DISCUSSION

Cervical cancer ranked as the third most common cancer among women worldwide.[128] The majority of cervical cancer-related deaths occur in developing countries, such as Egypt where a population of 25.76 million women over 15 years of age are at risk of developing cervical cancer.[129] Indeed, it has been estimated that around 514 women are diagnosed with cervical cancer and 299 die from the disease in Egypt each year; thus cervical cancer ranks as the second most frequent cancer among Egyptian women.[130]

The treatment of cervical cancer has been and still the domain of radiotherapy. Brachytherapy (BT), in conjunction with External-beam radiation and chemotherapy, is the standard of care in the curative management of locally advanced cervical cancer.[131]

In the last decade, effort has been put into combining radiotherapy with other treatment modalities, mainly chemotherapy resulting in better locoregional control rates and improved survival rates.[74, 86, 132] External treatment using the four-field box technique with field borders generated according to the bony anatomy fail to encompass the target volume adequately in a number of patients .

Therefore, visualization of the primary tumor process and its surrounding organs is one of the crucial steps in the process of improving radiotherapy. Imaging techniques such as computed tomography (CT), magnetic resonance (MR) imaging, and positron emission tomography (PET) visualize the primary cervical tumor, the pathologic lymphatic nodes, and the surrounding organs. [103]

Newly developed treatment strategies and planning techniques make it possible to optimize the doses to the target volumes without increasing the dose to the critical organs. Three dimensional conformal radiation therapy (3D-CRT) as well as intensity-modulated radiation therapy (IMRT) clearly improve dose conformity compared with conventional planning. [133]

However, during the course of radiotherapy, target volumes change position due to internal organ motion and tumor regression . The conformal dose distributions and the steep dose gradients generated around target volumes created by 3D-CRT and IMRT planning require an accurate treatment setup and repeated monitoring to prevent a geographic miss during radiotherapy.

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 this study were divided into two groups. Group A (therapeutic group) included 30 female patients and Group B (imaging group) included 15 female patients with locally advanced cervical cancer.

Group A was be 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.

Whole pelvic radiotherapy (WPRT) is a major component of definitive radiotherapy of cervical cancer. (126) In definitive radiotherapy; external beam radiotherapy (EBRT) is usually combined with intracavitry brachytherapy (BT) to boost the tumor site.[132] WPRT treatment results in the irradiation of large volumes of small and large bowel, rectum and bladder. Therefore, gastrointestinal and genitourinary symptoms are among the most important acute and chronic toxicities in these patients.

To improve treatment side effects , advanced techniques are required to allow delivering adequate doses to both tumor and areas of lymphatic drainage, while at the same time sparing normal structures. Intensity modulated radiation therapy (IMRT) is an approach conforming the high dose region to the shape of irregular and concave target volumes in three-dimensions.[134]

Additionally, steep dose gradients are created, which limit the dose to surrounding normal tissues. In initial planning studies of patients with cervical or endometrial cancer, with or without para-aortal nodal irradiation, it was shown that IMRT reduced the volume of bladder and rectum receiving high dose.[107]

The superiority of intensity modulation for sparing the organs at risk in whole pelvic radiotherapy is well established for both gynecological and urological malignancies. Several studies have reported that IMRT reduces the volume of normal tissues irradiated and decreases acute toxicity compared with conventional techniques.[133]

The purpose of this study was to report the clinical outcomes using IMRT for treatment of local advanced cervical cancer, comparing it with conformal radiotherapy in terms of acute and chronic toxicity. Treatment was well tolerated in our patients.

Most of the patients experienced mild acute toxicity and none required interruption of treatment. Moreover, the toxicity profile of the IMRT patients compared favorably with that of the conformal RT group. There were higher incidence of acute GIT toxicities occurred in patients treated with 3D CRT than in those treated with IMRT. Diarrhea was the most frequent acute GIT toxicity. Diarrhea and abdominal pain developed in 73.3% and 40% of patients of group A1 compared to 60% and 13% of group A2 respectively.

The rate of grade 2 acute GIT toxicity was lower in the IMRT group and the frequency of medication (anti-diarrheal) used was reduced. Also late GIT toxicities were developed more frequently in patients treated with 3D CRT where 60% of patients of group A1 developed GIT toxicities compared to 46.7% of group A2. only one patients in group A2 suffered from late sever GIT toxicity as she had rectovaginal fistula.

The same was reported for genitourinary toxicity where All acute genitourinary symptoms were frequently higher in patients received 3D CRT compared to patients received IMRT. The most frequently encountered symptom was frequency of urination where grade II was reported in 20% and 6% of patients of groups A1 and A2 respectively. Also Acute grade I haematuria was seen in 26.7% of patients in group A1 and in 6.7% of group A2.

These reported patterns of acute and late GIT and GU toxicities in the present study were comparable to the same patterns reported by Chen LA, et al.,[135] who evaluated toxicity of intensity modulated radiation therapy (IMRT) versus 3-dimensional conformal radiation therapy (3DCRT) in the treatment of patients with cervical cancer. In their study, the toxicity rates were reduced with IMRT versus 3DCRT and women who received IMRT had numerically lower rates of late gastrointestinal and genitourinary toxicity and significantly lower rates of late overall toxicity at 3years (16% vs. 45%, p=0.04).

The present results were consistent with results of Gandhi et al,[136] who evaluated the toxicity and clinical outcome in patients with locally advanced cervical cancer . They found that patients in the IMRT arm experienced significantly fewer grade ≥2 acute gastrointestinal toxicities (31.8% vs 63.6%, P=.034) than did patients receiving 3D CRT and had less chronic gastrointestinal toxicity (13.6% vs. 50%, P=.011).

Another retrospective study assessed the acute and chronic toxicity with intensity-modulated radiation therapy (IMRT) in treatment of cervical cancer. In this study; IMRT was well tolerated, with significant reduction in acute gastrointestinal (GI) and genitourinary (GU) toxicities compared with the Box-RT group.[137]

Chinese study[138] evaluated the dosimetry, efficacy and toxicity of reduced field intensity-modulated radiation therapy (IMRT) for patients with advanced cervical cancer. IMRT patients experienced lower acute and chronic toxicities with comparable short-term effects than did those treated with box technique. No significant differences were found between treatment groups for 1year, 3year, and 5year overall survival (OS) levels, while a significantly higher progression-free survival (PFS), (P=0.031) was seen for IMRT.

In the present study there was a statistical significant reduction in the volume of small bowel receiving high radiation dose where the mean radiotherapy dose received by the small bowel in patients who received IMRT radiotherapy was 27.16 ± 1.43 Gy. In patients treated by 3D conformal radiotherapy, the mean radiotherapy dose received by small bowel 41.07 ± 1.33Gy.

Also there was a statistical significant reduction in the mean dose of radiotherapy received by the rectum in patients of group A2 compared to that of patients of group A2 (p=0.003). The mean rectum dose in patients receiving IMRT was 41.46 Gy ± 0.93 while it was 47.93Gy ± 7.51 in patients receiving 3D CRT.

The median mean bladder radiotherapy dose was significantly higher in group A1 compared to group A2 (p value = <0.001) where the mean bladder dose was 45.20 Gy ± 1.26 in group A1 and was 41.40Gy ± 1.35 in group A2. The results of present study suggested that minimizing the volume of small bowel, rectum and bladder irradiated to high dose translates into less acute GI and GU toxicity.

Previous investigators have reported that IMRT provided significant reduction in the volume of small bowel receiving 30–40 Gy .[111, 139] Roeske et al [110] showed that the volume of small intestine irradiated to 75% of the prescribed dose (33.75 Gy) or more are significantly associated with clinically significant acute GI toxicity, and the volume of rectum irradiated to 110% of the prescribed dose (49.5 Gy) with borderline significance.

Also another study showed that significant reductions in the volume of normal tissues irradiated to high doses were seen in patients treated using IMRT. At the 45-Gy dose level, the average volume of small bowel irradiated was reduced by a factor of 2 (17.4% vs 33.8%,). [111]

Also the results of present study was comparable with results of Georg P et al,[140] that compared a conformal four field technique and a seven field IMRT plan (prescription dose 50.4 Gy) in terms of DVH and various target parameters. At doses between 40 and 50.4 Gy statistically significant improvements ($P<0.05$) were observed for IMRT-WPRT for irradiated volume of rectal wall and bladder. This study reported that IMRT significantly reduced the absolute volume of rectal wall, bladder and bowel irradiated at the prescribed dose level in gynaecological patients and bladder filling is an important co-factor influencing the benefit of IMRT with respect to OAR sparing.

Retrospective study determined the influence of target-volume expansion on the reduction in the small-bowel dose achieved with the use of intensity-modulated radiation therapy (IMRT) vs. standard conformal treatment of the pelvis. Significantly less small bowel was irradiated by IMRT than by 2 field ($p < 0.0001$) or 4field conformal radiotherapy ($p < 0.0001$) for doses greater than 25 Gy. Significantly less rectum was irradiated by IMRT than by 2FC ($p < 0.0001$) or 4FC ($p < 0.0001$). Significantly less bladder was irradiated by IMRT than by 2FC ($p < 0.0001$). Accurate target delineation, highly reproducible patient immobilization, and a clear understanding of internal-organ motion were needed to achieve optimal advantage in the use of IMRT over conventional methods of pelvic radiation therapy. [111]

Also same result was described by doesimetric study that evaluated the ability of intensity-modulated radiation therapy (IMRT) to reduce the volume of small bowel irradiated in women with gynecologic malignancies receiving whole pelvic radiotherapy (WPRT). Ten women with cervical cancer undergoing WPRT were selected and two plans were created: a standard "4-field box" with apertures shaped to the PTV in each beam's eye view and an IM-WPRT plan designed to conform to the PTV while minimizing the volume of normal tissues irradiated. [107]

In this doesimetric study IM-WPRT plan reduced the volume of small bowel irradiated in all 10 patients at doses above 30 Gy. At the prescription dose, the average volume of small bowel irradiated was reduced by a factor of two (17.4 vs. 33.8%, $p = 0.0005$). In addition, the average volume of rectum and bladder irradiated at the prescription dose was reduced by 23%.[107]

Group B (Imaging Group):

Brachytherapy plays an essential role in definitive radiotherapy of cervix cancer. In 2D BT, the doses are prescribed to specific points with only limited information on patient anatomy and tumour extension. This may result in inadequate estimation of dose to tumour

and OAR. The 3D based BT allows the proper delineation of target and permits the optimization of dose to individual tumour topography while sparing adjacent OARs.

However, in many institutions, it may remain difficult to perform MRI guided BT because of limited resources, i.e. unavailability of MRI near the BT unit. 3D CT-based brachytherapy may be considered as alternative under such circumstances. The present study evaluated CT based HR CTV delineation and compared this to the MRI guided approach.

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 at time of BT. T2-weighted MRI studies after BT applicator placement were generated in 5 mm slice intervals. The HR CTVMRI was contoured according to the Gyn GEC-ESTRO recommendations. HR CTVCT was delineated on CT images.

In order to evaluate the potential improvement of a fully CT-based delineation protocol, for settings without access to MRI at the time of brachytherapy, the use of information based on FIGO stage with adding precise documentation of gynaecological findings was investigated in this study. The quality of the CT-based HR CTV contours was assessed by comparison with the gold standard, i.e. MRI based target delineation.

In present study; there was a statistically significant differences between the volume of HR CTV CT and volume of HR CTVMRI where the volume of HR CTVCT were significantly larger ($p < 0.05$) than the volumes of HR CTVMRI. The widths of the CT-based HR CTV were larger than the widths of HR CTVMRI as the place and extent of parametrial infiltration was often not detectable on CT in more than 60% of cases. The differences between the mean widths of HR CTVCT and HR CTVMRI was statistical significant difference. No statistically significant differences were noticed in regard thickness.

Also we included most of the height along the uterine cavity into the HR CTV in advanced stages as the height of the individual uterine tumour invasion could not be assessed in the study population, as neither CT nor clinical examination were capable of assessing uterine tumour invasion in cervix carcinoma.

A straightforward approach for CT-based treatment planning was to keep the full loading of intrauterine tandem length up to its tip as planning aim according to traditional practice. The potential dosimetric benefit of these improved CT-based target structures has not been assessed in the present study. Overall, the reported DVH-parameters for CT-based target structures are expected to underestimate systematically the dose (in range between 20-40%)to the corresponding MRI-based HR CTV, which is usually smaller according to present findings, in particular in regard to height and width.

While MRI remains the standard for contouring HR CTV for 3D IGBT, CT-based delineation of HR CTV may be applied in situations with limited imaging resources. However, to arrive at a clinically acceptable accuracy such CT-contouring always has to be based on a comprehensive 3D-documentation of repetitive gynaecologic examination.

These findings are in agreement with other reports and were due to the inferior soft tissue contrast of CT which does not allow identification of macroscopic tumour. The comprehensive information of disease spread based on clinical examination may contribute to reduce the inaccurate CT-based volume determination, (in particular in width) and. additional value most likely would be gained if also the same person doing the gynaecological examination is also doing the contouring.

Several studies compared CT-guided BT with conventional BT and demonstrated that CT-based planning is superior to conventional planning, improving conformity of target coverage. Shin et al.,[141] compared in patients with cervical cancer intracavitary BT conventional point A plan (conventional plan) and computed tomography (CT)-guided clinical target volume-based plan (CTV plan) by analysis of the quantitative dose-volume parameters and irradiated volumes of organs at risk.

The macroscopic residual cervical tumour was delineated on CT images with information of CGE and pre-treatment MRI. He found that Computed tomography-guided CTV planning of ICR is superior to conventional point A planning in terms of conformity of target coverage and avoidance of overdosed normal tissue volume.

Also the results of present study was comparable to results of Viswanathan et al., study.[142] Viswanathan et al., compared the contours and dose-volume histograms (DVH) of the tumor and organs at risk (OAR) contoured on computed tomography (CT) vs. magnetic resonance imaging (MRI) in cervical cancer brachytherapy. This study found that computed tomography-based or MRI-based scans at brachytherapy are adequate for OAR DVH analysis. However, CT tumor contours can significantly overestimate the tumor width, resulting in significant differences in the D(90), D(100), and volume treated to the prescription dose or greater for the HR-CTV compared with that using MRI. MRI remains the standard for CTV definition.

Moreover Eskander R et al[143] evaluated the differences between target and normal tissue delineation between magnetic resonance imaging (MRI) and computed tomography (CT) in cervical cancer patients and The CT- and MRI-based brachytherapy tissue delineation seems adequate for evaluation of OAR and target tissues, although the shapes of HR-CTV and OAR do differ. When adopting volume-based prescription, these differences may lead to altered target dosing. The clinical impact of these differences seems to be small and may demonstrate that planning with CT, if combined with one MRI, may be sufficient.

Overall, CT-based contouring can be significantly improved by careful integration of comprehensive CGE at diagnosis and at time of BT, in particular for appropriate width to improve the accuracy of dose optimization in settings with limited access to imaging facilities at the time of brachytherapy. The height of the HR CTV should be determined by applying standard heights.

The results presented here, are based on a medium-size cohort of patients who were evaluated retrospectively. Therefore, these findings need to be validated within a larger (multi-institutional) prospective trial.

SUMMARY AND CONCLUSIONS

Cervical cancer ranked as the third most common cancer among women worldwide. Brachytherapy (BT), in conjunction with External-beam radiation and chemotherapy, is the standard of care in the curative management of locally advanced cervical cancer. WPRT treatment results in the irradiation of large volumes of small and large bowel, rectum and bladder. Therefore, gastrointestinal and genitourinary symptoms are among the most important acute and chronic toxicities in these patients.

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receiving high radiation dose where the mean radiotherapy dose received by the small bowel in patients who received IMRT radiotherapy was 27.16 ± 1.43 Gy. In patients treated by 3D conformal radiotherapy, the mean radiotherapy dose received by small bowel 41.07 ± 1.33Gy.

Also there was a statistical significant reduction in the mean dose of radiotherapy received by the rectum in patients of group A2 compared to that of patients of group A2 (p=0.003). The mean rectum dose in patients receiving IMRT was 41.46 Gy ± 0.93 while it was 47.93Gy ± 7.51 in patients receiving 3D CRT. The median mean bladder radiotherapy dose was significantly higher in group A1 compared to group A2 (p value = <0.001) where the mean bladder dose was 45.20 Gy ± 1.26 in group A1 and was 41.40Gy ± 1.35 in group A2.

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