의학석사 학위논문

Comparison of 4D CT, USG, and ^{99}mTc Sestamibi SPECT/CT in Localizing Single-Gland Primary Hyperparathyroidism

단일 병변 일차성 부갑상선 항진증의 정위를 위한 4D CT, USG, ^{99}mTc Sestamibi SPECT/CT 비교

2014년 2월

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Master of Science in Medicine

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Abstract

Comparison of 4D CT, USG, and ^{99}mTc Sestamibi SPECT/CT in Localizing Single-Gland Primary Hyperparathyroidism

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Introduction: Four-dimensional computed tomography (4D CT) provides surgeons with anatomical and functional information about parathyroid glands for minimally invasive parathyroidectomy (MIP). The purpose of this study was to evaluate the usefulness of 4D CT for localizing single-gland primary hyperparathyroidism (HPT).

Methods: Twenty-four patients were selected, who underwent focused parathyroidectomy for single gland primary HPT between June 2011 and February 2013. Three imaging modalities of ultrasonography (US), ^{99m}Tc sestamibi scanning with single positron emission computed tomography/CT (SeS), and 4D CT, were performed for each patient. Data were reviewed retrospectively and imaging modalities were compared in terms of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Associations between correct 4D CT localization of abnormal parathyroid glands and demographic, clinical, and pathological characteristics were assessed.

Results: Compared to US, 4D CT was more sensitive (91.7% vs. 62.5%; p=0.015) and specific (97.2% vs. 88.9%; p=0.05), and had higher positive predictive value (91.7% vs. 65.2%; p<0.001), negative predictive value (97.2% vs. 87.7%; p=0.021), and accuracy (95.8% vs. 82.3%; p=0.005). 4D CT did not differ significantly from SeS in terms of any measure.

However, in 6/24 (25%) patients, where neither US nor SeS yielded convincing data, 4D CT provided correct localization for MIP. 4D CT localization correlated with maximal diameter (p=0.004) and volume (p=0.002) of parathyroid glands.

Conclusions: 4D CT is a valuable imaging technique for detecting lesions in primary HPT. Compared to conventional imaging, including SeS, its sensitivity is similar or higher; it is also more specific than either US or SeS.

Keywords: Primary Hyperparathyroidism, Minimally Invasive Surgical Procedures, Four-Dimensional Computed Tomography

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Introduction

Primary hyperparathyroidism (HPT) occurs in about 1% of the adults (1, 2). It is most frequently resulted from a single adenoma consisting of a clonal population (3). The definitive treatment is surgery for patients with primary HPT symptomatic or asymptomatic, if they fulfill specific criteria (4, 5). The traditional bilateral neck exploration (BNE) is currently being replaced with the more modern directed parathyroidectomy or minimally invasive parathyroidectomy (MIP) methods (6, 7). MIP is associated with reduced hospital stay and better cosmetic outcome than BNE (8). Other merits of MIP include less cervical dissection, smaller surgical incision, decreased postoperative pain, and decreased cost (9).

For performing MIP, an imaging study must be conducted to localize the abnormal parathyroid gland(s). Available imaging methods include cervical ultrasonography (US), thallium-201 scanning, 99mTc-sestamibi scanning with single photon emission computed tomography combined with computed tomography (SPECT/CT) (SeS), contrast-enhanced US, CT, magnetic resonance imaging, three-dimensional virtual neck exploration, three-dimensional metabolic and radiologic gathered evaluation, US-guided biopsy, selective venous sampling/arteriography, and intraoperative US (10).

Four-dimensional computed tomography (4D CT) was introduced in 2006. It differs from conventional CT in having a fourth dimension; namely, it provides perfusion information that is generated by precontrast, 30, 60, and 90 seconds images (9). 4D CT rapidly provides anatomic and functional information and can detect supernumerary parathyroid glands present in 5-13%; it can detect the ectopic parathyroid glands present in 4-16% (11-13). Its multiplanar reconstruction images provide spatial information (14). 4D CT is also less invasive than US-guided biopsy, venous sampling or parathyroid arteriography, which reduces the risk of seeding or spreading parathyroid cells (15). To address this issue, the present study compared the abilities of 4D CT, US, and SeS to localize parathyroid lesions preoperatively.

Methods

Patients

A total of 24 patients with single parathyroid disease who underwent three imaging modalities were selected for the study between June, 2011 and February, 2013. The demographic data, biochemical values, preoperative imaging reports, operative procedure details, intraoperative findings, and pathology were obtained in accordance with the institutional review board of Seoul National University Hospital (Seoul, Korea).

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of the three imaging techniques for localization were calculated. The measures were generated by matching preoperative imaging reports for each parathyroid gland to its intraoperative finding and final pathology. During surgery, an intraoperative PTH (IoPTH) assay was performed and a frozen biopsy was analyzed. After the operation, the surgically resected specimens were confirmed by final pathology. The patients were followed up for at least 6 months to determine whether there was persistent HPT.

The gold standard reference was the pathology together with the rate of IoPTH drop. Imaging study data were reviewed independently and in a blinded fashion by a radiologist (J.H.K) or a nuclear medicine physician (G.J.C) with more than 10 years of experience. For the purpose of accurate localization, lesions were categorized into 4 quadrants in the neck.

Ultrasonography

US examinations were performed with a 7.5-15 MHz linear transducer (Accuvix XG, Medison, Seoul, Korea, iU22, Philips Healthcare, Best, The Netherlands, or Aixplorer, SuperSonic Imagine, Aix-en-Provence, France). Color Doppler was performed to assess the vascularity. The patients were examined in the supine position with neck extended and the shoulders lowered. Longitudinal and transverse images were taken from the clavicles to the mandible. In US, no contrast was used for enhancement and concomitant thyroid pathology evaluation was possible. By guiding the position of the patient and instructing the patient when to breathe and swallow, the sonographer was able to obtain diverse real-time views with and without compression.

^{99m}Tc-sestamibi scanning with SPECT/CT

Dual phase acquisitions were performed on the anterior neck at 15 and 150 minutes after the intravenous injection of ^{99m}Tc-Sestamibi (Dong-A pharmaceutical, Seoul, Korea or Lantheus Medical Imaging, North Billerica, USA). On average, 740 MBq (20 mCi) was injected. A dedicated SPECT/CT system fitted with free angle dual-head detectors (Discovery NM/CT 670, GE Healthcare, Chalfont St. Giles, UK) was used for the 15 and 150 minutes planar scans and a delayed SPECT/CT scan. A single detector equipped with a LEHR parallel collimator (256×256 matrix, 2.0× zoom) was used for the 15 and 150 minutes planar scans. The ^{99m}Tc window was centered at 140 keV and had a 10% width (range 133–147 keV). After completing the SPECT acquisition, the patient remained static on the table for the next CT acquisition. A scout scan (120 kVp, 30 mA, anterior view) was obtained and an axial FOV was set from the neck to the middle of the chest. A helical CT scan was then performed (120 kVp, 80 mA; 3.75 mm slice thickness; 512×512 matrix).

Four-dimensional CT

A 64-slice multi-detector CT system (Brilliance 64, Philips Healthcare, Best, the Netherlands) was performed to obtain 4D CT images. Automatic exposure control was used (range, 140-240 mA) at 120 kV. Craniocaudal coverage was from the external auditory meatus to 2 cm below the carina, and a small field of view (168x168 mm) was used. Detector configuration for the acquisition was 2.0 mm, and images were reconstructed at a 3 mm thickness with 3 mm spacing in the axial and coronal planes. An initial unenhanced scan was obtained. This scan was followed by an intravenous injection of 90 mL of contrast material (Xenetics 300; Guerbet, Paris, France). Scanning was then repeated at 30, 60, and 90 seconds after the initiation of IV contrast administration. The mean volume CT dose index per imaging phase was 11.4 mGy (range, 10.2-11.9 mGy).

Surgery

All patients underwent planned MIP using lateral approach (15). We routinely performed IoPTH monitoring (Roche cobas e 411 analyzer, Roche Diagnostics, Indianapolis, USA). PTH values were acquired at preincision, preexcision, 5, 10 minutes after excision. The operation could be terminated, if the hormone level decreased by more than 50% (the Miami criterion (16)).

Statistical analysis

SAS version 9.2 (SAS institute, Cary, USA) was used for statistical analysis. Continuous variables were analyzed using Student's *t* test or Mann-Whitney U test, while categorical data were analyzed using Fisher's exact test. Obuchowski proposed a statistical method for the comparison of correlated proportion of the clustered data, and found that this method is more suitable than McNemar test or generalized estimating equations (17). This method was used to compare the measures of each imaging modality in the present study (17). The statistical method described by Leisenring *et al*. was used to compare PPVs or NPVs (18). An adjusted *P*-value was used to correct the Type I error that occurs during multiple comparisons of imaging modalities. Adjusted *P*-values that did not exceed 0.05 were considered significant.

Results

Patients

Of the 24 patients, six were male and 18 were female with a mean age of 58.0±12.1 years. Table 1 shows their clinicopathological characteristics. None of the patients had previously undergone neck surgery. MIP was successfully performed in all patients. The operation time in the MIP group was 64.1±22.7 minutes and the length of hospital stay was 3.3±0.6 days. The IoPTH dropped by 79.4±7.3% during the operation. All patients satisfied the Miami criterion.

Table 1 Demographic and Clinical Characteristics of 24 Patients with Single Hyperparathyroid Disease Who Underwent All Three Imaging Modalities

Characteristic (n = 24)		**Mean±SD**
Age (years)		58.0±12.1
Sex (n)	Male	6
	Female	18
BMI (kg/m^2)		23.6±3.4
Tumor	Size (cm)	1.9±0.9
	Volume (mm^3)	1010±1084
Preoperative test	iPTH (pg/ml)	233.5±117.4 (10.0-65.0)
	25 Vitamin D3 (ng/ml)	18.1±7.8 (9.0-37.6)
	1, 25 Vitamin D3 (pg/ml)	44.3±22.3 (15.0-60.0)
	Ca (mg/dl)	11.7±0.8 (8.8-10.5)
	P (mg/dl)	2.6±0.5 (2.5-4.5)
DXA T-score		-1.6±1.1
Drop in IoPTH (%)		79.4±7.3
6 months after surgery	iPTH (pg/ml)	46.3±25.0 (10.0-65.0)
	25 Vitamin D3 (ng/ml)	29.4±8.2 (9.0-37.6)
	1, 25 Vitamin D3 (pg/ml)	38.6±16.5 (15.0-60.0)
	Ca (mg/dl)	9.3±0.3 (8.8-10.5)
	P (mg/dl)	3.4±0.5 (2.5-4.5)

SD standard deviation; *BMI* body mass index; *iPTH* intact parathyroid hormone; *DXA* dual-energy X-ray absorptiometry; *IoPTH* intraoperative parathyroid hormone
Reference ranges were presented in parentheses.

Localization studies

Table 2 shows the sensitivity, specificity, PPV, NPV, and accuracy of the three imaging modalities. Compared to US, 4D CT was significantly more sensitive (91.7% vs. 62.5%; p=0.015) and specific (97.2% vs. 88.9%, p=0.05), had a higher PPV (91.7% vs. 65.2%; p<0.001), NPV (97.2% vs. 87.7%, p=0.021), and was more accurate (95.8% vs. 82.3%; p=0.005). 4D CT did not differ significantly from SeS in terms of any measure. Although there was no statistical difference between 4D CT and SeS, 4D CT provided correct localization for MIP in 6/24 (25%) patients, where neither US nor SeS yielded convincing data (Table 3).

Table 2 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy with Which Three Imaging Modalities Indicate the Location of Pathological Parathyroid Glands

	4D CT		**US**		**SeS**	
	Rate (%)	**95% C.I.**	**Rate (%)**	**95% C.I.**	**Rate (%)**	**95% C.I.**
Sensitivity	91.7	80.4-100.0	62.5	42.7-82.3	87.5	74.0-100.0
Specificity	97.2	93.5-100.0	88.9	81.4-96.4	90.3	81.1-99.5
PPV	91.7	81.3-100.0	65.2	48.1-82.3	75.0	57.4-92.6
NPV	97.2	93.6-100.0	87.7	81.9-93.5	95.6	91.1-100.0
Accuracy	95.8	92.0-100.0	82.3	74.8-89.8	89.6	82.4-96.8

4D CT four –dimensional computed tomography; *US* cervical ultrasonography, *SeS* ^{99m}Tc sestamibi scanning with single positron emission computed tomography/computed tomography; *C.I.* confidence interval; *PPV* positive predictive value; *NPV* negative predictive value

Table 3 Detailed Anatomic Information Provided by 4D CT, Which neither Ultrasonography nor ^{99}mTc Sestamibi Scanning with SPECT/CT Yielded

Patient	**Age (years)**	**Sex**	**Anatomic Location**	**US**	**SeS**	**Result**
1	57	F	LU	Left	Left	Inconclusive
2	59	F	LU	Four Quadrants	None	Unsuccessful
3	76	F	LU	Left	Right	Discordant
4	68	M	RL	Right	Right	Inconclusive
5	64	F	LU	None	Left	Inconclusive
6	48	F	LU	Left	Left	Inconclusive

4D CT four –dimensional computed tomography; *US* cervical ultrasonography; *SeS* ^{99}mTc sestamibi scanning with single positron emission computed tomography/computed tomography; *LU* left upper; *LL* left lower; *RU* right upper; *RL* right lower

Identification of variables that correlated with 4D CT success

All resected parathyroid glands were confirmed as adenoma in the final pathology. 4D CT failed to localize the lesion in two cases, while it was successful in 22 cases. Table 3 shows the incorrectly localized group compared to the correctly localized group in terms of various demographic and clinical variables. Analysis of the 4D CT data revealed that the maximal diameters of the glands in the cases of incorrect and correct localization groups were 1.0±0.1 and 1.9±0.9 cm, respectively. Their volumes were 211±116 and 1087±1101 mm^3, respectively (Table 4). Thus, correct 4D CT localization correlated with parathyroid gland maximal diameter (p=0.004) and volume (p=0.002).

Table 4 Association of Variables with Correct Localization of Abnormal Parathyroid Glands by Four-Dimensional Computed Tomography

Variable (n=24)	**Incorrect (n=2)**	**Correct (n=22)**	***p*-value**
Sex (male, n)	1	5	1.000
Age (years)	53.7±13.7	59.3±12.2	0.467
BMI (kg/m2)	22.56±3.84	23.77±3.35	0.567
Tissue PTH (pg/ml)	915.00±1093.95	2542.49±1585.63	0.108
Calcium (mg/dl)	11.4±0.4	11.8±0.8	0.368
Phosphorus (mg/dl)	2.2±0.5	2.7±0.5	0.408
25(OH) Vitamin D3 (ng/ml)	19.7±4.5	15.0±6.0	0.318
iPTH (pg/ml)	194.0±95.8	236.6±118.8	0.560
Volume (mm3)	211±0.116	1087±1101	0.002
Size (cm)	1.3±0.1	1.9±0.9	0.004

BMI body mass index; *PTH* parathyroid hormone; *iPTH* intact PTH
The preoperative laboratory values were presented.

Short-term outcomes

The follow-up duration was 16.4±5.4 months. During the hospital stay, none of the patients experienced complications such as bleeding, surgical site infection, or recurrent laryngeal nerve (RLN) injury. Six months after surgery, the calcium value was 9.3±0.3 mg/dL, the phosphorus value was 3.4±0.5 mg/dL, the 25(OH) vitamin D3 value was 29.4±8.2 ng/mL, and the iPTH value was 46.3±25.0 pg/mL. Those laboratory values are normal or near-normal. None of the patients required reoperation for persistent or recurrent HPT.

Discussion

Although MIP is not generally performed in patients with thyroid disease or in those that have undergone previous neck surgery, it is increasingly being used for parathyroid surgery because more than 80% of primary HPT cases are caused by a single lesion (2, 7, 19, 20). Several studies have assessed the utility of various imaging modalities (3). Recurrent or persistent HPT occurs in 2–5% of patients whose initial parathyroidectomy failed (1, 21, 22). A second cervical exploration is more difficult than the initial surgery; moreover, it raises the risk of RLN injury from less than 1% to 15% (23).

The efficacy of three imaging modalities was assessed in the current study. 4D CT was superior to US in terms of sensitivity, specificity, PPV, NPV, and accuracy, but did not differ significantly from SeS in terms of these measures. The inferior sensitivity of US called for complementary imaging modalities. While it was reassuring that SeS was as sensitive as 4D CT, 4D CT tended to be more specific and accurate than SeS. In six cases (25% of the 24 cases), neither US nor SeS yielded convincing data regarding the location of the lesion. By contrast, 4D CT provided successful localization in these six cases, and allowed MIP. A comprehensive analysis of the demographic and pathological characteristics between the incorrect and correct localization groups revealed that the correct 4D CT localization correlated with the maximal diameter and volume of parathyroid glands.

Rodgers et al., in their pioneering research, found that US and sestamibi imaging is unsuitable for patients with previous neck surgery, coexisting thyroid disease, or unfavorable body habitus (9). A meta-analysis of 43 studies on preoperative localization techniques in primary HPT reported pooled sensitivity and PPV values of 89.4% and 93.5% for 4D CT, respectively (24). In a few retrospective studies, 4D CT showed impressive results (14), or the superiority to sestamibi with SPECT or US (25). However, the study by Lubitz et al. was not consistent with the present study (21). Their reported sensitivity for localization was only

60% lower than our presented measure. In their study, 21 patients had prior neck explorations and 4D CT were considered in patients with poor localization by sestamibi and US. Their higher BMI of 28.9±6.2 kg/m2 compared to our 23.6±3.4 kg/m2 could affect the way to differentiate parathyroid glands from circumjacent soft tissue. Moreover, their median largest dimension and volume of 1.2 cm and 300 mm3 in the group localized by 4D CT, were smaller than our 1.9±0.9 cm and 1087±1101 mm3.

The present study has a number of strengths. First, the author used the comparative statistical method for correlated proportions for clustered data (proposed by Obuchowski) to assess the efficacy of the three imaging modalities. Second, the imaging data were reviewed in a blinded fashion. Third, only patients who underwent all three imaging studies were analyzed. Fourth, clinicopathologic features that correlated with successful 4D CT localization could be identified.

Kunstman et al. in their algorithmic approach suggested that when US and SeS provide negative or contradictory results, 4D CT should be considered, albeit with great care where young patients are concerned because of the radiation risk (3). Indeed, the utility of 4D CT is limited by the fact that 4D CT involves exposure to radiation (25-27). The authors in the present study also suggest that 4D CT should only be used once the risks and benefits have been carefully considered.

One decision-analysis study demonstrated that the mean cost for US plus SeS plus 4D CT was $6,572 per patient, whereas US plus SeS alone cost $6,306 per patient (8). The other similar study showed that US followed by 4D CT was the least expensive diagnostic combination (28). In our own country, 4D CT costs about $213.5 compared with about $150 for US and $316.7 for SeS. However, this approach is hampered by the fact that US is not covered by our national health insurance. Thus, given its many clinical benefits, 4D CT can be a cost-effective modality for parathyroid gland localization in patients with primary HPT.

Diagnostic accuracy can be increased by including 4D CT as a preoperative localization test along with US and SeS. While US helps to detect concomitant thyroid disease, 4D CT adds anatomical details that complement the more functional imaging provided by SeS. The increased accuracy obtained by adding 4D CT reduces the possibility of localization errors and the need for re-operations. Therefore, the author believe that when it is necessary to localize parathyroid glands preoperatively, 4D CT might be performed along with US and SeS, unless the patient is young and, thus, sensitive to the radiation exposure.

The present study is limited by the fact that it is retrospective in nature and only examined a small cohort of patients. The fact that all the patients included in this study came from single-gland primary hyperparathyroidism, may have introduced selection bias. In addition, although 4D CT at our institution has been performed with high measures, variability may occur due to differences between interpreters in terms of their experience, and/or differences in study protocols.

Conclusions

4D CT may be a valuable imaging technique for detecting lesions in patients with primary HPT. Compared to conventional imaging, including SeS, its sensitivity is similar or higher; it is also more specific than either US or SeS. Because the superior spatial resolution of 4D CT greatly aids the localization of the lesion, 4D CT facilitates the use of MIP over BNE.

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국문초록

서론: 4D CT는 최소침습 부갑상선 절제술을 위해 부갑상선의 해부학적이고 기능적인 정보를 외과의에게 제공한다. 이 연구에서는 단일 병소의 일차성 부갑상선선 항진증 환자에서 비정상 부갑상선의 정위를 위한 4D CT의 유용성을 확인하고자 한다.

방법: 2011년 6월 2013년 2월까지 단일 병소의 일차성 부갑상선 항진증으로 최소침습 부갑상선 절제술이 시행된 24명의 환자들을 대상으로 연구하였다. 각 환자에서 3개의 영상 검사 즉 ultrasonography (US), ^{99}mTc sestamibi scanning with single positron emission computed tomography/CT (SeS), 4D CT가 시행되었다. 검사 결과는 후향적으로 검토되었으며 민감도, 특이도, 양성예측도, 음성예측도, 정확도의 측면에서 영상 검사들을 비교하였다. 또한 4D CT에서의 비정상 부갑상선의 정확한 정위와 어떠한 인구학적, 임상적, 병리적 특징들이 연관되었는지 살펴보았다.

결과: US와 비교하였을 때 4D CT는 민감도 (91.7% vs. 62.5%; p=0.015), 특이도 (97.2% vs. 88.9%; p=0.05), 양성예측도 (91.7% vs. 65.2%; p<0.001), 음성예측도 (97.2% vs. 87.7%; p=0.021), 정확도 (95.8% vs. 82.3%; p=0.005)에서 유의한 차이가 있었다. SeS와는 통계적으로 유의한 차이를 확인하지 못하였다. 그러나 US나 SeS가 정확한 위치 정보를 주지 못했던 6명 (25%)의 환자에서 4D CT는 최소침습 부갑상선 절제술을 위한 정확한 위치 정보를 제공하였다. 4D CT의 정확한 정위는 부갑상선의 최대 직경 (p=0.004), 부피 (p=0.002)와 유의한 상관 관계가 있었다.

결론: 4D CT는 일차성 부갑상선 항진증에서 병변을 찾아내는 유용한 영상 검사 방법이다. SeS를 포함한 기존의 영상 검사 방법들과 비교하였을 때, 그 민감도가 유사하거나 높았으며 US 또는 SeS보다 특이도가 높았다.

주요어: 일차성 부갑상선 항진증, 최소침습 부갑상선 절제술, 4D CT

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감사의 말

평생 외과의로서 살 수 있는 영광을 주신 것만도 과분한데 외과학 석사 과정에 입문하여 학문적 연구를 진행할 수 있었으며 이렇게 잘 마무리를 지을 수 있게 도움 주셔서 여러 선생님들께 다시 한 번 감사의 말씀을 드립니다.

그러한 은혜에 보답하는 길은 임상의사로서 동시에 의학자로서 소임을 다하는 길 뿐이라 생각합니다. 더불어 맺어진 인연의 끈을 소중하게 이어가며 더욱 풍부한 겸양과 소양의 미덕으로 한 인간으로서 좋은 모습 보여드리도록 노력하겠습니다.