Parathyroid Hormone Venous Sampling Before Reoperative Surgery in Renal Hyperparathyroidism

Comparison With Noninvasive Localization Procedures and Review of the Literature

Daniel Seehofer, MD; Thomas Steinmüller, PhD; Nada Rayes, MD; Peter Podrabsky, MD; Julia Riethmüller; Jochen Klupp, PhD; Frank Ulrich, MD; Ralph Schindler, PhD; Ulrich Frei, PhD; Peter Neuhaus, PhD

Objectives: To analyze the predictive values of selective venous sampling (SVS) in our own experience and in a systematic meta-analysis of the international literature and to compare them with the results of noninvasive localization studies before reoperative parathyroid surgery.

Data Sources: Twenty-one consecutive patients with persistent or recurrent renal hyperparathyroidism underwent preoperative SVS and noninvasive imaging. These data were added to a systematic review of the literature on localization studies before reoperative surgery. The literature search included localization studies, recurrent hyperparathyroidism, and reoperation.

Study Selection: Prospective and retrospective studies that provided at least the true-positive rate of 1 procedure were included. Data from initial surgery, hyperfunctioning autografts, and case reports were excluded.

Data Extraction: Thirty-one publications reported on SVS (n=22), technetium Tc 99m sestamibi scintigraphy (n=17), thallium-technetium scintigraphy (n=11), ultrasonography (n=18), magnetic resonance imaging (n=12), and computed tomography (n=13). The overall analysis was performed by dividing the overall number of true- and false-positive results by the total number of patients.

Data Synthesis: Localization by SVS was correct in 20 of 21 patients. In 1 patient with 2 localizations, only 1 was predicted correctly. Therefore, the sensitivity of SVS was at least 90%, with no false-positive results. Overall true- and false-positive rates, respectively, in 31 studies were 71% and 9% for SVS, 69% and 7% for technetium Tc 99m sestamibi scintigraphy, 54% and 16% for magnetic resonance imaging, 55% and 15% for thallium-technetium scintigraphy, 50% and 18% for ultrasonography, and 45% and 14% for computed tomography.

Conclusions: With its high sensitivity, SVS is the gold standard in patients with persistent or recurrent renal hyperparathyroidism and negative results of noninvasive localization procedures. The noninvasive procedure of choice is now technetium Tc 99m sestamibi scintigraphy, with high sensitivity and a low rate of false-positive results.

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EVEN IN EXPERIENCED MEDICAL centers, the failure and complication rates of reoperative parathyroid surgery are markedly increased compared with those of initial operations because of scarring of the tissue planes. Therefore, preoperative localization studies are mandatory before surgery for persistent or recurrent hyperparathyroidism (HPT) to minimize the surgical effort and the complication rate and to minimize the number of nerves at risk. This is particularly true for patients with persistent secondary renal HPT in whom extensive bilateral preparation of the neck was performed during adequate initial surgery.

Owing to the variety of localization techniques available, several algorithms have been suggested for the preoperative workup of patients undergoing reoperative parathyroid surgery. In addition to noninvasive procedures such as ultrasonography (US), scintigraphy (thallium-technetium or, more recently, technetium Tc 99m sestamibi), computed tomography (CT), and magnetic resonance imaging (MRI), the invasive procedure of selective venous sampling (SVS) completes the repertoire of localization procedures. This method was first described in 1969 by Reitz et al[1] in 6 patients with primary HPT. Since then, it has been used mainly before reoperative sur-

Author Affiliations: Departments of General, Visceral, and Transplantation Surgery (Drs Seehofer, Steinmüller, Rayes, Klupp, Ulrich, and Neuhaus and Ms Riethmüller), Radiology (Dr Podrabsky), and Nephrology (Drs Schindler and Frei), Charité Campus Virchow, Humboldt University of Berlin, Berlin, Germany.
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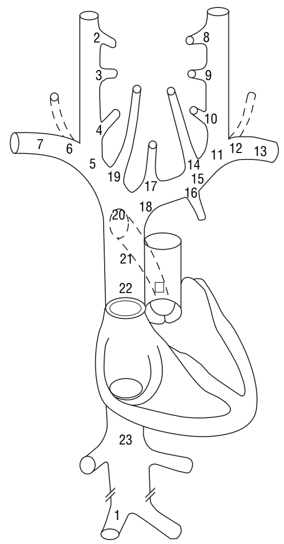

Figure 1. Routine sampling positions for selective venous sampling. If deemed necessary during the procedure, additional samples were obtained.

gery. Owing to the development of more sophisticated radiologic and laboratory methods, results of SVS have improved with time.

The development of technetium Tc 99m sestamibi scintigraphy and the introduction of new MRI techniques have, in parallel, improved the accuracy of noninvasive localization procedures, but SVS is still frequently indispensable when noninvasive procedures have negative or inconclusive findings. Also, the possibility of intraoperative quick measurement of intact parathyroid hormone (iPTH) levels has facilitated intraoperative localization and improved the quality of reoperative parathyroid surgery.[2,3] Intraoperative iPTH measurement is also feasible in patients with renal HPT,[4] but it has not replaced the requirement for preoperative localization studies.

Whereas the results of localization studies, including SVS, before reoperation for primary HPT have been frequently reported, almost no data exist on the use of localization studies, in particular SVS, in patients with persistent or recurrent secondary renal HPT. Therefore, we investigated the value of SVS in our reoperative series for renal HPT and compared the results with those of noninvasive localization studies and the literature in primary and—as far as available—renal HPT.

METHODS

PATIENTS

Twenty-one consecutive patients who underwent reoperative surgery for renal HPT at the Charité Virchow Clinic between January 1, 1999, and December 31, 2002, underwent preoperative SVS as a major localization procedure. All patients had previous conventional bilateral neck exploration at Charité Virchow Clinic (n=4) or were referred after exploration to that clinic (n=17). All patients initially underwent either subtotal or total parathyroidectomy.

Patients were prospectively included if they had either no autotransplantation in the forearm or a negative "Casanova test" result.[5] A modified Casanova test was performed in the present study by side-specific determination of iPTH values in both arms and by determination of systemic iPTH levels 10 minutes after suprasystolic exclusion of the graft-bearing arm. In the case of an iPTH level decrease of 50% or more, the autograft was removed, and further management depended on the iPTH values afterward. Besides SVS, other localization studies were performed in all patients, but no uniform regimen of these investigations was performed. Study choice partially depended on the available studies at the time of referral. The mean age of the patients was 51 years (range, 10-69 years); 11 patients were men and 10 were women. Indications for reoperative surgery were persistent HPT in 8 patients and recurrent disease in 13 patients.

SELECTIVE VENOUS SAMPLING

After puncture of the right femoral vein, a 100-cm 5F cobra or headhunter catheter was introduced and advanced via the right atrium to the superior caval vein with fluoroscopic control. From here, the cervical and mediastinal veins were catheterized following a defined scheme. Blood samples were obtained at fixed positions in the cervical and mediastinal veins (**Figure 1**). Further samples were collected if additional branches or anatomic variations were identified during the investigation so that all accessible side branches were sampled (Figure 1). In addition, the catheter position was documented in a fluoroscopic image after injection of a small amount of contrast medium. All blood samples, approximately 25 to 30 per procedure, were numbered and put on ice immediately. They were sent to the laboratory after completion of the SVS procedure. The whole procedure was performed with electrocardiographic monitoring. All patients were investigated by 1 of 2 radiologists experienced in this technique. Levels of iPTH were measured using routine clinical methods (Elecsys electrochemiluminescence assay; Roche Diagnostics GmbH, Mannheim, Germany). Selective venous sampling was defined as positive when a 1.5-fold increase in iPTH concentration compared with the femoral vein was found, followed by a decreasing gradient in consecutive samples. Based on the obtained results, patients were categorized into 1 (or 2) of the following groups: right cervical, left cervical, thymic/mediastinal region, or no positive gradient.

SURGERY

Patients with suspected cervical recurrence underwent reexploration of the neck via the previous standard transverse incision, mostly by the standard anterior approach. Patients with suspected mediastinal manifestation underwent standard median sternotomy. If deemed necessary or if no parathyroid tissue was localized, intraoperative blood samples at large cervical or mediastinal veins were obtained for quick iPTH measurement.

DEFINITIONS

Intraoperative findings (the gold standard) were correlated with preoperative localization studies. In SVS, prediction of the correct cervical side was considered to be a true-positive result.

Results of the other localization studies (US, CT, MRI, and scintigraphy) were deemed to be true positive if the correct side and localization (upper or lower) were predicted. The sensitivity of a localization study was defined as the proportion of scans that correctly localized all abnormal glands in patients with abnormal glands. If the actual localization of the hyperfunctioning parathyroid tissue remained unknown after reoperation, it was classified as localization unknown. A successful surgical outcome was defined as removal of the major source of PTH secretion, with a decrease in the PTH level to less than 3 times the upper limit of normal and a concomitant decrease in or normalization of the level of calcium phosphate product.

ANALYSIS OF THE LITERATURE

A systematic analysis of the international literature was performed using MEDLINE. The literature search was performed using the following search terms, individually and in combination: *recurrent hyperparathyroidism, localization, ultrasound, MRI, CT, scintigraphy, sestamibi, thallium-technetium, selective venous sampling,* and *reoperation*. In addition, the reference lists of the obtained publications were screened for further relevant publications. Articles on localization studies before initial parathyroid surgery and studies not differentiating between initial and reoperative parathyroid surgery were not included. Prospective and retrospective studies were considered. Studies dealing only with localization of hyperfunctioning autografts and case reports were excluded from the analysis. The following localization studies were included if at least the patient-based (relative) number of true-positive results was available: SVS, technetium Tc 99m sestamibi scintigraphy, thallium-technetium scintigraphy, CT, MRI, and US. If also available, the relative number of false-positive results of the different tests was analyzed. When more than 1 publication included the same patient population, only the most recent publication was included in the overall analysis. The overall true-positive rate was calculated by dividing the overall number of patients with true-positive results by the overall number of patients investigated. In parallel, the overall false-positive rate was calculated.

STATISTICAL ANALYSIS

Descriptive statistics were used to evaluate the individual patient results and the literature review. All values are given as mean and, if applicable, SEM. No statistical tests were considered necessary for the literature analysis.

RESULTS

SURGICAL RESULTS

Twenty (95%) of the 21 patients underwent successful surgery; 19 of them were treated successfully during the first reoperation. One patient (patient 8) underwent initial mediastinal exploration with removal of a parathyroid gland in the aortopulmonary window, but the postoperative iPTH level was still elevated. A second reoperation revealed additional right cervical hyperplastic parathyroid tissue. In 1 patient who underwent 2 surgical explorations at external medical centers previously, no parathyroid tissue was found intraoperatively despite 2 reexplorations. After 23 reexplorations (patients 4 and 8 underwent the procedure twice), the following reasons for recurrence or persistence were found: supranumeric parathyroid glands (n=5), missed glands during the initial operation (n=9; only 2 of them were at ectopic localizations), cervical parathyromatosis (n=3), recurrence caused by the remnant after subtotal parathyroidectomy (n=3), and unknown (n=1, after 2 unsuccessful reexplorations [patient 4]).

The hyperactive parathyroid tissue was removed via cervical incision in 19 patients and via sternotomy in 2 patients (**Table 1**). Histologic investigation confirmed the presence of parathyroid tissue in all 20 patients: 19 had hyperplastic parathyroid tissue and 1 had a parathyroid carcinoma. The mean ± SEM iPTH value in successfully treated patients decreased from 950 ± 150 pg/mL (100.0 ± 15.8 pmol/L) before surgery to 128 ± 47 pg/mL (13.4 ± 4.9 pmol/L) on postoperative day 1. Seven postoperative complications occurred in 5 (24%) of the 21 patients. Unilateral transient recurrent nerve palsy was found in 2 patients (10%), and permanent recurrent nerve palsy was found in 1 patient (5%). One patient each developed a wound infection, thrombosis of the dialysis fistula, transient palsy of the ulnaris nerve, and postoperative bleeding.

RESULTS OF LOCALIZATION STUDIES

Localization was correctly predicted by SVS in 19 of 20 patients who underwent successful surgery. The maximum gradient at the positive site ranged from 1.67 to 29.8 compared with the iPTH value measured at the femoral vein. In patient 8, with 2 different sites of hyperplastic parathyroid tissue, SVS before the initial procedure correctly localized the dominant mediastinal gland, but no right cervical gradient was found. Repeated SVS after the first reexploration revealed an additional right cervical gradient, which was confirmed intraoperatively by removal of hyperplastic parathyroid tissue at this position. In 1 patient, no parathyroid tissue was found during surgery despite 2 extensive surgical explorations; therefore, the correct or incorrect prediction of localization by SVS could not be determined. The suspected localization by SVS was mediastinal, and the other localization studies (US, MRI, and thallium-technetium scintigraphy) showed negative results. Therefore, the sensitivity of SVS was at least 90% in the present series. The only 2 patients who were calculated as having incorrect localization in this definition were 1 with unknown localization and 1 with true-positive plus false-negative results of the first SVS investigation (patient 4). No serious complications occurred during the SVS procedure. One patient developed an inguinal hematoma, which did not require surgical intervention.

The results of the noninvasive localization studies in our patients are given in Table 1 and **Table 2**. The best prediction of localization was reached by technetium Tc 99m sestamibi scintigraphy, with 6 of 8 true-positive results and only 1 false-positive result.

REVIEW OF THE LITERATURE

Thirty-five publications fulfilled the inclusion criteria[6-40]; 4 of these 35 publications[12,15,18,23] were excluded from the overall analysis because of overlapping data, in which case only the most recent publication was included. Thus, 31 publications reporting on the following investigations were

Table 1. Results of Localization Studies, Intraoperative Localization, and Laboratory Values in the Individual Patients

Patient No.	Rec	SVS	US	Sestamibi	ThTc	CT	MRI	Localization of Removed Parathyroid	PTH, pg/mL Pre	PTH, pg/mL Disc	Ca × Po Pre	Ca × Po Disc
1	1	TP	FP	NP	NP	NP	NP	Anterior mediastinum	624	18	3.1	2.6
2	1	TP	NP	TP	NP	NP	NP	High left carotid sheath	1057	36	2.6	2.3
3	2	TP	CN	NP	CN	CN	NP	Left cervical (carcinoma)	1133	105	1.8	1.5
4	1	UK	CN	NP	UK	NP	UK	None	412	392	7.1	4.6
5	1	TP	CN	NP	NP	NP	NP	Lower right cervical	460	98	4.1	3.0
6	1	TP	NP	NP	TP	NP	NP	Lower left cervical	1790	126	4.8	2.4
7	1	TP	CN	NP	TP	NP	CN	Right carotid sheath	2410	3	4.2	1.8
8a	3	FN + TP	CN	NP	NP	NP	FN + TP	Aortopulmonary window	1560	847	5.9	3.2
9	2	TP	NP	TP	CN	NP	NP	Left thyrothymic horn	650	209	3.0	2.2
10	1	TP	CN	TP	NP	NP	NP	Right paraesophageal	727	2	7.2	3.0
11	1	TP	NP	NP	NP	NP	NP	Upper left cervical	525	4	5.8	3.8
8b	4	TP	NP	NP	NP	NP	NP	Right parathyromatosis	847	303	3.2	2.6
12	1	TP	CN	TP	NP	CN	NP	Left thymus	812	3	2.6	3.0
13	1	TP	CN	NP	NP	NP	NP	Left thyrothymic horn	220	75	2.3	2.3
14	1	TP	NP	NP	NP	NP	FP	Upper + lower left cervical	190	19	4.2	2.9
15	1	TP	TP	NP	TP	NP	TP	Lower left cervical	350	171	5.3	3.0
16	1	TP	NP	NP	NP	NP	TP	Upper left cervical	1492	142	5.9	3.4
17	1	TP	TP	TP	NP	NP	CN	Upper left cervical	1719	184	7.9	2.1
18	3	TP	NP	CN	NP	NP	NP	Right parathyromatosis	480	175	4.4	3.2
19	2	TP	TP	TP	NP	NP	TP	Lower left cervical	518	181	2.3	1.9
20	1	TP	FP	FP	NP	NP	NP	Upper left cervical	1800	28	7.9	1.5
21	2	TP	NP	NP	TP	NP	TP	Left thymus	1230	139	5.1	2.1

Abbreviations: Ca × Po, calcium phosphate product; CN, completely negative; CT, computed tomography; disc, at discharge; FN, false negative; FP, false positive; MRI, magnetic resonance imaging; NP, not performed; pre, preoperatively; PTH, parathyroid hormone; Rec, number of recurrent explorations; sestamibi, technetium Tc 99m sestamibi scintigraphy; SVS, selective venous sampling; ThTc, thallium-technetium scintigraphy; TP, true positive; UK, unknown localization; US, ultrasonography.

Table 2. Predictive Value of Localization Procedures in the Study Cohort

	Patients, No. (%) True-Positive Results	Completely Negative Results	False-Positive Results	Unknown Localization*
Ultrasonography (n = 16)	5 (31)	8 (50)	2 (13)	1 (6)
Thallium-technetium scintigraphy (n = 7)	4 (57)	2 (29)	0	1 (14)
Technetium Tc 99m sestamibi scintigraphy (n = 8)	6 (75)	1 (13)	1 (13)	0
Magnetic resonance imaging (n = 9)	5 (56)	2 (22)	1 (11)	1 (11)
Selective venous sampling (n = 21)	20 (95)	0	0	1 (5)

*In 1 patient, no parathyroid tissue was found during surgery; therefore, the correct or incorrect prediction of the tests is unknown.

included: SVS (n=22), technetium Tc 99m sestamibi scintigraphy (n=16) (**Figure 2**), thallium-technetium scintigraphy (n=11) (**Figure 3**), US (n=17) (**Figure 4**), MRI (n=13) (**Figure 5**), and CT (n=13) (**Figure 6**). The overall rate of true-positive results for correct prediction of all hyperfunctioning parathyroid tissue was highest for SVS (71%) (**Table 3**) and technetium Tc 99m sestamibi scintigraphy (69%). In all studies analyzed, only 22 false-positive results (7%; range, 0%-18%) in 323 patients were obtained using technetium Tc 99m sestamibi scintigraphy. Selective venous sampling revealed 57 false-positive results (9%) in 633 patients. All other procedures had markedly lower rates of true-positive results and higher rates of false-positive results (**Figure 7**). For US, the relative number of true-positive results was markedly higher in most studies when only patients with cervical adenomas were analyzed.

COMMENT

The present study of patients with recurrent or persistent renal HPT revealed excellent sensitivity and specificity for SVS. These results were achieved with a standardized, meticulous realization of the procedure by experienced investigators. Despite successful preoperative localization studies in more than 90% of patients and the resulting limited exploration, the complication rate of reoperative parathyroid surgery was relatively high in the present series. This parallels the experience of other medical centers and emphasizes the importance of preoperative localization studies before reoperative parathyroid surgery.

Most cases of persistent or recurrent HPT were due to missed cervical glands at the primary operation or su-

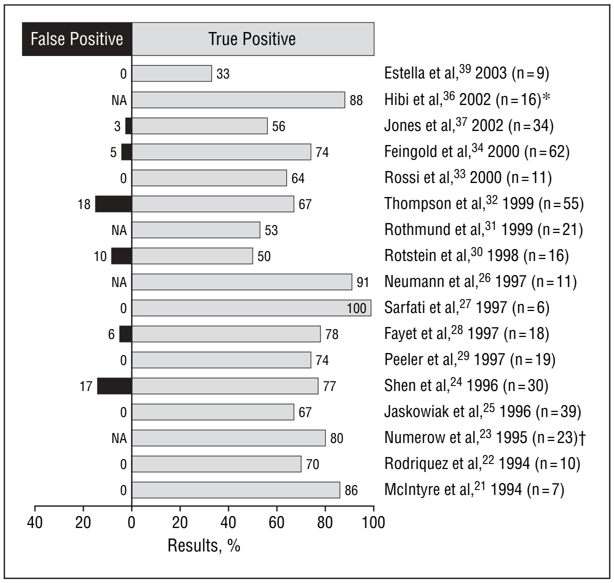

Figure 2. Literature overview of technetium Tc 99m sestamibi scintigraphy results before reoperative parathyroid surgery. Asterisk indicates study of patients with renal hyperparathyroidism; dagger, excluded from the overall analysis because of inclusion of the same patients in a more recent publication by the same group; and NA, not available.

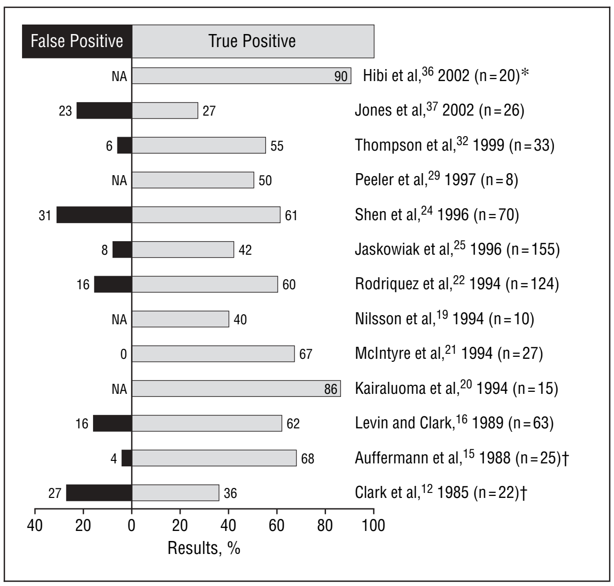

Figure 3. Literature overview of thallium-technetium scintigraphy results before reoperative parathyroid surgery. Asterisk indicates study of patients with renal hyperparathyroidism; dagger, excluded from the overall analysis because of inclusion of the same patients in a more recent publication by the same group; and NA, not available.

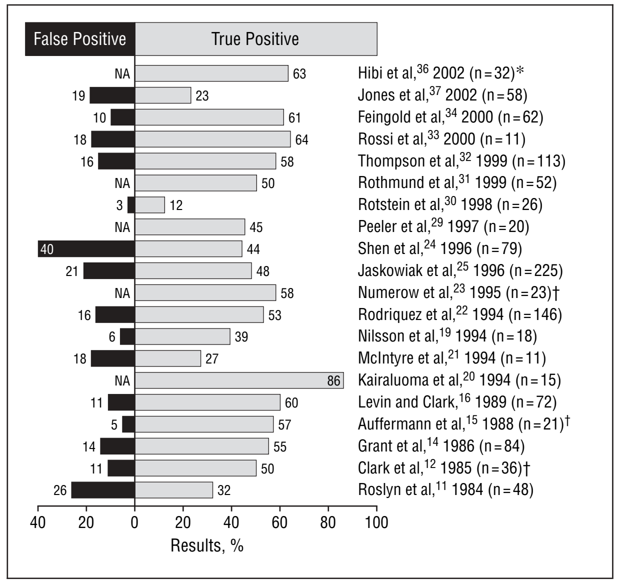

Figure 4. Literature overview of ultrasonography results before reoperative parathyroid surgery. Asterisk indicates study of patients with renal hyperparathyroidism; dagger, excluded from the overall analysis because of inclusion of the same patients in a more recent publication by the same group; and NA, not available.

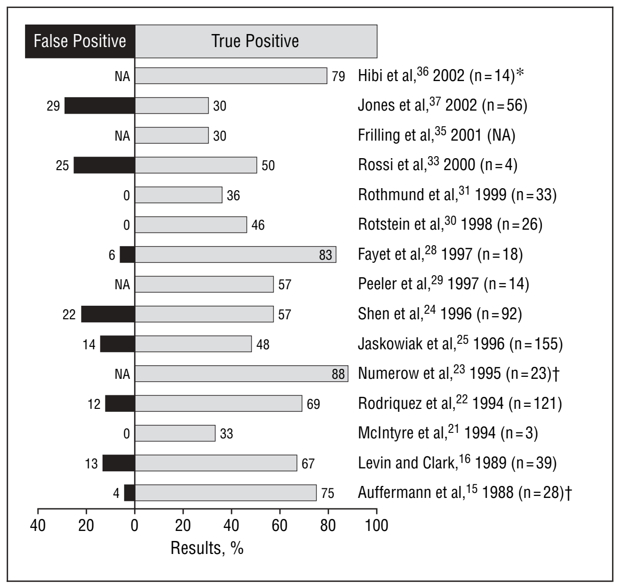

Figure 5. Literature overview of magnetic resonance imaging results before reoperative parathyroid surgery. Asterisk indicates study of patients with renal hyperparathyroidism; dagger, excluded from the overall analysis because of inclusion of the same patients in a more recent publication by the same group; and NA, not available.

pranumeric glands. Only 10% of the patients had parathyroid tissue in the mediastinum, which was not reachable via the collar incision. These numbers are similar to the experience of most medical centers[32] and underline the importance of an adequate initial operation.

Analysis of the literature revealed very few data on invasive and noninvasive localization studies in patients with persistent or recurrent renal HPT. Therefore, all of the literature on localization procedures before reoperative primary and renal HPT was analyzed. The overall true- and false-positive rates of the different procedures were similar in primary HPT and the few published series in patients with renal HPT.

Computed tomography had an overall low rate of true-positive results (45%) and, in most studies, a relatively high rate of false-positive results (14%) (Figures 6 and 7). In 10 of 13 studies, the rate of true-positive results was less than 50%. Therefore, in general, CT adds little useful information to the other investigations. Only in difficult cases with otherwise negative localization studies might CT be indicated. In several studies, the predictive value of CT was better in enlarged mediastinal than in enlarged cervical parathyroid glands. The analyzed studies revealed no trend toward better results in the more recent studies. This might be related to the fact that several studies cover a relatively long study period with different qualities of CT. In future analyses, superior rates of true-positive results might be achievable because of technical progress.

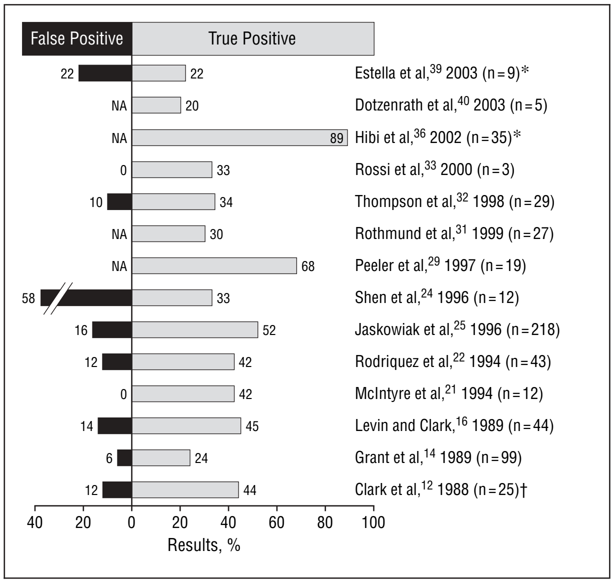

Figure 6. Literature overview of computed tomography results before reoperative parathyroid surgery. Asterisk indicates study of patients with renal hyperparathyroidism; dagger, excluded from the overall analysis because of inclusion of the same patients in a more recent publication by the same group; and NA, not available.

Magnetic resonance imaging had a true-positive rate of 50% in our experience, which correlates with the overall true-positive rate of 54% in the literature review (Figures 5 and 7). In total, the true-positive rate for MRI is 10% better than for CT before reoperative parathyroid surgery. From the single studies, 7 of 13 revealed a true-positive rate of 50% or more. Thus, from the present experience, MRI rather than CT should be used. Regarding the technical progress in MRI studies, the same might be true as stated previously for CT.

High-resolution US (10 MHz) is efficacious in showing the parathyroid glands in the neck. Particularly before primary surgery, excellent results have been reported. In the reviewed literature, most studies report a low rate of true-positive results before reoperative parathyroid surgery (Figures 4 and 7). This rate is markedly increased in the case of cervical localization of the enlarged parathyroid glands by an experienced investigator. On the other hand, atypically localized enlarged cervical parathyroid glands are occasionally difficult to detect; for example, adenomas in the tracheoesophageal groove or in the carotid sheath, as described even by skilled investigators.[41] Nevertheless, US is a cheap and useful first-line diagnostic procedure. In experienced hands, it is an ideal completion to technetium Tc 99m sestamibi scintigraphy, especially if cervical localization is predicted. The sensitivity of US might be increased by aspiration and iPTH measurement.[42,43] In addition, US is useful for the evalu-

Table 3. Reported Results of Selective Venous Sampling in Patients With Persistent or Recurrent Hyperparathyroidism

	Patients, No.		Results, %		
Source	**Total**	**With SVS**	**True Positive**	**False Positive**	**Complications**
Eisenberg et al,[6] 1974	50	20	85	5	NA
Wang,[7] 1977	112	16	88	12	NA
Edis et al,[8] 1978	51	9	44	56	None
Roslyn et al,[11] 1981	26	17	88	6	NA
Prinz et al,[9] 1981	27	18	50	1	NA
Brennan et al,[10] 1981	75	75	55	5	NA
Clark et al,[12] 1985*†	36	16	75	0	None
Granberg et al,[13] 1986	46	46	80	13	NA
Cheung et al,[17] 1989	83	23	39	26	NA
Levin and Clark,[16] 1989	81	31	68	0	NA
Sugg et al,[18] 1993†	223	86	88	10	None
Nilsson et al,[19] 1994	29	29	93	0	None
Rodriquez et al,[22] 1994‡	174	67	69	15	None
McIntyre et al,[21] 1994	43	15	53	0	NA
Shen et al,[24] 1996	102	30	77	23	NA
Jaskowiak et al,[25] 1996	288	98	76	4	NA
Peeler et al,[29] 1997	16	4	75	NA	NA
Fayet et al,[28] 1997	18	12	83	0	NA
Rotstein et al,[30] 1998	28	26	50	0	NA
Rothmund et al,[31] 1999	68	15	53	NA	NA
Frilling et al,[35] 2001	34	NA	82	NA	NA
Jones et al,[37] 2002§	235	64	75	12	NA
Udelsman et al,[38] 2003	56	7	86	0	NA
Estella et al,[39] 2003	9	9	89	0	None

Abbreviations: NA, not available; SVS, selective venous sampling.
*Includes 5 patients with renal hyperparathyroidism.
†Excluded from the overall analysis because of inclusion of the same patients in a more recent publication from the same group.
‡Includes 19 patients with renal hyperparathyroidism.
§Includes 6 patients with renal hyperparathyroidism.

ation of thyroid nodules, and it might be used during surgery for the detection of parathyroid adenomas.[44]

Thallium-technetium scintigraphy has a markedly lower rate of true-positive results combined with more false-positive results. Therefore, technetium Tc 99m sestamibi scintigraphy should be preferred (Figures 3 and 7).

Technetium Tc 99m sestamibi scintigraphy revealed the highest overall true-positive rate of the noninvasive localization studies (69%), and its false-positive rate was very low. In the analyzed literature, only 22 false-positive results (7%) in 323 patients were reported. Only the present study and 1 other study[36] report the use of technetium Tc 99m sestamibi scintigraphy before reoperative surgery in renal HPT with a good true-positive rate of 75% to 90%. This is in contrast to the situation before initial surgery for renal HPT, in which only 53% of hyperplastic glands were detected by technetium Tc 99m sestamibi scintigraphy.[45] The use of technetium Tc 99m sestamibi scintigraphy for primary and reoperative parathyroid surgery has been reviewed recently in a meta-analysis.[46]

Better results in patients with renal failure are reported by using iodine I 123 and technetium Tc 99m sestamibi subtraction scintigraphy combined with single-photon emission CT, which correctly localized 77% of hyperplastic glands.[47] With this modified technique, excellent results (93% true-positive results) have been demonstrated before reoperation for renal HPT.[48] Although increased experience with technetium Tc 99m sestamibi scintigraphy in patients with persistent or recurrent renal HPT is required, initial results are promising. Particularly because of its low rate of false-positive results, technetium Tc 99m sestamibi scintigraphy is the imaging procedure of choice before reoperation of primary and renal HPT.

Selective venous sampling has been demonstrated to be a highly sensitive and specific localization procedure in persistent or recurrent primary HPT in the literature. Excellent results have also been found in secondary HPT in the present analysis and a few other studies.[12,22,36,37] However, in 7 (33%) of 22 publications (Table 3), the true-positive rate of SVS was only approximately 50%, which might be due to acquisition of too few blood samples during SVS, extensive previous exploration, or a difficult patient population. However, SVS also has limitations, as shown in the present analysis in the patient with 2 adenomas, in whom initially only the dominant one was localized correctly.

In the only other available publication involving a reoperative series in patients with renal HPT, Hibi et al[36] reported good results in 30 patients using noninvasive localization procedures without applying SVS. Their high sensitivity for thallium-technetium and technetium Tc 99m sestamibi scintigraphy (89%), CT (89%), and MRI (79%) could not be confirmed in the present study or in most other studies in patients with primary HPT (Figure 7).

The disadvantage of SVS is its invasive character, although in our own experience, morbidity with SVS is low. In the literature, most researchers do not include information about the complication rate. In the relatively few publications that include this information,[8,12,18,19,22,39] no single complication is reported in all 124 investigations. However, the risks of applying contrast medium, including renal failure (which was present in most of our patients with renal HPT) and anaphylactic reactions, remain, although the incidence is low. In addition, SVS is a relatively expensive investigation that requires high technical and personal effort, although the costs of SVS could be reduced over the years. Comparison of costs in different countries and even different hospitals is difficult. In our hospital, SVS costs approximately €500, including laboratory costs for 25 iPTH measurements. Magnetic resonance imaging is only marginally more expensive, at approximately €550, but technetium Tc 99m sestamibi scintigraphy costs about half (approximately €310). Cervical US is the cheapest investigation (€35). However, in other medical centers and other countries, much higher expenses are reported.

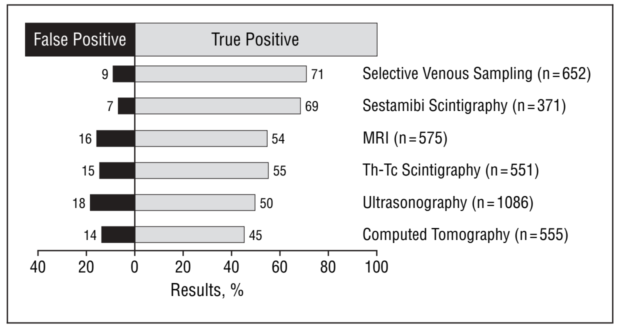

Figure 7. Comparison of overall true-positive and false-positive results of localization studies before reoperative parathyroid surgery in patients with persistent or recurrent hyperparathyroidism. Sestamibi indicates technetium Tc 99m sestamibi; MRI, magnetic resonance imaging; and Th-Tc, thallium-technetium.

The previously mentioned characteristics make SVS inappropriate as a first-line localization study in patients undergoing reoperative parathyroid surgery but the gold standard in cases of negative results for noninvasive localization procedures.

In summary, although one has to consider the high costs of localization studies (especially SVS), the reduced complication rate and the improved success rate with correct localization procedures surpass financial considerations for cervical reexploration. In our opinion, 2 concordant localization procedures should be available before reoperative parathyroid surgery. The algorithm used should depend on the experience of the investigators, the specificity and sensitivity of the different procedures at every medical center, and the center-specific costs of these procedures. On the basis of the literature review and our own experience, we suggest the following algorithm of localization studies before reoperation for renal HPT. First, if present, exclusion of a hyperfunctioning autograft in the forearm is required; for example, by technetium Tc 99m sestamibi scintigraphy or Casanova test. Thereafter, cervical US (as a cheap first-line study and especially for the exclusion of concomitant thyroid disease) and technetium Tc 99m sestamibi scintigraphy are recommended. Despite improvements in CT and MRI, both have relatively low sensitivity in reoperative parathyroid surgery and are now recommended only in cases with negative or inconclusive scintigraphy and SVS findings. Selective venous sampling, performed by an experienced investigator acquiring 20 to

30 samples per investigation, shows excellent results and is the gold standard in cases of inconclusive noninvasive localization studies.

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Correspondence: Daniel Seehofer, MD, Department of General, Visceral, and Transplantation Surgery, Charité Campus Virchow, Humboldt University of Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany (daniel.seehofer@charite.de).

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