Minimally invasive surgery of solitary parathyroid adenomas in patients with primary hyperparathyroidism;

Role of ultrasonography with supplemental computed tomography

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Abstract

Purpose To determine the role of ultrasound (US) with supplemental computed tomography (CT) in patients with primary hyperparathyroidism (pHPT) to undergo minimally invasive surgery (MIS) instead of conventional neck exploration.

Materials and methods US and CT were performed in 61 consecutive patients with pHPT (part I) to identify and localize solitary adenomas for resection by MIS and to provide a surgical roadmap. In part II, involving 33 consecutive patients, CT was performed only when no solitary adenoma was identified with US, or for roadmap information. MIS was considered successful when serum calcium levels normalized and remained stable.

Results In part I, 46 definite solitary adenomas were found by US and two additional ones by CT. MIS was successful in 45 patients and failed once. In part II, US identified 23 solitary adenomas and CT found one. MIS was successful in 22 patients and failed in two. Combined results of 94 patients demonstrated successful MIS in 67 (71%), with 64 of them selected by US alone (95% CI: 61-80).The sensitivity of US in diagnosing solitary adenomas was 78% (95% CI: 67-86) with a positive predictive value of 96% (95% CI: 88-99).

Conclusion US evaluation of patients with pHPT allowed successful selection for MIS in more than two thirds of cases, with additional CT being chiefly useful for surgical road-mapping.

Introduction

Primary hyperparathyroidism (pHPT) is a relatively uncommon disease in adults with an estimated prevalence of 1 : 700 in the United States [1]. Women, particularly postmenopausal, are affected 2 to 3 times more frequently than men [2]. Clinical manifestations of pHPT include renal calculi, gastric ulcers, bone cysts and mental depression. Its diagnosis is based on elevated serum calcium and parathyroid hormone levels. In the vast majority (approximately 85%) of patients, a solitary parathyroid adenoma is the cause of the disease [3 4 5]. Multiglandular involvement, either caused by multiple adenomas (4%) or diffuse hyperplasia (10%), is much less common [4]. Rare causes of pHPT are parathyroid cyst and carcinoma.

The common treatment of pHPT is conventional neck exploration (CNE) [6]. With this procedure, the neck is explored in order to identify all parathyroid glands and to remove the enlarged ones. CNE is a time consuming and surgically demanding procedure because of the many vulnerable structures of the neck that need to be explored to allow identification of the parathyroid glands. Nevertheless, in experienced hands, CNE is curative in 95% of cases with few reported complications [6 7 8].

Recently, we introduced minimally invasive surgery (MIS) by use of US and CT imaging to treat patients in whom the disease is caused by a solitary adenoma, and in this earlier report, which included 61 patients of the current study, we highlighted the clinical aspects of this method [9]. During the MIS procedure, the surgeon, guided by an imaging-based roadmap, carefully approaches the lesion through a small incision in the skin and removes it with minimal damage to the vulnerable structures of the neck. Advantages of MIS compared to CNE include reduction in operation time and hospital stay with subsequent decreased costs, improved cosmetic results, and restriction of postoperative fibrosis to the immediate area of the removed gland, facilitating re-operation in case of recurrence of disease [10].

The typical adenoma is small, usually not palpable because its consistency is equal to that of fat, and is often hidden among the structures of the neck. Consequently, a high accuracy is required in diagnosing and localizing the solitary lesion. In addition, accurate determination of its relationship with the surrounding structures is needed in order to perform MIS successfully.

The purpose of the current study was to investigate prospectively the role of ultrasonography (US) as the primary imaging modality for identification and localization of parathyroid adenomas in patients with pHPT to undergo MIS. As the surgical technique was relatively new when we initiated this study and we were uncertain about the full potential of US in facilitating the surgery, we used computed tomography (CT) as a supplemental test to increase confidence in lesion diagnosis and to provide an operator-independent roadmap for the surgeon.

Materials and methods

Overall design

The study population consisted of consecutive patients admitted to our institution who were scheduled for surgical treatment of clinically proven pHPT, i.e. a blood serum parathyroid hormone level higher than 8 pmol/L and/or a serum calcium level higher than 2.60 mmol/L. Ninety-four patients with pHPT were enrolled, 21 of them were men and 73 women, with a mean age of 58 (range 17-84). The median serum calcium level was 2.82 mmol/L (normal 2.20-2.60 mmol/L; range 2.42-3.60 mmol/L), the median serum parathormone was 12.2 pmol/L (normal <8 pmol/L in normocalcemic state; range 4.9-234.0 pmol/L). One or more manifestations of the disease were present in 40 (43%) patients; 21 had renal stones, 20 suffered from malaise/fatigue and 10 patients from bone/joint pain.

Two distinct diagnostic strategies were followed. In the first (part I, 61 patients), performed from October 1994 through April 1997, all patients underwent both US and CT imaging of the neck. In the second (part II, 33 patients), performed from May 1997 through April 1998, all patients underwent US, and supplemental CT was performed only when no solitary adenoma was identified by US or when requested by the surgeon for additional road-mapping. Eighty-nine of the 94 US examinations were performed and interpreted by one radiologist (AvD). This radiologist also interpreted the US findings of the remaining five patients whose examinations were performed by an experienced sonographer. In all cases the US findings were interpreted without knowledge of any prior imaging studies, if present. All CT images were interpreted by the same radiologist with knowledge of the US findings, and the final diagnosis was based on the combined results. When the final preoperative diagnosis of a definite solitary adenoma was made, the patient was scheduled for MIS, and in all other cases CNE was performed. The study was approved by the Institutional Review Board, and informed patient consent was obtained in all cases. All patients who were scheduled for MIS had a repeat US examination immediately prior to the operation with the neck extended in the position in which surgery was going to be performed. The previously diagnosed solitary adenoma was then localized again in the presence of the surgeon, the surgical approach assessed and the optimal incision site marked on the skin of the patient.

Ultrasound imaging

The equipment used were real time units with 4-7 mHz and 5-10 mHz transducers (HDI 900 and 3000, Advanced Technical Laboratories, Bothel WA, USA). Examination was performed with the patient in supine position and the neck extended. The area from the carotid bifurcation to the deepest accessible part of the mediastinum was scanned in longitudinal and transverse planes. Graded compression was used to improve visualization of the deep paratracheal and para-esophageal areas, and, in case of doubt, to differentiate between an intra- or extrathyroidal location of a lesion. When a possible parathyroid lesion was identified, color-Doppler was applied to determine the presence of vascularity of the lesion and/or to identify a vascular pedicle favoring the diagnosis of a parathyroid adenoma. Lesion mobility during swallowing and/or deep breathing was also observed to allow differentiation from structures such as para-carotid cervical lymph nodes or the longus colli muscle. The thyroid gland was also evaluated and assessed for the presence of disease. The initial US examination required approximately 15 minutes and the preoperative repeat examination about 5 minutes.

Spiral Computed Tomography imaging

Contrast-enhanced CT scanning was performed with the patient in supine position and the neck in slight extension with the shoulders pulled down as much as possible. Ninety mL of non-ionic contrast medium (Isovist, Schering M, Berlin, Germany) were given intravenously with a rate of 2 mL/sec. Imaging was initiated 25 sec. after the beginning of the administration of the contrast medium. In a single breath-hold the volume from the level of the mandibular angle to that of the aortic root was scanned. A table speed of 5 mm/sec. and a slice thickness of 5 mm with a gantry rotation time of 1 sec. were applied with a reconstruction index of 3 mm. The obtained images were evaluated on hard copy and in cine loop using a dedicated computer workstation (EasyVision workstation; Release 2.1, Philips Medical Systems, Best, The Netherlands).

Grading of adenomas by Ultrasound and Computed Tomography

Ultrasound: The normal parathyroid glands are oval or bean-shaped and measure on average 6 mm in length with a mean weight of 40 mg. They contain a considerable amount of stromal fat [11] and are generally not visualized with current US equipment [12]. The US diagnosis of a typical 'definite' adenoma was made when a lesion was visualized with a homogeneous hypo-echoic reflection pattern relative to thyroid tissue (**Figure 1**) and showing the following characteristics. Typically, the shape varied from round/oval to elongated with an alignment in a craniocaudad orientation and a diameter of at least of 8 mm when round or up to 3 cm long when elongated [5 13 14 15]. In addition, the typical adenoma was located closely to the

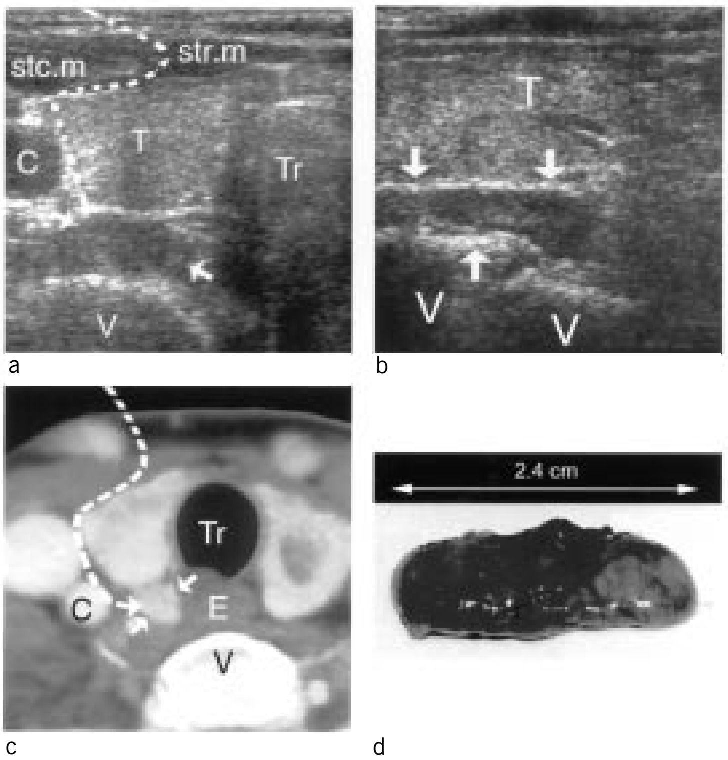

Figure 1 *Patient with a solitary adenoma, superior type.*

(a) Transverse US image of the neck demonstrating the adenoma (between arrows) as a hypoechoic lesion behind the right thyroid lobe, allowing the diagnosis of a definite adenoma. The surgical approach is drawn with a dotted line.
(b) Longitudinal US image showing the adenoma as an elongated mass (between arrows) located behind the thyroid, consistent with a 'superior type' adenoma.
(c) Transverse CT image of the neck at the same anatomic level as figure 1a showing the adenoma (between arrows) and surrounding structures. The surgical approach is drawn with dotted line.
(d) Surgical specimen of the adenoma. Weight 705 mg.
Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus, stc.m = sternocleidomastoid muscle, str.m strap muscles.

thyroid gland, or more caudad in the paratracheal or para-esophageal space. Essential for the diagnosis of a parathyroid adenoma was that the lesion retained its relationship with the thyroid gland during swallowing and deep breathing and did not show a central hilum.
Furthermore, any oval, elongated or lobulated lesion in the same location and with

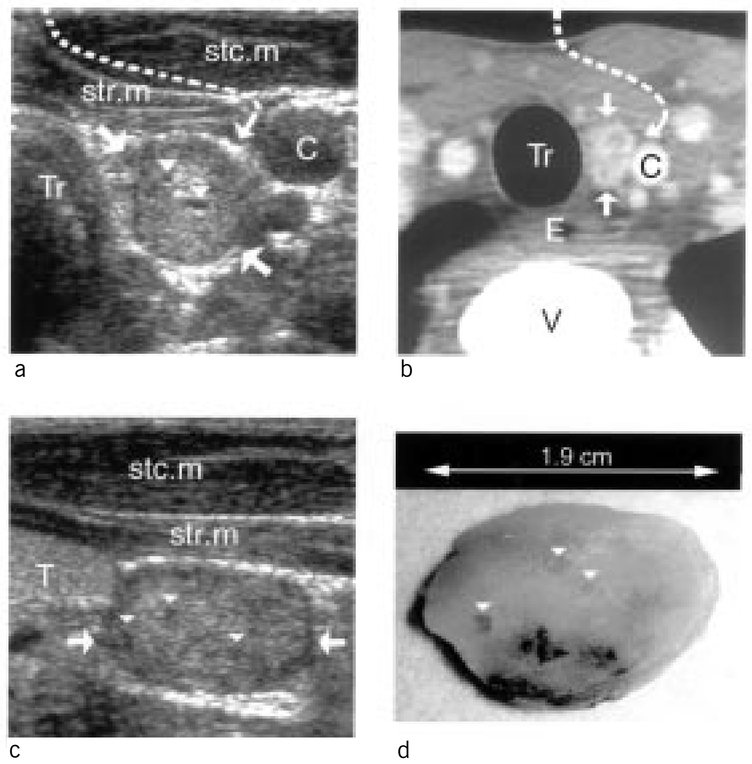

Figure 2 *Patient with a solitary adenoma, inferior type.*

(a) Transverse US image demonstrating the adenoma as an oval echogenic lesion (arrows) with small cystic changes (arrow heads). The surgical approach is drawn with dotted line.
(b) Transverse CT image corresponding to figure 2a demonstrating the adenoma (arrows) and the surgical approach (dotted line).
(c) Longitudinal US section showing that the adenoma (arrows) is located just caudad to the thyroid gland and close to the strap muscles, corresponding with an 'inferior-type' adenoma. Few small cysts (arrow heads) are present.
(d) Surgical specimen of the adenoma demonstrating the multiple small cysts (arrow heads). Weight 1287 mg.
Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus, stc.m = sternocleidomastoid muscle, str.m strap muscles.

the same mobility, but with an increased and/or irregular reflection pattern, cystic changes (**Figure 2**) and/or calcifications representing degeneration [13 14] and measuring from 1-2 cm to approximately 5 cm in length, was also considered a definite adenoma. A subcapsular, intrathyroidal lesion with the characteristics of a parathy-

roid adenoma was considered a definite parathyroid adenoma when the thyroid was otherwise normal and when there was no evidence of an adenoma elsewhere. A poorly visualized lesion with localization and movement at swallowing suggestive of adenoma was also considered a definite adenoma when the lesion showed clear vascularity by color Doppler (**Figure 3**).
A lesion was considered an 'equivocal' adenoma in case its characteristics did not completely fulfill the criteria given above. A lesion was diagnosed as no adenoma when its mobility during swallowing was not related to that of the thyroid unless an aberrant location e.g. in the carotid sheath was considered or when an evident central hilum was visualized and also the shape, size and reflection pattern were compatible with a lymph node. A patient was considered to have a definite 'solitary' adenoma when a definite adenoma as described earlier was the only identified lesion. In all other instances, i.e. when an equivocal solitary lesion, definite or equivocal multiple lesions, or no lesions were found, the diagnosis of 'no definite solitary adenoma' was made. When the solitary adenoma was located posterior to the thyroid lobe near the mid portion, it was called a 'superior type' adenoma (**Figure 1**). It was called an 'inferior type' when it was located near the lower pole of a thyroid lobe or inferior to it and having, at least in part, a close relationship with the anterior muscular wall of the neck (**Figure 2**). Any other location was considered 'aberrant'.

Computed Tomography: The images were analyzed with knowledge of US findings. In a case of a definite adenoma by US the diagnosis was not changed when the CT and US findings were compatible; otherwise the final diagnosis was equivocal adenoma. Criteria were that either the adenoma was visualized by CT as a contrast-enhancing lesion in the same location and with the same size as seen with US or, in case of a close relationship with the thyroid gland by US, the lesion was only recognized as a local bulge of the contour of the thyroid at the same location as seen with US.
When a lesion was diagnosed by US as an equivocal adenoma because of poor visualization, it was considered a definite adenoma when it was visualized by CT as a contrast enhancing lesion in the same location and with the same size as seen with US. In case of a lesion, well visualized by US but diagnosed as an equivocal adenoma because it did not fulfill the other criteria as described earlier, the US diagnosis was not changed by the CT findings.

When by CT an enhancing lesion with the size and location compatible with a parathyroid adenoma was found which was not visualized by US, it was considered a definite adenoma only if it was located in an area not well accessible to US examination, such as the deep para-esophageal and mediastinal regions; otherwise the lesion was considered an equivocal adenoma.

Surgical procedure, histopathology and follow-up

Guided by the imaging-based 'road map', MIS was begun with a 2-cm, transverse incision at the medial border of the sternocleidomastoid muscle at the site of the skin marking. After lateral mobilization of the muscle, internal jugular vein and common carotid artery and medial mobilization of the strap muscles and thyroid gland, the tracheo-esophageal groove was entered and the enlarged gland was identified and removed (**Figure 1**). If during MIS no lesion could be identified, the surgery was converted to CNE. Surgery was qualified as successful when the serum calcium levels normalized within 24 hours and remained stable for at least 6 months. The surgical specimens were weighted in the pathology department, and histopathological examination was performed by the pathologist to assess the presence of parathyroid tissue. The lesions were considered to represent adenoma when at histological evaluation parathyroid tissue was found. Histological differentiation between adenoma and hyperplasia was not made in our institution [16].

Statistical analysis

The data were analyzed statistically using two different approaches. The first analyses were performed while considering the *patients as the units of analysis.* As only definite solitary adenomas were considered eligible for MIS, the imaging results were categorized as patients with the preoperative diagnosis 'solitary adenoma' or 'no solitary adenoma'. In other words, the imaging was used as a screening test yielding either 'solitary adenoma - eligible for MIS' or 'no solitary adenoma - not eligible for MIS'. To obtain sensitivity, specificity and predictive values of this screening test, a gold standard test indicating whether a patient in reality was suitable for MIS, is required. In this study, the latter can only be established with confidence after surgery and follow-up. Therefore, the final diagnosis serves as the gold standard in this study. The final diagnosis was made on the basis of the findings during surgery combined with the course of post-surgical serum calcium levels. If at surgery a single adenoma was removed and calcium levels normalized and remained stable as described earlier, the final diagnosis was 'solitary adenoma'. In all other cases, the final diagnosis was 'no solitary adenoma'. Using this approach, sensitivity of US denotes, among patients with a final diagnosis of solitary adenoma, the probability of a US diagnosis of a solitary adenoma at the same location as observed at surgery. The positive predictive value of US denotes, among patients with a solitary adenoma on US, the probability of a final diagnosis of solitary adenoma at the predicted location. The negative predictive value denotes, among patients with no solitary adenoma on US, the probability of a final diagnosis of no solitary adenoma. Specificity denotes, among patients with a final diagnosis of no solitary adenoma, the probability of no solitary adenoma on US. All probabilities from this analysis are presented as percentages with exact binomial 95% confidence intervals [17].

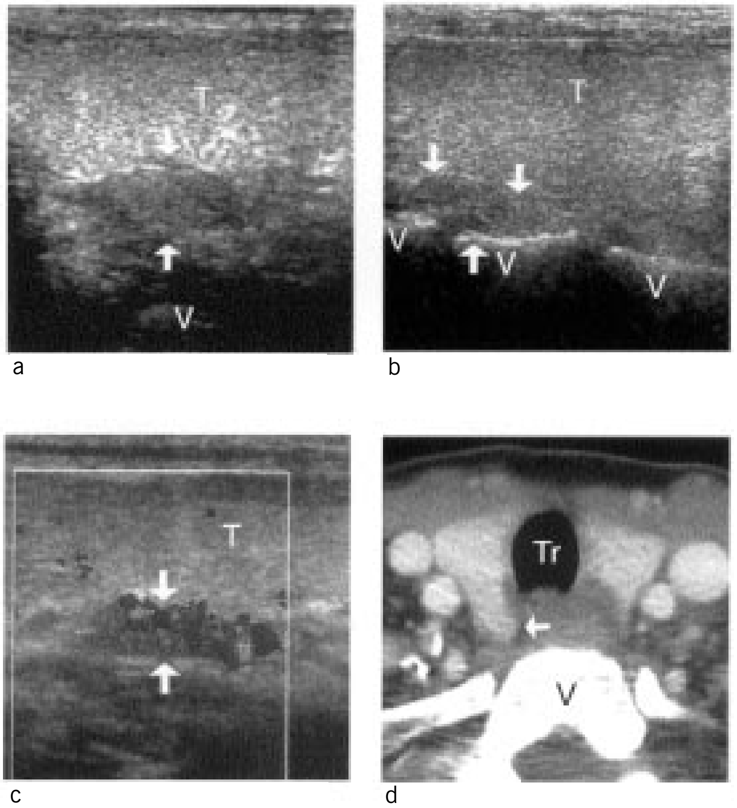

Figure 3 *Patient with a solitary adenoma, superior type.*

(a) Transverse US section shows ill-defined hypoechoic lesion (arrows) behind the right thyroid gland indicative of an 'equivocal' adenoma.

(b) Longitudinal section demonstrates again poor visualization of the lesion (arrows) which is compressed between thyroid and cervical spine.

(c) Transverse color Doppler US image at the same level as figure 3a showing extensive vascularization of the lesion, allowing diagnosis of a 'definite' adenoma.

(d) Transverse CT section showing the adenoma only as enlargement of the posterior aspect of the right thyroid lobe (arrow), due to its close relation to the thyroid and the identical enhancement.

Note: T = thyroid, Tr = trachea, C = carotid artery, V = vertebral body, E = esophagus.

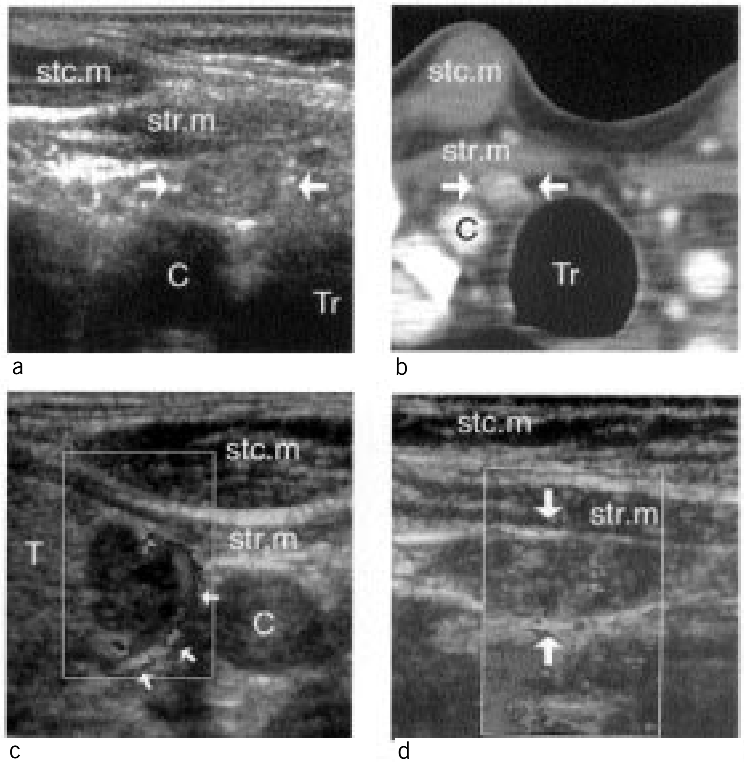

Figure 4 *Patient with incorrectly diagnosed solitary adenoma.*

(a) Transverse US image at level caudad to thyroid gland shows a moderately echogenic lesion (arrows) between the right carotid artery and the anterior muscular wall of the neck. The lesion was believed to be a solitary parathyroid adenoma.

(b) Transverse CT image at same level as 4a showing the same lesion (arrows), which was removed by MIS. Histopathologic examination of the specimen revealed only thyroid tissue.

(c) Transverse US section of the neck showing the solitary parathyroid adenoma found at subsequent CNE. The lesion is located subcapsularly in the thyroid gland and was believed to be a thyroid nodule at initial US examination. Doppler US shows the presence of a vascular pedicle (arrows).

(d) Longitudinal US section of the adenoma showing the oval shape but with rather sharp edges probably caused by the subcapsular position. In retrospect, these edges favor the diagnosis of a parathyroid adenoma above a thyroid nodule.

Note: T = thyroid, Tr = trachea, C = carotid artery, stc.m = sternocleidomastoid muscle, str.m strap muscles.

Second, we carried out analyses with *adenomas as units of analysis.* Because in this situation the number of no solitary adenoma diagnoses (both on ultrasound and at surgery) is undefined, only sensitivity and positive predictive value were calculated. Using this approach, the sensitivity denotes the probability that an adenoma found at surgery had also been identified at that site by US, and the positive predictive value is defined as the probability that an adenoma identified by ultrasound was present at surgery at the same location. As in this analysis the observations may not be independent within patients, confidence limits were omitted.

Results

The results of US, CT and surgery evaluation for both series are given in **Table 1**. In part I there were 61 patients; in 46 of those a definite solitary adenoma was diagnosed by US and the diagnosis was not changed by CT. In the remaining 15, CT changed the US diagnosis to a definite solitary adenoma in two cases. In one of them, CT changed the initial US diagnosis of equivocal to a definite solitary adenoma. In the other one, in whom no lesion was seen by US, CT identified a solitary adenoma in a deep paratracheal/mediastinal location (this lesion was later visualized, with knowledge of the CT findings, on the repeat US examination performed immediately before surgery). Thus, in part I there were 48 patients with the final diagnosis of a definite solitary adenoma. All underwent MIS except for one patient who underwent primary CNE because the MIS procedure was considered surgically impossible due to the presence of extensive multinodular goiter and resulting deep location of the lesion demonstrated by imaging. Of the 47 patients undergoing MIS, surgery was converted to CNE in one because during MIS the lesion could not be found due to extensive fibrosis in the operation area caused by prior thyroiditis. In the remaining 46, MIS was completed without surgical complications. Serum calcium levels normalized in 45 of these, resulting in a 98% success rate of the MIS procedure. Calcium levels did not normalize in one of the 46 patients, and histological examination of the specimen in this case revealed normal thyroid tissue without parathyroid components. In retrospect, the lesion that was diagnosed as a definite solitary adenoma by US and confirmed by CT, appeared to be an accessory thyroid gland, located two cm inferior to the right thyroid lobe (**Figure 4a,b**). CNE performed two days later revealed a small (274 mg) intrathyroidal parathyroid adenoma located subcapsular in the left lobe (**Figure 4c,d**). In another patient undergoing successful MIS, the visualized lesion proved to consist of two abutting adenomas rather than one solitary lesion, and the final postoperative diagnosis in this case was therefore multiple adenomas.

Table 1 Results of part I (n=61), part II (n=33) and combined results (n=94): Imaging diagnosis, type of surgery, failures and final findings.

	Imaging Diagnosis		Type Surgery		Failures	Final findings	
	US	combined US and CT	MIS	primary CNE		solitary	no solitary (multiple)
Part I							
Definite solitary adenoma	46	48	46+1*	1	1	47	1
No definite solitary adenoma	15	13	-	13	-	9	4
Total (patients)	61	61	46+1*	14	1	56	5
Part II							
Definite solitary adenoma	23	24	24	0	2	23	1
No definite solitary adenoma	10	9	-	9	1	6	3
Total (patients)	33	33	24	9	3	29	4
Combined results							
Definite solitary adenoma	69	72	71	1	3	70	2
No definite solitary adenoma	25	22	-	22	1	15	7
Total (patients)	94	94	70+1*	23	4	85	9

* Converted to CNE.

In part II there were 33 patients. In 23 of these a definite solitary lesion was diagnosed by US and they were directly scheduled for MIS. In the remaining 10, CT was subsequently performed which identified only one additional solitary adenoma in a deep para-esophageal location. Thus, in this series there were 24 patients with a solitary adenoma who all underwent primary MIS. In no case the operation was converted to CNE, and in all the removed lesion proved to contain parathyroid tissue at histopathological examination. In two of the 24 patients, however, serum calcium levels did not normalize following MIS. On subsequent CNE, a large (900 mg) second adenoma was found in one patient at the same location at which initially a small (230 mg) adenoma was removed during MIS. In this case only the large adenoma had been identified by imaging. In the other one, CNE revealed a large part of an adenoma at the same location where during prior MIS fragments of an adenoma were removed with total weight of 1,020 mg. In this case a much larger lesion (44x22x11 mm with estimated weight of 6,000 mg) had been diagnosed by the initial US. Thus, 22 of the 24 MIS procedures were successful resulting in a 92% success rate. In 6 of the 23 cases additional CT was performed at request of the surgeons, particularly by one who was new on the team and who had therefore less experience with the US-guided MIS procedure. In these patients, the CT scans were used exclusively for road-mapping in case of a deep para-esophageal location of the adenoma by US [3], severe enlargement of the thyroid due to goiter (2), or when there was an extremely large parathyroid adenoma diagnosed by US (n=1, weight of the specimen 16.010 mg). However, in these cases CT findings were not used for lesion diagnosis.

In part I and II combined, 69 definite solitary adenomas were diagnosed by US, in three of these the diagnosis was incorrect. Of the 66 solitary adenomas correctly diagnosed by US, 34 were in a ‘superior’ location, 27 were ‘inferior’ and 5 had an ‘aberrant’ location (intrathyroidal (n=1), para-esophageal (n=3) and cranial to the thyroid (n=1).

Histopathological results

At histopathological examination parathyroid tissue was identified in all 107 surgical specimens with exception of one, where only normal thyroid tissue was found. The median weight of the parathyroid specimens was 610 mg (range 90 -16,020 mg).

Statistical results

The results of the combined parts I and II in selecting patients with a solitary adenoma by US for MIS are depicted in **Table 2**. In total, there were 85 (90%) patients with a solitary adenoma according to the gold standard, i.e. the final operative results and change of the serum calcium levels. The sensitivity of US for diagnosing and localizing solitary parathyroid adenomas was 78% (66/85; 95%CI: 67-86) and the specificity also 78% (7/9; 95%CI: 40-97). The positive predictive value was 96% (66/69; 95%CI: 88-99) and the negative predictive value 28% (7/25; 95%CI: 12-49). In two of the three false positive cases there was multiglandular disease as described before, and in one there was a solitary adenoma which was not located at the predicted site.

In total, there were 106 adenomas in the 94 patients (85 with a solitary adenoma, and 21 adenomas in 9 patients with multiple lesions). The sensitivity of US for correctly diagnosing and localizing parathyroid adenomas was 74% (78/106); the positive predictive value was 98% (78/80). A false positive diagnosis of an adenoma was made in two patients. In one, the imaging-identified lesion proved to be aberrant thyroid tissue, and in the other, a small (8x7x3 mm) lesion identified by US, was not found at surgery.

Table 2 Results of US in correctly finding patients with a solitary parathyroid adenoma (part I and II combined).

	Results surgery		Total
Results US	present	not present	
Solitary adenoma	66	2+1*	69
No solitary adenoma	18	7	25
Total	84	9+1*	94

* one present, but not at predicted location.

Sensitivity	66/(84+1*)	78%
Positive predictive value	66/69	96%
Specificity	7/9	78%
Negative predictive value	7/25	28%

Discussion

The results of the first series of 61 patients with pHPT (part I) made it clear that, in more than two thirds (77%) of patients, successful MIS could be performed using the combined US-CT preoperative evaluation. In this series CT played only a limited role as additional diagnostic imaging modality, as there was no change in diagnosis in any of the 46 (75%) patients who harbored a definite US-diagnosed solitary adenoma, and it identified only two additional patients with such a lesion. These findings, combined with the increased confidence of the surgeon in the role of US, made us decide to initiate the second part of the study, in which CT was only used selectively. In this series (part II), CT only added one additional case for MIS.
The combined results of part I and II demonstrate that US is an excellent tool for selecting those patients with pHPT in whom successful MIS can be performed. In the 70 completed MIS procedures, three cases were selected by CT and thus 67 by US alone. Three of the 70 MIS procedures were unsuccessful, resulting in a 96% (67/70) success rate of the surgical procedure. This success rate for MIS is similar to that reported for primary CNE performed by experienced surgeons in patients who did not undergo preoperative imaging [6 7 8]. Thus, considering the results of the entire group of 94 patients, preoperative imaging was of major benefit to more than two thirds (71%) of our patients because they were able to undergo a limited, but equally successful operation for treatment of their pHPT instead of an extensive, complicated conventional surgical procedure.

It is well recognized, in case of ectopic adenomas with mediastinal or deep paratracheal and/or para-esophageal location, that US is of limited value because the lesions are generally inaccessible to the US beam; however, in these cases, they are usually well visualized by CT [3 5 13 14 18]. Nevertheless, in selecting patients for MIS, the added value of CT scanning was limited in our study because it identified only three additional definite solitary adenomas out of the entire group of 25 patients with 'no solitary adenoma' diagnosed by US. In two of these, the adenoma was located deeply in an area inaccessible to US, and in one the diagnosis of an equivocal lesion was changed to a definite solitary adenoma. Although in both cases of deep localization the adenoma was visualized at repeat US with knowledge of the CT findings, it is conceivable that visualization may be impossible at repeat US. In such a situation MIS could still be considered; however, the deep location of the lesion and the absence of preoperative localization of the adenoma and determination of the optimal incision site may make a surgical approach through a small opening in the skin very difficult, if not impossible.

In our study we used CT exclusively as an adjunctive test and we did not evaluate its role as primary imaging tool. However, in our experience, application of spiral

CT with cine loop presentation of images allows easy identification of a number of lesions and provides an excellent display of the visualized adenoma in its surrounding anatomical structures. Therefore, CT could potentially also be used as the primary test for selecting patients for MIS. However, the cost of CT is generally much higher than that of US, and the modality involves the use of ionizing radiation to a vulnerable area (thyroid gland) with associated risks [19]. For these reasons together with its good results we prefer to use US as the primary modality for selection of the patients for MIS. Nevertheless, in selected cases the surgeon may still want to have an additional CT for road mapping, as has been our experience, particularly in cases when the lesion is located deeply, or when the thyroid gland is enlarged.
Magnetic resonance (MR) imaging and scintigraphy have also been used for identification of parathyroid adenomas with results comparable to those of US and CT [4,20]. In our study we preferred to use CT as additional modality over MR imaging for reasons of availability and costs, and therefore the role of this modality in selecting patients for MIS was not determined. Conventional scintigraphy is, in our opinion, not well suited for selecting patients for our MIS procedure because of the relatively poor image resolution and anatomical information obtained. Recent studies have shown, however, that a minimally invasive surgical procedure is possible in cases where the uptake of the administered radiopharmacon is sufficient to allow localization of the parathyroid adenoma intra-operatively with a small gamma probe [21,22].

In one patient with two, contiguous adenomas simulating one lesion by imaging, MIS was successfully performed because during the surgery a discrepancy was noted between the size of the lesion that was first removed and the size predicted by imaging. Technically, MIS allows removal of multiple lesions through the same incision; however, since in case of multiglandular disease all parathyroid glands may be involved and identification by US is less successful due to the small average size of the enlarged glands [13], it is important that all glands be surgically inspected. Therefore we prefer to perform CNE in case enlargement of more than one gland has been diagnosed.

In three patients MIS was unsuccessful. One of these treatment failures was caused by an incorrect imaging diagnosis, in which an accessory thyroid gland was misinterpreted as being a parathyroid adenoma. In another case, there were two adenomas close to each other in the same anatomical location, and only the largest was visualized by preoperative imaging. However, in this case the MIS procedure was terminated after removal of the smaller one because no notice was made of the discrepancy between the size of the removed adenoma and that of the larger one visualized by US and found later at CNE. In the third case, the surgeon removed initially only a part of the predicted large adenoma and the remainder was left behind, which was later removed at CNE. These experiences emphasize the importance to correlate during MIS the size of the removed adenoma with the size predicted by imaging. Application of a test that allows rapid determination of the parathyroid hormone level in the blood at the end of the surgical procedure may also alert the surgeon to incomplete resection or the presence of a second adenoma in case the hormone level remains elevated. Such a test, which takes only 40 minutes to complete, was recently introduced at our institution as a routine procedure, allowing to perform re-operation within an hour in case of initial failure [23].

US showed an overall sensitivity in identifying parathyroid adenomas of 74% (solitary and multiple adenomas combined). Although we considered in our conservative approach all equivocal adenomas as 'negative' findings, these results are within the range (65%-85%) of those reported by others in identifying parathyroid adenomas with US imaging [13 15 18 20 24]. However, our positive predictive value of 98% in diagnosing parathyroid adenomas, and thus the nature of the lesions, by US was high compared to that of others (range 80%-97%) [13 15 18 20 24]. Because of the high accuracy in determining the nature of the lesions, we were also able to diagnose solitary parathyroid adenomas with high consistency (predictive value of 96%), something that is of crucial importance for successful MIS. In our study less then 10% of the patients had multiglandular disease, supporting the suggestion by some authors [25] that the true frequency of multiglandular involvement is lower than the 15% that is usually reported [3 4 5].

In our experience, characterizing the location of the solitary adenomas as 'superior', 'inferior' or 'aberrant' was very useful in the communication with the surgeon because it gave essential information about the anatomical localization of the lesion with its surrounding structures, needed for the implementation of the MIS procedure. Our approach to diagnosing a definite solitary adenoma was rather conservative to minimize the number of unsuccessful MIS procedures. Whether a definite adenoma was diagnosed or not, in all patients with the presentation of one or more equivocal lesions, primary CNE was performed. If we had considered the equivocal lesions to be all 'definite' adenomas or all 'negative', in both instances we would have been able to perform more successful MIS procedures; however, this would have been at the expense of substantially more surgical failures.

A limitation of our study is that the patient groups were taken as convenience samples (group I came before group II). As a result, temporal effects on the results cannot be excluded. For instance, in group II the clinicians could have been more familiar with the advantages of MIS compared to CNE. They may therefore have lowered their threshold by referring patients with minimal or no clinical symptoms of pHPT for group II of the study. Such patients are more likely to harbor relatively small adenomas which are more difficult to diagnose and operate upon. On the other hand, learning effects may have resulted in superior diagnostic and surgical performance in group II. As the magnitudes of these effects are unknown, comparison of the results of part I and part II of the study, should therefore be done cautiously. However, the goal of our study was not to compare the two patient groups but to determine the overall role of US as the primary imaging modality for identification and localization of parathyroid adenomas in patients with pHPT to undergo MIS.

In conclusion, MIS is an imaging-guided surgical technique for treatment of parathyroid adenomas that has considerable advantages compared to CNE. We have demonstrated that, using the criteria outlined above, US permitted successful selection of patients with pHPT for MIS in more than two thirds of the cases. The adjunctive diagnostic use of spiral CT scanning allowed the selection of only a few more patients for MIS and therefore, the added diagnostic value of CT may not have been worth the effort, cost and risk of a radiation hazard. However, in selected cases CT may play an important role in providing an operator-independent roadmap for the surgeon. Close cooperation between surgeon and radiologist is essential, because the MIS procedure can only be performed successfully when the surgeon is informed in detail about location and size of the adenoma that needs to be removed.

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