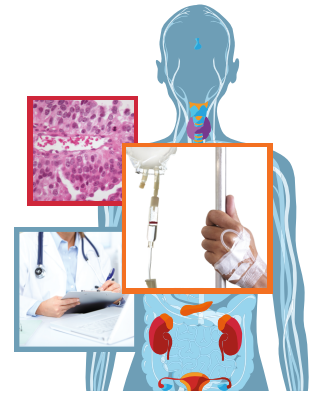
Case Series



International Journal of Endocrine Oncology

Preventing blind thyroid lobectomy in patients with intrathyroidal hyperfunctioning parathyroid glands with radioguided enucleation

Sophie Dream*[1], Brenessa Lindeman[2] & Herbert Chen[3]

[1]Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

[2]University of Alabama at Birmingham, 1808 7th Ave S, Boshell Building, Birmingham, AL 35233, USA

[3]University of Alabama at Birmingham, 1808 7th Ave S, BDB 603, Birmingham, AL 35233, USA

*Author for correspondence: Tel.: +1 414 955 1457; Fax: +1 414 955 0197; sdream@mcw.edu

Aim: Hyperfunctioning intrathyroidal parathyroid glands are rare and often result in thyroid lobectomy. This study examines the utility of radioguided surgery to guide enucleation of intrathyroidal parathyroids. **Methods:** Between December 2002 and March 2018, 2291 patients underwent parathyroidectomy by one surgeon for primary hyperparathyroidism. A total of 74 (3%) patients had an ectopic intrathyroidal parathyroid gland and underwent radioguided. **Results:** All of intrathyroidal parathyroid glands were localized with the gamma probe. *In vivo* radionuclide counts were above 120% of the background in all but three patients. All intrathyroidal parathyroids were enucleated with the guidance of the gamma probe. **Conclusion:** Radioguided surgery is useful for intraoperative identification of hyperfunctioning, intrathyroidal parathyroid glands. This technique allows for enucleation of the abnormal parathyroid gland, avoiding thyroid lobectomy and preserving healthy thyroid parenchyma.

First draft submitted: 1 November 2019; Accepted for publication: 19 December 2019; Published online: 14 February 2020

Keywords: blind thyroidectomy • hyperparathyroidism • hypothyroidism • intrathyroidal parathyroid • parathyroid enucleation • parathyroid imaging • parathyroidectomy • radioguided surgery • thyroid lobectomy • thyroidectomy

Primary hyperparathyroidism (PHPT) affects approximately 1% of the population with 75–85% of cases being attributable to a single parathyroid adenoma. Multigland disease accounts for 5–15% of PHPT and may result from double adenoma or hyperplasia [1,2]. Definitive treatment of PHPT remains as surgical excision of the hyperfunctioning parathyroid glands. The use of localization techniques and intraoperative parathyroid hormone (PTH) assay has advanced surgical treatment of PHPT, with cure achieved in >95% of cases [3]. Surgical failure leads to persistent hyperparathyroidism, which may result from a missed adenoma, inadequate resection or a parathyroid gland in an ectopic location [4].

Ectopic parathyroid glands are most frequently located within the thymus, anterior mediastinum and rarely within the thyroid. Hyperfunctioning intrathyroidal parathyroid glands have been reported to occur in approximately 1–18% of patients, with higher rates of abnormal intrathyroidal parathyroid glands in hyperplastic disease [5–7].

While they are rare, a missing parathyroid adenoma after thorough neck exploration may result in blind thyroid lobectomy without intraoperative visualization of the ectopic parathyroid gland. However, the risk of hypothyroidism after thyroid lobectomy ranges from 14.3 to 35% [8–11]. Therefore, blind thyroid lobectomy for a suspected ectopic intrathyroidal parathyroid may commit a patient, with an otherwise normal thyroid, to lifelong thyroid supplementation. Radioguided techniques have been shown to be helpful in localizing intrathyroidal parathyroids, permitting radioguided enucleation of these lesions without the need for thyroid resection [12]. Our study examines the utility of radioguided surgery to facilitate enucleation of intrathyroidal parathyroids, thus preserving normal thyroid tissue.

Future Medicine

Table 1. Comparison of demographic and laboratory data.

Variable	All Patients	Adenoma	Double adenoma	Hyperplasia	p-value
N	74	43	12	19	
Age (year)	60 ± 2	60 ± 2	58 ± 4	59 ± 3	0.885
Preoperative Ca (mg/dl)	10.9 ± 0.1	11 ± 0.1	10.6 ± 0.3	10.7 ± 0.2	0.084
Preoperative PTH (pg/ml)	152 ± 20	139 ± 13	128 ± 27	198 ± 70	0.395
Postoperative Ca (mg/dl)	9.3 ± 0.1	9.23 ± 0.1	9.56 ± 0.1	9.17 ± 0.2	0.143
Postoperative Ca (mg/dl) at 6 months	9.3 ± 0.1	9.2 ± 0.1	9.8 ± 0.1	9.3 ± 0.1	0.551
Postoperative PTH (pg/ml)	49 ± 5	47 ± 6	40 ± 7	59 ± 12	0.158
Postoperative PTH (pg/ml) at 6 months	52 ± 4	49 ± 6	46 ± 6	62 ± 8	0.606

Comparison of demographic data, preoperative and postoperative laboratory work across etiology groups.
PTH: Parathyroid hormone.

Materials & methods

We performed a retrospective review of patients undergoing parathyroidectomy for primary hyperparathyroidism, by a single surgeon between December 2002 and March 2018, from a prospectively collected database. There were 2291 patients who underwent parathyroidectomy during that time and of these patients, 74 (3%) were identified to have an abnormal, ectopic intrathyroidal parathyroid gland. We defined an intrathyroidal parathyroid gland as parathyroid gland, which is located within the thyroid parenchyma. The decision for preoperative imaging was made at the surgeon's discretion. Demographics, imaging, pre- and post-operative laboratory work and intraoperative radioguided probe data for this group were evaluated.

All patients underwent radioguided parathyroidectomy with preoperative injection of 10 mCi of TC-99m sestamibi. A background radionuclide level was obtained with the collimated gamma probe (Neoprobe Gamma Detection System, Devicor Medical Products, Inc., part of Leicia Biosystems, OH, USA) over the thyroid isthmus. Parathyroid glands that appeared to be enlarged were excised and placed on the gamma probe directed away from the patient. *Ex vivo* radionuclide counts were used to confirm hyperfunctioning parathyroid excision with specimen radioactivity of >20% of the background level [13].

In cases where a parathyroid gland was missing, the ipsilateral thyroid is examined and meticulously scanned with the gamma probe for regions with increased radionuclide counts. Thyroidotomy is performed over the area of highest gamma counts using the electrocautery. The parathyroid adenoma was enucleated and excision is confirmed with *ex vivo* counts >20% above the background level. Intraoperative PTH monitoring was used in all cases. Curative excision was confirmed using postoperative PTH and calcium levels at 6 months.

Statistical analysis was performed using SPSS Statistics software (version 25, IBM Corp.). Data are reported as mean ± standard error of the mean. Groups were compared using one-way analysis of variance (ANOVA). A p-value <0.05 was considered statistically significant. This study was approved by the University of Alabama at Birmingham Institutional Review Board.

Results

Demographics & preoperative labs

The mean patient age was 60 ± 2 years with 80% of the patients being female. Mean preoperative calcium was 10.9 ± 0.1 ml/dl and the mean preoperative parathyroid hormone level was 152 ± 20 pg/ml. A total of 20 patients were referred for persistent hyperparathyroidism and underwent remedial parathyroid exploration.

Patients were divided into groups based on the etiology of their hyperparathyroidism; these groups were: single adenoma, double adenoma or hyperplasia. A total of 43 patients (58%) had a single adenoma, 12 (16%) had double adenoma and 19 (26%) had hyperplasia. Comparison was performed across these groups (Table 1). There was no difference in age of the groups (60 ± 2 vs 58 ± 4 vs 59 ± 3 years; p = 0.885). Mean preoperative calcium and PTH were not significantly different among the groups (11.0 ± 0.1 vs 10.6 ± 0.2 and 10.7 ± 0.2 mg/dl; p = 0.084) and (139 ± 13 vs 128 ± 27 and 198 ± 70 pg/ml, p = 0.395) (Table 1).

Preoperative imaging

Of the patients in this study, the majority underwent preoperative imaging, with five of the 74 patients (7%) undergoing parathyroid exploration without preoperative imaging. There were 62 patients who underwent pre-

Table 2. Preoperative imaging results.

Preoperative imaging modality	N	Preoperative imaging detected parathyroid adenoma within the thyroid	Sensitivity (%)
Sestamibi scan	62	37	60
US	19	12	63
CT	14	9	64
Sestamibi and US	8	5	63
Sestamibi and CT	6	4	67
US and CT	5	3	60
Sestamibi, CT and US	4	3	75

Retrospective evaluation of preoperative imaging accuracy, CT was the most accurate single image while obtaining all three images was the most likely to identify an intrathyroidal parathyroid gland.
CT: Computed tomography; US: Parathyroid ultrasound.

Table 3. Radioguided excision data.

Variable	All Patients	Adenoma	Double adenoma	Hyperplasia	p-value
Mean *in vivo* counts (% background)	160 ± 10	170 ± 8	119 ± 3	145 ± 7	0.280
Mean *ex vivo* counts (% background)	80 ± 10	89 ± 8	52 ± 10	75 ± 20	0.209
Background counts	207 ± 11	200 ± 14	186 ± 23	238 ± 27	0.277
Ex vivo counts	157 ± 16	183 ± 25	96 ± 22	135 ± 19	0.209

Intraoperative radionuclide results from background, *in vivo* and *ex vivo* counts: all patients had *ex vivo* counts >20% of the background, *in vivo* radionuclide counts were above 120% of the background in all but three patients.

operative sestamibi scan, which detected a parathyroid adenoma within the thyroid in only 37 patients (60%). Ultrasound was performed in 19 patients and predicted an intrathyroidal adenoma in 12 patients (63%). CT scan was performed in 14 patients and correct in nine patients (64%). Additionally, of those patients who had multiple imaging studies, eight patients had both an ultrasound and sestamibi scan preoperative, five had a ultrasound and CT scan, six had a sestamibi scan and a CT scan and four patients had all three images (Table 2).

Radioguided data

The mean background radionuclide count on the thyroid was 207 ± 11, with mean *in vivo* radionuclide counts of the intrathyroidal parathyroid glands at 234 ± 15. All of the intrathyroidal parathyroid adenomas in this study were localized with the gamma probe. The *in vivo* radionuclide count of the intrathyroidal parathyroid ranged from 105 to 289% of the thyroid background, with a median of 147%. *In vivo* radionuclide counts were above 120% of the background in all but three patients. All intrathyroidal parathyroid glands were enucleated with the guidance of the gamma probe without the need for thyroid lobectomy. The mean *ex vivo* parathyroid radionuclide count was 157 ± 16, with 100% of *ex vivo* counts of removed glands in >20% of all patients.

Postoperative outcomes

The mean postoperative calcium was 9.3 ± 0.1 mg/dl at 2 weeks postoperatively and 9.3 ± 0.1 mg/dl after 6 months postoperatively. The mean postoperative parathyroid hormone level was 49 ± 5 pg/ml at 2 weeks postoperatively and 52 ± 4 pg/ml at 6 months postoperatively. No statistically significant differences were identified in postoperative lab values among the groups (Table 3).

Discussion

The detection of an intrathyroidal parathyroid adenoma provides a challenge to the endocrine surgeon. These patients often receive a workup, which involves multiple imaging studies, including ultrasound, radionuclide imaging, CT scan, MRI and venous sampling. The identification of intrathyroidal parathyroid glands preoperatively with routine sestamibi and ultrasound is difficult, as they may be mistaken for a thyroid nodule. Ultrasound can be used to distinguish parathyroid adenomas from thyroid nodules, which are both hypoechoic on ultrasound evaluation, as a parathyroid within the thyroid has hyperechoic line on the ventral surface of the gland; but requires a trained observer to do so [14].

Abboud *et al.* evaluated 178 patients undergoing cervical exploration for PHPT over a 7-year period who had an ultrasound preoperatively. There were six patients with a parathyroid adenoma within the thyroid, which was predicted in four patients on preoperative ultrasound [15]. We have similarly demonstrated that preoperative imaging may heighten the suspicion of an intrathyroidal parathyroid adenoma but does not reliably provide definitive information.

Additionally, fine needle aspiration of thyroid nodules to distinguish thyroid adenoma from a parathyroid adenoma preoperatively may be useful when parathyroid hormone washout is utilized, as cytology is not reliable [16–20]. Fine needle aspiration with PTH washout may only confirm a surgeon's preoperative suspicion, when imaging suggests a parathyroid adenoma within the thyroid. Its utility is further limited as biopsy of a suspected parathyroid adenoma may cause a fibrotic reaction that complicates surgical dissection and is generally avoided [21].

When faced with a missing parathyroid gland, a thorough neck exploration should be carried out, assessing areas where ectopic parathyroid glands are commonly found. Missing upper parathyroid gland may be identified in the retropharyngeal space, tracheoesophageal groove and the posterior superior mediastinum, while a missing lower gland may be within the anterior superior mediastinum or the thymus. Failure to identify a missing parathyroid gland in these locations has classically led to the opening of the carotid sheath for exploration and, finally, thyroid lobectomy or partial lobectomy on the side of the missing parathyroid gland [22,23].

Goodman *et al.* demonstrated the incidence of intrathyroidal parathyroid adenoma to be 1.9% in a retrospective review of 10,000 patients undergoing parathyroidectomy for PHPT. They examined 1163 reoperations for failed parathyroidectomy and demonstrated that a thyroid lobectomy was performed in 77% of cases, with the initial surgeon identifying two or fewer parathyroid glands. Additionally, they identified the parathyroid adenoma on the side of the lobectomy in 64% of cases and on the contralateral side in 36% of cases [24]. With the overall risk of hypothyroidism after thyroid lobectomy being 22%, blind thyroid lobectomy for missing parathyroid gland may put patients that otherwise have no indication for thyroidectomy at undue risk. Goodman *et al.* report a lower incidence of intrathyroidal parathyroid adenomas due to a conservative definition of an intrathyroidal parathyroid gland. Our 3% rate of intrathyroidal parathyroid glands is similarly on the lower end as we only included parathyroid glands within the thyroid parenchyma.

We utilize radioguidance in all parathyroidectomy cases, therefore familiarity with the gamma probe and experience with interpretation of radionuclide counts facilitates use of the technology to aid in localizing ectopic glands. Our study is limited as it is a retrospective review of a single surgeon's experience. Unfortunately, our study lacks a control group due to unreliable preoperative identification of intrathyroidal parathyroid glands prior to surgery, which has been demonstrated in prior studying and with our imaging results (Table 2). Additionally, there may be selection bias in patient distribution and other factors, as the patient population consisted of only those who were referred to an endocrine surgeon for definitive treatment of primary hyperparathyroidism. Lastly, postoperative thyroid function testing on postparathyroidectomy patients is not performed routinely. Therefore, we are unable to assess the effect thyroidotomy may have on thyroid function. However, since no thyroid tissue was resected in these operations, we would predict that thyroid function should not be diminished.

In conclusion, radioguided surgery is useful for intraoperative identification of hyperfunctioning ectopic intrathyroidal parathyroid glands. Identification of an intrathyroidal parathyroid gland with this technique allows for enucleation of the abnormal parathyroid gland, avoiding thyroid lobectomy and thereby preserving healthy thyroid parenchyma.

Future perspective

Radioguided surgery for hyperparathyroidism has been established as an intraoperative adjunct, that allows for the confirmation of the excision of hyperfunctioning parathyroid tissue, without the need for PTH aspiration of the resected tissue or frozen section. The present study further suggests that in difficult cases, routine use of radioguided techniques may aid in intraoperative decision making. Should the described technique be adopted, surgeons may be able to prevent blind thyroid lobectomy.

Author contributions

S Dream contributed to study design, statistical analysis and manuscript preparation. H Chen contributed to study design, database preparation and manuscript revision. B Lindeman contributed to database preparation and manuscript revision.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. This study was approved by the University of Alabama at Birmingham Internal Review Board.

Summary points

- A total of 3% of patients had an ectopic intrathyroidal parathyroid adenoma.
- Preoperative imaging ultrasound, sestamibi and CT scan were able to detect an intrathyroidal parathyroid adenoma with a sensitivity of 60%, 63% and 64%, respectively.
- Combined use of sestamibi, ultrasound and CT scan suggested intrathyroidal parathyroid adenoma in only 75% of cases.
- Five patients had no preoperative imaging; radioguidance identified an intrathyroidal parathyroid adenoma in all of these cases.
- All of intrathyroidal parathyroid gland were localized with the gamma probe.
- *In vivo* radionuclide counts were >120% of the background in all but three cases.
- All intrathyroidal parathyroid glands were enucleated with the guidance of the gamma probe, preserving normal, healthy thyroid parenchyma.
- Radio guided surgery is useful for intraoperative identification and enucleation of hyperfunctioning intrathyroidal parathyroid glands.

References

Papers of special note have been highlighted as: • of interest

1. Fraser WD. Hyperparathyroidism. *Lancet* 374(9684), 145–158 (2009).
- **Provides the reader with a thorough overview of hyperparathyroidism.**
2. Dream S, Lindeman B, Chen H. Prevalence of thymic parathyroids in primary hyperparathyroidism during radioguided parathyroidectomy. *Clin. Med. insights Endocrinol. Diabetes* 12, 1179551419869917 (2019).
3. Boggs JE, Irvin GL 3rd, Carneiro DM, Molinari AS. The evolution of parathyroidectomy failures. *Surgery* 126(6), 998–1002 (1999).
4. Levin KE, Clark OH. The reasons for failure in parathyroid operations. *Arch. Surg.* 124(8), 911–914 (1989).
- **Evaluates causes for failed parathyroidectomy in the era of preoperative imaging and intraoperative parathyroid hormone monitoring.**
5. McIntyre RC Jr, Eisenach JH, Pearlman NW, Ridgeway CE, Dale Liechty R. Intrathyroidal parathyroid glands can be a cause of failed cervical exploration for hyperparathyroidism. *Am. J. Surg.* 174(6), 750–754 (1997).
6. Phitayakorn R, McHenry CR. Incidence and location of ectopic abnormal parathyroid glands. *Am. J. Surg.* 191(3), 418–423 (2006).
7. Roy M, Mazeh H, Chen H, Sippel RS. Incidence and localization of ectopic parathyroid adenomas in previously unexplored patients. *World J. Surg.* 37(1), 102–106 (2013).
8. Verloop H, Smit JWA, Louwerens M, Dekkers OM, Kievit J, Schoones JW. Risk of hypothyroidism following hemithyroidectomy: systematic review and meta-analysis of prognostic studies. *J. Clin. Endocrinol. Metab.* 97(7), 2243–2255 (2012).
- **Evaluates the risk of clinical and subclinical hypothyroidism after thyroid lobectomy.**
9. Stoll SJ, Pitt SC, Liu J, Schaefer S, Sippel RS, Chen H. Thyroid hormone replacement after thyroid lobectomy. *Surgery* 146(4), 554–560 (2009).
10. McHenry CR, Slusarczyk SJ. Hypothyroidisim following hemithyroidectomy: incidence, risk factors, and management. *Surgery* 128(6), 994–998 (2000).

11. Lee DY, Seok J, Jeong WJ, Ahn SH. Prediction of thyroid hormone supplementation after thyroid lobectomy. *J. Surg. Res.* 193(1), 273–278 (2015).
12. Mazeh H, Kouniavsky G, Schneider DF *et al.* Intrathyroidal parathyroid glands: small, but mighty (a Napoleon phenomenon). *Surgery* 152(6), 1193–1200 (2012).

- **Describes a single institution's experience with intrathyroial parathyroid glands, including gland size and laboratory profile as they compare to nonintrathyroidal parathyroid adenomas.**

13. Chen H, Mack E, Starling JR. Radioguided parathyroidectomy is equally effective for both adenomatous and hyperplastic glands. *Ann. Surg.* 238(3), 332–337 (2003).
14. Yabuta T, Tsushima Y, Masuoka H *et al.* Ultrasonographic features of intrathyroidal parathyroid adenoma causing primary hyperparathyroidism. *Endocr. J.* 58(11), 989–994 (2011).

- **Evaluates the effectiveness of preoperative ultrasound in the detection of intrathyroidal parathyroid glands and serves to describe distinct ultrasonographic features of an intrathyroidal parathyroid gland.**

15. Abboud B, Sleilaty G, Ayoub S *et al.* Intrathyroid parathyroid adenoma in primary hyperparathyroidism: can it be predicted preoperatively? *World J. Surg.* 31(4), 817–823 (2007).
16. Maser C, Donovan P, Santos F *et al.* Sonographically guided fine needle aspiration with rapid parathyroid hormone assay. *Ann. Surg. Oncol.* 13(12), 1690 (2006).
17. Abdelghani R, Noureldine S, Abbas A, Moroz K, Kandil E. The diagnostic value of parathyroid hormone washout after fine-needle aspiration of suspicious cervical lesions in patients with hyperparathyroidism. *Laryngoscope* 123(5), 1310–1313 (2013).
18. Tseleni-Balafouta S, Gakiopoulou H, Kavantzas N, Agrogiannis G, Givalos N, Patsouris E. Parathyroid proliferations: a source of diagnostic pitfalls in FNA of thyroid. *Cancer* 111(2), 130–136 (2007).
19. Abraham D, Sharma PK, Bentz J, Gault PM, Neumayer L, McClain DA. Utility of ultrasound-guided fine-needle aspiration of parathyroid adenomas for localization before minimally invasive parathyroidectomy. *Endocr. Pract.* 13(4), 333–337 (2007).
20. Owens CL, Rekhtman N, Sokoll L, Ali SZ. Parathyroid hormone assay in fine-needle aspirate is useful in differentiating inadvertently sampled parathyroid tissue from thyroid lesions. *Diagn. Cytopathol.* 36(4), 227–231 (2008).

- **Clinical utility of fine needle aspiration for distinguishing thyroid nodule from parathyroid adenoma.**

21. Norman J, Politz D, Browarsky I. Diagnostic aspiration of parathyroid adenomas causes severe fibrosis complicating surgery and final histologic diagnosis. *Thyroid* 17(12), 1251–1255 (2007).
22. Feliciano DV. Parathyroid pathology in an intrathyroidal position. *Am. J. Surg.* 164(5), 496–500 (1992).
23. Bahar G, Feinmesser R, Joshua BZ *et al.* Hyperfunctioning intrathyroid parathyroid gland: a potential cause of failure in parathyroidectomy. *Surgery* 139(6), 821–826 (2006).
24. Goodman A, Politz D, Lopez J, Norman J. Intrathyroid parathyroid adenoma: incidence and location – the case against thyroid lobectomy. *Otolaryngol. Head Neck Surg.* 144(6), 867–871 (2011).