Surgeon-Performed Ultrasound as Preoperative Localization Study in Patients with Primary Hyperparathyroidism

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Key Words
Minimally invasive approach ∙ Parathyroid hormone ∙ Primary hyperparathyroidism ∙ Ultrasound

Abstract
Background: Minimally invasive parathyroidectomy is the treatment of choice for single-gland primary hyperparathyroidism. However, the exact location of the abnormal gland has to be established. Sestamibi scintigraphy, computed tomography and ultrasound (US) are commonly used modalities. We describe our experience in a non-academic center with surgeon-performed US (S-US) of the neck as preoperative localization study in patients with primary hyperparathyroidism (PHPT). Methods: Patients with a biochemically proven diagnosis of PHPT and preoperative S-US were included. Data were recorded prospectively. Perioperative gland location was compared to the preoperative S-US to determine sensitivity, specificity and accuracy rates. Results: Two of the 50 patients who underwent S-US were not subjected to surgery. In 85\% of the patients analyzed by S-US, the appropriate abnormal gland(s) were identified. In 11\%, no gland was identified, but abnormal glands were found during surgery. Sensitivity of S-US in our hospital is 85\%, with a positive predictive value of 97\%. Conclusions: We achieved a satisfactory sensitivity rate. S-US provides anatomic information to the surgeon which enables a more detailed operation planning, and it is a valuable diagnostic modality for patients with PHPT in our opinion. We hope that our data encourage other centers to implement this technique as well.

Introduction

Primary hyperparathyroidism (PHPT) is most often due to one parathyroid adenoma secreting excessive parathyroid hormone (PTH) [1]. These patients are characterized by a persistent hypercalcemia with a concomitant increase or inappropriately high level of serum PTH. The standard of care for PHPT is surgical removal of all hyperfunctioning parathyroid tissue. In experienced hands, parathyroidectomy by conventional neck exploration (CNE) is successful in 95–99\%, with a very low complication rate [2, 3]. However, >90\% of the patients have only one abnormal parathyroid gland, which makes it suitable for a focused approach (minimally invasive parathyroidectomy, MIP). Large studies have compared CNE with the minimally invasive approach (MIA) showing equal cure and complication rates [4–7]. The latter has the potential to be more cost effective with...
a shorter operation time and a shorter hospitalization 
Nowadays, MIP is the standard of care in case of uni-
glandular PHPT with preoperatively localized disease. 
Once the biochemical diagnosis of PHPT is established, 
preoperative localization of the abnormal glands is the 
next step towards MIP. Various imaging modalities can 
be used to identify the diseased glands. Technetium 
99m-sestamibi scintigraphy (MIBI), which is commonly 
used, is based on a difference in absorption of sestamibi 
between normal and hyperfunctioning glands. The ac-
curacy of MIBI depends on the particular scanning 
technique used [9], and reported sensitivity rates range 
from 54 to 88% [10, 11]. Sestamibi scintigraphy is repro-
ducible and investigator independent, and abnormal 
parathyroid glands are relatively easy to detect. The scan 
does not allow precise anatomical localization, and only 
roughly indicates at which side and level of the neck the 
lesion is situated.

Computed tomography (CT) provides high-quality 
two (sometimes three)-dimensional anatomical images 
and has a reported sensitivity of 66% and specificity of 
89% [12]. It is possible to use positron emission tomog-
raphy in combination with CT to detect the hyperfunc-
tioning gland, but this is not yet widely implemented [13]. 
Magnetic resonance imaging is another possible imaging 
modality with a reported sensitivity rate of 43.4–57.1% 
[14, 15]. Ultrasound (US) is quick, non-invasive and does 
not require the use of radioactive materials. Unfortunate-
ly, US is highly operator dependent [16] and much infor-
mation is lost when the two-dimensional images are 
stored. US performed by radiologists (R-US) have report-
ed sensitivity rates of 59–96% [11, 17]. An increasing 
number of surgeons are using US as an extension of the 
clinical examination (surgeon-performed US, S-US). The 
use of office-based S-US to localize abnormal parathy-
roid glands preoperatively is not new. In several pub-
lished studies, sensitivity rates of 66–76% have been re-
ported [18–20].

The majority of data on S-US published in the last 
years were collected from university hospitals and refer-
ral centers. Results from non-academic hospitals remain 
scarce, which gives the impression that S-US is a modali-
ity which is mainly performed in an academic setting. 
Whether S-US measurements are useful in a non-acade-
mic hospital setting, usually treating a lower number of 
patients, remains obscure. The aim of this study is to 
describe the experience in performing S-US as an addi-
tional preoperative localization study in patients with 
PHPT in a non-academic center.

Materials and Methods

Data were collected at the Reinier de Graaf Hospital from Au-
the participating patients were retrieved using operation-specific 
codes and relevant hospital coding systems. Thereafter, results 
were collected prospectively. All patients with a biochemically 
proven diagnosis of PHPT who were scheduled to undergo sur-
gery underwent a preoperative US performed by the dedicated 
surgeon and were included in the analysis. Baseline characteris-
tics (gender, age and preoperative laboratory values) were collect-
ed. All patients received preoperative localization studies consist-
ing of MIBI and/or US investigation (R-US and/or S-US) and/or 
CT. MIBI and CT scans were performed using similar settings 
(slice thickness, timing and amount of radioactive material) dur-
ing the whole study period.

Surgeon-Performed Ultrasonography

One of our endocrine surgeons (P.C.S.) performs neck US 
(Philips Envisor HD) at the outpatient clinic since 2004. No S-US 
were performed in the operating room just prior to surgery. The 
linear ray probe with a frequency of 3–12 MHz is used with the 
software set on thyroid modus. The patient is examined in supine 
position with the neck in hyperextension. US provides an image of 
the entire neck, from the angles of the jaw to the sternal notch. 
When the probe is aimed downwards, the upper mediastinum can 
be visualized. However, the retrocervical tracheal space cannot be 
studied by ultrasound as the air in the trachea hinders the passage 
of the ultrasound waves. Previous neck surgery, radiation therapy 
and goiter negatively affect US. When a possible enlargement of 
the parathyroid gland was identified, color Doppler US was used 
to determine the vascularity of the lesion to identify a vascular 
pedicle strengthening the diagnosis of a parathyroid adenoma. 
Parathyroid adenomas were defined as any oval, elongated, or lob-
ulated lesion connected with the thyroid gland during swallowing 
without a central hilum (characteristic for a lymph node). Lesions 
with the same characteristics but an increased and/or irregular 
reflection pattern, cystic changes and/or calcifications represent-
ing degeneration and measuring from 1–2 to ~5 cm in length were 
also considered to be an adenoma. When the solitary adenoma was 
located posterior to the thyroid lobe near the middle portion, it 
was considered an adenoma of the superior type. It was considered 
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. Any other location 
was considered aberrant. US takes approximately 10–15 min, and 
findings are directly recorded in the patient’s chart, with a detailed 
map (US pictures, drawings and text) for the scheduled surgical 
approach. The location of the future incision is described using the 
midline and the clavicular as landmarks.

Surgery

All procedures, both conventional neck explorations and MIP, 
were performed under general anesthesia by one of the two dedi-
cated endocrine surgeons, either P.W.d.G. or P.C.S. P.C.S., who 
also performed S-US, carried out >80% of the operations. The 
MIP, consisting of a small incision (<3 cm) above the suspect 
gland, was the operation of choice for single-gland disease. PTH 
levels were assessed intraoperatively to support the success of the 
minimally invasive procedure. After surgery, all normo- and hy-
distributed data are presented as means ± SD. Non-normally distributed data are reported as medians and ranges. For each imaging modality, any gland that was identified as abnormal parathyroid tissue by imaging, and confirmed as such by operative findings was scored as true positive (TP). A finding was false positive (FP) if operative findings did not confirm an abnormality of the gland detected by imaging. A finding was true negative (TN) if the gland was identified as normal by imaging and this was confirmed by intra-operative PTH levels and operative findings (among patients who underwent bilateral neck exploration). A finding was false negative (FN) if S-US failed to identify the abnormal gland but an abnormality was detected during the operation. Sensitivity was defined as TP/(TP + FN), specificity was defined as TN/(TN + FP), positive predictive value was defined as TP/(TP + FP), and negative predictive value was defined as TN/(TN + FN). The S-US localization was scored correct if the imaging technique predicted the proper quadrant (namely, upper left, upper right, lower left or lower right). The prediction was compared to the ‘gold standard’, which is for abnormal glands perioperative surgical findings combined with an abnormal gland during pathological analysis (abnormal glands include: adenomas (characterized by a neoplastic monoclonal process), hyperplastic glands (characterized by a polyclonal proliferation) or unsure (adenoma or hyperplasia). A cured patient indicates that there is no abnormal tissue left and all ‘abnormal’ glands have been removed, thus rendering the difference between adenoma and hyperplasia less important in this study. For normal glands, the prediction was compared to the pathological analysis or, if the gland remained in situ, a cured patient. Therefore, uncured patients are left out of this part of the analysis.

Statistical Analysis

Only descriptive statistics are used. Data were tested for normality using the Shapiro-Wilk test and visual assessment. Normally distributed data are presented as means ± SD. Non-normally distributed data are reported as medians and ranges. For each imaging modality, any gland that was identified as abnormal parathyroid tissue by imaging, and confirmed as such by operative findings was scored as true positive (TP). A finding was false positive (FP) if operative findings did not confirm an abnormality of the gland detected by imaging. A finding was true negative (TN) if the gland was identified as normal by imaging and this was confirmed by intra-operative PTH levels and operative findings (among patients who underwent bilateral neck exploration). A finding was false negative (FN) if S-US failed to identify the abnormal gland but an abnormality was detected during the operation. Sensitivity was defined as TP/(TP + FN), specificity was defined as TN/(TN + FP), positive predictive value was defined as TP/(TP + FP), and negative predictive value was defined as TN/(TN + FN). The S-US localization was scored correct if the imaging technique predicted the proper quadrant (namely, upper left, upper right, lower left or lower right). The prediction was compared to the ‘gold standard’, which is for abnormal glands perioperative surgical findings combined with an abnormal gland during pathological analysis (abnormal glands include: adenomas (characterized by a neoplastic monoclonal process), hyperplastic glands (characterized by a polyclonal proliferation) or unsure (adenoma or hyperplasia). A cured patient indicates that there is no abnormal tissue left and all ‘abnormal’ glands have been removed, thus rendering the difference between adenoma and hyperplasia less important in this study. For normal glands, the prediction was compared to the pathological analysis or, if the gland remained in situ, a cured patient. Therefore, uncured patients are left out of this part of the analysis.

Results

From August 2004 until September 2008, 50 patients were included in the study. The analysis comprised 33 (66%) women and 17 (34%) men, with a median age of 58 years (range 20–82). The preoperative median serum calcium level was 2.79 mmol/l (range 2.56–3.26, normal range 2.20–2.60) and the median serum PTH level was 12.40 pmol/l (range 5.6–70.4, normal range 1.0–5.5). One patient had (high) normal calcium levels under calcium-lowering medication (PTH = 8.6). All other patients were hypercalcemic.

Surgery

In 2 patients, it was decided to refrain from surgery due to the mild character of the disease combined with high comorbidity of the patients. They were excluded from further analysis. Forty-four patients underwent a first surgical procedure for PHPT. The MIP was chosen in 38 patients (86%); 6 patients (14%) underwent CNE. Reasons for CNE were multiple gland disease, recurrent nerve paresis due to unknown etiology, unequivocal imaging results or no reason specified.

In 4 patients, only the second operations for persistent hypercalcemia (reoperation) are included in the study, as the first operations were performed prior to the start of our study. Two patients could be cured by means of MIP. The other 2 patients are discussed in more detail as they had persistent disease. One patient developed recurrent disease after surgery in 1979. The patient was operated by means of a targeted approach to the left lower parathyroid, based on the results of the sestamibi scan. As intra-operative PTH levels failed to decrease, the surgical procedure was converted to a conventional neck operation. No abnormal parathyroid glands were identified. This patient was referred to a tertiary center. The last communication reports that, based on low urinary calcium levels, the diagnosis of hypocalciuric hypercalcemia is considered. The other patient was also treated for recurrent disease years after her first operation. CNE revealed an adenoma which was removed from a location different to that detected by S-US. This patient has, at the time of reporting, a normal calcium level with a high PTH level. Regrettably, during follow-up, a malignancy with metastasis (non-parathyroid) was diagnosed in this patient and evaluation of the hyperparathyroidism was discontinued.

Results of Surgeon-Performed Ultrasound

In total, 50 US were performed by the surgeon at the outpatient department. Four patients were excluded from the following analysis as no definite conclusion can be made about all 4 parathyroid glands (n = 2, not operated; n = 2 not cured). Preoperative S-US identified all the important anatomical landmarks: namely trachea, esophagus (par aesophageal groove), thyroid gland, carotid artery and jugular vein in all patients. All patients underwent both MIBI scanning and S-US. A CT scan was performed in 20/46 (44%) patients and R-US in 26/46 (57%) patients. Results from MIBI, R-US and S-US are shown in table 1.

In 40 of the 46 (87%) S-USs, the suspected lesions seen on S-US truly were hyperfunctioning glands, however in 2 cases multiple-gland disease was overlooked (4%). In 1 case, multiple-gland disease was adequately predicted. In
5 cases (11%), no gland was identified by S-US, while an abnormal gland was found during surgery. In 1 patient (2%), S-US identified an abnormal gland, but the gland was in the wrong quadrant (adequate side of the neck).

**Follow-Up and Complications**

The mean calcium level of all cured patients (1-year follow-up) was 2.36 mmol/l (range 2.25–2.53, normal range 2.20–2.60). Two patients are not considered cured, one of them is currently being treated for a metastatic disease and the other is diagnosed with hypocalciuric hypercalcemia (both are described in the Surgery section).

Three of the 48 operated patients (6%) had temporary postoperative hypocalcaemia for which 1 patient needed calcium supplementation. One patient had temporary hoarseness, most likely due to irritation by intubation, which restored rapidly. A re-operation for hemorrhage was needed in 1 patient.

**Discussion**

This study encompasses patients with PHPT who underwent preoperative S-US. The aim of our article is to describe the experience of US performed in a single non-academic center by a surgeon. As surgeons become more familiar with the use of US, it is more often applied as an extension of the physical examination during the initial office visit [20]. This trend is not restricted to parathyroid disease, it is also observed in other fields of medicine [21–23]. In our opinion, one of the main benefits of S-US is the support of sonographic findings prior to and during surgical treatment. The knowledge of the exact gland location enables the surgeon to perform a targeted tissue dissection, thereby possibly decreasing the risk of recurrent nerve injury and reducing scar formation. A prospective trial in a large cohort should be conducted to determine whether S-US leads to lower complication rates and shorter operation times.

Although it may require more logistical planning, it may be beneficial to perform S-US directly before surgery in the operating room. This enables the surgeon to directly plan the operation and the incision site, without the need for ‘remembering’ the case from the outpatient department. However, if no gland is found and more imaging is needed, the operation needs to be rescheduled. In addition, in our hospital, we use S-US as an additional imaging modality. We feel that if the S-US shows no abnormal glands, the other imaging modalities (MIBI, CT, R-US) must show an abnormal gland in order to proceed to MIP. Otherwise, CNE must be considered.

We acknowledge the fact that the number of patients in this study is limited and therefore these results should be interpreted with care. We also emphasize that it was not our intention to compare S-US with R-US, as our data were not suitable for this purpose. For example, S-US results cannot be compared with R-US results as the latter have been done by various radiologists, instead of one investigator. Secondly S-US is most of the times performed after the MIBI results were available, whereas some R-US were the first imaging modality applied.

Recent studies have shown US to be highly accurate in localizing parathyroid adenomas with reported sensitivity rates of up to 70–92.5% [17, 19, 24]. Our sensitivity rate is 85%.

The incidence of multiglandular disease in this study was 6%, which is within the normal range, but in the lower region of the incidence rates reported in the literature [18, 25–27]. This could be due to the relatively small numbers of patients in our study. As previously reported, preoperative localization is less accurate in multiglandular disease compared to single-gland disease [26]. The lower incidence of multiglandular disease in our study population may be a bias towards the results.

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Table 1. Results of preoperative localization studies

<table>
<thead>
<tr>
<th>Glands, n</th>
<th>TN</th>
<th>TP</th>
<th>SN</th>
<th>SP</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>total</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>abnormal</td>
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<tr>
<td>normal</td>
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</tr>
<tr>
<td>MIBI (n = 46)</td>
<td>184</td>
<td>40</td>
<td>144</td>
<td>135</td>
<td>37</td>
<td>80%</td>
<td>98%</td>
</tr>
<tr>
<td>S-US (n = 46)</td>
<td>184</td>
<td>42</td>
<td>142</td>
<td>135</td>
<td>41</td>
<td>85%</td>
<td>99%</td>
</tr>
<tr>
<td>R-US (n = 26)</td>
<td>104</td>
<td>14</td>
<td>90</td>
<td>76</td>
<td>13</td>
<td>48%</td>
<td>99%</td>
</tr>
</tbody>
</table>

TP = True positive; SN = sensitivity; TN = true negative; SP = specificity; PPV = positive predictive value; NPV = negative predictive value. Numbers of patients are shown in parentheses.
Several studies suggest that if S-US shows one abnormal gland, no further examination/imaging is needed and one may perform MIP [19]. Our study is not suited to draw conclusions regarding this statement. Many S-US are performed while knowing the results of the MIBI scanning, thus introducing bias. Although we report test characteristics of our imaging modalities, we cannot directly compare them due to the aforementioned bias.

Altogether, we regard S-US as a unique opportunity for the surgeon to plan the operation in detail by means of the detailed anatomical information provided by S-US. Despite the limitations of US (multiglandular disease/interobserver variety), the benefits (non–invasive approach with detailed real-time anatomical information which is easy to use) have led us to use S-US in every patient visiting our outpatient clinic and achieve a very acceptable sensitivity rate. We recommend the use of S-US and hope that our data encourage other non-academic centers to apply S-US.

References