REPORTS OF PRACTICAL ONCOLOGY AND RADIOTHERAPY 21 (2016) 195–200

Available online at www.sciencedirect.com

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Original research article

Should we customize PTV expansions for BMI? Daily cone beam computerized tomography to assess organ motion in postoperative endometrial and cervical cancer patients

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ARTICLE INFO

Article history:
Received 29 July 2015
Received in revised form
4 November 2015
Accepted 7 February 2016
Available online 2 March 2016

Keywords:
BMI
Postoperative pelvic radiation
IMRT
IGRT
Organ motion

ABSTRACT

Aim: A single-institution review assessing patient characteristics contributing to daily organ motion in postoperative endometrial and cervical cancer patients treated with intensity-modulated radiotherapy (IMRT).
Background: The Radiation Therapy Oncology Group has established consensus guidelines for postoperative pelvic IMRT, recommending a 7 mm margin on all three axes of the target volume.
Materials and methods: Daily shifts on 457 radiation setups for 18 patients were recorded in the x axis (lateral), y axis (superior–inferior) and z axis (anterior–posterior); daily positions of the planning tumor volume were referenced with the initial planning scan to quantify variations.
Results: Of the 457 sessions, 85 (18.6%) had plan shifts of at least 7 mm in one of the three dimensions. For obese patients (body mass index [BMI] $\geq$ 30), 75/306 (24.5%) sessions had plan shifts $\geq$7 mm. Odds of having a shift $\geq$7 mm in any direction was greater for obese patients under both univariate (OR 4.227, 95% CI 1.235–14.466, $p = 0.021$) and multivariate (OR 5.000, 95% CI 1.341–18.646, $p = 0.016$) analyses (MVA). Under MVA, having a BMI $\geq$ 30 was associated with increased odds of shifts in the anterior–posterior (1.173 mm, 95% CI 0.281–2.065, $p = 0.001$) and lateral (2.074 mm, 95% CI 1.284–2.864, $p < 0.000$) directions but not in the superior–inferior axis (0.298 mm, 95% CI −0.880 to 1.475, $p = 0.619$) exceeding 7 mm.
Conclusions: Based on these findings, the standard planned tumor volume expansion of 7 mm is less likely to account for daily treatment changes in obese patients.

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http://dx.doi.org/10.1016/j.rpor.2016.02.003

1. Background

Over two-thirds of the United States population is currently overweight or obese with the trend continuing to increase.[1] Obesity is known to contribute to increasing rates of commonly occurring cancers including endometrial, where approximately 50–90% of all cases in the United States are attributable to obesity.[2,3] The World Cancer Research Fund published data concluding endometrial cancer to have the highest relative risk (RR = 3.40) of development from obesity with 49% of U.S. diagnoses being preventable.[4] Both pre-menopausal and postmenopausal obese women have been found to have higher rates of endometrial cancer.[3] In addition, increasing rates of obesity appears to be contributing to higher rates of endometrial cancer in the younger age population as well.[5]

Many patients who have undergone hysterectomy for endometrial or early-stage cervical cancer require postoperative pelvic radiotherapy with a number of randomized trials showing improvements in local control and progression free survival.[6] To reduce surrounding normal tissue dosing and overall short-term and long-term side effects from treatment, radiation oncologists have transitioned away from conventional external beam plans with large treatment fields and have trended to more conformal plans. Much of this is made possible by intensity-modulated radiotherapy (IMRT) which has become increasingly used for postoperative cervical and endometrial cancers.[7,8] Studies have suggested significantly lower rates of acute and late toxicity using postoperative pelvic IMRT.[9–12] IMRT compared to 3D planning is currently being studied in an ongoing clinical trial (RTOG 1203).

IMRT requires precise targeting with tumor and organ delineation and therefore requires accurate daily setup to prevent under-dosing of tumor or over-dosing organs at risk.[13] The incorporation of daily image guidance (IGRT) has ensured that these conformal treatment plans align precisely to the targeted field.[14]

2. Aim

In 2008, the RTOG established a contouring atlas with consensus guidelines for postoperative pelvic IMRT for endometrial and cervical cancer.[15] The guidelines established two separate clinical tumor volumes (CTVs) encompassing the vaginal cuff and parametrial tissue based on the bladder being full and empty. This volume was defined as the internal target volume (ITV). The guidelines also recommend a 7 mm margin on all three axes of the target volume for radiation treatment for postoperative cervical and endometrial cancers. However, the concern we look to address may be that these margins are inadequate for patients with increasing body mass index (BMI) or other related factors. In our department, a number of postoperative cervical and uterine cancer patients undergo daily position verification using cone beam computed tomography (CBCT). Daily volume shifts from the original planning CT scan are then recorded. Based on our observation, patients with higher BMI tend to have greater treatment shifts. Therefore, the goal of this retrospective single-institution study was to review daily CBCT shifts to better understand whether current recommended margins are sufficiently accounting for organ and tumor motion and if certain patient characteristics including BMI predict for greater motion.

3. Material and methods

3.1. Patient selection

Chart review of 94 consecutive patients treated with post-operative IMRT for endometrial or cervical cancer from 2012 through 2014 performed at our institution were reviewed. Of those, 18 patients, who had undergone daily cone beam computed tomography (CBCT) using kilovoltage (kV) imaging, were included in the study. All patients were treated using the Varian TrueBeam system (Varian Medical Systems, Inc.). We excluded patients without upfront surgery and those who did not undergo daily CBCT prior to each treatment. The 18 patients underwent a total of 457 radiation treatment sessions. The median number of treatments was 27. This retrospective analysis was reviewed and approved by the institutional review board.

3.2. Treatment volumes and planning

At the time of CT Simulation, all patients were set up supine, arms overhead, and a custom alphacradle was made for daily immobilization. Tattoos were placed to be used daily during treatment for initial positioning with lasers. Treatment volumes were created using the ASTRO 2008 gynecologic post-operative consensus guidelines. The vaginal and parametrial clinical tumor volume (CTV) was contoured with full and empty bladder scans. The vaginal cuff CTVs from the full and empty bladder were combined to create an internal target volume (ITV). Lymph node CTV, included a 1 cm expansion off the common, internal, and external iliac vessels including any clinical or pathologically enlarged lymph nodes. An expansion of 7 mm was generated from the nodal CTV and ITV to create the planning tumor volume (PTV). The treatment plans were generated using the Varian Eclipse Planning System v11.

3.3. Daily imaging

All patients were treated with a full bladder; patients were instructed to have 300 ml of water one hour prior to treatment. Daily kilovoltage CBCT scans were used for pretreatment verification and setup confirmation. The CBCT scans were compared and matched to the full bladder simulation scan used for treatment planning, aligning to bony pelvic landmarks for nodal coverage and soft tissue for vaginal cuff matching. Three-dimensional image registration was used. Automatic registration followed by manual adjustments were performed daily by therapists and verified by physicians. Shifts were recorded in the x axis (lateral dimension), y axis (superior–inferior dimension) and z axis (anterior–posterior dimension). These daily recorded coordinates were compared to the planned isocenter placed on the original simulation scan used for planning. Daily changes in the X, Y, and Z direction were recorded.

3.4. Statistical analysis

Daily adjustments from the initial treatment planning scan were recorded and extracted for data analysis. Binary outcomes (yes/no) were reported based on any of the (X, Y, Z) adjustments exceeding 7 mm in absolute value. Euclidean distance from the origin of adjustment were also calculated, using $\sqrt{(X^2+Y^2+Z^2)}$. Absolute distance from the origin (based on individual shifts in X, Y, Z) were also measured. Each of these outcomes were initially assessed using simple regression models, using BMI of the patients prior to radiation therapy to predict the outcome. Additional analysis was performed looking at other predictors including age, stage, histology, time from surgery, surgery for cervical versus uterine, robotic versus laparoscopic, symptoms (GI versus other), and other clinical measures.

Generalized estimating questions (GEE) were used to assess the association between BMI and each of our measures to account for the correlation between measurements on the same individual. When the outcome was dichotomous (yes/no), a logit link was assumed and, thus, GEE was analogous to logistic regression when there were repeated measurements. With continuous outcomes, the GEE model was fairly analogous to repeated measures ANOVA. BMI was categorized as obese (BMI ≥ 30) versus non-obese (BMI < 30). Categorization of BMI was deemed necessary after inspection of the data suggesting that treatment of the BMI as a continuous variable would violate several assumptions required for generalized linear models. For each outcome, we initially assessed the association with BMI without adjusting for other factors. The final analysis for each measure was adjusted for type of surgery the subject had, the age of the patient, and time (days) between surgery and the radiation treatment. The adjustment variables were selected a priori but were chosen from the full list of possible adjustment variables after determining if there were sufficient observations to support the regression analysis for each level of the predictors. The data analysis was done in R version 3.1.0 (2014-04-10)[16] with the GEE model fitted via the geepack package[17]. Statistical significance was set at the 0.05 level.

4. Results

4.1. Patient and treatment characteristics

Patient data summary is included in Table 1. From January 2012 to January 2014, 18 patients were included in the study, all of whom had daily CBCT for treatment position verification. The majority ($n = 17$) were postoperative endometrial cancers, with a single postoperative cervix cancer. Mean age was 56. International Federation of Gynecology and Obstetrics (FIGO) staging varied from 1A ($n = 4$), 1B ($n = 1$), 2A ($n = 2$), 3A ($n = 4$), 3C1 ($n = 5$), 4B ($n = 1$), and unknown ($n = 1$). Mean tumor size was 4.9 cm. Patients either underwent laparoscopic ($n = 11$) or robotic ($n = 7$) hysterectomies. Time between surgery and radiation start day was 163 days. At the time of radiation planning, there was a mean full bladder volume of 228 cm,[3] bladder empty volume of 89.5 cm,[3] rectal volume of 85.8 cm,[3] ITV of 73.1 cm,[3] and final PTV size of 1239 cm.[3] Mean radiation dose was 49.7 Gy and mean duration of treatment was 39 days. The mean BMI before and after treatment was 31.2 and 30.7, respectively.

4.2. Daily shifts and BMI

The 18 patients in the study underwent 457 radiation treatment sessions. Of those, 85 (18.6%) had a plan shift of

Table 1 – Patient and treatment characteristics.

Variable	All patients	BMI < 30	BMI ≥ 30	P-value
Primary site (n, %)				1.000
Cervix	1 (5.6%)	0 (0.0%)	1 (8.3%)	
Uterus	17 (94.4%)	6 (100.0%)	11 (91.7%)	
Age (years)				0.865
Mean (SD)	55.83 (8.75)	56.33 (8.29)	55.58 (9.33)	
FIGO (n, %)				0.510
1A	4 (22.2%)	2 (33.3%)	2 (16.7%)	
1B	1 (5.6%)	0 (0.0%)	1 (8.3%)	
2A	2 (11.1%)	1 (16.7%)	1 (8.3%)	
3A	4 (22.2%)	0 (0.0%)	4 (33.3%)	
3C1	5 (27.8%)	2 (33.3%)	3 (25.0%)	
4B	1 (5.6%)	1 (16.7%)	0 (0.0%)	
Unknown	1 (5.6%)	0 (0.0%)	1 (8.3%)	
Tumor size (cm)				0.004
Mean (SD)	4.86 (1.55)	3.53 (1.07)	5.58 (1.27)	
Radiation dose (Gy)				0.888
Mean (SD)	49.65 (3.98)	49.87 (4.78)	49.54 (3.75)	
Number of fractions				0.355
Mean (SD)	27 (1.5)	27 (1.6)	26 (1.6)	
Dose per fraction (Gy)				0.559
Mean, SD	1.88 (0.15)	1.85 (0.12)	1.89 (0.17)	

Abbreviations: BMI, body mass index; SD, standard deviation; FIGO, international federation of gynecology and obstetrics; ITV, internal target volume; PTV, planned tumor volume.

Table 2 – Summary of shifts by body mass index.

Variable	All patients	BMI < 30	BMI ≥ 30
AP shift (*n*, %)			
<7 mm	420 (91.9%)	147 (97.4%)	273 (89.2)
≥7 mm	37 (8.1%)	4 (2.6%)	33 (10.8%)
SI shift (*n*, %)			
<7 mm	428 (93.7%)	145 (96.0%)	283 (92.5%)
≥7 mm	29 (6.3%)	6 (4.0%)	23 (7.5%)
Lateral shift (*n*, %)			
<7 mm	425 (93.0%)	151 (100.0%)	274 (89.5%)
≥7 mm	32 (7.0%)	0 (0.0%)	32 (10.5%)
Absolute AP shift (mm)			
Mean (SD)	2.77 (2.47)	1.94 (1.63)	3.18 (2.70)
Absolute SI shift (mm)			
Mean (SD)	2.25 (2.23)	2.19 (2.00)	2.27 (2.33)
Absolute lateral shift (mm)			
Mean (SD)	2.76 (2.57)	1.70 (1.32)	3.28 (2.86)

Abbreviations: BMI, body mass index; SD, standard deviation; AP, anterior–posterior; SI, superior–inferior.

at least 7 mm or more in one of the three dimensions of adjustment (*X*, *Y* or *Z*). Patients were categorized in two groups: healthy/overweight (18.5 ≤ BMI < 30) and obese (BMI ≥ 30). The lowest BMI observed was 21.2, maximum 41.7 and median 32.9. Of the 457 scans performed, ≥7 mm shifts in the anterior–posterior dimension for healthy/overweight and obese patients were observed in 4 (2.6%) and 33 (10.8%) scans, respectively. Superior-inferior shifts ≥7 mm occurred 6 (4.0%) and 23 (*n* = 7.5%) times, respectively, and shifts ≥7 mm laterally were seen in 0 (0.0%) and 32 (10.5%) occasions, respectively. Of the 306 radiation treatment sessions for those with BMI ≥ 30, 75 (24.5%) had a plan shift of at least 7 mm. In comparison, of those with a BMI < 30, 10 out of 151 sessions (6.6%) had a plan shift of at least 7 mm (Table 2). On univariate analysis, the odds of having a shift ≥7 mm in at least one of the three axial directions were significantly higher in patients with a BMI ≥ 30 (OR 4.227, 95% CI 1.235–14.466, $p = 0.0213$). Multivariate analysis was also statistically significant with a BMI ≥ 30 associated with shifts ≥7 mm (OR 5.000, 95% CI 1.341–18.646, $p = 0.0163$) (Table 3).

When looking at magnitude of shifts from the center, in both univariate (2.086 mm, 95% CI 0.833–3.339, $p = 0.0011$) and multivariate analysis (2.440 mm, 95% CI 0.959–3.921, $p = 0.0012$), the magnitude of the shift was greater in patients with a BMI ≥ 30. Shifts in the anterior–posterior direction were also found to be statistically significantly greater in patients with BMI ≥ 30 under both univariate (1.203 mm, 95% CI 0.348–2.058, $p = 0.0057$) and multivariate (1.173 mm, 95% CI 0.281–2.065, $p = 0.0097$) analysis. Changes in lateral daily shifts were also significant when looking at BMI for univariate (1.694 mm, 95% CI 0.943–2.446, $p < 0.0001$) and multivariate analysis (2.074 mm, 95% CI 1.284–2.864, $p < 0.0001$). Magnitude shifts in the superior–inferior direction were not found to be statistically significant on univariate (0.150 mm, 95% CI −0.914 to 1.213, $p = 0.7823$) or multivariate (0.298 mm, 95% CI −0.880 to 1.475, $p = 0.6194$).

5. Discussion

Modern techniques for postoperative pelvic treatment using IMRT and IGRT have substantially improved conformity, reduced dose to organs at risk, with the ultimate goal of reducing toxicity. Increased conformity does, however, cause the risk of potentially missing the target, leading to lower doses delivered to the PTV. We demonstrated a significant proportion of our patients with a BMI ≥ 30 to have shifts greater than the expected 7 mm that our PTV accounts for. While daily IGRT allowed for adjustments to account for this variability, this raises the concern that in cases without the use of daily IGRT (which is not currently standard at all institutions including ours), certain target volumes may be off greater than their PTV margins account for.

This study confirms an earlier report that obese patients may not set up as consistently in a new dataset, leading credence to the thought of treating these patients differently.[18] Our study supports their findings with increasing shifts in the lateral directions with increasing BMI, supporting the use of IGRT in these individuals. Several other studies analyzing organ motion during postoperative pelvic radiation using fiducial markers have been published.[19–21] Rash et al.[19] reviewed 145 daily images in patients receiving postoperative pelvic radiation using IMRT. Fiducial markers were placed in the vaginal cuff to monitor daily motion. They found shifts of

Table 3 – Univariable and multivariable regression results for estimating the odds of a shift of ≥7 mm On at least one of the three axila directions.

Variable	Univariable			Multivariable		
	OR	95% CI	P-value	OR	95% CI	P-value
BMI						
<30	1			1		
≥30	4.227	1.235–14.466	0.0213	5.000	1.341–18.646	0.0163
Age						
Per year increase	1.000	0.952–1.051	0.997	1.015	0.959–1.074	0.6101
Time since surgery						
Per additional year	0.999	0.998–1.001	0.3123	0.998	0.997–1.000	0.0669
Type of surgery						
Laparoscopic	1			1		
Robotic	0.985	0.314–3.087	0.979	0.81	0.252–2.577	0.7152

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

7 mm, 3 mm, and 2.9 mm in the anterior–posterior, lateral and superior–inferior dimensions, respectively. Rectal distension correlated with motion in the anterior–posterior direction. Two interesting points were made from this study. One discussion topic was whether ITV is enough to account for motion, as it does not take into account rectal filling. The other point made was in regards to BMI and whether body habitus could contribute to altered tissue doses. The example alluded to in the study showed that patients with higher BMI had more adipose tissue in the retrouterine space which could contribute to a lower dose to the rectum during brachytherapy. Another study used daily magnetic resonance imaging (MRI) during the course of postoperative pelvic radiation for 15 patients and found vaginal CTV shifts of 2.3 cm, 1.8 cm and 1.5 cm in the anterior–posterior, lateral, and superior–inferior directions, respectively.[21] They also showed rectal volume to correlate with motion in the anterior–posterior direction ($p < 0.001$). Harris et al.[20] also analyzed twenty-two patients undergoing postoperative pelvic IMRT and used fiducial markers placed in the vaginal apex to monitor daily motion. They found shifts of 12.1 mm, 3.1 mm and 9.5 mm in the anterior–posterior, lateral and superior–inferior axis. These studies correlate with our findings in that the anterior–posterior dimension had the greatest degree of shift. This was again significantly greater in the obese cohort and is likely due to variability of skin folds, abdominal distention, and intra-abdominal organ filling that can vary daily at the time of treatment. These factors alter the source to skin distance (SSD) originally set using the CT simulation scan and are likely to be the dominant driving factors for setup error.

As discussed earlier, IGRT plays a significant role in radiation oncology, especially to targeted sites such as the pelvis where daily organ motion is expected. As treatment plans become more conformal and IMRT is more frequently used, incorporation of daily imaging to verify proper coverage and dose delivery becomes essential. Daily shifts seen in our obese population, especially in the anterior–posterior axis cannot be resolved at this time with better immobilization techniques or use of surface anatomy/marks for positioning as there appear clearly to be substantial internal anatomy changes on a daily basis. Therefore, those with greater BMI or other risk factors predisposing them to greater inter-fraction motion may need daily IGRT to verify accurate positioning to reduce setup error. For some clinical situations, IGRT may need to be implemented on a more frequent basis.[22]

Limitations of the study include a relatively small number of patients evaluated, although 457 radiation treatments were included. Additional daily factors not accounted for were rectal and bladder filling which may contribute to daily motion in addition to obesity, although this is built into the planning ITV for bladder filling. We would expect, however, that variability in the bowel and bladder would be consistent on average for all patients and is already accounted for with ITV. ITV size did not contribute to increasing motion shifts, making bowel and bladder variability less likely to contribute to daily position changes. Further, while all patients received pelvic radiotherapy, PTV size varied between them creating some heterogeneity in the group. PTV size was included in our analysis and not found to contribute to the increase in daily shifts. Lastly, by measuring set up shifts based on IGRT alignment and not skin marker alignment, the potential confounding impact of daily skin motion variability in more obese patients was not an issue in this study.

6. Conclusions

Current RTOG guidelines call for a 7 mm expansion of the final treatment volume to form the PTV.[15] Results in our study demonstrate certain patients with greater BMI may have greater daily shifts than 7 mm, which becomes important when daily CBCT is not routinely done. For obese patients, clinicians may need to consider daily imaging to verify positioning or expand their initial volumes to account for larger degrees of motion. As radiation oncologists continue to treat patients with postoperative pelvic IMRT, we must remain cognizant of tight margins and degrees of inter-fraction variation that may exist based on anatomy and patient body habitus as demonstrated in this study. Daily IGRT and/or margin adjustments based on each individual may be necessary to ensure adequate coverage.

Conflicts of interest

None declared.

Financial disclosure

None declared.

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