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A Comparison of dosimetric parameters of volumetric modulated arc therapy and three dimensional conformal radiotherapy in locally advanced Carcinoma Cervix.

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Abstract: *The standard of care for locally advanced carcinoma cervix is concurrent chemoradiotherapy followed by brachytherapy. Recent advances in radiotherapy treatment delivery include three-dimensional conformal radiotherapy (3DCRT), Intensity-modulated radiotherapy(IMRT), Volumetric modulated radiotherapy(VMAT) have been in use and have shown to decrease the doses to normal tissues. Fifteen patients of biopsy proven locally advanced non metastatic cervical cancer patients were chosen for this study, VMAT and 3DCRT plans were generated for all the fifteen patients and plan parameters were compared. Our study showed no statistically significant difference between VMAT and 3DCRT plans in mean bowel dose (p=0.446), V30(p=0.08) and V45(0.132) doses. There was significant difference in mean rectal dose(p=0.001), V30(0.001) and V50(p=0.05) dose. For bladder dosimetric parameters there was significant difference for mean bladder dose(0.001) but not V30(p=0.056) and V50(0.852).*

Keywords: *Cervix, radiotherapy, VMAT.*

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I. Introduction

Cervical cancer is the third most common cancer in women and the seventh most common cancer worldwide [1]. Concurrent cisplatin-based chemoradiation in combination with brachytherapy has been established as the standard treatment for locally advanced cervical carcinoma (LACC) [2]. However, the survival rates remain modest, with a 5-year disease-free survival (DFS) and overall survival (OS) of approximately 50% to 60%, respectively and 5-year pelvic failure rates approximating 30% with a combined modality approach [2]. Traditionally, whole pelvic radiation therapy with either a 2-field or a 4-field technique has been used, but it is associated with significant rates of gastrointestinal (GI) and hematologic toxicities [3]. Dosimetric studies have shown that intensity-modulated radiation therapy (IMRT) can reduce bowel,rectal,bladder,and bone marrow dose [4-6], and early clinical studies have demonstrated lower rates of GI,genitourinary (GU), and hematologic toxicity compared with conventional techniques[4, 7, 8]. Yet, although clinical outcome has been reported to be comparable to that of conventional techniques [9-11], prospective studies comparing IMRT with conventional techniques for LACC are lacking. We conducted a dosimetric study to compare the bowel, rectum and bladder doses between 3DCRT and VMAT plans of 15 cases.

II. Materials and methods

Fifteen patients of biopsy proven locally advanced non metastatic cervical cancer patients were chosen for this study. All patients underwent CT-based planning in a supine position and were immobilized with custom thermoplastic immobilization devices. All patients received a bowel preparation before simulation. If a full rectum was noted on the simulation study, patients were instructed to repeat the bowel preparation, and a repeat simulation scan was done the next day. A bladder filling protocol (after voiding, patients were asked to drink 1 liter of water 30 to 45 minutes before treatment and to hold urine) was followed at the time of simulation and subsequently before each treatment to limit interfraction or intrafraction variability. A radio-opaque cervical marker measuring 0.5 mm was placed in the vagina at the most distal portion of the cervical growth for orientation. After the administration of oral and intravenous contrast medium, 3-mm CT images were obtained from the upper border of the L2 vertebral body to 3 cm below the ischial tuberosity. All patients were treated on a linear accelerator, Clinac iX-3665 (Varian Medical System, Palo Alto, CA).

The clinical target volume (CTV) included both the primary tumor site and regional lymphatics. The primary CTV included the entire uterus, cervix, parametrium, and vagina up to 3 cm below the vaginal marker. The nodal CTV included the common iliac, external and internal iliac, obturator, and presacral nodes. The inguinal lymph nodes were included in cases of lower vaginal involvement, and all lymph nodes were contoured

according to the guidelines by Taylor et al (13). The planning target volume (PTV) was defined as a 1-cm isotropic expansion of the primary CTV and a 0.7-cm isotropic expansion of the nodal PTV. Organs at risk, including the bowel bag, rectum and bladder were also contoured. In particular, the small bowel was contoured en bloc from the axial slice situated 1 cm superior to the most superior slice containing the PTV and continued to its most inferior extent in the pelvis. Individual loops of bowel were not contoured separately. The outer rectal wall was contoured separately, the organ being treated as a solid continuous structure, and was defined from the level of the sigmoid flexure to the anus. The outer bladder wall was similarly contoured as a solid continuous structure. Target planning constraints used were as follows: (1) 95% prescription isodose surface to encompass _95% of the PTV; (2)< 1% of PTV to receive _110% of the prescription dose; and (3) maximum dose _110%, limited to within the PTV. Planning constraints for normal tissues were as follows: (1) small bowel: volume receiving 40 Gy (V40) <32%; maximum dose <50 Gy; (2) rectum: V40 <40%; maximum dose <50 Gy; and (3) bladder: V40 <40%; maximum dose <50 Gy. The volume of the small bowel receiving 90% and 100% of the prescription doses was also noted because it has been shown to correlate with acute GI toxicity (6).

Volumetric modulated arc therapy planning The VMAT plans consisted of two optimized coplanar arcs, one with beam‐ on gantries rotating in the clockwise direction and the other arc used the same beam‐ on gantries but rotating in the counter‐ clockwise direction oriented tangentially. Collimation of 20° was used for all plans. Both used the same gantry angles. For all plans, 6 MV photons with a dose rate of 600 MU were used. DVH parameters studied, Mean dose in Gy, V30(%), V50(%) of Rectum (volume of Rectum receiving 30Gy, 45Gy, mean dose in Gy, V30 (%), V50 (%) of Bladder (volume of Bladder receiving 30Gy, 50Gy, mean dose in Gy, V30(%), V45 (%) of Bowel bag (volume of Bowelbag receiving 30Gy, 45Gy). A set of 3DCRT plans were generated for all the fifteen patients with standard four field technique.

The data on parameters of VMAT and 3DCRT were expressed as mean with standard deviation. The comparison of the difference in parameters between VMAT and 3DCRT was carried out by using the unpaired t‐ test. The dosimetric profiles of the OAR were expressed as frequencies and percentages and were compared by using the Chi‐ square test. All statistical analysis was carried out at 5% level of significance, and $p < 0.05$ was considered significant. The unpaired t‐ test was used for comparing the means of all the dosimetric parameters, and the two‐ tailed p values were obtained using the SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) software.

III. Results

All the individual plan parameters of VMAT and 3DCRT of the fifteen patients were compared including the dose volume histogram parameters.The volume of each organ of interest receiving doses in excess of 30 Gy was compared in the 3D and IMRT treatment plan. The mean volume of small bowel receiving doses in excess of 30 Gy was reduced by 18% (p=0.08) with IMRT compared with 3D. A similar advantage was noted for the rectum (26.7% reduction p=0.001) and the bladder (22.6% reduction, p=0.05). At all dose levels, the dose-volume histogram for IMRT was superior to those seen with the 3D plan. Comparative dose distributions of an IMRT plan and a 3D plan were evaluated. The mean dose to Bowel was lower for the VMAT plans (25.94±7.07 for the 3DCRT plans and 23.14 ± 6.01 for the VMAT plans, p=0.44). The mean values of V30 Gy and V45 Gy for Bowel were 36.53 ± 18.37 and 17.96 ± 12.84 for the 3DCRT plans and 32.36 ± 11.87 and 8.06 ± 2.13 for VMAT plans, p-value being 0.08 for V30 and 0.132 for V45 respectively. The mean dose to Rectum was lower for the VMAT plans (49.52± 2.03 for the 3DCRT plans and 41.09 ± 5.10 for the VMAT plans, p=0.001). The mean values of V30 Gy and V50 Gy for Rectum were 97.39± 4.18 and 75.62 ± 14.70 for the 3DCRT plans and 76.83 ± 14.80 and 42.36 ± 10.24 for VMAT plans, p-value being 0.001 for V30 and 0.05 for V50 respectively. The mean dose to Bladder was lower for the VMAT plans (50.34± 1.77 for the 3DCRT plans and 40.96 ± 4.30 for the VMAT plans, p=0.001). The mean values of V30 Gy and V50 Gy for Rectum were 97.71 ± 7.85 and 84.73 ± 9.39 for the 3DCRT plans and 79.68 ± 10.56 and 42.43 ± 11.35 for VMAT plans, p-value being 0.05 for V30 and 0.852 for V50 respectively.

IV. Discussion

Several authors have correlated the volume of normal tissue and treatment-related acute and late toxicity [9,14,20,32–35]. Gallagher et al. conducted a prospective trial to evaluate the impact of several techniques to reduce the volume of small bowel in a group of patients undergoing pelvic radiotherapy [5]. They found that the severity of acute effects closely correlated with the volume of small bowel irradiated. More troubling was the finding that the more severe the acute toxicity, the greater the incidence of late bowel effects. Both acute and late effects were inextricably correlated with the dose of small bowel receiving more than 45 Gy [23,27,36].

The importance of radiation-associated genitourinary and gastrointestinal toxicity is best understood when viewed from a quality-of-life perspective. It is therefore important to minimize treatment-related late effects in a group of patients who are likely to have significant survival posttreatment. Intensity-modulated radiotherapy can deliver treatment to a complex geometrical target in close proximity to nearby critical structures. As such, IMRT appears to offer several advantages over conventional 3D treatment planning for gynecologic malignancies. These include a significant reduction in treatment volume for bladder, rectum, and small bowel. In our study, the normal structures were preferentially spared with the IMRT plan as a result of the use of conformal avoidance, i.e., limiting the radiation dose below the designated threshold limit. In fact, at some dose levels, the dose to the small bowel and rectum was reduced by factors of 2 while maintaining full dose to the target tissues. More importantly, doses in excess of 45 Gy have been associated with an increased risk of late radiation complications. Using IMRT, the volume of rectum, bladder, and small bowel irradiated was reduced by a factor of at least 10. If the dose and volume of normal tissues irradiated can be significantly reduced, the incidence and severity of acute and late gastrointestinal and genitourinary toxicity may be ameliorated. Several authors have suggested that the use of IMRT for gynecologic cancer has resulted in significantly lower rates of grade 2 gastrointestinal and genitourinary symptoms, without interruption of treatment [19]. This relative sparing with IMRT may allow for dose escalation while maintaining the relative dosimetric advantage for normal tissues. This has been successfully exploited in the treatment of prostate cancer and has resulted in a significant improvement in local control while decreasing the rates of late treatment effects compared with conventionally treated patients [38]. At the very least, treatment with IMRT has the potential to change the risk-benefit ratio in favor of fewer treatment-related toxic effects There are admittedly several limitations with our current study. First, there is a relative lack of data on organ motion, particularly as it relates to pelvic and abdominal structures. Several reports have detailed the movement of the kidneys, prostate, bladder, and rectum in the treatment of prostate cancer [10,26,39,40]. Data gathered on rectal movement from prostate and rectal cancer using 3D CRT and serial CT have confirmed the variability of movement to be approximately 1.5–2 cm at most [34]. However, the targets for adjuvant radiotherapy for gynecologic malignancies are less likely to be as mobile. Because the vagina is not attached to the bladder as in the normal state, the movement as a result of bladder filling is likely significantly diminished. We reviewed the isodose distribution in all cases with particular attention to the vagina and paravaginal tissues and the DVH showed full coverage of this volume. The combination of a larger contoured target volume to actual volume and the presumed limited vaginal motion may allow for a more predictable inclusion in the high dose field. The regional lymphatics are unlikely to attain the same degrees of freedom as other pelvic structures although this has not been convincingly proven in the literature. In our study, we intentionally did not outline specific loops of bowel, but instead we contoured the peritoneal cavity in which the bowel was likely to be encountered. This methodology, as others have found, is more likely to overestimate the dose to small bowel as represented in the DVH since the probability of small bowel residing in a specific region of the pelvis is variable from day to day [41]. Pioneering work on lymph node location based on bony landmarks from researchers at the Mallinckrodt Institute of Radiology was presented at the American Society of Therapeutic Radiology and Oncology (ASTRO) 2001, San Francisco [42]. Lin and Chao used lymphangiogram-assisted CT evaluation of pelvic nodal regions in relationship to the bony structures of the pelvis. They found a predictable relationship of the internal, external, and common iliac nodes using referenced anatomical landmarks on cross-sectional CT.

Our study showed no statistically significant difference between VMAT and 3DCRT plans in mean bowel dose (p=0.446), V30(p=0.08) and V45(0.132) doses. There was significant difference in mean rectal dose(p=0.001), V30(0.001) and V50(p=0.05) dose. For bladder dosimetric parameters there was significant difference for mean bladder dose(0.001) but not V30(p=0.056) and V50(0.852).

V. Conclusion

The study demonstrates the dosimetric superiority of VMAT over 3DCRT in the treatment of carcinoma cervix. It is anticipated that this reduction in normal tissue irradiated volume would translate into an overall reduction in acute and potentially late treatment-related toxicity. Prospective trials are necessary to further evaluate the advantages and cost-effectiveness in a larger group of patients.

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