Cone-beam computed tomography for lung cancer - validation with CT and monitoring tumour response during chemo-radiation therapy

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Abstract:

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Introduction: Cone-beam computed tomography (CBCT) is a valuable image-guidance tool in radiation therapy (RT). This study was initiated to assess the accuracy of CBCT for quantifying non-small cell lung cancer (NSCLC) tumour volume compared to the anatomical “gold standard”, CT. Tumour regression or progression on CBCT was also analysed.

Method: Patients with Stage I-III NSCLC, prescribed 60 Gy in 30 fractions RT with concurrent platinum-based chemotherapy, routine CBCT and enrolled in a prospective study of serial PET/CT (baseline, weeks two and four) were eligible. Time-matched CBCT and CT gross tumour volumes (GTVs) were manually delineated by a single observer on MIM software, and were analysed descriptively and using Pearson’s correlation coefficient (r) and linear regression (R²).

Results: 94 CT/CBCT pairs from 30 patients were eligible for inclusion. The mean ($\pm$ SD) CT GTV vs CBCT GTV on the four time-matched pairs were 95 ($\pm$ 182) vs 98.8 ($\pm$ 160.3), 73.6 ($\pm$ 132.4) vs 70.7 ($\pm$ 96.6), 54.7 ($\pm$ 92.9) vs 61.0 ($\pm$ 98.8) and 61.3 ($\pm$ 53.3) vs 62.1 ($\pm$ 47.9), respectively. Pearson’s correlation coefficient (r) was 0.98 (95% CI 0.97 – 0.99, $p < 0.001$).

The mean ($\pm$ SD) CT/CBCT Dice’s similarity coefficient was 0.66 ($\pm$ 0.16). Of 289 CBCT scans, tumours in 27 (90%) patients regressed by a mean ($\pm$ SD) rate of 1.5% ($\pm$ 0.75) per fraction. The mean ($\pm$ SD) GTV regression was 43.1% ($\pm$ 23.1) from the first to final CBCT.

Conclusion: Primary lung tumour volumes observed on CBCT and time-matched CT are highly correlated (although not identical), thereby validating observations of GTV regression on CBCT in NSCLC.

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Introduction

Cone-beam computed tomography (CBCT) is a volumetric on-board imaging tool in image-guided radiation therapy (IGRT) for lung cancer [1-4]. Many factors influence gross tumour volume (GTV) and location both inter- and intra-fractionally including patient position, organ movement due to respiration, tumour regression or progression, and lung deformation due to collapse or re-expansion [5]. CBCT is currently the optimal, most readily available quality assurance procedure to verify GTV location and detect any gross set-up misalignments prior to radiation therapy (RT) [6].

There are limited publications reporting direct comparisons of lung tumours delineated on CBCT compared to CT. In a study of 12 non-small cell lung cancer (NSCLC) patients, Altorjai et al. (2012) reported that mean GTVs were on average 30% larger on CBCT than CT [7]. This may be explained by the slower CBCT acquisition time capturing GTV motion during the ventilatory cycle. Conversely, Liu et al. (2013) in their analysis of 71 NSCLC internal target volumes (ITV) reported that CBCT GTVs were smaller than 4D CT volumes by 11.8% [8]. The strength in the design of Liu's study was the use of 4D CT, accounting for tumour motion during respiration.

The conduct of a prospective study of sequential PET/CT in NSCLC patients at our institution presented a unique opportunity to compare the CT component of these scans to CBCT routinely acquired in this study cohort. The primary objective of this sub-study was to validate the accuracy of CBCT for monitoring primary lung tumours during RT by comparing GTVs on CBCT to those on time-matched CT. Informed by these findings, the

secondary objective was to study patterns of primary tumour progression and/or regression as observed on serial CBCT, particularly as there is interest in relating to changes in GTV during treatment to prognosis [9, 10]

Material and methods

Patient selection and treatment details

The institutional clinical research and ethics boards approved this study and patients provided written, informed consent. Patient data were sourced from a prospective cohort study of serial PET/CT imaging during concurrent chemo-radiation therapy (cCRT) for patients with NSCLC (Australian Clinical Trials Registry ACTRN12611001283965). Patient eligibility included Stage I-III NSCLC and cCRT of 60 Gy over 30 fractions in six weeks and concomitant chemotherapy (weekly carboplatin and paclitaxel, or cisplatin on days 1, 8, 29 and 36 of cCRT and etoposide during weeks 1 and 5). Additional sub-study eligibility included CBCT according to institutional protocol (CBCT scheduled four times in week one and weekly thereafter). Exclusion criteria included an indeterminate primary tumour, when the CBCT field of view did not encompass the entire tumour and when the tumour was not assessable due to poor image quality.

PET/CT acquisition

During PET/CT acquisition (baseline, weeks two and four), patients were aligned using in-room lasers and skin tattoos in a RT immobilisation device. Scans were acquired under free-breathing conditions and without contrast with a Discovery STE 8 or Discovery 690 hybrid PET/CT (GE Healthcare, Milwaukee, WI, USA). CT imaging was acquired in helical mode at 140 kV, using an automatically variable mA dependent on patient size (40-150 mA). Images were reconstructed with slices of thickness 3.75 mm.

Data were exported from GE eNTEGRA (GE Healthcare, Milwaukee, WI, USA) via the Picture Archiving and Communication System (PACS, Siemens Healthcare, Malvern, PA, USA) to Focal (Computerised Medical Systems, St Louis, MO, USA). RT target delineation and dosimetry were performed using the baseline FDG PET/CT scan on Focal and XiO (CMS, St Louis, MO, USA). To avoid cross-software modification of images, all study scans were exported directly from PACS to MIM (version 6.3.2, MIM Software Inc., Cleveland, OH, USA) for contouring and analysis. All images were exported between workstations using

Digital Imaging and Communication in Medicine (DICOM) RT protocol (Rosslyn, VA, USA).

CBCT acquisition

Patients were treated on a Varian CLINAC 21iX or Trilogy (Varian Medical Systems, Palo Alto, CA, USA) with an On-Board Imager (OBI – Varian Medical Systems, Palo Alto, CA, USA). In accordance with departmental policy, CBCT scans were acquired following patient set-up and immediately prior to treatment, to verify patient position and isocentre placement. Scans were taken under free-breathing conditions at 110 kVp, 32 mA and 20 ms using half-fan bowtie and copper filters. Once acquired, CBCT scans were exported from MOSAIQ (IMPAC Medical Systems Inc., Sunnyvale, CA, USA) to MIM using DICOM RT protocol.

Primary objective: comparison of GTV CT and GTV CBCT

The CT GTV was initially contoured using a mediastinum window width/level (500/0 HU) and then viewed and modified using a lung window width/level (1500/-250 HU). Since patient weight and composition greatly influence CBCT image quality [11, 12], an experienced radiation oncologist (NP) optimised three mediastinal window settings (45-80kg 480/-40 HU, 81-110kg 540/-90 HU and 111-150kg 550/-210 HU). As for CT delineation, CBCT GTVs were modified if necessary using the standard lung width/level (1500/-250 HU). In accordance with our departmental protocol, the lung window was primarily used where the tumour abutted lung, and mediastinum window where the tumour abutted mediastinum, chest wall, diaphragm or atelectasis [13].

To avoid inter-observer variation, one observer (AM) delineated all abnormal CT and CBCT signals consistent with visible primary tumour. This observer was resourced with viewing rights to the treatment GTV contoured at baseline and a thoracic anatomy text to verify tumour-mediastinal boundaries [14]. The primary observer contoured the entire tumour perimeter when the tumour appeared heterogeneous or displayed cavities, and when tumour and adjacent atelectasis could not be differentiated. Each scan was contoured in a single session to prevent unlimited contour refinement. The CT component of the PET/CT scans were time-matched to the closest CBCT in order to compare GTVs on CT vs CBCT for a given patient. PET scans were not viewed or incorporated into the contouring process. Upon completion, every contour was checked by an independent observer (SJE) and all contours abutting mediastinum were further checked by a radiation oncologist (NP).

MIM workflows were utilised to maintain standardised contouring procedures. In brief, each CBCT was automatically rigidly registered to its time paired CT using bony anatomy. The observer manually contoured the CT GTV on each axial slice using a 2D brush tool and the contouring protocol described above. This process was repeated for the CBCT GTV. For each scan the CT and CBCT GTVs were contoured in an alternating fashion. To reduce intra-observer and inter-modality bias, all contours were delineated on previously un-marked scans and alterations were not permitted between scans.

Secondary objective – monitoring GTV on CBCT over time

All evaluable CBCTs were considered in the analysis of tumour progression and regression. GTVs contoured on time-matched CBCT scans in the primary objective were maintained. Consistent with the primary objective, a standard MIM workflow and procedure were used to manually contour GTVs on all remaining CBCTs. Patients were randomly selected and scans were contoured in chronological order for each patient. Duplication from the previous scan followed by alteration of the contour was permitted. All contours were independently verified by an independent observer (SJE).

Statistical considerations

Verdi (IP Health, Melbourne, AUS) was used to access patient demographics (sex and age), tumour characteristics (disease stage, histology and tumour location) and treatment details (radiation dose, fractionation and chemotherapy regimen). Patient weight and scanner details were extracted from each scan's corresponding DICOM image file. Statistical analyses were performed using MIM, Microsoft Excel (Microsoft, Redmond, WA, USA), GraphPad Prism 6 and GraphPad QuickCalcs (GraphPad Software, La Jolla, CA, USA).

MIM workflows generated the absolute CT and CBCT GTVs, performed Boolean operations (i.e. volume of CT GTV not covered by CBCT), and RECIST long and short measurements [15]. Data were summarised descriptively using mean (SD), CT/CBCT ratios and mean percent difference between the modalities across all patients. Intermodal volumetric correlation was assessed using Pearson's correlation coefficient (r) and linear regression (R^2), and intermodal agreement was analysed using difference between volumes Bland-Altman plot. For all analyses, $p < 0.05$ was considered statistically significant. MIM also generated Dice's similarity coefficient between each CT and its time matched CBCT [16]. This

coefficient, reported as a fraction, provided an analysis of the volumetric overlap between the two contoured volumes, both in their size and position relative to each other. A value of 1 indicates perfect unity, while 0 indicates disunity.

Results

Of the 60 NSCLC patients enrolled in the prospective trial, 37 (62%) underwent CBCT scans during cCRT. Of these, seven (19%) patients were ineligible for this sub-study; one patient had no baseline CBCT, one patient presented with severe lymphangitis carcinomatosa which complicated GTV delineation, two patients had Stage TX primary tumours and three patients had incomplete GTVs due to the limited CBCT field of view. This resulted in 30 patients, recruited between November 2011 and August 2013 suitable for analysis. A summary of patient demographics is provided in Table 1. Tumour location varied between patients, with the majority (21, 70%) of tumours located in the upper lobes.

Primary objective

94 CT & CBCT pairs were selected and contoured, with a median (range) of three (2 to 4) scans per patient. The median (range) CT and CBCT inter-scan acquisition time was two (0 to 10) days, including 22 (23%) pairs acquired on the same day. At time-point 1, 2, 3 and 4 comparisons were available for 30, 30, 28 and 6 scan pairs, respectively. At each of the four time-points, the median (range) difference was 7 (0-10) days, 3 (0 to 5) days, 1 (0 to 7) days and 1 (0 to 3) days. The mean ($\pm$ SD) CT GTV vs CBCT GTV at time-point 1, 2, 3 and 4 were 95 ($\pm$ 182) vs 98.8 ($\pm$ 160.3), 73.6 ($\pm$ 132.4) vs 70.7 ($\pm$ 96.6), 54.7 ($\pm$ 92.9) vs 61.0 ($\pm$ 98.8) and 61.3 ($\pm$ 53.3) vs 62.1 ($\pm$ 47.9), respectively. Of these time-matched comparisons, the combined mean CBCT GTVs were 10.8% larger than their paired CT contours. When comparing absolute volumes, Pearson's correlation coefficient (r) was 0.98 (95% CI 0.97 – 0.99, $p < 0.001$). Of all tumour volumes, eight (27%) were lower lobe lesions, which appeared on average 23.8% larger on CBCT than CT. CBCT was larger in 66 (70%) scan pairs by an average volume of 20.3%. In the remaining 28 (30%) pairs, CT was larger by an average of 11.3%. The CT/CBCT ratio was 0.89. The modalities were highly correlated using a linear regression model, with $R^2 = 0.96$ ($p < 0.001$) as shown in Figure 1. Figure 2 shows time-matched CT and CBCT images of one patient across three time-points.

As shown in Figure 3, a difference-against-mean volume Bland-Altman plot reported a bias of -2.2 (two standard deviations 95% limits of agreement were -65 and 61) suggesting the

two scanning techniques are in good agreement, with a low average discrepancy. The two values greater than the upper 95% level of agreement belong to a single patient who presented with a very large tumour (996.72 mL on CT) with mediastinal and chest wall involvement and close proximity to the diaphragm, as shown in Figure 4. The single datum point observed below the lower 95% level of agreement belongs to a patient with a left pericardial effusion which clouded the right upper lobe and made GTV delineation difficult on the second CT and CBCT pair.

When analysing geographic miss, the mean ($\pm$ SD) CBCT GTV not included by the CT GTV was 36.7% ($\pm$ 16.8). Conversely, the mean ($\pm$ SD) CT GTV not included by the CBCT GTV was 29.3% ($\pm$ 16.6). The overall mean ($\pm$ SD) Dice's similarity coefficient between CT and CBCT was 0.66 ($\pm$ 0.16) and individual values are shown in Figure 5. Contour congruence was observed to decrease as patient weight increased (0.69, 0.65 and 0.52 for custom CBCT window W/L 1, 2 and 3 respectively), with the poorest overlap in the heaviest of patients.

The mean RECIST long measurement was 5.68 cm (SD $\pm$ 2.87) for CT and 5.98 cm (SD $\pm$ 2.93) for CBCT. CT appeared longer across 31 (33%) scans by 8.5% and in 62 (66%), CBCT appeared longer by 10.7%. The average CT/CBCT ratio across all 94 scan pairs was 0.96. Mean RECIST short measurements for CT and CBCT were 3.61 cm (SD $\pm$ 1.92) and 3.75 cm (SD $\pm$ 2.04), respectively. CT short measurement appeared longer across 35 (37%) scan pairs by 26.5% and in 58 (62%) scans, CBCT appeared longer by 26.5%. The average CT/CBCT ratio across all 94 scan pairs was 1.00.

Secondary objective

A total of 289 CBCT scans were acquired across all patients during CRT. 11 individual image exclusions were then made across seven patients to give a total of 278 CBCT suitable for analysis (median 9 per patient, range 6 to 14). The median frequency of CBCT acquisition was four scans in the first week of cCRT (range 1 to 6), then once weekly thereafter (range 0 to 4).

Overall, 27 (90%) patients displayed GTV regression. The mean ($\pm$ SD) regression rate was 1.5% ($\pm$ 0.75) per fraction. The mean ($\pm$ SD) GTV regression was 43.1% ($\pm$ 23.1) from the first to final CBCT. The remaining three (10%) patients displayed GTV progression (mean $\pm$ SD, 37.1 $\pm$ 31.1%) by a rate of 1.2% ($\pm$ 1.0) per fraction. Of these patients, one remained stable

throughout cCRT (overall change from baseline to final CBCT of 0.60 mL). The remaining two exhibited small initial tumour volumes which changed by 3.2 mL (51.2%) and 3.9 mL (58.5%), respectively. The relative volume difference from the baseline CBCT scan per week of cCRT and overall tumour response is presented in Figure 6. The overall average reduction in tumour diameter was 0.83 cm for RECIST long and 0.57 cm for RECIST short.

The lowest tumour regression rate was noted in the two patients with T4 disease; average tumour volume regression for T1, 2, 3 and 4 was 47.2%, 40.8%, 50.8% and 32.8%, respectively ($p=0.7792$). Right upper lobe tumours displayed the least average regression compared to right lower, left upper and left lower lobe patients (32.1%, 44.2%, 50% and 86.2%, respectively). No trends of significance were noted across different ages, nodal status, histologies, tumour sizes or chemotherapy regimens.

Discussion

The unique opportunity to compare sequential CT with time-matched CBCT has enabled our team to establish that the volumetric characteristics of primary lung tumour volumes are highly correlated on these distinct imaging modalities. These findings suggest that CBCT produces images of comparable quality to the anatomical imaging gold standard CT, which validates the accuracy of observed tumour volume changes on CBCT during cCRT.

In the current study, CBCT overestimated GTV by an average of 10.8% when compared to the current “gold-standard” of CT. Atorjai et al. (2012) reported considerably larger average CBCT contours of 30%, when compared to CT in 12 stereotactic NSCLC patients and concluded that CBCT provided adequate tumour localisation for this highly conformal technique [7]. When sub-divided into tumour location, almost one third of our patients had lower lobe lesions, which appeared on average 24% larger on CBCT than CT. Atorjai’s reported CBCT GTVs were more than 50% larger than CT in three patients with lower lobe tumours [7]. Together, this suggests that larger average CBCT GTVs result from respiratory-induced motion artefacts. The greatest bias is expected in lower lobe lesions which experience the greatest movement with ventilation, with cranio-caudal drifts of up to 15 mm intra-fractionally [7, 17-22]. Given the significant effects of motion in the treatment and imaging of NSCLC, further research comparing 4D acquisition of CBCT and CT would be of interest.

In addition to motion, CBCT is also more susceptible to image artefacts than CT, particularly where the patient's diameter is greater than the field of view (FOV) [11, 23, 24]. We observed a reduction in CT and CBCT GTV congruence as patient weight increased, with the poorest overlap in the largest patients. In the four (13%) patients who weighed ≥ 111 kg, the average Dice's co-efficient was 0.52 (compared to a combined 0.68 for patients < 110 kg). All four patient diameters were larger than the CBCT FOV, resulting in CBCT with extensive image noise and notable streaking, cupping and ring artefacts. To our knowledge, there are no published reports of Dice's similarity co-efficient or Boolean functions in the comparison of 3D CT with CBCT of lung lesions. Although CBCT and CT volumes were highly correlated in our cohort, each modality had a geographic miss of approximately 30% and comparatively low Dice co-efficients. This suggests discrepancies in tumour position, which could be attributed to tumour motion, patient size and/or image registration. As recommended previously, 4D imaging would provide further insight into the cause and significance of these discrepancies.

With respect to tumour growth between scans, the longest median (range) inter-scan acquisition time of 7 (0 to 10) days was observed between the baseline PET/CT and first CBCT. We have previously investigated NSCLC tumour growth using serial pre-treatment FDG PET/CT scans and observed that a scan interval of seven days is associated with an estimated progression rate (95% CI) of 11% (6-18%) [25]. Based on these data a small amount of tumour growth may have occurred during this period.

With regard to RECIST measurements, Biederer et.al. (2009) assessed tumour diameter using four inflated porcine lungs implanted with artificial agarose nodules [26]. The authors reported larger lesion diameters across all dimensions by an average of 7% on CBCT than CT, which was consistent with our RECIST long measurements of 4.1% larger on CBCT than CT. Our RECIST short measurements, however, were more reliable between the modalities, with a difference of only 0.5%.

Analysing sequential volumetric changes over time demonstrated an overall GTV regression of 43.1% from baseline to final CBCT acquisition in 27 (90%) patients. This is slightly more than published regression rates of 30-40% [10, 12, 27-29]. Van Zwienen et al. (2008), Kupelian et al. (2005) and Lim et al. (2011), reported regression rates of 0.6%, 1.2% and

1.5% per fraction respectively, which are consistent with our observed regression rate of 1.5% per fraction ($SD \pm 0.75$) [12, 27, 30]. Lim et al. (2011) and Kupelian et al. (2005) reported that larger initial tumour volumes were associated with the greatest rate of tumour regression [12, 30]. Our observations were consistent with Knap et al. (2010), who reported no correlation between initial GTV shrinkage [28]. We did however note the lowest rates of tumour regression, of 1.1% per fraction, were in two (7%) patients with T4 disease, and in 9 (30%) patients with right upper lobe lesions.

Of our three (10%) patients with overall volumetric progression, one patient displayed minimal GTV change of 45.52 mL (± 2.24 mL) throughout cCRT. In the remaining two patients, initial GTVs were small (<11 mL) and therefore highly susceptible to partial volume effects. It is therefore likely these volumes were under-represented in one or more CBCTs, leading to an observed volumetric progression. Van Zweinen reported progression in one (1%) patient; however, the overall progression rate was not specified

We acknowledge that our observations are based on anatomical imaging alone. There is significant evidence documenting that CT is limited by its low contrast sensitivity and specificity when compared to PET/CT [31, 32]. Incorporating functional information from PET would have influenced tumour delineation in this study, especially in cases where adjacent collapsed or consolidated lung was included in the anatomic tumour volume. Despite these known limitations of 3D anatomical imaging, the emphasis of our study was on the consistent contouring of anatomical tumour volumes between modalities.

Routine tumour monitoring strategies should be validated, readily accessible and capable of accurately visualising tumour volume changes during treatment. Based on our findings, CBCT is a suitable method to assess most NSCLC patients for this purpose and is straightforward to acquire as it does not require an additional appointment. With large volumes of CBCT data readily accessible in many centres, innovative applications of this technology are now being investigated including CBCT-based adaptive RT. Yoo et al. (2006) reported that CBCT-based treatment planning is feasible when tumour volumes are homogeneous, but careful validation is required in lung cancer [33]. Caution was also advised by Tanyi and Fuss (2008), who concluded that CBCT should not be used as a platform for dose re-calculation due to motion-induced artefacts, although it does provide adequate information to encourage re-scanning and dose adjustment using conventional CT [34]. As discussed, our patients were

treated based on combined FDG PET/CT. Since CBCT is only capable of visualising tumour anatomy, we do not recommend the use CBCT in redefining interim GTVs. Consistent with Tanyi and Fuss, our results indicate that CBCT is a readily assessable tool that could play an important role in prompting re-scanning with PET/CT if clinically significant tumour volume changes are observed during cCRT.

Conclusion

Results of this study have established that the volumetric characteristics of primary lung tumours observed on sequential CT during cCRT are highly correlated to those observed on time-matched CBCT. Caution is advised, however, when comparing the tumour location, especially in very large patients.

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Table 1: Patient, disease and tumour characteristics at baseline (N=30)

Characteristic	Number (percent)
Gender, n (%)	
Male	21 (70)
Age (years)	
Median	67.5
Range	31 – 86
Histology, n (%)	
Adenocarcinoma	16 (53)
Squamous cell carcinoma	10 (33)
Neuroendocrine origin	2 (7)
Poorly differentiated	2 (7)
Tumour location, n (%)	
Right upper lobe	9 (30)
Right lower lobe	7 (23.3)
Left upper lobe	12 (40)
Left lower lobe	1 (3.3)
Mediastinum (left hilum)	1 (3.3)
Overall disease stage, n (%)	
Stage IA	1 (3.3)
Stage IB	1 (3.3)
Stage IIA	4 (13.3)
Stage IIB	0 (0)
Stage IIIA	15 (50)
Stage IIIB	9 (30)
Stage IV	0 (0)

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Mean Difference in Volume per Week of Treatment

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