Original Research

AMERICAN ACADEMY OF OTOLARYNGOLOGY–HEAD AND NECK SURGERY
FOUNDATION

OTO Open
2025, Vol. 9(2):e70122

DOI: 10.1002/oto2.70122
http://oto-open.org
WILEY

Effectiveness of Bilateral Internal Jugular Parathyroid Hormone Measurements in Optimizing Hyperparathyroidism Surgery Outcomes

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Abstract

Objective. This study aimed to assess the effectiveness of intraoperative parathyroid hormone (PTH) measurements from bilateral internal jugular veins (BIJVs) in determining parathyroid gland laterality during surgery for primary hyperparathyroidism (PHPT).

Study Design. Prospective cohort study.

Setting. Single tertiary care center, February 2021 to February 2023.

Methods. All patients underwent intraoperative BIJV PTH measurements during parathyroidectomy. Preoperative localization of abnormal parathyroid glands was performed using cervical ultrasound (USG) and sestamibi scans (MIBI). Receiver operating characteristic (ROC) analysis was performed to determine the best performance (sensitivity and specificity) for predicting parathyroid gland laterality.

Results. A total of 124 patients underwent surgery during the study. PTH measurements from BIJV successfully confirmed the laterality of parathyroid adenomas in 102 cases (82.3%, $P = .001$). Intraoperative BIJV PTH measurements proved to be the most effective method for determining parathyroid gland laterality, with an accuracy of 82.3%. ROC curve analysis identified an optimal cutoff point of 16.7% for the percentage difference between right and left BIJV PTH values. The area under the curve (AUC) was 0.882, indicating high diagnostic accuracy. This cutoff yielded a sensitivity of 76.5% and a specificity of 95.5%. Additionally, no patients experienced complications related to the internal jugular vein (IJV) procedure.

Conclusion. Intraoperative BIJV PTH measurement is a valuable adjunct in parathyroidectomy, improving localization and enhancing surgical outcomes in PHPT patients.

Keywords

intraoperative parathyroid hormone, parathyroidectomy, primary hyperparathyroidism

Received December 11, 2024; accepted April 15, 2025.

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in nonhospitalized patients[1] and ranks third among endocrinological disorders.[2] It affects 1 in 700 individuals,[3] approximately 3% of postmenopausal women[4] and 0.73% of men.[5] The diagnosis is established through clinical and biochemical evaluations, with imaging reserved for patients undergoing surgical consideration.[6] Parathyroidectomy remains the gold standard for definitive treatment.[7] Over time, surgical approaches have shifted from routine bilateral neck exploration to targeted parathyroidectomy, aided by the advent of localizations studies and rapid PTH assays.[8] As 85% to 90% of cases are attributable to a single adenoma,[9] preoperative identification of abnormal glands enables minimally invasive unilateral neck exploration, reducing

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This article was presented at the AAO-HNSF 2024 Annual Meeting & OTO EXPO; September 27-October 1, 2024; Miami Beach, Florida.
Review board: IRB – CAAE: 43412821.4.0000.5505. Federal University of São Paulo.

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operative time and morbidity without compromising cure rates.[10]

For targeted parathyroidectomy, two concordant imaging studies are required, along with intraoperative rapid PTH monitoring.[9] Most surgeons in the United States use a combination of parathyroid ultrasonography (USG) and methoxyisobutylisonitrile parathyroid scintigraphy (MIBI) for surgical planning.[11] The sensitivity of ultrasound and sestamibi in PHPT is 76% and 78%, respectively.[12] If both imaging modalities are negative, surgical success rates decline.[13] In this scenario of negative imaging modalities, central PTH collection from the bilateral internal jugular veins (BIJVs) can aid in decision-making by confirming gland laterality.

Differential venous sampling of PTH concentration from the BIVJ, though invasive, is a practical technique that may help identify the side of the hyperfunctioning parathyroid gland. Despite limited literature,[14-17] Irvin and Carneiro's initial work in 1999 on intraoperative PTH monitoring to confirm surgical success briefly mentions central PTH collection from the BIJV as a potential tool.[18] Two prominent studies also performed PTH sampling from the internal jugular veins (IJVs) to determine adenoma lateralization. In 2007, Ito, with a cohort of 168 patients, described that this difference exists but preestablished a threshold of 5% between sides. Similarly, Barczynski et al[16] in 2009, with 78 patients, set a preestablished difference of 10% between sides. Although these prior studies have explored the utility of performing PTH sampling from the BIJV, the threshold differences are quite variable among studies, and there is no established reliable value for the potential application of this diagnostic method to date.

The concept of this study is to demonstrate the efficacy of selective parathyroid hormone (PTH) sampling from the IJVs to determine whether there is a difference in PTH concentration values between the veins that supports the method for accurately identifying adenoma lateralization and serves as a tool for the surgeon.

The aim of this study was to determine whether PTH values collected from the BIJV in patients with PHPT could assist in surgical decision-making and to establish a concentration gradient, particularly in cases with previously negative localization studies.

Methods

With approval from the institutional review board IRB – CAAE: 43412821.4.0000.5505, we conducted a prospective study of patients who underwent parathyroidectomy for PHPT at the Department of Otolaryngology–Head and Neck Surgery, Federal University of São Paulo, from February 2021 to February 2023. Data regarding sex, age, localization exams, surgeries performed, and complications were collected.

Inclusion criteria consisted of patients diagnosed with PHPT (defined by hypercalcemia and PTH levels above the normal reference range) who underwent preoperative imaging studies with USG and MIBI and provided written informed consent. Exclusion criteria included patients with a history of previous neck surgery and those with jugular vein thrombosis.

All patients underwent preoperative cervical ultrasound and sestamibi scans to localize abnormal parathyroid glands. Patients were classified into three categories based on preoperative imaging results: concordant, discordant, or negative. The concordant group included patients with positive findings in both USG and MIBI, identifying the same gland. Patients were classified as negative if all preoperative imaging results were negative. In the discordant group, one modality identified a localized abnormality, whereas the other did not, or the scans localized different parathyroid glands. Patients with concordant preoperative USG and MIBI scans (double positive), where both identified the parathyroid adenoma on the same side, underwent unilateral neck exploration. Those with discordant or negative scans underwent conventional bilateral neck exploration. Regardless of the groups, all patients underwent PTH sampling from the IJVs (five samples as described below).

Parathyroidectomy was guided by the Miami criteria,[19] which require a decrease in PTH levels of ≥50% relative to baseline (peripheral limb) 10 minutes after adenoma excision. Central PTH values did not influence the surgical strategy employed. As part of the study protocol, blood samples were collected in the operating room after general anesthesia, with the patient in a supine position and the neck extended. In addition to standard peripheral limb (leg) blood collection for evaluating intraoperative PTH decay (peripheral—time zero [T0] and peripheral—time 10 minutes [T10]), ultrasound-guided blood samples were taken from the right internal jugular vein (RIJV) at T0 and from the left internal jugular vein (LIJV) at T0 using a 23-G percutaneous needle and a 3-mL syringe. A central sample was also collected from the IJV ipsilateral to the excised gland (under direct visualization—directly from the exposed IJV in the operative field) at T10, totaling five PTH samples:

1. Peripheral T0
2. RIJV T0
3. LIJV T0
4. Peripheral T10
5. IJV (side of adenoma) T10.

All T0 samples were collected after general anesthesia and before the surgery began, whereas the T10 samples were collected 10 minutes after adenoma removal during the surgical procedure.

For statistical analysis, numerical variables were expressed as mean ± standard deviation, and categorical variables were expressed as numbers and percentages. For nonparametric values, analysis of variance

(Wilcoxon) was applied for comparisons at the same time point. Receiver operating characteristic (ROC) analysis was then performed to determine the best performance (sensitivity and specificity) for predicting parathyroid gland laterality, based on ROC curve coordinates between the percentage difference in PTH values from the IJVs. Statistical significance was defined as a *P*-value < .05.

Results

The final sample comprised 124 patients (**Figure 1**), including 97 females (78.2%) and 27 males (21.8%), with a mean age of 59.4 years, ranging from 18 to 86 years. Patients were divided into three groups based on the results of USG and MIBI: 49 cases (39.5%) were positive, 25 cases (20.2%) were negative, and 50 cases (40.3%) were discordant. MIBI successfully identified the diseased gland in 96 cases (77.4%), whereas USG identified it in 52 cases (41.9%).

A total of 76 bilateral surgeries and 48 unilateral surgeries were performed. Although the group with positive results from both tests included 49 patients, one case required bilateral exploration due to a lack of peripheral PTH decline. Central PTH declined in 100% of cases, and peripheral PTH declined in 96.8% (120 patients), according to the Miami criteria (**Table 1**).

The average central PTH decay was higher than peripheral decay in all follow-ups, according to the Miami criteria, with peripheral decay at 75.4% (median) and central decay at 85.7% (median) (**Table 2**).

The sample was segmented based on the position of the diseased parathyroid glands (inferior and superior), and peripheral and central PTH decay was compared. A statistically significant difference was observed between the PTH decay values for glands located in the superior and inferior positions. When analyzing central PTH decay values, the median decay for inferior parathyroids was 80.2%, compared to 89.9% for superior parathyroids (*P*-value = .001) (**Table 3**).

Using the ROC curve, we aimed to determine the optimal cutoff point for the percentage difference in PTH levels from the IJVs at T0 to accurately detect the side of the parathyroid adenoma. The area under the curve (AUC) was 0.882 with 95% confidence (**Table 4**). A cutoff point of 16.7% for the percentage difference in PTH levels from the IJVs at T0 was identified when performing a ROC curve coordinate analysis measuring sensitivity and specificity in diagnoses the side of the adenoma, considering the percentage difference in PTH values from IJV (**Table 5**), yielding a sensitivity of 76.5%, and specificity of 95.5% (**Figure 2**).

The 16.7% cutoff point proposed by the ROC curve was applied to the groups with positive, negative, and discordant test results. In the negative test group, this cutoff demonstrated an accuracy of 80%, sensitivity of 81%, and specificity of 75% (**Table 6**).

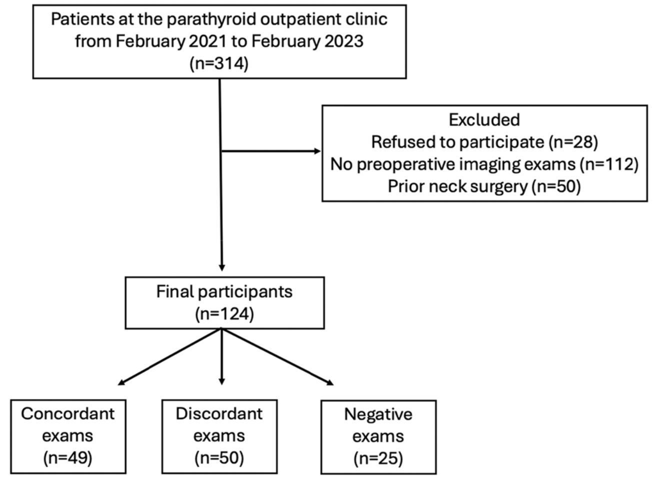

Figure 1. Flow chart of selection of study participants.

Table 1. Distribution of Qualitative Factors

		N	%
MIBI	Negative	28	22.6
	Positive	96	77.4
USG	Negative	72	58.1
	Positive	52	41.9
Preoperative imaging	Discordant	50	40.3
	Negative	25	20.2
	Positive	49	39.5
Surgery performed	Bilateral	76	61.3
	Unilateral	48	38.7
Laterality of the diseased gland	Right	61	49.2
	Left	63	50.8
% central PTH decay	Failure	0	0.0
	Success	124	100.0
% peripheral PTH decay	Failure	4	3.2
	Success	120	96.8

Abbreviations: MIBI, methoxyisobutylisonitrile parathyroid scintigraphy; PTH, parathyroid hormone; USG, ultrasonography.

Discussion

Our study confirms that there is a difference in PTH concentration values between the IJVs, which can be utilized by the surgeon to determine adenoma lateralization, particularly in cases where localization imaging is negative.

In addition to standard localization methods, PTH values from BIJV were analyzed to determine adenoma laterality. The ROC curve identified a cutoff of 16.7% for the percentage difference in PTH values from BIJV at T0, with an accuracy of 79.8%, sensitivity of 76.5%, and specificity of 95.5%. These findings indicated that BIJV PTH measurement is as effective as MIBI. The objective of this study is not to compare these modalities, particularly given that MIBI provides a functional assessment. Instead, the aim is to incorporate BIJV

Table 2. Percentage of Peripheral and Central Parathyroid Hormone (PTH) Decay by Segmentations

% PTH decay			Mean, %	Median, %	Standard deviation, %
Sex	Female	Peripheral	73.3	76.4	12.2
		Central	84.5	86.0	10.5
	Male	Peripheral	67.6	67.1	16.5
		Central	84.7	83.4	9.8
Surgery performed	Bilateral	Peripheral	71.2	74.4	13.6
		Central	84.2	83.8	9.5
	Unilateral	Peripheral	73.4	76.5	13.0
		Central	85.1	88.0	11.6
Preoperative imaging	Positive	Peripheral	73.6	76.8	13.1
		Central	86.3	88.5	10.2
	Negative	Peripheral	70.1	72.7	12.9
		Central	83.8	85.1	9.9
	Discordant	Peripheral	71.5	74.8	13.9
		Central	83.3	82.9	10.7
Laterality of the diseased gland	Left	Peripheral	70.6	71.9	12.9
		Central	84.2	86.0	12.0
	Right	Peripheral	73.6	76.7	13.7
		Central	85.0	85.1	8.4
Total		Peripheral	72.0	75.4	13.4
		Central	84.6	85.7	10.3

Table 3. Percentage of Peripheral and Central Parathyroid Hormone (PTH) Decay Relative to Inferior and Superior Parathyroids

		Mean, %	Median, %	Standard deviation, %	*P*-value
% peripheral PTH decay T0 – T10	Inferior	71.2	75.2	13.6	.511
	Superior	72.8	76.3	13.2	
% central PTH decay T0 – T10	Inferior	81.4	80.2	10.3	.001
	Superior	87.4	89.9	9.5	

Table 4. Receiver Operating Characteristic Curve Area for Detecting the Laterality of the Diseased Gland (>Parathyroid Hormone)

	AUC	*P*-value	Lower bound	Upper bound
Correct side	0.882	<.001	0.818	0.947

Abbreviation: AUC, area under the curve.

Table 5. Coordinate of Receiver Operating Characteristic Curve

% difference in PTH from jugular veins – T0	Sensitivity, %	Specificity, %
0.3	100.0	9.1
0.6	100.0	13.6
16.0	76.5	90.9
16.7	76.5	95.5
17.0	75.5	95.5
41.0	50.0	100.0
44.0	49.0	100.0

Abbreviation: PTH, parathyroid hormone.

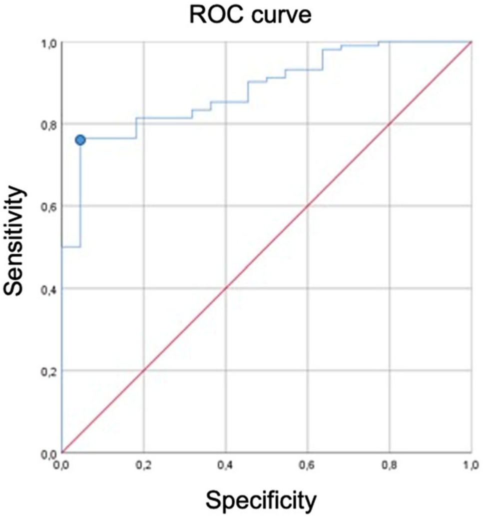

Figure 2. Receiver operating characteristic (ROC) curve.

PTH sampling into the surgeon's toolkit, especially in cases with negative preoperative imaging, where the method demonstrated a sensitivity of 80%.

A survey of the literature indicates a limited number of studies on central PTH sampling. The earliest reference can be traced back to 1996, when Taylor et al at the Royal Liverpool University reported a study involving 21 patients with a single adenoma.[14] Central PTH sampling correctly lateralized the adenoma in 76% of cases, though no reference values were specified to confirm lateralization, providing only a description of the method. In a 1999 study by Irvin and Carneiro,[18] the authors briefly mentioned central PTH sampling in cases of "difficult to find glands" while developing what is now known as the Miami criteria. This cohort of 42 cases demonstrated a 74% success rate in lateralizing the adenoma, but no specific values or parameters were provided to confirm lateralization.

It was not until 2007, in a study by Ito et al[15] from the University of Wisconsin involving 216 patients, that a 5% difference in central PTH sampling was empirically described as a marker for lateralization, with a sensitivity of 78.9%, closely matching our findings. They also reported no intraoperative or postoperative complications related to the procedure. The most recent study, published in 2016 by Sun et al,[17] applied a predefined gradient value (≥2.0), achieving lateralization in 17 out of 18 patients with negative prior localization studies.

In our analysis of central PTH collection at T0, we examined results from the RIJVs and LIJVs, as well as from inferior and superior parathyroid glands. In terms of laterality, the values were nearly identical, with 61 patients (49.2%) having the diseased gland on the right and 63 (50.8%) on the left, showing central PTH decay percentages of 85.1% (median) and 86.0% (median), respectively. These findings on laterality were not addressed in previous studies.

Regarding gland position (inferior vs superior), two studies reported results consistent with ours. In our sample, 65 glands were located superiorly, with a central PTH decay of 87.4%, whereas 59 glands were located inferiorly, with a central decay of 81.4% ($P < .05$). Taylor et al noted that in five cases where central PTH collection at T0 failed to lateralize the adenoma, the glands were positioned inferiorly.[14] Similarly, Barczynski et al[16] reported higher accuracy for central PTH sampling when glands were located superiorly. A possible explanation is that the inferior parathyroid glands may drain directly into the innominate vein rather than into the IJVs.[20]

In terms of the quantitative values and percentage decay of peripheral and central PTH, our study confirmed findings from previous literature that both peripheral and central PTH values are valid for intraoperative monitoring of PTH decay. In our study, peripheral PTH decay was 72%, whereas central PTH decay was 84.6%. As Neves et al[21] concluded, intraoperative peripheral PTH provides reliable results, correlating cure with a drop in its levels and disease persistence with its maintenance. Thus, the measurement of intraoperative peripheral and central PTH decay proved effective in predicting surgical success in PHPT.

After data analysis, a potential contraindication to the collection of PTH from the IVs to confirm adenoma laterality would be in previously operated cases, as venous drainage is altered due to the ligation of the middle thyroid vein. Future studies may further support the inclusion of this technique in surgical guidelines for cases with negative preoperative imaging studies.

This study has some limitations that should be considered. First, the sample size may limit the generalizability of the findings, and a larger cohort would be necessary to validate the results in a broader population. Second, although our sample included patients with negative MIBI scans, we did not have patients with multiglandular disease in our sample, which prevents us from determining the behavior of BIJV PTH sampling in this group of patients. Additionally, variations in protocols and laboratory methods across different centers may impact the reproducibility of the proposed cutoff point.

Conclusion

The evaluation of the present study suggests that collecting PTH values from BIJV is a valuable tool for confirming the laterality of the diseased gland, particularly in cases with negative imaging results. A value close to 16.7% between collections may demonstrate the method's highest sensitivity and specificity.

Table 6. Receiver Operating Characteristic Curve Prediction Metrics

		True class		Statistics		
		Correct	Wrong	Accuracy, %	Sensitivity, %	Specificity, %
Discordant localization exams	Correct	30	0	84.0	78.9	100.0
	Wrong	8	12			
Negative localization exams	Correct	17	1	80.0	81.0	75.0
	Wrong	4	3			
Positive localization exams	Correct	31	0	75.5	72.1	100.0
	Wrong	12	6			

Author Contributions

Davi Knoll Ribeiro, data analysis and interpretation, writing and editing manuscript; **Murilo Catafesta das Neves**, data analysis, contributions to writing manuscript, editing manuscript; **Rodrigo Oliviera Santos**, data interpretation, contributions to writing manuscript, editing manuscript; **Monique Nakayama Ohe**, data interpretation, contributions to writing manuscript, editing manuscript; **Marise Lazaretti-Castro**, data interpretation, contributions to writing manuscript, editing manuscript; **Marcello Rosano**, data interpretation, contributions to writing manuscript, editing manuscript; **Marcio Abrahao**, data interpretation, editing manuscript, project conception/design.

Disclosures

Competing interests: None.

Funding source: None.

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