MINIMALLY INVASIVE RADIO-GUIDED REOPERATIVE SURGERY WITH INTRAOPERATIVE iPTH ASSAY IN PRIMARY HYPERPARATHYROIDISM

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The aim of the study was to present the experience of the authors in employing minimally invasive radio-guided parathyroid reoperative surgery (MIRP) combined with intraoperative iPTH assay (IOPTH) in persistent and recurrent primary hyperparathyroidism (PHP) and in patients with a history of thyroidectomy.

Material and methods. A prospective analysis included the results of 12 reoperations performed employing the minimally invasive method using an intraoperative hand-held gamma camera (Gamma Finder II) following IV administration of 10 mCi 99mTc-MIBI, combined with IOPTH (Future Diagnostics) in six patients with persistent PHP, one patient with recurrent PHP and five patients after subtotal strumectomies without planned parathyroidectomies (F : M = 10 : 2; mean age 54±10.7 years; mean preoperative iPTH concentration 233.3±80.6 ng/L). Prior to surgery, all the patients had been subjected to diagnostic imaging studies (parathyroid scintiscans, USG of the neck, in selected cases, SPECT and CT of the neck and mediastinum). The validity of MIRP and IOPTH in minimizing the extent of intraoperative neck exploration was assessed. Therapeutic results were evaluated in six-month postoperative follow-up.

Results. All the patients were cured. The mean incision length was 3.5±0.5 cm. The mean operative time was 49±10 min. All the patients had a single parathyroid adenoma (in five cases – in the tracheoesophageal groove, in 3 – in the retroesophageal region in the neck, in one – in the retroesophageal region in the superior posterior mediastinum, in one – in the thyrothymic ligament and in two – in the thymus). The mean ratio of adenoma to background neck radioactivity was 25.7±5.4%. The mean iPTH concentration 10 min after adenoma resection was 38.5±17.4 ng/L. No postoperative complications were noted. In six-month postoperative follow-up, all the patients demonstrated normal serum calcium values.

Conclusions. MIRP has proven to be highly successful in reoperations in patients with PHP. The procedure performed using a hand-held gamma camera allows for a safe execution of a minimally invasive procedure focused on resection of a single parathyroid adenoma, eliminating the need for bilateral neck exploration, which is extensive, time-consuming and associated with a higher risk of damaging the recurrent laryngeal nerve and normal parathyroids.

Key words: persistent hyperparathyroidism, recurrent hyperparathyroidism, minimally invasive radio-guided parathyroidectomy, intraoperative parathormone assay

When performed by the experienced surgeon, bilateral neck exploration (BNE) executed in patients with primary hyperparathyroidism (PHP) results in a cure rate approximating 95%–98% (1, 2). Similarly, minimally invasive procedures focused on resection of a single parathyroid adenoma that has been localized in preoperative scintigraphy allow for curing 99%–
100% of patients (3-6). However, in individuals with negative findings of preoperative imaging, surgical results are significantly poorer, what is a consequence of the 30-50% risk of multiglandular disease, while in the remaining patients, the poor outcome is associated with a small-sized parathyroid adenoma, oftentimes situated ectopically and difficult to find, especially by an operator who is less experienced in parathyroid surgery (7, 8, 9). Thus, in spite of considerable progress observed recently in locating pathological parathyroids (scintiscan, SPECT, ultrasound, MRI, CT, SVS) and possibilities of intraoperative monitoring the quality of surgical treatment offered by intraoperative serum parathormone assay (IOPTH), instances of persistent hyperparathyroidism following a negative first neck exploration occur also today (10, 11, 12). These patients, similarly as patients with recurrent primary hyperparathyroidism and individuals with newly diagnosed primary hyperparathyroidism who have had prior thyroid surgery, require reoperations, which are technically difficult and laborious, since they are performed in the operative fields with cicatrical lesions and are associated with a significantly higher risk of recurrent laryngeal nerve damage, permanent hypoparathyroidism and surgical failures (13, 14). The effectiveness of reoperations in restoring normocalcemia is estimated as 80-85% (2, 10-13). Recently, several reports have been published that positively evaluate the method of intraoperative adenoma detection by means of a handheld gamma camera, what has allowed for limiting the extent of neck exploration also in reoperated patients (15-18).

The objective of the report was to present the experience of the authors in minimally invasive radio-guided parathyroid reoperations employing a hand-held gamma camera (MIRP) and IOPTH in patients with persistent or recurrent hyperparathyroidism or after past thyroid surgery.

MATERIAL AND METHODS

Between June 2005 and December 2007, 12 PHP patients after at least one past neck exploration were referred for surgical treatment at the Department of Endocrine Surgery, 3rd Chair of General Surgery, Jagiellonian University Medical College. The group included six patients diagnosed with persistent hyperparathyroidism, one patient with recurrent PHP and five patients after subtotal thyroidectomies without planned parathyroidectomies, who were subsequently diagnosed with PHP (within 3 to 15 years following the original surgery). All the patients had been operated on elsewhere and were referred for reoperations to our referral center. The group was composed of ten females and two males, with the mean age of 54±10.7 years. Preoperative indirect laryngoscopy revealed unilateral vocal cord palsy in two patients (No. 3 and 8). While preparing the patients for reoperations, their past operative reports were reviewed, paying special attention to the number of identified and resected parathyroids, their localization and the extent of thyroid surgery. The analysis also included histopathology of surgical specimens obtained during primary operations. Selected demographic data, medical histories and results of localization examinations of 12 subsequent patients qualified for reoperations are presented in tab. 1.

Preoperative diagnostic management

In all the presented patients, the diagnosis of primary hyperparathyroidism was confirmed preoperatively in keeping with the current diagnostic standards at the Department of Endocrinology, Jagiellonian University Medical College in Cracow. All the patients presented with elevated serum total calcium levels (range of 2.63 to 3.19 mmol/l, mean value 3.04±0.12 mmol/l) and increased serum parathormone values (range of 95.1 to 352.5 ng/L, mean value 233.3±80.1 ng/L).

Radioisotope diagnostics was carried out in the Nuclear Medicine Laboratory, Chair and Department of Endocrinology, Jagiellonian University Medical College. The patients were subjected to subtraction scintigraphy of the neck and upper mediastinum. During the examination, they were immobilized with the head extended.

The scan was done in the frontal plane using a gamma camera (Orbiter; Siemens, Erlangen, Germany) 20 minutes following intravenous administration of 2 mCi (74 MBq) $^{99m}$Tc, and subsequently 5 mCi (185 MBq) $^{99m}$Tc-MIBI, with additional image acquisition after 30 and 45 minutes. The final subtraction image was obtained following digital signal processing and subtracting the image acquired after $^{99m}$Tc administration from the image obtained following
Table 1. Demographics, history and preoperative localization tests in 12 consecutive reoperated patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Primary surgery</th>
<th>Scintigraphy</th>
<th>SPECT</th>
<th>USG</th>
<th>Localization</th>
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<td>brak</td>
<td>+</td>
<td>szyja – PPG</td>
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<td>sTX</td>
<td>–</td>
<td>+</td>
<td>-</td>
<td>szyja – PLD</td>
</tr>
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<tr>
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<td>brak</td>
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<td>szyja – PPG</td>
</tr>
<tr>
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<td>-</td>
<td>grasia – PLD</td>
</tr>
<tr>
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<td>56</td>
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<td>sTX</td>
<td>+</td>
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<td>+</td>
<td>szyja – PPD</td>
</tr>
</tbody>
</table>

PNP – primary hyperparathyroidism; pPNP – persistent PNP; rPNP – recurrent PNP; sTX – subtotal thyroidectomy; OESz – bilateral neck exploration; JESz – unilateral neck exploration; PPG – right upper parathyroid; PPD – right lower parathyroid; PLG – left upper parathyroid; PLD – left lower parathyroid; # ectopic localization in the posterior superior mediastinum; + positive result; +/- dubious result; – negative result; * unilateral vocal cord palsy before reoperation; † complementary result of SPECT and mediastinal CT.

The administration of $^{99m}$Tc-MIBI. The thus acquired images were evaluated by the nuclear medicine specialist (AHD), who used them as the basis for indicating the localization of a pathological parathyroid (fig. 1).

In dubious cases, single photon emission computed tomography (SPECT) of the neck and upper mediastinum was employed (fig. 2). The examination was performed using a dual-head E.CAM gamma camera (Siemens, Erlangen, Germany) equipped with parallel low energy high resolution (LEHR) collimators. Data acquisition was achieved at 360° gamma camera rotation (180° for each head), using the „step and shoot” mode (30 seconds per image) and a 128 x 128 matrix for image storage in the computer. Data processing was done by an e.soft workstation. SPECT reconstruction was performed using the filtered back-projection technique and a Butter-worth filter (cut-off 0.6 cycles/pixel, order – 5).

When a parathyroid adenoma was suspected of being ectopically situated in the mediastinum, an additional sixth-order spiral computed tomography scan with contrast enhancement and digital signal processing (Somatom Emotion 6; Siemens, Erlangen, Germany) was performed.

While qualifying the patients for surgery, the surgeon experienced in ultrasonographic parathyroid imaging (MB) performed a Doppler ultrasound of the neck using 7.5 MHz and 12 MHz linear transducers (Logiq 7; GE, Söllingen, Germany). The patients were examined in supine position, with extended neck; a transverse and a sagittal scan was performed. In order to better visualize the most common ectopic sites in the paraesophageal and prevertebral regions of the neck, the patients were also scanned with the head rotated to the right and subsequently to the left. Ultrasound images showed the enlarged parathyroids as

Fig. 1. Subtraction scintigraphy in a patient no 5 with persistent PHP after negative BNE. An adenoma of the right inferior parathyroid gland was confirmed intraoperatively.
oval, sharply delineated structures with uniform, decreased echogenicity, with peripheral vasculature. Additional evaluation included the thyroid echostructure and in cases when focal lesions 10 mm or more in diameter were detected, a fine needle aspiration biopsy was performed. The ultrasound image was subsequently correlated with the results of isotope studies in order to assess their complementarity (19).

Surgical technique MIRP with IOPTH

All the patients were operated on under general anesthesia by the same surgical team. Sixty minutes before the planned procedure, the patient was administered IV 10 mCi 99mTc-MIBI to prepare him for radio-guided surgery with the use of a hand-held cordless gamma camera (Gamma Finder II; World of Medicine, Orlando, USA). Following anesthesia induction and intubation and having placed the patients on the operating table with extended neck, approximately 90 minutes after radioisotope administration, the focus of the strongest isotope uptake (the hot spot) was localized in the neck (20% above the background level at the minimum) to optimally select the site for surgical access (fig. 3). The effectiveness of the procedure was monitored using the IOPTH method (Future Diagnostics, Wijchen, the Netherlands), evaluating iPTH concentration levels in peripheral blood samples prior to surgery,

Fig. 2. SPECT in a patient no 10 with parathyroid adenoma localized within left lobe of the thymus, 10 cm below the upper margin of the sternum

Fig. 3. Preoperative localization of the suspicious parathyroid lesion with Gamma Finder II. A signal at least 20% higher than background indicates the site of the neck harbouring a parathyroid adenoma and guides the placement of the skin incision
prior to parathyroid adenoma resection, as well as 10 and 20 minutes following the adenomectomy. The MIRP procedure was generally started from a 3-4 cm long incision bordering the scar left after the previous procedure. No complete cicatrectomy was performed (the main scar length was 8±2.5 cm), but only its polar fragment situated at the side of the highest isotope uptake was excised. The surgeons used the lateral approach to the deeper structures of the neck, between the external margin of the subhyoid muscles and the sternocleidomastoid muscle, to avoid extensive dissection of cicatrical tissues left after the previous operation, which had involved division of the subhyoid muscles in the median line.

Further tissue dissection was blunt, and gamma camera measurements were repeated to direct the surgeon to the hot spot (fig. 4). Having identified the parathyroid adenoma and having determined – if possible – the course of the recurrent laryngeal nerve, the lesion was resected and the gamma camera was used to evaluate the degree of radioactivity in the ex vivo material. Radioactive emission of the resected lesion equal to or exceeding 20% of the background value in the neck was regarded as confirmation of resection adequacy. The resected surgical material was referred to paraffin histopathology; no extemporaneous examination was performed. Instead, the effectiveness of MIRP was assessed intraoperatively by evaluating changes in serum parathormone concentration values. The procedure was completed if the iPTH level at 10 minutes after the adenomectomy dropped by at least 50% relative to the initial value (either preoperative or measured immediately before adenoma resection) and iPTH values normalized, falling within the reference range (10-65 ng/L) at 10 or 20 minutes after parathyroid adenoma resection.

Postoperative follow-up

Data on the surgical patients and details of the performed procedures were collected prospectively. As a rule, the patients were hospitalized for two days postoperatively and discharge was effected if their serum total calcium levels were above 2 mmol/l 48 hours after the operation. Indirect laryngoscopy was performed 24 hours postoperatively to assess the vocal cord mobility. All the patients received prophylactic substitution with calcium preparations and active vitamin D metabolites (Calperos 3 g in a divided dose and Alphadiol 1 µg per day). A follow-up examination on day 7 postoperatively included total calcium determinations, modification of substitution therapy and assessment of wound healing. In another follow-up examination performed 4 weeks after the procedure, the result of histopathology was evaluated and serum total calcium and parathormone levels were determined. Six months after the surgery, the patients were again examined and their serum total calcium and parathormone values were assessed. All the 12 patients completed the planned six-month early postoperative follow-up.

RESULTS

Normalization of total calcium and parathormone levels was achieved in all the surgical patients within the follow-up period up to 6 months postoperatively (mean values 6 months after MIRP: calcium 234±0.06 mmol/l, iPTH 34.6±10.7 ng/L).

Among the 12 reoperated patients, PHP – primary, persistent or recurrent – was caused
thyroid adenoma was situated ectopically. In none of the above patients was thyroid tissue resected on the operated side. Histopathologic findings pertaining to prior thyroidectomies described the presence of a single parathyroid gland with an intact structure in the surgical material originating from two of five patients.

The radioactivity ratio of the resected parathyroid adenoma to the background level in the neck was 25.5±5.4%. The mean iPTH concentration at 10 minutes after parathyroid adenoma resection was 38.5±17.4 ng/L, being within the reference range in 11 patients. Only in one patient with the initial iPTH level above 400 ng/L a repeated IOPTH determination at 20 minutes after adenomectomy was necessary; the value normalized and fell within the reference range. None of the patients demonstrated post-adenomectomy iPTH levels below 10 ng/L, what prognosticated a low risk of fixed hypoparathyroidism development.

No complications occurred after MIRP procedures; no repeated hospitalization was necessary, either.

DISCUSSION

Development of methods aiming at intraoperative identification of pathological parathyroids based on the technique of parathyroid radioisotope labeling and detection by means of a hand-held gamma camera has provided the surgeon with yet another tool that potentially

Fig. 5. An intraoperative view – a right superior parathyroid adenoma in a patient nr 11, localized in a retroesophageal ectopic site

Fig. 6. An intraoperative view – a left inferior parathyroid adenoma in a patient nr 10, localized in an ectopic site within thymus 10 cm below upper margin of the sternum, soon after transcervical mobilization

thyroid adenoma was situated ectopically.
facilitates the most difficult procedures in parathyroid surgery, i.e. operations performed in cicatrical cervical tissues. Today, the method is employed in numerous referral centers of endocrine surgery (15-18, 20). A cordless, handheld gamma camera allows the surgeon for performing the procedure from a small incision and for dissecting tissues at the site of the highest accumulation of radioisotope, without a need of an extensive and unnecessary dissection of the surrounding tissues. The method is especially useful in patients who require reoperation and when a single parathyroid adenoma is suspected that has been visualized in preoperative scintigraphy or SPECT. A positive result of preoperative radioisotope scan is necessary when MIRP is to be employed, since it allows for preselection of such patients that would derive the greatest benefit from a MIRP procedure (15-18, 21, 22, 23). A negative result of preoperative radioisotope imaging is associated with a high risk of multiglandular disease, which may be noted in as many as 50% of patients; in the remaining individuals, a negative result may indicate the presence of small adenomas, less than 0.5 g in weight, in the case of which intraoperative detection using MIRP is practically impossible in view of the too small difference between radioactivity accumulated by the adenoma and the background neck activity (16, 17, 18). Not all authors share the opinion that correlating the result of radioisotope test with the results of other imaging studies is necessary (16), but complementarity of ultrasonography results in the case of radioisotope accumulation in the neck, or concordance of spiral computed tomography if the radioisotope test with the results of other imaging studies is employed in numerous referral centers of parathyroid surgery, i.e. operations performed in cicatrical cervical tissues. Today, the method is employed in numerous referral centers of endocrine surgery (15-18, 20). A cordless, handheld gamma camera allows the surgeon for performing the procedure from a small incision and for dissecting tissues at the site of the highest accumulation of radioisotope, without a need of an extensive and unnecessary dissection of the surrounding tissues. The method is especially useful in patients who require reoperation and when a single parathyroid adenoma is suspected that has been visualized in preoperative scintigraphy or SPECT. A positive result of preoperative radioisotope scan is necessary when MIRP is to be employed, since it allows for preselection of such patients that would derive the greatest benefit from a MIRP procedure (15-18, 21, 22, 23). A negative result of preoperative radioisotope imaging is associated with a high risk of multiglandular disease, which may be noted in as many as 50% of patients; in the remaining individuals, a negative result may indicate the presence of small adenomas, less than 0.5 g in weight, in the case of which intraoperative detection using MIRP is practically impossible in view of the too small difference between radioactivity accumulated by the adenoma and the background neck activity (16, 17, 18). Not all authors share the opinion that correlating the result of radioisotope test with the results of other imaging studies is necessary (16), but complementarity of ultrasonography results in the case of radioisotope accumulation in the neck, or concordance of spiral computed tomography if the radioisotope accumulates in the mediastinum allows for focusing the planned extent of surgery and facilitating the execution of MIRP (24, 25).

Radioisotope, i.e. $^{99m}$Tc-MIBI, reaches its optimum accumulation level in parathyroid adenomas (having been leached from the thyroid in the early phase) within 90-150 minutes after its IV administration, hence, the procedure should be planned to fall within this period (15-18).

Reoperation in the neck region requires a detailed examination of previous operative reports and postoperative histopathology results. It also calls for assessment of vocal cord mobility in order to avoid missing asymptomatic impairment of vocal cord mobility in consequence of unilateral recurrent laryngeal nerve palsy resulting from the previous operation. Patients after previous negative neck exploration usually have one or two parathyroids resected (this was the case in the analyzed material), and in some of them, a normal parathyroid was incidentally resected in the course of thyroidectomy. In consequence, reoperated patients are not only at risk of persistent hyperparathyroidism in case a pathological parathyroid escapes identification, but also are in danger of permanent hypoparathyroidism (in case the only remaining adenomatous parathyroid is resected), or are at least at risk of severe transient postoperative hypocalcemia, if at least one normal parathyroid gland has been left in situ. From this viewpoint, the combination of MIRP with IOPTH is advisable, as it allows not only for intraoperative prognosticating of normocalcemia, but also for intraoperative identification of patients at risk of permanent hypoparathyroidism (in case the post-adenoectomy iPTH value drops below 10 ng/L – no such case was observed in the present series), what provides an opportunity for performing a simultaneous autotransplantation of the parathyroid tissue (25, 26, 27). While prognosticating postoperative normocalcemia, the authors employed the Rome criterion (post-adenoectomy normalization of iPTH levels to values in the reference range) rather than the Miami criterion (a post-adenoectomy drop in iPTH value by minimum 50% as compared to the initial value), what resulted from their concern not to miss a „dormant adenoma” in another parathyroid, which becomes activated when iPTH levels are below 100 ng/L (although no such case was observed in the presented group). The use of IOPTH also allowed for elimination of extemporaneous histopathologic examination.

In the presented group of reoperated patients with persistent PHP, the cause of persistent hypercalcemia was a single adenoma localized at the sites of the most common ectopy (in the neck – retroesophageal localization or localization within the thyrothymic ligament, in the mediastinum – localization within the thymus) (28). A more thorough exploration of these sites during the primary negative bilateral neck exploration might have resulted in curing the patients, but in such cases, the surgical result is a derivative of numerous factors, the most important of which is the experience of the surgeon (1, 2). Contrary to cases of persistent PHP, the patients after previous subto-
tal thyroidectomies who were later diagnosed with PHP presented with parathyroid adenomas localized at typical sites (14), but performing the procedure using the MIRP technique was easier in view of its allowing for limiting the dissection extent of cicatrical tissues.

The excellent MIRP outcomes, which allowed for curing all the reoperated patients, resulted on the one hand from the vast experience in parathyroid surgery of the team of operators, but on the other hand, achieving such results was possible thanks to precise imaging diagnostics prior to surgery (21, 22). Of special importance is limiting the percentage of falsely positive scintigraphy results, what has become possible in the presented group owing to relating radioisotope study results to neck ultrasonography findings, as well as through extending the scope of imaging diagnostics in dubious cases to include SPECT and also spiral computed tomography in patients with ectopic mediastinal localization of the lesion. Complementarity of imaging studies increases the chance of a successful operation employing MIRP (16). On the other hand, in the group of patients with negative results of imaging studies, the results of reoperations are significantly poorer and the percentage of postoperative normocalcemia as a rule does not exceed 60-70%, even after extensive blind bilateral neck explorations with blind thymectomies (13).

Summing up, the major advantage of MIRP in reoperations for PHP lies in limiting the extent of neck exploration to the radioisotope-accumulating region, what minimizes the risk of complications and shortens the operative time. Nevertheless, a prerequisite of qualifying patients for procedures performed using this method is the high accuracy of preoperative radioisotope diagnostics, which is the cornerstone of patient preselection.

**CONCLUSIONS**

The method of MIRP has proven to be highly effective in reoperations in patients with PHP and with positive preoperative scintiscans. The procedure done with the use of a hand-held gamma camera has allowed for performing safe minimally invasive operations focused on resection of a single parathyroid adenoma, without any need for bilateral neck exploration, which is much more extensive, time-consuming and associated with a higher risk to the recurrent laryngeal nerve and normal parathyroids.

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Received: 14.07.2008 r.
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