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Super-selective Venous Sampling in Conjunction with QuickPTH for Patients with Persistent Primary Hyperparathyroidism: Report of Five Cases

Running title: Super-selective Venous Sampling in pHPT

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Abstract

Background: Selective venous sampling (SVS) helps to interpret imaging results in patients with persistent primary hyperparathyroidism (pHPT). However, one of the drawbacks of conventional SVS may be low "spatial resolution", depending on the sample size.

Material and Methods: We modified SVS in the following way: First, patients underwent conventional SVS with up to 11 parathyroid hormone (PTH) samples taken. The quickPTH assay was used to measure PTH levels. The patients subsequently underwent super-selective venous sampling (super-SVS) in the region with the highest quickPTH level in the same session.

Results: The subjects were five consecutive patients with persistent pHPT investigated by various imaging techniques, none of which was considered conclusive. Therefore, all five patients underwent super-SVS, which was done successfully in four. Re-evaluation of the imaging results of these four patients resulted in localization of the parathyroid adenoma. Curative surgery was performed successfully in all patients during the study period .

Conclusion: Super-SVS increases the "spatial resolution" of conventional SVS and may have advantages when imaging results of patients with persistent pHPT are interpreted. Its true value must be analyzed in larger studies.

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disease with an estimated incidence of about 1/500-1,000 (1, 2). Most (80-85%) patients have one adenoma, but double-adenomas have been reported in up to 15% (3). About 10-15% of patients have multiglandular disease. Patients undergoing primary surgery are often cured, with success rates of 95-99% in experienced hands (4, 5). However, a minority of patients continues to suffer from pHPT (persistent pHPT) and may require reoperation. Imaging of the hyperfunctioning gland(s) is recommended prior to surgery in these patietns, to keep the increased morbidity associated with re-operation low (6). The non-invasive techniques used for this include ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), sestamibi scintigraphy (MIBI), and methionine-PET). Before re-operation, the sensitivity of US, CT, MRI, MIBI, and methionine-PET has been reported at 20-80 % (7-11), 40-90 % (9, 11, 12), 65-80 % (8, 11, 12), 50-90 % (8, 9, 11-13), and about 80% (14), respectively.

Selective venous sampling (SVS) is an invasive technique first described in 1969 (15). It may be useful when imaging studies are considered negative or discordant (16), and although the subclavian approach has been reported to be simpler, quicker, and less hazardous (17), it has not become the method of choice. SVS is usually performed via the inguinal approach. If only the large vessels; namely, the inferior and superior vena cava, the right and left innominate veins, and the right and left internal jugular veins, are catheterized, the source of parathyroid hormone over-production is often only roughly regionalized (18). The situation is made even more challenging by the fact that the venous drainage of each parathyroid gland is complex and often altered by the prior neck exploration (19). Practically, this low "spatial resolution" problem could be overcome if numerous (≥ 20) blood samples were taken from smaller venous branches (12, 13, 20). However, catheterizing many small venous branches can be costly, time-consuming and technically challenging. Alternatively, one could perform a "quick" first round, taking fewer samples from readily accessible locations of larger vessels, and then measuring the parathyroid hormone (PTH) level. In a subsequent second round, additional samples could be taken from few small

venous branches in the region with the highest PTH level; namely, "super-selective venous sampling" (super SVS). The problem with this approach was the time-consuming measurement of the PTH levels. Investigation of the smaller venous branches in the second round would have required reinvestigation of the patient in a second session. In 1994, Irvin and Deriso described a way of evaluating an intraoperative assay for intact PTH, which could be applied widely (21). These days, assays with a turn-around time of less than 20 min exist (22, 23) and the costs per sample are low (24). We conducted the present study to establish the applicability of super-SVS in conjunction with a quickPTH assay.

Material and Methods

We modified SVS in the following way: First, we performed conventional SVS. After administering local anaesthetic in the right groin (Xylocain 10mg/ml; 5-10 ml; AstraZeneca), a 5-F sheath (Brite Tip, 11 cm; Cordis, Johnson & Johnson) was placed in the right femoral vein. Through the sheath, a 4-F catheter with a short angled tip and no side holes (JB 1, 100 cm; Cordis, Johnson & Johnson) was advanced over a guide-wire (Teflon 35-150 cm; Boston Scientific) and then, under fluoroscopy, moved up through the inferior and superior vena cava, where the two first blood samples were taken; through the right and left innominate veins, where another three samples were taken, one proximal, one distal on the left side and one on the right side; and finally up to the internal jugular veins on both sides to just below the base of the skull, where three more blood samples were taken from the lower, middle, and upper part of each vein. Thus, in general a total of up to 11 samples were taken (Fig. 1, 1B). The left jugular vein can be difficult to catheterize because of the sharp angel between the left innominate vein and the left internal jugular vein and sometimes because of a competent valve in the lower part of the jugular vein.

The parathyroid hormone levels were then measured using a quickPTH assay (PTH STAT, Roche Diagnostics) (25). After receiving the results, the investigation was continued and the patients underwent super-SVS (26) of up to three additional small venous branches in the region with the highest quickPTH level. We proceeded with the super-selective catheterization, using a 4-F catheter (MP A2, 100 cm; Cordis or Cobra 2 100 cm; Cordis,
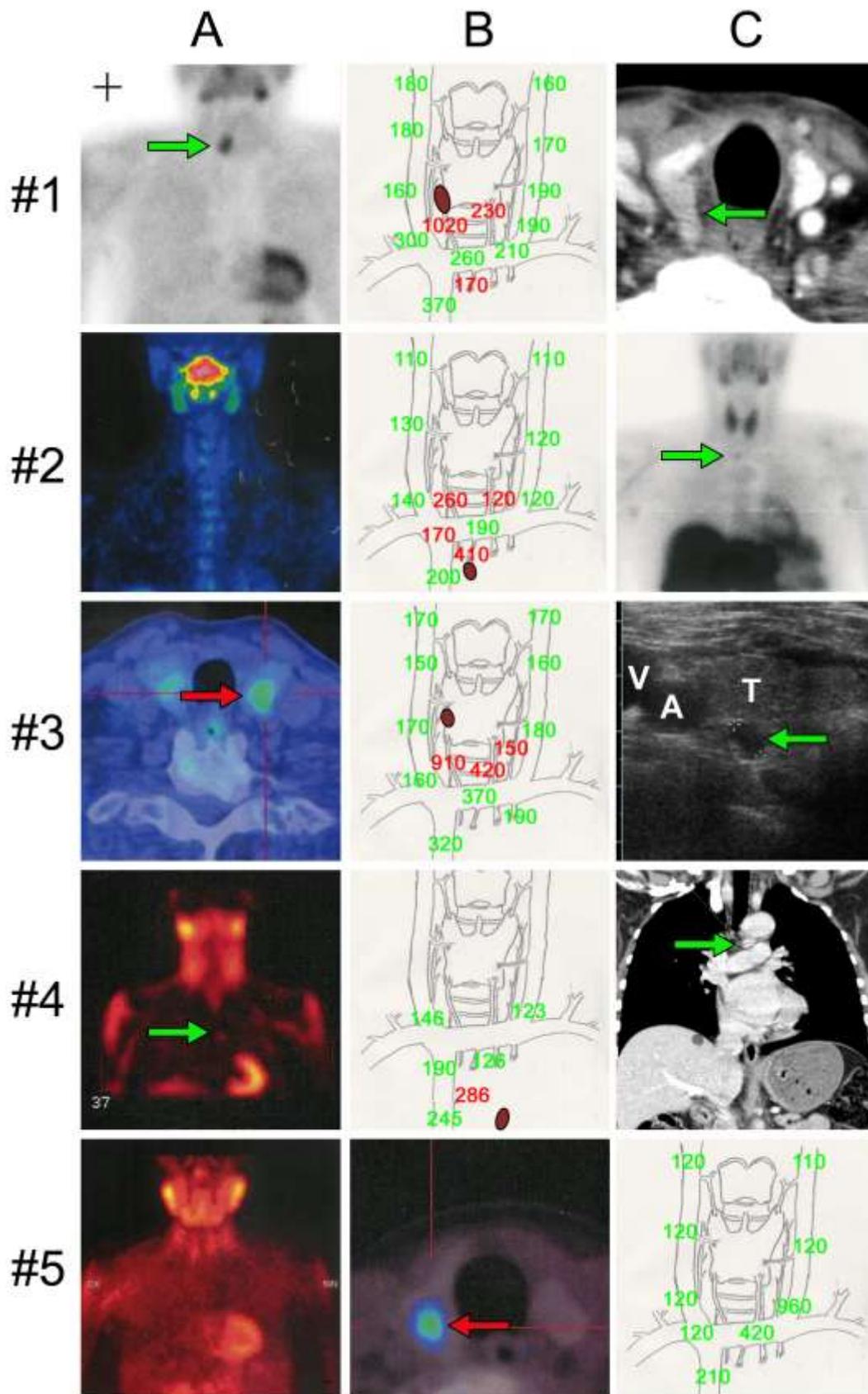
Fig. 1:   **Patient #1:** (A) MIBI suggested a right-lower parathyroid adenoma (true-positive); (B) super-SVS: green numbers, samples taken during the first round; red numbers, samples taken during the second round, suggestive of a right lower parathyroid adenoma (true-positive), final localization of parathyroid adenoma; (C) CT suggested a right parathyroid adenoma (green arrow, true-positive).

Patient #2: (A) Methionine-PET (false-negative); (B) super-SVS, suggestive of a parathyroid adenoma in the right upper-mediastinum (true-positive), final localization of parathyroid adenoma; (C) MIBI suggested a parathyroid adenoma in the right upper-mediastinum (green-arrow, true-positive).

Patient #3: (A) Methionine-PET suggested a left parathyroid adenoma (red-arrow, false-positive); (B) super-SVS suggested a right parathyroid adenoma (true-positive), final localization of parathyroid adenoma; (C) US suggested a right parathyroid adenoma (green-arrow, true-positive), V=internal jugular vein, A=carotid artery, T=thyroid.

Patient #4: (A) MIBI suggested a parathyroid adenoma in the left upper-mediastinum (green-arrow, true-positive); (B) super-SVS suggested a parathyroid adenoma in the left upper-mediastinum (true-positive), final localization of the parathyroid adenoma; (C) CT suggested a parathyroid adenoma in the left upper-mediastinum (green arrow, true-positive).

Patient #5: (A) MIBI (false-negative); (B) Methionine-PET suggested a right intrathyroidal parathyroid adenoma (red-arrow, false-positive); (C) SVS (no second round, see text) suggested a parathyroid adenoma in the left lower neck/upper mediastinum.

Johnson & Johnson) and a hydrophilic guide wire (Road runner, Nimble 35-180 cm; Cook or Terumo angled 35-180 cm; Radifocus Terumo) to access the small venous branches from the neck and upper mediastinum.

The investigation was conducted as part of the clinical routine. All patients gave informed consent to undergo super-SVS, which was performed in

accordance with the standards of the Helsinki Declaration of 1975, as revised in 1983.

Results

Five patients with persistent pHPT underwent this procedure, all of whom had previously undergone at least one operation for pHPT, despite which the postoperative PTH and ionized calcium (Ca) levels remained elevated. Various imaging techniques had been carried out, including ultrasound (US), CT/MRI, MIBI, and methionine-PET, but none of them was conclusive.

Case Reports

Patient #1

A 66-year old man presented to another hospital with a PTH level of 590 pg/ml [range: 15-65] and a total serum Ca level of 3.21 mmol/l [range: 2.15-2.50]. He underwent cervical exploration without preoperative imaging. Two normal parathyroid glands were identified on the left and although the lower gland on the right appeared normal, the upper gland on the right was enlarged and therefore, removed. Postoperatively, the PTH level and serum Ca only dropped to 180 pg/ml and 2.97 mmol/l, respectively. The patient then underwent MIBI-scintigraphy, which showed a suspected parathyroid adenoma on the right side, in concordance with the missing parathyroid gland (Fig. 1, 1A). During a second operation in the same hospital, tissue near the right lower thyroid lobe was removed. On frozen section, this tissue was considered to be parathyroid but final histology confirmed only thyroid tissue. The PTH level remained elevated, at 190 pg/ml. The total serum Ca was now 2.85 mmol/l and the ionized serum Ca was 1.41 mmol/l [range: 1.18-1.34 mmol/l]. The patient was referred to our hospital for further management. Ultrasound and CT findings suggested a right lower parathyroid adenoma but because no adenoma was found at the previous two operations, we decided that SVS was indicated. We had to change the catheter (Sim 2; 5-F, 100 cm; Cordis, Johnson & Johnson) to access the left jugular vein. Conventional SVS showed quickPTH peaks in the region of the right innominate vein and superior vena cava, which indicated a hyperfunctioning parathyroid gland either in the right lower part of the neck or in the upper

mediastinum. Following super-SVS, the highest quickPTH peak was found in the right inferior thyroid vein (Fig. 1, 1B) proving the existence of a PTH-producing tumor close to the lower right thyroid lobe (Fig. 1, 1B), as suspected from the US, MIBI and CT findings (Fig. 1, 1C; Table 1). The absence of a higher quickPTH level in the right internal jugular vein can probably be attributed to the dissection of venous branches draining into the internal jugular vein at the two previous operations. During subsequent surgery, we found and removed an adenoma, 24x21x12 mm in size. Postoperatively, the patient was cured. His PTH level normalized and the ionized serum Ca dropped to 1.2 mmol/l.

Patient #2

A woman was 33-years old when pHPT was diagnosed. The PTH level was 79 pg/ml and total serum Ca was 3.03 mmol/l, but there were no other signs or symptoms suggesting multiple endocrine neoplasia type 1 or other types of hereditary pHPT. Moreover, the patient's family history was negative for pHPT and preoperative ultrasound and MIBI-scintigraphy were negative. The patient underwent bilateral cervical exploration at another hospital and four normal parathyroids were identified. The findings of CT, MRI, MIBI-scintigraphy, and methionine-PET (Fig. 1, 2A) were all considered negative (Table 1). The patient subsequently underwent conventional SVS, at which time the highest quickPTH levels were found medially in the left innominate vein and the superior vena cava. This was indicative of a hyperfunctioning parathyroid gland either in the right lower part of the neck or in the upper mediastinum. After super-SVS, the highest quickPTH level was found in the right thymic vein, suggesting a PTH-producing tumor in the right upper mediastinum (Fig. 1, 2B). By re-evaluating the MIBI-scintigraphy (Fig. 1, 2C) increased uptake in the right upper mediastinum was identified (Table 1). An intrathymic parathyroid gland was suspected and the patient underwent thymectomy, which revealed a parathyroid adenoma 10x8x10 mm in size. Postoperatively, the patient was cured. Her PTH dropped to 21 pg/ml and ionized serum Ca, to 1.2 mmol/l.

Patient #3

A 71-year old man was admitted to another hospital with a total serum Ca of 2.91 mmol/l and a PTH level of 130 pg/ml. The preoperative ultrasound report documented suspicion of a right parathyroid adenoma. In retrospect, this investigation was most likely a "true positive". The patient underwent cervical exploration, which identified both lower parathyroid glands as normal. The two upper parathyroid glands were not identified. Postoperatively, the total serum Ca remained elevated and the patient was referred to our hospital. Subsequent ultrasound of the neck, as well as CT and MRI of the neck and thorax, revealed negative findings. Even MIBI-scintigraphy was negative (picture not available). Methionine-PET findings suggested a parathyroid adenoma on the left side of the neck (Fig. 1, 3A). Re-evaluation of ultrasound, CT and MRI could not confirm any parathyroid lesion on the left (Table 1). Therefore, the patient underwent SVS. Following conventional SVS, the highest quickPTH levels were found medially in the left innominate vein and in the superior vena cava. This indicated a hyperfunctioning parathyroid gland either in the right lower part of the neck or in the upper mediastinum. After super-SVS, the highest quickPTH peak was found in the right inferior thyroid vein (Fig. 1, 3B), but as no thymic vein was identified, no further samples from the mediastinal area were taken. A new cervical ultrasound showed an enlarged right parathyroid gland (Fig. 1, 3C; Table 1). The absence of a higher quickPTH level in the right internal jugular vein can probably be attributed to the dissection of venous branches draining into the internal jugular vein at the two previous operations. The patient then underwent re-operation and removed a parathyroid gland, 9x8x7 mm in size, found next to the middle part of the right thyroid lobe. Postoperatively, the patient was cured. His PTH level dropped from 150 pg/ml to the normal range and the ionized serum Ca decreased to 1.26 mmol/l.

Patient #4

A 49-year old woman was admitted to another hospital with a PTH level of 101 pg/ml and a total serum Ca level of 2.8 mmol/l. No imaging was done prior to surgery. Bilateral cervical exploration revealed two normal parathyroids on the left and one normal upper gland on the right, but the lower right parathyroid was

not identified. The postoperative PTH level and ionized serum Ca remained elevated. MIBI-scintigraphy then showed an uptake in the upper mediastinum (Fig. 1, 4A) but CT was initially considered inconclusive (Table 1). The patient then underwent SVS. During conventional SVS, we did not reach the upper part of the vein because of a competent valve in the lower third of the left internal jugular vein, where blood samples were taken instead. The highest quickPTH levels were found in the right innominate vein and the superior vena cava. This was consistent with a hyperfunctioning parathyroid gland either in the right lower part of the neck or the upper mediastinum. During super-SVS, only the thymic vein could be catheterized. The inferior thyroid veins were probably not able to be catheterized because they had been altered during the neck exploration. A high quickPTH peak was found in the thymic vein, suggesting a PTH-producing tumor in the upper mediastinum (Fig. 1, 4B). Re-evaluation of the CT scan then identified an adenoma cranial of the carina, caudal of the aortic arch (Fig. 1, 4C; Table 1). The patient underwent surgery and an adenoma, 13x6x10 mm in size, was found. Postoperatively, the patient was cured. Her PTH normalized and the ionized serum Ca was 1.26 mmol/l.

Patient #5

A 61-year old woman was admitted to our hospital with a PTH level of 91 pg/ml and a slightly elevated ionized serum Ca level of 1.36 mmol/l. Preoperative ultrasound was negative and she underwent bilateral cervical exploration. We identified two normal parathyroids on the left. On the right, the lower parathyroid appeared to be slightly enlarged and was removed, but the upper parathyroid was not identified. Postoperatively, the PTH remained elevated at 93 pg/ml and the ionized serum Ca increased to 1.4 mmol/l. The patient then underwent CT that was negative, as was MIBI-scintigraphy (Fig. 1, 5A). Methionine-PET then showed a suspected intrathyroidal parathyroid adenoma on the right side (Fig. 1, 5B; Table 1) and the patient underwent re-operation. The intrathyroidal nodule was thyroid tissue and no parathyroid tissue was identified. Following surgery, the PTH increased to 140 pg/ml and the ionized serum Ca stayed at 1.39 mmol/l. The patient then underwent conventional SVS and a peak in the right lower internal jugular vein was identified (Fig. 1, 5C). Unfortunately, no blood could be

drawn from the smaller veins in this region because of low back-flow. Thus, in this patient, super-SVS was not carried out successfully (Table 1).

Discussion

The findings of this study demonstrate the potential advantages of super-selective venous sampling over conventional selective venous sampling through the use of a quickPTH assay when interpreting the imaging results of patients with persistent primary hyperparathyroidism.

Conventional SVS is carried out in many ways and its sensitivity generally ranges from 50-95% (mean, 75%) (7-9, 11-13, 27-29). Depending on the sample size, the conventional method helps to regionalize the source of PTH excess to the right upper/lower neck, left upper/lower neck, low central neck and mediastinum. If the samples taken are restricted to the large vessels, it cannot localize the source precisely as the venous drainage of each parathyroid gland is complex and may even have been altered by prior neck exploration (19). This low "spatial resolution" problem can be overcome by taking numerous (≥ 20) blood samples (12, 20); however, catheterizing many small venous branches can be very time-consuming and technically challenging. This is where super-SVS may be of help. In a "quick" first round, the large vessels are catheterized and PTH levels are measured at up to 11 well-defined positions. After obtaining the results, smaller venous branches in the region with the highest PTH level are catheterized to increase the "spatial resolution" in that area. The advantage of this method over other techniques that require numerous (≥20) samples is that catheterizing all small veins in the neck may be time-consuming procedure and unnecessary. In this study, the time from when the first sample was taken during the first round until when the last sample was taken during super-SVS, including the quick PTH results, ranged from 90-135 min (mean, 115 min). This time has to be weighed against the time it would take to catheterize all small neck veins (29) and should be addressed in larger studies.

SVS is not the procedure of choice for patients with persisting pHPT because of its invasiveness. Only a few studies reported no complications (30), although most did not even mention the complication rate (12). We do not know if this reflects the real complication rate, but none of our patients suffered any

complications. Like other techniques, super-SVS has its flaws. For instance, super-SVS could not be carried out successfully in one patient because of low back-flow. Moreover, SVS may not enable regionalization of the parathyroid glands in patients with multiglandular disease, although none of the patients in this series had multiglandular disease. Thus, whether super-SVS may be more helpful than conventional SVS in such cases remains unclear, although most imaging techniques have a low sensitivity in this situation (31, 32). It was reported recently that fusion of MIBI-SPECT and CT might be helpful in patients with multiglandular disease (33). While SVS seems to be superior to MIBI-SPECT alone (18), the fusion of MIBI-SPECT and CT seems to be superior to MIBI-SPECT (34). However, to our knowledge, there has been no publication comparing the fusion of MIBI-SPECT and CT with SVS and we also have no experience of this. Another promising technique for detecting cervical parathyroid adenomas is three-dimensional ultrasonography (35). However, studies investigating its effectiveness in patients with persistent primary hyperparathyroidism have not been published yet.

When dealing with persistent pHPT, one should always look at the previous operation(s) from a critical point of view. In this series, the cervical parathyroid adenomas of two patients (patients #1 and #3) were not ectopic, as occasionally reported (36-38), but instead, missed during previous operations. Thus, these parathyroid adenomas could have been found by thorough cervical exploration. This may be explained by the fact that these patients underwent initial surgery at local hospitals that were not a referral center. Furthermore, thorough evaluation of the imaging results should have identified parathyroid adenomas in the mediastinum of two other patients (patients #2 and #4). However, identification of mediastinal parathyroid adenomas can be particularly difficult. In the early 1980s, the imaging method of choice to identify mediastinal parathyroids was CT, which has a sensitivity as low as 30% (39). Despite dramatic improvements in this technique, mediastinal glands may still be difficult to identify. In this instance, functional analysis using MIBI, methionine-PET, and SVS may be required. The parathyroid glands are then most often localized in the upper mediastinum, but rarely in the lower part (40).

In patients with persistent pHPT, we start looking for the hyperfunctioning gland(s) using ultrasound and MIBI. In the past, if the results were not concordant or if previous operations failed to identify the parathyroid gland(s), we performed conventional CT; however, now we perform dual-energy CT, as recently described (38), but not MRI. If still not concordant, we would then perform super-SVS. Thus, the indications for super-SVS in patients with persisting pHPT would be either a lack of concordance of functional and non-functional imaging techniques (as in patients #2, #3, #4, and #5) or concordance of functional and non-functional imaging techniques but a history of surgery with negative intraoperative findings (as in patient #1).

In summary, super-SVS can enhance the "spatial resolution" better than conventional SVS, by slightly increasing the sample size. Re-evaluation of the imaging results enabled localization of the parathyroid adenoma in all four patients in whom super-SVS was carried out successfully. Subsequent surgery rendered all of those patients cured during the observation period. Thus, if the low "spatial resolution" of SVS is the problem preventing accurate evaluation of conventional imaging results, super-SVS may be very helpful. Its true value must be addressed in a larger series.

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Table 1: Results of various imaging techniques before and after super-selective venous sampling

	US	CT	MIBI	PET	sSVS	US	CT	MIBI	PET
	before sSVS					after sSVS			
Patient #1	TP	TP	TP	NP	TP	TP	TP	TP	NP
Patient #2	TN	FN	FN	FN	TP	TN	FN	**TP**	FN
Patient #3	FN	FN	FN	FP	TP	**TP**	FN	FN	FP
Patient #4	TN	FN	TP	NP	TP	TN	**TP**	TP	NP
Patient #5	FN	FN	FN	FP	*	NA	NA	NA	NA

US – ultrasound; CT – computed tomography; MIBI – sestamibi scintigraphy ; PET – methionine positron emission tomography; sSVS – super-selective venous sampling

NP – not performed; TP – true positive; TN – true negative; FN – false negative; * - sSVS was not performed successfully; NA – not applicable