Radioguided occult lesion localization for minimally-invasive parathyroidectomy without quick PTH monitoring and frozen section: impact of the learning curve

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ABSTRACT

Objective: Minimally-invasive parathyroidectomy (MIP) is a surgical procedure that reduces the duration of operation, hospital costs, and hypocalcemia, and shortens the length of hospital stay. This study addressed the important procedural details of the radioguided occult lesion localization (ROLL)-MIP technique and evaluated the consequences of the learning curve from a series of patients.

Material and Methods: A total of 80 patients who underwent ROLL-MIP for a single parathyroid adenoma were included into this retrospective study. In order to analyze the effect of the learning curve, these subjects were then divided into 2 groups per time period and the operative times were compared. Group A consisted of 22 previously reported patients who served as the control group. Group B consisted of 58 consecutive patients.

Results: Serum calcium and parathyroid hormone (PTH) levels were normalized in all of the patients within 2 days and remained normal during the follow-up period (31 ± 18.5 months). None of the patients who underwent ROLL-guided parathyroidectomy suffered temporary or permanent recurrent laryngeal nerve injuries. Mean operation time (time from incision to excision of the adenoma) was 23 ± 6 min in Group A and 18 ± 7 min in Group B. Mean operative times were significantly shorter in group B.

Conclusion: The success of MIP administered with the ROLL technique in a single adenomatous patient was quite high. This method seems especially valuable in patients with atypically located or small adenomas.

Keywords: Parathyroid adenoma, minimally-invasive parathyroidectomy, radioguided occult lesion localization

INTRODUCTION

Primary hyperparathyroidism (pHPT) is a generalized disorder of calcium, phosphate, and bone metabolism caused by an increased secretion of the parathyroid hormone, with a prevalence of 1-3% in western countries. The most common clinical presentation of pHPT is asymptomatic hypercalcemia (1-4). It is explained by a single parathyroid adenoma in most of the cases (80%-85%), followed by hyperplasia, double adenomas, and parathyroid carcinoma.

Surgery continues to remain the mainstay of treatment for patients with symptomatic pHPT (nephrolithiasis, symptomatic hypercalcemia). Indications for surgery during the monitoring of asymomatic patients include an increase in serum calcium ≥ 1 mg/dL above the upper normal limit, a decreased glomerular filtration rate (< 60 mL/min), a reduction in bone density and/or the occurrence of fragility fracture, the occurrence of nephrolithiasis or nephrocalcinosis on the imaging study, and an age of < 50 years (5).

The unilateral focused surgical approach, known as minimally-invasive parathyroidectomy (MIP), is becoming more widespread, because it results in reduced operative time, lower hospital costs, a shorter hospital stay, and fewer events of transient hypocalcemia with cure rates equal to that of formal bilateral neck exploration.
Radioguided occult lesion localization (ROLL) is a new localization technique originally described for nonpalpable breast lesions (6). Recently, it has been reported that the use of ROLL for MIP in patients with pHPT due to a single parathyroid adenoma in the neck is technically safe and effective (7). It has also been shown that the ROLL technique does not impair the postoperative histopathological examination of the parathyroid glands.

Implementation of new procedures, including the ROLL-MIP, must be done in a responsible way to ensure that the procedures are performed correctly. This study addressed the important procedural details of the ROLL-MIP technique and evaluated the consequences of the learning curve from a series of patients.

**MATERIAL and METHODS**

A total of 80 patients who underwent ROLL-MIP for a single parathyroid adenoma were studied in this retrospective study. The study was conducted in accordance with the ethical standards set by the Declaration of Helsinki. Informed consent was obtained from all individual participants included into the study.

All diagnostic imaging studies and US-guided interventions were conducted by the same team member and all patients were operated on by the same surgical team headed by one of our senior endocrine surgeons.

All patients underwent a localization study consisting of dual-phase MIBI scintigraphy and high-resolution US. The parathyroid adenoma was localized preoperatively by scintigraphy and/or US. Diagnosis was confirmed by measuring the PTH in the needle aspirate of the suspicious lesions if scintigraphy and US were inconclusive or discordant. Since the recognition of an adenoma on a US is a prerequisite for ROLL, patients were excluded from the study when their cause of pHPT was neither correlated nor localized sonographically. Exclusion criteria were suspicion of multiple gland disease, multiple endocrine neoplasm syndrome, and thyroid disease requiring thyroidectomy. Surgical success was defined as the excision of the preoperatively identified lesions and normalization of the PTH and serum calcium levels.

**Statistical Analysis**

Analysis of the data was done using the IBM SPSS 25.0 statistical package program. Descriptive statistical methods (frequency, percentage, median, min-max) were used when the study data were evaluated. Normal distribution of the data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests, and the data were not normal. In the study, the Mann-Whitney U test was used for comparisons between the groups. Likelihood (P) values smaller than \(\alpha = 0.05\) were significant and there was a difference between the groups, with large values being insignificant and no differences between the groups.

**Patients**

The study group consisted of all of the surgical candidates presenting at the Department of Endocrine Surgery of Güven Hospital with pHPT due to a single adenoma between September 2011 and November 2017. In order to analyze the effect of the learning curve, these subjects were then divided into 2 groups per time period, and the operative times were compared. Group A consisted of the first 22 previously reported patients, who served as the control group. Group B consisted of 58 consecutive patients enrolled between January 2014 and November 2017.

Group A included 3 males and 19 females, with an average age of 56 ± 14 years (35-85 years) at the time of primary diagnosis. Four out of the 22 patients had previously undergone thyroid/parathyroid surgery. Group B included 19 males and 39 females, with an average age of 50 ± 14 years (22-87 years) at the time of primary diagnosis. Of the patients in both groups, 10 had previously undergone thyroid/parathyroid surgery (4 in Group A, 6 in Group B). Demographic data, preoperative and postoperative serum calcium and PTH levels, localization of the adenoma, and operative time (time from incision to excision of the adenoma) were available for all patients (Table I). Final diagnosis was confirmed histopathologically.

**Imaging studies and ROLL technique**

We have previously described our imaging techniques and interventions for ROLL MIP. Briefly, the diagnosed single parathyroid adenomas were injected with 3.7-5.55 MBq (0.1-0.15 mCi) of Tc-99m labeled macro-aggregated albumin (MAA) on the morning of surgery, using a tuberculin syringe equipped with a 22-G standard needle under US guidance. The total injected volume was 0.1-0.15 mL, depending on the size of the adenoma.

**Surgery**

All patients were operated on under general anesthesia. Surgery was focused on the preoperatively located and injected index gland. Parathyroid adenomas were searched for and localized over the skin with a gamma probe equipped with an 11-mm angled probe (Europrobe 3; EuroMedical Instrument, Paris, France) to decide the best incision level (Figure 1). Midline incisions were made in a skin fold at an appropriate level according to gamma probe measurements. The incisions were slightly weighted toward the expected side of the adenoma. Excised lesions were counted ex-vivo with the gamma probe to make sure that the preoperatively detected and injected lesion had been found (Figure 2,3). Frozen sections and intraoperative quick PTH monitoring were not routinely used. Time from incision to excision of the adenoma (operative time) was recorded. Postoperative follow-up consisted of the evaluation of serum calcium and PTH levels sampled at 6-8 h after surgery. The patients were discharged on calcium and vitamin D supplementation for 2 weeks, with a control visit after 1 week.
RESULTS

Localization of the adenoma was determined based on the PTH levels in the needle washout in 26 patients, by concordant US and scintigraphy results in 41 patients, and by only US results in 13 patients. The size of the successfully biopsied or injected lesions ranged from 7 × 3 mm to 40 × 33 mm in diameter. Parathyroid adenomas were found in inferior parathyroid locations in 59 (73.75%) patients (32 left inferior, 27 right inferior) and in superior parathyroid locations in 21 (26.25%) patients (11 left superior, 10 right superior). US-guided interventions were made without local anesthesia and were well-tolerated without complications in 78 patients. In the remaining 2 patients, who had a phobia of needle procedures, the injections were made after general anesthesia in the operating room.

Radioguided Surgery

All of the injected lesions were successfully located over the skin with the gamma probe. Despite previous cervical explorations in 10 patients, the gamma probe safely guided the surgeon to the preoperatively injected lesions. Mean operation time (time from incision to excision of the adenoma) was 23 ± 7 min in Group A and 18 ± 7 min in Group B. Mean operative times were significantly shorter in group B.

Serum calcium and PTH levels normalized in all of the patients within 2 days and remained normal during the follow-up peri-

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Table 1. Group demographics and comparisons

<table>
<thead>
<tr>
<th></th>
<th>Group A (n= 22)</th>
<th>Group B (n= 58)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>19 (86.4%)</td>
<td>37 (63.8%)</td>
<td>0.090a</td>
</tr>
<tr>
<td>Male</td>
<td>3 (13.6%)</td>
<td>21 (36.2%)</td>
<td></td>
</tr>
<tr>
<td>Age* (years)</td>
<td>57 (35-85)</td>
<td>46 (22-87)</td>
<td>0.091b</td>
</tr>
<tr>
<td>Operative time* (min)</td>
<td>23 (13-35)</td>
<td>16 (8-45)</td>
<td>0.000b</td>
</tr>
<tr>
<td>Adenoma Location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LI</td>
<td>7 (31.8%)</td>
<td>25 (43.1%)</td>
<td></td>
</tr>
<tr>
<td>LS</td>
<td>6 (27.3%)</td>
<td>5 (8.6%)</td>
<td>0.000a</td>
</tr>
<tr>
<td>RI</td>
<td>2 (9.1%)</td>
<td>25 (43.1%)</td>
<td></td>
</tr>
<tr>
<td>RS</td>
<td>7 (31.8%)</td>
<td>3 (5.2%)</td>
<td></td>
</tr>
<tr>
<td>Size on US* (mm × mm)</td>
<td>73 (21-248)</td>
<td>150 (21-1320)</td>
<td>0.000b</td>
</tr>
<tr>
<td>Previous cervical exploration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>18 (81.8%)</td>
<td>52 (89.7%)</td>
<td></td>
</tr>
<tr>
<td>TT</td>
<td>2 (9.1%)</td>
<td>5 (8.6%)</td>
<td></td>
</tr>
<tr>
<td>BST</td>
<td>--</td>
<td>1 (1.7%)</td>
<td></td>
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<tr>
<td>BST + CTx</td>
<td>1 (4.5%)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>UE</td>
<td>1 (4.5%)</td>
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</tbody>
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a: Chi-Square Test, b: Mann-Whitney U Test, *. Median (Min-Max).
Radioguided minimally invasive parathyroidectomy

**DISCUSSION**

pHPT is a complex endocrinopathy involving calcium metabolism and a potent hormone made by the parathyroid glands. Diagnosis is confirmed by inappropriately elevated parathyroid hormone levels accompanied by high-normal or elevated serum calcium. Although classic presentation of pHPT involves the presence of renal stones, bone loss, and gastrointestinal complaints, the screening of serum calcium levels during routine medical examinations has changed the clinical spectrum to include patients with minimally objective symptoms who are referred to as “asymptomatic”.

Over the past decade, there has been a shift towards MIP; a focused operation whereby only 1 parathyroid is removed. Compared to the conventional neck exploration, in which all 4 glands are investigated intra-operatively, MIP is associated with a shorter operating time, lower complication rates, smaller incision size, shorter hospital stay, and greater patient satisfaction (8-11).

Imaging is critical in order to enable successful MIP. Aside from its ability to localize the pathological gland(s), accurate imaging provides valuable anatomical information for the surgeon. Preoperative localization studies have been regarded as necessary but their use is still controversial (12). Some authors suggest that these studies may reduce surgical time, technical failures, complication rates (13) by improving pHPT operation by MIP (14), and radioguided surgery (15,16). Several imaging techniques, such as neck ultrasound (US) (17,18), computerized tomography (CT) (19), and dual-phase Tc-99m MIBI scan with single-photon emission CT (SPECT/CT) are currently available (20) although neck US and MIBI scans are generally used as the first tools in the diagnostic approach of pHPT (21).

ROLL-MIP seems to have several advantages over standard radioguided MIP with an intravenous injection of Tc-99m MIBI: 1) It is independent from the uptake potential of the diseased parathyroid glands and could be used in patients with negative MIBI scintigraphy, 2) It requires very small activity compared with the systemic injection of Tc-99m MIBI (0.1-0.15 mCi vs. 15-20 mCi), 3) The ROLL technique does not cause background activity and potentially gives the best lesion-to-background count ratios, 4) Contrary to the intravenous injection method, the lack of background activity makes the detection of injected adenomas with a gamma probe over the skin easier and facilitates the selection of the incision level as well, and 5) the technique warrants the excision of the preoperatively located adenoma since direct inoculation of Tc-99m labeled particles does not cause false-positive results like an intravenous injection of Tc-99m MIBI.

In our series, all of the preoperatively depicted parathyroid adenomas were found in a timely manner (23 ± 7 min in Group A, 18 ± 7 min in Group B) for the entire study group, including inpatients that had undergone previous neck explorations. In this study, we observed the effect of the learning curve over the duration of the operation, which generally showed a decrease in the duration of the operation as experience increased.

In general, MIP shortens operative and anesthesia time (22-24). In the literature, mean operation time of MIP ranges from 15 to 56 min (25,26). It also shortens hospitalization time (19). In this study, duration of the surgery was short 19.4 ± 7.2 (8-45 min) in the whole group and the patients were not hospitalized for longer than 1 day.

None of the patients had a permanent rise in their PTH and serum calcium levels or required a reoperation due to insufficient resection. In our study, we reached a 100% success rate without requiring additional tests like intraoperative quick PTH monitoring and frozen section.

In summary, the success of the ROLL-MIP technique without rapid PTH measurement and frozen section was quite high in patients with single adenoma. Repeated application of the ROLL-MIP technique resulted in a significant decrease in operative time, as expected. The technique seems to be particularly valuable in patients with atypically located or small adenomas.
Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Ankara Guven Hospital (18.03.2020)

Peer-review: Externally peer-reviewed.


Conflict of Interest: The authors have no conflicts of interest to declare.

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Hızlı PTH ölçümü ve frozen inceleme olmadan occult lezyonlarda radyolojik kılavuzlu minimal invaziv paratiroidektomi: öğrenme eğrisinin etkisi

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ÖZET

Giriş ve Amaç: Minimal invaziv paratiroidektomi (MIP); operasyon süresini, hastane maliyetlerini ve hipokalsemiyi azaltan ve hastanede kalış süresini kısaltan cerrahi bir işlemidir. Bu çalışma, radyoaktif madde ile küçük lezyon lokalizasyonunun (ROLL)-MIP tekniğinin önemli prosedürel detaylarını ele almakta ve bir dizi hastadan gelen öğrenme eğrisinin sonuçlarını değerlendirilmektedir.


Bulgular: Serum kalsiyum ve paratiroid hormonu (PTH) düzeyleri tüm hastalarda 2 gün içerisinde normalize edildi ve takiplerinde (31 ± 18.5 ay) normal kaldı. ROLL eşliğinde paratiroidektomi yapılan hiçbir hastada geçici veya kalıcı rekürren laringeal sinir yaralanması olmadı. Ortalama ameliyat süresi (insizyondan adenomun eksizyonuna kadar geçen süre) Grup A'da 23 ± 6 dakika ve Grup B'de 18 ± 7 dakika idi. Ortalama ameliyat süresi grup B'de anlamlı olarak kısaydı.


Anahtar Kelimeler: Paratiroid adenomu, minimal invaziv paratiroidektomi, radyoaktif madde yardımcılı occult lezyon

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