Project Name: Radiation Therapy for Localized Prostate Cancer
Project ID: CANT1209

Table 1: Invited Peer Reviewer Comments

Reviewer[1]	Section[2]	Reviewer Comments	Author Response[3]
1	General	The goal of this study was overall to evaluate specifically radiation therapy for localized prostate cancers answering the following questions. 1. Benefits and harms of radiation therapy for clinically localized prostate cancer compared to no treatment or no initial treatment i.e., watchful waiting in terms of clinical outcomes. 2. What the benefits and harms of different forms of radiation for clinically localized prostate cancer were in terms of clinical outcomes comparing stereotactic body irradiation vs. classically fractionated external beam including 3D vs. IMRT as well as particle therapy and also including high dose rate brachytherapy as well as low dose rate brachytherapy. 3. How do patient's specific characteristics such as age, race or ethnicity, presence or absence of co morbidities affect the outcomes of different forms of radiation? The results of this analysis revealed essentially no adequate data to answer any of the three questions posed. I agree that the data as available does not answer the questions posed in a prospective randomized way and clearly more data utilizing prospective randomized trials is needed to get answers to these questions, if one only considers low risk prostate cancer patients. Currently the START cooperative group trial between the United States and Canada looking at low risk patients and randomizing them to watchful waiting vs. their choice of a form of treatment surgery vs. radiation options would be an excellent one for nationwide support. But this trial only addresses patients with low risk disease. The results of this analysis unfortunately did not include patients with T3 disease many of whom have localized disease and there is phase III prospective randomized data (i.e., level 1 data) from Widmark et al (Lancet 2009: 373: 301-308) that demonstrates that the addition of radiation to the prostate improves overall survival and prostate cancer specific survival for patients with locally advanced disease. This data did include some patients with T1 and T2 tumors in addition to T3 tumors and should have been part of the analysis because it	Thank you for your comments and suggestions. 1) The START cooperative group trial was discussed in the Future Research section of the report. 2) We had a lengthy discussion on Widmark et al trial (Lancet 2009: 373: 301-308). Even though this trial is phase III prospective randomized data, it didn't meet more than one of our inclusion criteria. I) Treatments compared didn't meet our inclusion criteria (looking only at direct comparative studies) to be included under any of our key questions, including radiation therapy to no therapy or no initial therapy II) This trial had all patients treated with hormone therapy. III) This trial had included only 21% patients with T1/T2 disease. IV) The analogy of A+B vs. B → A vs. nothing is an inference and not direct evidence. 3) We searched the data sources with a broader net to obtain all the recent relevant articles and then screened them based on our inclusion criteria and key questions. Establishing objective inclusion and exclusion criteria is part of a "systematic" review process to ensure the studies selected are germane to the particular key questions posed. Asking a different set of key questions (but within the same topic) could very well have resulted in a different set of studies. The studies selected are those studies relevant for our set of key questions, which focused on *comparative* evidence, but are not necessarily representative of all the studies within the field. 4) We have adopted your suggestion regarding the reference to New York Times article and deleted it. Nevertheless, a lack of reporting on adverse event(s) with respect to quality assurance of radiation delivery was observed in the studies reviewed.

		shows a clear advantage to the use of radiation in terms of prostate cancer survival and overall survival for these patients. I do feel that this analysis was clear and organized the scope (except for the data listed in the paragraph above) was appropriate. One questions whether out of 1283 articles just how representative the 62 that were chosen are because they represent less than 5% of the published data on the role of radiation for localized prostate cancer yet the conclusions of no absolute answers regarding the questions posed is reasonable if one looks only at low risk patients Finally it is of considerable concern that the Executive Summary (ES-6) references the recent New York Times articles on prostate brachytherapy and suggests a lack of quality assurance with regards to LDR brachytherapy and radiation therapy in general. The questions posed and analysis done for this report did not address quality assurance within radiation therapy delivery and thus, this reference to the New York times articles should be deleted from the report. If the scope of this report had investigated quality assurance within radiation therapy delivery, a multitude of studies would have been found which would address these issues in detail. Thank you for the opportunity to comment on this report.	
2	General	I am concerned however that the scope of this review is too narrow. Specifically, I am concerned that the focus on T1-2 prostate cancer (and no consideration of T3 disease) precludes considering strong evidence on the role that radiotherapy plays in the curative treatment of prostate cancer. A seminal paper published by Widmark et al in 2009 (Lancet 2009; 373:301-308) demonstrated that radiotherapy improved survival in men with locally advanced disease. Approximately 20% of these patients had T1-2 disease. Another large Phase III study will be reported at the 2010 ASCO meeting (NCI-Canada Intergroup Study) that shows the same beneficial effect of radiotherapy on survival in men with locally advanced disease. Restricting this review to T1-2 disease limits the number of randomized trials that can be considered and does not tell the entire story. It is clear that radiotherapy changes the natural history of locally advanced prostate cancer (either in the definitive setting or when given postoperatively) and improves survival. I am concerned that the review uses a trade name (CyberKnife) throughout. Cyberknife is a specific machine that is being used to deliver stereotactic body radiotherapy (SBRT). It is possible to deliver SBRT with most linear accelerators. It would be better to use the generic term SBRT. The report doesn't use linear accelerator or brachytherapy source trade names and they shouldn't use	Thank you for your comments. Our report is an update of a previous AHRQ sponsored comparative effectiveness review; that report restricts to studies on patients with T1 or T2 disease. Given that vast majority of patients diagnosed today have clinically localized disease, and not locally advanced disease, our review of patients with T1-T2 disease provides valuable information about radiation therapy for these patients. The Widmark et al study (Lancet 2009; 373:301-308) did not meet our inclusion criteria. Please see response to reviewer 1. Your suggestion on the trade name Cyberknife® is noted. This has been replaced with a standard definition -stereotactic body radiotherapy delivered in one or few fractions (SBRT).

		CyberKinfe either.	
2	Specific	In answering Key Question 2 the authors state that *"there were no comparisons between EBRT and HDRBT."* There are no randomized trials comparing EBRT to HDRBT monotherapy BUT there are two randomized trials comparing EBRT to EBRT plus a BT boost; LDR in one study (Sathya, J Clin Oncol 2005; 23:1192-9) and HDR in another study (Hoskin, Radiother Oncol 2007; 84:114-120). Each study is small and the EBRT dose is unconventional but the BT boost arm is superior in each (without an increase in toxicity). In the conclusion section of the executive summary the authors state *"Available data also suggest that BT is associated with more genitourinary toxicity… compared with EBRT*." This statement is inconsistent with a previous statement from page 4 of the executive summary *"Two studies did and two studies did not show that LDRBT was associated with significantly more genitourinary toxicity than EBRT."* I favor a statement along the lines of "the observed and patient-reported genitor-urinary toxicities are similar between BT and EBRT". This is what I tell my patients. In the conclusion section of the executive summary the authors state *"EBRT administered as a standard fractionation or moderate hypofractionation does not seem to differ with respect to biochemical control and late genitourinary and gastrointestinal toxicities."* The authors should specify what they mean by standard fractionation and moderate hypofractionation. I presume that standard fractionation means 1.8-2 Gy per fraction five days per week; but I do not know what the authors mean by moderate hypofractionation. Do they mean >2.5 Gy per fraction? > 3 Gy per fraction?	The study by Sathya et al was included in our report, within the intra-EBRT modality comparison section. In the study by Hoskin et al, less than 80% of participants had T1-T2 prostate cancer, and therefore did not meet our inclusion criteria. Thank you for your comments and recommendations. The sentence has been modified after taking into consideration your suggestion. Thank you for your request for clarification regarding the definition of standard fractionation and moderate hypofractionation. We had added the definition of "standard fractionation" in the final report.
3	General	This section is adequate. No changes required.	Thank you.
3	Executive Summary	This section is adequate. No changes required.	Thank you.
3	Introduction/ Background	Cyberknife is a commercially available radiation therapy machine. In the description of different radiation therapy "types", it is presented as a particular treatment under the heading of "SBRT". This clearly inadequate. Although the Cyberknife is mostly utilized to deliver a few fractions per treatment course, therefore mostly going under the heading of SBRT, the treatment schedules and definitions of IMRT/IGRT/SBRT should not include individual radiation delivery devices. Cyberknife is not a different type of treatment, it's still a radiation-delivery device. For example, Cyberknife should be even listed in Figure 1. I would strongly suggest removing comments such as "stereotactic body radiation (including CyberKnife®)" from the entire document.	Thank you for your comments Your suggestion on the trade name Cyberknife® is noted. This has been replaced with a standard definition -stereotactic body radiotherapy delivered in one or few fractions (SBRT).

		The definition of SBRT is completely arbitrary with 5 fractions of less being defined as SBRT. There should be more discussion is clarifying that there is no clear distinction at 5 fractions… Similarly, Fig 2 suggests that IGRT is a treatment whereby Intensity modulation is also included. Image guidance (IG) has nothing to do with radiation delivery, but is simply the aiming process. Therefore, for ANY radiation delivery technique (2D to IMRT), image guidance could still be used. Including IGRT as a separate "treatment" does not help at all. This should almost be discussed in a different context.	
3	Methods	This section is adequate. No changes required.	Thank you.
3	Results	This section is adequate. No changes required.	Thank you.
3	Discussion/ Conclusion	The conclusions are very reasonable. The current state of the data on radiation therapy for prostate cancers does not support any conclusions beyond what the authors have discussed. The authors have done an excellent job at digesting the available information. As such, unfortunately, they are very bland and somewhat useless, if the aim was to determine necessity to treat or differences between treatments. Only one suggestion: The authors correctly note in the discussion that the natural history of prostate cancer is so long that conclusions are difficult to make with current trials. For example, the two trials that are most interesting in this context are the Canadian-sponsored START trial planning to enroll 2,130 men, with estimated primary completion date of April 2023 NCT00499174), and the British ProtecT trial that's been running since 1999 planning to enroll 2,050 men, with estimated primary completion date of December 2013 (NCT00632983). The Canadian trial will not have answers till 2023! Even these trials with 2000 patients will be too small to determine significant differences in outcome between treatments, and the techniques currently utilized will be significantly criticized whenever they are published. Much larger number of patient outcomes should be available for analysis for decent decision making; 2000 is not enough. Particularly in the context of prostate cancer, discussions should include alternative methods of evaluations other than randomized controlled trials, such as mandates of patient outcome reporting and high quality registry studies. Another related discussion should be a study of the factors that affect acceptance of results of trials, even studies considered "high quality". This might seem outside the context of this particular report, i.e. the discussion of the adequacy of "levels of evidence" the way they are defined today. However, it is actually very relevant in this context. If randomized trials are to be conducted the way they are conducted	The START trial was discussed in the Future Research section of the report. Your insight into alternative study designs is appreciated. We did include study designs other than randomized trials in our review of the literature. In fact, the large majority of included studies were not randomized trials, and registry-based studies were also included. With respect to safety data, again, we included trial designs other than randomized trials. Your comments on mandatory patient databases are interesting, but not within the scope of this review.

		today and considered as the only acceptable data, the end result will be a dramatic delay of reaching needed conclusions. The authors also mention at the end the “Future research” section that “Lastly, as has been mentioned earlier, no studies that we reviewed for this technology assessment reported safety data related to the delivery of radiation (e.g., errors in planning software, operator errors, machine malfunctions), it is vital that safety in radiation delivery be actively monitored and diligently recorded for every patient undergoing any form of radiation treatment.” These types of “studies” cannot be done in traditional ways (i.e. randomized studies). Mandates to report such incidents should lead to databases of patient outcomes/events/etc. This leads again to a need for high quality registries. This was somewhat a digression, but a very relevant one.	
3	Tables	This section is adequate. No changes required.	Thank you.
3	Figures	This section is adequate. No changes required.	Thank you.
3	Appendices	This section is adequate. No changes required.	Thank you.
3	References	This section is adequate. No changes required.	Thank you.

[1] Peer reviewers are not listed in alphabetical order.

[2] If listed, page number, line number, or section refers to the draft report.

[3] If listed, page number, line number, or section refers to the final report.

Project Name: Radiation Therapy for Localized Prostate Cancer
Project ID: CANT1209

Table 2: Public Review Comments

Reviewer Name[1]	Reviewer Affiliation[2]	Section[3]	Reviewer Comments	Author Response[4]
Anonymous Reviewer	American Society for Radiation Oncology (ASRO)	General	ASTRO, the largest radiation oncology society in the world with 10,000 members who specialize in treating patients with radiation therapies, appreciates the opportunity to comment on the draft report: "Radiation Therapy for Localized Prostate Cancer: an Update." In many respects, we think this report is well done. However, we have significant concerns about the decision to limit the review to T1-T2 disease with the primary key question focused on survival with radiation therapy compared to no treatment or no initial treatment. This doesn't seem like a good criterion to filter out articles that might illustrate the basic issue at hand: does RT provide benefit to patients? We appreciate the indolent nature of many prostate cancers and ASTRO members routinely counsel patients that active surveillance or watchful waiting may be the appropriate management for their disease. Yet, there is no well defined criterion that defines active surveillance or how patients should be managed if they select active management. Given that the role for active surveillance in 2010 remains controversial, ASTRO believes it is unreasonable to expect that this review would address the value of radiation relative to active surveillance looking at survival. To do so would imply that active surveillance was a legitimate option 10-20 years ago and that phase II studies could have reasonably been conducted. Even today, accrual to such a study would be limited by patient preference. We also agree with the statement, "Because of the differential survival rates based on tumor grade, there has been an increased focus on identifying and treating patients with aggressive subtypes whose overall survival is likely to be impacted by their cancer, while deferring treatment for patients with indolent subtypes and/or short life-expectancy, whose overall survival is not likely to be	Thank you for your comment. Our report is an update of a previous AHRQ sponsored comparative effectiveness review; that report restricts to studies on patients with T1 or T2 disease. Given that vast majority of patients diagnosed today have clinically localized disease, and not locally advanced disease, our review of patients with T1-T2 disease provides valuable information about radiation therapy for these patients. We had a lengthy discussion on the trial by Widmark et al. Even though this trial is phase III prospective randomized data, it didn't meet more than one of our inclusion criteria. I) Treatments compared didn't meet our inclusion criteria (looking only at direct comparative studies) to be included under any of our key questions. II) This trial had all patients treated with hormone therapy. III) This trial had included only 21% patients with T1/T2 disease. IV) The analogy of A+B vs. B → A vs. nothing is an inference and not direct evidence. A discussion regarding the small number of trials comparing radiation therapy and watchful waiting has been added to the report.

			impacted by their cancer" (page 2). At the same time, we consider it a major shortcoming of this report that T3 disease was excluded, as there are T3 patients with localized disease that have been proven to benefit from radiation therapy. In particular, the focus on T1-T2 prostate cancer (and no consideration of T3 disease) precludes considering strong evidence of the role that radiotherapy plays in the curative treatment of prostate cancer. A seminal paper published by Widmark et al in 2009 (Lancet 2009; 373:301-308) demonstrated that radiotherapy improved survival in men with locally advanced disease. This study shows an overall survival benefit associated with radiation therapy. Further, it is important to note that 20% of the patients in this study had T1-T2 tumors. We have serious concerns that this study was excluded, particularly since it shows survival benefit, including the T1-T2 subset group. The authors don't discuss why there are so few trials comparing radiation therapy to watchful waiting. ASTRO believes it is incredibly hard to conduct a clinical trial in which treatment is compared to surveillance for any cancer. For example, there have been no U.S. trials of surgery compared to watchful waiting that have been reported. We think that larger cultural issues are at play, and that broad outreach and education is needed so that patients can better understand their risks. Additionally, more biomarker research is needed so that patients with underlying risk of prostate cancer progression can be identified. Until such identification is reliable, some may question the ethics of a non-treatment arm of a possible study.	
Anonymous Reviewer	American Society for Radiation Oncology (ASRO)	Executive summary	We have identified a few issues and highlighted the discussion in the executive summary; we would note that these issues should be addressed where they appear in the report. "EBRT administered as a standard fractionation or moderate hypofractionation does not seem to differ with respect to biochemical control and late genitourinary and gastrointestinal toxicities." (page ES-7) We believe that if the terms "standard fractionation" and "moderate hypofractionation" are going to be used in this report, they should be specified. We would anticipate that by "standard fractionation," the authors mean 1.8-2.0 Gy per	Thank you for your request for clarification regarding the definition of standard fractionation and moderate hypofractionation. We had added the definition of "standard fractionation" in the final report. We have adopted your suggestion regarding the reference to New York Times article and deleted it. Nevertheless, a lack of reporting on adverse event(s) with respect to quality assurance of radiation delivery was observed in the studies reviewed.

			fraction. However, we are unclear what is meant by the term “moderate hypofractionation” (e.g., >2.5 Gy per fraction? > 3 Gy per fraction? OR “ 19 fractions” “5 fractions?). Similarly, we believe the total dose to which these conclusions apply should also be stated to avoid confusion with alternative dose-fractionation regimens that are not studied in this report. ASTRO is concerned that the report references recent New York Times stories, including a link to these stories (page ES-6), which report on very limited safety issues and implies that the quality assurance of radiation therapy may be insufficient. Patient safety is a comprehensive issue that is germane to all elements of a radiation oncology practice and is not limited to patients with prostate cancer. ASTRO has recently launched a “Target Safely” campaign to consolidate our efforts to enhance patient safety (http://www.astro.org/TargetSafely/). Further, radiation oncology literature is full of high quality publications about patient safety, machine safety, and quality assurance. However, none of the search terms for the literature review include quality assurance terms. ASTRO is deeply committed to the delivery of high quality care, but we believe this issue is outside the scope of this updated report. We believe the references to quality assurance and the New York Times articles should be removed, as their inclusion seems both outside the scope of the report and the references are prejudicial in nature. “There were also no comparisons between EBRT and HDRBT.” (pg ES-4). While there are no randomized trials comparing EBRT to HDRBT monotherapy, there is one published randomized trial during the January 1 2007 - December 2009 timeframe. In this study, an HDRBT boost was compared to EBRT (Hoskin, Radiother Oncol 2007; 84:114-120). While small and with an unconventional EBRT dose, this study shows that the BT boost arm is superior without an increase in toxicity. We find the following statements inconsistent: “Two studies did and two studies did not show that LDRBT was associated with significantly more genitourinary toxicity than EBRT.” (page ES-4) ?Available data also suggest that BT is associated with more genitourinary toxicity and less gastrointestinal toxicity compared with EBRT.? (page ES-7) Since the cited studies in the first statement have	The publication by Hoskin et al. was excluded because less than 80% of participants had T1-T2 prostate cancer, and therefore did not meet our inclusion criteria. Thank you for comment regarding the inconsistency with respect to the comparison between LDRBT and EBRT in the executive summary. The sentence has been modified after taking into consideration your suggestion.

			contradictory findings, ASTRO believes the later statement should be deleted or revised to state that there are similar toxicities between EBRT and BT.	
Anonymous Reviewer	American Society for Radiation Oncology (ASRO)	Methods	Again, we highlight our concern that the 2009 Widmark et al study was not included in this update and view its absence to be a major shortcoming of this report. While this study does include androgen deprivation therapy, it also includes data about the use of EBRT and therefore should have been included. Based on the statement, "All abstracts concerning technical aspects of radiation therapy were re-screened by a radiation oncologist," (page 9) it is unclear if radiation oncologists were involved in the literature review process and note that only one of the authors is a radiation oncologist. We believe inclusion of more specialists familiar with the topic is appropriate and would welcome the opportunity to work with AHRQ and its contractors in the future to identify recognized experts who might participate in literature reviews and drafting, lending expertise and insight that would likely be beneficial. We question why the authors rated the multiple phase III dose trials as "moderate" evidence. These are high quality randomized trials that show a biochemical control benefit with higher doses of RT yet the authors of the review consider this to be only "moderate" evidence. We believe that the grading of evidence for these dose trials should be reconsidered.	We had a lengthy discussion on the trial by Widmark et al. Even though this trial is phase III prospective randomized data, it didn't meet more than one of our inclusion criteria. I) Treatments compared didn't meet our inclusion criteria (looking only at direct comparative studies) to be included under any of our key questions. II) This trial had all patients treated with hormone therapy. III) This trial had included only 21% patients with T1/T2 disease. IV) The analogy of A+B vs. B → A vs. nothing is an inference and not direct evidence. Thank you for your suggestion about including more specialists in the development of this report. We will pass it on to AHRQ. The criteria for rating the strength of evidence is described in the method section of the report.
Anita McGlothlin	American College of Radiology (ACR)	General	The American College of Radiology (ACR), representing over 32,000 diagnostic radiologists, radiation oncologists, medical physicists, interventional radiologists, and nuclear medicine physicians appreciate this opportunity to submit comments on the draft report titled "Radiation Therapy for Localized Prostate Cancer: An Update", draft project ID CANT1209. The ACR fully endorses the American Society for Radiation Oncology (ASTRO) recommendations. Please refer to the ASTRO comments for the various aspects of the draft technology assessment report.	Thank you for your comment.
Sonja Schoeppel, MD	Baptist Regional Cancer Center	General	I have been treating patients with prostate cancer since 1986. This was before PSA found cancers earlier. Back then, most patients seen had metastatic prostate cancer. With the advent of finding patients with earlier disease and more effective local treatment with radiation (implants and EBRT with IMRT) it is uncommon for me to see men with	Thank you for your comment.

			prostate cancer which has spread outside of the prostate and metastasized to bone. Dying of cancer in the bones is painful. I have no doubt that finding prostate cancer earlier and eradicating it with radiation treatment prevents many men from dying of prostate cancer.	
ToddR Wasserman, MD	Washington University in St Louis	General	The data do not establish that RT in any form is better than no initial therapy, because the comparable data does not exist yet. The report does not state that the same lack of data does not prove the null hypothesis, that RT is only as good as no initial therapy. The report concludes that EBRT dose escalation leads to better biochemical control. Teleologically, this is likely to be true because EBRT is of benefit with a lack of comparative data yet	Thank you for your comment.
Linda Winger, MSc, FACHE	Georgetown University Medical Center	General	The CyberKnife® Coalition (CKC) congratulates the Agency on this thorough draft Technology Assessment, and welcome the opportunity to comment. In general we find it an excellent summary. Formed in 2003 and incorporated in 2005, the CKC is a non-profit association of CyberKnife® user institutions, dedicated to protecting patients? access to this life-saving technology by working to ensure accurate and adequate reimbursement through educational, payer, and government advocacy. With a large body of academic support, the CyberKnife has now treated more than 80,000 patients worldwide and been installed as a radiosurgery system of choice by more than 190 institutions globally and 117 in the United States and Puerto Rico, many of whom are members of our Coalition. There is, however, a crucial omission, for which we will provide specific comments, in the 'Introduction/Background' section related to the currently unique ability of CyberKnife to automatically compensate for movement of the target: the radiation beam moves with the tumor. We are sure that AHRQ representatives will have noted that clinicians who spoke in both the formal presentation, and public segment, of the meeting emphasized this point. It is critically important from a patient perspective, because it has obvious advantages in assuring that the prostate receives the planned dose and limiting collateral damage to healthy tissue.	Thank you for your comment. In response to peer review comments, the use of the trade name Cyberknife® has been replaced with a standard definition -stereotactic body radiotherapy delivered in one or few fractions.

			Given the importance of this issue, and the status of AHRQ, we would encourage the Agency either to meet with us, or to visit a CyberKnife center at a time and location of the Agency's choosing.	
Linda Winger, MSc, FACHE	Georgetown University Medical Center	Executive summary	Page ES-2 indicates "the intervention of interest was radiation treatment used as a first line treatment of prostate cancer." We note this sentence in particular since all forms of radiation therapy with the exception of proton therapy have data/literature that supports sole mode of delivery treatment for localized prostate cancer. All of the literature contained within the technology assessment for proton therapy is for proton therapy as a boost to photon-based treatment. We therefore recommend that the technology assessment be modified to reflect the lack of sole mode delivery data for proton therapy. A potential update could reflect the following: "all technologies except proton therapy were used as the sole mode of radiation delivery; proton therapy was used as a boost to photon-based treatment."	Thank you for your comment about proton therapy. We did not find any comparative studies between proton and photon therapy as the definitive (rather than boost) treatment. For the purposes of this review, proton therapy delivered using conventional fractionation was considered to be external beam radiation therapy, because single institution series with conventional fractionation, a large number of patients (>500), and relatively long median follow up (>5 years) have been published, detailing the use of proton therapy as a definitive modality (Slater JD, Int J Radiat Oncol Biol Phys. 2004 Jun 1;59(2):348-52.)
Linda Winger, MSc, FACHE	Georgetown University Medical Center	Introduction/ background	1. Page 4 indicates that two approaches are currently utilized to deal with the issue of intra-fraction motion "Calypso and CyberKnife. For the CyberKnife, the technology assessment indicates that ?implanted fiducial markers that are tracked prior to each treatment beam every few seconds." Xie 2008 (Xie Y, et al. ?Intrafractional motion of the prostate during hypofractionated radiotherapy.? Int J Radiat Oncol Biol Phys 2008;72:236-246) indicates the following regarding the importance of utilizing the CyberKnife to TRACK PROSTATE MOTION AND TO AUTOMATICALLY CORRECT THE AIM OF THE TREATMENT BEAM WHEN PROSTATE MOVEMENT IS DETECTED? Our study shows the importance of real-time image guidance and motion-compensation techniques such as the robotic linear accelerator used in CyberKnife during hypofractionated prostate radiation treatment. Given the magnitude and random nature of prostate motion as well as recent technical advancements in various related fields, real-time monitoring of prostate position to compensate for the motion should be part of future prostate radiation therapy to ensure adequate dose coverage of the target while maintaining adequate sparing of adjacent structures.?	Thank you for your detailed information about the Cyberknife® system. Based on our search criteria, we did not find any comparative studies between Cyberknife® and other radiation therapy delivery systems that reported clinical outcomes. Thank you for your comment about the different types of SBRT systems. Based on our search criteria, we did not find any comparative studies between Cyberknife® and other radiation therapy delivery systems that reported clinical outcomes. Thank you for your comment about possible reduction in adverse events with Cyberknife®. Based on our search criteria, we did not find any comparative studies between Cyberknife® and other radiation therapy delivery systems that reported clinical outcomes including rates of adverse events.

			The central technological benefit of the CyberKnife System since its first clinical use in 1994 has been to use its image-guidance system to determine the location of the target, detect any target movement, and automatically correct the aim of the treatment beam. As Murphy put it in 2000 (Murphy MJ, et al. ?Image-Guided Radiosurgery for the Spine and Pancreas. Computer Aided Surgery 2000;5:278-288.), ?During each treatment, the image guidance system monitored the position of the target site and relayed the target coordinates to the beam-pointing system at discrete intervals. The pointing system then dynamically aligned the therapy beam with the lesion, automatically compensating for shifts in target position.? This unique ability of the CyberKnife System, to detect prostate motion and automatically correct the beam aim to assure accurate radiation delivery, gives clinicians confidence that they are delivering high-dose radiation precisely to the prostate and not to surrounding tissues. We strongly request that the technology assessment be updated to reflect the ability of CyberKnife to utilize real-time image guidance to automatically compensate for shifts in target position. 2. Page 5 indicates that “incorporation of various body immobilization systems into IMRT with IGRT, together with increased daily dose, and limiting the number of treatments to at most 5, is known as stereotactic body radiation therapy.” However, the technology assessment fails to point out the differences between the many different treatment options considered SBRT. Martin and Gaya (Martin A, Gaya A. ?Stereotactic Body Radiotherapy: A Review.? Clinical Oncology 2010, doi:10.1016/j.clon.2009.12.003) indicated that a number of modern linacs with on-board imaging capabilities meet the basic image-guidance requirements for SBRT delivery, e.g. Varian Trilogy and Elekta Synergy. More recently there has been the introduction of linacs fully adapted as integrated stereotactic delivery systems. These include the Novalis TX, BrainLAB, Elekta Axesse, TomoTherapy Hi-Art System, and CyberKnife. Sahgal 2008 (Sahgal A, et al. ?Stereotactic Body Radiosurgery for Spinal Metastases: A Critical Review. Int J Radiat Oncol Biol Phys 2008;71:652-665) provides details regarding the differences between the SBRT systems. The article indicates that the CyberKnife and Novalis systems are	

			equipped with in-room stereoscopic kilovoltage (kV) X-ray imaging. However, the article goes on to state that the CyberKnife is unique in that it uses intrafractional X-ray imaging (typically obtained every 30-60 s), and automatic LINAC position adjustments to compensate for any detected changes in target positioning. We request that the technology assessment be updated to reflect two key differences between CyberKnife and other SBRT technologies: (1) no stereotactic immobilization is necessary with CyberKnife; and (2) CyberKnife is the only technology that automatically compensates for target movement throughout treatment, thereby keeping the radiation beams on target. 3. Page 5 indicates that ?despite the technical advances in delivery of external beam radiation, it may not be possible to deliver sufficiently high dose without incurring unacceptable normal tissue toxicity.? Several CyberKnife publications point to the contrary; these publications indicate that CyberKnife toxicity is equal to or better than other external beam radiation treatment options in avoiding normal tissue toxicity. For example, King et al. (King CR, et al. ?Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial.? Int J Radiat Oncol Biol Phys 2009;73:1043-1048) concluded based on a median 33-month follow-up that ?the outcomes from the clinical trial demonstrate that a hypofractionated course of stereotactic radiotherapy for localized prostate cancer is associated with urinary and rectal toxicity that are of the expected nature and severity as those experienced with conventionally fractionated courses of external beam radiotherapy.? In addition, Katz et al. (Katz AJ, et al. ?Stereotactic body radiation therapy for organ confined prostate cancer.? BMC Urology. 2010:10:1) noted based on a median 30-month follow-up that ??although our therapeutic doses were higher than [several reviewed IMRT] studies our observed rate of acute urinary and rectal toxicity was lower, with less than 5% of patients experiencing any Grade II urinary or rectal toxicity and none experiencing any higher grade acute toxicity.? Friedland et al. (Friedland J et al. ?Stereotactic body radiotherapy: an emerging treatment approach for localized prostate	

			cancer.? Technol Cancer Res Treat 2009;8:387-392.) also reported very low rates of toxicity at a median of 2 years. The literature supports the proposition that the very precise targeting will limit collateral damage to healthy tissue to well within acceptable levels while high radiation doses are delivered to the prostate. We therefore contest the suggestion that ?it may not be possible to deliver sufficiently high dose without incurring unacceptable normal tissue toxicity?, and request that this language should be moderated.	
Linda Winger, MSc, FACHE	Georgetown University Medical Center	Discussion/ Conclusion	1. The section labeled ?Future Research? indicates that ?randomized trials to address the question of extremely hypofractionated (SBRT or HDRBT) radiation therapy should be conducted.? However, we are sure that the Agency will have noted two key comments made by the MEDCAC panel at the April 21, 2010 MEDCAC (Radiation Therapy for Localized Prostate Cancer) meeting. First, the panel recognized that randomized clinical trials or observational studies are necessary for ALL forms of radiation therapy for localized prostate cancer, rather than limiting this comment to extremely hypofractionated (SBRT or HDRBT) radiation therapy. Second, the panel discussed that, while randomized controlled trials (RCTs) are desirable, there are practical difficulties associated with them which, together with a rate of innovation that renders a technology obsolete by the time the RCT conclusions are known. The MEDCAC suggested that registries may be a more practical solution. Given the panel?s comments at the MEDCAC meeting (which will be publically available), we request that the sentence be changed to note that ?randomized clinical trials, retrospective studies, or observational studies including registries should be used in order to address all types of radiation therapy for localized prostate cancer.? 2. The section labeled ?Future Research? indicates, ?our current review did not identify any comparative studies evaluating the role of particle radiation therapy (e.g., proton) in the treatment of prostate cancer. Data from such studies will help decide how to best use these limited resources.? Given the fact that there are no publications for proton therapy as the sole mode of radiation delivery (proton therapy was used as a boost to photon-based	Your comment on study designs other than RCT is appreciated. We did include comparative study designs other than randomized trials in our review of the literature. In fact, the large majority of included studies were not randomized trials, and registry-based studies were also included.

			treatment), we request that the ?Future Research? sentence be changed to reflect the lack of sole mode proton therapy data. We request the sentence read, ?Our current review did not identify any comparative studies evaluating the role of particle radiation therapy (e.g., proton) as a sole mode delivery in the treatment of prostate cancer. Data from future studies may highlight proton therapy as a sole mode of radiation delivery for prostate cancer will help decide how to best use these limited resources.?	
Linda Winger, MSc, FACHE	Georgetown University Medical Center	Tables	Table 2 on page 7 provides a comparison of the different types of external beam radiation therapy (EBRT) modalities including SBRT. However, the technology assessment lumps together different types of technologies considered SBRT and fails to point out the differences especially for CyberKnife. Martin and Gaya (Martin A, Gaya A. ?Stereotactic Body Radiotherapy: A Review.? Clinical Oncology 2010, doi:10.1016/j.clon.2009.12.003) state that a number of modern linacs with on-board imaging capabilities meet the basic image guidance requirements for delivery of SBRT, e.g., Varian Trilogy and Elekta Synergy. More recently there has been the introduction of linacs fully adapted as integrated stereotactic delivery systems. These include the Novalis TX, BrainLAB, Elekta Axesse, TomoTherapy Hi-Art System, and CyberKnife. Sahgal 2008 (Sahgal A, et al. ?Stereotactic Body Radiosurgery for Spinal Metastases: A Critical Review. Int J Radiat Oncol Biol Phys 2008;71:652-665) provides details regarding the differences between the SBRT systems. The article indicates that the CyberKnife and Novalis systems are equipped with in-room stereoscopic kilovoltage (kV) X-ray imaging. However, the article goes on to state that the CyberKnife is unique in that it uses intrafractional X-ray imaging (typically 30-60 s), and automatic LINAC position adjustments to compensate for any detected changes in target positioning. Since Table 2 on page 7 is demonstrably inaccurate in referring to the use of Stereotactic Immobilization for CyberKnife, and since CyberKnife has the ability to automatically track and compensate for target motion during treatment, we request that either additional columns should be added to the table, or that a new	Thank you for your detailed information about the Cyberknife® system. Based on our search criteria, we did not find any comparative studies between Cyberknife® and other radiation therapy delivery systems that reported clinical outcomes.

			?Advanced SBRT, such as CyberKnife? category should be created.	
Linda Winger, MSc, FACHE	Georgetown University Medical Center	Figures	It is of interest within Figure 2 that proton therapy, which based upon the literature, is used only as boost therapy and has extremely limited data/publications, would be categorized as EBRT and not called out specifically just as SBRT was.	Thank you for your comment about proton therapy data. We agree that proton therapy should ideally be compared to modern photon therapy, and have noted so in our report.

[1] Names are alphabetized by last name. Those who did not disclose name are labeled "Anonymous Reviewer 1," "Anonymous Reviewer 2," etc.

[2] Affiliation is labeled "NA" for those who did not disclose affiliation.

[3] If listed, page number, line number, or section refers to the draft report.

[4] If listed, page number, line number, or section refers to the final report.