Four-dimensional Computed Tomography for Preoperative Localization of Parathyroid Adenomas

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ABSTRACT: **Background:** Four-dimensional parathyroid computed tomography (4DCT) is a relatively new parathyroid imaging technique that provides functional and highly detailed anatomic information about parathyroid tumors.

Objectives: To assess the accuracy of 4DCT for the preoperative localization of parathyroid adenomas (PTAs) in patients with biochemically confirmed primary hyperparathyroidism (PHPT) and a history of failed surgery or unsuccessful localization using ^{99m}Tc-sestamibi scanning and ultrasonography.

Methods: Between January 2013 and January 2015, 55 patients with PHPT underwent 4DCT at Hillel Yaffe Medical Center, Hadera, Israel. An initial unenhanced scan was followed by an IV contrast injection of non-ionic contrast material (120 ml at 4 ml/s). Scanning was repeated 25, 60 and 90 seconds after the initiation of IV contrast administration. An experienced radiologist blinded to the earlier imaging results reviewed the 4DCT for the presence and location (quadrant) of the suspected PTAs. At the time of the study, 28 patients had undergone surgical exploration following 4DCT and we compared their scans with the surgical findings.

Results: 4DCT accurately localized 96% (27/28) of abnormal glands, all of which were hypervascular and showed characteristic rapid enhancement on 4DCT that could be distinguished from level II lymph nodes. Surgery revealed hypovascular cystic PTA in one patient with a negative 4DCT scan. All patients had solitary PTAs. The scan at 90 seconds provided no additional information and was abandoned during the study.

Conclusions: 4DCT accurately localized hypervascular parathyroid lesions and distinguished them from other tissues. A three-phase scanning protocol may suffice.

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KEY WORDS: primary hyperparathyroidism (PHPT), parathyroid adenoma, four-dimensional parathyroid computed tomography (4DCT), parathyroid imaging, parathyroid hormone (PTH), multiple detector computed tomography (MDCT)

Primary hyperparathyroidism (PHPT) is a common condition, occurring in 0.3–0.7% of the general population [1,2]. In approximately 85–88% of patients the cause is a solitary adenoma [3]. Surgical resection is regarded as the definitive treatment once the adenoma is identified accurately [4].

Bilateral neck exploration, which entails examining four parathyroid glands to definitively identify or exclude the presence of multi-gland disease and removing the abnormal gland(s), constituted the gold standard for the management of hyperparathyroidism from 1930 to 1990 and resulted in reported cure rates of more than 95% [4,5]. This approach is still in widespread use but is extremely time consuming; potential complications include postsurgical hypocalcemia and damage to the recurrent or superior laryngeal nerve [5,6]. An increase in the number of cases of primary hyperparathyroidism led to a corresponding increase in the number of operative procedures performed and a rapid evolution in parathyroid surgical techniques [7]. Over the last two decades, following the advent of intraoperative parathyroid hormone (iPTH) assays and improved imaging techniques, surgeons have increasingly adopted minimally invasive techniques, with the aim of reducing tissue trauma and the complication rate, decreasing the duration of hospitalization, and reducing costs compared with those associated with bilateral cervical exploration [7,8]. Minimally invasive unilateral imaging-directed parathyroidectomy has impressive curative rates exceeding 98% and significantly reduces surgical complications. However, it requires sophisticated, reliable and accurate imaging to localize the lesion(s) prior to surgery [3].

Non-invasive imaging studies have included cervical ultrasound, nuclear scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography [9]. Currently, ultrasound and/or ^{99m}Tc-sestamibi (MIBI) combined with single-photon emission computed tomography (SPECT), which provides three-dimensional localization, are the two most widely used imaging modalities [10]. More recently, four-dimensional computed tomography (4DCT) imaging, also known as dynamic multiple detector computed tomography (4D-MDCT) [11], was developed and the first report in the literature of its use for parathyroid imaging was in 2006 [12]. The first dimension in 4DCT is acquired axially and combined with coronal and sagittal reformations to produce a three-dimensional image, while the fourth dimension is provided by the differential uptake and washout of an iodinated contrast agent over time [12]. In 4DCT, parathyroid adenomas (PTAs) show low attenuation on the non-contrast-enhanced images, peak enhancement of the contrast agent on the arterial phase, and washout of contrast material from the arterial to delayed phase. Localization in four dimensions enables the surgeon to assess both anatomy and function and makes 4DCT a potentially more robust method of localization than other non-invasive imaging modalities [11-14].

The aim of this retrospective study was to assess the accuracy of 4DCT in the preoperative detection of PTAs in patients with biochemically confirmed PHPT and a history of failed surgery or unsuccessful localization by conventional imaging.

PATIENTS AND METHODS

The Institutional Review Board at Hillel Yaffe Medical Center approved this retrospective study and waived the requirement for informed consent. We compiled data on all patients with biochemically confirmed PHPT who were referred to 4DCT examination for PTA localization in our institution between January 2013 and January 2015. Only patients with one of the following characteristics were included in this study: negative ultrasound and MIBI scans for PTA, a discrepancy between the results of the ultrasound and MIBI scans, failed previous parathyroidectomy without identification of the adenoma, or high values of PTH after resection. Fifty-five patients met our inclusion criteria and were included in this study. At the time this retrospective study was undertaken, 28 patients had undergone parathyroid surgery following 4DCT. The surgical reports, pathology reports, iPTH assays, and clinical follow-up of all patients were reviewed. An endocrinology surgeon and head and neck surgeon in different health care centers performed the surgeries.

4DCT TECHNIQUE

All CT examinations were performed using a 64-MDCT scanner (Brilliance-64, Philips Healthcare, Cleveland, Ohio, USA). The 4DCT technique used was a slightly modified version of that reported previously by Beland and colleagues [11]. All MDCT images were obtained using the following parameters: tube voltage 120 kVp, tube current 400 mAs, collimation 64 x 0.625, pitch 0.484, rotation 0.75, and matrix 512. Images were reconstructed at a 3 mm thickness with 3 mm spacing in the axial and coronal planes. Craniocaudal coverage was from the external auditory meatus to 2 cm below the carina. An initial unenhanced scan was obtained. This scan was followed by an IV contrast injection of 120 ml of a non-ionic contrast material (Iomeron® 350 mg/ml, Bracco, Milan, Italy) equivalent to 35% iodine or 350 mg iodine/ml at 4 ml/s. Scanning was then repeated at 25, 60 and 90 seconds after the initiation of IV contrast administration.

4DCT IMAGE ANALYSIS

Each CT examination was retrospectively reviewed by two board-certified radiologists, each with more than 10 years of experience, who were blinded to the surgical results, clinical history and prior imaging. Image review was performed on a PACS (picture archiving and communication system) station. During the consensus review, the two radiologists recorded the following for all adenomas: location by side and quadrant as well as relationship to the thyroid gland when adjacent, size (mm) in greatest long-axis measurement, and the transformed attenuation coefficients (measured in Hounsfield units, HU). Following Rodgers et al. [12], results were correlated with the surgical findings using a four-quadrant classification with right and left sides in relation to the midline. Superior quadrants were defined as at the level of or superior in relation to the inferior extent of the lower pole of the thyroid gland, and inferior quadrants were defined as inferior in relation to the inferior extent of the thyroid gland and superior in relation to the sternal notch [15]. Adenomas were defined as ectopic when located in an unusual anatomic location, such as the carotid sheath, thoracic mediastinum, or retro-esophageal space [Table 1]. Histologic confirmation of PTA was obtained in all cases.

In 13 of 28 patients, the mean CT densities (in HU) for the surgically confirmed adenomas were measured in all phases using ellipsoid region-of-interest (ROI) measurements that encompassed as much of the lesion as possible without including adjacent blood vessels or soft tissues. In these 13 patients (who also had surgically confirmed PTAs), normal level II lymph nodes were visualized. Ellipsoid ROI density measurements of the lymph nodes were performed in all four phases of the CT examination.

In 10 patients with a negative ultrasound examination for PTA and a positive 4DCT examination result, the ultrasound examination was repeated by a senior radiologist (with at least 10 years of experience) after that radiologist had been presented with the 4DCT examination results, i.e., after he knew the exact location of the PTA.

Table 1. The number and location of parathyroid adenomas on 4DCT

4DCT adenoma location	n=28
Right upper	2
Right lower	7
Left upper	5
Left lower	5
Ectopic (retrotracheal, retroesphageal, retrosternal)	9

4DCT = Four-dimensional computed tomography

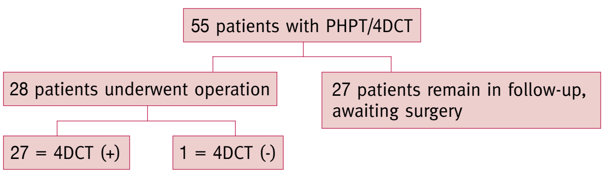
STATISTICAL ANALYSIS

Statistical analysis was performed using SAS software, version 9.2 (SAS Institute Inc., Cary, NC, USA). Data were entered in an Excel worksheet for storage (Microsoft, Redmond, WA, USA). Mean ROI measurements of the surgically proven PTAs and measured level II cervical lymph nodes were compared in the unenhanced phase and all contrast-enhanced phases. Student's *t*-test was used to calculate *P* values in continuous data. A *P* value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 32 women (mean age 58 years) and 23 men (mean age 57 years) underwent 4DCT examination for PTA localization. At the time of this study, 28 patients had undergone parathyroid surgery after 4DCT. The other 27 patients were enrolled in a strict clinical follow-up program or were awaiting surgery [Figure 1].

Figure 1. The flow of consecutive patients with primary hyperparathyroidism (PHPT) who underwent four-dimensional parathyroid computed tomography (4DCT)



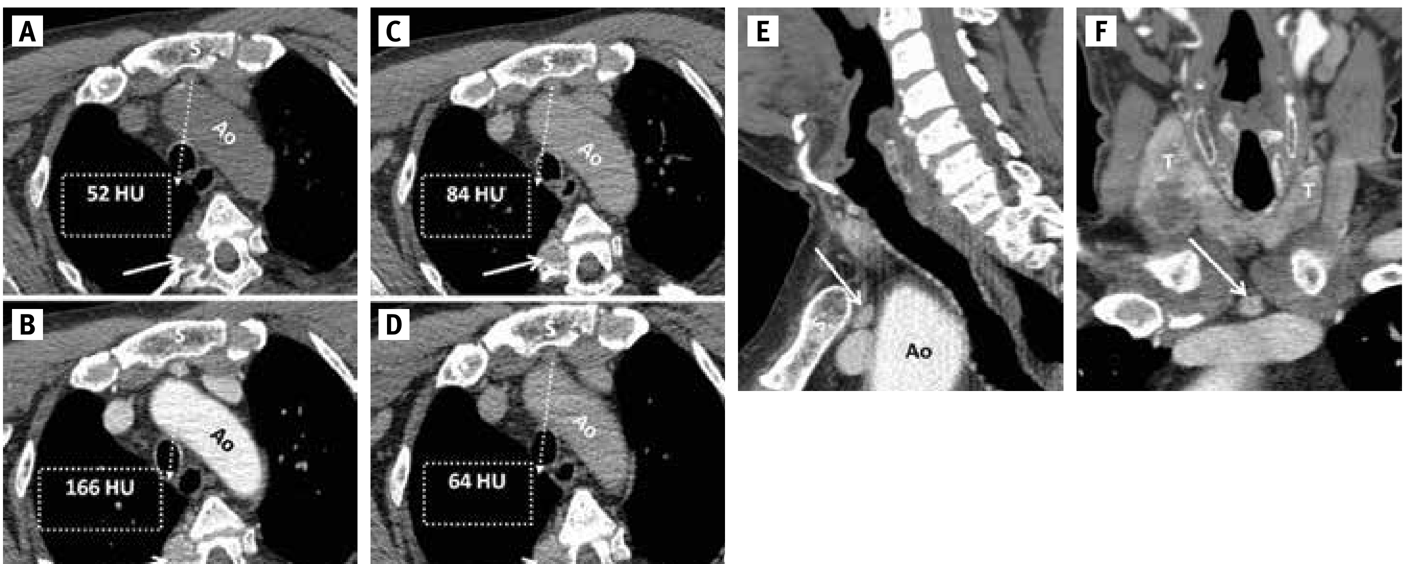
A total of two right superior, seven right inferior, five left superior, five left inferior, and nine ectopic glands were identified surgically as adenomatous [Table 1]. Of the ectopic adenomas, two were primary and seven were postoperative cases.

Adenomas were clearly visible on 4DCT and correlated with surgical findings in 27 of 28 patients (96%). Of the 28 resected adenomas, 27 (96%) appeared as hypervascular lesions (i.e., they showed early enhancement in the arterial phase and washout in the venous phase) at 4DCT [Figure 2]. In one patient (4%) the 4DCT was negative for PTA. In this patient the adenoma was hypovascular/cystic (non-enhancing). The size of the correctly localized adenomas as measured by 4DCT was 6–40 mm (mean 14.4 mm). All patients with surgically resected adenomas showed a biochemical response.

The maximum mean densities of the confirmed adenomas (in 13 of the 27 patients for whom this was calculated) were 41, 168, 132 and 110 HU at 0, 25, 60 and 90 seconds, respectively. Mean level II lymph node densities were 33, 59, 76 and 92 HU at 0, 25, 60 and 90 seconds, respectively.

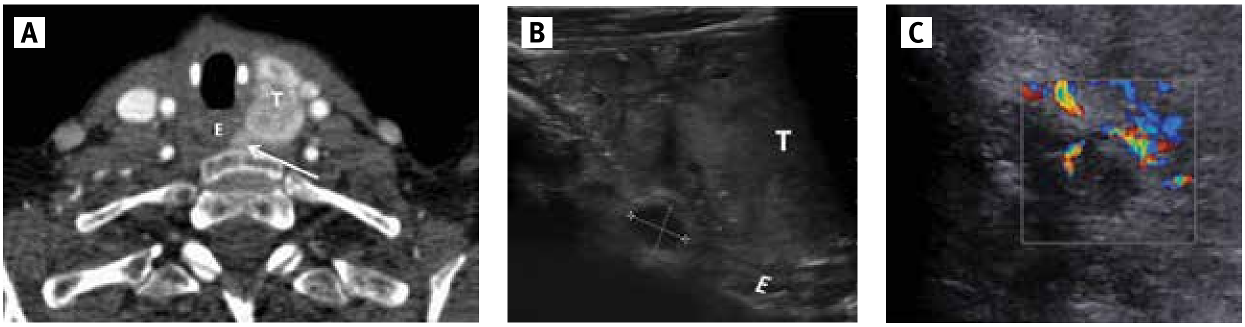
Compared to enhancement of the lymph nodes, enhancement of the adenomas was significantly greater in the same patients at 25 ($P < 0.0001$) and 60 ($P < 0.0001$) seconds, but not at 90 seconds ($P = 0.07$). Consequently, we concluded that the last scan (the fourth) is not necessary for diagnosis of PTAs, and we stopped performing it in subsequent patients in order to reduce radiation exposure. PTA was identified in all 10 repeated ultrasound examinations performed by a radiologist who was aware of the 4DCT results [Figure 3].

Figure 2. Representative images from parathyroid four-dimensional computed tomography (4DCT). **[A]** Axial non-enhanced CT image. **[B-D]** Axial CT images obtained 25, 60 and 90 seconds, respectively, after intravenous contrast administration. The CT images show the rapid uptake of the contrast agent by an ectopically located retrosternal parathyroid adenoma and its subsequent washout from that adenoma. Note the osteolytic lesion in the right costovertebral joint representing a brown tumor (arrow). Coronal **[E]** and sagittal **[F]** reformatted CT images showing the retrosternal parathyroid adenoma (arrow)



Ao = aortic arch, S = sternum, T = thyroid, HU = Hounsfield units

Figure 3. Four-dimensional computed tomography (4DCT) performed a few months after an unsuccessful right cervical surgical exploration for parathyroid adenoma in a 58 year old woman. Axial contrast-enhanced CT image **[A]** shows a small (about 8 mm) hypervascular para-esophageal lesion (arrow) consistent with parathyroid adenoma. The lesion was not detected on ultrasound performed before the 4DCT examination. **[B]** Ultrasound image shows a subtle hypoechoic parathyroid adenoma located posterior to the left lobe of the thyroid. **[C]** Color Doppler ultrasound shows a peripheral feeding vessel characteristic of parathyroid adenoma. Also note typical arc vascularity. The ultrasound examination was performed by a senior radiologist after he was presented with the 4DCT examination results and learned the exact location of the parathyroid adenoma



E = esophagus, T = thyroid

DISCUSSION

Preoperative localization of PTAs may significantly reduce operative and postoperative complications and costs [16]. 4DCT is emerging as a powerful non-invasive tool for the detection and localization of PTAs. Using 4DCT, we accurately localized 96% of adenomas to the correct quadrant of the neck prior to surgery, a rate in agreement with previous reports [11,17] or better than those achieved previously with this modality [18,19]. Accordingly, 4DCT is considerably more sensitive than the traditional modalities of MIBI scanning and ultrasound, which have reported sensitivities of 40% and 48%, respectively, in accurately localizing an adenoma to the correct quadrant [17].

Most institutions that perform 4DCT utilize non-enhanced phase followed by three contrast-enhanced phases [11,17,19-21], as we initially did. Some combine a non-enhanced phase with a single post-contrast phase beginning 25 or 50 seconds after infusion [22,23] or eliminate the non-enhanced phase and use solely post-contrast arterial and venous phases [22]. All protocols reportedly have the ability to verify the PTAs while differentiating them from other structures, mainly lymph nodes. Consistently with others [14], who found that contrast washout information and enhancement changes assist in assessing potential lesions and in differentiating them from high-attenuation iodine-containing thyroid nodules, we found that PTAs differed significantly in their density from lymph nodes during the second and third scans (at 25 and 60 seconds). However, we found no statistically significant difference between PTAs and lymph nodes during the fourth scan (at 90 seconds), and therefore stopped performing the fourth scan during the study. We suggest that a shorter protocol comprising only three scans (pre-contrast, arterial, and venous) is sufficient for the localization of PTAs. Furthermore, a three-phase protocol has the benefit of reducing radiation exposure below the approximately 92 mGy absorbed radiation dose to the thyroid that was calculated for the commonly used four-phase protocol [21]. We note that Hoang et al. [24] recommend a very similar approach, in which they first undertake a non-enhanced CT study to cover the thyroid gland and thus help differentiate a candidate parathyroid lesion from other thyroid tissue, and follow it with arterial and delayed phases acquired 25 and 80 seconds, respectively, from the start of the injection.

Identification and localization of PTAs using 4DCT enabled two experienced radiologists to subsequently localize them on the previously obtained ultrasound. All PTAs not detected during the initial ultrasound examination were found upon reexamination of the ultrasound following 4DCT. We believe that proper characterization of PTAs by ultrasound (in addition to 4DCT) prior to surgery is beneficial. First, combining ultrasound and 4DCT may provide additional morphological characterization that can further substantiate the diagnosis, especially in borderline or questionable cases. Second, it may provide a target lesion for cytology sampling or for guided aspiration for PTH measurement. Third, it may assist during follow-up studies, which may be indicated in cases of failed surgery or suspected recurrence. Knowing the location and characteristics of the PTA, the sonographer can focus on the area where the lesion was first detected. This approach can reduce the need for additional expensive 4DCT scans and lower the radiation burden [3]. These conclusions are consistent with those of a very recent prospective, blinded, head-to-head comparison of several first-line imaging modalities, including 4DCT and ultrasound, that was conducted in consecutive patients with hyperparathyroidism eligible for parathyroidectomy [25]. That study found no statistically significant differences in sensitivity between dual-phase 4DCT and ultrasound, although considerably more positive scans received a rating of "certain" or "probable" rather than "uncertain" for 4DCT (71%, 20%, 9%) compared with ultrasound (56%, 36%, 8%), and the specificity of 4DCT (86%) was significantly lower than that of ultrasound (95%).

The limitations of this study include a relatively small cohort of patients with known hyperparathyroidism (which potentially introduces a selection bias) and the lack of a control group (such as patients evaluated with only MIBI scanning or ultrasound). In addition, all imaging studies were performed at a single institution, which, while ensuring protocol standardization and reducing inter-rater disagreements, could have introduced a sample bias.

CONCLUSIONS

Our results show 4DCT to be a sensitive and specific second-line imaging modality for hypervascular parathyroid lesions. It is particularly valuable in combination with ultrasound imaging. The common four-phase 4DCT scanning protocol appears unnecessary, and we have successfully replaced it in our institution with a three-phase protocol involving a pre-enhancement scan followed by arterial and venous phases acquired 25 and 60 seconds later.

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"If A is a success in life, then A equals x plus y plus z. Work is x; y is play; and z is keeping your mouth shut"

Albert Einstein (1879–1955), German-born theoretical physicist and Nobel Laureate. He developed the theory of relativity, one of the two pillars of modern physics. Einstein's work is also known for its influence on the philosophy of science. Einstein is best known in popular culture for his mass–energy equivalence formula, $E = mc^2$, which has been dubbed the world's most famous equation