Epidemiology

Epidemiology 550 for April 29, 2015

- Review homework 6
- Review article on palliation for vertebral bone metastases
- Review article on preventive therapy for malaria during pregnancy
- Provide information about final examination
- Elicit student feedback about this year's course

Original Investigation

Routine Magnetic Resonance Imaging for Idiopathic Olfactory Loss
A Modeling-Based Economic Evaluation

Luke Reid, MD, MSC; Kristine A. Smith, MD; Zachary N. Soree, MD; Michael C. Schlosser, MD; Timothy L. Smith, MD, MPH


Author Affiliations. Division of Otolaryngology-Head and Neck Surgery, Department of Surgery, University of Calgary, Calgary, Alberta, Canada (Reid); Division of Rhinology and Sinus Surgery, Department of Otolaryngology-Head and Neck Surgery, Medical University of South Carolina, Charleston, S.C. (Smith); Division of Otolaryngology and Head and Neck Surgery, University of Toronto, Toronto, Ont. (Soree); Division of Otolaryngology and Head and Neck Surgery, Department of Dermatology, University of British Columbia, Vancouver, B.C. (Schlosser); Division of Otolaryngology and Head and Neck Surgery, Oregon Health and Science University, Portland (Smith)

Conflict of Interest Disclosures. Dr Reid has received support from a grant from the National Institute on Deafness and Other Communication Disorders, National Institute of Health (R01DC 022454), and served as consultant to Biocom, Inc, and Ossur, Inc. Dr Reid has received honoraria from Ossur, Inc. Dr Reid, Dr Soree, and Dr Smith have served as consultants for Intersect ENT Inc. Dr Reid has received honoraria from the National Institute on Deafness and Other Communication Disorders, and Mr Reid and Dr Smith have received grant support from the National Institute on Deafness and Other Communication Disorders. No other disclosures were reported by the other contributing authors.
The objective of this economic evaluation is to determine the cost-effectiveness of routine MRI in patients presenting with idiopathic optic nerve loss. The purpose of this study was to inform decision making for this challenging clinical scenario. The primary outcome was the incremental cost per dis-
RESULTS: The mean (SD) cost for the MRI strategy was $2400.00 ($7175.54) and was effective 100% of the time, whereas the mean (SD) cost for the no-imaging strategy was $865.01 ($7175.40) and was effective 78% of the time. The incremental cost-effectiveness ratio (ICER) for the MRI strategy compared with the no-imaging strategy was $115659.50, which is higher than most acceptable willingness to pay thresholds. The threshold analysis demonstrated...

Sensitivity Analysis:
A univariate threshold analysis was performed to elucidate what the probability of having a treatable intracranial abnormality would have to be to make the MRI strategy a more cost-effective decision. We provide the increase in...

Table 1: Outcomes From the Threshold Sensitivity Analysis.

<table>
<thead>
<tr>
<th>Probability of Having a Treatable Intracranial Abnormality (%)</th>
<th>ICER for MRI vs No Imaging</th>
<th>Degree of Converting, $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.9</td>
<td>24 654.13</td>
<td>65</td>
</tr>
<tr>
<td>4.6</td>
<td>41 019.83</td>
<td>48</td>
</tr>
<tr>
<td>1.6</td>
<td>121 813.52</td>
<td>19</td>
</tr>
</tbody>
</table>

Abbreviations: ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging.

* Indicates rate at which the MRI strategy is cost-effective, assuming willingness to pay of $50000.
More Important Strengths

• Problem is important and topical
• Modeling is an appropriate method for addressing the problem
• Clear description of model and its inputs
• ICERs were used to summarize results
• Sensitivity analyses were done, both deterministic and probabilistic
• This effort was contrasted with previous efforts
More Important Weaknesses

- Many important costs and values were left out of the analysis, for example, those for outcomes beyond the 1-yr horizon and those for treatments, clinical outcomes, out-of-pocket costs, and lost productivity.
- One result of omitted costs was that the promised analysis from a societal perspective was not done.
- The outcome was “correct diagnosis of idiopathic olfactory loss,” but it should have been QALYs.
- The willingness to pay values used by the authors are the consensus values for a QALY, not the values for a correct diagnosis in this clinical situation.
- The MRI was perfectly sensitive and specific.*

Table 1. Number of responses by item and grade.

<table>
<thead>
<tr>
<th>Item</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevance</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Accuracy</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
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<tr>
<td>Completeness</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Appeal</td>
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<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Educational Value</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 2. Number of responses by recommendation about publication.

<table>
<thead>
<tr>
<th>Publication Recommendation</th>
<th>Number of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject</td>
<td>2</td>
</tr>
<tr>
<td>Reconsider after major revision</td>
<td>7</td>
</tr>
<tr>
<td>Accept after satisfactory revision</td>
<td>1</td>
</tr>
<tr>
<td>Accept</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
</tr>
</tbody>
</table>
Table 3. Number of responses by recommendation for an editorial.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Number of Responses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>No</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
</tr>
</tbody>
</table>

Advice for Less Experienced Reviewers

- Resist the temptation to summarize what the authors did
- Comments for editors should emphasize and complement the comments for authors, not duplicate or summarize them
- Focus on bigger problems, especially “fatal errors”
- Divide author comments into distinct ideas and number them consecutively because doing so will facilitate author responses
- Separate comments for authors into “more important” and “other” categories (or similar categories with other labels)
- Sort comments for editors and authors in descending order of importance
- Provide all the information requested by the journal
- What is the best way to write comments for authors? Is it, “I think you should . . .” or “The authors should . . .”?
Conventional fractionated EBRT (largely 30 Gy in 10 fractions) has been mostly accepted for palliative treatment (6, 7). Radiation Therapy Oncology Group (RTOG) 97-14, which randomized patients to either 8 Gy in a single fraction or 30 Gy in 10 fractions for radiation treatment of bone metastases, showed similar pain relief (the primary endpoint of this study) between the two study arms (1, 6). For this reason, 8 Gy in a single fraction is one of the acceptable options from the American Society for Radiation Oncology consensus evidence-based standard of care for symptomatic bone metastases (2). Recently, stereotactic body radiation therapy (SBRT) has demonstrated better pain control and neurologic function in comparison with historical results with conventional EBRT for spine metastases (8-10). Unlike with EBRT, where concerns of spinal cord myelopathy have limited dose escalation because of the proximity of the spinal cord to the vertebral body, improved precision of dose delivery with SBRT creates a sharp dose falloff between the target and adjacent spinal cord. This high targeting accuracy allows higher single fraction radiation dose to the vertebral target while maintaining a safe spinal cord dose previously not feasible with EBRT (10).

![Fig. 1. Markov state transition model. Arrows represent transition between health states. EBRT = external beam radiation therapy; SBRT = stereotactic body radiation therapy.](image-url)

<table>
<thead>
<tr>
<th>Table 1: Radiation therapy doses</th>
<th>Amount administered</th>
<th>Consequence of Event</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT vs. SBRT</td>
<td>8 Gy in a single fraction</td>
<td>Similar pain relief</td>
<td>Favor SBRT</td>
</tr>
<tr>
<td>Low dose EBRT</td>
<td>30 Gy in 10 fractions</td>
<td>Similar pain relief</td>
<td>Favor EBRT</td>
</tr>
<tr>
<td>High dose EBRT</td>
<td>30 Gy in 10 fractions</td>
<td>Similar pain relief</td>
<td>Favor EBRT</td>
</tr>
</tbody>
</table>

Note: Dose escalation with SBRT creates a sharp dose falloff between the target and adjacent spinal cord, allowing higher single fraction radiation dose to the vertebral target while maintaining a safe spinal cord dose previously not feasible with EBRT (10).
Sensitivity analysis

We performed 1-way, 2-way and probabilistic sensitivity analyses to account for uncertainty in decision model assumptions. A 1-way sensitivity analysis, where all parameters are varied individually, was examined to detect the effect of these variations on model results. A 2-way sensitivity analysis varies 2 parameters simultaneously and denotes where a particular strategy is preferred. We performed a 2-way sensitivity analysis to determine the optimal treatment strategy when median survival rate and pain relief difference were varied. The probabilistic sensitivity analysis using a Monte Carlo simulation was conducted to vary all parameters simultaneously. This is, distributions for each parameter (Table 1) were sampled at random during 5000 trials, and results were reported as the percentage of trials in which a strategy is most-effective at a series of WTP (willingness to pay) thresholds. Costs were modeled using a normal distribution with a standard deviation of 25% of the base case value. For utilities and probabilities, we used a beta distribution function for sampling.

Table 3: Incremental cost-effectiveness ratios (ICER) for EBRT compared with EBRT

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost ($1000)</th>
<th>Incremental cost ($1000)</th>
<th>Effectiveness</th>
<th>Incremental effectiveness</th>
<th>Incremental ICER ($1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBRT</td>
<td>6000</td>
<td>0</td>
<td>0.35</td>
<td>0.05</td>
<td>12,352</td>
</tr>
<tr>
<td>EBRT</td>
<td>6000</td>
<td>0</td>
<td>0.35</td>
<td>0.05</td>
<td>12,352</td>
</tr>
</tbody>
</table>

* Alternatives: EBRT = external beam radiation therapy, EBRT = external beam radiation therapy.

Fig. 2. One-way sensitivity analysis. Incremental cost-effectiveness ratio (ICER). Sensitivity diagram for 1-way sensitivity analysis. The vertical line represents the base case value of $12,352 (35%). Utility of unadjusted pain: range, 0.75-0.35 to 0.75-0.35 (35%); utility of unadjusted pain after the mental treatment (range, 0.75-0.35 to 0.75-0.35 (35%); and median survival rate range: 0.5 to 0.75 to 0.5 to 0.75 (35%).
Conclusion: SIRT for palliation of splanchnic bone metastasis is noncost-effective compared with EBRT at a $300,000 per QALY gained WTP threshold. However, if median survival is ≥11 months, SIRT costs ≤$300,000 per QALY gained, suggesting that selective SIRT use in patients with longer expected survival may be the most cost-effective approach.
More Important Strengths

• Problem is important and topical
• Markov modeling is an appropriate method for addressing the problem
• Clear description of model and its inputs
• ICERS were used to summarize results
• Sensitivity analyses were done, both deterministic and probabilistic
• Effort was contrasted with previous efforts

More Important Weaknesses

• RTOG 0631 will finish enrollment in July 2015, so the information in this article will be outdated soon, because “…our clinical assumptions for SBRT may not accurately reflect reality.”
• An analysis from a societal perspective was not done
• Other?
Background: In 2015, WHO changed its recommendations for intermittent preventive treatment of malaria during pregnancy (IPTp) from twice to three times. We conducted a cost-effectiveness analysis to evaluate the impact of the decision of policy makers. We compared the incremental cost-effectiveness of IPTp in a trial evaluating IPTp with concomitant treatment (IPTp-CT) versus IPTp alone (IPTp).

Figure: The decision tree. The decision tree model follows the example in [18]. All estimates and results published by Saman and colleagues were used to populate the model. The model was designed to be used in a scenario in which IPTp alone or IPTp-CT were evaluated. IPTp was assumed to be given at three doses: at the start of the pregnancy, at the 36th week, and at the 40th week of pregnancy. The probabilities of each outcome were estimated from the literature.
Disability-adjusted life year (DALY)

From Wikipedia, the free encyclopedia

- The disability-adjusted life year (DALY) is a measure of overall disease burden, expressed as the number of years lost due to ill-health, disability or early death. It was developed in the 1990s as a way of comparing the overall health and life expectancy of different countries.
- The DALY is becoming increasingly common in the field of public health and health impact assessment. It extends the concept of potential years of life lost due to premature death...to include equivalent years of 'healthy' life lost by virtue of being in states of poor health or disability. In so doing, mortality and morbidity are combined into a single, common metric.
The cost of delivering 1776-974a to 1000 pregnant women in the base case scenario table 2 gives an incremental cost-effectiveness ratio of $2.7A per DALY avoided. For the deterministic sensitivity analysis, figure 2 and table 1 show the results and percentage change for changes in parameter inputs, changes to methodological assumptions, or subgroup analysis in which the variation resulted in at least 5% change in the incremental cost-effectiveness ratio. The base case incremental cost-effectiveness ratio was substantially below the low willingness-to-pay threshold of $30-72 per DALY avoided. Although some variations in the deterministic sensitivity analysis resulted in substantial percentage changes in the incremental cost-effectiveness ratio, none substantially altered outcomes which relative risks for all outcomes and subgroups were varied. The upper bound of the 95% CI shows a lower than the low willingness-to-pay threshold of $30-72 and none of them resulted in a change beyond the middle willingness-to-pay threshold of $25-35.
Discussion
Our findings suggest that at just $7.20 per DAILY packet, EFPs-SFPs can be a highly cost-effective intervention when incorporated into an existing antimalarial care package. In settings with moderate malaria transmission, EFPs-SFPs has a 95.4% probability of being highly cost-effective using a threshold of $30.7 per DAILY packet. It is substantially more cost-effective than many health interventions recommended for implementation in sub-Saharan Africa (e.g., intermittent preventive treatment in early infancy at $4.9 per DAILY packet or PMTCT at $35-60 per DAILY packet). Furthermore, cost effectiveness...
More Important Strengths

- Problem is important and topical
- Decision tree modeling is an appropriate method for addressing the problem
- Many inputs were based on a meta-analysis
- Society’s perspective was used
- Outcomes were measured in DALYs
- ICERS were used to summarize results
- Sensitivity analyses were done, both deterministic and probabilistic
- Lifetime horizon
- 3% discount rate

More Important Weaknesses

- Confusing presentation of how DALYs were calculated from separate models of LBW, maternal anemia, and clinical malaria
- DALYs are not as familiar to clinicians as they are to public health practitioners
- Attendance at prenatal care was assumed
- Perfect adherence to preventive therapy by attendees was assumed

The Final Examination

- Available 9:00 AM Monday May 4
- Due 5:00 PM Monday May 11
- One question asks you to review an article
- The other question asks you to solve a problem using a cost-effectiveness analysis
- “Open book” with access to all resources except other people (no working together)
- Henry and I will answer email questions that do not compromise the examination
Student Feedback for 2015

- Room, Time of Day, Day of Week
- Canvas
- Class notes
- Assigned reading
- Homework
- Frequency and amount
- TreeAge software
- Individual vs. group responsibility
- Critical analyses
- Quiz 1 and Quiz 2
- In class exercise
- Grading
- Inclusion, exclusion, and sequence of material
- Class discussion
- Other issues