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FULL PAPER

Split-bolus contrast injection protocol enhances the visualization of the thoracic vasculature and reduced radiation dose during chest CT

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Objective To investigate the visualization of mediastinal lymph nodes during thoracic CT employing a multiphasic contrast media (CM) protocol.

Methods Institutional review board approved retrospective study consisting of 300 patients with known chest malignancy. Patients were allocated to one of two CM protocols: Protocol A, consisted of dual bolus (Phase 1: 100 ml CM followed by 100 ml saline chaser) i.v. injected at 2.5 ml s⁻¹; Protocol B employed 100 ml of CM using a multiphasic injection protocol (Phase 1 and 2: 60 ml contrast and saline, followed by Phase 3 and 4: 40 ml contrast and saline injected at 2.5 ml s⁻¹) with a fixed scan delay of 70 s for each acquisition. Attenuation profiles of the thoracic arteries and veins were calculated as well as the arterio-venous contrast ratios (AVCR). Receiver operating characteristic (ROC), visual grading characteristic (VGC), and Cohen's kappa analysis were assessed.

Results Arterial opacification was up to 24% ($p < 0.032$) higher in protocol B than A, whereas, in the veins it was

significantly lower in protocol B than A, with a maximum reduction of up to 84% ($p < 0.0001$). There was no statistical significance between the central and peripheral pulmonary arteries [>263 Hounsfield units (HU)] in each protocol. Protocol B, demonstrated significant improvement in AVCR at various anatomical sites ($p < 0.002$). Radiation dose was significantly reduced in protocol B compared to A ($p < 0.004$). Both ROC and VGC demonstrated significantly higher Az score for protocol B compared to A ($p < 0.0001$) with an increased inter reader agreement from poor to excellent.

Conclusion Employing a multiphasic CM protocol significantly improves opacification of the thoracic vasculature and visualization of mediastinal lymph nodes during thoracic CT.

Advances in knowledge Uniform opacification between thoracic arteries and veins increases the delineation between vasculature and lymph nodes, reduces radiation dose when employing a multiphase contrast media injection protocol.

INTRODUCTION

Lung cancer is the major oncological public health burden for males and females.¹ Approximately 85% of lung cancer patients have non-small cell lung cancer (NSCLC).¹ Although patients with early stage NSCLC may be cured by surgery, post-operative survival rates are relatively low.² Neoplasia in the lymph nodes occurs in two ways: lymphatic or haematogenous spread. For patients with mediastinal lymph node metastases (local or distant), it is clinically unfavorable even after surgery and/or adjuvant chemotherapy.³ Lymph node involvement in patients with

chest pathology is pivotal for setting the staging, management, and treatment outcome.

CT technology is rapidly evolving with its submillimeter contrast and spatial resolutions, providing superior image quality and increasing reader confidence and agreement during chest CT. Texture and shape analysis has the potential to accurately differentiate between malignant and benign mediastinal nodes in lung cancer imaging.⁴ However, the current sensitivity and specificity of CT in staging patients with NSCLC are 57% and 82%, respectively, vs 84 and 89%,

78 and 71% for positron emission tomography (PET) and endoscopic ultrasound (EUS), respectively.⁵ Moreover, according to Song et al, the greater the extent of lung cancer in the mediastinum or the more the encroachment to the regional lymph nodes, the harder it is to detect lymph node involvement.⁶ The primary concern is the separation between lymph nodes and poor enhanced vasculature may lead to difficulty in detecting these lymph nodes that are adjacent to vasculature in the mediastinum.

With the evolution of CT technology, contrast media (CM) related artifacts, such as those in the superior vena cava (SVC), right and left brachiocephalic veins (BCVs) have emerged as a serious issue since they obscure the visualization of lymph nodes at the level of the cervico-thoracic junction and SVC pathway, resulting in poor image quality.^{7–10} Nevertheless, the synchronization between the scanner and CM administration during a routine CT, has been recently developed by employing patient-specific contrast formulae and adjusting CM volume based on the patient's variables leading to a significant reduction in the SVC artifact during CT angiography.^{11–13} This has resulted in an increase in sensitivity and specificity of image quality using previous CT techniques to almost 100% during thoracic CT angiography.^{7,9} The aim of the current study is to compare the opacification of thoracic vasculature and visualization of mediastinal lymph nodes during CT of the thorax employing a conventional vs multiphasic CM injection protocol.

METHODS AND MATERIALS

Study population

The institutional review board approved this retrospective study, and the written informed consent was waived since all studies were clinically indicated and patient data was evaluated anonymously. 300 consecutive patients (mean age 68 years, range 54–82 years, 140 male, 160 female) were included in this study. Patients with biopsy-confirmed malignant mediastinal nodal involvement were referred to the Radiology Department at our institution for further evaluation with contrast-enhanced CT. Pregnant females, patients allergic to iodine-based pharmaceuticals, and those with renal insufficiency (estimated glomerular filtration rate $<50 \text{ ml min}^{-1}$ per 1.73 m^2) were excluded from this study.

Thoracic CT acquisition

The subjects were reviewed in a continuous fashion where, 153 underwent protocol A (previous contrast technique), while, 147 employed protocol B (new scanning technique that was approved by radiology faculty). All scanning examinations were performed using a 64-slice CT scanner (VCT, GE Healthcare, WI) and patients were positioned supine with arms above their head. Anteroposterior scout scan was performed prior to scan acquisition, with a scan range from the lung apices to the lower edge of the costo-phrenic angles. The patients were asked to breath in and hold their breath prior to scan acquisition. For each protocol, the scanning parameters included 120 kVp, 120 mA with mA modulation, 0.4 s rotation time, pitch 0.889 mm rot^{-1} , and a craniocaudal scan. The image reconstruction parameters for each protocol employed $64 \times 0.625 \text{ mm}$ slice thickness

and reconstruction intervals of 0.5 mm, field of view $350 \times 350 \text{ mm}$, and a window width and window level of 420 and 65, respectively.

Contrast media administration

CM and saline chaser were injected with an automated dual barrel power injector (Optivantage, Optiray 320 mg ml^{-1} , and Mallinckrodt) via a 20G venous catheter placed in the right cubital fossa. The right antecubital vein was the preferred site for injection since it provides a shorter route for CM flow and subsequently, a less dilution effect.¹⁴

Protocol A entailed a single bolus of 100 ml CM volume, followed by 100 ml saline, at a flow rate of 2.5 ml s^{-1} and a fixed scan delay of 70 s. CM volume was not tailored to the patient's body mass index¹⁵ but was based on current departmental work practice and in line with the current literature.¹⁶ Protocol B utilized the multiphasic injection protocol (Phase 1 and 2: 60 ml contrast and saline, followed by Phase 3 and 4: 40 ml contrast and saline injected at 2.5 ml s^{-1}) with a fixed scan delay of 70 s prior to the acquisition.

Image assessment

Transaxial images were reconstructed with 0.625 mm slice thickness (0.5 mm increment) using a smoothing convolution kernel (field of view $380 \times 380 \text{ mm}$, image matrix, 512×512). Image quality was assessed using a reporting workstation (IMPAX 6.3.1, AGFA) with a GSDF-calibrated 3 megapixel monitor.

Attenuation measurements

Attenuation in the region of interest (ROI) was measured in the axial images, in HU, by encircling the greatest possible diameter; embracing the lumen of the vessel but excluding its wall to avoid any possible calcified plaques. The mean and standard deviation (SD) within the ROI in each vessel were recorded. Arterial measurements took place at nine anatomical levels (Figure 1): At the level of the ascending aorta,¹ sinus of valsalva²; sinotubular junction³; mid segment of the ascending aorta⁴; distal segment of the ascending aorta;⁵ first segment (between innominate and left common carotid artery);⁶ second segment (between the left common carotid and left subclavian artery);⁷ aortic isthmus opposite to the left subclavian artery;⁸ descending aorta proximally at the level of the aortic valve, and⁹ descending aorta at the aortic hiatus.

Attenuation in the veins (SVC and BCVs), adjacent to and at the same anatomical levels as the arteries, was recorded. Additionally, the opacification profile of 3 central segments and 10 peripheral pulmonary arteries was measured. The locations of the ROI were: central pulmonary vasculature (trunk, right and left pulmonary arteries); pulmonary segments; right upper lobe (anterior and posterior), right middle lobe (lateral and medial), right lower lobe (anterior and posterior basal), left upper lobe (apico-posterior and inferior lingular), and left lower lobe (anteromedial basal and posterior basal). The arterio-venous contrast ratio (AVCR) was obtained through expressing the ratio of the attenuation of the contrast (in HU) of the artery to that of the corresponding vein, at each of the aforementioned two levels

Figure 1. Anatomical location of measurements of the thoracic vasculature. Image (1) sinus of valsalva, (2) sinotubular junction, (3) mid segment of the ascending aorta and (4) distal segment of the ascending aorta, (5) first segment (between innominate and left common carotid artery), (6) second segment (between the left common carotid and left subclavian artery) and (7) aortic isthmus is opposite to the left subclavian artery, (8) descending aorta, proximally at the levels of the aortic valve; and (9) descending aorta, at the level of the aortic hiatus.

(sternal notch and third thoracic vertebrae). Levels with multiple arteries and veins had their vessel group averaged.

Contrast-to-noise ratio measurement

Contrast to noise ratio (CNR) analysis was calculated using a 0.625 mm thick trans-axial image. The ROI was constructed as to mark the vessel lumen excluding any calcification or plaques present within the wall. When calculating the CNR, the attenuation of the right pectoralis major muscle (ROI_{PM}) was measured at the level of the fifth thoracic vertebra followed by the second measurement of noise as the SD in the foam mattress of the CT table. The mean opacification of the thoracic aorta for each patient was measured just below the tracheal bifurcation (ROI_{TF}). Finally, the CNR was calculated based on the measured parameters described above, with an empirically derived formula: $CNR = (ROI_{TF} - ROI_{PM}) / \text{Noise}$.

Radiation dose measurement

For each of the CT scans, individual effective dose [E_{eff} (mSv)] was calculated from the dose-length products (DLP [$\text{mGy} \times \text{cm}$]), which were recorded from the patient protocol. A normalized conversion factor [k ($\text{mSv/mGy} \times \text{cm}$)] for the mediastinum— $0.0054 \text{ mSv/mGy} \times \text{cm}$ —was used to calculate the E_{eff} ¹⁷: $E_{\text{eff}} = \text{DLP} \times k$.

Receiver operating characteristic (ROC) analysis

100 randomly chosen cases were selected for each CM protocol (total $n = 200$). Cases showing lymphadenopathy of varying

degrees were defined by two radiologists' reports (based on complete patient series, previous and subsequent examinations, and clinical indications). The ordering of protocol viewing was performed in a blinded, and randomly assigned throughout the entire case base.

All visible pathology (greater than 1 cm with complete and circular hyperenhancement) present on the transaxial images, the prevalence of lymphadenopathy, the CM protocol, and the scanning techniques were not revealed to the readers. Technical criteria ensuring correct scan range and anatomical inclusion were considered by an expert medical imaging scientist (not included in the study proper).

Two general radiologists, with a mean of 14 years of experience, being certified by The Royal Australian and New Zealand College of Radiologists, assessed the images selected for ROC analysis. All reviewers were specialists in cardio-thoracic imaging, and each observer was allowed to manipulate the window width and the level of the images. The score scale from 1 to 6 (Likert Scale) was used to assess each imaging, where a score of 6 denotes an absolute nodal pathology unlike the score of 1, which refutes the presence of any nodal pathology, and 3 is defined as equivocal.

Visual grading characteristic (VGC) analysis

The VGC method of Bath and Mansson¹⁸ was employed by the radiologists to determine viewer preference of one technique

Table 1. Mean attenuation (HU) of arteries at each anatomical segment of the aorta during thoracic CT

Anatomical segment	Arterial location	Regimen A	Regimen B	<i>p</i>
Ascending aorta	Aortic sinus	257 ± 86	316 ± 86	0.03
	Sinotubular junction	252 ± 89	317 ± 88	0.001
	Body	244 ± 91	318 ± 86	0.002
	Distal	243 ± 94	316 ± 85	0.001
Transverse aorta	First segment	242 ± 92	316 ± 84	0.001
	Second segment	236 ± 96	315 ± 84	0.001
	Aortic isthmus	230 ± 96	316 ± 86	0.001
Descending aorta	Proximal	236 ± 93	311 ± 83	0.001
	Diaphragm	230 ± 92	306 ± 81	0.001

HU, Hounsfield units;

Data are mean ± standard deviation,

over another based on the visibility of lymph node distribution relative to vascular opacification. Specifically, for this work, nodal visualization scaling was performed using a 4-point classification scale; where score 0 indicated poor visualization of lymph nodes and 3 represented the complete visualization of the entire lymph node tree of the mediastinum.

Statistical analysis

Data entry and statistical analyses were performed using SPSS (v.23, 2009, Chicago, IL). Descriptive analyses for age distribution between the two CM groups was carried out by reporting frequencies and percentages. Continuous variables were presented as means and SDs were calculated using

independent-samples *t*-test. The ROC analyses employed the Dorfman-Berbaum-Metz approach using readers as random and cases as fixed.¹⁹ Cases were treated as fixed on the basis that the limited image sample size should not be taken as representative of all images. A statistically significant *p*-value was set to be less than 0.05.

In each scanning acquisition and CM protocol, the inter- and intra observer agreements were calculated using Cohen's kappa analysis. A *k* value 0.60–1, 0.41–0.60, 0.21–0.40, and less than 0.20 was considered excellent, moderate, fair, and poor agreement, respectively.

Table 2. Mean venous enhancement during thoracic CT

	Anatomical location	Protocol A	Protocol B	<i>p</i> value
Sternal notch	BCV	1506 ± 828	240 ± 76	<0.0001
Third thoracic vertebra	SVC	796 ± 464	127 ± 66	<0.0001
Pulmonary trunk	Mediastinum	309 ± 73	302 ± 81	0.24
Right main pulmonary arteries		315 ± 44	337 ± 19	0.32
Left main pulmonary arteries		305 ± 26	317 ± 49	0.34
Pulmonary arteries				
Right superior anterior	Right upper lobe	300 ± 49	301 ± 72	0.13
Right superior posterior		289 ± 38	293 ± 49	0.15
Right medial	Right middle lobe	271 ± 68	277 ± 37	0.08
Right lateral		263 ± 76	269 ± 75	0.11
Right anterior-basal	Right lower lobe	317 ± 59	318 ± 76	0.31
Right posterior-basal		305 ± 83	312 ± 81	0.22
Left apico-posterior	Left upper lobe	306 ± 99	308 ± 79	0.25
Left inferior-lingular		319 ± 48	314 ± 86	0.26
Left anteromedial-basal	Left lower lobe	289 ± 55	299 ± 82	0.27
Left posterior-basal		301 ± 76	304 ± 83	0.19

BCV, Brachiocephalic vein; SVC, superior vena cava;

Data are mean ± standard deviation.

Table 3. Arterio-venous contrast ratio during thoracic CT

Anatomical Location	Regimen A			Regimen B		
	Arterial	Venous	AVCR	Arterial	Venous	AVCR
Sternal notch	240	1506	0.16	318	240	1.33
Third thoracic vertebra	230	796	0.29	316	127	2.50

AVCR, arterio-venous contrast ratios;

RESULTS

Patient demographics, scanner acquisition, and radiation dose

There was no significant difference in the gender, age, height, weight, and body mass index between the two protocols (all $p > 0.05$). The E_{eff} dose was significantly reduced in protocol B, compared to that of protocol A (E_{eff} was 2.9 ± 0.6 mSv for protocol A; and 2.1 ± 0.3 mSv for protocol B, $p < 0.004$), consistent with a decrease in the DLP measuring the total exposure time of patient who underwent protocol B compared to protocol A. There was no significant difference in mean scan time in protocol B (3.22 ± 1.2 s) compared to A (3.01 ± 1.3 s), and in scan range in each protocol (A: 33.2 ± 2.01 cm and B: 32.9 ± 3.03 cm) ($p > 0.05$).

Opacification of the thoracic arteries and veins and contrast-to-noise ratio

Statistical analysis has shown that the mean arterial opacification were up to 24% ($p < 0.03$) higher following protocol B, compared to that of A (Table 1). Mean venous opacification (SVC and BCVs) were significantly lower following protocol B than those following protocol A, with a maximum reduction of up to 84% ($p < 0.001$) (Table 2). The opacification profile of 3 central segments and 10 peripheral pulmonary arteries demonstrated no statistical significance with the mean opacification of all segments in each protocol above 263 HU. As for AVCR, significant improvement

($p < 0.002$) was attained at the level of the sternal notch (90%) and the third thoracic vertebrae (86%) (that included the thoracic aorta, BCV, and SVC (Table 3). At the level of the fifth thoracic vertebra, the mean CNR in protocol B was significantly higher than that of protocol A (B; 34.4 ± 9.0 , A; 14.5 ± 14.0 HU) ($p < 0.032$).

Image evaluation

Receiver operating characteristic

The 6-point scale demonstrated a significant difference ($p < 0.0001$) between protocols with mean ROC values demonstrating increased reader confidence between protocols A and B being 0.87 and 1.0 (Figure 2).

Visual grading characteristic

The 4-point scores individually graded by the two readers for each CM protocol were expressed as a graph shown in Figure 3. When a preference is shown towards one protocol, the curve becomes convex to the axis of the corresponding protocol. The graphs clearly demonstrate that when the thoracic CT was assessed for opacification, the preference is for protocol B over A with reader confidence increasing from 0.76 to 0.99 ($p < 0.0001$).

Figure 2. ROC curve. The curves demonstrate significant increases in the area under the curve and 95% confidence intervals. AUC, area under the curve; ROC, receiver operating characteristic.

Figure 3. VGC curve. The graph represents protocol A compared with B during thoracic CT employing the conventional vs the split-bolus contrast injection protocol. AUC, area under the curve; VGC, visual grading characteristic.

Figure 4. Axial and coronal reformats of the chest: image (a) demonstrates the incoming redundant contrast (arrow head) in the SVC. Image (b) reveals the SVC (arrow head) without contrast media related artifact along with clear visualization of the axillary lymph nodes (small arrow head). Image (c) shows loss of visualization in the axilla (large arrow head) due to the high contrast media concentration in the subclavian veins (small arrow) causing a streak artifact when scanning was performed at 70 s post injection with poor visualization of the lymph nodes. Image (d) depicts the SVC (large arrow) filled with an encroaching primary lung carcinoma and artifact-free images visualized within the mediastinum. SVC, superior vena cava.

Kappa analysis

Thoracic CT yielded an excellent inter observer agreement with protocol B ($k = 0.71$), compared to that of A ($k = 0.43$) for the detection of lymph node pathology. Also, there was a strong positive relationship between the mean arterial and venous opacification, image quality, and reader confidence in protocol B compared to that in A ($r = 0.68$, $p < 0.001$).

DISCUSSION

Thoracic oncology imaging application is employed (a) to confirm a clear status of the chest, in terms of an absence of regional lymphadenopathy, (b) to document lymphadenopathy contralateral to the primary location, if any, (c) to assess the

regional extent of the disease especially in relation to vascular and lung structures, and (d) to survey lymph nodes for follow-up.²⁰ Our study highlights that the use of a multiphasic CM technique reduces the perivenous artifacts in the cervico-thoracic junction (BCV and SVC) while, significantly increasing the visualization of lymph nodes surrounding the SVC by uniformly distributing the CM throughout the vasculature and the parenchyma.

The CT patterns of mediastinal lymph nodes are the primary landmarks used to narrow down the list of differential diagnosis.²¹ Especially, clear visualization of lymph nodes is crucial for approaching mediastinal pathology.²² Even though the use of contrast-enhanced CT technique reveals more enlarged

mediastinal nodes than what unenhanced CT does, the occurrence of CM related artifacts significantly degrades image quality (Figure 4).²³ Our study showed that reduced SVC density/artifact increased reader confidence, lymph node visualization, and inter observer agreement in our split-bolus CM technique. Nevertheless, different chest malignancies display different lymph node enhancement patterns.^{21,24–27}

Previous studies have shown a cost to achieving optimal image quality with CT chest examinations, in particular in regard to radiation dose.²⁸ Exceptionally, in our work, radiation dose was reduced with reduced CM volume. This was due to the flying focal spot detecting changes in tissue attenuation in the region of the SVC, resulting in the scanner not increasing the radiation dose in the split-bolus CM protocol. However, the higher radiation dose in protocol A, was due to the increased iodine concentration in the SVC, that significantly increased the radiation dose due to the changes in the linear attenuation coefficient. This dose saving offers significant benefits to the examination, since radiation levels at adjacent radiosensitive anatomical structures such as the adrenal glands and liver, are reduced. The interplay between radiation dose and CM protocols have often been overlooked, with the chief focus being on perivenous artifact reduction via patient-specific CM formulas during CT angiography,^{9,29} reduced X-ray tube voltage,³⁰ and CM with low iodine concentration, while attempting to maintain image quality.³¹ The current study highlights the value of multiphasic CM administration technique that can reduce radiation dose to patients during chest CT. This decrease in CV and radiation comes at

no cost since it is associated with increased image quality and reader confidence. Currently, it is somewhat difficult to draw an accurate comparison with the literature, and to our knowledge, we are the first to compare the multiphasic to conventional CM approach for lymph node detection during chest CT.

There were shortcomings in this study. While the results presented are promising, the use of PET/CT with histopathological dissections could further clarify the surgical outcome based on our split-bolus CM protocol. Also, our image evaluation focused mainly on the quantitative and qualitative image criteria while it did not include the diagnostic accuracy of chest malignancies in terms of sensitivity and specificity according to a reference standard. Therefore, to accurately predict patient clinical outcomes, regional and distant lymph node metastasis in the chest could only be confirmed with the use of PET/CT and the histopathology consideration with our split-bolus CM technique.

The split-bolus CM technique has certain advantages over conventional CM injection protocols. The future scope for this technique lies in the head, neck, chest, and whole body PET/CT imaging with the use of CM. This CM technique would also benefit follow-up imaging of lymph node metastases in either CT and/or PET/CT with CM.

In summary, we present a multiphasic CM protocol which significantly improves the visualization of mediastinal lymph nodes during thoracic CT at a reduced radiation dose.

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