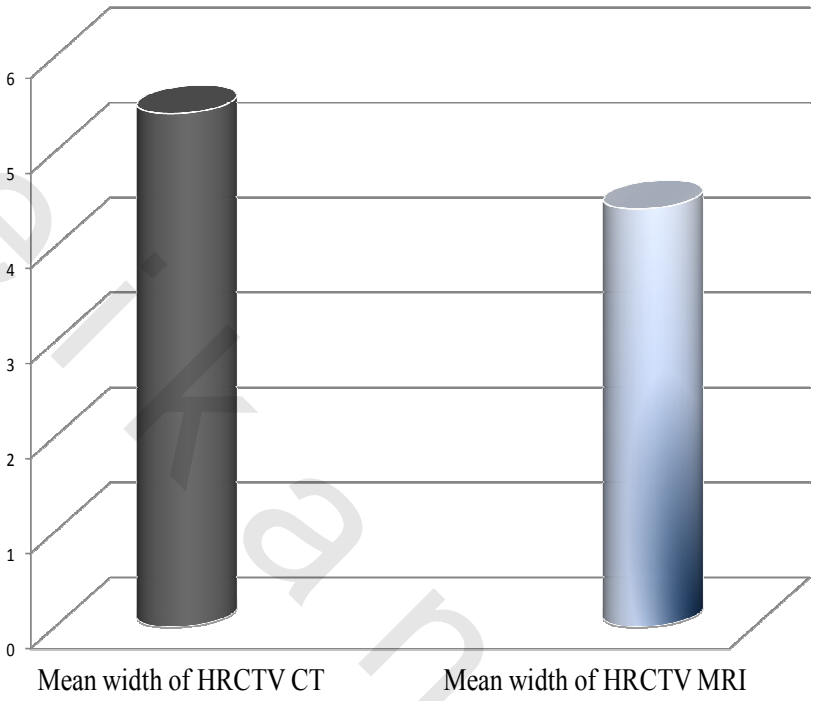


Figure (75): Comparison between Mean width of HRCTV CT and HRCTV MRI

For the HR-CTV, this difference in width resulted in statistically significant differences in the volume treated to the prescription dose. Evaluation of the volume treated to the prescription dose (D90, and D100), showed statistically significant differences between HR CTVCT and HR CTV MRI.

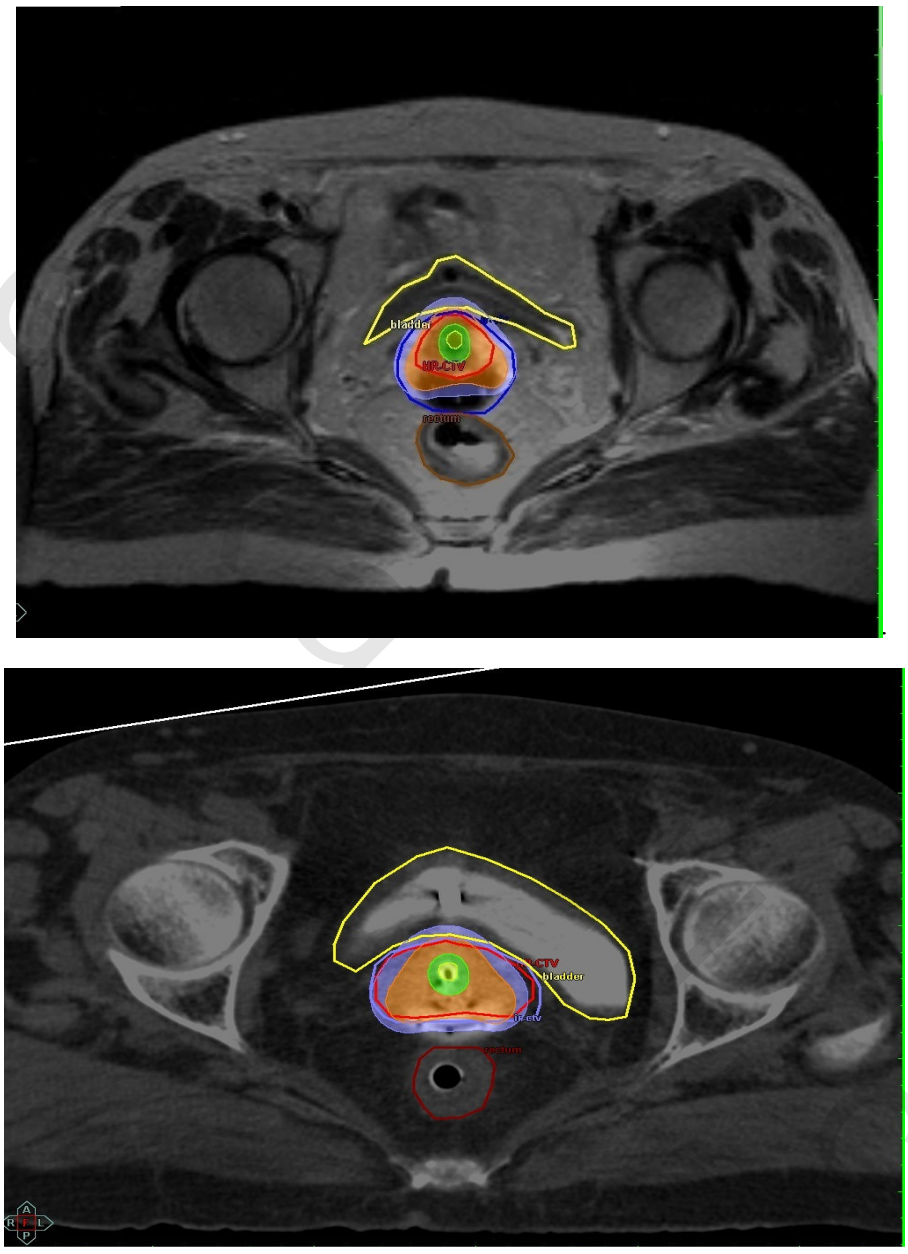


Figure (76): Comparison between coverage of HRCTV CT and HRCTV MRI by prescribed dose.