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ORIGINAL ARTICLE

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Hyperparathyroidism subsequent to radioactive iodine therapy for Graves' disease

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Abstract

Background: The development of primary hyperparathyroidism (PHPT) after radioactive iodine (RAI) treatment for thyroid disease is poorly characterized. The current study is the largest reported cohort and assesses the disease characteristics of patients treated for PHPT with a history of RAI exposure.

Methods: A retrospective analysis comparing patients, with and without a history of RAI treatment, who underwent surgery for PHPT.

Results: Twenty-eight of the 469 patients had a history of RAI treatment, all for Graves' disease. Patients with a history of RAI exposure had similar disease characteristics compared to control; however, patients with a history of RAI treatment had a higher rate of recurrence (7.4% vs 1.2%, $p = 0.012$).

Conclusion: PHPT in patients with a history of RAI treatment can be approached in the same manner as RAI naive PHPT patients; however, the risk of recurrence of PHPT in RAI exposed patients may be higher.

KEYWORDS

Graves' disease, hypercalcemia, hyperparathyroidism, parathyroid surgery, radioactive iodine

1 | INTRODUCTION

The development of primary hyperparathyroidism (PHPT) after radioactive iodine (RAI) treatment for thyroid disease has been described, but not well studied. The literature on this topic consists mostly of case reports and case series.[1–16] The overwhelming majority of patients in these reports received RAI for Graves' disease,[2,3,5,8,9,16,17] but other indications include thyroid malignancy[2,6,7,10,14,18] and benign goiters.[1,3,4,11,14] In terms of etiology, the existence of RAI-induced PHPT as a truly unique entity has been debated; some studies report no increased risk of PHPT after exposure to RAI,[6,10,13,19] while others suggest an association with PHPT development.[2–4,7,14,15,17,20] Additionally, it remains unclear if PHPT occurring after RAI exposure presents with a distinct clinical phenotype. In the reports on these patients, there is a female predominance and a higher predilection in the middle aged and elderly. While most patients reportedly present 10–20 years after administration of RAI,[2,3,5,6,11,14,17,18,21] the time lapse is highly variable.

Previous studies describing PHPT in patients with a history of RAI consisted of small sample sizes, having fewer than 11 patients in their reports. As a result, there are fewer than 100 cases documented in the medical literature. This current study describes the largest cohort to date. The aim of this study was to better characterize this disease entity by examining the clinicopathologic characteristics of patients presenting for surgical

management of PHPT with and without a history of RAI treatment.

2 | MATERIALS AND METHODS

This was a single institution retrospective cohort study of 497 patients undergoing first time parathyroidectomy for PHPT from July 2015 to February 2020. The study was approved by the Henry Ford Health System's Institutional Review Board, IRB #14143. This study conforms to the ethical principles for medical research involving human subjects as described in the Declaration of Helsinki. The diagnosis of PHPT was established by an elevated or inappropriately suppressed serum parathyroid hormone (PTH) in the setting of hypercalcemia. No patients with normocalcemic hyperparathyroidism were included in this study, as the senior author does not routinely operate on patients with this diagnosis. Patients with a history of parathyroid surgery were excluded from this study.

Information collected via chart review included patient demographics, symptoms, history of RAI treatment, prior neck surgeries, results of imaging studies, preoperative, intraoperative and postoperative laboratory values, operative time, and pathology reports. Two groups were created from the database: patients with PHPT with a history of RAI treatment and patients with PHPT without a history RAI treatment. The two groups were compared. A subgroup analysis was also performed.

2.1 | Surgical technique

Surgical intervention entailed either a minimally invasive (focused) parathyroidectomy or bilateral neck exploration. The type of surgery was dictated by multiple patient and disease factors, including results of imaging studies and intraoperative findings. A sestamibi scan and a surgeon-performed ultrasound (US) were routinely obtained. In the overall cohort, a 4D CT scan was obtained in select patients if both the former imaging modalities were nonlocalizing. In all patients previously treated with RAI, a 4D CT was obtained if the US and sestamibi were nonlocalizing.

In all minimally invasive cases, intraoperative PTH (ioPTH) levels were used to determine cure. Early in the experience, the ioPTH criteria were a drop of ≥50% from baseline ioPTH level by 10 min and into the normal range. The more recent cases were performed using a stricter protocol, which included a third criterion of the ioPTH dropping below 40 pg/mL. If the ioPTH levels did not meet these standards, the remainder of the parathyroid glands was sought and assessed.

2.2 | Determination of postoperative cure

Cure was defined by becoming eucalcemic and maintaining calcium (ionized, serum, and corrected serum calcium) levels in the normal range for ≥6 months from the time of surgery. Persistence was defined by continued hypercalcemia postoperatively that did not normalize. Recurrent disease was characterized by a period of eucalcemia that lasted at least 6 months following surgery, followed by a return of the hypercalcemia.

2.3 | Statistical analysis

The continuous variables in this data set were not normally distributed. Medians and their interquartile range (IQR; 25th to 75th percentile) were used as a result. Nominal variables were described with percentiles. The two groups, those with PHPT with a history of RAI exposure and those with PHPT who were not exposed to RAI, were compared with a two-sample Wilcoxon test for continuous variables or a chi-square test for nominal variables. The same statistical methodology was employed to compare those with multiglandular disease to those without multiglandular disease within the RAI exposed group. All analyses were done using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). A p-value less than 0.05 was considered evidence of significance. A power analysis could not be conducted as the incidence is not well described in the literature with the literature only consisting of case reports and case series. The study was conducted with a sample size greater than previous studies.

3 | RESULTS

Of the 497 patients in the PHPT cohort, 469 patients met criteria to be included in the study; 441 patients were in the control group and 28 patients were in the RAI exposure group (Table 1). At least 6 months of follow-up data were available for 27/28 RAI exposed patients and 426 patients in the control group. In the control group, 76.9% (339) were female and 82.1% (23) were female in the RAI group. The incidence of PHPT with RAI exposure in the total study cohort was 5.97% (28/469). The median ages were 61.0 years (IQR 52.0–68.0) and 65.0 years (IQR 52.0–71.5) for the control group and RAI group, respectively ($p = 0.142$). There was no statistical

TABLE 1 Comparison of preoperative and intraoperative metrics control versus RAI

	Control			RAI			
Variable	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***p***
Age (years)	441	61.0	52.0–68.0	28	65.0	52.0–71.5	0.142
BMI (kg/m^2)	440	30.3	25.9–34.7	28	30.8	26.0–33.2	0.787
Preoperative							
Intact PTH (pg/mL)	440	114.0	83.0–155.0	28	118.0	92.5–169.5	0.666
Vitamin D (ng/mL)	436	24.0	19.0–31.0	28	25.5	18.5–35.0	0.608
Ionized calcium (mmol/L)	436	1.44	1.35–1.54	28	1.38	1.33–1.49	0.103
Corrected calcium (mg/dL)	436	10.9	10.5–11.3	28	11.0	10.6–11.4	0.573
Creatinine (mg/dL)	438	0.82	0.68–1.04	28	0.84	0.70–1.05	0.559
Intraoperative							
Baseline ioPTH (pg/mL)	439	160.5	114.0–228.6	28	170.7	118.9–210.7	0.801
Last ioPTH (pg/mL)	440	22.6	15.9–33.4	28	25.1	17.7–36.9	0.523
Operative time (min)	441	69.0	58.2–91.0	28	73.7	57.2–89.0	0.829
Maximum mass adenoma (mg)	420	700.0	350.0–1402.0	27	723.0	300.0–1600.0	0.872

Abbreviations: BMI, body mass index; ioPTH, intraoperative parathyroid hormone; IQR, interquartile range; N, number of patients in the respective group; PTH, parathyroid hormone; RAI, radioactive iodine.

TABLE 2 Comparison of cure rate and disease subtype control versus RAI

Variable	**Control % (R/N)**	**RAI % (R/N)**	***p****
Female	76.9 (339/441)	82.1 (23/28)	0.519
Kidney stones	26.3 (116/441)	17.9 (5/28)	0.322
Multiglandular disease	16.6 (73/439)	14.3 (4/28)	0.746
Disease type			0.129
Single gland	83.4 (366/439)	85.7 (24/28)	
Double gland	7.5 (33/439)	14.3 (4/28)	
4-gland hyperplasia	9.1 (40/439)	0 (0/28)	
Recurrence/ persistence			***0.032***
Cured	98.4 (419/426)	100 (27/27)	0.508
Persistence	1.6 (7/426)	0 (0/27)	0.508
Recurrence	1.2 (5/419)	7.4 (2/27)	**0.012**

Abbreviations: %, percentage; N, total number of patients in the respective group; R, number of patients with the characteristics as dictated by the respective variable; RAI, radioactive iodine.
*Significant *p* values are bolded and italicized.

difference with regard to the history of nephrolithiasis between the two groups (Table 2). The median time from the RAI treatment until diagnosis with PHPT was 20 years (IQR 18–30). The median preoperative intact PTH and corrected calcium levels were similar between the groups (Table 1). There were no statistically significant differences in the vitamin D, ionized calcium, and creatinine levels between the two groups (Table 1). With regard to imaging, 22/28 patients had a localizing, surgeon-performed US, and/or sestamibi scan. The remaining six patients additionally underwent a 4D CT scan. Of these, three provided localizing information.

Of the 28 patients, 16 were managed with the initial ioPTH regimen and 12 with the modified protocol. The median baseline ioPTH levels were 160.5 pg/mL (IQR 114.0–228.6) and 170.7 pg/mL (IQR 118.9–210.7) for the control and RAI groups, respectively ($p = 0.801$), with a median reduction in ioPTH levels at 10 min postexcision of the pathologic gland(s) to 22.6 pg/mL (IQR 15.9–33.4) and 25.1 pg/mL (17.7–36.9), respectively ($p = 0.523$). There were no statistical differences in operative time or adenoma mass (or largest pathological gland if multiple were present) between the two groups (Table 1). There was also no statistical difference in rate for multiglandular disease between the two groups ($p = 0.129$). Of note, the RAI group did not have any patients with 4-gland hyperplasia (Table 2). The cure rate was similar in the two groups, 98.4% (419/426) in the control group compared to 100% (27/27) in the RAI group ($p = 0.508$).

Perhaps, the most notable difference between the groups was in recurrence rate. Only 1.2% (5/419) of the control group was found in follow-up to have recurrent disease, in contrast with the RAI group in which the recurrence rate was 7.4% (2/27) ($p = 0.012$). In both of the patients with recurrence, at the time of surgery a

TABLE 3 Subgroup analysis of RAI group—single gland versus multiglandular disease

	RAI single gland			RAI multiglandular			
Variable	**N**	**Median**	**IQR**	**N**	**Median**	**IQR**	***p****
Age (years)	24	66.5	55.0–72.0	4	58.0	54.4–62.0	0.177
BMI (kg/m^2)	24	30.6	26.0–32.5	4	32.4	28.2–34.3	0.512
Preoperative							
Intact PTH (pg/mL)	24	118.0	92.5–165.0	4	133.5	87.5–190.0	0.844
Vitamin D (ng/mL)	24	25.5	18.5–32.5	4	29.0	20.0–38.5	0.532
Ionized calcium (mmol/L)	24	1.38	1.33–1.49	4	1.36	1.28–1.50	0.599
Corrected calcium (mg/dL)	24	11.0	10.6–11.5	4	11.0	10.5–11.1	0.554
Creatinine (mg/dL)	24	0.84	0.66–1.05	4	0.91	0.79–1.46	0.341
Intraoperative							
Baseline ioPTH (pg/mL)	24	178.0	132.3–239.9	4	135.1	94.6–193.6	0.431
Last ioPTH (pg/mL)	24	29.1	18.2–38.0	4	18.4	8.8–21.8	0.088
Operative time (min)	24	70.5	56.3–79.6	4	127.8	110.3–179.6	***0.004***
Maximum mass adenoma (mg)	23	800.0	500.0–1600.0	4	355.0	200.0–1250.0	0.269

Abbreviations: BMI, body mass index; ioPTH, intraoperative parathyroid hormone; IQR, interquartile range; N, number of patients in the respective group; PTH, parathyroid hormone; RAI, radioactive iodine.
*Significant *p* values are bolded and italicized.

TABLE 4 Comparison of cure rate for RAI subgroup analysis—single gland versus multiglandular disease

Variable	**RAI single gland % (R/N)**	**RAI multiglandular % (R/N)**	***p***
Female	79.2 (19/24)	100.0 (4/4)	1.000
Kidney stones	20.9 (5/24)	0 (0/4)	1.000
Recurrence/persistence			1.000
Cured	91.3 (21/23)	100 (4/4)	1.000
Recurrence	8.7 (2/23)	0 (0/4)	1.000

Abbreviations: %, percentage; N, total number of patients in the respective group; R, number of patients with the characteristics as dictated by the respective variable; RAI, radioactive iodine.

single, adenomatous gland was removed and ioPTH levels were consistent with cure. Both were operated on during the period when the stricter ioPTH criteria were being employed. However, after experiencing a period of eucalcemia of at least 6 months, both demonstrated recurrent hypercalcemia.

A subgroup analysis was performed for the RAI group comparing patients with single gland disease to those with multiglandular disease. There were no statistically significant differences between groups in the preoperative, intraoperative, or postoperative metrics except for operative time (Tables 3 and 4). As mentioned, there were no cases of 4-gland hyperplasia in the RAI group, but there were two cases of double adenomas, which required additional time for exploration. The median operative times were 70.5 min (IQR 56.3–79.6) and 127.8 min (110.3–179.6) for the single gland group and multiglandular group, respectively ($p = 0.004$). There was no statistical difference in cure rates between these two groups (Table 4).

4 | DISCUSSION

The available literature on the development of PHPT after the RAI treatment for thyroid disease consists mostly of case reports and small case series.[1–16] In these publications, a majority of the patients were treated with RAI for the treatment of Graves' disease. Additional indications include adjuvant therapy for thyroid cancer and benign goiters. Little is known about the characteristics of the PHPT in these patients. Some reports suggest that there is no increased risk in developing PHPT after RAI treatment,[6,10,13,19] while others suggest that there is an

association between RAI exposure and the development of PHPT.[2–4,7,14,15,17,20]

The incidence and prevalence of this entity is not known, but in this cohort nearly 6% of the patients undergoing surgery for PHPT had a history of prior RAI treatment. While the percentage of the general population that has been treated with RAI is not known, the incidence in this cohort seems comparatively high, suggesting a possible causative relationship. However, it remains unclear if this causative association is real. Is RAI exposure just a confounder? External beam radiation to the thyroid gland has been shown to increase the risk of developing PHPT and is a more well-established risk factor than RAI.[20,22–24] Studies with murine models have shown an increased incidence or more rapid development of PHPT after exposure to RAI when compared to control rodents.[3,25,26] Unfortunately, there are no large prospective studies examining this question in humans. Although there is some evidence to support the entity of RAI-induced PHPT, the mechanism of how RAI increases the risk of developing of PHPT is unknown and speculative at best.[3] The question of what dose and duration of RAI exposure puts patients at a higher risk for developing PHPT also remains unknown.[19] To better characterize the possible relationship and mechanism of RAI-induced PHPT, larger prospective studies would be needed. RAI is known to have a number of potential side effects and it is possible that the risk of developing PHPT should be added as a potential consideration.[27]

As the literature on this topic is limited, the clinical presentation of these patients remains unclear. The latency period from the time of RAI treatment to the development of PHPT is not well studied.[2,3,5,6,11,14,17,18,21] Bondeson et al. quote a latency period range of 3–27 years in their 10 patient case series.[2] Wei et al. report a latency range of 12–14 years in their cohort of 11 patients.[17] One study, which combined an institutional cohort of 11 patients with 36 patients described in the literature, describes a range of 3–30 years with a mean of 35 ± 19.5 years.[3] This group also reported that with increasing age at the time of RAI treatment, the latency period to developing PHPT decreased. In our cohort, the average latency period was 20 years.

The current study, which includes the largest cohort studied to date, found that with regard to most clinical measures, the RAI exposed patients were similar to non-RAI patients. There were no statistically significant differences in gender, incidence of nephrolithiasis, preoperative calcium, vitamin D, creatinine or PTH levels, or gland weights. Wei et al.'s study, the only other retrospective cohort study examining this topic (which included 11 patients exposed to RAI), described similar findings. As RAI ablates the thyroid and consequently can alter the normal anatomy, these cases could potentially be more challenging and time intensive. However, we found no difference in average operative time between the cohorts.

Several relevant findings from this study have not previously been reported. Given that RAI may induce mutations in the parathyroid glands of the RAI exposed cohort, a higher rate of multiglandular disease might be expected in these patients. However, in our cohort, the overall rate of multiglandular disease was similar between the groups. Interestingly, none of the RAI exposed patients were found to have 4-gland hyperplasia. These results suggest that patients with PHPT who have had prior RAI exposure have a similar disease phenotype as those without prior RAI exposure. Importantly, we found no statistically significant difference in cure rates between the RAI and control group. This includes a large number of patients who were managed with minimally invasive parathyroidectomy (and ioPTH levels).

While the cure rate was similar between the two groups, the recurrence rate was statistically greater in patients who had been exposed to RAI. Historically, recurrence after a curative parathyroidectomy (in which a single adenoma was excised) was thought to be quite uncommon. However, more recent data suggest that recurrence is a more common issue than traditionally thought.[28,29] The higher recurrence rate in our cohort calls for some speculation regarding possible etiology. The two RAI exposed patients who recurred had a single gland removed during surgery and met the stricter ioPTH protocol. Consequently, these patients appear to have experienced true sequential adenomas. While this can occur in any patient with PHPT, it is possible that RAI exposure does in fact increase the risk. It is important to recognize that while statistically significant, this result was found in a very limited sample size. Consequently, the strength of this finding should be considered carefully by surgeons. In addition, a potential confounding factor to this finding is that due to the history of Graves' disease and RAI therapy, a greater percentage of these patients compared to the control group might have been under the continued care of an endocrinologist, leading to a higher rate of diagnosis. Nonetheless, greater vigilance when counseling and monitoring these patients after surgery is likely prudent.

One limitation of the current study was that some patients did not remember when they received RAI treatment and it was not in the medical record; as a result, the ability to precisely determine the median latency time was limited. There were also limitations due to the retrospective nature of this study. A larger prospective cohort study would provide stronger evidence. Although this is the largest retrospective cohort study, the true incidence

of RAI-induced PHPT is not known and therefore a power analysis could not be accurately calculated.

5 | CONCLUSION

In this study, patients with PHPT with a history of treatment with RAI were found to present with a similar clinical presentation to RAI naïve PHPT patients. Importantly, the frequency of multiglandular pathology was similar between the two groups. Consequently, RAI exposed patients can be approached in the same surgical manner typically employed by surgeons. While surgeons and patients in this scenario can expect a similar cure rate with surgery, they should be aware that the risk of recurrence may be increased.

CONFLICTS OF INTEREST

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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