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## **A pilot study evaluating the effectiveness of dual registration image guided radiotherapy in patients with oropharyngeal cancer**

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## **ABSTRACT**

### **PURPOSE**

The purpose of the article was to determine the impact of Dual Registration (DR) image-guided radiotherapy (IGRT) on clinical judgement and treatment delivery for patients with oropharyngeal cancer prior to implementation.

### **METHODS**

Ninety Cone Beam Computed Tomography images from ten retrospective patients were matched using standard clipbox registration (SCR) and DR. Three image guided radiotherapy specialist radiographers performed all registrations and evaluated by; intra-class correlation to determine interrater agreement, Bland-Altman with 95% Limits of Agreement to determine differences between SCR and DR procedures, changes in clinical judgment, time taken to perform registrations and radiographer satisfaction.

### **RESULTS**

Interrater agreement between radiographers using both SCR and DR was high (0.867 and 0.917  $p < 0.0001$ ). The 95% Limits of Agreement between SCR and DR procedures in the medio-lateral, cranial caudal, and ventro-dorsal translational directions were -6.40 to +4.91, -7.49 to +6.05, and -7.00 to +5.44 mm respectively. The medio-lateral direction demonstrated significant proportional bias ( $p < 0.001$ ) suggesting non-agreement between SCR and DR. 80% of DR matches resulted in a change in clinical judgement to ensure maximum target coverage. Mean registration times for SCR and DR were 94 and 115 seconds respectively and radiographer's found DR feasible and satisfactory.

### **CONCLUSION**

The standard method using SCR in patients with oropharyngeal cancer underestimates the deviation in the lower neck. In these patients DR is an effective

IGRT tool to ensure target coverage of the inferior neck nodes, and has demonstrated acceptability to radiotherapy clinical practice.

## INTRODUCTION

Accurate localisation of soft tissue volumes is vital for the effective delivery of radiotherapy in patients with oropharyngeal cancer. There have been many advances in image guided radiotherapy (IGRT) <sup>1</sup>, including Cone Beam Computed Tomography (CBCT). The practice of using CBCT for IGRT allows tumour volumes to be precisely localised, and avoid healthy tissues <sup>2-3</sup>. This is important for patients receiving head and neck radiotherapy for primary and locoregional lymphatic nodal involvement, as the inferior neck nodes can move independently of the primary tumour volume. Several studies have described and evaluated the problem of regional anatomical differences in the head and neck by utilising megavoltage portal imaging<sup>4-6</sup>, stereoscopic kilo-voltage (kV) <sup>7</sup>, CBCT<sup>4, 8</sup> and computed tomography (CT) on rails<sup>9</sup>.

The problem of deviations in different regions of the head and neck is compounded by the increasing use of intensity modulated radiotherapy (IMRT) techniques<sup>10</sup>, which require CBCT scans to visualise soft tissues. It is common for commercial CBCT software packages to only allow for one region of interest (ROI) <sup>1</sup>, <sup>11</sup>, which inevitably encompasses a large volume comprising the primary cancer site, inferior regional neck nodes that may degrade the effectiveness of the image matching algorithm. Registering such a large ROI fails to accurately quantify larger set up errors in the inferior neck <sup>4-9</sup>. This could lead to a suboptimal treatment to the inferior neck nodes that may result in recurrence for the patient<sup>10-13</sup>.

A study by van Beek and colleagues<sup>12</sup> addressed this problem through the development of an automated multiple ROI algorithm for CBCT and tested their first clinical experience undertaken by radiographers. Radiographers found the multiple ROI easy to use with little additional workload and that it helped to identify patients for re-planning<sup>12</sup>. This software is not commercially available for routine clinical use; however, Elekta Dual Registration (DR) is available<sup>14</sup>. DR allows the registration of

two separate regions of anatomy, calculating their positional offsets independently, and proposing joint correction that best fit both ROIs. Manual corrections can be made to the proposed correction via applying a sliding-scale weighting to favour one ROI's over the other prior to applying the correction. Pre-set limits also alert the radiographer if a treatment target structure has moved closer to a critical structure<sup>14</sup>. In anatomical sites other than head and neck, Campbell et al<sup>14</sup> demonstrated in post prostatectomy patients that DR can be a more efficient registration which could improve patient experience such as comfort<sup>15</sup> while also reducing inter-observer variability. There is limited evidence to demonstrate the clinical impact and processes of using DR in head and neck patients. Therefore, the aim of this pilot study was to evaluate the impact of DR on clinical judgement and treatment delivery for patients with oropharyngeal cancer prior to clinical implementation.

## **MATERIALS AND METHODS**

A retrospective pilot study was planned and reported as per Standards of Quality Improvement Reporting Excellence (SQUIRE 2.0) guidelines<sup>16</sup>. The pilot study was considered a service evaluation by the Department of Clinical research at Taunton and Somerset NHS Foundation Trust following good clinical practice<sup>17</sup>.

### **Patient data**

Ten retrospective patient CBCT datasets, a sample size recommended by Herzog<sup>18</sup> for pilot studies, who completed radiotherapy to an oropharyngeal primary and nodal area in 2015 to 2016 were anonymised.

### **Standard procedures**

Patients received their treatment supine immobilised in a Qfix Aquaplast™ (Avondale, USA) nine point thermoplastic immobilisation mask covering head, neck and shoulders. The mask is mounted on a Qfix Curve board which itself was affixed and indexed to the Elekta iBEAM® evo Couchtop. Patients were also tattooed on

their sternum for medio-lateral positional alignment. Radiographers followed a positioning protocol to ensure standardisation across patients<sup>19</sup>. CT planning scans were acquired using 2 mm slices (Philips Brilliance® CT Big Bore CT simulator, Guildford, UK) planned using Pinnacle treatment planning system (Philips version 9.10). Prior to treatment, CBCT scans (XVI® [5.02] 2016, Elekta AB Stockholm, Sweden) were acquired using 1 mm slices as per departmental protocol. This is justified by sampling theory which dictates that in relation to slice thickness of scans the ideal scenario is to sample at twice the rate of the resolution trying to achieve<sup>20</sup>. The CBCT preset selected was filter F0 and collimator S20 with a lens sparing gantry rotation of 335° to 180° with a gantry speed of 360° per minute. The correction reference point was set to the Planning Target Volume (PTV). Goals for planning target volume doses are guided by recommendations contained in ICRU50/62/83<sup>21-23</sup>, with near minimum (V99%) dose not less than 95% of the prescription dose and a near maximum dose (V2%) not greater than 107% of the prescription dose. Gross Tumour Volume (GTV) outlined includes primary tumour (or resection site/ tumour bed, if post-operative) and involved lymph nodes. Clinical Target Volume (CTV) will usually be taken as GTV with a margin of 5-10mm, taking account of normal tissue boundaries and barriers to spread (e.g. vertebral body). An appropriate margin for an involved nodal level will be taken as the next inferior nodal level clear of disease if this can be feasibly included. The Oncologist will indicate the high (macroscopic), intermediate (microscopic) and low (prophylactic) risk CTVs as CTV 1, CTV 2, and CTV3 respectively which will result in multiple phases of photon or concurrent dose regimes using Volumetric Modulated Arc Therapy (VMAT) or IMRT. A margin of 5mm around all CTVs delineates the PTVs<sup>21-23</sup>

A total of nine CBCT scans for each patient were scheduled for acquisition at treatment fractions 1-5, then weekly. An offline No Action Level correction strategy was standard practice using a 3mm translational, and 3° rotational tolerance to

ensure treatment is delivered within the PTV<sup>24</sup>. A 3 mm translational and 3 rotational registration was performed using Elekta 6 degrees of freedom automatic rigid body registrations<sup>25</sup> to auto-register<sup>26</sup>.

### **Dual registration procedure**

DR enables radiographers to register two separate locations of anatomy using a “clipboard” which encompasses a cuboidal area, and a “mask” in one CBCT scan. This technique enables users to have the option to make corrections based on the critical structure registration (mask/clipboard), or on the tumour registration (mask/clipboard), or a combination of the two, based on a clinical decision depending on the priority match structure. Discussions with a consultant clinical oncologist and radiographers determined the most appropriate clipbox and mask structure for clinical practice within the patients’ treatment plan<sup>13</sup>. At the host radiotherapy department CTV 2 was chosen to include the lower neck nodes.

This is confined only to the predefined anatomical structure of interest, delineated on a planning CT scan, with or without a margin depending on tissue contrasts required (Fig. 1). A 3mm translation and 3° rotation image tolerances were set as the registration limits to alert the operator when the differences between the mask or clipboard exceeds the limit and a compromise or clinical judgement needs to be made of whether to treat a patient or not<sup>3</sup>.

### **Data collection**

Three participating IGRT specialist radiographers matched the images and collected the data. All three had undertaken a recognised IGRT training programme such as the European Society of Therapeutic Radiology and Oncology IGRT course or an MSc module in IGRT and are designated IGRT specialist radiographers as per National Radiotherapy Implementation Group Report<sup>27</sup>. Their in-depth knowledge and clinically expert skills were deemed appropriate for this study<sup>27</sup>.

A preliminary evaluation of local set-up errors for two regions<sup>28</sup>, the superior neck (location of the oropharynx primary tumour) and the inferior neck, was undertaken (Fig. 2)<sup>6-9</sup>.

Three separate clipbox ROIs (Fig. 2) were prepared and checked independently by two of the IGRT specialist radiographers and offline registrations were performed by two radiographers. For standardisation each ROI clipbox was prepared by one IGRT specialist radiographer (Fig.2), and verified by a 2<sup>nd</sup> IGRT specialist radiographer following a local study protocol to ensure consistency. ROI 1, ROI 2 and ROI Total were generated from one reference CT dataset and individually registered and matched against the treatment localisation CBCT dataset. Multiple ROI registration is not available at the host radiotherapy department therefore each CBCT scan was registered and matched 3 times for each ROI.

The evaluated geometric displacements were those captured prior to correction to observe the effect of geometric error for each ROI<sup>3,28</sup>. The values obtained were compared to the available evidence prior to proceeding to the pilot study.

All three IGRT specialist radiographers retrospectively registered and matched the CBCT datasets of 10 patients using an SCR and then each dataset was re-matched using DR procedures as described and the final correction values were evaluated. A custom Excel sheet was created to collect the geometric displacement data and IGRT specialist radiographers were asked to select whether an adjustment has been made for DR. Firstly each CT reference scan was prepared according to dual registration procedures (Fig.1) by one IGRT specialist radiographer and verified by a second IGRT specialist radiographer following a study protocol. Each IGRT specialist radiographer followed a local IGRT protocol for SCR registration match criteria and a study protocol for the registration match criteria for DR. The SCR criteria for image matching is to auto register using the bone translation and rotation (Bone T&R) algorithm which is a chamfer match registering to the high electron

density regions such as bone. If the Bone T&R registration fails, then auto-registration is performed using the grey translation and rotation (Grey T&R) algorithm which is a voxel to voxel match of the entire ROI. IGRT specialist radiographers then review the registration of the clipbox area, focusing on bony anatomy such as the vertebrae and mandibular arch then review the PTV coverage and making a manual adjustment if required based on their judgement. The DR criteria for image match registration is to first register the clipbox (Fig.1) using the Bone T&R algorithm, assess the match using the above criteria as for SCR, and then register the mask which is CTV2 which covers the lower neck nodes. IGRT specialist radiographer will then review the match to the mask ensuring that the lower neck nodes are covered and then checking the clipbox to ensure primary tumour coverage and making a compromise if required prior to converting to correction. For both SCR and DR the IGRT specialist radiographer also review contour changes and avoidance of organs at risk such as the spinal cord or lacrimal glands.

An evaluation of inter-rater agreement between radiographers was followed by the evaluation of agreement between the SCR and DR procedures. Percentage of occasions DR change radiographers clinical judgement, along with the time taken to perform registrations, and validated radiographer satisfaction<sup>32-33</sup> were completed for both SCR and DR. The validated radiographer satisfaction questionnaire was an adapted 4 item Likert scale with a scoring scale of 0–3 (0 - least satisfactory, 1 – slightly satisfied, 2 – moderately satisfied, 3 - most satisfactory). Satisfaction scores were calculated for SCR and DR for each patient.

Finally, correction errors were calculated for SCR and DR for comparison (Fig.1).

### **Statistical analysis**

Systematic ( $\Sigma$ ) and random ( $\sigma$ ) geometric errors were analysed as per van Herk<sup>28</sup> with respect to the average geometric displacement with standard deviation per patient and population between the CT reference scan and the CBCT localisation

scan for the multiple ROI displacements and SCR and DR correction values to determine geometric errors<sup>3</sup>. Systematic errors are a constant observed trend in geometric displacements. Random errors are geometric displacements not consistent with a trend.

Population error used in our study was:

$\Sigma_{pop}$ = The standard deviation of the patient groups' systematic errors;

$\sigma_{pop}$ = The root mean square of the patient groups' random errors.

Population systematic and random errors were evaluated against a 3mm local tolerance threshold<sup>3</sup>. This methodology was used for corrective values too.

Intra-class correlation coefficients (ICC) were used to evaluate agreement between three radiographers using both SCR and DR. An interclass correlation was considered significant at the  $p < 0.05$  level<sup>29</sup>. A Bland-Altman method with 95% limits of agreement (LoA)<sup>30</sup> was then used to determine the agreement of geometric displacement between the registration matches of SCR and DR procedures, using a clipboard and a mask of a suitable inferior neck node clinical target volume.

A modified Bland-Altman approach was used to define the 95% LoA between the two registration procedures. A clinical threshold of 3mm in each direction was determined as standard clinical practice, as such that the different registrations could be considered equivalent or used interchangeably if the 95% LoA were within 3mm<sup>31</sup>. In the case where there is no obvious relation between the differences and the mean, a summary of the potential lack of agreement was completed by a calculation of bias estimated by the mean difference and the standard deviation of the differences. The rejection of agreement was considered significant at the  $p < 0.05$ <sup>31-32</sup>. The percentage of occasions that DR changed the clinical judgement of radiographers was also calculated to determine the appropriateness of implementing DR. Efficiency of DR was assessed by measuring the times radiographers' commenced SCR or DR, made a final judgement on the registration including any

adjustments were recorded for every fractional image. Mean times for radiographers to complete this were calculated for SCR and using DR.

Statistical analyses were performed using SPSS Statistics Version 23 (IBM, Portsmouth, UK).

## RESULTS

Ten selected patient datasets consisting of seven male and three female patients with diagnosed oropharyngeal cancers, mean age of 69 years (standard deviation =9), were included (Table.1). All received Volumetric Arc Radiotherapy (VMAT) of 66Gy in 30 fractions to a primary tumour in the head and neck including the inferior neck nodes. A total of 90 CBCT images were registered and matched.

A preliminary evaluation of set up errors found systematic errors in the total and superior ROI were within a 3mm imaging threshold tolerance, although in the medio-lateral and ventro-dorsal direction the random error breached the threshold in some patients. In the medio-lateral, cranial-caudal and ventro-dorsal directions, errors up to 5mm were measured. In the inferior ROI, the systematic errors were within the 3mm tolerance in the medio-lateral and cranial-caudal directions, although breaching the 3mm tolerance in the ventro-dorsal direction. Rotational errors were within a local clinical threshold tolerance of 3° (Table 2).

Inter-rater agreement between radiographers was analysed finding an ICC for the SCR was 0.867 and for DR 0.917 demonstrating statistically significant agreement ( $p < 0.000$ ).

The 95% LoA between SCR and DR procedures in the medio-lateral, cranial-caudal, and ventro-dorsal translational directions were -6.40 to + 4.91, -7.49 to +6.05, -and - 7.00 to + 5.44mm respectively (Figure 3). Variation existed in the medio-lateral and ventro-dorsal directions (mean differences -0.57mm to -0.77mm) suggesting that there are systematic differences between registrations mainly in medio-lateral

direction. This can be observed in the Bland-Altman Plot with many values beyond the clinical threshold with some outlier's plotted beyond the LoA. There is an observed trend suggesting that a larger geometric displacement results in a greater difference between registrations, which is more pronounced in medio-lateral direction. The medio-lateral direction demonstrated proportional bias which was statistically significant ( $p < 0.001$ ) suggesting non agreement between registrations. In the cranial-caudal and VD directional there was no proportional bias which was not statistically significant ( $p = 0.074 - 0.207$ ) suggesting agreement between registrations. To compare the consistency of registrations, the percentage of values within a 3mm clinical threshold were evaluated for the medio-lateral, cranial-caudal and ventro-dorsal direction. The percentage of registrations within the clinical 3mm threshold was 32 to 65% demonstrating variation in all directions (Figure 3). The 95% LoA between SCR and DR procedures in the roll, pitch, and yaw rotations were  $-2.09$  to  $+ 1.86$ ,  $-3.24$  to  $+2.06$ , -and  $-1.74$  to  $+ 1.57^\circ$  respectively (Figure 4). Little variation existed in the roll, pitch, and yaw rotations (mean differences  $-0.08$  to  $-0.59$ ) suggesting systematic differences between registrations in the pitch rotation. This can be seen in the Bland-Altman plot with tight clusters of data points around the mean and difference lines in the roll and yaw rotations. The pitch rotation plot demonstrates a greater spread of data. However, there are a few outliers outside of the clinical threshold and LoA. Roll and Yaw rotations demonstrated no proportional bias which was not statistically significant ( $p = 0.493$  to  $0.453$ ) suggesting agreement. However the pitch rotation demonstrated proportional bias which was statistically significant ( $p < 0.001$ ) suggesting non agreement between registrations. 80% of DR image matches resulted in a change in clinical judgement to ensure the inferior nodes were sufficiently covered. Mean registration and matching times (seconds) for SCR and DR were 94 and 115 respectively. The radiographer satisfaction scores were 73% (3 – Most satisfied), 26% (2 – moderately satisfied), 1% (1 – slightly

satisfied) and 0 (0 – least satisfactory) for DR and 46% (3 – Most satisfied), 33% (2 – moderately satisfied), 18% (1– slightly satisfied) and 3% (0– least satisfactory) for SCR. The use of DR resulted in greater geometric correction values demonstrating that SCR could underestimate the correction required. (Table.3).

## **DISCUSSION**

The results of this pilot study demonstrate there is a clinical difference between using a SCR and DR in patients with oropharyngeal cancer based on these parameters. Consistent with other studies<sup>4-9</sup>, the preliminary set-up error data demonstrated that there is a distinct variation in head and neck anatomy in regards to systematic and random errors. Systematic and random errors were greater in the lower neck. The preliminary data justified piloting DR as a viable method for IGRT in patients with oropharyngeal cancer.

ICC inter-rater reliability demonstrated statistically significant agreement between radiographers using either a SCR or DR. This is encouraging as DR is designed to be a thorough method of image guidance and good levels of agreement suggest reliability among radiographers comparable to results demonstrated by Campbell et al<sup>14</sup> in patients with prostate cancer. A Bland-Altman analysis evaluated the differences between the two registration procedures finding that in medio-lateral direction there was proportional bias suggesting non-agreement between the SCR and DR. A difference between the two registration procedures was demonstrated, which corresponded to a 80% change to radiographers clinical judgement after using DR. The data suggests the change in clinical judgment using DR was mainly to ensure that the lower neck nodes were adequately covered by the PTV in 70% of cases. This is consistent findings from Hawkins et al suggesting that the image volume chosen has an impact on the overall registration. The timing data demonstrates that DR takes on average 21 seconds longer than the SCR, which is

logistically acceptable to clinical practice. Considering that DR is new to our department it was encouraging that radiographers took little time in learning to become independent operators of this procedure as well as finding DR a little more satisfactory than SCR.

Our findings contrast with Campbell et al<sup>14</sup> who found no change in clinical judgement, but did demonstrate that DR was a more efficient procedure. However, these authors were evaluating the use of DR in patients with prostate cancer which could explain the difference in results. There are no known studies evaluating the use of DR in head and neck cancer, therefore the current study should help to fill this gap. Furthermore, this work builds upon Hawkins et al<sup>13</sup> in optimising the registrations of CBCTs to maximise clinical outcomes. However, it is acknowledged that DR is a feature only available in Elekta systems.

The set-up error data using DR were lower than using large clipbox ROI. This could be due to the precision of DR, specifically the focus on soft tissue which is known to move independently of bony anatomy and in this case resulting in lower correction errors. The data from tables 1 and 2 contrast, but are demonstrating different clinical implications. Using large ROI, specifically in the lower neck suggest that there is need to develop the thermoplastic mask immobilisation to improve stability which will reduce set-up errors. This is consistent with other studies finding thermoplastic immobilisation to lack stability in the lower neck<sup>34-38</sup>. A recent publication titled 'ESTRO ACROP guidelines for positioning, immobilisation and position verification of head and neck patients for radiation therapists'<sup>19</sup> gives recommendations to improve methods of producing thermoplastic masks have the potential to improve stability. However, the data from suggest that DR is a highly suitable instrument for IGRT to monitor this variability in patients with oropharyngeal cancer.

## **Limitations**

Some limitations need to be addressed. A sample size of 10 is small. However, this was a pilot study prior to a larger substantive study which will require effect size calculations. Another limitation is that DR is only available on Elekta systems and not available on other commercial systems which may exclude wide clinical uptake. The implications of the results on whether a re-plan was required was not undertaken, and should be included in future work.

## **CONCLUSION**

Dual registration might be an effective method of image guidance than using a SCR in patients with oropharyngeal cancer. Adequate inter-rater agreement was found between radiographers using DR. Dual registration was found to deviate from the SCR but supported radiographers' clinical judgement.

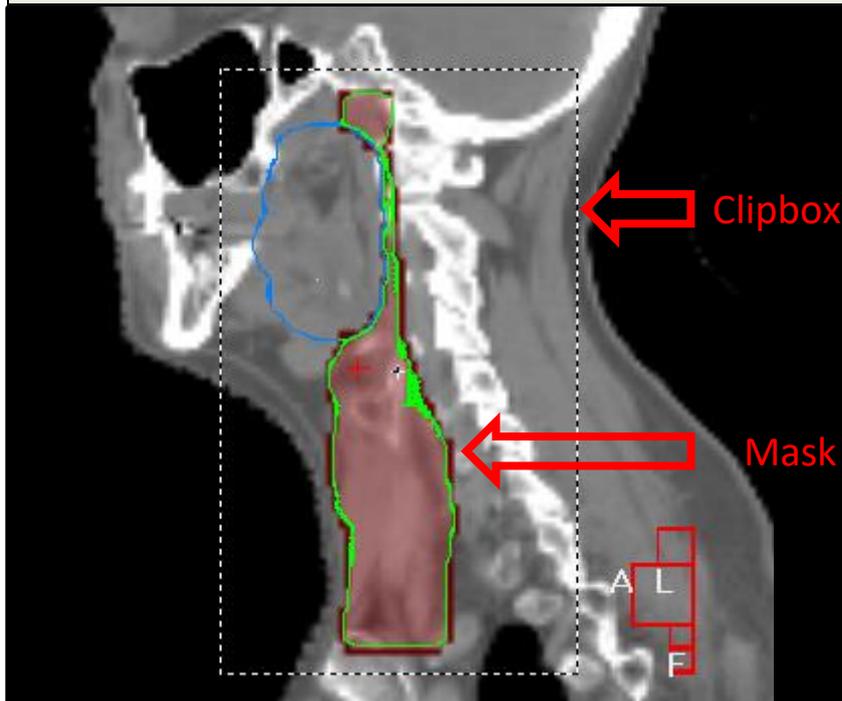
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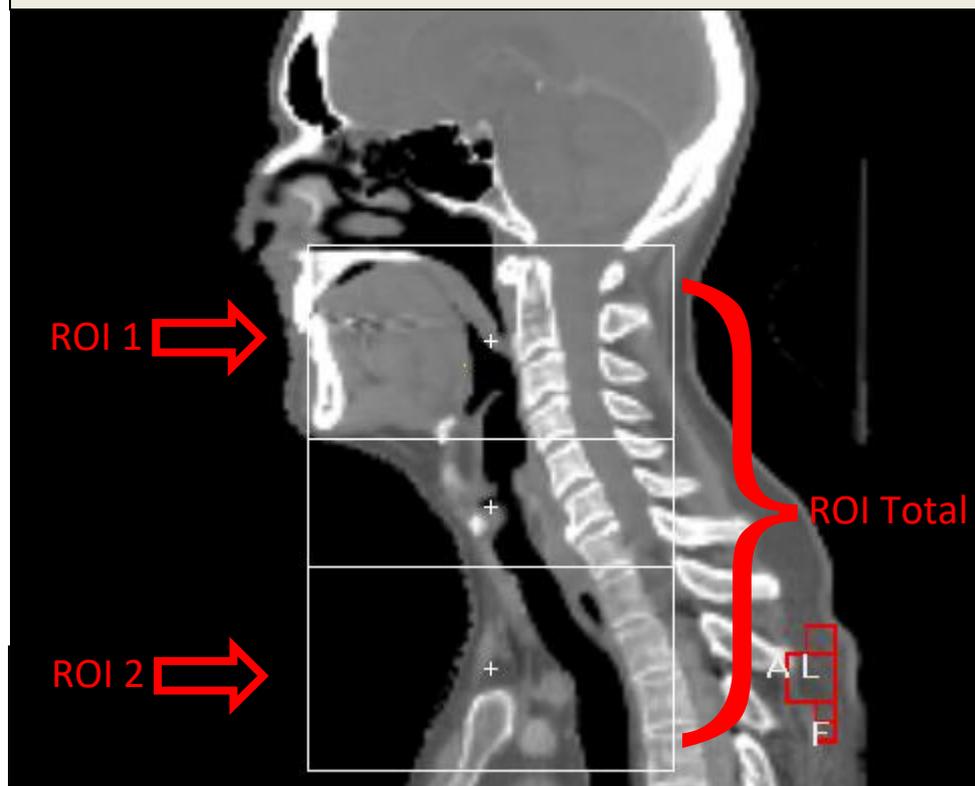
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**Figure 1 - Example of dual registration**



**Figure 2 - Separate Regions of Interest (ROI); ROI1, ROI2, ROI-Total**



Three ROI (clipboxes) were selected; upper neck; base of skull to C4 (ROI1), lower neck; T1 to T4 (ROI2), and standard large clipbox (ROI Total) for comparison.

**Table 1. Patient demographics**

Patient demographics	Mean/standard deviation or count
Participants	10
Age in years	69 (9)
Sex	
Female	3
Male	7
Primary tumour	
Tonsil	6
Tongue	2
Parotid	2

**Table 2. Systematic and random displacement errors of three ROI (ROI-Total, ROI-1, ROI-2)**

		ML (mm)		CC (mm)		VD (mm)		Roll (Rot°)		Pitch (Rot°)		Yaw (Rot°)	
		$\Sigma\rho_{op}$											
ROI	Total	1.03	0.73	1.20	1.47	1.43	1.14	0.5	1.0	0.26	0.43	0.31	0.43
	1	1.17	1.30	1.25	1.90	1.39	1.97	0.61	0.55	0.82	0.63	0.70	0.63
	2	2.89	2.30	3.00	2.50	3.37	3.01	1.44	1.25	0.86	0.85	0.70	0.85

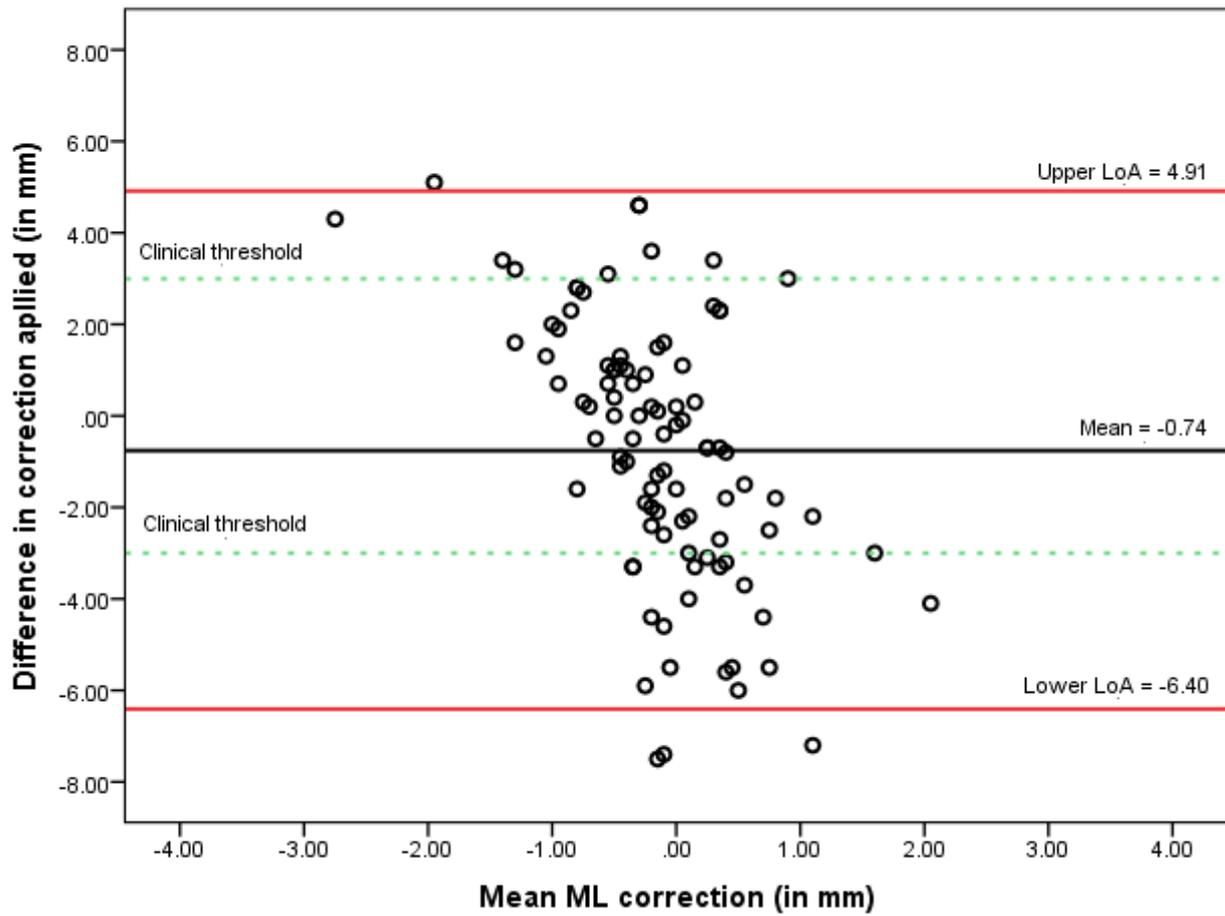
(ML= Medio-Lateral, CC = Cranio-Caudal, VD = Ventro-Dorsal, Rot = rotation,  $\Sigma\rho_{op}$ = The standard deviation of the patient groups' systematic errors;  $\sigma\rho_{op}$ = The root mean square of the patient groups' random errors.)

**Table 3. Systematic and random correction values for standard clipbox registration and dual registration**

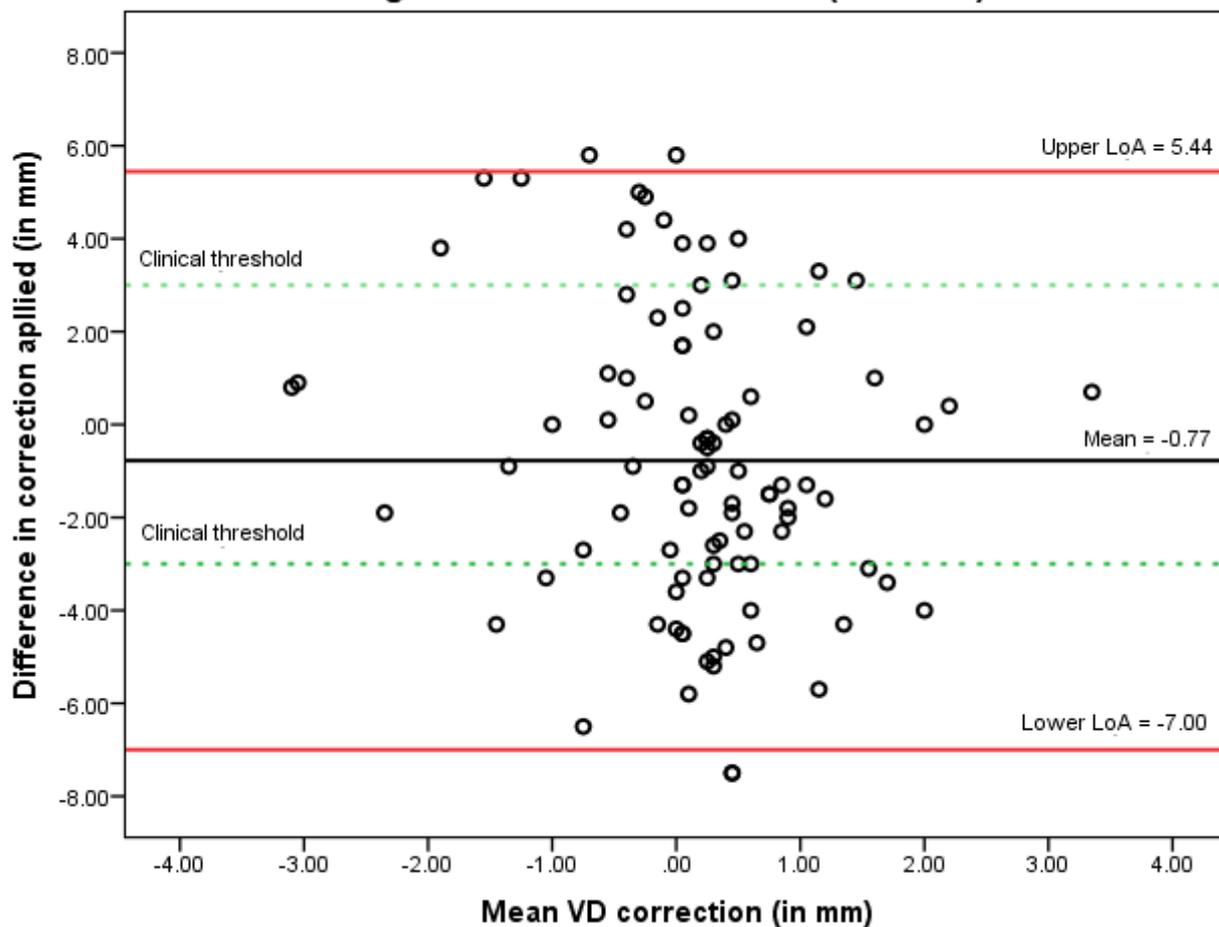
	ML (mm)		CC (mm)		VD (mm)		Roll (Rot°)		Pitch (Rot°)		Yaw (Rot°)	
	$\Sigma\rho_{op}$											
SCR correction	1.03	0.73	1.20	1.47	1.43	1.14	0.5	1	0.26	0.43	0.31	0.43
DR correction	1.56	1.54	1.41	1.79	1.57	1.71	0.40	0.41	0.77	1.40	0.33	0.45

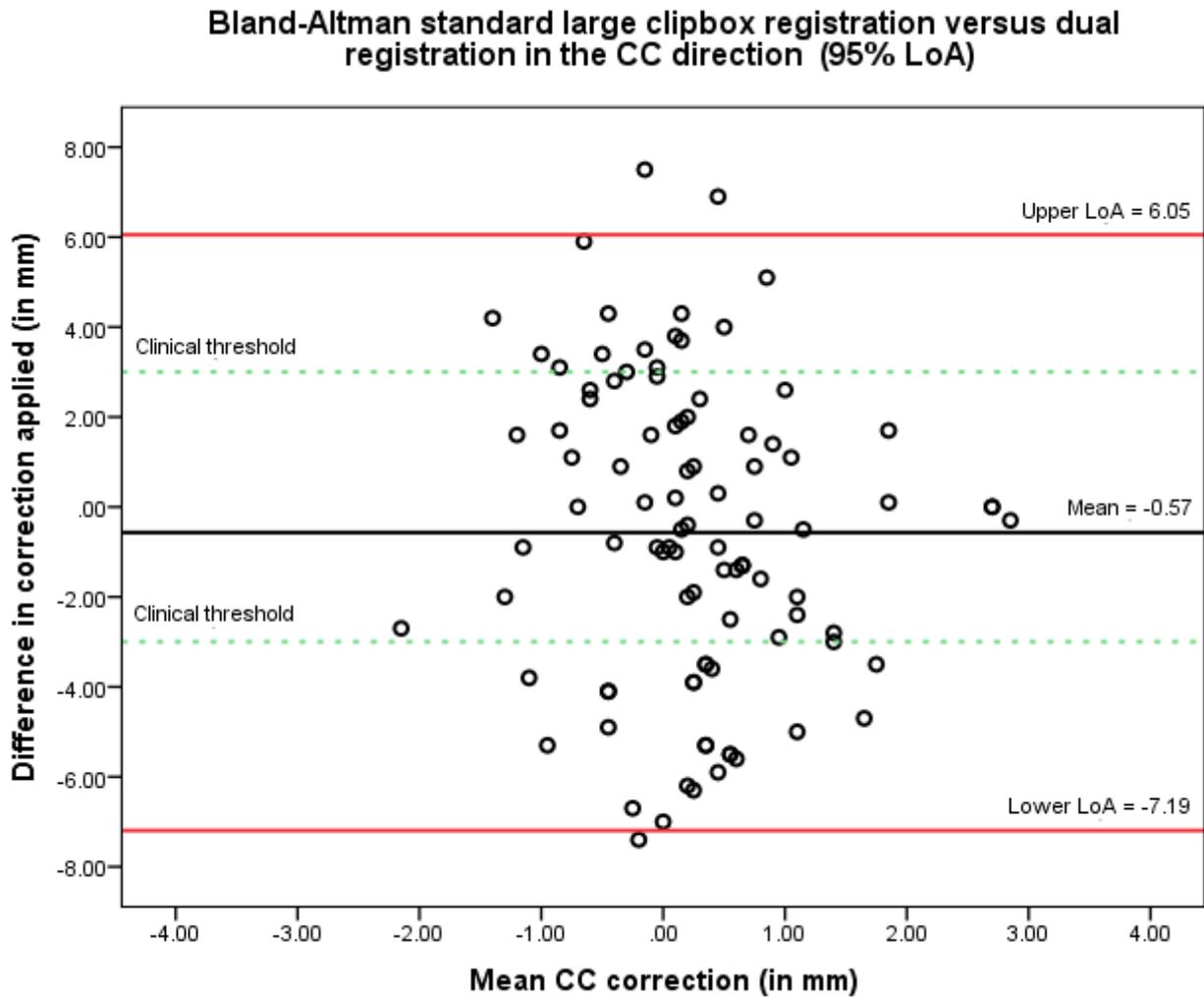
(ML= Medio-Lateral, CC = Cranio-Caudal, VD = Ventro-Dorsal, Rot = rotation,  $\Sigma\rho_{op}$ = The standard deviation of the patient groups' systematic errors;  $\sigma\rho_{op}$ = The root mean square of the patient groups' random errors)

**Bland-Altman standard large clipbox registration versus dual registration in the ML direction (95% LoA)**



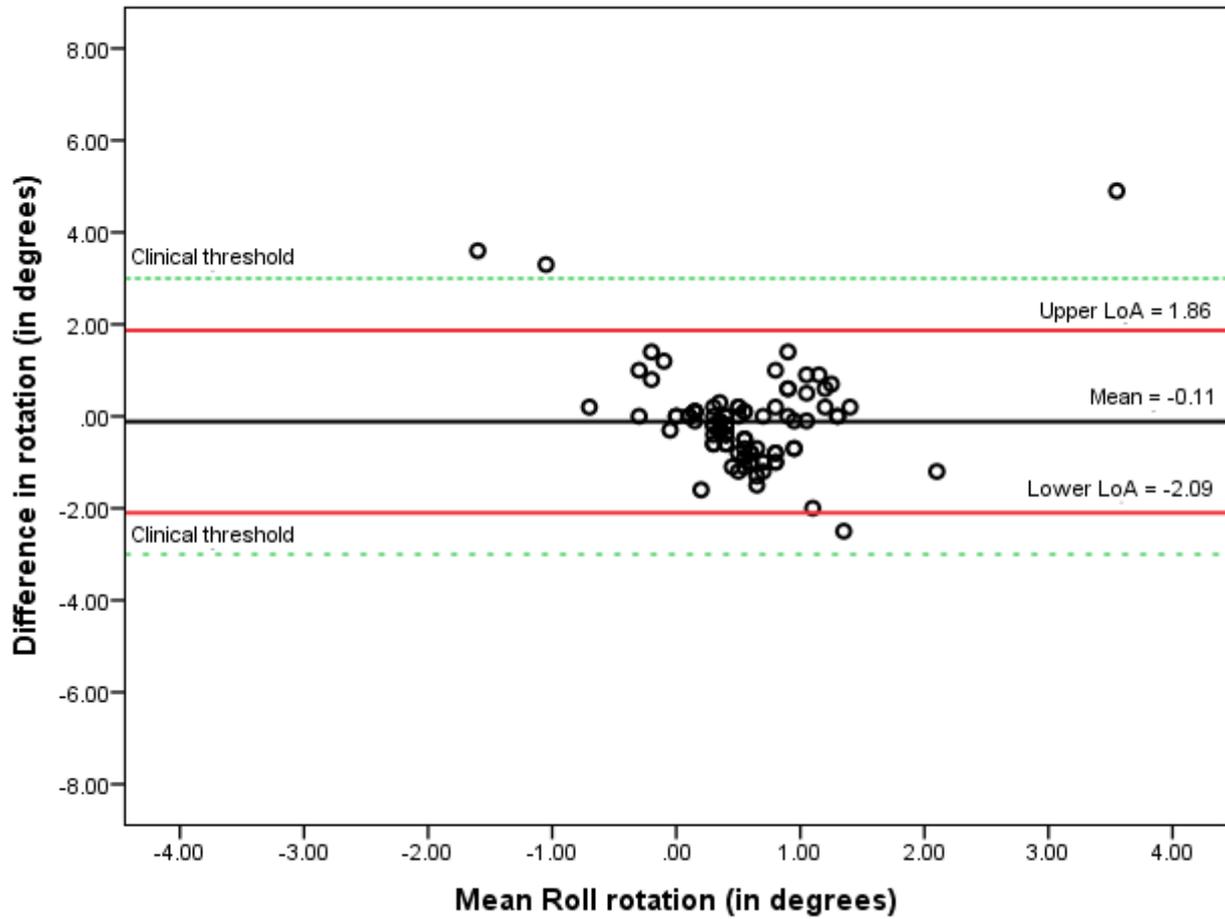
**Bland-Altman standard large clipbox registration versus dual registration in the VD direction (95% LoA)**

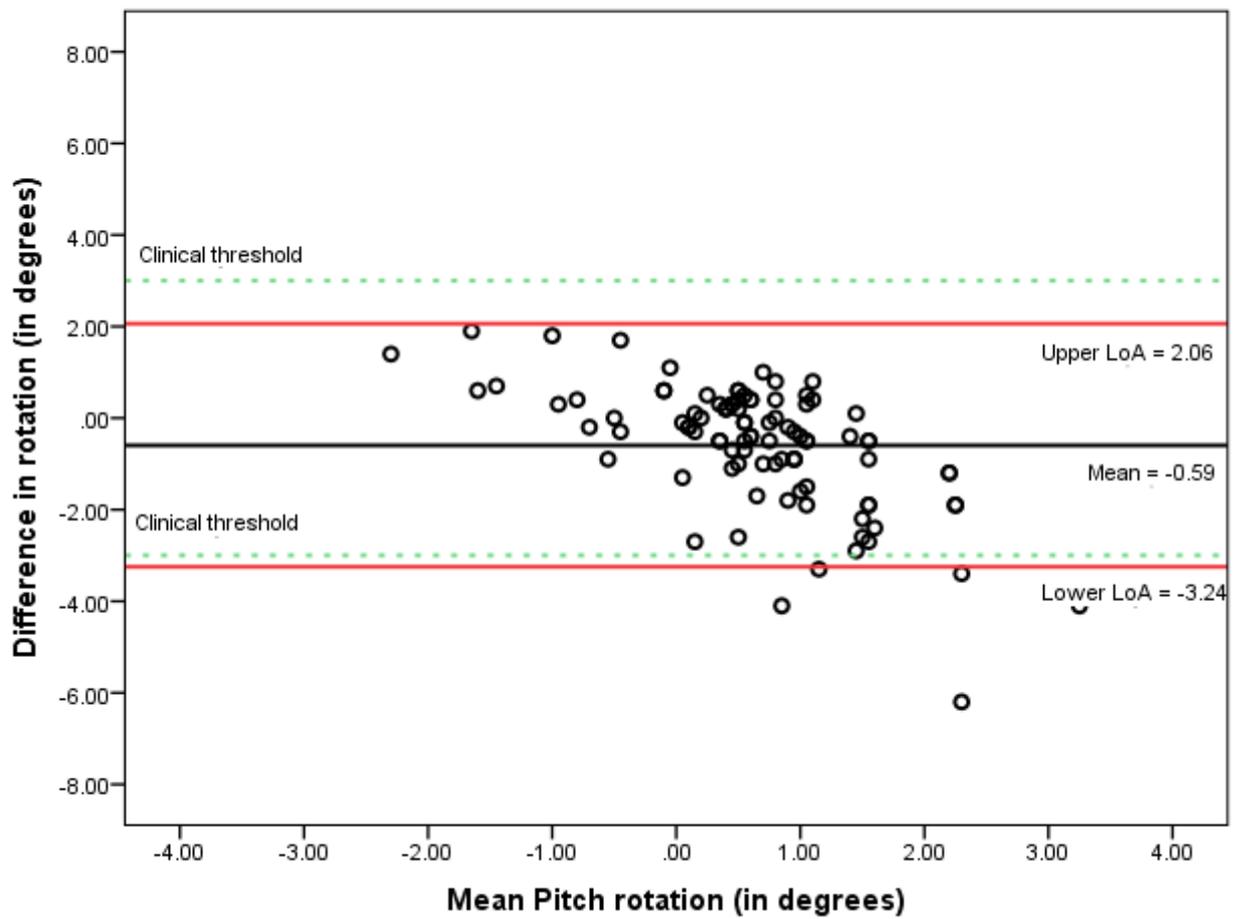


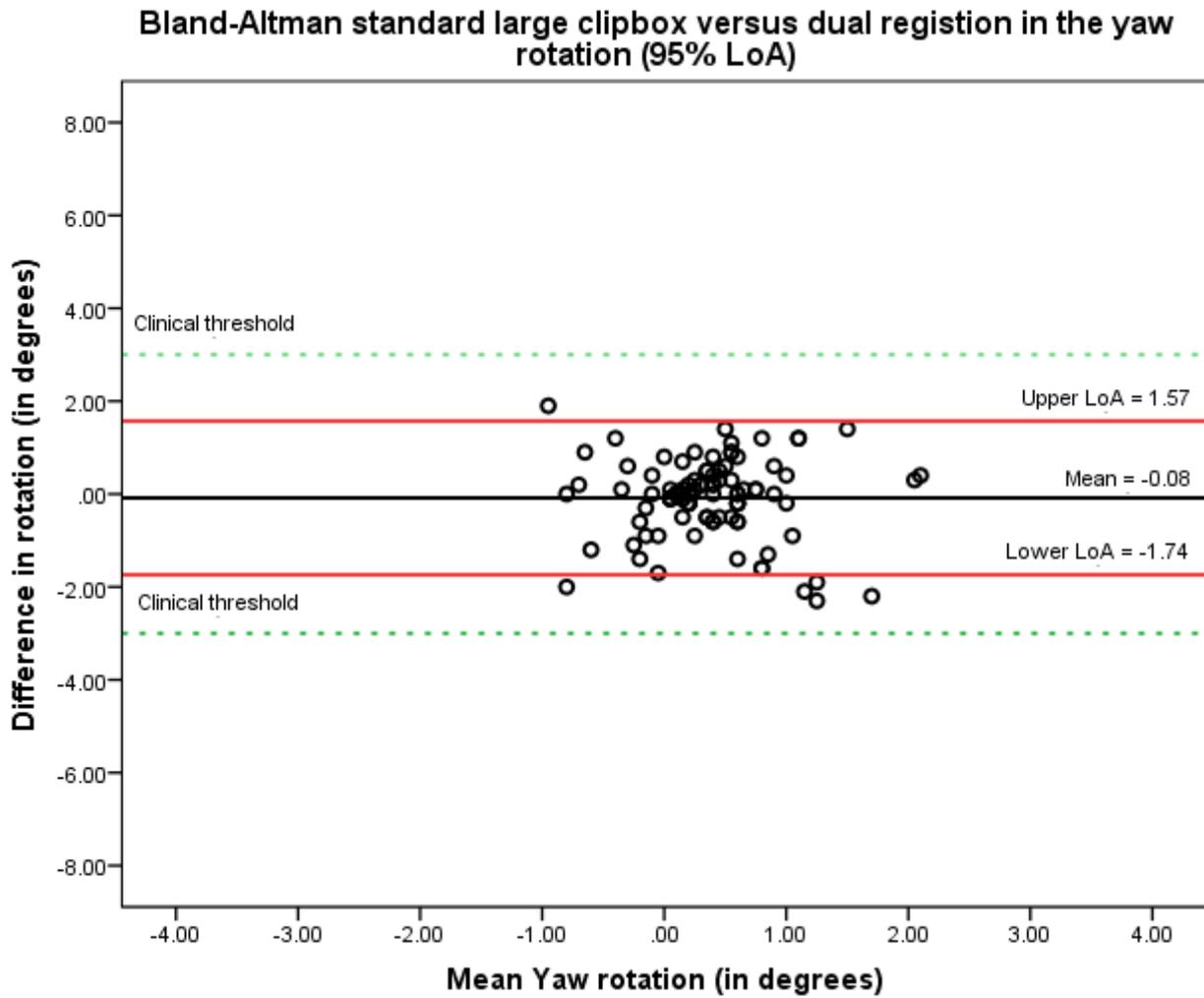


**Fig.3** Agreement between SCR and DR the medio-lateral (ML), cranio-caudal (CC), and ventro-dorsal translational directions using a Bland-Altman approach

**Bland-Altman standard large clipbox versus dual registration in the roll rotation (95% LoA)**



**Bland-Altman standard large clipbox versus dual registration in the pitch rotation (95% LoA)**



**Fig.4** Agreement between a SCR and DR in the roll, pitch, and yaw rotations using a Bland-Altman approach