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Clinical adaptation of auxiliary methods and multidisciplinary approach to changing trends in parathyroid surgery

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Abstract

To examine the effects of multidisciplinary approach and adjunct methods, on the surgical strategy, complications and treatment success of parathyroid surgery.

Patients, who were operated for primary hyperparathyroidism (n = 411) at our institution between 2012 and 2019 were reviewed retrospectively. Preoperative imaging studies, surgical method, additional diagnostic methods used during surgery, frozen section results, and histopathology findings, complications, persistence, and recurrence were examined.

Localization was determined by first-line examinations in 79.9% (n = 348). Four-dimensional computed tomography was used with an 83.3% success rate. Lateralization success for angiographic selective venous sampling was 80.3% and exact localization success was 65.1%. Bilateral neck exploration was performed in 10.6% (n = 37) of the patients, and in the remaining 89.4% (n = 311), minimally invasive parathyroidectomy (MIP) was performed. While the complication rate was higher in the bilateral neck exploration group ($P = .019$), persistence and recurrence rates were similar between 2 groups. During the study period, annual case volume increased from 9 cases to 103 cases ($P < .001$) and the rate of MIP increased from 44.4% to 92.8% over the years ($P < .001$).

Effective use of adjunct techniques has increased the rates of MIP. The multidisciplinary approach has also provided low complication rates with the increasing number of cases.

Abbreviations: 4D-CT = four-dimensional computed tomography, ASVS = angiographic selective venous sampling, BNE = bilateral neck exploration, IO-GP = intraoperative gamma probe, IO-PTH = intraoperative parathormon, MEB = Multidisciplinary Endocrine Board, MIBI = sestamibi scans, MIP = minimally invasive parathyroidectomy, MRI = magnetic resonance imaging, USG = neck ultrasonography.

Keywords: parathyroid adenoma, parathyroidectomy, primary hyperparathyroidism

1. Introduction

Hyperparathyroidism, which was first defined by Albright in the 1930s, is seen more frequently today and is generally diagnosed at the asymptomatic stage.[1–3] Over the years, not only the clinical findings of this disease but also the surgical strategies have changed. Recognition of the patients in an early clinical stage was achieved owing to advances in laboratory and imaging techniques and easy accessibility. The accurate detection of the pathological gland and the development of intraoperative techniques have increased the surgical success.[4] Changing

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trends in the selection of appropriate type of surgery created a shift from bilateral neck exploration (BNE) to minimally invasive parathyroidectomy (MIP) over the past 15 years.[3,4]

Although BNE is acknowledged as the standard approach by many authors, MIP has gained popularity as a minimally invasive surgical method that allows shorter operation time, decreased postoperative pain, smaller incision, and less scar tissue.[5] The main factor that enables minimally invasive surgery to be performed safely is the precise localization of the pathological gland before surgery. Although there is no consensus regarding the number and order of imaging methods, American Association of Endocrine Surgeons recommends experienced clinicians to make decisions according to their imaging capabilities.[6]

Neck ultrasonography (USG) and sestamibi scans (MIBI) are the 2 most commonly used methods for the detection of the pathological gland before the surgery. Conventional computed tomography and magnetic resonance imaging (MRI) are the traditional second-line imaging methods used in patients when localization with USG and scintigraphy is unsuccessful. Nowadays, a novel method called four-dimensional computed tomography (4D-CT) has increasingly been used for detecting the parathyroid gland instead of conventional computed tomography in available institutions.[7] 4D-CT is based on visualization of hyper functioning parathyroid tissue with early contrast uptake and rapid wash-out in images taken within 25 to 30 and 30 to 60 seconds following ionized contrast administration.[8–10] The sensitivity of 4D-CT is close to 90% and it is effective especially in cases where USG and/or sestamibi are negative or discordant and in the presence of an ectopic parathyroid adenoma.

Angiographic selective venous sampling (ASVS) is one of the most valuable third-line techniques to localize the pathologic gland and it might be preferred when non-invasive investigations fail to localize the adenoma. However, it is an invasive method and generally used for recurrent or persistent disease.[11,12]

In addition to preoperative imaging studies, there are also some auxiliary methods used as a guide during surgery. While the use of an intraoperative gamma probe (IO-GP) is a helpful guide in finding the pathological gland, intraoperative parathormon (IO-PTH) allows us to make sure that the pathological gland is removed and to safely terminate the operation.[13]

One of the most important stages of parathyroid surgery is the management of the disease with a multidisciplinary approach. In this way, the quantity of complex cases increases and the effectiveness of disease management improve.[14,15]

Hereby, we aimed to evaluate the effects of adjuncts methods, multidisciplinary approach and operation type, which we have used at our institution on the treatment success.

2. Methods

Patients, who were evaluated by the Multidisciplinary Endocrine Board (MEB) and underwent parathyroid surgery (n = 411) at our institution between 2012 and 2019 were reviewed retrospectively. Preoperative imaging studies, laboratory tests, surgical method, additional surgery requirement, additional diagnostic methods used during surgery, frozen section results, postoperative laboratory and histopathology findings, complications, persistence, and recurrence were examined. Patients with concomitant thyroid pathology requiring surgery due to nodules or diffuse goiter and those who were operated for secondary or tertiary hyperparathyroidism were excluded (n = 63). USG and MIBI were used as the first-line imaging methods in all patients. One of the second-line cross-sectional imaging modalities were used in cases of undetermined location (CT or MRI). 4D-CT or ASVS was used as a third-line method for advanced examination in cases, where the pathological glands could not be localized despite conventional cross-sectional imaging. 10% difference in PTH levels was accepted as the cut-off value for the correct localization of the pathological gland.[12] IO-PTH and IO-GP were used as peroperative adjunct methods within the availability of our hospital during the study period. Parathyroidectomy with the use of gamma probe was performed fallowing the intravenous injection of the radioisotope (10–20 mCi Tc99m sestamibi) approximately 1 hour before surgery. When IO-PTH was used, the patients were evaluated according to the Miami Criteria and it was expected that pre-incision PTH value decreased by >50% at the 10th minute after excision.[16]

The surgical method to be applied was determined according to the preoperative imaging studies. While MIP was performed in patients with preoperative pathological gland localization, BNE was performed in patients whose localization could not be achieved despite localization studies or whose MIP procedures failed. All operations were performed under general anesthesia. All patients were operated by experienced endocrine surgeons in the general surgery department.

2.1. Operative approaches

MIP and BNE were performed under general anesthesia, patient was placed in a semi-fowler position with both arms tucked at the sides. A silicone pillow was put under the shoulder to slightly extend the neck. For MIP, 1.5 cm skin incision was made over the estimated area of the localized gland. Then, strep muscles were medialized and sternocleidomastoid muscle was lateralized to reach the thyroid gland. The tissues were dissected meticulously and the parathyroid gland searched carefully using with loupes magnification for protecting recurrent nerves and vascular structures.[17]

In BNE, midline was opened in the avascular plane following a small Kocher incision. Strep muscles were divided in the midline and thyroid gland was reached. Then, 4 parathyroid glands were examined and enlarged glands were resected. Intraoperative cure was confirmed histopathologically with frozen section in all cases. And according to availability cure was confirmed radioactively with IO-GP in former cases and biochemically with IO-PTH in the later. In addition, all samples were evaluated by the pathologists participating in the MEB by peroperative frozen section followed by hematoxylin eosin staining of paraffin blocks. The operation was terminated according to the IO-PTH value and frozen section results. Patients were discharged on oral calcium regimen at postoperative day 1.

2.2. Statistical analysis

Data were evaluated using JMP software version 9.0.1 (SAS, Cary, NC). Continuous variables were expressed as mean ± SD. Categorical variables were expressed as frequencies and percentages. Comparison of parametric continuous variables was performed using Student *t* test. The chi-square test was used in the comparison of categorical variables. *P* values of ≤.05 were considered as statistically significant.

2.3. Ethical standards

All procedures performed in this study involving human participants were in accordance with the ethical standards of

the institutional ethics committee (Ref. No: 2020-12-09, Date: June 8, 2020) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

3. Results

The female/male ratio of the patients (n = 348) was 293/55, and 45.7% were diagnosed because of high calcium levels in laboratory findings (Table 1). Localization was determined by first-line examinations in 79.9% (n = 348). While cross-sectional imaging was required in 91 patients, the rate of localization detection in cross-sectional imaging was only 52.5% for MRI and 42.8% for conventional CT. 4D-CT was used in 12 patients with an 83.3% success rate. Invasive tertiary examinations (ASVS) were used in 66 of the patients. Lateralization success for ASVS was 80.3% and exact localization success was 65.1% (Table 2).

Bilateral neck exploration was performed in 10.6% (n = 37) of the patients, and in the remaining 89.4% (n = 311), MIP was performed. The operation time was shorter in the MIP group than in the BNE group ($P < .001$). IO-GP was used in 29.3% of the patients (n = 102). While 90 of the IO-GP were used in MIP, 12 of them were used in BNE ($P = .661$). IO-PTH was used in 50% of patients (n = 174) and used more frequently in patients who underwent MIP (n = 162) than patients who underwent BNE (n = 12), ($P = 0.022$). The rate of conversion to 4-gland exploration was 2.6% (n = 8) in patients who underwent MIP (Table 3).

The laboratory examinations (preoperative Ca, PTH, phosphorus, 25-OH Vitamin D, and postoperative 3rd and 6th month Ca and PTH) were similar between both groups (Table 4). While the complication rate was higher in the BNE group ($P = .019$), persistence and recurrence rates were similar between 2 groups ($P = .635$) (Table 5).

During the study period, IOPTH replaced IOGP, ASVS, one of the preoperative examinations, was always used to a certain extent, and 4D-CT was started to be used as an effective preoperative test (Fig. 1). Also, annual case volume increased from 9 cases to 103 cases ($P < .001$) and the rate of MIP increased from 44.4% to 92.8% over the years ($P < .001$) (Fig. 2).

4. Discussion

The minimally invasive surgery trend that started in the 1980s has increased the tendency from bilateral neck exploration to focused surgery in parathyroidectomy since the 90s with the advances in auxiliary diagnostic methods. Besides, it has many advantages for patients, and also reliable for the surgeon because of reduced complication rates.[18] In our center, we established a standard treatment algorithm with the multidisciplinary endocrine council for evaluating patients with PHPT. With the

Table 1

Demographic findings.

Demographic findings	n
Age, mean (SD)	56.17 (10.8)
Gender, n (%)	
Female	293 (84.2)
Male	55 (15.8)
Clinical manifestations n (%)	
Skeletal symptoms	52 (14.9)
Nephrolithiasis	25 (7.2)
Neuromuscular symptoms	80 (22.9)
Neurocognitive symptoms	11 (3.2)
Cardiovascular symptoms	10 (2.9)
Gastrointestinal Symptoms	11 (3.2)
Hypercalcemia	159 (45.7)

Table 2

Preoperative adjunct technics.

Preoperative imaging technics	n	Accuracy (%)
USG + MIBI	348	79.9
Cross-sectional imaging	91	56.0
MRI	59	52.5
CCT	14	42.8
4D-CT	12	83.3
ASVS		
Lateralization	53	80.3
Localization	43	65.1

4D-CT = four-dimensional computed tomography, ASVS = angiographic selective venous sampling, CCT = conventional computed tomography, MIBI = sestamibi scans, MRI = magnetic resonance imaging, USG = neck ultrasonography.

Table 3

Intraoperative findings.

Intraoperative findings and tools	MIP	BNE	*P* value
n, (%)	311 (89.4)	37 (10.6)	N/A
Operation time, min, mean (SD)	93 (75.1)	126 (41.6)	<.001
Use of IO-GP, n (%)	90 (25.9)	12 (3.4)	.661
Use of IO-PTH, n (%)	162 (46.6)	12 (3.4)	.022
Convertion to BNE, n (%)	8 (2.6)	–	N/A

BNE = bilateral neck exploration, IO-GP = intraoperative gamma probe, IO-PTH = intraoperative parathormon, MIP = minimally invasive parathyroidectomy.

Table 4

Laboratory findings.

Laboratory findings, mean (SD)	MIP (n = 311)	BNE (n = 37)	*P* value
Pre-op calcium, mg/dL	11.4 (0.1)	11.4 (0.1)	.934
Pre-op PTH, pg/mL	270.3 (49.8)	274.9 (38.7)	.956
Pre-op phosphorus, mg/dL	2.7 (2.3)	2.7 (0.8)	.981
Pre-op 25 (OH) D, mmoL/L	21.2 (16.6)	21.3 (14.9)	.911
Post-op 3rd month calcium, mg/dL	9.6 (0.9)	9.3 (1.1)	.121
Post-op 3rd month PTH, pg/mL	72.4 (7.1)	74.1 (17.2)	.925
Post-op 6th month calcium, mg/dL	9.6 (0.6)	9.4 (0.5)	.421
Post-op 6th month PTH, pg/mL	64.6 (5.5)	52.1 (12.1)	.493

Serum calcium reference range: 8.4–10.5 mg/dL.
Serum parathormone (PTH) reference range: 10–65 pg/mL.
Serum phosphorus reference range: 2.5–4.5 mg/dL.
Serum 25-hydroxyvitamin D [25 (OH) D] reference: <20 mmoL/L is considered as Vitamin D deficiency.
BNE = bilateral neck exploration, MIP = minimally invasive parathyroidectomy.

Table 5

Differences between 2 surgical methods.

Postoperative Findings	MIP (n = 311)	BNE (n = 37)	*P* value
Histopathological, n (%)			.247
Adenoma	306 (98.4)	34 (91.9)	
Double adenoma	1 (0.3)	1 (2.7)	
Hyperplasia	4 (1.3)	2 (5.4)	
Complication, n (%)	1 (0.3)	2 (5.4)	.019
Persistence, n (%)	1 (0.3)	0 (0.0)	.635
Recurrence, n (%)	1 (0.3)	0 (0.0)	.635

BNE = bilateral neck exploration, MIP = minimally invasive parathyroidectomy.

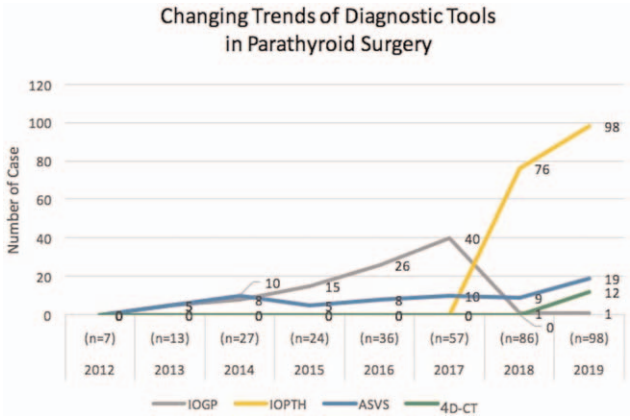

Figure 1. Different preoperative and peroperative auxiliary methods. 4D-CT = 4 dimension computed tomography, ASVS = angiographic selective venous sampling, IOGP = intraoperative gamma probe, IOPTH = intraoperative parathormone, n = total number of case.

application of adjunct techniques such as 4D-CT, IO-PTH, and ASVS within the availability of our hospital, the rate of MIP increased and complication rates decreased.

Our results have shown the success of first-line imaging methods in detecting the pathological gland. Although 4D-CT has been used in a limited number of patients at our hospital for the last few years, very successful results have been obtained (Table 2).

Failure to detect adenoma with conventional preoperative studies, may result in unsuccessful surgery requiring reoperation, prolonged hypercalcemia, and possible future complications.[14] For this reason, in selected cases, we use ASVS with the approval of the MEB in order to eliminate the need for a second operation in patients with adenomas whose localization cannot be determined. Although ASVS is an invasive technique, prolonged hypercalcemia, patient stress, and additional costs due to complications of a possible reoperation can be prevented with the meticulous use of ASVS. Considering all these aspects, ASVS may be less invasive than a second operation requirement.[12] Our study showed that, increased rates of successful ASVS, also increased the applicability of MIP.

IO-GP, which has also been used as an intraoperative auxiliary method in a certain period of time at our clinic, is no longer

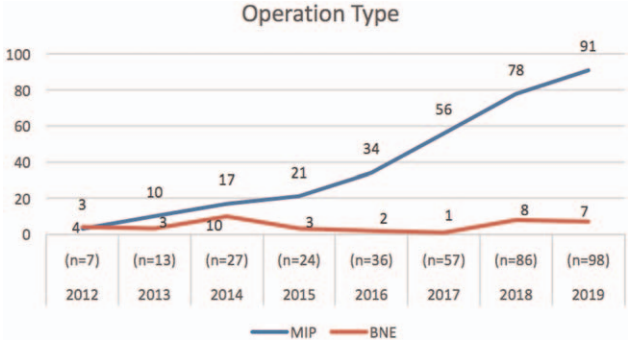

Figure 2. Operative technique and volume of approaches. BNE = bilateral neck exploration, MIP = minimally invasive parathyroidectomy, n = total number of case.

applied because of its systemic effects, and using difficulties in small exploration area for MIP procedures. Also, Perrier et al[19]. stated that, they no longer use gamma prop because it contributes little to the preoperative radionuclide study results and prolongs the operation time. However, Pasta et al[20] used this method with 10% Lugol's solution to prevent radioisotope uptake by the thyroid gland. In this way, it was possible to clearly distinguish the radioactivity of the parathyroid adenoma from the surrounding tissues and ensure the treatment success of parathyroid surgery.

Although there was no difference between the persistence and recurrence rates for MIP and BNE, the complication rates were found to be significantly higher in those with BNE. Jinih et al[21] reported similar persistence, recurrence and complication rates in a large meta-analysis comparing BNE and MIP results. The most common complication in their study was reported as transient hypocalcemia. In our study, 1 transient hoarseness in the MIP group, 1 permanent hoarseness, and 1 postoperative hemorrhage were found in the BNE group, contrarily, we did not encounter any transient hypocalcemia. We believe that the relatively low complication rates in our series are due to our high volume endocrine specific working strategy. The absence of transient hypocalcemia in our study was attributed to the patients being prescribed oral calcium preparations in the early postoperative period.

The retrospective design of the study is one of the main limitations. Another major limitation is the heterogeneity of radiological and nuclear medicine evaluations of the patients. Ultrasonographic examinations are carried out not by a single radiologist, instead by various radiologist at our institution, and some MIBI studies were performed at an external center. Although all of the visualization studies were evaluated in the MEB, by our radiology and nuclear medicine specialists.

As a result, developing and changing diagnostic trends in PHPT surgery always plays a role in the choice and success of the surgical method. It is undeniable that additional imaging and laboratory techniques that facilitate localization increase the applicability of MIP. Effective use of these techniques in our clinic has increased the rates of MIP. The multidisciplinary approach has also provided low recurrence rates with the increasing number of cases.

Author contributions

Statistical analysis (A. Cem Dural, Husnu Aydin, Murat Sipahi); final approval (all authors).
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