Langenbeck's Archives of Surgery
https://doi.org/10.1007/s00423-022-02711-5

RESEARCH

Check for updates

Persistence of primary hyperparathyroidism: a single-center experience

Dmitrii M. Buzanakov[1] · Ilya V. Sleptsov[1] · Arseny A. Semenov[1] · Roman A. Chernikov[1] · Konstantin Y. Novokshonov[1] · Yulia V. Karelina[1] · Natalya I. Timofeeva[1] · Anna A. Uspenskaya[1] · Viktor A. Makarin[1] · Igor K. Chinchuk[1] · Elisey A. Fedorov[1] · Natalya A. Gorskaya[1] · Ilya V. Sablin[1] · Yuriy N. Malugov[1] · Svetlana A. Alekseeva[1] · Ksenya A. Gerasimova[1] · Alexander A. Pushkaruk[1] · Mikhail V. Lyubimov[1] · Dina V. Rebrova[1] · Shamil S. Shikhmagomedov[1] · Timur A. Dzhumatov[2] · Anna V. Zolotoukho[2] · Alexander N. Bubnov[1]

Received: 27 April 2022 / Accepted: 9 October 2022

Abstract

Background Parathyroidectomy is the only definitive treatment for primary hyperparathyroidism (PHPT). Precise localization of abnormal glands is a key to a successful surgery. Most patients are expected to be successfully treated with focused parathyroidectomy. However, this approach is associated with a risk of existing multiglandular disease which may lead to the postoperative persistence of PHPT.

Methods Eight hundred ten patients who underwent an initial surgery for PHPT at SPBU Hospital in 2017–2018 were included in the study. Preoperative imaging results were evaluated. Multivariate logistic regressions were calculated to estimate predictive values of preoperative data for the risk of postoperative persistence and risk of MGD.

Results Multiglandular disease was found to be a leading cause of persistent hyperparathyroidism. An anamnesis of thyroid surgery was found to be a significant risk factor for the persistence of hyperparathyroidism. The rate of persistence did not differ significantly between groups with bilateral neck exploration and focused parathyroidectomy. Age, sex, body mass index as well as negative results of preoperative US, MIBI, and 4D CT were not independently associated with a higher risk of MGD. All preoperative imaging modalities showed from low to moderate sensitivity for the detection of MGD. The frequency of cases of a missed second adenoma did not differ significantly between patients with concordant and discordant preoperative data. There were 7 cases with previously unsuspected second adenomas found solely due to bilateral neck exploration.

Conclusions None of the combination of preoperative visualization modalities was able to rule out the MGD and reliably identify patients for focused parathyroidectomy. Additional preoperative visualization failed to improve overall results. Bilateral neck exploration appeared to have a slight benefit for the patients with concordant preoperative imaging results.

Keywords Primary hyperparathyroidism · Bilateral neck exploration · Focused parathyroidectomy · Preoperative imaging · Multiglandular disease

Introduction

The number of operations performed for primary hyperparathyroidism (PHPT) is increasing, as surgery remains the only definitive treatment for the disease, and the procedure is safe and cost-effective, compared to conservative treatment [1, 2].

Meanwhile, there is still no consensus on the optimal surgical treatment of PHPT. Most patients could be successfully treated with the focused parathyroidectomy (FPTX) based on preoperative visualization data. Sestamibi scintigraphy and ultrasound imaging are considered to be the "gold standard" for parathyroid imaging, allowing for an accurate preoperative localization of parathyroid adenomas [3, 4].

The development of additional options for preoperative visualization is expected to improve the accuracy of patient selection for FPTX. 4D-CT has proven to be a useful

✉ Dmitrii M. Buzanakov
dmitrybuzanakov@gmail.com

1 Saint Petersburg State University Hospital, Saint Petersburg, Saint Petersburg, Russian Federation

2 Faculty of Medicine, Saint Petersburg State University, Saint Petersburg, Russian Federation

imaging modality even as a first-line imaging [5, 6] with a demostrated high diagnostic accuracy of up to 93% [7]. Positron emission tomography (PET) with 11C-Choline showed even more outstanding results with an accuracy of nearly 99% [8]. However, despite its excellent accuracy rivaling exploratory surgery in cases of non-localized adenoma, PET has some considerable limitations mostly related to its cost and availability [9]. Even then, a focused approach still may face a risk of postoperative persistence of PHPT due to an undetected multiglandular disease (MGD). MGD itself may stand for 3–33% of all PHPT cases [10].

At the present time, up to 30% cases of MGD remain undetected preoperatively [11]. Preoperative predictors of MGD have been actively investigated for the past decades [12]. Several preoperative scoring systems for the prediction of multiglandular disease were developed and evaluated. The most frequently used systems were CaPTHUS score and the Wisconsin index. The former is a scoring model based on preoperative total calcium and intact PTH serum levels, positive ultrasound and sestamibi scan results for a single enlarged gland, and concordant ultrasound and sestamibi scan findings [13], while the latter employs multiplication of preoperative serum calcium by preoperative parathyroid hormone [14].

Further investigations showed limited usefulness of these models, indicating that they cannot reliably rule out MGD. [15, 16]. More recent studies reported diabetes mellitus, elevated serum osteocalcin levels, and negative sestamibi scintigraphy to be significant factors associated with MGD [12].

Intraoperative PTH test (ioPTH) is currently widely used to confirm intraoperatively the removal of hyper-functioning parathyroid gland and thus excluding the possibility of MGD during the FPTX [17]. Nevertheless, there are certain drawbacks associated with ioPTH use including additional cost and operation time spent waiting for the results [18]. At the same time the accuracy of the test may vary significantly, showing little to no difference in success rate, compared with the same surgical procedure without ioPTH, in patients with concordant preoperative imaging [19, 20]. The rate of false positive results of the ioPTH (i.e., significant decrease in serum PTH following the removal of just one of the multiple adenomas) must also be taken into consideration [21, 22]. Our own previous data [23] for standard and modified (with shortened time of analysis) ioPTH test showed 50–60% specificity. The overall risk of disease persistence after FPTX is 2–3% as reported by various large studies, raises the question of the role of conventional parathyroidectomy versus bilateral neck exploration (BNE) as routine surgery for PHPT [24]. Although the widespread use of focused parathyroidectomy over past decade has shown high rate of success [25], they seem to have approached their maximum possible efficiency. Also, there are published data of the extent of preoperative imaging that does not affect surgical outcomes or complications rate [26].

BNE may be viewed as a reasonable alternative [27]; however, it is associated with higher requirements for the surgical technique and a higher number of possible surgical complications. Besides, BNE is still strongly questioned in terms of its cost-effectiveness [28, 29]. The data on its influence on outcomes are controversial A 2017 meta-analysis of 19 studies showed no significant difference in the rate of the persistence between BNE and FPTX [30]. A 2020 Cochrane systematic review reported the similar success rates of minimally invasive parathyroidectomy and BNE with higher rate of symptomatic hypocalcemia in BNE group [24].

Methods

Data on consecutive patients who underwent surgery for PHPT at Saint Petersburg State University Hospital during the years of 2017–2018 (from January 2017 to December 2018) have been collected into a database, containing information about the patients' medical history, clinical variables, surgical records and histology reports. The total number of patients was 827. Initial operations for PHPT were performed in 810 cases. All patients with normocalcemic PHPT had been previously treated with cholecalciferol and had normal kidney function.

Outcome

Persistence of hyperparathyroidism was defined as the presence of one of the following: (1) reoperation for PHPT during the observed hospital stay, (2) ionized calcium levels above the upper margin of reference (1.31 mmol/L) with inadequate PTH level at the time of discharge, (3) absence of PTH decrease up to the moment of discharge along with normal calcium level in patients with normocalcemic PHPT. Long-term follow-up data were not collected. MGD was defined as one of the following: (1) more than one histologically confirmed parathyroid adenoma excised during surgery within the observed hospital stay, (2) more than one enlarged gland excised with none of the glands reported as adenomas on histological examination, and a resolution of hyperparathyroidism following surgery, (3) persistence of PHPT following the excision of a single parathyroid adenoma. Long-term outcomes were not investigated.

Preoperative localization studies

The results of the visualization studies were encoded as nominal: present or missing; and further specified retrospectively for each gland: positive or negative, uncertain findings were considered as negative. Neck US was performed preoperatively in all cases and assessed by several endocrine surgeons. All radionuclide studies were performed in various medical facilities others than SPBU Hospital before the admission to the hospital. All 4D CTs were performed in SPBU Hospital and reviewed by a surgeon and a radiologist. Patients could have an additional 4DCT performed after their admission to the Hospital by their surgeon's appointment.

Biochemistry

The following biochemical markers were analyzed preoperatively: serum ionized calcium and PTH. Serum ionized calcium concentrations were analyzed through ISE technology using an EasyLyte Calcium-MEDICA analyzer. The reference range was 1.13–1.31 mmol/L. Serum ionized calcium was assessed preoperatively and on the day following surgery. PTH was measured by immunochemiluminescent assay using a Beckman Coulter analyzer. The reference range was 1.3–9.3 pmol/L. PTH was assessed preoperatively, at 1 h after surgery and on the day following surgery. Genetic testing was not performed preoperatively, as it is not covered by standard insurance. All patients with MGD were recommended to perform genetic testing after surgery.

Surgery

Surgeries were performed by a team of 14 experienced endocrine surgeons. Each surgical team included at least one surgeon with over 10-years-experience of parathyroid surgery.

Surgery was performed through a 3–4 cm (based on the patient's constitution) standard Kocher incision. The strap muscles were divided in the midline. Ninety patients underwent concomitant thyroid surgery (total thyroidectomy, lobectomy, or atypical thyroid resection): 49 for follicular thyroid neoplasm, 15 for thyroid cancer, 16 for toxic goiter, and 10 for non-toxic goiter. Intraoperative neuromonitoring of recurrent laryngeal nerves was performed selectively according to the patients' preferences, as this procedure was not covered by standard public healthcare insurance.

In each case, the surgeon was free to choose the type of operation: with or without bilateral neck exploration. At the time of the study, there were no preferences concerning the surgical approach among all surgeons. The algorithm for neck exploration was not standardized and was left to the operating surgeon's discretion with due consideration as to each clinical situation details. Central neck dissection and thymectomy were not mandatory for BNE. Intraoperative measurement of PTH was not performed due to technical limitations. Frozen section was not used as it would increase the time of operation. Normal parathyroid glands were not routinely biopsied.

Statistical analysis

Pearson's chi-square test was used to compare categorical variables between groups. Multivariate logistic regression models were developed to identify preoperative factors independently associated with postoperative persistence and risk of MGD. The following independent variables were included in the analysis: age, sex, body mass index, negative scintigraphy (yes or no), negative US (yes or no), negative CT (yes or no), number of preoperative visualization studies (1, 2, or 3), previous operations on the neck (yes or no). Odds ratios (*OR*) and 95% confidence intervals (*CI*) were calculated. P value < 0.05 was considered statistically significant. All tests were two-tailed.

Statistical analysis was performed in R.

Results

Median age was 58 years (range from 9 to 87). Most of them were female; male patients accounted for 6.1%. There were 21 cases of normocalcemic PHPT. In all cases of normocalcemic PHPT, the localization of an abnormal gland was discovered by at least one visualization method.

Persistence of PHPT was found in 43 cases. There was no significant difference between the BNE and non-BNE groups. ($p = 0.616$). An undetected complementary adenoma in a typical position on the neck was the most frequent cause of the persistent disease ($n = 24$) (Table 1). Of 42 patients with the persistence, 30 were reoperated during the present hospital stay and became cured. Twelve patients were discharged without re-operation due to the absence of a localized adenoma, according to the data by postoperative 4D CT.

Total number of cases of MGD was 54 (6.67%), 5 of which were identified as MEN1 and were genetically verified by the time of data collection (Table 3).

Negative results of preoperative visualization, body mass index, sex, and age were assessed. No significant predictors were found among estimated variables (Table 4).

In all cases, neck ultrasound (US) was performed preoperatively by a surgeon. In 109 cases, only US was performed. Three hundred fifty-six patients had sestamibi scintigraphy (MIBI) performed at the prehospital stage. In 181 cases, computed tomography with intravenous contrast injection (4D CT) was performed either at prehospital stage or during the observed hospital stay instead of scintigraphy. In 164 cases, 4D CT was added as a third visualization study.

Different studies independently showed a weak to moderate sensitivity for the diagnostics of MGD, with 4D CT showing higher sensitivity values (Table 5).

In 673 cases, a single adenoma was localized by at least one imaging modality with no direct indication of MGD (Table 6). MGD and total persistence rates were significantly lower in this group, while the rate of persistence caused by MGD did not differ significantly from the group of patients with discordant imaging results, suspected MGD, or without localized adenoma.

Out of the 200 cases with BNE, in 131 cases BNE was performed in patients with a single localized adenoma,

Table 1 Cases with postoperative persistence of PHPT

Sex	Age	Ionized calcium level (mmol/L)	PTH level (pmol/L)	Total number of adenomas	Previous thyroid surgery	BNE performed	MEN 1 confirmed	Cause of the persistence	Missed gland localization
f	59	2.23	60.8	3	No	No	No	Second adenoma on the neck missed	RS + RI
m	55	1.59	56.7	2	No	No	No	Second adenoma on the neck missed	RS
f	42	1.35	23.3	3	No	Yes	No	Second adenoma on the neck missed	RS + RI
f	30	1.59	7	3	No	Yes	Yes	Adenoma estimated as normal	RI
f	37	1.4	4.4	1	No	No	No	Enlarged parathyroid gland taken for an adenoma	LS
f	55	1.26	43.9	Unknown	No	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	58	1.35	12.1	2	No	No	No	Second adenoma on the neck missed	LS
f	55	1.49	9.3	2	No	No	No	Second adenoma on the neck missed	RI
f	84	1.36	5	Unknown	No	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	50	1.36	7.9	2	No	No	No	Second adenoma on the neck missed	RI
f	67	1.53	11.6	Unknown	No	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	51	1.45	19	1	No	Yes	No	Supernumerary mediastinal adenoma	5th Mediastinal
f	63	1.35	14.1	1	Yes	No	No	Lymph node taken for an adenoma	RS
f	58	1.74	22.7	2	No	No	No	Second adenoma on the neck missed	LS
f	54	1.63	13.7	1	No	No	No	Thyroid nodule taken for an adenoma	RS
f	57	1.3	12.5	2	No	No	No	Second adenoma on the neck missed	RS
f	56	1.43	6.1	1	No	Yes	No	Adenoma in aortopulmonary window	APW
f	56	1.61	19.2	2	Yes	No	No	Second adenoma on the neck missed	RS
f	74	1.53	37.8	1	No	No	No	Thyroid nodule taken for an adenoma	LI
f	69	1.42	13.8	3	No	No	No	Second adenoma on the neck missed	RI + LS
f	69	1.33	12.7	1	No	Yes	No	Thyroid nodule taken for an adenoma	RI
f	72	1.52	64.5	Unknown	No	Yes	No	Lymph node taken for an adenoma	Unknown
f	29	1.46	8.1	2	No	No	Yes	Second adenoma on the neck missed	RS
m	52	2.01	44	2	No	No	No	Second adenoma on the neck missed	LS

Table 1 (continued)

Sex	Age	Ionized calcium level (mmol/L)	PTH level (pmol/L)	Total number of adenomas	Previous thyroid surgery	BNE performed	MEN 1 confirmed	Cause of the persistence	Missed gland localization
f	60	1.4		1	No	No	No	Enlarged parathyroid gland taken for an adenoma	LI
f	68	1.44	18.5	2	Yes	Yes	No	Second adenoma on the neck missed	RS
m	45	1.71	18.5	2	Yes	Yes	No	Second adenoma in aortopulmonary window	APW
f	43	1.43	14.6	2	No	No	No	Second adenoma on the neck missed	LI
f	67	1.34	31.8	2	No	No	No	Second adenoma on the neck missed	RS
f	53	1.38	9.6	Unknown	Yes	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	57	1.7	20.4	2	No	No	No	Second adenoma on the neck missed	RS
f	81	1.35	27.2	Unknown	No	No	No	Second adenoma on the neck missed	RI
f	57	1.48	13.6	Unknown	No	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	87	1.31	14.3	2	No	No	No	Second adenoma on the neck missed	RI
f	63	1.57	17.1	1	Yes	No	No	Lymph node taken for an adenoma	LS
f	53	1.19	10.3	2	No	No	No	Second adenoma on the neck missed	RI
f	69	1.42	19.2	2	No	Yes	No	Second adenoma on the neck missed	RS
f	68	1.34	15.2	2	Yes	No	No	Second adenoma on the neck missed	LS
f	65	1.53	21.5	2	No	Yes	No	Second adenoma on the neck missed	LS
f	33	1.25	15	Unknown	No	No	No	Enlarged parathyroid gland taken for an adenoma	Unknown
f	61	1.39	18.3	1	No	No	No	Second adenoma on the neck missed	RI
f	49	1.48	20.8	2	No	No	No	Second adenoma on the neck missed	RS
f	53	1.31	7.9	1	No	No	No	Thyroid nodule taken for an adenoma	LS

An anamnesis of the thyroid surgery was found to be the only factor significantly associated with a higher risk of the persistence of the disease ($OR = 4.649142$, 95% $CI = [1.2685791, 17.038373]$) (Table 2).

RS right superior, *RI* right inferior, *LS* left superior, *LI* left inferior, APW aortopulmonary window.

according to at least one visualization modality. There were 3 cases of a second adenoma found intraoperatively in this group, and no MGD was missed.

Improvement in MGD detection achieved by adding BNE was found to be significant using a comparison of relative predictive values for paired samples $NPV = 100\%$ vs 91.7% ($p = 0.0456$).

Patients with two or three preoperative studies ($n = 681$) were further divided in 2 groups: (1) with concordant visualization — patients with at least two preoperative

Table 2 Multivariate logistic model of the risk of postoperative persistence

	OR	2.5%	97.5%
Negative US (yes/no)	0.6125619	0.1640335	2.287532
Negative CT (yes/no)	2.516499	0.2205314	28.715936
Negative MIBI (yes/no)	1.443112	0.3496298	5.956504
BMI	1.077409	0.9917539	1.170462
Thyroiditis (yes/no)	1.600668	0.4171979	5.956504
Sex (m/f)	1.42772	0.1695557	12.021922
Age	1.42772	0.9831090	1.075972
Thyroid Nodules (yes/no)	1.028493	0.5168269	4.011337
Thyroid surgery anamnesis (yes/no)	4.649142	1.2685791	17.038373*
BNE performed (yes/no)	0.8722553	0.1149205	6.620484
Number of preoperative visualization studies (3 or less)	2.179062	0.8141141	5.832487

Table 3 Characterization of patients with a single adenoma vs MGD

Number		MGD 54	Single adenoma 756
Age		55.0 ± 13.1	56.9 ± 12.0
Sex	m	4	49
	f	49	708
Preoperative ionized calcium (mmol/l)		1.47 ± 0.19	1.49 ± 0.17
Postoperative persistence		24	19

Table 4 Multivariate logistic model of the risk of MGD

	OR	2.5%	97.5%
Negative US (yes/no)	1.12243	0.4403378	2.861095
Negative CT (yes/no)	4. 282339	0.8479477	21.626835
Negative MIBI (yes/no)	1.24263	0.4066877	3.796844
BMI	1.000079	0.9834466	1.016993
Sex (m/f)	1.259609	0.3726131	4.258078
Age	0.9871979	0.9643682	1.010568

visualization studies each indicating a single parathyroid adenoma at the same site ($n = 461$; 2) with uncertain imaging results — all other cases, including negative results by at least one method of visualization, discordant imaging data, or suspected MGD ($n = 240$).

The rate of MGD was a significantly higher group with discordant imaging while as well as a total persistence rate, while the rate of persistent cases caused by MGD did not differ significantly (Table 7).

In 175 cases, BNE was performed. In 87 cases, BNE was performed for patients with concordant results; no MGD was missed in this group with 2 cases when second adenomas were found only intraoperatively. Improvement in MGD detection received by adding a BNE was found to be significant using a comparison of relative predictive values for paired samples for paired samples $NPV = 100\%$ vs 94.3% ($p = 0.0254$).

Forty-six patients with at least two visualization studies performed had at least one adenoma which was not preoperatively localized. Twenty-six of them had a single adenoma which localization was not correctly identified at preoperative stage; 20 patients had MGD with only one abnormal gland localized preoperatively. There were 7 cases with previously unsuspected complementary adenomas found solely due to BNE.

Discussion

During the 2 years covered in the study, the leading cause of the persistent PHPT was a missed adenoma in undetected MGD on the neck. In contrast to other works [12], we have not found the negative MIBI scans to increase the risk of MGD. No combination of preoperative visualization modalities was able to reliably rule out MGD and precisely identify patients for FPTX. Even within the cohort of patients with completely concordant imaging, MGD is frequently observed, accounting for nearly one-third of the total prevalence.

Additional preoperative visualization (4D CT as a third modality) was unable to improve overall results. This may partially be due to the effect of a "challenging" case. Patients with small and/or atypically located adenomas, which were not seen through standard imaging, received more extensive

Table 5 Independent diagnostic values of different visualization studies for MGD

	US		MIBI		4D CT	
	Value	95% *CI*	Value	95% *CI*	Value	95% *CI*
Sensitivity	22.92%	12.03% to 37.31%	33.33%	17.29% to 52.81%	62.16%	44.76% to 77.54%
Specificity	97.99%	96.65% to 98.90%	92.69%	89.78% to 94.98%	90.13%	86.21% to 93.24%
Positive predictive value	44.00%	27.39% to 62.07%	24.39%	14.93% to 37.23%	43.40%	33.44% to 53.92%
Negative predictive value	94.85%	94.04% to 95.56%	95.16%	93.84% to 96.20%	95.14%	92.82% to 96.74%

Table 6 Characterization of patients with a single adenoma localized by preoperative imaging vs patients with uncertain imaging results

	Localized single adenoma	No localization, discordant imaging results or suspected MGD	Chi-sq	*p*-value
Number of patients	673	137		
Number of MGD	22	32	73.826	< 0.001
Number of persistent cases	28	15	10.435	0.002
Number of persistent cases caused by missed MGD	19	5	0.270	0.604
BNE performed	131	69		

Table 7 Characterization of patients with completely concordant imaging results vs uncertain imaging results

	Concordant data	Negative results by at least one method of visualization, discordant data or suspected MGD	Chi-sq	*p*-value
Number of patients	461	240		
Number of MGD	15	39	37.494	< 0.001
Number of persistent cases	18	23	9.243	0.003
Number of persistent cases caused by missed MGD	13	11	1.484	0.224
BNE performed	87	88		

preoperative examination along with more thorough intraoperative exploration, while apparently simple cases received less attention with regard to the possible risk of MGD. That is perhaps why discordant preoperative visualization results were not associated with the higher risk of persistence caused by neck MGD, as one might intuitively expect. These findings may suggest an underestimated role of BNE in a group of patients with preoperative data indicating a single adenoma. It is important to note that the imaging discordant data from patients, who underwent a FPTX and had a persistent disease, were obviously misinterpreted by a surgeon, which led to a wrong choice of a surgical treatment. This implies that none of the visualization modalities should be considered as having a priority for the planning of FPTX.

Negative preoperative imaging while seeming to pose a challenge [31, 32] was not associated with a lower rate of the success of treatment. Indeed, clinically significant parathyroid glands in a typical position on the neck are often reported to be successfully found through the blind exploration [33] after an ectopic (intravagal or mediastinal) adenoma has been ruled out [34].

Stricter demands for visualization improve the identification of adenoma but still fail to reliably rule out MGD. We see that the rate of undetected neck MGD did not significantly decrease following the selection of patients with at least two studies with completely concordant results.

The retrospective character of the study puts considerable limitations on drawing any conclusions. For example, the large number of cases with discordant visualization results where BNE was not performed suggests that retrospective evaluation of preoperative does not always correspond to that in actual clinical practice, and the results should not be directly applied.

All imaging methods are operator-dependent thus affecting the results of the study. We cannot be confident that imaging data we classify as "concordant" were viewed the same way by a surgeon who made the decision to perform BNE or not. There may have been findings one could interpret as "suspicious" or "uncertain" which may have led to the performing of BNE. Heterogenity within the group with performed scintigraphy affects our estimation of its accuracy. For this method performed in accordance to the standard protocols in a single facility, the MGD detection rate is expected to be higher. Additional visualization methods may be successfully applied in order to increase the cure rate. However, the increasing of the number of imaging studies may delay the surgery, which is even more important for the healthcare system where patients have irregular or limited access to diagnostic options. The cost-effectiveness of this approach in comparison with the broader use of BNE requires further investigations. The performance of BNE for patients with a localized single adenoma in such circumstances may help to overcome limitations of misinterpreted preoperative data.

The overall low rate of both MGD and postoperative persistence demands for a larger cohort of patients in order to obtain clear evidence for or against routine BNE. However, in that case the future findings may still be biased due to the gradually increasing cumulative experience of a surgical team. Additionally, we believe that the selection criteria for FPTX are being continuously optimized and may affect the sample. Moreover, a higher the rate of BNEs performed, a better understanding of parathyroid anatomy is expected; therefore, the overall incidence of treatment failure may decrease. The use of frozen section increases the time of operation. However, it helps to eliminate the risk of the removal of non-parathyroid tissue and therefore may be efficiently applied to BNE, as we observe that BNE itself does not positively affect this type of surgical failures. BNE may be approached as a diagnostic surgical maneuver rather than as an alternative type of the surgery. With this approach an improvement of the diagnostics of MGD may be obtained. Thus, either the criteria for FPTX should be further specified or the role of BNE expanded, particularly, for high-volume endocrine clinics. At the same time the safety of BNE is still under question and further investigations are required.

Conclusion

To this date, no combination of preoperative visualization modalities seems to reliably rule out MGD. The higher overall success rate apparently cannot be achieved by increasing the number of preoperative visualization studies performed on a single patient. The routine performance of BNE may decrease the rate of the persistence of PHPT and therefore may be recommended for high-volume centers as a routine procedure, though further investigation is required.

Author's contributions Study conception and design: Dmitrii M. Buzanakov, Ilya V. Sleptsov, Roman A. Chernikov, Arseny A. Semenov. Surgeons: Ilya V. Sleptsov, Roman A. Chernikov, Arseny A. Semenov, Konstantin Y. Novokshonov, Julia V. Karelina, Viktor A. Makarin, Anna A. Uspenskaya, Natalya I. Timofeeva, Igor K. Chinchuk, Elisey A. Fedorov, Natalya A. Gorskaya, Ilya V. Sablin, Yuriy N. Malugov, Svetlana A. Alekseeva. Acquisition of data: Svetlana A. Alekseeva, Alexander A. Pushkaruk, Ksenya A. Gerasimova, Shamil S. Shikhmagomedov, Mikhail.V. Lyubimov, Dina.V. Rebrova. Data analysis: Dmitrii M. Buzanakov, Timur A. Dzhumatov, Anna V. Zolotoukho. Writing — original draft preparation: Dmitrii M. Buzanakov, Anna V. Zolotoukho. Writing — review and editing: Ilya V. Sleptsov, Roman A. Chernikov, Arseny A. Semenov, Anna V. Zolotoukho. Supervision: Alexander N. Bubnov.

Declarations

Competing interests The authors declare no competing interests.

Conflict of interest The authors declare no competing interests.

References

1. Nilsson IL (2019) Primary hyperparathyroidism: should surgery be performed on all patients? Current evidence and residual uncertainties. J Intern Med 285:149–164. https://doi.org/10.1111/joim.12840
2. Zanocco K, Heller M, Sturgeon C (2011) Cost-effectiveness of parathyroidectomy for primary hyperparathyroidism. Endocr Pract 17:69–74. https://doi.org/10.4158/EP10311.RA
3. Coakley AJ, Kettle AG, Wells CP et al (1989) 99Tcm sestamibi–a new agent for parathyroid imaging. Nucl Med Commun 10(11):791–794
4. Johnson NA, Tublin ME, Ogilvie JB (2007) Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. Am J Roentgenol 188:1706–1715. https://doi.org/10.2214/AJR.06.0938
5. Kelly HR, Hamberg LM, Hunter GJ (2014) 4D-CT for preoperative localization of abnormal parathyroid glands in patients with hyperparathyroidism: accuracy and ability to stratify patients by unilateral versus bilateral disease in surgery-naïve and re-exploration patients. Am J Neuroradiol 35:176–181. https://doi.org/10.3174/ajnr.A3615
6. Starker LF, Mahajan A, Björklund P et al (2011) 4D parathyroid CT as the initial localization study for patients with de novo primary hyperparathyroidism. Ann Surg Oncol 18:1723–1728. https://doi.org/10.1245/s10434-010-1507-0
7. Day KM, Elsayed M, Beland MD, Monchik JM (2015) The utility of 4-dimensional computed tomography for preoperative localization of primary hyperparathyroidism in patients not localized by sestamibi or ultrasonography. Surgery 157:534–539. https://doi.org/10.1016/j.surg.2014.11.010
8. Orevi M, Freedman N, Mishani E et al (2014) Localization of parathyroid adenoma by 11C-choline PET/CT. Clin Nucl Med 39:1033–1038. https://doi.org/10.1097/rlu.0000000000000607
9. Tay D, Das JP, Yeh R (2021) Preoperative localization for primary hyperparathyroidism: a clinical review. Biomedicines 9:390. https://doi.org/10.3390/biomedicines9040390
10. Barczyński M, Bränström R, Dionigi G, Mihai R (2015) Sporadic multiple parathyroid gland disease—a consensus report of the European Society of Endocrine Surgeons (ESES). Langenbeck's Arch Surg 400:887–905. https://doi.org/10.1007/s00423-015-1348-1
11. Shah US, Mccoy KL, Kelley ML et al (2022) How and when is multiglandular disease diagnosed in sporadic primary hyperparathyroidism? Surgery 171(1):35–39. https://doi.org/10.1016/j.surg.2021.09.018
12. Thier M, Daudi S, Bergenfelz A, Almquist M (2018) Predictors of multiglandular disease in primary hyperparathyroidism. Langenbeck's Arch Surg 403:103–109. https://doi.org/10.1007/s00423-017-1647-9
13. Kebebew E (2006) Predictors of single-gland vs multigland parathyroid disease in primary hyperparathyroidism. Arch Surg 141:777. https://doi.org/10.1001/archsurg.141.8.777
14. Mazeh H, Chen H, Leverson G, Sippel RS (2013) Creation of a "Wisconsin Index" nomogram to predict the likelihood of additional hyperfunctioning parathyroid glands during parathyroidectomy. Ann Surg 257:138–141. https://doi.org/10.1097/SLA.0b013e31825ffbe1
15. Serradilla-Martín M, Palomares-Cano A, Cantalejo-Díaz M et al (2021) Usefulness of the Wisconsin and CaPTHUS indices for predicting multiglandular disease in patients with primary hyperparathyroidism in a southern European population. Gland Surg 10:861–869. https://doi.org/10.21037/gs-20-857
16. De Pasquale L, Lori E, Bulfamante AM et al (2021) Evaluation of Wisconsin and CaPTHUS indices usefulness for predicting monoglandular and multiglandular disease in patients with primary hyperparathyroidism through the analysis of a single-center experience. Int J Endocrinol 2040284:1–8. https://doi.org/10.1155/2021/2040284
17. Dobrinja C, Santandrea G, Giacca M et al (2017) Effectiveness of intraoperative parathyroid monitoring (ioPTH) in predicting a multiglandular or malignant parathyroid disease. Int J Surg 41:26–33. https://doi.org/10.1016/j.ijsu.2017.02.063
18. Morris LF, Zanocco K, Ituarte PHG et al (2010) The value of intraoperative parathyroid hormone monitoring in localized

primary hyperparathyroidism: a cost analysis. Ann Surg Oncol 17:679–685. https://doi.org/10.1245/s10434-009-0773-1
19. Barczyński M, Gołkowski F, Nawrot I (2015) The current status of intraoperative iPTH assay in surgery for primary hyperparathyroidism. Gland Surg 4(1):36–43. https://doi.org/10.3978/j.issn.2227-684X.2015.01.01
20. Badii B, Staderini F, Foppa C et al (2017) Cost-benefit analysis of the intraoperative parathyroid hormone assay in primary hyperparathyroidism. Head Neck 39:241–246. https://doi.org/10.1002/hed.24567
21. Haciyanli M, Lal G, Morita E et al (2003) Accuracy of preoperative localization studies and intraoperative parathyroid hormone assay in patients with primary hyperparathyroidism and double adenoma. J Am Coll Surg 197:739–746. https://doi.org/10.1016/S1072-7515(03)00676-8
22. Sugg SL, Krzywda EA, Demeure MJ, Wilson SD (2004) Detection of multiple gland primary hyperparathyroidism in the era of minimally invasive parathyroidectomy. Surgery 136:1303–1309. https://doi.org/10.1016/j.surg.2004.06.062
23. Sleptsov IV, Vybornova NB, Chernikov RA, et al (2015) Modified quick parathyroid hormone test in surgery of primary hyperparathyroidism. Endocr Surg 9(4):12–21. (In Russ.) https://doi.org/10.14341/serg201541221
24. Ahmadieh H, Kreidieh O, Akl EA, El-Hajj Fuleihan G (2020) Minimally invasive parathyroidectomy guided by intraoperative parathyroid hormone monitoring (IOPTH) and preoperative imaging versus bilateral neck exploration for primary hyperparathyroidism in adults. Cochrane Database Syst Rev. https://doi.org/10.1002/14651858.CD010787.pub2
25. Sleptsov IV, Chernikov RA, Bubnov AN et al (2012) Minimally invasive surgery of primary hyperparathyroidism. Endocrine Surgery 6:24–33 (In Russ.)
26. Fazendin JM, Lindeman B, Chen H (2020) Preoperative parathyroid localization does not improve surgical outcomes for patients with primary hyperparathyroidism. Am J Surg 220(3):533–535. https://doi.org/10.1016/j.amjsurg.2020.04.029
27. Norman J, Lopez J, Politz D (2012) Abandoning unilateral parathyroidectomy: why we reversed our position after 15,000 parathyroid operations. J Am Coll Surg 214:260–269. https://doi.org/10.1016/j.jamcollsurg.2011.12.007
28. Walsh NJ, Sullivan BT, Duke WS, Terris DJ (2019) Routine bilateral neck exploration and four-gland dissection remains unnecessary in modern parathyroid surgery. Laryngoscope Investig Otolaryngo 4:188–192. https://doi.org/10.1002/lio2.223
29. Norlén O, Wang KC, Tay YK et al (2015) No need to abandon focused parathyroidectomy. Ann Surg 261:991–996. https://doi.org/10.1097/SLA.0000000000000715
30. Jinih M, O'connell E, O'leary DP et al (2017) Focused versus bilateral parathyroid exploration for primary hyperparathyroidism: a systematic review and meta-analysis. Ann Surg Oncol. 24(7):1924–1934. https://doi.org/10.1245/S10434-016-5694-1
31. Dy BM, Richards ML, Vazquez BJ et al (2012) Primary hyperparathyroidism and negative Tc99 sestamibi imaging: to operate or not? Ann Surg Oncol 19:2272–2278. https://doi.org/10.1245/s10434-012-2325-3
32. Elaraj DM (2010) Are Additional localization studies and referral indicated for patients with primary hyperparathyroidism who have negative sestamibi scan results? Arch Surg 145:578. https://doi.org/10.1001/archsurg.2010.108
33. Wachtel H, Bartlett EK, Kelz RR et al (2014) Primary hyperparathyroidism with negative imaging. Ann Surg 260:474–482. https://doi.org/10.1097/SLA.0000000000000875
34. Ellika S, Patel S, Aho T, Marin H (2013) Preoperative localization of parathyroid adenomas using 4-dimensional computed tomography: a pictorial essay. Can Assoc Radiol J 64:258–268. https://doi.org/10.1016/j.carj.2012.03.002

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.