Original Article

Four-Dimensional Computed Tomography Pattern Enhancement of Parathyroid Lesions in Preoperative Localization of Hyperparathyroidism

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Background: Four-dimensional computed tomography (4D-CT) improves the precision of pre-operative localization of hyperfunctioning parathyroid glands (HPGs).

Objective: To analyze the role of pattern enhancement in 4D-CT imaging in hyperparathyroidism for differentiating HPGs from surrounding tissues for precision pre-operative localization of HPGs.

Materials and Methods: The present retrospective study was conducted in patients who underwent 4D-CT scan of the parathyroid at the Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between January 2013 and October 2016. Lesions were plotted for pattern enhancement, and mean Hounsfield units (HUs) of HPGs, lymph nodes, thyroid nodules, and thyroid glands were measured and analyzed.

Results: Twenty-seven patients with 119 lesions were included. Significant difference was observed between both parathyroid adenoma and hyperplasia and thyroid gland during non-contrast phase and delayed 90-second phase. Attenuation value of less than 60 HUs in pre-contrast phase could differentiate HPGs from thyroid gland with 60% sensitivity and 85% specificity. Sensitivity of 4D-CT was 100% (95% Cl 73.5 to 100) for localization of all HPGs.

Conclusion: Integration of clinical history data, conventional imaging, and 4D-CT imaging could improve differentiation of HPGs from surrounding tissues, thereby improving the precision of HPG localization during minimally invasive parathyroidectomy.

Keywords: Thailand, 4D CT pattern enhancement, Parathyroid lesions, Preoperative localization, Hyperparathyroidism

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Hyperparathyroidism (HPT) is a rare disease, with clinical presentations that can vary from region to region. HPT is characterized by excessive secretion of parathyroid hormone (PTH). Patients with HPT generally present with hypertension and multiple somatic signs and symptoms of systems that include skeletal, renal, nervous, and gastrointestinal system. Routine check-up programs have increased the rate of diagnosis of asymptomatic cases. Previous study found that primary hyperparathyroidism (PHPT) is seldom underdiagnosed, and rarely has delayed detection among patients in Thailand(1).

Parathyroidectomy, via bilateral exploration, remains the operation of choice in patients with HPT. However, the direction of surgery is beginning to shift to minimally invasive parathyroidectomy, which has

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shorter operative time, smaller incision, and reduced number of complications. An essential requirement of minimally invasive parathyroidectomy is precision localization imaging[2].

Pre-operative localization combined parathyroid scan (Tc-99m pertechnetate/Tc-99m MIBI subtraction and dual phase Tc-99m MIBI and SPECT) and ultrasound (US) is the most commonly selected imaging modality for primary investigation. Combined sestamibi-SPECT and US is comparable to parathyroid scan and US relative to pre-operative localization of parathyroid adenomas in patients with PHPT. However, current studies suggest that primary localization using four-dimensional computed tomography (4D-CT) may be more effective than combined sestamibi-SPECT and US[3]. The 4D-CT showed higher sensitivity (88%) than both MIBI scan (65%) and US (57%) for pre-operative planning for directed parathyroidectomy[4-9]. Payne et al[10] reported that 4D-CT could localize HGPs in patients whose HGPs could not be localized by US or MIBI scan. The improved efficacy of localization by 4D-CT reduces medical risk to the patient by helping to facilitate a higher surgical success rate[11].

The 4D-CT involves acquisition of image enhancements over time during the non-contrast-enhanced, arterial, and delay phases over the parathyroid region. The characteristic contrast enhancement pattern in parathyroid adenoma is low attenuation on pre-contrast images, peak enhancement during the arterial phase, and then washout of contrast medium during transition from the arterial to the delayed phase[4].

The aim of the present study was to analyze the pattern of enhancement in 4D-CT imaging relative to differentiation between hyperfunctioning parathyroid gland (HPGs) and surrounding tissues for precision preoperative localization of HPG. The sensitivity of 4D-CT was analyzed and compared with pathologic evaluation, which is regarded as the gold standard for diagnosing HPGs.

Materials and Methods

Patients

The present retrospective study was conducted in patients that underwent 4D-CT scan of the parathyroid at the Siriraj Imaging Center of the Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between January 2013 and October 2016. The protocol for the present study was approved by the Siriraj Institutional Review Board (SIRB), COA No. Si006/2016).

Imaging protocol and CT image analysis

Four-dimensional CT scanning was performed using a 64-row multidetector CT scanner (Discovery CT750 HD; GE Healthcare, Milwaukee, WI, USA). The research protocol was modified from the technique tips reported by Huang et al by extending the coverage axis and scan to four phases from the sternal notch to the midbrain during the pre-contrast and arterial phases[5]. Attenuation in Hounsfield units (HUs) was used to differentiate HPGs, lymph node, thyroid nodule, and thyroid gland during the pre-contrast, arterial, venous, and delayed phases. The scan setting used to interpret the disease was, as followed, scan of head of clavicle to mandible angle during the venous and delayed phases at 0.625 mm section thickness, 0.4 seconds tube rotation time, pitch factor of 0.516:1, and exposure of 120 kVp with automatic tube current modulation (range 200 to 300 mA). Non-ionic contrast (100 ml) was given intravenously to all patients. The scanning phases were at 30, 60, and 90 seconds, and the mean effective radiation dose was 8.3 mSv.

An author of the present study, a board certified sub-specialist in neuroradiology (Songsaeng D) interpreted all 119 lesions for consistency of image comparison, and measurement of characteristic enhancement (mean HU density) during the four phases at the location of HPGs (n = 27), lymph node (n = 47), thyroid nodule (n = 20), and thyroid gland (n = 25). Of the 12 pathologically proven lesions of HPGs, seven were adenoma and five were hyperplasia.

Statistical analysis

Data analyses were performed using PASW Statistics version 18 (SPSS Inc., Chicago, IL, USA). Kruskal-Wallis test was used to compare several parameters. The sensitivity and specificity of non-contrast phase for differentiating HPGs from thyroid gland were calculated. Sensitivity and 95% confidence interval (CI) was calculated for comparison of 4D-CT and MIBI scan. Findings were reported as mean HUs. A p-value of less than 0.05 was considered statistically significant.

Results

Twenty-seven patients with 119 lesions were included. The mean age of patients was 65.8 years (range 41 to 85 years) and 70.4% were female. Two patients had history of total thyroidectomy. Twenty-four patients had undergone parathyroid scintigraphy. Only 12 patients underwent 4D-CT scan of parathyroid, parathyroid scintigraphy, and parathyroidectomy with

Table 1. Comparison of mean Hounsfield units (HUs) of lesions during non-contrast and each phase of contrast study (4D-CT) among tissue groups

Houfield units	Group				
	Parathyroid adenoma (n = 7)	Parathyroid hyperplasia (n = 5)	Thyroid nodule (n = 20)	Lymph node (n = 47)	Thyroid gland (n = 25)
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Non-contrast	41.00±19.97	34.78±25.31	65.06±31.69	41.02±14.89	80.96±26.25
30-second phase	164.73±54.17	134.63±39.41	112.59±55.80	80.26±25.77	198.92±44.96
60-second phase	152.73±55.75	95.28±33.20	112.82±45.73	103.09±27.20	181.84±51.47
90-second phase	125.18±63.13	95.18±37.35	108.53±41.56	108.96±27.61	165.76±46.95

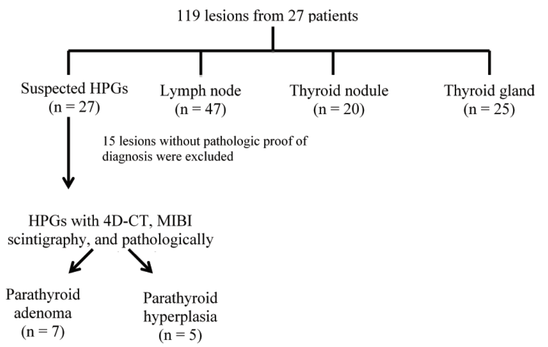

Figure 1. Flow diagram of study protocol.

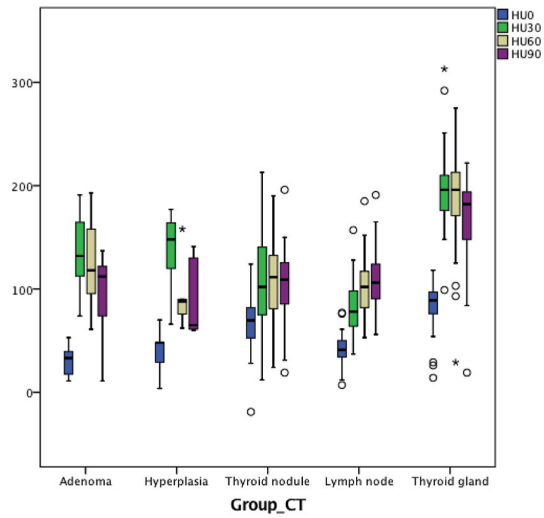

Figure 2. Box plot showing characteristic pattern enhancement of parathyroid adenoma, parathyroid hyperplasia, thyroid nodule, lymph node, and thyroid gland. Only lymph node revealed progressive enhancement. Parathyroid adenoma, parathyroid hyperplasia, thyroid nodule, and thyroid gland showed early arterial enhancement and contrast washout during delayed phase. Attenuation of thyroid gland during pre-contrast phase was higher than the attenuation observed in HPGs.

pathologically-proven diagnosis (Figure 1). The 119 lesions were categorized, as followed, suspected HPGs (n = 27), thyroid nodule (n = 20), lymph node (n = 47), and thyroid gland (n = 25). Fifteen lesions were excluded due to an absence of pathologic proof. Twelve cases were defined to be either parathyroid adenoma (n = 7) or parathyroid hyperplasia (n = 5) (Figure 1).

Pattern enhancement of both parathyroid adenoma and parathyroid hyperplasia showed the characteristic pattern of peak arterial enhancement and washout of contrast material from the arterial phase to the delayed phase. However, no difference in mean attenuation during any of the phases among those with parathyroid adenoma or hyperplasia was observed (Table 1, Figure 2). Significant difference was observed between both parathyroid adenoma and parathyroid hyperplasia and thyroid gland during the non-contrast phase and the delayed 90-second phase (Table 2, Figure 3-6). Parathyroid hyperplasia was also significantly different from thyroid gland during the delayed 60-second phase.

HPGs revealed lower attenuation compared with thyroid gland during the pre-contrast phase. An attenuation value of less than 60 HUs during the pre-contrast phase could differentiate HPGs from thyroid gland with a sensitivity of 60% and a specificity of 86%. In contrast lymph node enhancement showed a different pattern with progressively increasing enhancement, and peak enhancement during the delayed 90-second phase (Figure 7).

The sensitivity of 4D-CT in the present study was 100% (95% Cl 73.5 to 100) for localization of HPGs in any of the four quadrants (i.e., right-upper, right-lower, left-upper, and left-lower) when compared to the gold standard of pathologic proof. In contrast, MIBI scan

Table 2. Difference of mean Hounsfield units (HUs) of lesions during non-contrast and each phase of contrast study (4D-CT) among tissue groups

Group	Compare with	p-value			
		Non-contrast	30-second phase	60-second phase	90-second phase
Parathyroid adenoma	Parathyroid hyperplasia	0.989	0.710	0.111	0.705
	Thyroid nodule	0.108	0.032	0.180	0.885
	Lymph node	1.000	0.000*	0.014*	0.883
	Thyroid gland	0.000*	0.254	0.425	0.107
Parathyroid hyperplasia	Thyroid nodule	0.093	0.859	0.935	0.947
	Lymph node	0.981	0.056	0.995	0.959
	Thyroid gland	0.001*	0.021*	0.001*	0.007*

p-value <0.05 indicates statistical significance

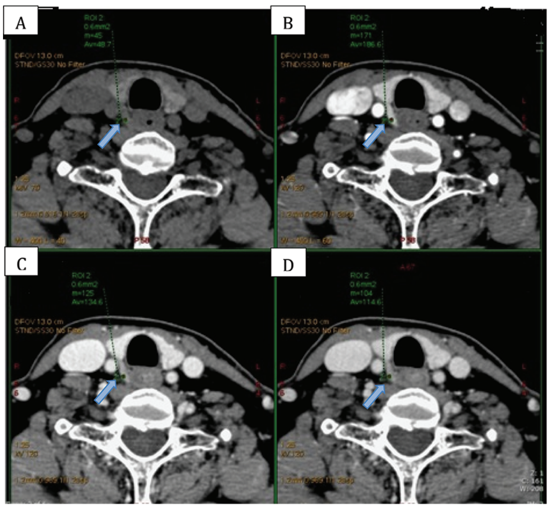

Figure 3. A 60-year-old female with PHPT. Prior MIBI scan was negative. 4D-CT showed early enhancement with contrast washout lesion at right lower aspect of thyroid gland, which is suggestive of HPG. This lesion was pathologically proven parathyroid adenoma.

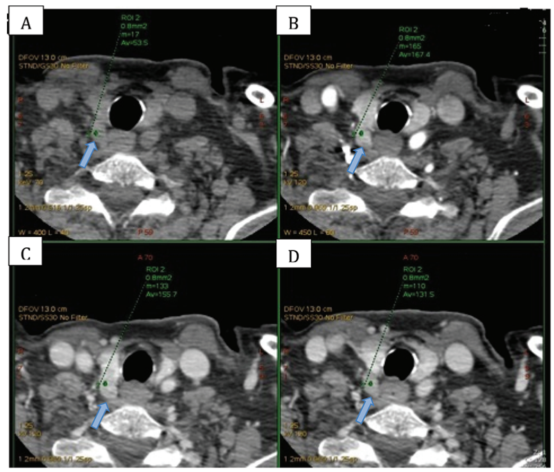

Figure 4. A 63-year-old female with PHPT. 4D-CT: (A) noncontrast; (B) post-contrast 30-second delay; (C) post-contrast 60-second delay; and (D) post-contrast 90-second delay revealed suspected HPG at the right upper aspect of thyroid gland. The lesion was surgically-proven parathyroid adenoma.

was positive in only seven lesions, with a sensitivity of 58.3% (95% CI 27.7% to 84.8%).

Discussion

The present study established a modified 4D-CT scanning technique by using a simplified scanning protocol yielded valuable interpretive images while exposing the patient to a low effective dose of radiation (8.3 mSv). The authors' study found the pattern enhancement of parathyroid scanning characteristics similar to those reported in the previous studies(4-7). However, imaging data in parathyroid hyperplasia is scarce. Pattern enhancement in parathyroid hyperplasia was found to be the same as pattern enhancement in parathyroid adenoma in the current study, which means that, these two conditions cannot be differentiated by using 4D-CT alone.

The strength of the present study is that the authors found significant difference in mean HUs between HPGs and normal thyroid gland in non-contrast images. Based on the literature reviewed, no previous study has recommended a HU cut-off as the lower limit in normal thyroid gland. Accordingly, and based on the present data, the authors propose 60 HUs as the cut-off value in this condition. As previously described in the present report, attenuation value of less than 60 HUs in pre-contrast phase could

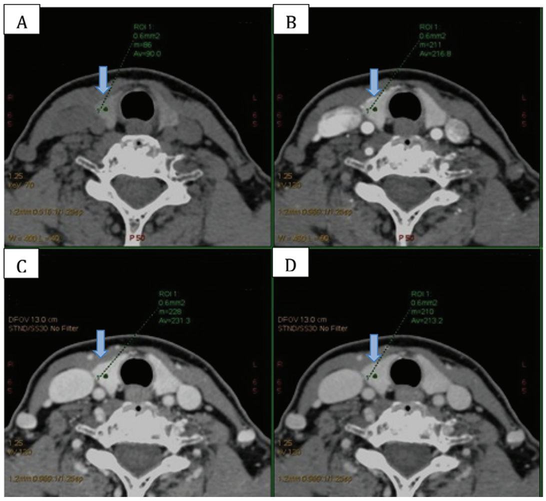

Figure 5. 4D-CT: (A) noncontrast; (B) post-contrast 30-second delay; (C) post-contrast 60-second delay; and (D) post-contrast 90-second delay of the same patient profiled in Figure 3 shows arterial enhancement and contrast washout of thyroid gland, and high attenuation during the pre-contrast phase as 90 HU.

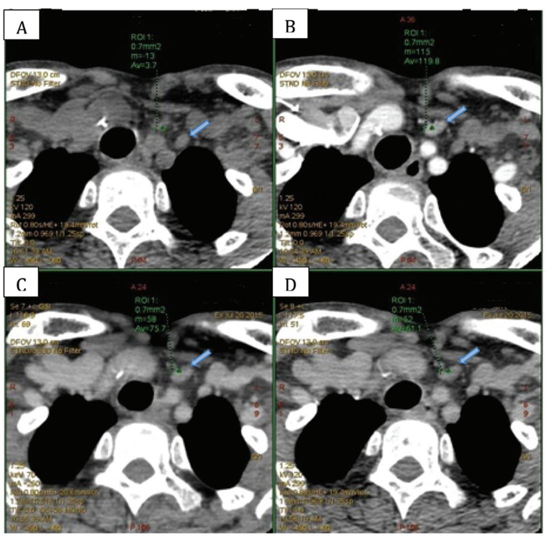

Figure 6. A 63-year-old female with PHPT. 4D-CT: (A) noncontrast; (B) post-contrast 30-second delay; (C) post-contrast 60-second delay; and (D) post-contrast 90-second delay, revealed surgically-proven ectopic parathyroid hyperplasia, which showed peak arterial enhancement and contrast washout at left upper paratracheal region.

differentiate HPGs from thyroid gland with 60% sensitivity and 85% specificity.

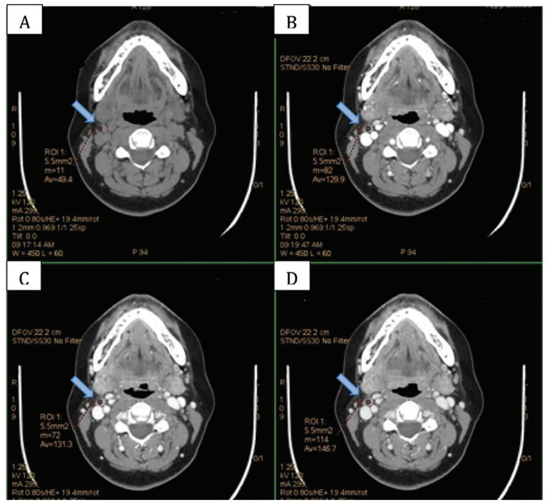

Figure 7. 4D-CT: (A) noncontrast; (B) post-contrast 30-second delay; (C) post-contrast 60-second delay; and (D) post-contrast 90-second delay of a 54-year-old female with PHPT showed progressive enhancement of right cervical lymph node.

The present study also demonstrated the superiority of 4D-CT over MIBI. The authors found 4D-CT to have 100% sensitivity for localization of HPGs, which is higher than the sensitivity values described in reports from Rodgers et al and Gafton et al[5,7].

Small sample size and single-center study is the present study limitation that might need to be considered.

Conclusion

Integration of clinical history data, conventional imaging, and 4D-CT imaging could improve differentiation of HPGs from surrounding tissues, thereby, improving the precision of HPG localization during minimally invasive parathyroidectomy.

What is already known on this topic?

HPGs was verified by MIBI study and US for localization, which was the guideline for investigation. A few studies revealed that 4D-CT of parathyroid examination may be more effectively localized than the guideline protocol.

What this study adds?

The 4D-CT of parathyroid with four phase protocol (pre-contrast, 30 seconds, 60 seconds, and 90 seconds) was powerful in differentiate the HPGs from thyroid gland when using lower than 60 HU as criterion with fare sensitivity and high specificity and lymph node was enhanced more time by time. New guideline of HPG localization is suggested.

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Conflicts of interest

The authors declare no conflict of interest.

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