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ORIGINAL SCIENTIFIC REPORT

Rapid Relief: Thyroidectomy is a Quicker Cure than Radioactive Iodine Ablation (RAI) in Patients with Hyperthyroidism

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Abstract

Background Time to hormonal control after definitive management of hyperthyroidism is unknown but may influence patient and physician decision making when choosing between treatment options. The hypothesis is that the euthyroid state is achieved faster after thyroidectomy than RAI ablation.

Methods A retrospective review of all patients undergoing definitive therapy for hyperthyroidism was performed. Outcomes after thyroidectomy were compared to RAI.

Results Over 3 years, 217 patients underwent definitive therapy for hyperthyroidism at a county hospital: 121 patients received RAI, and 96 patients underwent thyroidectomy. Age was equivalent ($p = 0.72$). More males underwent RAI (25% vs 15%, $p = 0.05$). Endocrinologists referred for both treatments equally ($p = 0.82$). Both treatments were offered after a minimum 1-year trial of medical management ($p = 0.15$). RAI patients mostly had Graves (93%), versus 73% of thyroidectomy patients ($p < 0.001$). Thyroidectomy patients more frequently had eye symptoms (35% vs 13%, $p < 0.001$), compressive symptoms (74% vs 15%, $p < 0.001$), or were pregnant/nursing (14% vs 0, $p < 0.001$). While the thyroidectomy patients had a documented discussion of all treatment modalities, 79% of RAI patients did not have a documented discussion regarding the option of surgical management ($p < 0.001$). Both treatment groups achieved an euthyroid state (71% vs 65%, $p = 0.39$). Thyroidectomy patients became euthyroid faster [3 months (2–7 months) versus 9 months (4–14 months); $p < 0.001$].

Conclusions Thyroidectomy for hyperthyroidism renders a patient to an euthyroid state faster than RAI. This finding may be important for patients and clinicians considering definitive options for hyperthyroidism.

Introduction

Uncontrolled hyperthyroidism adversely affects both a patient's quality of life and physical well-being [1]. The ideal treatment for hyperthyroidism would result in a rapid resolution of symptoms with low complication rates or side effects. While many patients may be successfully managed with antithyroid drugs (ATDs) alone, definitive therapy will be required for those patients needing high dosages of ATDs or experiencing toxic side effects, progressive ophthalmopathy, compressive symptoms, or concerns regarding the ongoing costs of ATDs. Physicians and patients must consider the risks and benefits of I^{131} radioactive

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iodine ablation (RAI) and thyroidectomy to determine which definitive therapy best fulfills the needs and concerns of the individual patient [2]. In the USA, RAI is more frequently utilized than thyroidectomy for definitive management [3, 4]. However, thyroidectomy provides absolute control of a patient's hyperthyroidism without exposure to radioactivity and avoiding potential side effects from prolonged ATDs usage.

The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) have published guidelines giving preference to thyroidectomy in individuals with large thyroid glands (>80 g), compressive symptoms, retrosternal extension, needing rapid control of a thyrotoxic state, coexisting hyperparathyroidism, insufficient RAI uptake, and significant exophthalmos [5]. The ATA also recommends that if surgery is selected, the patient should be referred to a high-volume thyroid surgeon [5, 6]. Patient characteristics help decide an appropriate treatment plan for most scenarios. Absolute contraindications for RAI include pregnancy, lactation, suspicious thyroid nodules, and noncompliance with radiation safety guidelines. The time to hormonal control after definitive treatment is currently unknown, but may be an important factor for many patients when deciding on a treatment modality [2].

This study compared total thyroidectomy to RAI ablation with regard to time to establish a post-intervention euthyroid state. While both treatment options can ultimately result in hypothyroidism requiring hormone supplementation, the hypothesis was that thyroidectomy would allow for a more rapid transition to euthyroid hormone supplementation in comparison with treatment with RAI ablation.

Methods

After Institutional Review Board approval, a retrospective review was performed to evaluate the definitive management of hyperthyroid patients at a large, urban, safety-net hospital. All patients age 18 years or older undergoing RAI or thyroidectomy for hyperthyroidism from 2014 to 2017 were included. The criteria used to define hyperthyroidism, as well as specific cause of hyperthyroidism, were the presence of signs and symptoms of an overactive thyroid gland, elevated T4 or T3 with suppressed TSH level, pattern of isotope uptake on the radionuclide scan, and/or the clinician's noted diagnosis. Reasons of hyperthyroidism included Graves' disease, toxic multinodular goiter, and toxic adenoma. Exclusion criteria included age, inadequate pre- or post-treatment follow-up evaluations and laboratory data, and previous definitive treatment at an outside facility.

Trial of ATDs was defined as at least 12 months of therapy before receiving RAI or thyroidectomy. Preoperative thyroid hormone status was defined by the last set of laboratory values before initiating definitive treatment. Thyroid hormone status was defined by T4 and T3 levels rather than TSH, as TSH is known to lag in response to declining thyroid hormones [5, 7].

Patients receiving RAI were compared to patients undergoing thyroidectomy. Baseline information from the patient's medical record including demographics, laboratory and imaging findings, and treatment course was collected. Time to euthyroid state was the main study outcome. Secondary outcomes included ability to achieve euthyroid state, treatment failures, number of medication adjustments, and adverse effects of treatment. Treatment failure was defined as continued hyperthyroidism requiring ongoing ATDs, and/or a second RAI dosage, or subsequent thyroidectomy. Medical noncompliance was based on documentation from the physician's notes.

Institutional protocol requires patients to maintain a low-iodine diet and hold their ATD medication for 1 week prior to RAI ablation. During preoperative visit, thyroidectomy patients were started on calcium and vitamin D supplementation [5, 8]. Potassium iodide (SSKI) was also prescribed to thyroidectomy patients with nonurgent Graves' disease who were without concern for poor medical compliance [7, 9]. All postsurgical patients were kept on scheduled calcium supplementation and titrated off based on laboratories and/or symptoms. Parathyroid hormone levels drawn in the recovery room were used along with calcium levels to dictate the addition of calcitriol [10].

After thyroidectomy, ATDs were stopped and patients started on Levothyroxine (weight-based dosing) with laboratories checked 6–8 weeks postoperatively [11]. Medication adjustments were made based on laboratories and followed every 6–8 weeks after any additional modifications until euthyroid state was established. For RAI patients, the ATD was continued usually until laboratories were checked 4–8 weeks after ablation therapy proving a trend toward hypothyroidism. Patients were then transitioned to Levothyroxine with laboratories checked 4–8 weeks later and repeated as needed until euthyroid state was established.

Capture of complication data was limited to what was documented within the medical record. RAI-related complications were defined by physician documentation related to both expected acute risks such as dry mouth, ageusia, nausea, and long-term complications such as sialoadenitis, xerostomia, dental caries, and nasolacrimal outflow obstructions [5, 7, 12, 13]. Post-thyroidectomy hypocalcemia was defined by symptoms requiring treatment in the postoperative setting and/or collecting a serum calcium level below reference range. Prolonged hypocalcemia was

defined as persistence beyond 6 months. Permanent hypoparathyroidism required supratherapeutic calcium and/or vitamin D supplementation with low parathyroid hormone levels beyond 12 months post-surgery. Transient RLN injury was defined as a loss of intraoperative nerve signal, complaints of hoarseness, or demonstrated vocal cord palsy/paresis by laryngoscopy in the first 6 months following surgery. Persistence beyond 6 months was defined as permanent RLN injury. Routine intraoperative nerve monitoring was performed for all cases, and laryngoscopy was performed selectively based on nerve monitoring results and/or patient-reported complaints.

Data are expressed as number (percentage), mean ± SD, or median (25th–75th percentile). IBM SPSS Statistics Version 25e (SPSS Inc, Chicago, IL) was used to perform all statistical analyses. Chi-square, Fisher's exact, unpaired t test, and Mann–Whitney test were utilized for univariate analysis as appropriate. Kaplan–Meier survival analysis was performed to determine time to euthyroid state after definitive treatment, with the comparison of the curves using Mantel–Cox log-rank test. A p value of ≤ 0.05 was determined to be significant.

Results

Between 2014 and 2017, 217 patients underwent definitive management for hyperthyroidism: 96 patients underwent thyroidectomy, and 121 patients underwent RAI. Baseline characteristics prior to definitive therapy for both cohorts can be found in Table 1. Of the thyroidectomy cohort, 70 patients (72.9%) were treated for Graves' disease, while 24 (25%) had a toxic multinodular goiter and 2 (2.1%) had a toxic solitary adenoma. Of the RAI cohort, 112 patients (92.6%) were treated for Graves' disease, while 4 (3.3%) had a toxic multinodular goiter and 5 (4.1%) had a toxic solitary adenoma.

At presentation, majority of the patients (206 patients, 95.4%) were treated with Methimazole (MMI) leading into their definitive therapy. 3.7% of patients were using Propylthiouracil (PTU); one patient did not improve on MMI so was changed to PTU, two patients developed rashes with MMI, and the other two patients were desiring pregnancy. Two patients (0.9%) failed MMI without trial of additional ATD prior to definitive therapy. 70% of the thyroidectomy group and 60% of the RAI group underwent a trial of ATD before opting for definitive therapy ($p = 0.148$). Endocrinologists were the primary referring specialty for both treatments (91% vs 89% $p = 0.82$). While all thyroidectomy patients had a documented discussion regarding all of treatment modality options, 79% of RAI patients did not have a documented discussion regarding the option of surgical management ($p < 0.001$). Two patients were referred directly to RAI by their primary care provider after notation of suppressed TSH with mild T4 elevation, without documented discussion of treatment options, and without initiation of ATDs. History of prior neck surgery was documented on all surgical patients, but was not well documented in the RAI cohort leading to an inaccurate comparison. As expected, thyroidectomy

Table 1 Patient characteristics

	Thyroidectomy $N = 96$	RAI $N = 121$	p value
Demographics			
Age of patient at presentation, years	45.8 ± 11.9	45.0 ± 12.4	0.720
Male gender	14 (14.6%)	30 (24.8%)	0.063
Etiology			
Graves' disease	70 (72.9%)	112 (92.6%)	<0.001
Toxic multinodular goiter	24 (25%)	4 (3.3%)	<0.001
Toxic solitary adenoma	2 (2.1%)	5 (4.1%)	<0.001
Pretreatment variables			
Referred by endocrinologist	87 (90.6%)	108 (89.3%)	0.823
Eye symptoms	34 (35.4%)	16 (13.3%)	<0.001
Pregnant, breastfeeding mother, or desiring pregnancy	13 (13.5%)	0 (0%)	<0.001
Thyrotoxicosis requiring hospital admission	29 (30.5%)	19 (15.7%)	<0.001
Compressive symptoms	71 (74%)	17 (14.2%)	<0.001
Given trial of ATDs prior to definitive therapy	67 (69.8%)	73 (60.3%)	0.148
Imaging studies			
US	94 (97.9%)	66 (54.5%)	<0.001
RAI uptake scan	43 (45.3%)	119 (98.3%)	<0.001

patients more frequently had eye symptoms (35% vs 13%), compressive symptoms (74% vs 14%), or were pregnant/nursing (14% vs 0, all $p < 0.001$).

Preoperative ultrasound (US) was performed in 94 (97.9%) of thyroidectomy patients and 66 (54.5%) of RAI patients ($p < 0.001$). Of the 33 patients with suspicious US findings who underwent preoperative fine-needle aspiration (FNA), 6 patients were placed in the Bethesda criteria of "suspicious for malignancy" or "known malignancy." Appropriately these patients received definitive surgery with final pathology for all confirming papillary thyroid carcinoma (PTC). Fourteen FNAs were "atypia of undetermined significance" (AUS), with 13 of these patients proceeding to thyroidectomy. Final operative pathology for these 13 AUS patients' revealed 9 benign, 3 incidental micro-PTC, and one follicular thyroid carcinoma (FTC). Interestingly, one patient with a benign FNA who underwent thyroidectomy was found to harbor an incidental FTC on final pathology. In total, final pathology revealed 16 thyroid cancers: 8 PTC, 2 FTC, and 6 micro-PTC). Six of these 16 patients were later treated with RAI for their cancer. Of the thyroidectomy cohort, 89 patients received total thyroidectomy, 4 patients underwent hemi-thyroidectomy for toxic adenoma/toxic uni-nodular goiter, and 3 patients required staged thyroidectomy due to the loss of recurrent laryngeal nerve signal with completion thyroidectomy performed after nerve recovery and normal vocal cord movement demonstrated on laryngoscopy.

The mean dose of RAI administered to the RAI cohort was 17.27 ± 6.15 mCi. Recurrence rate in the RAI group was 10.2% (12 patients); one with persistent Graves' disease and worsening eye symptoms elected thyroidectomy, one awaiting surgical consultation, two underwent repeat ablation, and the rest of the patients remain on low dosages of ATDs. The recurrence rate after thyroidectomy was 0% ($p < 0.001$).

Summary for post-treatment results can be found in Table 2. Duration of follow-up showed a more prolonged course for the RAI group, 8 months (range 3–17) versus 12 months (range 5.5–24.5, $p < 0.001$). Both treatment groups achieved a similar percentage for a euthyroid state at time of last follow-up (70.8% vs 65.3%, $p = 0.386$). Importantly, thyroidectomy patients became euthyroid faster, 3 months (range 2–7) vs 9 months (range 4–15, $p < 0.001$, Fig. 1). Thyroidectomy patients also underwent half the medication adjustments in the post-treatment setting (1.37 ± 1.23 vs 2.63 ± 1.45, $p < 0.001$). Medication adjustments accounted for increases or decreases in ATDs and/or Levothyroxine. Both groups showed similar patterns for documented medical noncompliance in the post-intervention setting, thyroidectomy (37.5% vs RAI 34.2%, $p = 0.611$).

Complications for the thyroidectomy cohort included one (1%) surgical site infection, three expanding hematomas (3.1%) requiring exploration, three (3.1%) transient RLN injuries, one (1%) permanent RLN injury, thirteen (13.5%) transient hypocalcemia cases, and four (4.1%) cases of prolonged hypocalcemia. For the patients with prolonged hypocalcemia, one patient had PTC with nodal metastasis requiring central neck dissection and modified lateral neck dissection, and the other three patients were documented having continued medical noncompliance for calcium and calcitriol with persistent low serum calcium levels but a normal PTH level.

Only one documented complication following RAI treatment was noted with a case of pancreatitis treated with conventional management. It is important to note that documentation regarding inquiry of common post-RAI symptoms was not found, making it difficult to determine true rates of post-RAI complications.

Discussion

Physicians and their patients can opt for definitive treatment of hyperthyroidism with either surgery or RAI. Choosing between these modalities requires an informed conversation which should include rates for success and complications, and for some patients an important variable for discussion will regard time to attain a post-intervention euthyroid state. The primary outcome of interest in our study was time to achieve euthyroid state. Thyroidectomy patients became euthyroid three times faster than the RAI group, 3 months versus 9 months.

It is well known that hypothyroidism following total thyroidectomy is immediate, while RAI-induced

Table 2 Post-intervention findings

	Thyroidectomy $N = 96$	RAI $N = 121$	p value
Recurrence rate	0	12 (10.2%)	<0.001
Avg. no. of post-treatment medication adjustments	1.37 ± 1.23	2.63 ± 1.45	<0.001
Achieved euthyroid state	68 (70.8%)	79 (65.3)	0.386
Time to euthyroid state, months	3 (2–7)	9 (4–14)	<0.001

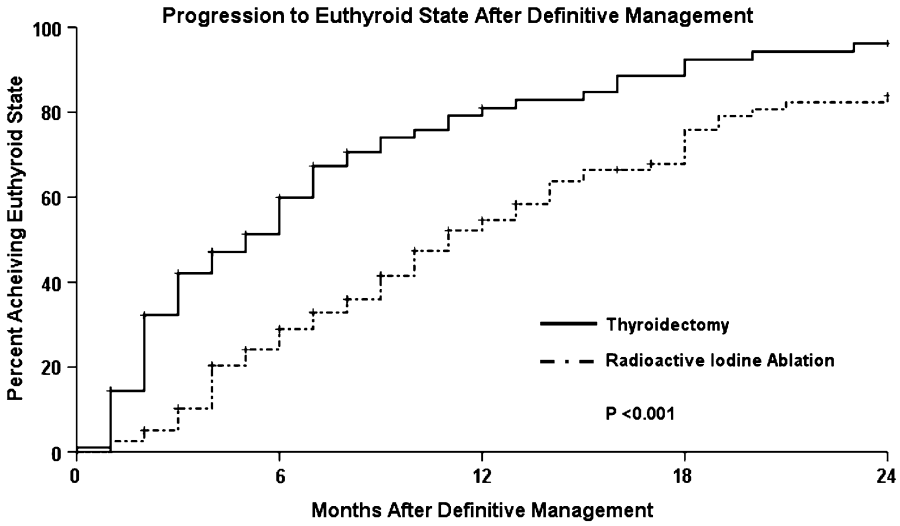

Fig. 1 Reverse Kaplan–Meir curve comparing thyroidectomy to RAI treatment for months needed for return to euthyroid state after definitive management

hypothyroidism is more gradual in onset, typically occurring within 3–6 months [14]. As full-dose thyroid hormone replacement can start immediately after surgery, this is the likely explanation for our results. To our knowledge, this is the first study to directly compare therapies for time to achieve euthyroid state. This was also the first study to directly compare therapies for the number of medication adjustments needed to achieve euthyroid state. Both of these variables may prove important for discussion with patients regarding differences in therapies, especially in populations that suffer from medical noncompliance as seen in our study. Early qualitative studies looking at Graves' patient satisfaction with all three management modalities have demonstrated both rapid control and rapid resolution as important factors for patients [2].

With expected indications for surgery, thyroidectomy patients in our study more frequently had eye symptoms, compressive symptoms, or were pregnant/nursing. One troubling statistic was that 79% of the RAI patients did not have a documented discussion regarding the option of surgical management. Reasons speculated to explain this finding include ease of error for electronic medical record systems do not capture the true conversation, and possibly RAI being a favored treatment with bias to downplay/omit discussion of the surgical option. RAI seems to be the preferred therapy in the USA, whereas long-term ATD therapy or thyroidectomy is more popular treatment choices in Europe [3, 5]. However, recent publications have shown thyroidectomy to be equivalent to RAI for long-term quality of life and some US institutions serving patients with low socioeconomic status are using surgery as their preferred treatment modality [3, 15–17]. As our study population was treated at an urban safety-net hospital, they were predominantly from a low socioeconomic status.

A full understanding of both RAI and thyroidectomy as definitive therapies is necessary for the patient, including disclosure of possible consequences. ATDs are almost always used as a bridge to definitive therapy, but they have high relapse rates (20–75%) and known side effect profiles to include hepatotoxicity, agranulocytosis, and skin manifestations [18]. For RAI, the insidious and often slow trend toward hypothyroidism may come with consequences such as radiation thyroiditis (1%) and new or worsened Graves' ophthalmopathy (13–33%), as well as a failure rate of 8–15% [5, 12, 13]. When considering surgery, providers should disclose an unrivaled relapse rate of 0% for total thyroidectomy with the procedure shown to be a safe and effective intervention. The most common complication after thyroidectomy for hyperthyroidism is transient hypocalcemia ranging from 3 to 40%, with the incidence of prolonged hypocalcemia being 0.6–6% [7]. The more feared complication of transient or permanent injury to the RLN ranged from 0–24% to 0–2% [7]. Other possible complications include superior laryngeal nerve injury (<1%), postoperative bleeding (0.3–4.9%), and anesthetic obstacles [5, 12, 13, 19]. Our study demonstrated similar thyroidectomy complications rates to previously reported literature with most of the concerns regarding hypocalcemia and hoarseness proving to be short-lived.

As with any retrospective review, this study is limited to the documented data in the patient's EMR. In particular, with regard to the RAI cohort, discussion of all treatment options was not documented, nor was potential complications clearly inquired about to ensure none occurred. Late complications following RAI treatment may not be

accurately captured in this 3-year study period. This report reflects the results of high-volume surgeons (>150 thyroidectomy procedures per year) at an urban safety-net hospital, and its findings may not be generalizable to all patient populations or surgeons [6]. To the authors' knowledge, this study represents a respectable population size in comparison with prior studies evaluating best therapeutic options for hyperthyroidism. This study sheds further light on treatment outcomes for hyperthyroidism and allows additional dialogue for selecting the most appropriate management for the patient. Future investigations regarding patient's quality of life measurement from patients from both cohorts would be helpful. A direct long-term cost analysis considering the impact of hormonal regulation after definitive management may be beneficial.

Thyroidectomy for hyperthyroidism renders a patient to an euthyroid state faster than RAI. Also, thyroidectomy patients enjoyed on average half the number of medication adjustments in the post-treatment setting. These findings may be important for patients and clinicians considering definitive options for hyperthyroidism.

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