Intraoperative ultrasound imaging and sono-scintigraphic concordance improves success rates of minimally invasive parathyroidectomy

Abstract

Background/aim: This study aimed to evaluate the effect of sono-scintigraphic correlation on the success of minimal invasive parathyroidectomy (MIP) via surgeon performed continuous intraoperative sonographic guidance in patients operated for primary hyperparathyroidism (PHPT) without intact parathormone (PTH) measurement.

Materials and Methods: A retrospective analysis of a prospective database was conducted to review patients who underwent MIP (July 2017-October 2019). The screened parameters were preoperative PTH level, preoperative ultrasonography (US), preoperative scintigraphy, intraoperative US, intraoperative frozen section analysis, postoperative PTH level and permanent pathology report. Intraoperative intact PTH measurement was not employed due to institutional policy.

Results: Preoperative US alone localized the specific side (right/left, inferior/superior) of abnormality in 54 out of 74 (72.97%) cases. Scintigraphy alone localized the specific side in 58 (78.37%) cases. The sensitivity of preoperative US and scintigraphy alone was 76.05% and 86.56%, respectively. Sono-scintigraphic discordance was present in 6 cases (8.1%) and intraoperative real-time US predicted accurate localization of adenoma in 4 (66.6%) and scintigraphy in 2 (44.4%) patients. The frozen section analysis confirmed parathyroid cells in all cases evaluated.

Conclusion: Sono-scintigraphic concordance with intraoperative real-time imaging increases surgical success rates in cases where MIP is planned under the circumstances of limited resources regarding unavailability of intact PTH measurement.

Key words: Parathyroid adenoma, ultrasonography, minimally invasive surgery, scintigraphy

1. Introduction

Primary hyperparathyroidism (PHPT) is a disorder due to overactivation of one or more of the parathyroid gland/glands. The most frequent type of the pathology is the parathyroid adenoma of a single gland (75–90 %), parathyroid hyperplasia (8–21 %) and double parathyroid adenoma (3–6 %) [1]. PHPT can cause dramatic changes on calcium levels leading to serious health problems such as bone thinning and kidney stones. The recommended treatment of choice for PHPT is surgery with the major goal of treating disease at the index surgical procedure and protect patients from the devastating consequences of secondary interventions [2]. Conventionally, bilateral neck exploration has been the gold standard of care to accurately localize the over functioning gland/glands with intraoperative intact PTH level measurements [3]. Fortunately, with the current invent of minimal invasive procedures (MIP), focused parathyroidectomy became a rational option for PHPT in cases when the diseased gland is accurately localized prior surgery. Regarding localization methods, there are multiple modalities with various success rates [4]. Ultrasonography (US) is one of the most exclusively performed imaging method which is safe and non-invasive with the limitation of direct operator-dependence [4]. On the other hand, application of nuclear medicine imaging including planar scintigraphy and single photon emission computed tomography (SPECT) has been considered as gold standard to localize adenoma with an average sensitivity and positive predictive value up to 90% and 97% for patients without thyroid pathology, respectively [5,6]. The aim of the presented study is to evaluate the effect of preoperative sono-scintigraphic correlation and surgeon performed intraoperative continuous real-time US imaging on the success of MIP for PHPT without intact PTH measurement.

2. Materials and methods

Institutional ethical approval was obtained from the ethics committee of Zonguldak Bulent Ecevit University (Approval no: 2020/18). A retrospective analysis of a prospectively maintained database was conducted to review patients who underwent surgeon performed intraoperative US guided MIP between July 2017 and October 2019 with the diagnosis of parathyroid adenoma. All patients with secondary or tertiary causes of hyperparathyroidism and who did not undergo intraoperative US and sestamibi scan were excluded (Intraoperative ultrasound not intraoperative sm scan). Patients at least one positive imaging regarding localization was included. The scintigraphy was conducted in planar (Tc-99 m Sestamibi-Two phase imaging) and SPECT fashion. Continuous real-time intraoperative US was performed by primary surgeon experienced in sonography. All patients underwent the same preoperative evaluation and all MIP procedures were performed under the guidance of intraoperative real-time US (Figure a.,b.,c.,d).

In the operating theater, the surgeon scanned the neck after positioning using 6-12-MHz high-frequency linear array transducer (Hitachi HI Vision 5500system, equipped with color Doppler; Hitachi, Tokyo, Japan) to mark incision and to image the adenoma during surgery. The second look US scanning of bilateral neck after lesion removal was standard of care to confirm the resection and to verify the absence of a missing adenoma. Intraoperative intact PTH measurement was not employed due to institutional policy. Surgical cure was defined as achieving normocalcemia at 6 months postoperatively. Accuracy of the sonography was measured in association with intraoperative sonographic data documented by the operating surgeon.

The evaluated parameters were as follows; age, gender, body mass index (BMI), preoperative PTH and calcium (Ca) level, preoperative US, preoperative scintigraphy, intraoperative US, intraoperative frozen section analysis, postoperative PTH and Ca level and permanent pathology report. The outcomes of surgery confirmed by definitive histology as well postoperative Ca and PTH results was taken as golden standard to determine sensitivity and positive predictive values of each imaging. Outcomes measures regarding complications included nerve injury as evidenced by postoperative indirect laryngoscopy as well as postoperative hematoma requiring secondary intervention.

3. Parameters evaluated and outcomes measured

The evaluated parameters were as follows; age, gender, body mass index (BMI), preoperative PTH and calcium (Ca) level, preoperative US, preoperative scintigraphy, intraoperative US, intraoperative frozen section analysis, postoperative PTH and Ca level and permanent pathology report. The outcomes of surgery confirmed by definitive histology as well postoperative Ca and PTH results was taken as golden standard to determine sensitivity and positive predictive values of each imaging. Outcomes measures regarding complications included nerve injury as evidenced by postoperative indirect laryngoscopy as well as postoperative hematoma requiring secondary intervention.

4. Results

4.1. Patient Characteristics

Of the 118 patients, 62.7% underwent both of the imaging studies pre-operatively. Basic patient demographics are listed in Table 1. The sample size that met study criteria was 74 patients. Considering the demographic structure of the study, 62 out of the 74 patients who met the criteria were female. The median age of the patients was 53 years (range 32-72) with an average BMI of 29 kg/m2. 4.2. Operative data, imaging and outcomes Solitary adenoma was assigned in 71 patients (95.9 %) and intrathyroidal adenoma in 2 patients, as well. There were one multiple-gland-disease with 2 adenomas which was determined via intraoperative ultrasound after removal of the adenoma localized with preoperative imaging.

In all 42 cases (56.75 %) with sono-scintigraphic concordance, the parathyroid adenoma was accurately localized in the predefined region and successfully excised which was confirmed via normalization of postoperative Ca. and PTH levels. Preoperative US alone localized the specific side (right/left, inferior/superior) of abnormality in 54 out of 74 (72.97%) and sestamibi scan alone localized the specific side in 58 (78.37%) cases. The sensitivity of preoperative US and sestamibi alone was 76.05% and 86.56%, respectively. In only 1 out of 9 cases (11.1%) that were not scintigraphically visualized but sonographically localized, the adenoma could not be found in sonographic localization. In 3 out of 17 cases (17.64%) with scintigraphically imaged, but cannot sonographically detected, the adenoma was not found on scintigraphic localization. Sono-scintigraphic discordance was present in 6 cases (8.1%) and intraoperative real-time US predicted accurate localization of adenoma in 4 (66.6%) and scintigraphy in 2 (44.4%) patients (Table 2).

In these 4 discordant patients, the adenoma was localized on the right superior (1 case) and the left posterior (3 cases) side of tracheoesophageal groove via intraoperative US imaging performed after retracting strap muscles and thyroid lobe and excised successfully. The positive predictive value of US and sestamibi scan was 94.73% and 89.23%, respectively (Table 3).

The frozen section analysis confirmed parathyroid cells in all cases evaluated. Only two patients who had confirmed parathyroid adenoma by permanent histopathology and decreased postoperative calcium and PTH levels after index surgery, experienced recurrent disease after 6 months. Eventually, only 2 of the 118 patients had a recurrence 6 months after the operation, and the rest had no recurrence. There was no recurrent laryngeal nerve injury. Finally, it's worth mentioning that no new focus was found in localization studies at follow-up in terms of recurrent cases. Since the patients did not want the neck exploration, medical treatment was continued.

5. Discussion

In last few decades there has been a tremendous paradigm shift in the surgical management of PHPT from more extensive interventions including bilateral neck exploration, which has been conventionally the gold standard method, towards more conservative approaches employing focused parathyroidectomy. With the evidence-based data reporting higher complication rates of redo surgeries, to establish the best diagnostic and surgical algorithm to treat PHPT at the very first intervention became the major goal of the endocrine surgeons [7]. The most crucial criterion of success for MIP is the accurate localization of hyperfunctioning gland or glands before index surgical intervention. Current improvement in imaging technology made it possible to identify the localization of diseased parathyroid via various techniques [8]. One of the safest being sonography, requiring some experience to become proficient. Preoperative sonographic evaluation of the neck performed by radiologist is a standard of care globally and serves as a main road map guiding surgeon to decide which side of the neck to begin to explore first. Nevertheless, intraoperative sonography performed by principal surgeon allows surgeon many advantages with real-time manner. Moreover, sonographic guidance during surgery leads to design the most appropriate incision and alleviates dissection to reach the pretended region [9]. Sonography is a safe, reproducible and non-invasive method without ionizing radiation providing real-time imaging. However, has a limitation of direct operator-dependence and experience to achieve competence [10]. On the other hand, nuclear medicine applications and other imaging procedures could be utilized in order to accurately localize the lesion to prevent secondary interventions and more complicated extensive neck procedures particularly in patients with unequivocal sonographic evaluations. Currently, most of the imaging protocols utilizes USG and scintigraphy together for better diagnostic quality during surgical planning with intraoperative intact PTH measurement after resection [11]. There are various historic trials demonstrating great success employing combined modalities of US and sestamibi scan; however, the unique aspect of the presented study is the association of continuous performance of intraoperative US by operating surgeon with preoperative US and scintigraphy data without intact PTH measurement. More advanced techniques, one of which is 4D-CT parathyroid scan is promising with the reported sensitivity of 93.9 % and positive predictive value of 85.7 % even for multiglandular disease [12,13]. Nevertheless, the widespread use and accessibility of these techniques are limited due to costs globally. Accordingly, the accurate prediction of the localization of parathyroid adenoma via intraoperative sonography or scintigraphy is crucial. The intraoperative quick PTH assay is another important adjuct that is proposed and extensively used to confirm that the adenoma is excised and the patient's PTH level is within normal ranges which defines the success of the operation [14]. However, this technique is somewhat costly and not available in every institution. In the presented study, none of our patients undergoing focused exploration regarding preoperative imaging had intraoperative PTH performed. In all 42 patients with sono-scintigraphic concordance the adenoma was found precisely at the predicted localizations which means the requirement of intact PTH measurement could be excluded in this subgroup and more selective use of intact PTH might be rational. Moreover, the results of this study clearly demonstrate that preoperative and continuous intraoperative real-time US performed by an experienced surgeon is an accurate method in determining the localization of parathyroid adenoma. Surgeon's knowledge of three-dimensional anatomy, anatomic variations and embryology would improve more precise localization leading to success at the initial surgical procedure with reduced reoperation and complication rates. In addition to providing a great advantage to surgeon, the performance of second look intraoperative US scanning bilateral neck compartments after removing the adenoma is invaluable, to confirm the removal of the predicted lesion and to exclude the presence of additional second adenomas, if intact PTH measurement is not available. In the presented study positive predictive value of surgeon performed intraoperative US was 94.73% which was higher than sestamibi scan with a rate of 89.23%, confirming the importance of surgeon's proficiency and experience on neck US which is an invaluable tool guiding surgical dissection. These findings strongly encourage to adapt the practice of preoperative and intraoperative sonographic evaluation of neck to identify parathyroid glands. The concordance of US with sestamibi scan regarding localization not only improve operative accuracy and decrease the extension of dissection, but US as the diagnostic tool in the hands of the operating surgeon serves to improve the quality of surgical care. In this study, the limitations that occur for the researchers can be divided into three groups in general. One of the limitations in this study is that rapid parathyroid hormone values cannot be measured during the operation. After the parathyroid adenoma is removed, intraoperative PTH measurement is performed to demonstrate the appropriateness of resection. PTH measurement is convenient because it is produced only in the parathyroid gland and is cleared from the circulation in less than 5 minutes due to the short half-life. For intraoperative quick hormone measurement, an immunochemulsant method that can be installed in the operating room has been developed, and the results can be obtained in approximately 10 minutes in the operating room. However, this method is more expensive than checking PTH in the central laboratory. It cannot be applied in many centers in our country and in the world. The second limitation of our study is its retrospective nature and the general limitations of retrospective studies. Finally, we can mention the disadvantage of not being able to make an evaluation with a different eye, since the preoperative ultrasonography examination and operation were performed by a single surgeon. To conclude; in the era of value-based medicine, therapies which are patient-centered, cost-effective and curative at the very first surgical intent should always be prioritized. Precise localization of adenoma preferentially with the minimum diagnostic tools required and an experienced surgeon is the key factor to successfully treat PHPT. Not only will this improve surgical accuracy and decrease operative extent, but it will spare patients from more complicated redo surgeries and will allow selective use of more advanced costly imaging modalities. Moreover, sono-scintigraphic concordance with intraoperative real-time sonographic imaging eliminates the necessity of intact PTH measurement in this subgroup leading to resource management. However, in the presence of discordance, additional imaging methods and the possibility of bilateral neck exploration should be considered and discussed with the patient before ultimate surgical decision.

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None

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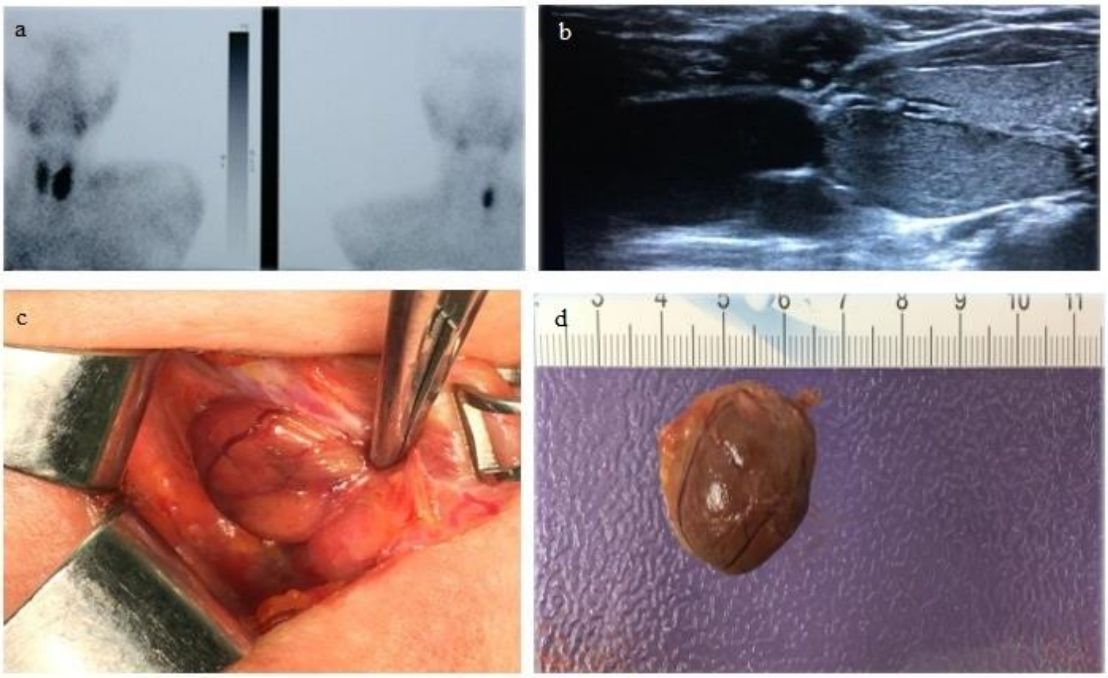

Figure. Case description **(a)** Scintigraphic view **(b)** Sonographic view **(c)** Intraoperative in-vivo image of parathyroid adenoma **(d)** Intraoperative ex-vivo image of parathyroid adenoma.

Table 1. Demographics

Patient Characteristics	No.
Age (years)	53 (median) (range 32-72)
Gender (F/M)	62/12
BMI (kg/m^2)	29±2
Preoperative PTH (pg/mL)	145±14
Preoperative Calcium (mg/dL)	11.2±0.1
Postoperative PTH (pg/mL)	33±4
Postoperative Calcium (mg/dL)	8.6±0.2

Averages with standard error of the mean reported

Note: The values are presented as mean +/- SD or median (min-max)

Table 2. Patient outcomes and operative data in the ultrasonography versus scintigraphy cohorts

Patient outcomes (N)	Ultrasonography (N)	Scintigraphy (N)
Solitary Adenoma (73)	53	58
Double adenoma (1)	1	0
Inaccurate localization (10)	3	7
Sono-scintigraphic discordance (6)	4	2
Nerve injury	0	0
Hematoma	0	0
Recurrence	1	1

Table 3. Preoperative outcomes of Localisation Modalities

Modality	Sensitivity (%)	PPV (%)	Accuracy (%)
Ultrasonography	76.05	94.73	72.97
Sestamibi Scan	86.56	89.23	78.37