Reviewer's report

Title: Neoadjuvant or adjuvant therapy for resectable esophageal cancer: a practice guideline

Version: 1 Date: 19 November 2003

Reviewer: John Urschel

Reviewer's report:

General

The manuscript can be artificially broken down into two components: systematic review (exhaustive and complete) and practice guideline (lacking in depth). The authors were probably exhausted from the former, and ran out of energy for the latter.

The systematic review is simply outstanding. It is extremely thorough. The methodology is top notch. It will be an important reference for the future.

The guideline component is weak. I am going to draw an analogy to the field of economics, where data analyses may be positive or normative ("what is", or "what should be"). For this manuscript the "what is" component (systematic review) is excellent, but the "what should be" (practice guideline) component represents an opinion based on the data. It is an opinion that reflects a cautious approach to accepting new treatments. A general question not explicitly addressed in the guideline, or in others from CCO, is as follows: If we know that our current standard treatment (surgery alone) is not very good, what is the threshold of evidence for adopting a new treatment? That is a difficult normative question, and one that is not addressed in the guideline part of the manuscript.

Discretionary Revisions (which the author can choose to ignore)

Minor Compulsory Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

The systematic review part of the manuscript is excellent, and revisions are not needed. I suggest either revision of the guidelines component, or separation of the paper into two separate papers (systematic review accepted without revision, and guideline reworked and resubmitted).

The Guideline Component -

While data analysis is often black or white, the underlying issues are not. The clinician authors should address the "gray" underlying issues that the statisticians do not see or understand. The key issue relates to esophageal cancer resectability. This is not mentioned in the manuscript. The term "resectable esophageal cancer" is discussed as a distinct entity, without qualification.
A few points to consider:

1. Surgery alone for esophageal cancer fails for two reasons: systemic disease is often lurking (mentioned in the manuscript) and we are often unable to completely resect the cancer (not mentioned in the manuscript).
2. If a complete (R0) resection is not accomplished, surgery alone will not be curative (this statement does not necessarily mean that multimodality treatment would have been curative).
3. It is often difficult to be certain (preoperatively) if a complete resection will be possible.
4. One of the main reasons for "success" of induction therapy, followed by surgery, is its impact on the rate of complete resection. Surprisingly, it does not seem to have much effect on systemic disease.
5. If the authors look at their data they will see that patients treated with induction chemotherapy or chemoradiotherapy have a higher rate of complete resection than those treated with surgery alone. The overall rate of resection (any resection, even if incomplete) is lower in patients treated with induction therapy. So, induction therapy probably improves the rate of complete resection in two ways - "downstaging" and patient selection. Complete resection is not an endpoint; I grant the authors this. However, it is crucially important.
6. Recognizing the "gray" area of resectability, the authors might reconsider their conclusions. The data would support a statement that surgery alone is the current standard if there is a reasonable probability of a complete resection (R0 resection) being performed. That is probably what the authors were trying to say (implicitly) when they used the word "appropriate".
7. If there is preoperative evidence of regionally advanced disease, as is often the case, and the prospects for complete resection seems grim, what are we to do? Offer an incomplete resection, with "palliative" intent (an outdated concept that should be condemned)? Treat with definitive chemoradiotherapy (discussed in a separate CCO practice guideline)? Try induction therapy followed by surgery, even though the evidence to support it is scanty? These are the questions that clinicians and patients face. I do not see how "surgery alone when appropriate" answers these questions.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

I previously worked in Hamilton, Ontario, Canada, and was a faculty member at McMaster University. I held an appointment with Cancer Care Ontario, and had some involvement in the lung cancer practice guideline initiative. Therefore, I am familiar with CCO's practice guideline "environment". I have great respect for the authors' scientific rigour and honesty.