

October 22, 2009

Ms. Laura I. Thevenot  
Chief Executive Officer  
American Society for Radiation Oncology  
8280 Willow Oaks Corporate Drive  
Suite 500  
Fairfax, VA 22031

Dear Ms. Thevenot:

Thank you for your thoughtful and insightful comments on ICER's draft report on management options for low-risk prostate cancer. We greatly appreciate ASTRO's continued engagement with our process and work products, and sincerely hope that we can continue to communicate on this and other topics of mutual interest. With your permission, we would like to publish your response document as well as our reply on our web site. Our specific responses to your concerns can be found below, using the same headings that were used in your letter.

***Bias Toward Active Surveillance***

We agree that there is a lack of long-term data with active surveillance (AS), and that this reduces the certainty of our conclusions (see page 33 of the report). It is important to note, however, that our consideration of the literature on AS used the entire continuum of surveillance protocols, including the watchful waiting studies. As such, there was more certainty in our designation of the comparative clinical effectiveness of AS as "comparable" for older patients, who have been studied much more extensively across the entire literature continuum. There is less certainty regarding AS for younger patients, which we have reflected in our rating of the evidence as "unproven with potential".

Your comments have crystallized a general concern for us, however, regarding our attempts to summarize the technically-detailed individual appraisals of these management options in a single document. While limitations of the evidence base for AS are described on page 33 and again when we discuss our rationale for integrated evidence ratings (pp. 54-55), this issue is discussed in more detail in our appraisal report of AS and radical prostatectomy (<http://www.icer-review.org/index.php/as-rp.html>). A detailed discussion of the ERG deliberations and rationale for the ratings can be found on pages 24-26 of this document, and issues with the evidence base for all management options are documented in detail starting on page 64. We will modify the summary report to cite the detailed appraisal documents wherever necessary.

### *Risk Adjustment for Comorbidities*

We agree that there may be substantial differences in the profile of patients undergoing the definitive treatment options of interest, an issue that is compounded by the lack of randomized trials or other prospective evaluations explicitly comparing these options. However, any attempt to “risk adjust” the findings from these largely single-center studies to reflect differences in patient populations would be problematic for several reasons. For example, necessary data are often missing from the study reports; in addition, there are other influences on outcome, such as surgery or procedure learning curve.

### *Issues with the ICER Model*

As noted on page 50 of the summary report, we conducted a sensitivity analysis in which brachytherapy (BT) was selected as the definitive treatment of choice for patients on AS, rather than IMRT. With BT as the treatment option, AS becomes cost-saving relative to surgery in 65 year-old men.

We also conducted a sensitivity analysis in which AS was assumed to have a higher risk of prostate cancer-specific mortality than definitive treatment – in this case, we assumed an absolute risk difference at 10 years that was approximately one-half that observed in the Scandinavian trial of watchful waiting (2.5%, also noted on page 50). The difference in quality-adjusted survival between AS and immediate treatment was reduced slightly by this change, but AS still produced an additional 9-12 months compared to immediate treatment.

Finally, we did assume that the low-risk, organ-confined nature of the disease in the target population would result in a relatively low rate of adjuvant radiation, based on findings from recent studies (Louie-Johnsun, 2009; Griffin, 2007) suggesting rates of positive surgical margins that are under 10% in low-risk patients. This is a limitation of the model, however, as results are then slightly biased in favor of surgery, and we will modify the report to highlight this limitation.

### *Issues with the CVET Table*

We hope that the following explanation will clarify the apparent disconnect between the rates of treatment-related side effects in the CVET table and the findings from our systematic review. First, it should be noted that our estimates of short- and long-term side effects were restricted to rates reported by clinicians, and may therefore be lower than patient-reported rates. Second, while the side-effect estimates from our systematic review were used as inputs to the model (page 37), rates of urinary incontinence and erectile dysfunction were adjusted to reflect only treatment-attributable risk (i.e., risk over and above the baseline risk due to age and/or comorbidity in 65 or 55 year-old men). This construct is described on page 47 of the summary report.

*Review of Alternative Management Strategies*

We believe there are several sections of the report that state the relative contraindications to BT, including the decision guide on page 6 and the procedure description on page 15. While our systematic review found no data to distinguish rates of urinary toxicity for BT from other radiation modalities, history of urinary obstruction is listed as a contraindication, and acute urinary retention is considered separately (page 39). Differences in gastrointestinal toxicities between BT and other radiation modalities are also noted (page 38), with the caveat that there is again limited evidence with which to distinguish these options.

*Technical Questions/Corrections*

Thank you for these insights. We will remove the NCI letter from the list of IMRT guidelines, as we agree that it does not truly reflect guidelines for use. We will also include references for our statement regarding IMRT vs. 3D-CRT use in the U.S., and also agree that there is likely variation in BT practice, involving both inpatient and outpatient treatment. Finally, we will increase the cutoff for large prostates as a contraindication to brachytherapy.

Thank you again for your comprehensive and thorough review of our report. We appreciate ASTRO's willingness to work with us as both an active participant and key stakeholder in our processes. If you have any further questions or concerns, please do not hesitate to contact us.

Sincerely,



Steven D. Pearson, MD, MSc, FRCP  
President