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# Prospective Randomized Trial for Image Guided Biopsy Using Cone Beam Computed Tomography Navigation compared to Conventional Computed Tomography

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## Abstract

**Purpose:** To compare cone beam computed tomography (CBCT) navigation to conventional computed tomography (CT) image guidance during biopsies.

**Materials and methods:** Patients scheduled for image-guided biopsies were prospectively and randomly assigned to conventional CT vs. CBCT navigation guidance. Radiation dose, accuracy of the final needle position, rate of histopathological diagnosis, number of needle repositions to reach the target (defined as pullback to adjust position) were compared.

**Results:** A total of 58 patients (mean age 57years, 62.1% men) were randomized, 29 patients underwent 33 biopsies with CT and 29 patients with 33 lesions using CBCT navigation. The average body mass index was similar between the two groups, 28.8± 6.55 (p=0.18). There was no difference between the two groups in terms of patients and lesion characteristics i.e. size, depth. The number of needle repositions in the CBCT group was 0.3±0.5 vs. 1.9±2.3 in the CT group (p<0.001). The average skin entry dose was 29% less with CBCT vs. CT group (p<0.04

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Trial registration:
This trial was registered at clinical trials.gov, the registration number was NCT01287013

Conflict of Interest Disclosures:
Alessandro Radaelli and Imramsjah Martijn Van der Bom are clinical scientists employed by Philips healthcare. Brad Wood is the principal investigator on the collaborative research and development agreement between Philips and the NIH.
Nadine Abi-Jaoudeh has no personal conflicts of interest however there is a collaborative research and development agreement between Philips and the NIH.
Robert Wesley, John Jacobus, Marlene Skopec and Teresa Fisher have no conflicts of interests.

accounting for BMI). The average estimated effective dose for the planning scan from phantom data was 49% lower with CBCT vs. CT (p=0.018). The accuracy defined as the difference in mm between the planned and final needle position, was 4.9±4.1mm for the CBCT group vs. 12.2±8.1mm for the CT group (p<0.001). Histopathological diagnosis rate was similar in both groups 90.9% for CT vs. 93.9% for CBCT (p=0.67).

**Conclusion:** Biopsies using CBCT navigation improved targeting accuracy with fewer needle repositions, lower skin entry dose and lower effective dose for planning scan and comparable histopathological diagnosis rate.

## Introduction:

Adequate and representative tissue samples are essential for identification of specific biomarkers and activated pathways to determine the appropriate therapy[1,2]. Percutaneous biopsies performed under ultrasound and computed tomography (CT) guidance are standard of care for tissue procurement[3]. However, lesion heterogeneity and lack of conspicuity limit the quality of specimens as well as feasibility of biopsies[4]. Navigation technologies including cone beam CT (CBCT) were introduced during to improve technical feasibility of difficult biopsies[5]. Several case series have shown that navigation technologies facilitated biopsies of PET avid areas without anatomical correlates as well as lesions only visible with MR or after contrast administration[6,7]. With potentially increased precision, navigation technologies might enable targeting smaller lesions or heterogeneous lesions more accurately. However it is unclear whether these technologies provide any advantages in standard biopsies compared to conventional image guidance. Comparing real-time imaging vs. static imaging with or without navigation systems was identified as a research avenue in the proceedings from the Society of interventional radiology research consensus panel[8]. In this prospective randomized trial, conventional CT was compared to CBCT navigation for routine biopsies.

## Methods and Materials:

This trial was a prospective open label randomized trial conducted at a single site. The institutional review board approved this protocol (NCT01287013 (URL: https://clinicaltrials.gov/ct2/show?term=xperguide&rank=1). All CBCT (XperCT, Philips Healthcare, Best, NL) and CT (Philips Healthcare, Best NL) technologies in this study were commercial products cleared by the U.S. Food and Drug Administration.

### Study patients:

Eligible study participants were older than 18 years of age, scheduled for a CT image-guided biopsy of a lesion deeper than 3 cm. Subjects were excluded if they weighed more than 375 pounds (table limit), were unable to hold still or hold their breath (assessed prior to consent) and if they were unable to give consent. Patients whose lesions could be biopsies using ultrasound guidance were excluded from the trial.

### Study design:

A pilot phase of the trial consisted of the operators performing 5 cases using CBCT navigation before enrolling patients on the main phase of the protocol. The pilot subjects were not included in the analysis. CBCT is a newer technology compared to CT, so the 5 initial cases were excluded by design. During the main phase of the study, the patients were randomly assigned in a 1:1 ratio to undergo biopsy with conventional CT or CBCT navigation guidance. The randomization sequence was computer-generated by an interactive Web-based response system and performed in permuted block sizes of 6. The randomization sequence was kept concealed from the operators until the start of the procedure after consent had been obtained to minimize selection bias. . The patients were divided into three cohorts according to the anatomic site: lung, kidney and other abdominal consisting of retroperitoneal lymph nodes (n=16 patients, 8 in each group) and adrenal lesions (n=4 patients 2 in each group)). Of note, the protocol initially included a liver cohort that was removed because no patient was recruited as hepatic lesions were visible with ultrasound and therefore not eligible. Fifty-five procedures on the trial were performed by one operator (with 7 years of experience); the remaining 3 were performed by two other operators (8 and 20 years of experience).

### Imaging:

In the CBCT group, all patients except 4 were performed using a 4 sec CBCT scan (120 kV tube voltage, 250 mA tube current with automatic modulation, 0.9 Cu filtration, 4×4 binning) acquiring 242 images over a 240 degrees rotation of the C-arm in “propeller” position at the head of the patient. The remaining patients were performed using a 5 CBCT sec scan with the same trajectory and acquisition settings but acquiring 312 projection images (n=1) and an 8 sec CBCT scan with the C-arm in the “roll” position at the side of the patient, which involves a shorter 180 degrees rotation with 240 projection images (n=3). The CT technique was performed using the biopsy mode protocol with an initial larger scan and limited repeat scans centered around the needle, in 16 patients, a “wider” post scan to detect complications i.e. pneumothorax or bleeding. The CT technique was designed to reproduce usual clinical practice as much as possible.

### Outcome measures and endpoints:

The primary outcome measures were accuracy of the final needle position, number of needle repositions to reach the target, definitive pathology diagnosis and skin entry radiation dose. Definitive pathology diagnosis was defined as an adequate specimen as judged by the pathologist and a diagnosis confirmed by surgery or clinical follow-up. The accuracy of the needle position was calculated in mm using the difference between the x, y, z coordinates of the tip of the “planned” needle compared to the x, y, z coordinates of the tip of the actual needle before specimen collection. In addition, the planned path was compared to the actual path using the difference in mm between the x, y, z coordinates of the planned and actual skin entry point as well as the x, y, z coordinates of the planned and actual needle tip. Repositions were defined as a needle pullback to adjust its position including pullbacks due to traversing the lesion through and through. Changes in needle angulation without pullback were not considered a reposition.. The revised National Institutes of Cancer Common

Terminology Criteria for Adverse Events (CTCAE) version 4.0 was utilized for adverse event recording and reporting[9].

Four optical stimulated luminescent dosimeters (OSLD) were placed on each side of the patient (front, back, right and left) at the level of the projected needle entry (within a 3cm imaginary band), to ensure that they were included in the field of view and could directly measure the skin entry dose. The dosimeters were processed after the procedure and dose was provided in mGy. Fluoroscopy, CBCT and CT settings during the procedures were also recorded. The dose length product (DLP) provided by CT and dose area product (DAP) for CBCT are radically different measured quantities. Therefore, comparison of the effective dose between the two modalities was performed using an anthropomorphic phantom (The Phantom laboratory Rando-alderson phantom). In order to accommodate the 1cm × 1cm OSLDs in the phantom, 186 cavities measuring 1cm × 1cm were created throughout the phantom at locations that were identified to best represent the organs and tissues deemed significant for estimating effective dose to all organs irradiated by primary and scatter radiation with CBCT and CT (Figure 1) . Four acquisition types (lung prone, lung supine, abdomen prone and abdomen supine) were obtained with each modality using the parameters of the typical procedural planning scan. The comparison of the effective dose between the two modalities was made based on specific phantom measurements of the internal organs for that modality and scan type e.g. prone or supine, lung or abdomen[10]. The reported DLP or DAP for the planning scan of each subject was multiplied by the specific phantom effective dose for the type of scan the patient received and then multiplied by the ratio of the patient's body mass index (BMI) to the phantom's BMI to obtain the effective dose. Of note, the DLP of the planning scan was available for all CT patients included in the analysis while the DAP for the planning scan was recorded for 13 patients only in the CBCT group.

## Statistics:

The primary analysis was a standard "superiority" comparison between conventional CT to CBCT navigation based on the four endpoints discussed above[11]. The endpoint chosen for sample size determination was the number of needle repositions since it was deemed more sensitive to detect a difference between the two modalities. During the procedure, the operator was able to reposition the needle as needed until the lesion was reached, although reaching the exact "planned" target was not required. Based on previous non-prospective, non-randomized publications, the number of repositions for conventional CT was 2 (standard deviation 1.22) and 0.2 (standard deviation 0.5) for CBCT navigation[12,13]. Therefore with 42 patients (21 with each modality/ 14 per anatomical site), the study would have 90% power to detect a difference between the groups with a 2-sided type I error of 0.05, assuming unequal variances and a t-test based on Sattherwaite's approximation. Assuming that 30% of patients would be non-evaluable due to technical difficulties or lack of follow-up, the study should have a final sample size of 60 patients (30 per modality/ 20 per anatomical site). Baseline clinical characteristics between the two groups such as age, gender and BMI were compared using Student's t-test or Fisher's exact test as appropriate. In case a patient underwent biopsy of multiple sites in one session, the patient data was included once in the analysis and the lesion characteristics were tabulated as separate data

points. In these cases with multiple lesions, radiation was excluded from statistical analysis; however other outcome measures were averaged per patient. However, the overall histopathological diagnosis rate is based on all lesions, although the group comparison P-value is based on a summary rate per patient using a nonparametric test.

A Shapiro-Wilk test was performed for each outcome measure to ensure normal distribution. For measures with non-normal distribution, a log transformation was applied before statistical analysis. For lesion characteristics such as size and depth, ANOVA test was used stratified on anatomical site. Other endpoints including needle repositions, accuracy of needle position, histopathological diagnosis, and number of verifications scans as well as time to target were all compared with a stratified nonparametric Wilcoxon test. A log transformation was applied to the radiation data. An ANCOVA (analysis of covariance) analysis taking into account the body mass index was used to compare the average skin entry dose from the dosimeters in the CBCT vs. CT group. A t-test comparison of the logs of the raw values was used to compare the effective doses of the planning scan with CBCT vs. CT. Means and standard deviations are reported, in all cases based on the raw values (even when analyses may have been done on log values). All P-values are two-sided.

### Study patients:

Between April 2011 and May 2014, a total of 58 patients were enrolled and randomly assigned to conventional CT or CBCT navigation guided biopsy. Two patients were randomized to CT procedure but due to non-diagnostic procedure, CBCT navigation biopsy was performed per protocol. In both cases, CBCT navigation biopsy was diagnostic but the repeat procedures were excluded since they were not enough “repeat” procedures for a matched sub-analysis. After excluding the repeat procedures, 20 patients underwent biopsy for lung lesions and were assigned to the lung cohort (10 CT and 10 CBCT), 20 patients were in the “other abdominal” cohort (10 CT and 10 CBCT) and 18 patients underwent biopsy of the 3$^{rd}$ anatomical location (9 CT and 9CBCT). Twenty-nine patients underwent biopsy of 33 lesions with conventional CT guidance and 29patients with 33 lesions were performed with CBCT navigation guidance (see figure 2). The mean age of the participants was 57 and 62.1% (n=36) were men. The average body mass index was 28.8± 6.55 and no difference was detected between the groups (p=0.18). The baseline lesion characteristics of the two groups were similar (see table 1). The average lesion size was 29.1±12.7mm for the CT group vs. 31.2±16.8mm for the CBCT group (p=0.59). The average lesion depth was 82.4±31.5mm for the CT group and 87.0±28.6mm for the CBCT group (p=0.48).

### Procedures:

Most procedures were performed under conscious sedation except for 3 cases performed under general anesthesia due to comorbidities and one whose procedure was performed with local sedation only. A co-axial technique was used to initially obtain fine needle aspirates then 18 gauge cores. In both groups, after an initial scan was obtained, the operator would mark the ideal needle entry point and tip position. An image with the coordinates of the planned needle entry and tip was saved. For the CBCT group this was the trajectory, for CT, a marking tool that provides the coordinates of each voxel, was used. Once the operator deemed the needle in good position i.e. the location where the specimens were collected, the

operator would save another image with the coordinates of the actual needle entry and tip position. The images were used for the accuracy calculations.

## Results:

### Study endpoints:

The number of needle repositions to reach the target in the CBCT group was 0.3±0.5 vs. 1.9±2.3 in the CT group ($p<0.001$). The accuracy defined as difference in mm of the final needle tip position from the planned tip position, was 4.9±4.1mm for the CBCT group vs. 12.2±8.1mm for the CT group ($p<0.001$). The deviation of needle path was 8.8±5.4mm for the CBCT group vs. 28.3±20.5mm for the CT group ($p<0.001$). Diagnostic accuracy defined as an adequate specimen with histopathologic diagnosis was similar in both groups, 90.9% in the CT group vs. 93.9% in the CBCT group ($p=0.67$) (see table 2).

Seven patients with two or more lesions biopsied in one session were excluded from the radiation analysis as discussed above. The average skin dose recorded by the dosimeters in the CBCT group (53.3± 33.3mGy) was 29% less than the average skin dose in the CT group (75.4± 62.6mGy) ($p<0.04$) (See figure 3). The average effective dose of the planning based on anthropomorphic phantom acquisitions in CBCT group was 4.63mSv vs. 8.7mSv in the CT group, a 49% reduction using CBCT over CT.

The number of verification scans obtained in the CBCT group was 2.9± 1.1 vs. 7.3± 3.6 in the CT group ($p<0.001$). The average procedure time for CBCT was 23± 11 minutes (median 18minutes) vs. 30± 18 minutes in the CT group (median 27minutes) ($p=0.38$). There were 2 complications in each group, one asymptomatic self-limiting pneumothorax in each group. In the CT group, there was one large pneumothorax requiring a chest tube and additional hospitalization. In the CBCT group, a retroperitoneal lesion, accessed through a transhepatic route resulted in a self-limited bleed however the patient did not require hospitalization or transfusion. The small number of complications did not allow for a comparison between the two groups.

## Discussion:

This prospective randomized trial in patients undergoing percutaneous biopsies demonstrated that CBCT guidance was significantly more favorable than conventional CT with respect to the number of repositions, accuracy of the final needle tip position, and with a lower radiation dose. The histopathologic diagnosis rate and procedure times were similar in both groups but operators were allowed to reposition the needle until successful tissue procurement. In this study, reposition was counted if it entailed a pullback before re-advancement, since this meant that a greater amount of normal adjacent parenchyma was traversed potentially resulting in increased risk of complications. Indeed greater number pleural passes, increased needle manipulations, increased length of normal lung parenchyma traversed have been documented to be significantly associated with increased rate and severity of pneumothorax[13,14]. Some of the aforementioned factors have also been associated with pulmonary hemorrhage[13]. A population based risk assessment study revealed that patients with post biopsy hemorrhage or pneumothorax requiring chest tubes

had worse outcomes, increased hospital stays and more likely respiratory failure requiring mechanical ventilation[15]. In Eiro et al.'s prospective study, a logistic multivariate analysis revealed that frequency of renal puncture during biopsies even without any tissue collection was an independent risk factor for moderate complications[16]. Length of normal parenchyma traversed increased risk of bleeding in general[17]. Thus, reducing needle manipulations during biopsies resulted in decreased complications. The cohort was too small and the number of complications too few for a realistic comparison.

The ease to reach the target for specimen collection in the CBCT group translated into a significantly reduced radiation skin entry dose in patients. The patient's skin dose was 29% less with CBCT compared to CT as measured by dosimeters placed on each side of the patient. The effective dose of the planning scan derived from the anthropomorphic phantom was 49% lower with CBCT compared to CT. Previous publications suggested that CBCT navigation reduced radiation during biopsy procedures[14,18–20]. One non-randomized study of bone biopsies used 3 dosimeters for skin entry dose in two thirds of their cohort and demonstrated reduced radiation with CBCT compared to CT[20]. Most of the literature otherwise consisted of effective dose estimates using software programs or estimates provided by the imaging equipment itself[14,18,19]. However considerable differences between CBCT and CT imaging technologies and techniques limit the value of such estimates. Indeed, CT has a narrow beam that rotates 360° around the patient whereas CBCT has a wider beam that rotates 220° (Figure 4). Also, CT machines provide radiation estimates using dose length products (DLP) whereas angiography suites provide the dose area product (DAP). Direct comparison between the two is not possible. Models such "Monte Carlo", attempt to estimate dose length product of CBCT, however several major assumptions are made[21,22]. An anthropomorphic phantom, although more time consuming, is more accurate than conversion factors to obtain organ dose estimates.

Previous retrospective and non-randomized case series have shown safety and feasibility of lung or abdominal biopsies with CBCT[14,23–25]but did not examine accuracy due to their study design. The accuracy of the final needle position in relation to the pre-determined target was significantly better with CBCT (4.9±4.1mm) compared to CT (12.2±8.1mm) with an average lesion size of 30mm. With larger homogeneous lesions, precise needle placement may not be as critical as with smaller or heterogeneous lesions. Indeed, exact positioning is vital in partly necrotic or partly PET avid lesions to avoid non-diagnostic specimens or to better search for biomarkers.

This study has several limitations; indeed it was carried out in a single center with the majority of the cases performed by one operator. The results do need to be validated by outside institutions. Moreover, the study was powered according to number of needle repositioning not improved diagnostic accuracy. This study was performed at quaternary center, biopsy specimens are vital and a cytopathology technician is available on site during all biopsies. The operator will reposition the needle until adequate specimens are seen. Although it was prospective and randomized, blinding the operators was not possible during the procedure. To minimize selection bias, the randomization remained unknown to the operator until the procedure was about to start. Nonetheless this affected the selection of patients since the operators avoided smaller lesions or lesions visible on PET or MRI.

Radiation dose to the operator was not measured, and represents a potential weakness of CBCT, in that it may expose the operator to some level of radiation, highly dependent upon technique. Finally CBCT was not compared to fluoroscopic CT which provides real-time guidance however fluoroscopic CT delivers higher radiation doses to the patient and operator compared to conventional CT which itself provides higher radiation than CBCT. Indeed, as published recently by Mammarappallil et al.[26] CT fluoroscopy demonstrated an improvement in technical success of core biopsy at the expense of a significant increase in radiation dose. The authors therefore recommended that the choice between CT fluoroscopy and conventional CT be determined by operator preference.

In conclusion, this prospective randomized study demonstrated that CBCT navigation improved accuracy of targeting with fewer needle repositions and lower overall skin entry radiation dose as well as effective dose of planning scan, during pulmonary and abdominal biopsies.

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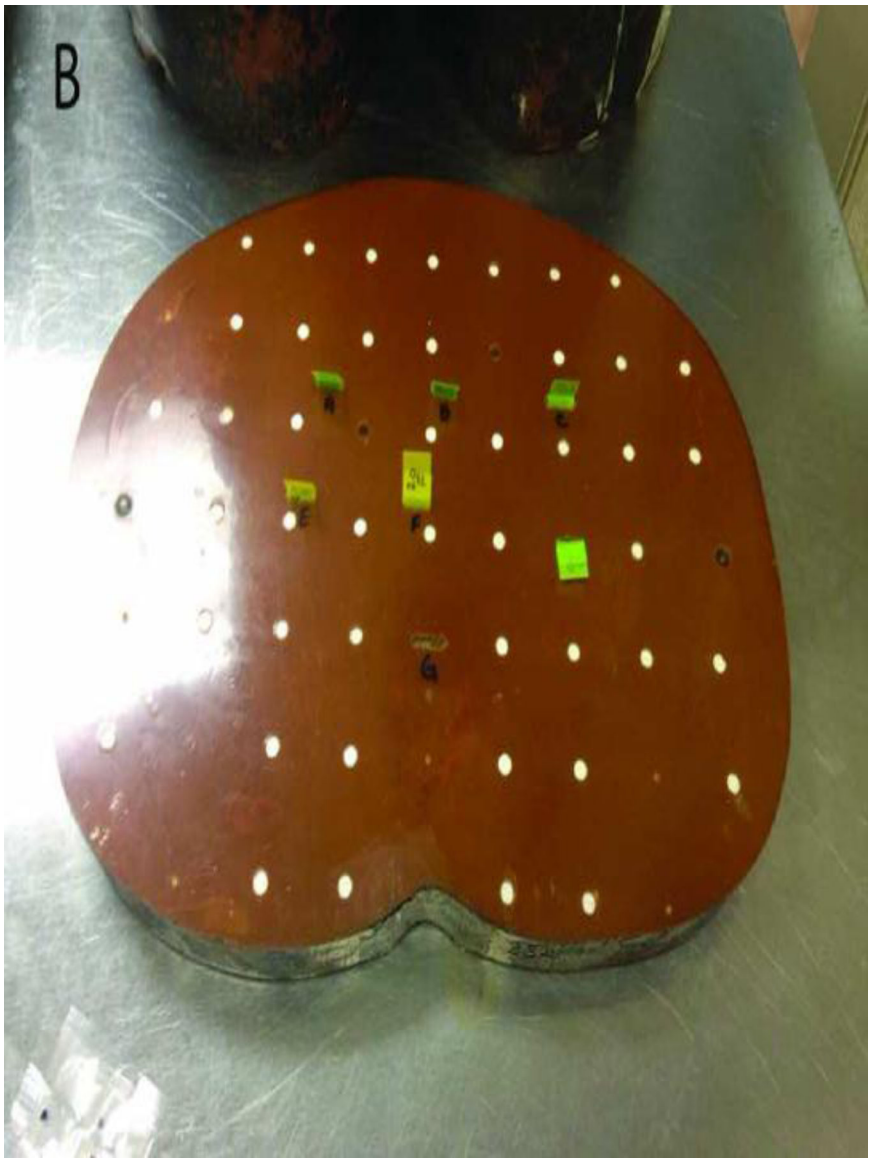
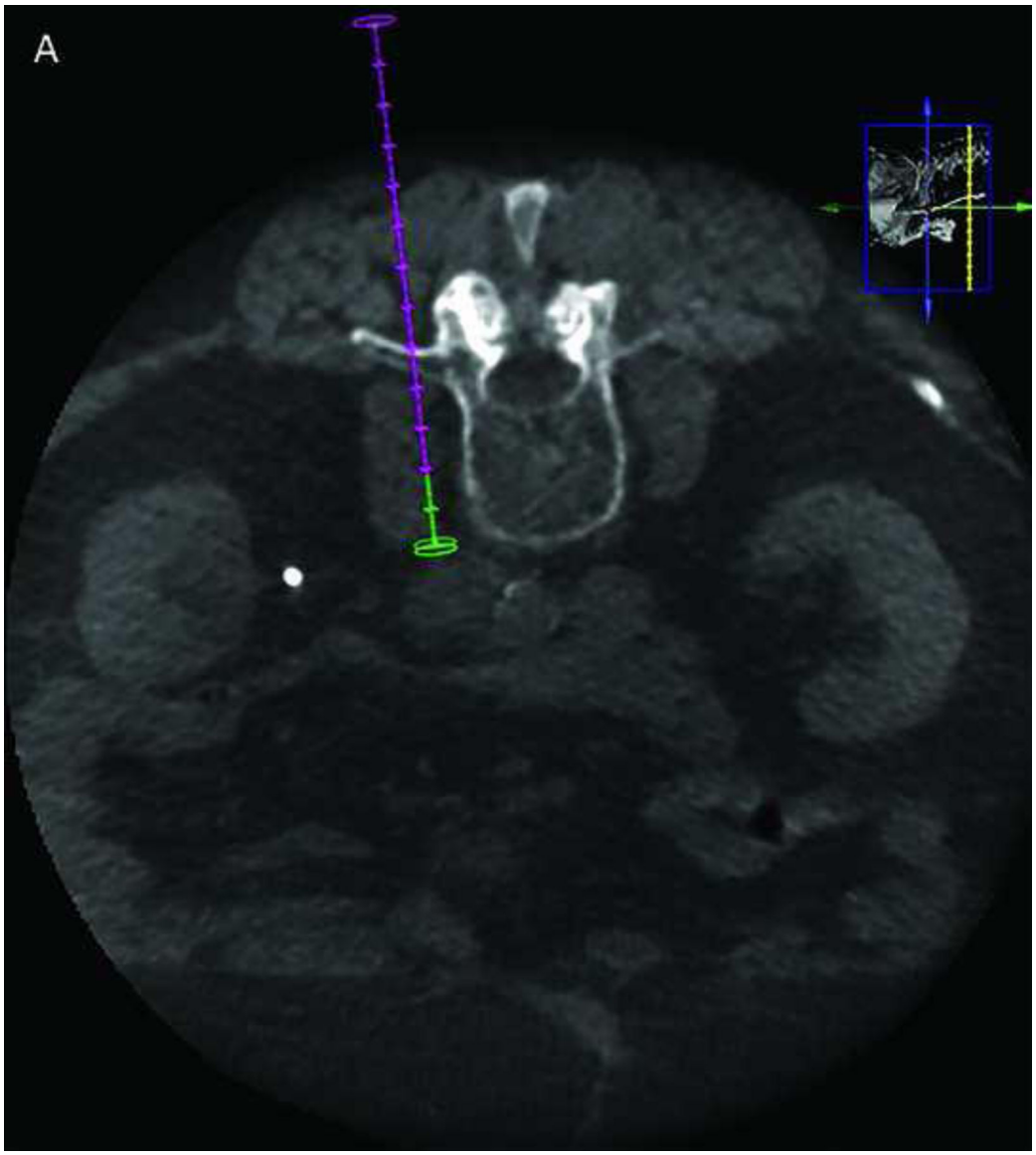
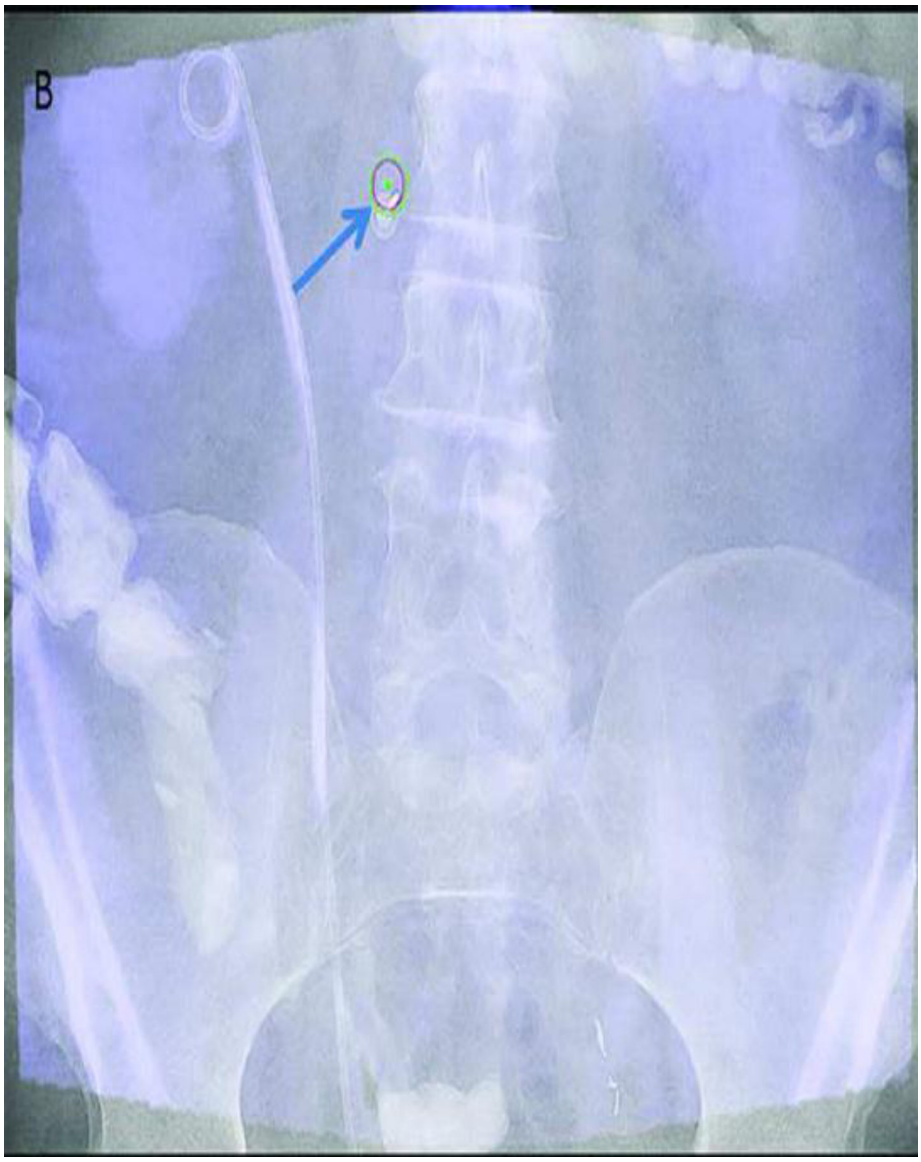
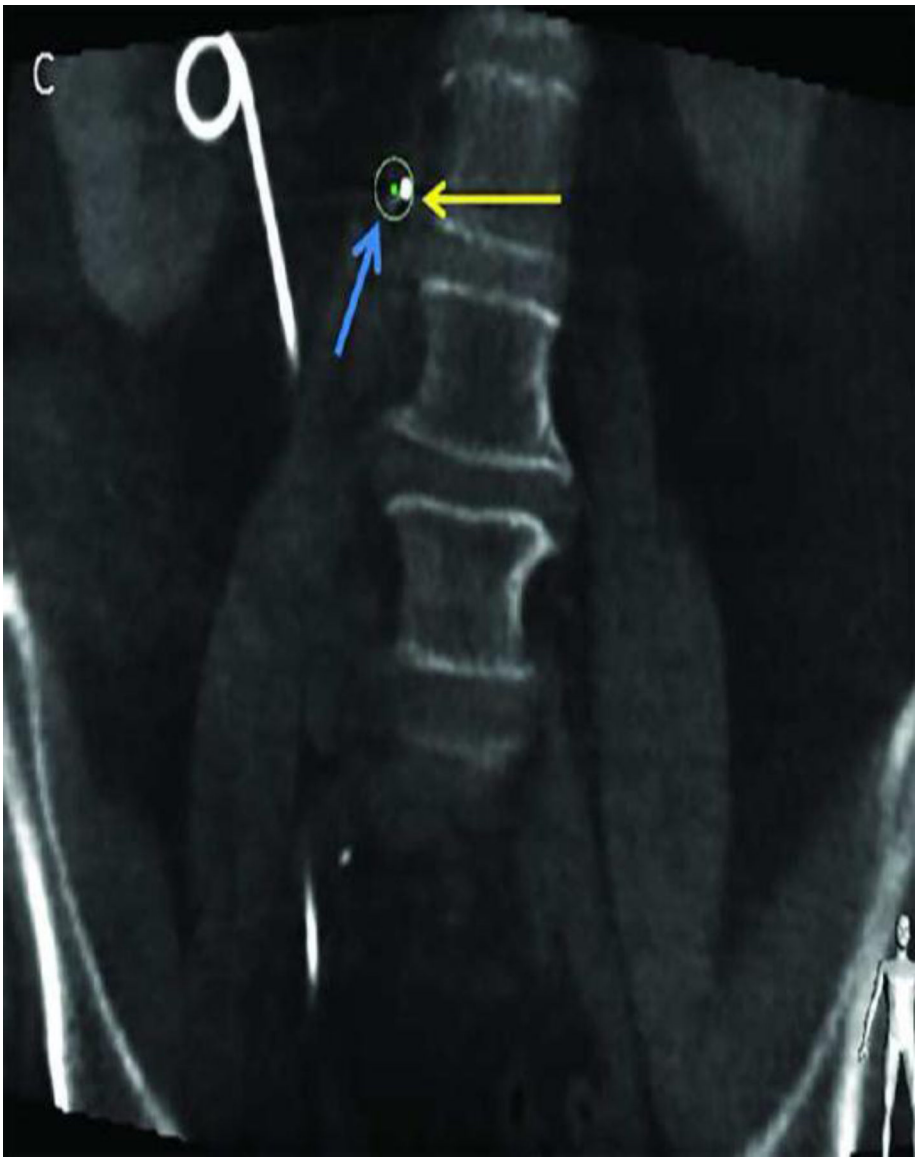



**Figure 1:**
1a is a picture of the anthropomorphic phantom with the cavities. 1b is a close up with the OSLDs inside the cavities.







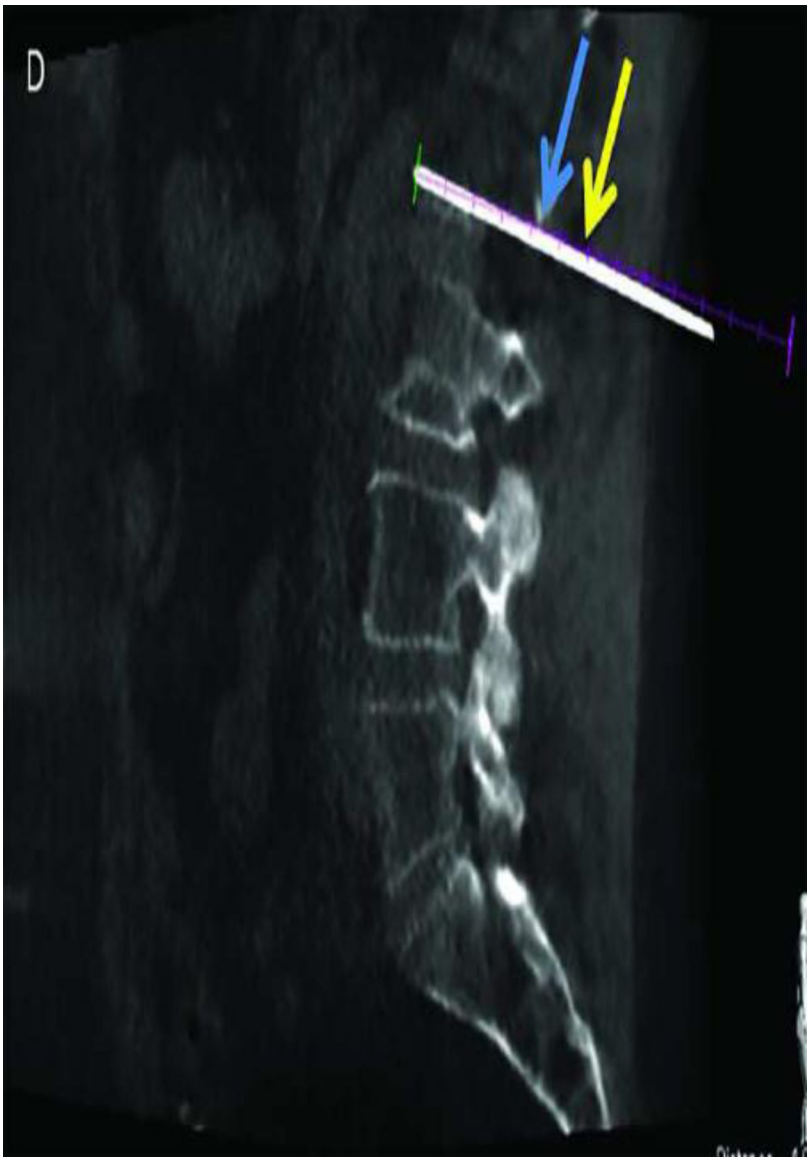



**Figure 2:**

59 year old female with history of spindle cell carcinoma and a newly enlarged retroperitoneal peri-aortic lymph node. 2a: axial image of the procedural CBCT demonstrating the planned needle path on an axial image displayed as the green and magenta line. 2b: Real-time fluoroscopy image with overlaid CBCT and the planned target are shown. The operator aligns the needle with the planned target seen as the green dot inside the magenta circle (blue arrow). 2c and d: CBCT images in the entry point view and progress view respectively obtained once the operator deemed that the target is reached. Yellow arrow points to the needle seen as a white dot on image C and white line on image D. A blue arrow highlights the planned path seen as white circle with green dot on image C and a magenta dotted line on image D. Both the needle and planned trajectory are superimposed in both images meaning that the needle was advanced along the desired trajectory to reach

the specific target point. The deviation between the needle tip and the planned target was calculated based on the x, y, z coordinates of each.

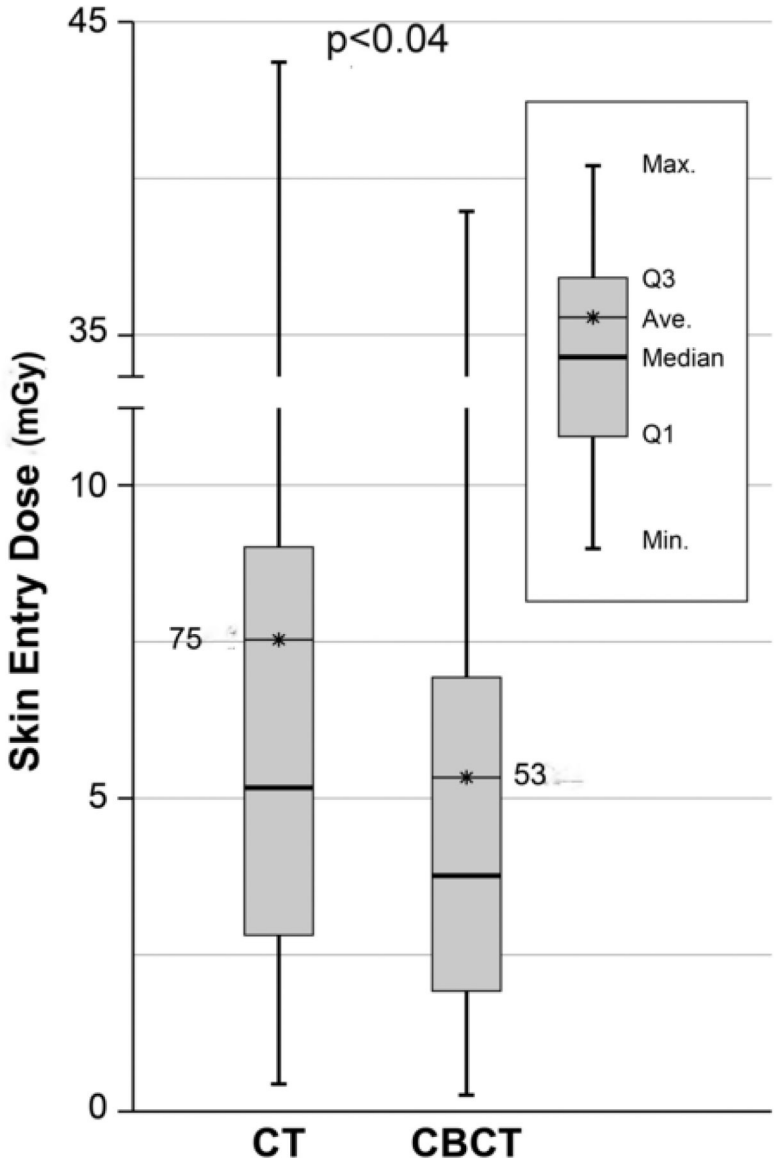



**Figure 3:**

The box plots depict the average skin entry dose recorded by the patient's OSLDs. The median is thicker straight line and the average is thinner line with a star. The doses are provided in their initial mGy value. The P-value for the group comparison, based on a test of the log values mGy taking BMI into account, is statistically significant.

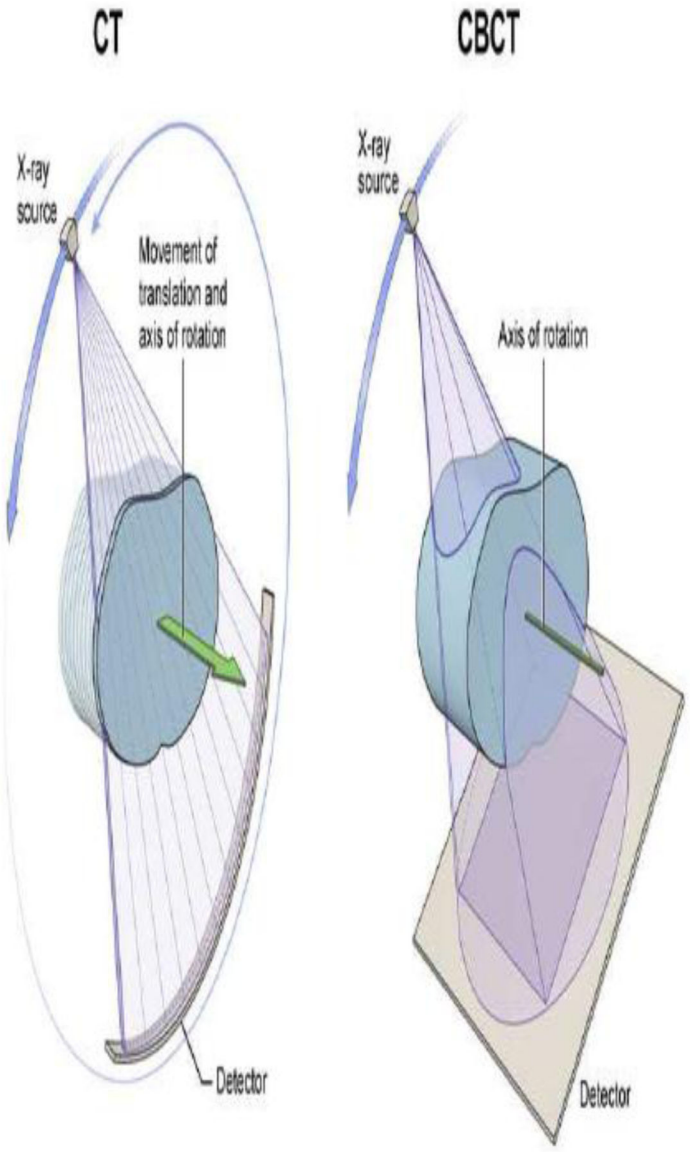



**Figure 4.**

Figure 4 displays the CT beam on the left and the CBCT beam on the right. The CBCT has a single x-ray source that delivers a wide beam with a single rotation while the CT has several x-ray sources (only one depicted) that radiate a narrow area requiring multiple rotations while the table/patient are moving to radiate an entire area.

**Table 1**

Table 1 is a summary of the patient and lesion characteristics

| | CT group | CBCT group | p values |
|---|---|---|---|
| Age | 56.9±14.1 | 56.5±13.6 | 0.91 |
| Body Mass Index (BMI) | 27.6±5.4 | 30.0±7.5 | 0.18 |
| Gender (female/male) | 8/21 | 14/15 | 0.18 |
| Lesion size in mm | 29.1±12.7 | 31.2±16.8 | 0.59 |
| Lesion depth in mm | 82.4±31.5 | 87.0±28.6 | 0.48 |

## Table 2

Table 2 is a summary of the results

| | CT group | CBCT group | p values |
|---|---|---|---|
| Reposition maneuvers | 1.9±2.3 | 0.3±0.5 | P<0.001 |
| Histopathological diagnosis (diagnostic/non-diagnostic) | 30/3 (90.9%) | 31/2 (93.9%) | p=0.67 |
| Accuracy of needle position in mm | 12.2±8.1 | 4.9±4.1 | P<0.001 |
| Accuracy of needle trajectory (vector) in mm | 28.3±20.5 | 8.8±5.4 | p<0.001 |
| Skin entry dose in mGy | 75.4± 62.6 | 53.3± 33.3 | p<0.04 |
| Effective dose of planning scan in mSv | 8.7 | 4.63 | p=0.018 |
| Number of verification scans | 7.3± 3.6 | 2.9± 1.1 | p<0.001 |
| Complications ** | 1(3)/1(1)** | 1(2)/1(1)** | Not applicable |
| Time to target in minutes | 30± 18 | 23± 11 | p=0.38 |

Complications** were tabulated per the revised National Institutes of Cancer (NCI)

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In the table the number of complications is listed for each grade, with the grade between parentheses.