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# The role of selective venous sampling in the management of persistent hyperparathyroidism revisited

Janneke E. Witteveen, Job Kievit, Arian R. van Erkel, Hans Morreau, Johannes A. Romijn, Neveen A.T. Hamdy

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**ABSTRACT**

**Introduction:**

Localization studies are mandatory prior to revision surgery in patients with persistent hyperparathyroidism in order to improve surgical outcome and reduce the risk of lengthy explorations. However, in this case noninvasive localization studies are reported to have a poor sensitivity. The aim of our study was to determine the accuracy of selective PTH venous sampling (SVS) in localizing residual hyperactive parathyroid glands in patients with persistent or recurrent hyperparathyroidism.

**Patients & Methods:**

We retrospectively evaluated the localizing accuracy of 20 PTH SVS performed prior to revision surgery in 18 patients with persistent or recurrent primary hyperparathyroidism (n=11) or autonomous (tertiary) hyperparathyroidism (n=7). Tc99m-MIBI-SPECT was also performed in all patients prior to revision surgery. Operative and pathology data were obtained from hospital records.

**Results:**

SVS was able to accurately localize 15 of the 20 pathological glands removed at revision surgery, representing a sensitivity of 75%. This sensitivity is significantly higher than that of Tc99m-MIBI-SPECT, which was only 30% ($P$=0.012).

**Conclusion:**

Our findings demonstrate that SVS is a valuable localization study in patients with persistent or recurrent hyperparathyroidism, with a sensitivity significantly higher than that of Tc99m-MIBI-SPECT. Our data suggest that SVS represents a useful addition to the pre-operative work-up of these patients prior to revision surgery.

## INTRODUCTION

In primary hyperparathyroidism (PHPT) parathyroidectomy is reported to have a cure rate of 94%-100% (1-10) with a complication rate of 0-2.7% in the hands of experienced surgeons (3,5,7-9). In contrast, revision surgery for persistent hyperparathyroidism poses a far greater challenge, due to distortion and scarring of surgical planes caused by previous interventions. In addition, the likelihood of supernumerary parathyroid glands, ectopic localizations and parathyromatosis (inadvertent seeding of parathyroid cells during previous surgeries) is also increased. For these reasons, preoperative localization studies are highly recommended prior to revision surgery for persistent hyperparathyroidism in order to decrease operating time, improve surgical outcome and reduce the risk of complications due to lengthy explorations (10-14). However, localizing residual hyperactive parathyroid tissue often represents an elusive task, particularly following previous surgery for PHPT. The most widely used localization study, Tc99m-MIBI-SPECT, has indeed been shown to hold significant limitations prior to revision surgery for persistent PHPT. Explanations for the poor localizing ability of Tc99m-MIBI-SPECT in persistent PHPT, as low as 50%, include the small size of residual pathological glands, higher probability of hyperplasia and potential distortion of the vascular supply to the residual hyperactive glands due to previous surgery (15-19).

Selective venous sampling (SVS) of parathyroid hormone (PTH) has been shown to be valuable in localizing hyperactive parathyroid glands (20-22), but this invasive technique has generally fallen out of favor since the introduction of non-invasive radionucleotide tests, initially thallium-technetium subtraction scanning (23), and subsequently the more sensitive Tc99m-MIBI-SPECT (10). The diagnostic value of SVS is based on the assumption that regional drainage of each one of the 4 parathyroid glands is into the adjacent superior, middle and inferior thyroid veins, respectively (20). Despite potential anatomical variations, SVS is successful in predicting the side of a pathological parathyroid gland in 39-93% of patients with PHPT (20-22,24-31) and, more importantly, in 66-75% of patients

with negative noninvasive studies (21,27,32). The major limitation of SVS, however, is that it pinpoints the area of venous drainage of a hyperactive gland rather than its exact anatomical location. There may indeed be many variations in regional venous anatomy of the parathyroids due to embryological differences. While each parathyroid gland thus tends to drain ipsilaterally and inferiorly, contralateral drainage has also been described (20). Variations in regional venous drainage may also occur as a result of previous surgical interventions, usually due to ligation of draining veins. In previously published studies, the predictive value of SVS was judged to be positive when a positive gradient was documented on the side of the neck where a pathological gland was found at subsequent surgery (15,27,29). The aim of the present study was to evaluate whether SVS for PTH could contribute to a more accurate preoperative localization of residual hyperactive parathyroid tissue in patients with persistent hyperparathyroidism.

## PATIENTS AND METHODS

### *Patients*

Using our hospital records, we selected all patients who had undergone Tc99m-MIBI-SPECT and selective venous sampling for PTH prior to revision surgery for persistent or recurrent PHPT or autonomous tertiary hyperparathyroidism (THPT) due to end-stage-renal failure between February 1994 and January 2009. Eighteen patients who had undergone a total of 20 revision surgeries were considered eligible and were included in the study. Fifteen of the 18 patients (83%) had their initial parathyroidectomy at another hospital and were referred to our hospital for revision surgery. All revision surgeries were undertaken by two surgeons with considerable experience in endocrine surgery.

### *Methods*

Demographic data, operative data and pre- and post-operative laboratory data were obtained from patients' hospital records. All Tc99m-MIBI-SPECT scans were

reviewed by an experienced nuclear medicine physician, blinded to the outcome of the subsequent revision surgery.

In our study, cure was defined as sustained normal serum calcium and PTH concentrations more than 6 months after parathyroidectomy (33). Persistent hyperparathyroidism was defined as persistently elevated serum calcium and PTH concentrations in consecutive samples within and beyond 6 months after surgery (33).

*Parathyroid selective venous sampling technique*

Parathyroid venous sampling was performed by an experienced intervention radiologist as follows: a 5 Fr MP catheter, with a selective end hole, was introduced via a sheath in the right femoral vein under local anaesthesia and guided by fluoroscopy to each of the jugular, subclavian and brachiocephalic veins, the azygos vein and the vena cava superior and inferior. Blood samples were obtained from several levels along these veins at close distances (1-2 cm), covering the venous drainage of normal anatomical locations as well as potential ectopic locations of parathyroid glands. A total of 30-40 blood samples were collected in whole blood tubes with spray-coated potassium EDTA and immediately put on ice before transportation to the laboratory for PTH measurement. The various sampling sites and any anatomical variation in venous drainage system found at the time of sampling by injecting contrast (Iomeron 300, Bracco Imaging, Konstanz, Germany) were accurately recorded during the procedure.

At the end of the procedure, the catheter was withdrawn and pressure was applied at the point of entry in the femoral vein for approximately 10 minutes until haemostasis was achieved. Regular checks were undertaken for the following 1-2 hours after which the patient was discharged home.

Blood samples were centrifuged and the separated serum was assayed in one batch using an immunochemiluminescent assay (Immulite 2500, Siemens, Deerfield, Il., USA)**.** Using this assay, the normal range of serum iPTH concentration is 1.5-8 pmol/L. The measured PTH concentrations were plotted at the corresponding anatomical sites on the sampling map (Figure 1).

Laboratory screening before the procedure included a coagulation screen and evaluation of renal and thyroid function to establish the safety of contrast administration. If anticoagulation was used, this was temporarily reversed and wherever possible NSAIDs and acetylsalicyl acid were discontinued for a few days before the procedure

Similar to other venous catheterisation procedures, potential complications of SVS include hematoma formation, venous thrombosis, perforation of blood vessels, pseudo-aneurysm, wound infection and side-effects of use of contrast material including anaphylactic reactions and deterioration of renal function (20,34). Patients with a glomerular filtration rate of less than 45 ml/min who underwent SVS were prehydrated using normal 0.9% saline solution.

A selective venous sampling for PTH was deemed to be positive when a gradient of >50% was found between PTH concentrations at a specific anatomical site of sample collection compared to peripheral blood samples obtained at the time of procedure (17,21).

For the purpose of the study, data of each selective venous sampling were reanalyzed by an experienced endocrinologist, blinded to the previously predicted localization and to the outcome of the surgical procedure.

*Non-invasive pre-operative localization studies*

The Tc99m-MIBI-SPECT scan was performed as follows: following intravenous injection of 500 MBq of Tc99m methoxy-isobutyle-isonitrile (MIBI), planar images of the head and neck region and chest were performed at a matrix size of 256 x 256 (10 minutes per frame). Scintigraphy was performed as a dual-phase single tracer examination before each of the 20 revision surgeries. Images were acquired in the supine position, 15 minutes and 2 hours after injection of the radiopharmaceutical. A gamma camera (Toshiba GCA-7200, Tokyo, Japan) equipped with low-energy high resolution (LEHR) collimators was used for image acquisition. Single photon emission computed tomography (SPECT) was performed in a 128 x 128 matrix size, using a step angle of $4^{o}$ and a step time of 35 seconds per step, 90 minutes after the

injection. The filtered back projection was used for image reconstruction, using a Butterworth filter (8 order, subset 12).

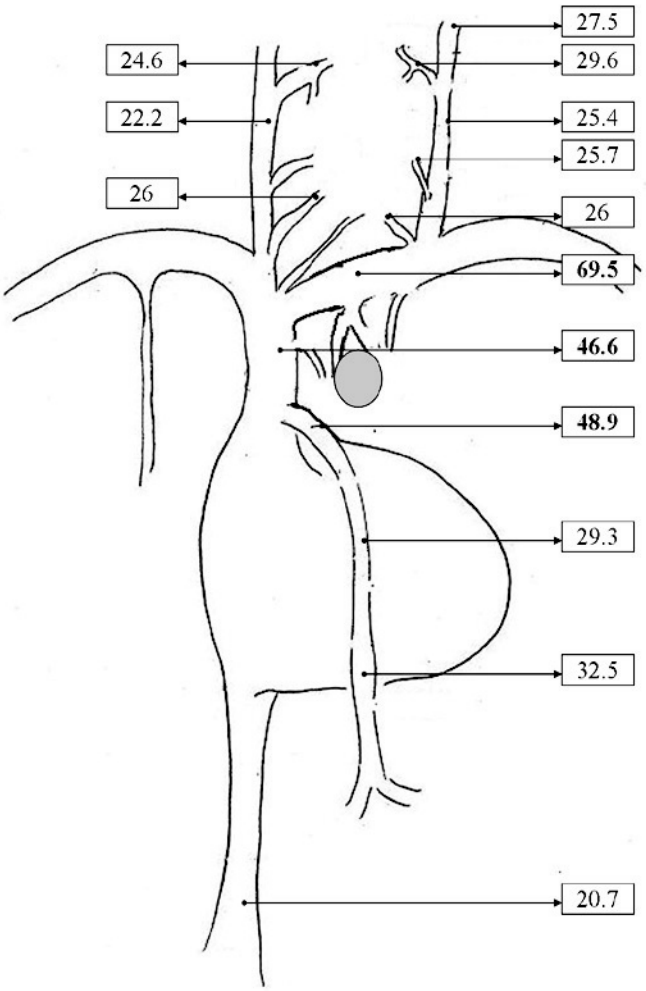


**Figure 1:** PTH concentrations (pmol/L) plotted on the sampling map demonstrating a gradient in the brachiocephalic vein, the superior vena cava and the azygos vein, suggesting a pathological parathyroid gland in the mediastinum, which corresponded with the subsequent operative finding of a pathological parathyroid gland in aorto pulmonary window (shaded area).

*Analysis of data*

For the purpose of the analysis, the neck was divided in 5 designated anatomical areas: four thyroid quadrants, and a fifth "elsewhere" area combining all possible ectopic localizations in the mediastinum (Figure 2). A true positive region was defined as a region from which a pathological parathyroid gland was removed at surgery, and in which the presence of hyperactive parathyroid tissue was suggested in the same region by the preoperative localization test. A true negative region was defined as a region in which no pathological parathyroid gland was found at surgery, and in which no presence of hyperactive parathyroid tissue was suggested in this region by the preoperative localization test. A false positive region was defined as a region in which no pathological parathyroid gland was found at surgery, although the presence of hyperactive parathyroid tissue was suggested in this region by the preoperative localization test. A false negative region was defined as a region from which a pathological parathyroid gland was removed at surgery, although no presence of hyperactive parathyroid tissue was suggested in this region by the preoperative localization test.

True negative and false positive scans, sides or regions could only be determined in patients who were cured after surgery by the finding and removal of a pathological parathyroid gland elsewhere in the neck or mediastinum (this latter condition precluding compromising the sensitivity and specificity by false-negative surgery).

Widely accepted definitions for sensitivity and specificity were used. Sensitivity was thus judged to be the power of the test to identify the presence of pathological parathyroid glands in an exact region of the neck. Specificity was judged to be the power of the test to recognize the absence of a pathological parathyroid gland in an exact region of the neck.

*Statistical analysis*

Statistical analysis was performed using the SPSS 16 software (SPSS inc., Chicago, IL., USA). Results are expressed as mean ± SE unless otherwise stated. The McNemar test was used to assess the difference in localization accuracy between

SVS and Tc99m-MIBI-SPECT scan. A probability level of random difference of $P<0.05$ was considered to be significant.

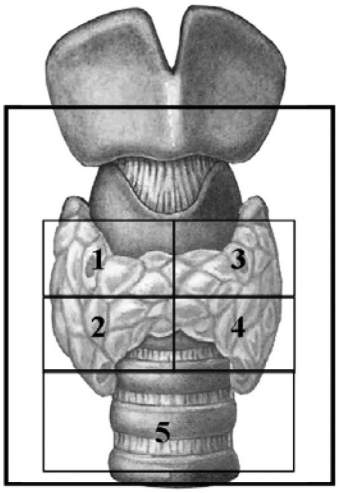


**Figure 2:** Analysis of the ability of SVS and Tc99m-MIBI-SPECT scan to correctly localize a pathological parathyroid gland as confirmed by localization at surgery by dividing the neck into 5 anatomical areas (the four thyroid quadrants and a 5$^{th}$ area of all possible ectopic localizations in the mediastinum).

*Ethical consideration*

The methods used in this study were part of the clinical routine work-up of patients undergoing revision surgery in our hospital. The study was approved by the local Ethics Committee and all patients consented to the use of their data.

## RESULTS

*Pre-operative data*

The study population consisted of 18 patients who underwent a total of 20 revision surgeries. Eleven patients had persistent or recurrent PHPT, which was sporadic in 9 patients, due to a *MEN-1* mutation in 1 patient and due to parathyroid carcinoma in 1

patient. Seven patients had persistent or recurrent autonomous tertiary hyperparathyroidism (THPT) due to end-stage renal failure. Patients had an average of 2 previous surgeries, during which an average of 3 pathological parathyroid glands were removed (Table 1).

*Operative and pathological data*

Surgical approach consisted of bilateral neck exploration in 10 cases, unilateral neck exploration in 8 cases and a sternotomy in 2 cases. Bilateral neck exploration was extended to include mediastinal exploration via sternotomy in 8 cases in which no pathological glands could be found after extensive exploration of the neck.

A single parathyroid adenoma was removed in 5 cases. In 3 of these 5 cases, this was a second adenoma, with an adenoma also removed at initial surgery. All of the 3 second adenomas were found in normal anatomical locations, in the right (n=2) or left (n=1) lower quadrant of the neck. Cure was achieved in 2 of these 3 cases. In the other 2 cases, no pathological glands were removed at initial surgery, and both adenomas were identified in ectopic locations, in the mediastinum (n=1) and high on the left side of the neck on the prevertebral fascia (n=1). Both of these revision surgeries resulted in cure.

One or more hyperplastic gland(s) (n=14) were removed in 12 cases. The majority of hyperplastic glands were identified in normal anatomical locations, in the left upper quadrant (n=4), left lower quadrant (n=3), right upper quadrant (n=1) or right lower quadrant (n=3) of the neck. Three glands were removed from ectopic locations, 2 were in the mediastinum and 1 was intrathyroidal. Only 5 of these 12 revision surgeries (42%) resulted in cure.

A metastasis of a parathyroid carcinoma was removed in 1 case, which resulted in cure lasting for more than 11 months. In the last two cases extensive bilateral neck exploration failed to identify pathological parathyroid glands. Cure was thus achieved in 10 of the 18 patients with persistent or recurrent hyperparathyroidism, 5 after a second surgery, 4 after a third surgery and 1 patient with parathyroid carcinoma was normocalcaemic for almost 1 year after his sixth surgery but has since developed recurrent hyperparathyroidism.

*Predictive value of Tc99m-MIBI-SPECT*

Tc99m-MIBI-SPECT scans performed before revision surgery were negative in 11 of 20 cases. Scans were only able to detect and accurately localize 6 of 20 surgically removed pathological glands and had thus a sensitivity of 30%.

*Selective venous sampling for PTH*

An average number of 36 ± 8 samples were collected during each of the 20 selective venous sampling procedures. A positive gradient in PTH concentration of >50% suggesting the presence of a hyperactive parathyroid gland was documented in all 20 cases. The median of the highest PTH concentration found at sampling was 35 pmol/L (range 16-2202 pmol/L) in patients with persistent or recurrent PHPT and 182 pmol/L (range 39-790 pmol/L) in patients with persistent or recurrent THPT ($P$=0.8). The average gradient was a 4-fold increase in PTH concentration (range 1.5-9), which was not significantly different between patient groups ($P$=0.7). There were no complications reported for any of the 20 sampling procedures.

Sensitivity of SVS for localizing pathological parathyroid glands

Selective venous sampling (SVS) for PTH was able to accurately localize 15 of 20 pathological parathyroid glands removed at 20 revision surgeries. Ten of these 15 glands: 7 hyperplastic glands and 3 adenomas, were found in normal anatomical locations in the left lower (n=3), right lower (n=4), and left higher (n=3) quadrants of the neck. Five of these 15 pathological parathyroid glands were found in ectopic locations: 4 in the mediastinum and 1 high in the left side of the neck on the prevertebral fascia.

All 5 pathological parathyroid glands that were not accurately localized by SVS were hyperplastic in nature with an average size of 7 mm. Four of these glands were removed from normal anatomical locations and one was intrathyroidal. In only 2 of these 5 glands was a gradient found in the correct side of the neck, but not in the correct quadrant.

**Table 1.** Demographic, Laboratory, Operative and Pathology Data of patients who underwent Tc99m-MiBi-SPECT and SVS for PTH prior to revision surgery for persistent or recurrent PHPT or autonomous tertiary hyperparathyroidism (THPT)

| | 11 patients with PHPT (13 operations) | 7 patients with THPT (7 operations) | P value |
|---|---|---|---|
| Age at time of SVS (years) | 52 ± 3 | 49 ± 5 | 0.628 |
| Sex (M/F) | 4:7 | 3:4 | 0.528 |
| Time after initial operation (months) | 121 ± 35 | 75 ± 26 | 0.388 |
| Previous operations (No) | | | |
| 1 | 5 | 4 | |
| 2 | 3 | 2 | |
| 3+ | 5 | 1 | |
| Glands removed at previous operations (No) | | | |
| 0 | 2 | 0 | |
| 1 | 5 | 1 | |
| 2 | 1 | 1 | |
| 3+ | 5 | 5 | |
| Pathology data at previous operation | | | |
| Adenoma | 3/13 (23%) | 2/7 (28%) | 0.787 |
| Hyperplasia | 7/13 (54%) | 5/7 (72%) | 0.444 |
| Carcinoma | 1/13 (8%) | 0 | 0.452 |
| No pathological parathyroid glands | 2/13 (15%) | 0 | 0.274 |
| Pre-operative laboratory data | | | |
| Corrected s-Calcium (mmol/L) | 2.72 ± 0.06 | 2.67 ± 0.08 | 0.623 |
| s-PTH (pmol/L) | 48.9 ± 31.8 | 50.6 ± 14.7 | 0.971 |
| Selective venous sampling | | | |
| Number of samples | 36 ± 3 | 36 ± 2 | 0.966 |
| Gradient of increase in PTH | 4 ± 0.5 | 4 ± 1 | 0.745 |
| Maximum PTH concentration (pmol/L) | 214 ± 166 | 277 ± 106 | 0.797 |
| Post-SVS operative data | | | |
| Bilateral neck exploration | 8/13 (62%) | 2/7 (29%) | 0.160 |
| Unilateral neck exploration | 4/13 (31%) | 4/7 (57%) | 0.251 |
| Sternotomy alone | 1/13 (8%) | 1/7 (14%) | 0.639 |
| Neck exploration combined with sternotomy | 4/13 (31%) | 2/7 (29%) | 0.919 |
| Post-SVS pathology data | | | |
| Adenoma | 4/13 (31%) | 1/7 (14%) | 0.417 |

| | | | |
|---|---|---|---|
| Hyperplasia | 7/13 (54%) | 5/7 (72%) | 0.444 |
| Carcinoma | 1/13 (8%) | 0 | 0.452 |
| No pathological parathyroid glands | 1/13 (8%) | 1/7 (14%) | 0.639 |

PHPT: primary hyperparathyroidism, THPT: tertiary hyperparathyroidism due to end-stage renal failure, s: serum, PTH: parathyroid hormone, No: number

Sensitivity of SVS in relation to parathyroid gland pathology

SVS was able to accurately localize all 5 adenomas (100%), 9 of 14 hyperplastic glands (64%) and one metastasis from a parathyroid carcinoma (100%) subsequently removed at surgery.

Sensitivity of SVS for pathological parathyroid glands in anatomically expected versus ectopic locations

SVS was able to accurately localize 10 of the 14 pathological glands found in normal anatomical locations (71%) and 5 of the 6 pathological glands found in ectopic locations (83%): mediastinum n=4 and high on the left side of the neck on the prevertebral fascia n=1.

A gradient in both the distal brachiocephalic and the left jugular vein (n=2) accurately corresponded with the finding of a pathological parathyroid gland in the neck at surgery in the 2 cases (100%). A gradient in both the proximal brachiocephalic vein and the vena cava superior (n=3) accurately corresponded with a pathological gland in the right lower quadrant of the neck in 2 of 3 cases (67%) and in 1 case no pathological gland could be found despite extensive neck and mediastinal exploration. A gradient in the vena cava superior and the azygos vein accurately corresponded to the presence of a gland in the mediastinum in 2 of 2 cases (100%).

Sensitivity of SVS in relation to pathological parathyroid gland size

SVS was able to accurately localize 8 of 9 pathological glands (89%) with a diameter greater than 1.5 cm, but only 6 of 11 pathological glands (55%) with a diameter smaller than 1.5 cm, 9 of which were hyperplastic (82%).

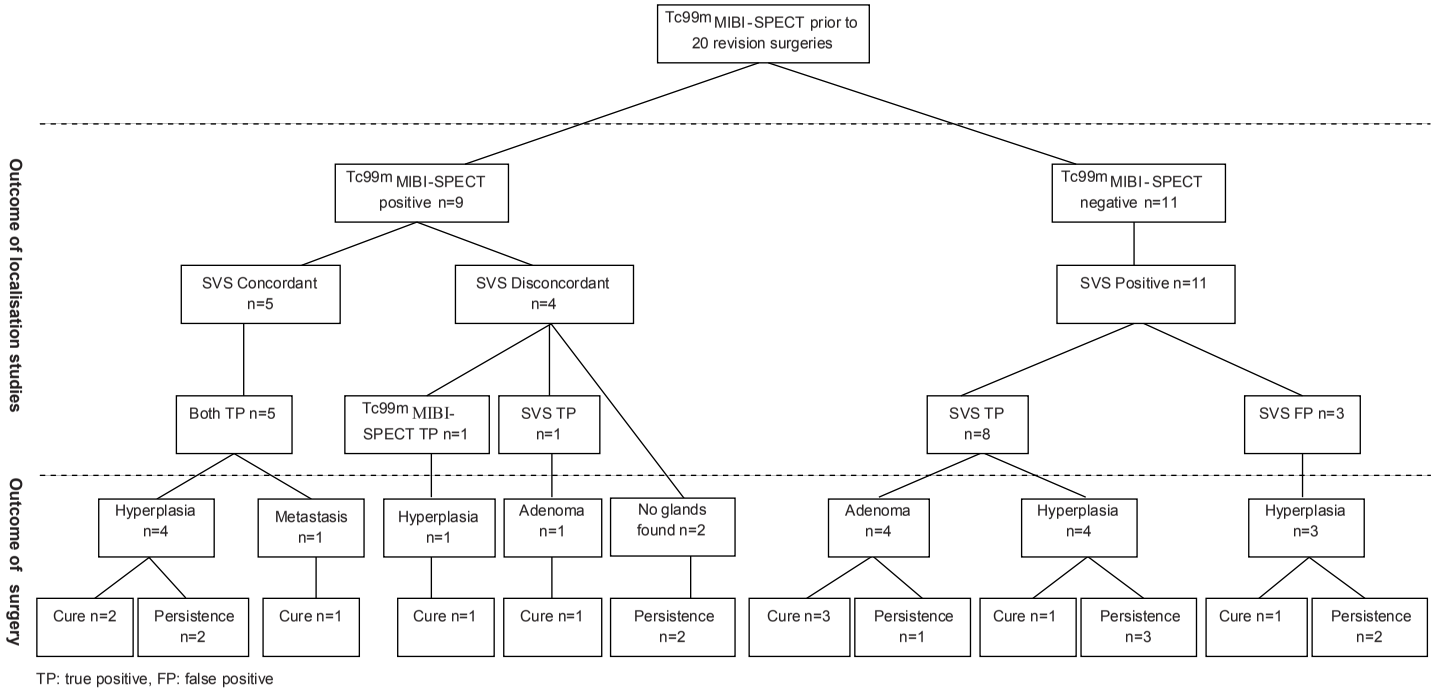


**Figure 3:** Flowchart of the outcome of Tc99m-MIBI-SPECT compared to SVS in 20 patients who underwent revision surgery.

*Sensitivity of SVS for localizing pathological parathyroid glands compared to that of Tc99m-MIBI-SPECT*

Tc99m-MIBI-SPECT and SVS were both performed prior to the 20 revision surgeries, during which 1 pathological parathyroid gland was removed in 16 patients, 2 pathological glands in 2 patients and none in 2 patients despite extensive neck and mediastinal exploration. Of these 20 surgically excised glands, 15 (75%) were accurately localized by SVS compared to only 6 (30%) by Tc99m-MIBI-SPECT. SVS was thus able to accurately localize 10 of the 14 pathological glands (71%), which had been inaccurately localized or completely missed by Tc99m-MIBI-SPECT, while Tc99m-MIBI-SPECT was only able to localize 1 of the 6 pathological glands (17%) inaccurately localized by SVS. Localization accuracy was highest when the outcome of Tc99m-MIBI-SPECT and SVS was concordant (n=5) (Figure 3). The overall ability of SVS to accurately localize pathological glands was significantly higher than that of Tc99m-MIBI-SPECT ($P$=0.012).

## DISCUSSION

The present study demonstrates that the ability of selective venous sampling for PTH to accurately localize residual hyperactive parathyroid glands in patients with persistent or recurrent hyperparathyroidism is significantly higher than that of the non-invasive Tc99m-MIBI-SPECT imaging technique. To date, Tc99m-MIBI-SPECT and US of the neck are the most widely used imaging techniques with a sensitivity of up to 90% prior to initial surgery for PHPT (1-5,7,10,35). However, the sensitivity of these techniques has been reported to be as low as 50% before revision surgery for persistent PHPT (15-17).

Because of the invasive nature of SVS and the high costs of the procedure, SVS has been generally used only prior to revision surgery. In keeping with previous observations, the present study shows the better performance of SVS in the accurate detection of residual pathological parathyroid tissue prior to revision surgery compared to that of the widely used Tc99m-MIBI-SPECT (15-17). In our hands, SVS was indeed able to accurately localize 71% of the pathological glands missed

by Tc99m-MIBI-SPECT. Of significant relevance to the operating surgeon is the localizing sensitivity of 100% when concordance is achieved between SVS and Tc99m-MIBI-SPECT, compared to a sensitivity of only 30% when localization is only dependent on Tc99m-MIBI-SPECT.

The disappointing low predictive value of the Tc99m-MIBI-SPECT imaging technique in patients with persistent PHPT is believed to be due to the usually small size of residual parathyroid glands and to their frequent hyperplastic nature (1,6,35-38). Our findings suggest that the sensitivity of SVS is also decreased in the case of pathological parathyroid glands smaller than 1.5 cm compared to glands greater than 1.5 cm (55% vs. 89%), and in the case of hyperplastic compared to adenomatous residual glands (64% vs. 100%), hyperplastic glands being smaller than adenomatous ones (1.45 cm vs 2.3 cm, $P$=0.21). Although gland size could potentially influence the predictive value of SVS by determining the amount of PTH secreted by the hyperactive parathyroid gland, we were unable to demonstrate a correlation between the gradient in PTH concentration as measured at SVS and the size of the pathological parathyroid gland removed at surgery.

One of the most frequently reported causes of persistent hyperparathyroidism is an ectopic mediastinal location of a pathological parathyroid gland (11,39). Our data and those of others demonstrate a high sensitivity of SVS ranging from 66% to 100% for the localization of these ectopically located glands (17,40). In keeping with previous reports (22), we also observed that SVS was able to accurately localize all ectopically located pathological glands in the mediastinum by the finding of a gradient in the superior vena cava (SVC) alone, or by the finding of a simultaneous gradient in the SVC and in the azygos vein and/or in the brachiocephalic vein. A PTH gradient found only in the brachiocephalic vein remains, however, an interpretational challenge. In contrast to Nilsson *et al.* (22), who suggested that a gradient in the proximal brachiocephalic vein or the SVC corresponded to a mediastinal parathyroid gland in all cases, we observed that a simultaneous gradient in the SVC as well as in the azygos vein was necessary for conclusive evidence for a hyperactive parathyroid gland in the mediastinum. A gradient in the distal brachiocephalic vein was less specific in the study reported by

Nilsson *et al.* (22), corresponding to a mediastinal gland in 86% of cases and to a cervical gland in 14% of cases. Our data suggest, however, that a gradient in the distal brachiocephalic vein corresponded to the localization of a pathological gland in the left side of the neck in 100% of cases.

In persistent or recurrent hyperparathyroidism, previous surgeries may disturb venous anatomy which jeopardizes the localizing ability of radiotracer techniques, such as Tc99m-MIBI-SPECT, and sometimes leads to challenging interpretation of venous sampling data. Notwithstanding, our findings demonstrate that in patients with persistent or recurrent hyperparathyroidism the ability of SVS for PTH to detect and accurately localize pathological parathyroid glands is significantly higher than that of the widely used Tc99m-MIBI-SPECT imaging technique. In experienced hands the SVS procedure is safe and devoid of complications. Concordance of both techniques leads to a reassuring sensitivity of 100%. Our data from this study clearly suggest that SVS for PTH should be reinstated as a valuable tool in the armamentarium of localization studies in the pre-operative work-up of patients with persistent or recurrent hyperparathyroidism.

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