Treatment Options for Graves' Disease

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The term *evidence-based medicine* was first coined by Sackett and colleagues[1] as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients." The key to practicing evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practice evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility, and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis, and economics as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program titled "Evidence-Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc and Ethicon Endo Surgery Inc. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS Web site. A listserve discussion is held where participants can discuss the monthly article. Fellows and candidates of the College can access Evidence Based Reviews in Surgery through the American College of Surgeons Web site (www.facs.org). All journal articles and reviews are available electronically through the Web site. Currently we have a library of 50 articles and reviews, which can be accessed at any time. Each October, a new set of articles will be available each month until May. Surgeons who participate in the current (modules) packages can receive CME credits by completing a series of multiple choice questions. Additional information about EBRS is on the ACS Web site or by email to the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS Web sites, 4 of the reviews are published in condensed versions in *the Canadian Journal of Surgery*, 4 in the *Journal of the American College of Surgeons*, and 4 in *Diseases of Colon and Rectum* each year.

REFERENCE

1. Evidence-Based Medicine Working Group. Evidence-based medicine. JAMA 1992;268:2420–2425.

SELECTED ARTICLE

Treatment Options for Graves' Disease: A Cost-Effectiveness Analysis

Haejin I, Pearce EN, Wong AK, et al. J Am Coll Surg 2009;209:170–179.

ABSTRACT

Objective: To determine the most cost effective option for treating Graves' disease after 18 months of antithyroid medication (ATM).

Design: A decision tree model was used to examine the cost effectiveness of 3 treatment options (lifelong antithyroid medication, radioactive iodine [RAI], and total thyroidectomy).

Setting: Treatment efficacy and complication data were derived from a literature review. Costs were examined from a health care system perspective using actual Medicare reimbursement rates to an urban university hospital.

Base case: Thirty-year-old nonpregnant woman without a large goiter, ophthalmopathy, or palpable nodules, who has failed to remain euthyroid after completion of 18 months of ATM.

Interventions: Each treatment option incorporated all associated events, their probabilities, and costs including

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medications, laboratory tests, clinic visits, treatment costs, costs associated with adverse events, such as agranulocytosis and recurrent laryngeal nerve damage; and costs associated with change in treatment for failed intervention.

Main outcomes: Outcomes were measured in quality-adjusted life-years (QALY).

Results: Total thyroidectomy was the most cost-effective strategy, resulting in a gain of 1.32 QALYs compared with RAI (at an additional cost of $9,594) and an incremental cost-effectiveness ratio of $7,240/QALY. RAI was the least costly option at $23,600, but provided the least QALY (25.08). Once the cost of total thyroidectomy exceeds $19,300, the incremental cost-effectiveness ratio of lifelong ATM and total thyroidectomy reverse, and lifelong ATM becomes the more cost-effective strategy at $15,000/QALY.

Conclusions: The findings demonstrate that total thyroidectomy is more cost effective than RAI or lifelong ATM in these patients; this continues until the cost of total thyroidectomy becomes greater than $19,300.

Commentary: Graves' disease is an autoimmune disorder that affects approximately 0.5% of the North American population. Graves' disease is the most common cause of primary hyperthyroidism. Treatment of hyperthyroidism is essential because overt manifestations of the condition can lead to long-term effects on the heart, bones, and psychological well being of the patient. Immediate control of symptoms is obtained with the use of beta-blockers; the antithyroidial drugs take effect and block further syntheses of thyroxin production. The goals of therapy are to control symptoms and restore the patient to a euthyroid state. There are 3 modes of therapy for the treatment of Graves' disease: antithyroidal medication, RAI, and total thyroidectomy.

Typically, patients with Graves' disease are treated with ATM for a period of time in hopes that the disease will resolve spontaneously. Remission, depending on the size of the gland, can occur in 30% to 50% of patients after a 12- to 18-month course of the drugs. After 12 to 18 months, most patients are faced with 3 possible treatment choices: continue the ATM for an indefinite period of time; receive RAI; or have a total thyroidectomy. The authors have correctly assumed that the best surgical option is a total thyroidectomy, and yet some surgeons continue to offer the option of a subtotal thyroidectomy to their patients. In contrast to a subtotal thyroidectomy, patients undergoing a total thyroidectomy will predictably require thyroid hormone replacement but will have a significantly lower risk of recurrence.

In counseling such patients with Graves' disease, the total thyroidectomy option is the one that has the most readily identifiable risks. As a result, many surgeons look at total thyroidectomy as something that should be strongly considered by patients only if there is a reason why ATM or RAI is not a safe option. For example, if the patient is pregnant or has suspicious nodules, RAI is not a safe option, or if a patient has had a bad reaction to the ATM, continuing medication is not a good option. Surgeons in the US are not commonly sent patients for total thyroidectomy for Graves' disease unless there is some other reason why RAI or continuing ATMs for long periods of time is not safe.

Total thyroidectomy, when done by experienced surgeons, is safe and provides an immediate and permanent solution to the hyperthyroid state. Surgery should continue to be used in all patients who fail to become euthyroid with other treatments, patients with very large goiters, in whom RAI would likely fail or is contraindicated, and those with significant Graves' ophthalmopathy. This analysis provides further evidence that thyroidectomy should also be considered the first line treatment option in patients with refractory Graves' disease because the long-term benefits and cost-effectiveness of this treatment are superior to lifelong medication and RAI. Although thyroidectomy is more costly up front, the benefit is realized in the long-term. It is important, however, to recognize that this benefit is realized only when the thyroidectomy is done by an experienced surgeon who has a low risk profile and understands the complexity of operating on a patient with Graves' disease. This study provides a rational basis for a physician to recommend a total thyroidectomy to patients even if they have no contraindication to ATM or RAI. Namely, total thyroidectomy is the most cost-effective strategy as long as the cost of total thyroidectomy does not exceed $19,300. The authors also report the results of sensitivity analyses for key variables that would influence medical decisions or have substantial medical consequences. The cost of thyroidectomy had the greatest influence on the results. As long as the cost of total thyroidectomy remained less than $19,300, total thyroidectomy remained the most cost-effective strategy. Other variables, including cost of medication, cost of RAI, patient age, probability of cancer with medication or RAI, success rate of RAI, rate of hypothyroidism with RAI, and complication rates of total thyroidectomy, did not influence the results. The sensitivity analyses are included as an online supplement (Appendix: 2).

This study has several limitations. It was based on retrospective nonexperimental data supplemented by expert opinion to generate probabilities and quality-of-life adjustment factors. In addition, utilities were not derived based

on patient opinions. So, it is possible that patient assessments of the utility or disutility of different disease states might differ considerably from those that were assigned by the authors. In addition, costs were based on the reimbursement structure for Medicare as representative of US payors. Actual 2007 Medicare reimbursements to a large urban university hospital were used to calculate the cost of treatment. Medication costs were obtained from average US wholesale prices. Future health care costs were computed using an inflation rate of 5%. A standard discount rate of 3% was applied to both cost and effectiveness, as recommended by the Panel on Cost-Effectiveness in Health and Medicine. However, although this methodology is the easiest, there are some concerns about it. The first limitation of this method is that the "price" is not always the same as the actual "cost" of delivering the service or product. These variances may occur because the price was established some time previously and does not reflect current costs; it may be due to the bargaining power of health care institutions, third-party payers, and the profit margin of for-profit health care systems. The second limitation is that the results of the analysis may not be generalizable to other systems. Because the cost of each resource is not explicitly stated, it is not possible to substitute the cost that may be incurred in another system in the analysis to determine if the results of the analysis are robust. Having said that, Medicare reimbursement is not a bad way of estimating cost in the US setting because these rates are established centrally and are not subject to bargaining and volume discounts.

In summary, the analysis by Haejin and colleagues is a timely article. This review brings to light the role that thyroidectomy can have in the treatment of Graves' disease. It is likely that the surgeon's role will expand in the years to come, with the increasing awareness and concerns about the long-term impact of RAI and the increasing emphasis on cost-effective therapies. Surgeons need to be more involved in the first line decision process when it comes to treatment of Graves' disease. Thyroidectomy is a valid treatment option and it is only the surgeon who can accurately explain the surgical risk vs benefit of this modality to the patient.