**Purpose:** Applying manual registration of CBCT to a reference image for prostate localization increases treatment time affecting prostate motion and patient setup. A reliable automatic registration can be more time efficient and accurate. This preliminary study demonstrates variability of manual fusion by multiple observers comparing manual to an in-house automatic fusion.

**Methods and Materials:** 7 patients with 7 CBCT scans each were studied by 4 observers. Off-line manual fusion between CBCT and Simulation CT was performed using On-Board Imaging (OBI) software by Varian version 1.2. We pre-defined our Region of Interest (ROI) and Organ of Interest (OOI) to be the pelvic bones and the prostate respectively. Offsets were recorded in 4 degrees of freedom (3 translations and couch rotation). To increase precision, one outlier observation was excluded. Interobserver variation in manual registration was studied by determining percentage of observations that fall within 1 mm and 1 degree standard deviation (SD). Automatic registration, utilizing the uphill simplex, gradient correlation and mutual information similarity measures, was compared to the manual matched results using frequency histograms of the differences between the two methods. System robustness is checked using prostate calcifications.

**Results:** Comparing different observers, 69% cranial-caudal (C-C), 83% anterior-posterior (A-P), 100% right-left (R-L), and 100% (couch rotation) of the observations fall within 1 mm,1 degree SD for ROI. 69% C-C, 75% A-P, 90% R-L, and 100% couch rotation were observed for OOI. ROI/OOI automatic fusion showed 92%/85% overall agreement with manual fusion within 2 mm respectively.

**Conclusion:** Manual registration is time consuming and demonstrates observers’ variations. The automatic method localizes the prostate within 15 seconds. More observers and measurements, methods utilizing drawn contours and implanted fiducial markers, will be required for system accuracy and precision. Our automatic registration with feedback from observers’ experiences would enable on-line correction for prostate motion.