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Comparison of Daily Couch Shifts Using MVCT (TomoTherapy) and B-mode Ultrasound (BAT System) During Prostate Radiotherapy

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Abstract

The purpose of this study was to compare daily couch shifts after prostate localization between megavoltage CT (MVCT, Hi-ART® TomoTherapy) and b-mode ultrasound (BAT system). Nine hundred and thirteen couch shifts from 22 consecutive patients treated using MVCT localization were compared to 853 shifts from 23 randomly selected patients treated using b-mode ultrasound prostate localization. Shifts were made in three principal axes based on prostate position after comparing daily images to the initial planning CT. Mean shift for each axis and the shift variability both between and within individual subjects were calculated. Variability was higher for BAT compared to MVCT for vertical and cranial-caudal (CC) shifts ($p = 0.0084$ and 0.01037 , respectively), while lateral shifts were significantly greater for MVCT. For each individual, the pairwise correlations between shifts in different axes were calculated. Among all the groups and pairings, only the pairing of vertical and cranial/caudal adjustments in BAT-localized patients showed significant evidence of correlation after adjustment for multiple pairwise comparisons ($p = 0.0006$). When compared to MVCT, the use of BAT for prostate localization results in greater variability of positional adjustments in vertical and CC directions. This likely reflects differences in the ability to precisely align b-mode ultrasound contours to KVCT images, as well as prostate excursion in vertical and CC direction caused by the ultrasound probe. These considerations need to be made when defining treatment volumes, and argue for the use of less disruptive techniques for daily prostate localization.

Keywords

Prostate; BAT; Ultrasound; MVCT; and Tomotherapy

Introduction

For definitive prostate radiotherapy, the use of image-guidance to adjust the radiation delivery to daily setup and organ motion variability can improve targeting while limiting dose to normal tissue below tolerance levels (1). A variety of techniques have been employed by various institutions to allow visualization of the prostate immediately prior to

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radiation treatment, including daily computed tomography (CT) scans (2), insertion of fiducial markers (3), B-mode ultrasound imaging (4), megavoltage (MV) CT as part of the Hi-ART® Tomotherapy system (5), and cone beam CT treatment systems (6).

One widely used technique is the ultrasound based system that can conveniently and efficiently acquire images which are then used for target alignment prior to treatment. There are at least five commercially available systems, the original and most widespread of which is the NOMOS B-mode acquisition and targeting system (BAT) (Nomos, Sawickley, PA). Several reports have demonstrated its reliability, efficiency, and cost-effectiveness. However it is highly operator dependent and is subject to inter-user variability, mostly related to subjectivity of aligning to ultrasound images which lack distinct soft tissue contrast (7).

Image-guided radiation therapy utilizing CT is attractive because of the superior soft tissue contrast and the ease of interpreting CT images. The types in clinical use are the “CT on rails” with a KVCT scanner located immediately adjacent to the treatment linear accelerator (2), a linear accelerator with onboard kilovoltage cone-beam CT (6), and a helical Tomotherapy unit with integrated megavoltage CT (MVCT) imaging capability (8). These methods allow the user to correct for interfraction prostate positional variation by performing couch adjustments (or shifts) based on image guidance following initial alignment to skin marks.

Several prior studies have evaluated BAT B-mode ultrasound image registration capability (2, 3, 9–13). An initial report comparing daily ultrasound versus repeat CT scans in the final boost phase of prostate radiotherapy found the couch shifts after alignment to skin marks to be similar between the modalities, with average shifts in the three axes ranging between 2.4 to 5.9 mm and no differences in directionality of isocenter shifts (2). A recent prospective comparison corroborated this result (14). In this study, comparison between daily ultrasound imaging and twice-per-week CT scan found a high level of correlation between the shifts, with the average absolute systemic and random differences being less than 2 mm in all directions (14). However, in contrast to these studies, other reports suggest that the distribution of the shifts made by ultrasound is not equal in all directions, with significant greater variation in the shifts in the anterior-posterior and the superior-inferior directions (15, 16). This directional bias is considered to be a systematic error introduced by the pressure of the ultrasound probe applied to the abdomen (17, 18).

Compared to ultrasound, Tomotherapy with onboard MVCT imaging is a relatively newer modality, with few reports on the recorded shifts made on this type of equipment (8, 19). Reports on the comparisons of image guidance using these two technologies are sparse (20). We have incorporated the use of BAT as part of daily prostate treatments since 2000. More recently we have acquired the Hi-ART® Tomotherapy treatment system as part of our ongoing initiative to bring image guidance and adaptive radiation therapy into common practice. As part of our quality assurance process, we undertook this study to assess the relative differences between these two modalities and to potentially elucidate any systematic biases in either imaging method.

Materials and Methods

BAT System

Eight hundred fifty-three couch shifts from twenty-three patients treated on a 21EX Varian linear accelerator equipped with the BAT system between 2002 and 2005 were randomly selected from medical records and form the BAT cohort for this study. All patients underwent CT-based simulation with an alpha cradle cast and urethrogram. CT contours of the prostate, rectum, and bladder were outlined by the physician and exported to the BAT

system. The BAT probe was aligned to the isocenter with registration to the linear accelerator gantry. Before each daily treatment, the therapist aligned the patient to skin marks with room lasers. Monthly quality assurance tests were performed on the alignment of the laser system to the linear accelerator isocenter, with tolerance of less than 1 mm. Sagittal and transverse ultrasound images were then acquired with the probe placed on the patient's pelvis. Virtual alignments were calculated with the BAT system by overlaying the CT contour structures. Particular emphasis was made on the alignment of the prostatic/rectal interface. The treatment couch was moved according to the virtual shifts made on the screen in three primary axes: lateral (right and left), vertical (up and down), cranial/caudal (CC, in and out). All virtual shifts were recorded but only adjustments greater than 1 mm were performed. Treatment was rendered after the adjustments. Screen captures of the alignment images displaying the actual shifts were printed and kept in the charts and reviewed by the treating physician.

Hi-ART® Tomotherapy (Tomo)

Nine hundred thirteen couch shifts from twenty-two consecutive patients treated on the Hi-ART® Tomotherapy system were evaluated. The technical aspects of the simulation and the IMRT planning parameters are the same as those patients treated on the BAT system. The CT contours of the prostate, rectum, and bladder were outlined by the physician and the IMRT planning was performed on a TomoPlan workstation. After initial patient setup on the treatment couch according to laser alignment with skin marks, a megavoltage (MV) CT image was acquired. Monthly quality assurance measurements were performed with respect to laser to mechanical isocenter alignment (-0.65mm , -0.03mm , and -0.41mm in sagittal, transverse, and coronal planes, respectively). Automated image registration was then performed between the original simulation KVCT and the current MVCT images, which is also verified by the therapist. The image registration was adjusted manually by the therapist if deemed appropriate. After image registration, the final couch position was adjusted accordingly to the amount of shift necessary for image alignment. Once verified, the couch was automatically moved in the CC or vertical directions by the computer, while the lateral movements were made manually by the therapist. Only shifts in lateral directions greater than 3 mm were made, because lateral couch shifts require manual turning of a crank, which was felt to be a risk for repetitive motion injury for the therapists if performed for every patient. However, for purposes of this analysis all lateral alignment data were included. After completing this process of adjustments, treatment was then rendered. Each coregistered image with the shift data was kept as a paper record in the treatment chart and reviewed daily by the treating physician.

Statistical Methods

Statistical analyses were performed using R version 2.2.0 (The R Foundation for Statistical Computing, Boston, MA). The demographic characteristics of the study population were summarized using medians, sample standard deviations, and ranges for continuous variables and counts and percentages for categorical variables. Due to the skewness of the data, a non-parametric estimate of sample standard deviation was used.

Summary statistics [mean, standard error (SE), and range] are calculated for the entire cohort for each of the three types of shift (lateral, vertical, and CC). The estimates of mean and SE are derived using a linear mixed effects model which takes into account the fact that multiple replicates are available for each individual. A conditional t-test is used to determine whether or not there is a significant shift (*i.e.*, the shift is significantly different from zero). Due to the existence of multiple replicates for each individual, there are two sources of variation: between subject variation and within subject variation. Estimates for the between and within subject variation are included with 95% confidence intervals. Comparisons

between the shifts for the patients treated with BAT and the patients treated with Tomo are made using a linear mixed effects model with treatment as a factor. In order to adjust for multiple comparisons, a Bonferroni correction is used to reduce the possibility of Type I error, resulting in a downward adjustment of each individual test's α level ($\alpha = 0.0167$) to determine a significance level of 0.05 (8).

To explore the relationships between shift directions for each treatment, pairwise scatterplots of the raw data, *i.e.*, not clustered by individual, were created. The pairwise correlations between the three types of shifts (lateral, vertical, and CC) were calculated for each individual. The pairwise Spearman's correlations are summarized for BAT and Tomo separately using medians, sample standard deviations, and ranges. The Wilcoxon signed-rank test, appropriate for non-parametric data, was used to determine whether or not the correlation for each pairing of adjustments was significant after using a Bonferroni correction.

Results

Table I shows the demographic profiles for the BAT and Tomo patients. In general the two groups are matched very similarly in all parameters except for one outlier (*e.g.*, PSA 162.9 in one patient). The number of daily images acquired for each individual ranged between 31 and 42 (median 37) for BAT and between 37 and 42 (median 41) for Tomo. Although all patients were prescribed 42 fractions, fewer ultrasound images were acquired either due to temporary inoperability of the BAT system or noncompliance on the part of the patients for complete bladder filling. A total of 2559 (853×3 axes) and 2739 (913×3 axes) data points were used in the analysis for the BAT and Tomo, respectively.

Table II shows the summary statistics for lateral (+, right/−, left), vertical (+, up/−, down) and CC (+, cranial/−, caudal) couch shifts for BAT and Tomotherapy. There is evidence of significant negative shift in the lateral direction for both the BAT and Tomo ($p = 0.0097$ and $p = 0.0059$, respectively). However, the magnitude of the lateral shift for BAT is -0.816 mm, which is not clinically significant. There is also a significant negative CC shift for the BAT cohort of -1.2 ± 0.4 mm ($p = 0.0009$). The corresponding CC shift for the Tomo group is in the positive direction and above 1 mm but is not significant ($p = 0.0527$).

Since multiple measurements were made on each individual patient, both inter-individual (between-person) and intraindividual (within-person) variations exist. In order to illustrate the two sources of variation we have created boxplots showing the CC shifts for the Tomo patients (Figure 1). The within-person variability relates to the range of values observed for each individual, *i.e.*, the length of the individual boxes. The between-person variability relates to the range of values taken on by the point estimate calculated for each individual (median), which is represented by a black line in the center of each box. Table III shows the components of between-person and within-person variability for BAT and Tomo. For all three types of shift, there does not appear to be a substantial difference in the between-person variability. However, we observed a significant difference in the within-person variability for BAT and Tomo in all three shift types ($p < 0.0001$ in each case). In nearly all cases, the within-person variation was larger than the between-person variation. This is reflected in the computation of the correlation using Spearman's correlation among replicate measurements which is the fraction of the overall variation accounted for by between-person variation (see Table III). Only BAT vertical and Tomo CC shifts show evidence of strong correlation among replicates. For lateral shifts, the within-person variability among replicate measurements is slightly larger for Tomo than for BAT. A larger variability in BAT replicates is observed for the vertical and CC shifts. These increases are reflected in the range of shift measurements observed (see Table II). We adjusted for these differences in the

within-person variation when comparing the two treatments. When comparing the shifts for the BAT and Tomo cohorts (Table II), only the CC direction showed a significant difference in shift (-2.2 ± 0.7 mm; $p = 0.0014$).

We have also explored the inter-relationships of the three measurements of shift for both BAT and Tomo. Figure 2 shows pairwise scatter-plots of the raw data without adjustment for individuals for BAT (a-c) and Tomo (d-f). There appears to be a strong positive correlation between vertical and CC shifts for the BAT individuals (see Fig. 2c). For each individual, the Spearman's correlation was calculated for each pair of shifts. The summary statistics for the pair-wise correlations for individuals in each group are presented in Table IV. Only the pairing of Vertical and CC adjustments in BAT patients showed significant evidence of an overall pattern of correlation ($p = 0.0006$).

Discussion

There have been a number of studies compared BAT B-mode ultrasound image registration capability compared to other modalities such as KVCT scans or gold seed implants (2, 3, 9–13). In this report we have made comparisons between the daily imaging setup of the Hi-ART® Tomotherapy system and the BAT system. A limitation of the study is that it is not a direct comparison between these two modalities since they are performed on separate patient populations. However, the data from two otherwise similar groups of patients would not be expected to have substantive differences in day-to-day prostatic variability. We have evaluated the statistical variances in shifts and compared these variances within 2 modalities as performed in a purely clinical workflow. Despite previous reports of similarity between CT-based image guidance systems and the ultrasound-based systems (2), our analysis reveals significant differences in the distribution of shifts made between these two systems. There is significantly greater within-person variability in the BAT for the vertical and CC shifts, with slightly greater variability in the lateral direction for the Tomo. Only the shifts in the CC direction differ significantly for the two methods (Table II). Furthermore, only the vertical and CC shifts for BAT patients showed significant evidence of correlation. Since there are no differences in how the patients are setup on the treatment table between these two modalities, we believe these differences could be explained by intrinsic differences in the way daily images are acquired between these two modalities.

For every treatment plan, the planning target volume (PTV) is the margin that accounts for setup error, which comes from both random and systematic sources. Hoogeman *et al.* describes systematic errors as those arising from the preparative phase of the treatment process such as the predictive filling or emptying of the rectum, whereas the random error could arise from daily setup error or contour delineation uncertainty (21). Hypothetically, if one assumes that random error is the major source of the daily variations, the spread in all three axes should be nearly equal. This approximates the result we see in the patients treated on Tomotherapy. However, there is significant difference in the shape of the shift “cloud” seen in the BAT system, with an oblong shape that is oriented at an oblique angle. The major source of this elongation is in the vertical axis, signifying a greater degree of variability in this direction.

Chandra *et al.* have also found a significant correlation between the CC and AP (vertical) shifts, but suggested that the prostate travels along this elongated axis due to a combination of daily bladder and rectal volume variations (15). If true, such phenomena would also be seen in the patients treated on Tomotherapy, but this was not the case in our patients. One suggestion is that large differences in the CC orientation for BAT is due to difficulty in imaging the prostate in the cranial direction because of the interference by the pubic arch, therefore ambiguity is cast in the cranial/caudal directions where optimal alignment must be

made at the bladder/prostate interface (11). This mechanism does not explain why there is a significant correlation between the CC and vertical axis, as observed by other investigators (15). The ability for the ultrasound probe to displace the prostate has been well documented in several studies. McGahan *et al.* (17) demonstrated in a pelvic phantom that a 10 mm separation between the phantom surface and the prostate model could be achieved with moderate ultrasound probe pressure. Artignan *et al.* (22) used a 3D ultrasound probe to visualize prostate displacement as a function of the amount of probe displacement (therefore pressure) on the abdomen above the pubic symphysis. To achieve adequate quality of ultrasound images, a minimum of 1.2 cm displacement must be attained which produces an average prostate displacement of 3.1 mm. Most of the prostate displacement was seen in the vertical and CC direction with the least movement in the lateral direction. Serago *et al.* (23) also found a prostate displacement of an average of 3.1 mm (range 2.3 to 5 mm) in 7 of 16 patients with 9 of 16 without any discernable movements. They also find that only 1.5% of the lateral shifts equal 10 mm, while 7% of the longitudinal and vertical shifts equal 10 mm. More recently, Dobler *et al.* (18) tracked the movement of the prostate by the I-125 implanted seeds as the ultrasound pressure is applied to the abdominal wall. They find the maximum displacement of 10 mm could be produced with heavy probe pressure, with an average 2.3 mm displacement seen with moderate probe pressure adequate to display good quality images. These investigators also found that maximum displacement were made in the vertical and CC directions (2.8 mm and 3.0 mm, respectively) with only 0.8 mm in the lateral direction. This displacement corresponded to a maximal rotational change of 2.5° clockwise and 1.9° counterclockwise (18).

It is known that interfraction prostate position can vary by as much as 2 cm based on differences in rectum and bladder volumes (24). We performed an analysis looking at the volumes of the respective organs at the time of the simulation and examined whether men who have substantial correlation in the CC and vertical shifts can be correlated based on the size of the organs seen at the time of simulation. We could not find any significant relationship between the magnitude or the correlation of the shifts and the size of the respective organs (data not shown). This implies that any influence on prostate excursion by altering intraabdominal pressure by the ultrasound probe is independent of the size or volumes of the adjacent structures.

Another source of systematic error is the ability to precisely align daily acquired images with the planning KVCT images or organ contours. It is often difficult to precisely identify organ contours with imaging modalities that produce lower tissue resolution when compared with higher resolution modalities such as MRI (25, 26). We believe it is partly due to this reason why we saw a much greater intra-individual variability for the BAT group compared to the Tomotherapy cohort in the vertical and CC directions. Ultrasound images, especially the day-to-day quality of the images, can vary substantially due to inter-operator (7) or bladder filling variations (27). The lower soft-tissue contrast in the ultrasound images also can affect the ability for therapists to accurately assess the best image overlap. Although both the BAT and the Tomotherapy systems require the user's judgement as to the best alignment, the Tomotherapy system does provide an automated registration tool to overlay the MVCT and KVCT images prior to verification by the therapist, whereas for the BAT such alignments are entirely carried out manually by the therapist. Although we did find the distribution of the shifts to be more uniform in all three axes for the Tomo compared to the BAT, we did find a significantly greater shift from zero in the lateral (in the negative, or leftward) direction for patients treated on the Tomotherapy system. The reason for this is not entirely clear, but the rectal-prostatic interface is the major landmark identified on the ultrasound image, and lateral displacement of this linear-appearing structure may be more difficult to assess on the axial ultrasound view than on MVCT, where the lateral prostatic boundaries are easily identified. Langen *et al.* (8) also found systematic shifts in the vertical

and lateral directions (9.9 ± 3.6 mm vertical and 4.0 ± 3.6 mm lateral) in their prostate cancer patients treated on the Hi-ART® Tomotherapy system. The excess vertical shift was attributed to the systematic drop in the couch position between where the patient is setup vs. where the patient is treated within the scanner on their particular unit, but the reason for their large systematic shift in the lateral direction was unclear. Unlike the Langen *et al.* study, we did not find a systematic shift in the vertical direction and had a substantially lower systematic shift to the lateral (-1.3 ± 0.4 mm) direction. Since we relied upon the automatic coregistration with the manufacturer software for image alignment, it is possible that there is a systematic error in the lateral direction within the image fusion algorithm, although this has not been evaluated. It is possible that our particular unit has a slight shift in lateral position when the couch is moved from scanning to treatment position, similar to the vertical shift of the couch described in the Langen paper. Another potential explanation is that all our patients got onto the couch from the left side, and the therapists also viewed the patient from the left side. These factors, along with the width of the setup laser being 2mm, could have caused a bias toward the left.

We have also analyzed for any trends in the spread of the shift over the course of each patient's treatment. We did observe a statistically significant trend in the negative direction in both the BAT and Tomotherapy treated patients, with magnitude of only fractions of a millimeter (0.03 and 0.04 mm, respectively). The relevance of this clinically inconsequential tendency is unclear, but it is potentially due to patients learning to better comply over the course of treatment with our directive to fill their bladder in preparation for treatment, which patients have noted to us on a subjective basis.

Conclusion

Imaging-guided radiation therapy by the daily imaging of the treated area, including measures to compensate for intrinsic motion of the organs/tumors due to respiration, is an evolving technology that improves the overall quality of the radiation delivered to the target while minimizing toxicities to surrounding normal tissues. Ultrasound acquisition is an efficient and effective means of acquiring daily imaging without the radiation exposure but has several limitations compared to less intrusive approaches such as daily MV or KVCT images. We find a much larger variability of shifts in the cranio-caudal and vertical directions in the BAT group relative to the Tomo group. This is likely due to the systematic error introduced when the prostate is displaced by the ultrasound probe as well as the relatively greater difficulty in the accurate alignment of the often fuzzy ultrasound images. Since the final goal of image-guided radiotherapy is to eliminate the uncertainty of daily setup errors, utilizing technologies that are less disruptive so as to avoid introduction of systematic errors is indicated.

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Figure 1. Boxplots of individual CC shifts for Tomo patients. The center line of each boxplot represents the median of the CC shifts for that individual.

Figure 2. Pairwise comparison of lateral, vertical and CC shifts for BAT (a–c) and Tomo (d–f). The gray dot represents the mean shift in each direction.

Table I

Demographic Characteristics for the Bat and Tomo Patients. Asterisks denote a single outlier with a PSA 162.9.

Demographic	Bat (n = 23)	Tomo (n = 22)
Number of measurements	2559	2739
Age		
Median (SSD)*	66.0 (9.27)	69 (9.82)
Range	(51, 83)	(47, 79)
Stage:		
T1C	15	13
T2A	2	6
T2B	2	0
T2C	2	1
T3A	1	1
T3B	1	1
Gleason Score		
6	9	10
7	9	7
8	2	3
9	3	1
10	0	1
PSA (ng/ml)		
Median (SSD)	9.90 (6.56)	7.3 (7.01)
Range	4.3–162.9*	1.0–40.0
Prostate Volume (cc)		
Median (SSD)	36.40 (10.19)	39.75 (22.04)
Range	22.10–109.10	20–95.66
Rectum Volume (cc)		
Median (SSD)	86.50 (28.50)	75.20 (56.54)
Range	32.70–173.60	38.70–212.40
Bladder Volume (cc)		
Median (SSD)	211.5 (108.01)	200.9 (112.60)
Range	93.8–632.7	98.1–611.3
Seminal Vesicles (cc)		
Median (SSD)	13.30 (5.30)	13.25 (5.61)
Range	4.90–28.90	3.86–36.30

All volumes are as measured on the initial planning simulation CT. SSD is the non-parametric estimate of the sample standard deviation.

Table II

The Mean and SE Estimates are Based Upon a Linear Mixed Effects Model. The range of all of the shifts, unadjusted for multiple measurements per individual, are also presented. Units are in millimeters. CC, Craniocaudal.

Individual Treatments	Lateral (mm)	Vertical (mm)	CC (mm)
BAT			
Mean (SE)	−0.8 (0.3)	1.1 (0.7)	−1.2 (0.4)
Range	(−18.4, 16.6)	(−23.5, 25.4)	(−19.8, 13.0)
p-value	0.0097	0.1511	0.0009
Tomo			
Mean (SE)	−1.3 (0.5)	0.3 (0.4)	1.1 (0.6)
Range	(−16.2, 26.9)	(−14.2, 12.6)	(−8.7, 10.4)
p-value	0.0059	0.5543	0.0527
Comparison of Treatments			
Difference (SE)	0.5 (0.6)	0.8 (0.8)	−2.2 (0.7)
p-value	p = 0.4191	p = 0.3535	p = 0.0014

Table III

Estimates (SD) of the Two Components of Variation: Between Subject Variation (σ_B) and Within Subject Variation (σ_W). The correlation represents the amount of correlation between replicate measurements on the same individual, $\sigma_B^2/(\sigma_B^2 + \sigma_W^2)$. Units are in millimeters.

	Lateral	Vertical	CC
BAT			
Between			
Estimate SD	1.4	3.4	1.6
95% CI	(1.0, 2.0)	(2.5, 4.7)	(1.1, 2.2)
Within			
Estimate SD	3.0	4.6	3.3
95% CI	(2.9, 3.2)	(4.3, 4.8)	(3.1, 3.4)
Spearman's Correlation	0.183	0.360	0.188
Tomo			
Between			
Estimate SD	2.1	1.9	2.6
95% CI	(1.5, 2.9)	(1.4, 2.7)	(1.9, 3.5)
Within			
Estimate SD	3.6	3.6	2.5
95% CI	(3.5, 3.8)	(3.4, 3.8)	(2.4, 2.7)
Spearman's Correlation	0.245	0.222	0.513

Table IV

Summary Statistics for Pairwise Spearman's Correlations Calculated for Each Individual. SSD is the non-parametric estimate of the sample standard deviation. Units are in millimeters. CC, Craniocaudal.

Treatment	Lateral vs Vertical	Lateral vs CC	Vertical vs CC
BAT			
Median (SSD)	0.8 (1.9)	0.6 (2.1)	4.3 (3.8)
Range	(-3.9, 4.8)	(-4.7, 3.9)	(-2.7, 7.8)
p-value	0.2345	0.3447	0.0006
Tomo			
Median (SSD)	-1.0 (1.3)	-0.2 (0.2)	1.0 (2.1)
Range	(-3.4, 2.9)	(-3.6, 4.7)	(-5.3, 4.7)
p-value	0.1560	0.6789	0.2099