Localization of parathyroid tumours in the minimally invasive era: which technique should be chosen? Population-based analysis of 253 patients undergoing parathyroidectomy and factors affecting parathyroid gland detection

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Abstract

A series of 253 consecutive patients with proved primary hyperparathyroidism due to parathyroid tumours was reviewed. There were 68 (26.9%) men and 185 (73.1%) women, with a median age of 57 years (range 13–82 years). All patients, prior to successful parathyroidectomy, underwent one or more preoperative localization procedures such as: neck ultrasonography (US) in 191 (75.5%), 201Tl/99mTc-pertechnetate subtraction scintigraphy (TPS) in 144 (56.9%), CT scan in 92 (36.4%), 99mTc-sestamibi/99mTc-pertechnetate subtraction scintigraphy (MPS) in 90 (35.6%), selective venous sampling (SVS) with parathyroid hormone (PTH) assay in 30 (11.9%), and magnetic resonance imaging (MRI) in 6 (2.4%) patients. The results were compared with operative and histological findings that showed 235 (92.9%) solitary parathyroid adenomas, 13 (5.1%) carcinomas and 5 (2.0%) double adenomas. Sensitivity and positive predictive value were 82.9% and 93.8% for US, 83.6% and 91.8% for TPS, 81.3% and 98.7% for CT scan, 85.1% and 96.1% for MPS, 65.4% and 80.9% for SVS, and 80.0% and 80.0% for MRI respectively. No different results (P=NS) were found using US, TPS, MPS or CT scan, whereas SVS and MRI sensitivity was lower (P<0.05). The combination of MPS and US was 94.0% sensitive (P<0.05) but when TPS, CT scan or MRI were also used overall sensitivity did not improve significantly (P=NS). In conclusion, MPS should be used as the starting preoperative localization procedure, while US and MPS together represent the most reliable noninvasive localization tool. If MPS and US are negative or not in agreement, further studies are not cost-effective and the patient should undergo bilateral neck exploration.

Introduction

Primary hyperparathyroidism is the most common cause of hypercalcaemia in outpatients, and its age-adjusted incidence is estimated to be 42 per 100 000 (Arnaud 1994). Most patients in whom the diagnosis of primary hyperparathyroidism is made require surgical treatment and bilateral neck exploration has represented for many years the standard procedure to perform parathyroidectomy. However, since 85–90% of primary hyperparathyroidism is caused by solitary parathyroid tumours, unilateral exploration and minimally invasive parathyroidectomy, both endoscopic and radioguided, may be currently performed (Borley et al. 1996, Bonjer et al. 1997a, Norman & Chheda 1997, Naitoh et al. 1998, van Vroonhoven & van Dalen 1998, Inabnet et al. 1997).
Lumachi et al.: Localization tests in primary hyperparathyroidism

1999, Miccoli et al. 1999, Pattou et al. 1999). In this setting, the interest for preoperative localization procedures is growing and consequently sensitivity and accuracy of non-invasive techniques have improved, but at present it has not been clearly established which procedure should be preferred when parathyroid gland imaging is required.

The aim of this study was to analyse the results obtained using preoperative localization procedures in a population-based study of patients with primary hyperparathyroidism due to parathyroid tumours, and to suggest the correct diagnostic tool to be used.

Patients and methods

A series of 253 consecutive patients with proved primary hyperparathyroidism were reviewed. There were 78 (26.9%) men and 185 (73.1%) women, with a median age of 57 years (range 13–82 years). The main preoperative laboratory data are reported in Table 1. Intact (1–84) parathyroid hormone (PTH) was measured in 192 (75.9%) patients using immunoochemiluminometric technique, whereas in 61 (24.1%) patients different PTH fragment (carboxy terminal (34–84 peptide), amino terminal (1–34 peptide), or mid-molecule (44–68 peptide)) assays were available.

Prior to surgery 191 (75.5%) patients underwent neck ultrasonography (US), 92 (36.4%) had computed tomography (CT) scan of the neck and mediastinum, 144 (56.9%) underwent 201Tl/99m Tc-pertechnetate subtraction scintigraphy (TPS), 90 (35.6%) 99mTc-methoxyisobutylisonitrile (sestamibi)/99mTc-pertechnetate subtraction scintigraphy (MPS), and in 30 (11.9%) patients selective venous sampling (SVS) with PTH assay was performed. The results were compared with operative and histological findings. The techniques of performing SVS, TPS, MPS and US have been previously described (Zotti et al. 1989, Borsato et al. 1989, Lumachi et al. 1999). Computed tomography scan images were obtained using standard contiguous 5 mm sections after intravenous radiographic contrast administration and spiral CT was available for 21/92 (22.8%) patients. Moreover, in the six (2.4%) patients who underwent magnetic resonance imaging (MRI), axial T1- and T2-weighted spin-echo images were obtained using an anterior neck surface coil (hyoid bone-sternal notch). Informed consent was obtained from each patient who underwent preoperative localization procedures.

The results were considered true-positive (TP) when one or two parathyroid tumours were correctly localized (right/ left side, upper/lower pole of the thyroid gland, mediastinum or other ectopic sites), false-positive (FP) when no parathyroid tumours were found in the site showed by the localization procedures, and false-negative (FN) when the technique did not detect any abnormal parathyroid gland. Sensitivity was defined as TP/(TP+FN) and positive predictive value was defined as TP/(TP+FP). All reported data are expressed as mean ± S.D. and comparisons between different groups were performed using two-tailed Student’s t-test, the Fisher exact test and the chi-squared test, when appropriate. The differences were considered significant at P < 0.05. The Pearson’s correlation coefficient (r) calculation was also used.

Results

There were no differences (P = NS) in mean serum calcium (Ca) and PTH levels between men and women. All patients underwent successful parathyroidectomy and were subsequently cured for their hyperparathyroidism. The removed parathyroid tumours were measured by the pathologist, who found 235 (92.9%) solitary adenomas, 13 (5.1%) carcinomas and 5 (2.0%) double adenomas. The mean maximum diameter (size) of the abnormal parathyroid glands was 20.7 mm (median 20 mm, range 8–45 mm) and they were in a typical site in 202 (79.8%) cases. The r coefficients between Ca and PTH, size and PTH, and size and Ca were 0.398271 (F = 381.39, P < 0.05), 0.238292 (P=NS) and 0.155881 (P=NS) respectively.

In the subgroups of patients with malignant (n = 13) and benign (n = 240) parathyroid tumours mean serum calcium (3.40±0.56 vs 3.01±0.36 mmol/l) and PTH (388.3±136.2 vs 178.2±133.7 ng/l) levels were significantly (P < 0.05, Student’s t-test) different, as well as the size of the removed parathyroid tumours (29.23±8.86 vs 20.32±7.68 mm) and the age of the patients (62.46±13.13 vs 54.47±13.12 years).

Table 1 Main preoperative laboratory data in the overall patients

<table>
<thead>
<tr>
<th></th>
<th>Serum calcium (mmol/l)</th>
<th>Serum 1–84 PTH (ng/l)</th>
<th>Serum creatinine (µmol/l)</th>
<th>Alkaline phosphatase (U/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>253 (100%)</td>
<td>192 (75.9%)</td>
<td>253 (100%)</td>
<td>247 (97.6%)</td>
</tr>
<tr>
<td>Median</td>
<td>2.95</td>
<td>139</td>
<td>77</td>
<td>125</td>
</tr>
<tr>
<td>Range</td>
<td>2.62–4.27</td>
<td>61–990</td>
<td>28–290</td>
<td>45–490</td>
</tr>
<tr>
<td>Mean values</td>
<td>3.02</td>
<td>185.96</td>
<td>82.2</td>
<td>152.43</td>
</tr>
<tr>
<td>S.D.</td>
<td>0.38</td>
<td>149.38</td>
<td>28.81</td>
<td>89.66</td>
</tr>
<tr>
<td>Normal values</td>
<td>1.90–2.60</td>
<td>10–55</td>
<td>53–97</td>
<td>53–141</td>
</tr>
</tbody>
</table>

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Table 2 shows the results obtained and the costs for each technique. No differences \((P = \text{NS}, \chi^2\text{-test})\) were found using US, TPS, MPS or CT scan, whereas SVS sensitivity was significantly lower. Table 3 reports the differences between patients with TP and FN results using US, TPS, MPS and CT scan. The few cases studied by SVS and MRI did not allow statistical analysis. Significant \((P < 0.05, \text{Student's } t\text{-test})\) differences were found between patients with TP and FN results: (1) in the mean serum Ca levels using US; (2) in the mean size of parathyroid tumours using TPS; (3) both in the mean size of parathyroid tumours, and in the mean serum Ca and PTH levels using CT scan; and (4) in the ectopic rate of parathyroid tumours using US, which was higher (Fisher exact test) in the patients with FN results. Such parameters did not affect MPS sensitivity. The combination of US and MPS was the most useful, showing a 94.0% sensitivity, which was significantly higher than the sensitivity of single US and MPS (Table 4). In fact, there were few patients \((52/84, 61.0\%)\) with TP results both with US and MPS and thus the two techniques should be considered complementary. Forty \((15.8\%)\) patients underwent US, MPS and CT scan and a 97.5% sensitivity \((TP = 39/40, 97.5\%)\) was obtained, but the difference was not significant \((P = \text{NS}, \chi^2\text{-test})\) in respect of the combination of MPS and US, although CT scan correctly localized three out of four parathyroid tumours undetected both by US and MPS. Few patients \((n = 4)\) underwent US, MPS and TPS and none US, MPS and SVS or MRI.

### Discussion

Immediate surgical neck exploration performed by an experienced surgeon was considered the treatment of choice for patients with primary hyperparathyroidism, with an

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**Table 2** Results obtained using different localization procedures, \(P\) value (\(\chi^2\) test), and costs for each technique at Padua University Hospital

<table>
<thead>
<tr>
<th>Technique</th>
<th>Patients</th>
<th>% TP</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity (%)</th>
<th>(P)</th>
<th>PPV (%)</th>
<th>Cost (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>191</td>
<td>75.5</td>
<td>150</td>
<td>10</td>
<td>82.9</td>
<td>NS</td>
<td>93.8</td>
<td>40</td>
</tr>
<tr>
<td>TPS</td>
<td>144</td>
<td>56.9</td>
<td>112</td>
<td>10</td>
<td>83.6</td>
<td>NS</td>
<td>91.8</td>
<td>120</td>
</tr>
<tr>
<td>CT scan</td>
<td>92</td>
<td>36.4</td>
<td>74</td>
<td>1</td>
<td>81.3</td>
<td>NS</td>
<td>98.7</td>
<td>100</td>
</tr>
<tr>
<td>MPS</td>
<td>90</td>
<td>35.6</td>
<td>74</td>
<td>3</td>
<td>85.1</td>
<td>NS</td>
<td>96.1</td>
<td>120</td>
</tr>
<tr>
<td>SVS</td>
<td>30</td>
<td>11.9</td>
<td>17</td>
<td>4</td>
<td>65.4</td>
<td>&lt;0.05</td>
<td>80.9</td>
<td>600*</td>
</tr>
<tr>
<td>MRI</td>
<td>6</td>
<td>2.4</td>
<td>4</td>
<td>1</td>
<td>80.0</td>
<td>–</td>
<td>80.0</td>
<td>300</td>
</tr>
</tbody>
</table>

Patients, number of patients who underwent each localization procedure; TP, true positive results; FP, false positive results; FN, false negative results; PPV, positive predictive value; US, neck ultrasonography; TPS, \(^{201}\)TI/\(^{99m}\)Tc-pertechnetate subtraction scintigraphy; MPS, \(^{99m}\)Tc-sestamibi/\(^{99m}\)Tc-pertechnetate subtraction scintigraphy; CT, CT scan of the neck and mediastinum; SVS, selective venous sampling. *SVS with 10 samples and PTH assay.

**Table 3** Differences between patients with true positive (TP) and false negative (FN) results obtained using different techniques. Mean values ± s.d. (Student’s \(t\)-test and Fisher exact test*)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Ca (mmol/l)</th>
<th>PTH (ng/l)</th>
<th>Creatinine ((\mu)mol/l)</th>
<th>Site</th>
<th>Typical/ectopic</th>
<th>Size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>TP</td>
<td>54.76±13.17</td>
<td>3.02±0.35</td>
<td>189.19±120.66</td>
<td>81.19±29.14</td>
<td>130/20</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>55.91±8.99</td>
<td>2.86±0.34</td>
<td>180.42±140.18</td>
<td>74.10±20.39</td>
<td>20/11</td>
</tr>
<tr>
<td></td>
<td>FN</td>
<td>52.93±12.08</td>
<td>3.12±0.39</td>
<td>116.23±112.55</td>
<td>89.54±32.54</td>
<td>88/24</td>
</tr>
<tr>
<td>TPS</td>
<td>TP</td>
<td>53.72±12.08</td>
<td>3.12±0.39</td>
<td>168.37±112.55</td>
<td>89.54±32.54</td>
<td>88/24</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>48.42±15.51</td>
<td>3.01±0.34</td>
<td>116.23±112.55</td>
<td>83.93±28.65</td>
<td>16/6</td>
</tr>
<tr>
<td></td>
<td>FN</td>
<td>55.89±14.41</td>
<td>2.94±0.90</td>
<td>207.12±170.05</td>
<td>81.33±34.78</td>
<td>60/14</td>
</tr>
<tr>
<td>MPS</td>
<td>TP</td>
<td>52.93±13.73</td>
<td>2.80±0.20</td>
<td>131.78±56.65</td>
<td>77.00±28.29</td>
<td>9/4</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>54.92±13.77</td>
<td>3.02±0.34</td>
<td>190.55±119.98</td>
<td>78.37±26.46</td>
<td>55/19</td>
</tr>
<tr>
<td></td>
<td>FN</td>
<td>55.44±12.96</td>
<td>2.83±0.34</td>
<td>113.08±42.23</td>
<td>72.54±16.07</td>
<td>10/7</td>
</tr>
</tbody>
</table>

US, neck ultrasonography; TPS, \(^{201}\)TI/\(^{99m}\)Tc-pertechnetate subtraction scintigraphy; MPS, \(^{99m}\)Tc-sestamibi/\(^{99m}\)Tc-pertechnetate subtraction scintigraphy; CT, CT scan of the neck and mediastinum.
overall cure rate greater than 90% (Arnaud 1994, Shen et al. 1997, Roe et al. 1998, Delbridge et al. 1998). However, most studies suggested that preoperative localization of abnormal parathyroid glands may be useful in reducing operative time, morbidity and hospital stay, facilitating parathyroidectomy especially in patients with ectopic parathyroid tumours (Wei & Burke 1995, Sfakianakis et al. 1996, Gupta et al. 1998, Sofferman & Nathan 1998, Vogel et al. 1998, Boggs et al. 1999, Chen et al. 1999, Lumachi et al. 1999, Song et al. 1999). Table 5 shows the results obtained from series in which two or more procedures were compared.

In 1990 the National Institutes of Health panel recommended against the use of imaging tests to locate parathyroid tumours (NIH Conference 1991). In fact, in the 1980s FN and FP rates in patients without previous surgery ranged from 26–65% and 7–32% (parathyroid scintigraphy), 8–66% and 4–25% (US), and 14–59% and 6–38% (CT scan) respectively (Miller 1991). However, in recent years sensitivity of noninvasive localization procedures has significantly improved, ranging from 95 to 100% for MPS (Sfakianakis et al. 1996, Caixas et al. 1997, Chen et al. 1997, Gallowitsch et al. 1997, Hindé et al. 1998), and from 80 to 90% for US (Ammor et al. 1998, Lane et al. 1998, Vogel et al. 1998). The use of different radiopharmaceuticals does not significantly modify the results, but should be considered that the radiation dosimetry expressed as effective dose equivalent is lower for 99mTc-sestamibi and 99mTc-pertechnetate than for 201Tl-chloride, due to longer physical half life of the latter (O’Doherty et al. 1992, Geatti 1999). The use of single-photon emission computer tomography (SPECT) is a promising procedure that may improve MPS sensitivity, as well as the colour and power Doppler for US (Billotev et al. 1996, Neumann et al. 1997, Lane et al. 1998, Varsamidis et al. 1999). We did not find any difference (P = NS) using parathyroid scintigraphy, US or CT scan, whereas ectopic parathyroid tumours were not satisfactorily detected by US, and CT scan was significantly influenced by the size and the functional status of parathyroid tumours.

If both reliable preoperative localizing tests and intraoperative quick-PTH assay are available, minimally invasive parathyroidectomy becomes a safe alternative procedure to bilateral neck exploration, and the most common causes of parathyroidectomy failure may be eliminated (Soffermann et al. 1998, Boggs et al. 1999, Chen et al. 1999).

Selective venous sampling is of little usefulness in the noninvasive era and should be abandoned because of its low sensitivity (41–65%) and positive predictive value, longer technical performing and high cost, and might be useful only in selected patients with persistent or recurrent hyperparathyroidism (Doppman et al. 1998, Pattou et al. 1999). Magnetic resonance imaging sensitivity does not seem to be different from other techniques, ranging between 77 and 84% (Lee et al. 1996, McDermott et al. 1996).

In patients with hyperplastic parathyroid glands sensitivity of preoperative localization procedures ranges between 41 and 62%, but the frequency of multiglandular disease is less than 15% (Malhotra et al. 1996, Molinari et al. 1996, Blanco et al. 1998, Pattou et al. 1999). It has also been suggested that MPS imaging can help to distinguish preoperatively hyperplasia from adenomatous disease (Johnston et al. 1996). However, such patients require bilateral neck exploration to correctly perform parathyroidectomy, and they should not undergo minimally invasive surgery.

Parathyroid carcinoma is a rare tumour, easy to detect because of its large size. Clinical and biochemical findings of such a tumour and analysis of causes of its prevalence in our experience have been discussed previously (Favia et al. 1998).

In conclusion, parathyroid scintigraphy, US and CT scan sensitivity did not differ significantly but, in any case, we suggest the use of MPS as the first diagnostic tool due to its higher sensitivity (>85%) and good (>96%) positive predictive value. Furthermore, MPS is not influenced (P = NS) by the age of the patients or their biochemical status, and by the size or the site (typical or ectopic) of abnormal parathyroid glands. The combination of US and MPS represents the most reliable noninvasive localization tool and

### Table 4: Results (TP/FN and sensitivity) obtained with a combination of two techniques, P values in respect of the results obtained with a single technique, number and percentage of patients with TP results who underwent both procedures and relative P value (chi-squared test)

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>95</td>
<td>83</td>
<td>84</td>
<td>42</td>
<td>6</td>
<td>41</td>
</tr>
<tr>
<td>Overall TP/FN</td>
<td>86/9</td>
<td>76/7</td>
<td>79/5</td>
<td>38/4</td>
<td>5/1</td>
<td>37/4</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>90.5</td>
<td>91.6</td>
<td>94.0</td>
<td>90.5</td>
<td>83.3</td>
<td>90.2</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>–</td>
<td>NS</td>
</tr>
<tr>
<td>No. of both TP</td>
<td>84</td>
<td>74</td>
<td>52</td>
<td>37</td>
<td>5</td>
<td>36</td>
</tr>
<tr>
<td>Percentage of both TP (%)</td>
<td>88.4</td>
<td>89.1</td>
<td>61.9</td>
<td>88.1</td>
<td>83.3</td>
<td>87.8</td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>NS</td>
<td>–</td>
<td>NS</td>
</tr>
</tbody>
</table>

US, neck ultrasonography; TPS, 201Tl/99mTc-pertechnetate subtraction scintigraphy; MPS, 99mTc-sestamibi/99mTc-pertechnetate subtraction scintigraphy; CT, CT scan of the neck and mediastinum; TP, true positive; FN, false negative.
the two techniques seem to be complementary. If MPS and US are negative or not in agreement further studies are not cost-effective and the patient should undergo bilateral neck exploration.

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Bonjer HJ, Bruining HA, Valkema R, Lamers JS, de Herden WW,


