Parathyroid Computed Tomography Angiography: Early Experience with a Novel Imaging Technique in Primary Hyperparathyroidism

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Abstract

Objectives. To describe parathyroid computed tomography angiography (PCTA), determine its accuracy, and, as a secondary objective, calculate its mean radiation dosimetry.

Study Design. Retrospective chart review of patients who underwent parathyroidectomy for primary hyperparathyroidism from 2007 to 2015.

Setting. Single-center tertiary care academic military hospital.

Subjects and Methods. PCTA is a 2-phase computed tomography imaging technique that uses individualized timing of contrast infusion and novel patient positioning to accurately identify parathyroid adenomas. Consecutive patients who underwent parathyroidectomy for primary hyperparathyroidism from 2007 to 2015 were reviewed; 55% of patients were women. The mean age was 50.9 years (range, 26-68 years). Sensitivity and specificity were calculated as well as mean radiation dosimetry and timing of contrast.

Results. A total of 108 procedures were performed during the study period. Twenty-one patients undergoing 22 PCTAs after prior sestamibi scans were nonlocalizing or equivocal. In this group, there were 15 true-positive, 3 false-positive, 4 true-negative, and 0 false-negative PCTAs. This represents a sensitivity of 100% (95% CI, 74.7%-100%) and a specificity of 57% (95% CI, 20%-88%). The mean calculated radiation dose was 5.15 mSv. In the most recent studies, a mean dose of 4.1 mSv was calculated. The ideal time of image acquisition contrast administration varied from 20 to 30 seconds after contrast infusion.

Conclusions. PCTA is a new technique in anatomic imaging for hyperparathyroidism. In a single-center, single-radiologist retrospective study, it demonstrates excellent accuracy for patients with parathyroid adenomas that are otherwise difficult to localize preoperatively. Preliminary experience suggests that its use may be indicated as a primary imaging modality in the future.

Keywords

primary hyperparathyroidism, parathyroid surgery, CT angiography, computed tomography, preoperative imaging

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Selective parathyroidectomy is gaining wide acceptance as the standard of care for primary hyperparathyroidism (PHPT) and has replaced bilateral neck exploration when reliable preoperative localizing imaging is available. Without successful preoperative localization, multigland exploration must be performed, which is a comparatively longer and riskier surgical procedure, with increased hospital stays and cost. The field of parathyroid imaging is actively evolving in the search for more sensitive examinations, without increasing radiation dosing. Traditional parathyroid imaging strategies are multimodality examinations, with ultrasound and technetium-99 sestamibi scans and cross-sectional nuclear imaging (single-proton emission computed...
tomography (SPECT/CT) becoming the more common adjunctive or primary imaging techniques.\(^5\)  

When successful, cross-sectional imaging has the added benefit of anatomic localization. Four-dimensional computed tomography (4DCT) is an important recent development in the field of parathyroid imaging. Variations of 4DCT have been reported with success in improving visualization of parathyroid adenomas (PAs).\(^6,5\) 4DCT involves the acquisition of multiple noncontrasted and contrasted studies at protocol-specific time intervals, allowing for the addition of time as the fourth dimension of 3-dimensional anatomic imaging. 4DCT in PHPT was first reported by Rodgers et al in 2006,\(^8\) and it has undergone investigation and evolution with various protocols (ie, 2, 3, or 4 phases). The standard 4-phase protocol was formally described by Mortenson et al in 2008 and Lubitz et al\(^10\) in 2010 and is the most frequently reported 4DCT variation, with a noncontrasted scan followed by arterial, venous, and delayed contrasted images. More recently, 3- and 2-phase imaging techniques have been described.\(^11-13\) Our technique represents a new strategy to harness the particular characteristics of PAs for diagnostic imaging.

The primary challenge of contrast-enhanced parathyroid imaging technique is to optimally harness the increased vascularity of hyperactive parathyroid glands. Additionally, this should be done while minimizing radiation exposure. In the search for a solution to these challenges, we have developed a novel computed tomography (CT) angiography technique for patients with PHPT for whom standard imaging failed to localize a PA. With this in mind, our technique implements individualized timing designed to ensure optimal enhancement of PAs—the parathyroid CT angiography (PCTA) with 2 phases: 1 nonenhanced and 1 contrast enhanced.

PCTA relies on 2 fundamental principles. First is the hypervascularity of PAs. Second is the quality of non–contrast enhanced parathyroid’s hypointensity relative to adjacent thyroid tissue,\(^12\) as parathyroid tissue does not concentrate iodine. The contrast-enhanced and nonenhanced phases harness these characteristics. Furthermore, we implement radiation-saving techniques developed for coronary imaging and refine the scans using volumetric reconstructions. This technique has been used with success for our patients with PHPT who had previous nonlocalizing nuclear imaging. We present the preliminary data over the period during which this technique was first developed and utilized.

The principal innovations represented by this technique are threefold: (1) novel patient positioning that reduces beam-hardening artifacts at the thoracic inlet; (2) low-volume, high–flow rate contrast infusions; and (3) individualized timing of contrasted imaging. The clinical results of this new technique presented here demonstrate high accuracy in identification of PAs with an acceptably low radiation exposure.

**Methods**

This study was approved by the Institutional Review Board of the Naval Medical Center San Diego and was performed in compliance with the Health Insurance Portability and Accountability Act. The need for informed consent was waived due to the retrospective study design.

We conducted a retrospective chart review to evaluate all consecutive patients who underwent PCTA imaging for PHPT prior to parathyroid surgery at the Naval Medical Center San Diego in the otolaryngology–head and neck surgery department. Patients who underwent parathyroidectomy from 2007 to 2015 were identified. Only patients who had nonlocalizing or inconclusive sestamibi with or without other imaging modalities and then had PCTA were included for analysis.

Data were collected regarding patient demographics, preoperative calcium and parathyroid hormone (PTH) levels, results of imaging studies (including radiation dose), operative findings, pathologic data (including pathologic diagnosis and weight of excised gland, where available), and surgical success.

**Imaging Technique**

The images are obtained with a Siemens Flash CT scanner with a Stellar Detector (Siemens, Forchheim, Germany). The bowtie filter is used, which reduces radiation exposure outside the central 16-cm field of view. Adaptive collimation at the beginning and end of the scan field of view further reduces the dose tail of penumbral nonimaged regions of the scan profile.\(^14\) The imaging reconstructions are obtained with 0.5-mm slice thickness with reconstruction overlapping every 0.3 mm.

Noncontrast, test bolus, and arterial phase contrast examinations are performed. Scan range is caudocranial from the carina to the skull base. Patients receive an 18-gauge intravenous line in the right antecubital vein. The scan technique is 120 kVp, with reference of 80 to 150 mA for the noncontrast examination and 300 to 470 mA for the contrast examination, varying by patient weight. Rotation time is 270 milliseconds with a pitch of 3.2 and subsecond scan duration.

The test bolus scan is performed with 15 mL of Isovue 370-mg/mL contrast (Bracco Diagnostics, Monroe Township, New Jersey) at 5 to 7 mL/s—varying by patient size—followed by 30 mL of normal saline at the same rate, with the region of interest centered on the proximal descending thoracic aorta. We observed over the evolution of the technique that optimal timing for enhancement of PAs occurred just as jugular venous return was visualized. It was then empirically determined that the optimal scan start time for the CT angiogram examination was time to peak enhancement of the descending aorta plus 6 seconds. For the contrasted image, 65 to 75 mL of contrast is injected at the same rate as in the test bolus, followed by 50 mL of normal saline at the same rate. The contrasted image is acquired at the individualized timing determined by the test bolus. Reconstructions were performed with the SAFIRE (Siemens) iterative reconstruction technique.

A novel patient positioning is employed: the right arm down and the left arm up, with the shoulders askew (**Figure 1**).

**Surgical Procedure**

All patients received general endotracheal anesthesia. When indicated by preoperative imaging, selective parathyroidectomy was performed. Intraoperative PTH (IOPTH)
monitoring was used to biochemically confirm the successful removal of hyperactive parathyroid glands. Surgical success was defined as a ≥50% decrease of IOPTH and within the reference range by 15 to 25 minutes after excision of the gland. Patients whose PCTA was not localizing or for whom selective parathyroidectomy was not successful per IOPTH monitoring underwent bilateral neck exploration.

Radiation dose determinations were based on all PCTA examinations performed on patients during the study period. To adjust for differing conversion factors between the neck and the upper chest for reporting estimated radiation dosimetry, the assumption is made that half of the total dose is administered each to the neck and to the chest and that appropriate corrections for differences in field of views are made.

**Statistical Analysis**

A true-positive study was defined as a study that correctly identified, lateralized, and localized a PA. A false positive was defined as a presumed PA identified on radiology report that was not confirmed by operative findings. If a PA was identified but incorrectly localized, this was also classified as a false positive. A true negative was defined as the absence of a PA on PCTA, confirmed by 4-gland hyperplasia on operative findings. A false negative was defined as a failure of PCTA to identify an adenoma that was later discovered in surgery. Sensitivity, positive predictive value, and specificity were calculated in standard fashion. Sensitivity analysis was performed on the VassarStats online calculator with 95% confidence intervals.

**Results**

Of 108 patients who underwent parathyroidectomy during the study period, 22 had nonlocalizing studies and received 23 PCTAs. One patient had unsuccessful initial surgery after having localizing sestamibi to the mediastinum. Subsequent PCTA demonstrated an ectopic PA in the middle mediastinum that was ablated by intravascular sclerosis. Because this study is more focused on the imaging technique than the surgical intervention, this patient was included. One CTA was performed by a nonstudy radiologist using a disparate technique from the study technique—this patient was excluded, leaving 21 patients who underwent 22 PCTAs. One patient received PCTA prior to each of 2 surgical procedures. This patient was considered 2 separate data points. During the study period, 2 additional PCTAs were performed on patients without a diagnosis of PHPT. These were excluded from the accuracy assessments, but their radiation dosimetry calculations are included.

Twelve patients were female (55%). Mean age was 50.9 years (range, 26-68; Table 1). All patients had previous sestamibi scans. Eight patients also had SPECT, and 13 patients also had ultrasound.

During PCTA, contrast was infused at a mean rate of 5.6 mL/s (range, 4-7). The mean dose length product was 368 mGy·cm (range, 137-1338), with a mean calculated dose of 5.15 mSv. Based on only the most recent 14 studies, there was a mean dose length product of 292 mGy·cm (range, 162-425), with a mean calculated dose of 4.1 mSv.

The individualized time to maximum enhancement based on the test bolus, which was used to determine the individualized timing of image acquisition, was available for 18 patients. Mean time to maximum enhancement was 17.7 seconds (SD, 3.4; range, 14-26).

Sixteen patients had a single gland removed. Two patients had 3 glands each removed, and 3 patients underwent subtotal parathyroidectomy. Fifteen scans (68.2%) demonstrated true-positive results, accurately identifying and localizing PAs. Three scans (13.6%) were false positive. Four patients (18.2%) had true-negative scans (Table 2). There were no false-negative examination. Of the false positives, 1 incorrectly localized a PA; 1 identified a single PA when 4-gland hyperplasia was found on the day of surgery; and 1 correctly localized a PA, but further surgery was...
required to achieve success after a repeat PCTA demonstrated a second, ectopic PA, which was subsequently removed successfully. The second adenoma was retrospectively present on the original scan but less apparent. Hypothesized reasons include earlier relative suppression of the second adenoma by the other hyperactive gland or possible patient factors, including a shorter neck for this individual. For the purposes of analysis, this patient was considered 2 separate data points—the original, a false positive because further surgery was needed to achieve surgical success despite accurate localization of 1 PA; and the second, a true positive. The overall sensitivity was 100% (95% CI, 74.7%-100%), with a specificity of 57% (95% CI, 20%-88%) and a positive predictive value of 83% (95% CI, 58%-96%; Table 2). Characteristic imaging findings are presented in Figure 2.

Discussion

Selective parathyroidectomy has become the standard of therapy for PHPT at many centers. Such directed procedures depend on accurate preoperative localization. The ectopic PA and the small PA (<350 mg) frequently elude traditional imaging modalities, such as sestamibi–SPECT/CT. Advanced analysis showed ultrasound to have a sensitivity and a positive predictive value of 76.1% and 93.2%, respectively, and those of sestamibi–SPECT, 78.9% and 90.7%. Advanced imaging techniques such as 4DCT imaging are important recent developments, demonstrating an improvement over older techniques for imaging PAs. Improved accuracy was described specifically for reoperative parathyroidectomy, nonlocalizing PAs by other modalities, and patients with low baseline PTH.

4DCT involves acquisition of multiple phases of imaging at set times relating to contrast infusion. The original and most widely reported 4DCT utilizes 4 imaging phases: noncontrasted, early arterial, venous, and delayed contrast. The literature regarding 4DCT contains variability in patient populations, statistical definitions, and analysis, but a consistently high accuracy has been reported. Four-phase studies reported 71.8% to 92% sensitivity and 92% to 95% specificity. Subsequently, 3- and 2-phase 4DCT protocols were reported, also demonstrating excellent accuracy, with sensitivity of 57% to 97%. A recent single-institution study describing trends of accuracy and utilization over time reported 82.3% overall sensitivity in 2- and 3-phase 4DCT over a 5-year study period. As can be expected, studies that limit their patient populations to those with previously nonlocalizing studies demonstrate a lower sensitivity than do those that do not differentiate. Highly accurate 4-dimensional magnetic resonance imaging protocols were recently described, but more study is required to elucidate the clinical role for this technique. Our results are consistent with the accuracy of these other advanced imaging protocols, with 100% sensitivity, 57% specificity, and 83% positive predictive value. Furthermore, these results were obtained in a specifically difficult population of patients with previously nonlocalizing sestamibi scans.

The added radiation from multiple irradiations of the same anatomic region is a persistent concern for the researcher or clinician in the search for more accurate imaging. 4DCT—specifically, the 4-phase imaging protocol—may expose patients to an unnecessarily high dose of radiation. Four-phase imaging protocols have demonstrated doses of 10 to 27 mSv. Three-phase imaging was reported with the following estimated radiation doses: a dose length product of 1200 to 1928 mGy·cm (28 mSv) by Bahl et al and a lower dose of 6.6 mSv by Sepahdari et al. Two-phase protocols continue to improve on this, with mean radiation doses of 5.2 to 6.8 mSv. Our technique further improves on this reduced dosing with a mean radiation dose of 5.15 mSv and a mean 4.1 mSv in our most recent studies.

The PCTA imaging technique presented here represents a modest but meaningful evolution of CT imaging in PHPT.

Table 2. Imaging Characteristics.

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Sensitivity                  100   75-100
Specificity                  57    20-88
Positive predictive value    83    58-96

% 95% CI

All Examinations Most Recent 14 Examinations
Dose-length product, mean (range), mGy·cm 368 (137-1338) 292 (162-425)
Mean calculated total dose, mSv 5.15 4.1

254 Otolaryngology–Head and Neck Surgery 161(2)
Where 4DCT relies on a fixed protocol of image acquisition timing, we have developed PCTA that uses individualized timing. Our results demonstrate meaningful variability in individual patients’ time to maximal enhancement, which supports the utility of individualized timing of image acquisition. This approach limits the study to 2 phases—one contrasted and 1 without contrast—which limits radiation without sacrificing imaging accuracy. Our novel patient positioning reduces noise, allows for further reduction of radiation dose, and may be considered in diverse protocols for imaging of the lower neck and thoracic inlet. Similar imaging characteristics are seen in our study when compared with 4DCT, including excellent anatomic localization and a frequent appearance of the polar vessel sign (Figure 2C). During the study period, each PCTA was directly overseen and interpreted by a subspecialized radiologist, which is consistent with methodology of other novel imaging protocols in PHPT.

The limitations of this study include its retrospective design. Additionally, the analysis reported here aggregates data that are acquired from a period of evolution of this technique—further analysis of the technique in its current form is underway, and we are hopeful that it will continue to demonstrate excellent clinical utility. The single-institution, single-radiologist design of the study precludes assessment of external validity.

**Conclusion**

We present the early results from a novel imaging technique among patients with PHPT. The PCTA has demonstrated success in localizing PAs among patients with previously nonlocalizing imaging. The technical innovations of the PCTA—the novel positioning, rapid infusion of contrast, and individualized timing of contrasted image acquisition—have yielded excellent results thus far. Furthermore, these results come with a reduced radiation dose compared to standard and other advanced parathyroid imaging. It is our intention here to describe the technique in full so that interested surgeons and radiologists may reproduce it wholly or in part, as it may suit their practice, and further the improvement of preoperative localization for this patient population. At this institution, PCTA is obtained before surgery for patients who have undergone sestamibi/SPECT without successful PA localization. Future work will involve prospective analysis of PCTA for all patients with PHPT.

**Author Contributions**

Isaac E. Schwartz, study design, data collection, data analysis, manuscript preparation; Gregory G. Capra, study design, data analysis, manuscript preparation; David P. Mullin, study design, data analysis, manuscript preparation; Terence E. Johnson, study
References


