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Clinical and Socioeconomic Factors influence treatment decisions in Graves' Disease

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Abstract

Background—Definitive treatment of Graves' disease includes radioactive iodine (RAI) and thyroidectomy, but utilization varies. We hypothesize that, in addition to clinical reasons, there are socioeconomic factors that influence whether a patient undergoes thyroidectomy or RAI.

Methods—Patients treated for Graves' disease between 8/2007 and 9/2013 at our university hospital were included. A comparative analysis of clinical and socioeconomic factors was completed.

Results—Of 427 patients, 300 (70%) underwent RAI while 127 (30%) underwent surgery. Multiple factors were associated with surgery: younger age (mean 36 vs. 41 years old, $p<0.01$), female gender (33% vs. 19% males, $p=0.01$), black race (56% vs. 28% non-black, $p<0.01$), Medicaid or uninsured (43% vs. 27% private insurance or Medicare, $p<0.01$), ophthalmopathy (38% vs. 26%, $p< 0.01$), goiter (35% vs. 23%, $p<0.01$), lowest quartile of median household income (38% vs. 27% upper three quartiles, $p=0.03$). Thyroidectomy increased annually, with 52% undergoing surgery during the final year ($p<0.01$). Adjusting for confounding, younger age (OR 1.04; 95% CI 1.02, 1.05), female gender (OR 2.06; 95% CI 1.06, 4.01), ophthalmopathy (OR 2.35; 95% CI 1.40, 3.96), and later year of treatment (OR 1.66; 95% CI 1.41, 1.95) remained significantly associated with surgery.

Conclusions—Surgery has now become the primary treatment modality of choice for Graves' disease at our institution. Clinical factors are the main drivers behind treatment choice, but patients with lower SES are more likely to have clinical features best treated with surgery, underlying the importance of improving access to quality surgical care for all patients.

Graves' disease is the most common type of hyperthyroidism in the United States, accounting for up to 80% of cases.(1) The prevalence of hyperthyroidism is approximately 1.2% in the United States.(2) Treatment options for this common disease include anti-thyroid medications, radioactive iodine (RAI), or surgical thyroidectomy. Practice patterns differ internationally; anti-thyroid medications are often used long-term in European countries, whereas in the United States, anti-thyroid medications are used to treat the initial thyrotoxicosis, but patients are offered definitive therapy with either RAI or surgery.(3) In the past, RAI has overwhelmingly been the definitive treatment of choice, with surgery

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reserved for patients who have failed other options or who have severe ophthalmopathy or other surgical indications. There has been an increased interest in total thyroidectomy for Graves' disease over the last few years as published complication rates are low and more clinicians are viewing it as a viable first-line therapy.(4-7)

Several factors should be taken into account when deciding whether a patient would be best treated definitively with surgery or RAI. Traditionally, clinical factors that are generally felt to be best treated with surgery include younger age, particularly in women who may be in the process of planning for a family, pregnancy, large goiters with compressive symptoms, nodules with a suspicion of cancer, concomitant hyperparathyroidism, or severe ophthalmopathy.(8) Other indications include failure or refusal of RAI therapy or complications associated with anti-thyroid medications. (9) One previous study reported a disproportionate number of patients with lower socioeconomic status (SES) undergoing surgery(10), and raised the possibility that social or economic factors such as insurance status, income, race, or education could also be influencing choice of treatment.

At our institution, we have seen an increase in the number of patients referred for surgical consultation for treatment of Graves' disease. The purpose of our study is to review our recent experience of the use of surgery or RAI for initial definitive treatment for Graves' disase. We hypothesize that, in addition to clinical reasons, there are socioeconomic factors that influence whether a patient undergoes thyroidectomy or RAI, and that health care disparities exist in the treatment of Graves' disease.

Methods

To determine if socioeconomic factors had any correlation with choice of treatment for GD, we performed an analysis at our institution of patients with Graves' disease treated with either RAI or thyroidectomy between August 2007 and September 2013. Patients who underwent surgery were identified by reviewing our prospectively collected endocrine surgery database of all thyroid operations at our institution, and including only those with a diagnosis of Graves' disease, as documented by hyperthyroidism and the presence of autoantibodies or documented diffuse uptake on radioactive uptake scan. Patients who underwent RAI treatment were identified using our institutions pharmacology database and extracting patients who were given I^{131} for a diagnosis of hyperthyroidism. Medical records for patients who received a dose of <50miCu were reviewed and since all patients had a thyroid uptake scan prior to administration of therapeutic doses, only patients with uptake scans that showed diffuse uptake consistent with Graves' disease were included. Patients with hot or cold nodules seen on thyroid uptake scan, ultrasound, or any mention of a nodule in a clinic note prior to treatment were excluded. In order to include only patients who were facing a genuine choice between RAI and surgery, we excluded patients who had conditions that stringently restricted that choice. Patients with absolute contraindications to RAI (iodine allergy, n=3, or pregnancy, n=10) and patients with other strong indications for surgery (suspicious or malignant nodules, n=20, or hyperparathyroidism, n=3) were excluded.

We included patients for whom surgery or RAI was their first definitive treatment. The initial management for almost every hyperthyroid patient at our institution is anti-thyroid

medications, but we did not restrict our sample based on the use or duration of use of those medications prior to definitive treatment with thyroidectomy or RAI. However, we did exclude anyone who had a previous treatment with either partial thyroidectomy or relapse after a previous dose of RAI.

A comparative analysis of age, gender, race, ethnicity, health insurance, primary language, year of treatment, ophthalmopathy, goiter, distance from hospital, median household income and education level was completed for patients who underwent thyroidectomy or RAI. Race and ethnicity (Hispanic or non-Hispanic) are self-reported at our institution and recorded in the medical record. Distance from hospital was calculated by drawing a straight line on a map between each patients address and the hospital, actual driving distance was not calculated. Patient addresses were geocoded and median household income and education level were derived from the census block from the 2010 US Census. When a complete address was unavailable (n=9), median income and education level was based on the zip code using the same US census data. Bivariate analysis and multivariate models were created using Stata v.11 (Stata Corporation; College Station, TX). This study was reviewed and approved by the institutional review board at the University of Wisconsin, informed consent was waived for patients, and all data was stored on secure, HIPAA-compliant servers within the health system.

Results

427 patients underwent definitive treatment for Graves' disease: 300 (70%) underwent RAI while 127 (30%) underwent surgery. Table 1 shows a comparison of all examined variable for patients who underwent RAI or surgery. This bivariate analysis revealed multiple factors that were associated with surgery. Patients who underwent surgery were younger (mean 36 vs. 41 years old, $p<0.01$). Female patients underwent surgery 33% of the time vs. 19% in males ($p=0.01$). The total number of black patients was small, but black patients underwent surgery 56% of the time as a first line vs. 28% non-black ($p<0.01$). Patients with Medicaid or who were uninsured underwent surgery in 43% of cases vs. 27% of the time for patients with private insurance or Medicare ($p<0.01$). Patients with ophthalmopathy or any eye complaints underwent surgery 38% of the time vs. 26% if there were no eye complaints ($p<0.01$). Patients with goiter underwent surgery 35% of the time vs. 23% of the time if the thyroid was felt to be near normal sized ($p<0.01$). In patients who lived in areas that had the lowest quartile of median household income, 38% of patients underwent surgery vs. 27% of patients from neighborhoods with higher incomes ($p=0.03$). Hispanic ethnicity, Spanish-speaking, education, and distance from the hospital did not vary significantly between the groups. Figure 1 shows the increasing use of thyroidectomy each year of the study, with 14% of patients undergoing surgery the first year, increasing each year to 52% during the final year ($p<0.01$).

After adjusting for confounding with a multivariate logistic regression model, Table 2 shows the variables that remained significantly associated with surgical treatment: younger age (OR 1.04; 95% CI 1.02, 1.05), female gender (OR 2.06; 95% CI 1.06, 4.01), ophthalmopathy (OR 2.35; 95% CI 1.40, 3.96), and later year of treatment (OR 1.66; 95% CI 1.41, 1.95).

Discussion

Radioactive iodine had been the definitive treatment of choice for Graves' disease in the United States for decades, and a 2011 survey found that only 1% of endocrinologists would recommend thyroidectomy as a first-line therapy(3). The subspecialty field of endocrine surgery is growing, and in 2007 the American Association for Endocrine Surgery formalized training of endocrine surgeons with a standard curriculum and training objectives. As with many surgeries, high surgeon volume is associated with improved outcomes and fewer complications after thyroidectomy(11), and since the formalization of endocrine surgery fellowships, more high volume endocrine surgeons are entering practice each year(12). With this improvement in thyroidectomy outcomes, we have seen a surge in the past three years of publications analyzing surgery as a first-line therapy for Graves' disease. At our institution over this time period, surgery was performed more often over each year of the study, and in the final year, thyroidectomy was performed more often than RAI as a first-line, definitive treatment for Graves' disease.

We report here that clinical features such as younger age, female gender, and ophthalmopathy remain the driving factors for surgery over RAI therapy. Black race, Medicaid or uninsured status, and lower income were all associated with surgery in the bivariate model, but dropped out as confounding was controlled for in a multivariate model. One must be careful about simply dismissing these social determinates of health as mere confounders, however. Taking a closer look at some of the relationships of the variables on Table 3, we found that 48% of black patients at our institution had ophthalmopathy vs. 33% of white patients. The mean age of black patients was 35 years vs. 42 years for white patients. Of patients with Medicaid, 42% had ophthalmopathy vs. 32% who had private insurance, and more than twice as many black patients lived in neighborhoods with the lowest quartile of income than white patients. These relationships are not all individually statistically significant, but when combined in our final model, they influence the odds ratios enough that some factors that seemed strong predictors on bivariate analysis no longer were independently predictive of surgery. However, it does appear that patients with lower SES seem to have clinical features of Graves' disease that are best treated with surgery. It is the clinical features that seem to drive the decision for surgery, but there are social determinates of health that are associated with those clinical features.

Noureldine, *et al.* recently reported that African Americans undergoing thyroid or parathyroid surgery had higher lengths of stay and overall complication rates, higher mortality, higher costs, and less access to high-volume surgeons than Caucasian patients(13). Combining this with our data that found that black patients were more likely to present with Graves' disease and clinical manifestations best treated with surgery, such as higher incidence of ophthalmopathy, our findings emphasize the importance of improving access to high-quality surgical care for these patients.

Our study is limited in its retrospective design and its relatively homogeneous population. The population of Wisconsin is 86% Caucasian, and our sample reflected the racial demographics of the state with only 6% African American. This is not reflective of the demographics of the country as a whole, and future studies are being planned that will

examine a larger, more diverse population of patients. Over half of the patients with Graves' disease at our institution are now treated with surgery, which is probably a higher number than at many institutions. We are a tertiary care center with high-volume endocrine surgeons who take referrals from a wide catchment area, whereas radioactive iodine is often administered locally. This likely accounts for a portion of the increased volume of surgery, and we cannot account for socioeconomic differences in patients who are referred to our center for surgery vs. those who have surgery or RAI in their local communities. Furthermore, clinicians at our institution take a multidisciplinary approach to patients with Graves' disease. There is good communication between endocrinologists and high-volume endocrine surgeons who have demonstrated excellent outcomes with thyroidectomy for Graves'(4). One aspect of the decision-making process that needs further rigorous investigation is the process by which patients themselves express a preference for one treatment over the other. Clearly, there are some clinical features that are best treated with surgery over RAI, and there seem to be some associations of these clinical features with certain racial, social, and economic factors. Ultimately, patients themselves need to weigh all the risks and benefits of the treatment options and decide which will work best for them. This decision can be very complex and should be individualized, and we need to explore and understand all the factors that go into that decision making process in order to improve clinical practice and reduce health disparities in the treatment of patients with Graves' disease.

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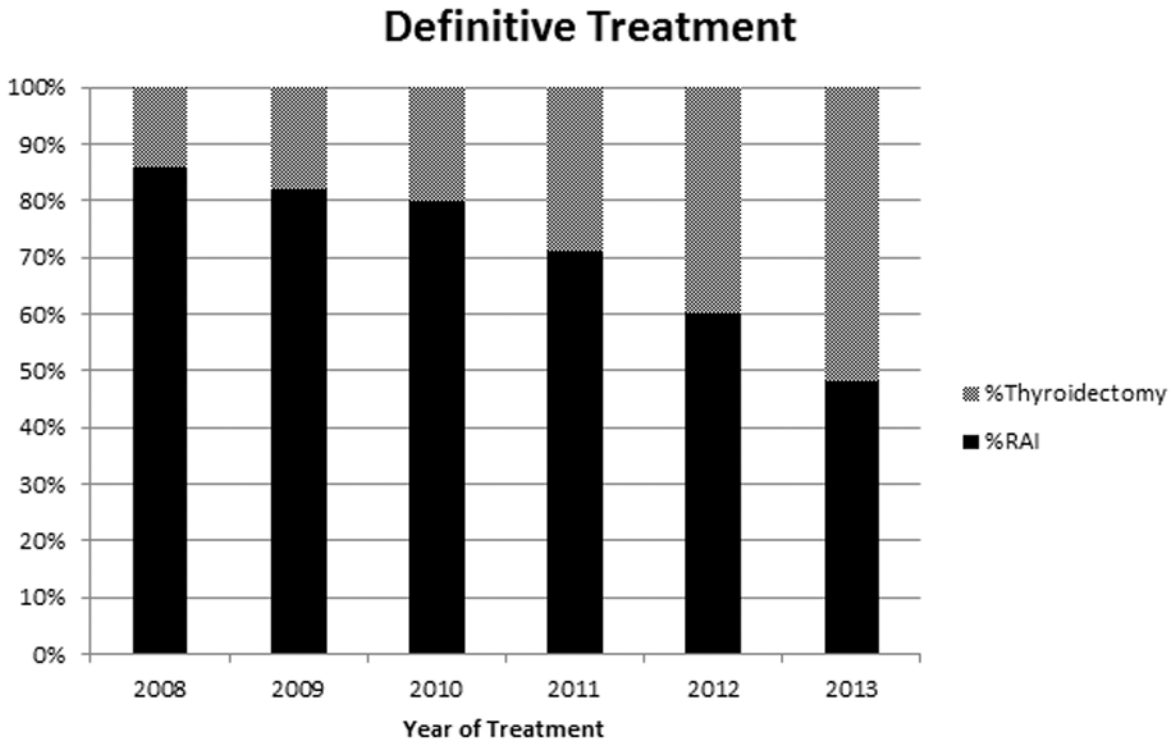

Figure 1.

Table 1

A comparison of all factors examined in patients who underwent thyroidectomy (Surgery) or RAI during the study period

Variable	Surgery n = 127 (30%)	RAI n = 300 (70%)	p
Age (mean ± SD in years)	36.1 ± 16.6	41.3 ± 16.3	<0.001
Female (%)	87.4	76.7	0.01
Black (%)	11	3.7	0.003
Hispanic (%)	5.6	4.1	0.49
Spanish primary language (%)	1.6	2.7	0.495
Medicaid (%)	28.4	16	0.003
Ophthalmopathy (%)	43.3	30.2	0.009
Goiter on Exam (%)	65.9	51.0	0.005
Lowest Quartile Income (%)	31.9	21.9	0.03
Lowest Quartile Education (%)	28.6	22.9	0.23
Distance from Hospital (mean ± SD, miles, straight line)	118 ± 310	96 ± 287	0.48

Table 2

Multivariate logistic regression model for variables associated with surgical treatment of Graves' disease

Variable	Odds Ratio, Surgery	95% C.I.
Younger Age (per year)	1.04	1.02, 1.05
Female	2.06	1.06, 4.01
Ophthalmopathy	2.35	1.40. 3.96
Later year of treatment (per year)	1.66	1.41, 1.95

Table 3

Association between the major clinical drivers of surgery and socioeconomic factors in patients with Graves' disease.

	% with Ophthalmopathy	Age (mean)	%Female
Overall cohort	34	41	80
Black	48	35	80
Non-black	33	42	80
Medicaid or Uninsured	42	39	83
Medicare or Private Insurance	32	42	79
Lowest Quartile Income	33	39	77
Upper Quartiles Income	36	42	81
Lowest Quartile Education	38	44	84
Upper Quartiles Education	24	40	78