Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: Local Nonsurgical Therapies for Stage I and Symptomatic Obstructive Non–Small-Cell Lung Cancer

Draft review available for public comment from: February 22, 2012 to March 21, 2012.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Reviewer 1 (Peer)	General Comment	This is a clinically meaningful report. The first two questions are likely the most clinically important as they address larger populations of lung cancer patients and one in which the goal of treatment of cure rather than palliation of end of life symptoms which is addressed in question 3.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 1 (Peer)	General Comment	Clarity and Usability: I am a bit unsure of how this report will used to guide policy, as it clearly states that the data published to date is insufficient to accurately compare one treatment modality to another in these three clinical scenarios. I am in complete agreement with the author's conclusions, but remain unsure of how such a finding can guide policy decisions.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 2 (TEP)	General Comment	The report is clinically meaningful but someone limited by the bias toward RCTs. While these are clearly the preferred and best means to assess any therapy, simply because a study is NOT a RCT, does not mean it is not meaningful or valuable.	For Key Question (KQ) 3, we identified RCTs for a number of interventions, as well as a number of single-arm studies. We made the decision to base the analyses of safety and efficacy on the more robust RCTs, because they are inherently less biased with greater internal validity, and permit us to grade the strength of evidence using systematic review methods specified by AHRQ. Other study designs can be useful in the absence of RCT evidence as they can be used to inform future comparative studies in design and appropriate outcomes to be measured. We identified no RCTS for KQ 1 and 2, so according to our study selection hierarchy, we included single-arm studies. We recognize that single-arm studies can provide valuable information on clinical outcomes such as overall survival, or toxicities important to patients, providing guidance for the design of more robust studies. However, single-arm studies themselves are insufficient to draw conclusions as to the relative effectiveness and safety of local (nonsurgical) interventions in the stage 1 NSCLC setting.
Reviewer 2 (TEP)	General Comment	Clarity and Usability: The report is well structured and organized although at 285 pages, difficult for anyone to digest in toto.	Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	General Comment	The key questions, particularly KQ1 and KQ2 and the associated report address important and clinically meaningful topics. Treatments for early stage non-small cell lung cancer will likely be used increasingly as disease is detected through screening low dose CT scans. Therefore, an evidence-based approach to the treatment options would be very helpful to clinicians and payers. The target audience is explicitly defined and the key questions are appropriate.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 3 (Peer)	General Comment	1. Clarity and Usability: The report is well organized and structured. The main points are clearly presented. Overall, the manuscript is well written. The recommendation for a prospective cohort study of patients with obstructing endobronchial lesions is particularly important and likely to yield important and relevant information. 2. A major concern regarding the conclusions and their relevance to the practicing community is the recommendation that comparative studies be performed among SBRT, IMRT, 3DCRT and RFA. There seems to be some confusion (as described above) regarding these terms and therefore, what would constitute a practical and clinically meaningful study. The field is in desperate need of well-designed and performed comparative trials. As a result, for KQ1 and KQ2, the current conclusions and recommendations are not likely to be used to inform policy, practice or clinical trial design decisions.	1. Thank you. We appreciate your efforts in reviewing this report. 2. We acknowledge the concerns of the reviewer in critiquing our call for RCTs of the interventions we assessed. We have revised these to reflect concerns revolving around technical differences in the RT modalities (e.g., differences in the biologically effective dose [BED] that can be safely delivered with SBRT compared to wither IMRT or 3DRT). This revision can be seen on Executive Summary page ES-26 and Research Gaps page 61 in body of the report. It also is replicated below in response to reviewer 3 comments on the Executive Summary and Discussion (page 11 and 24 of this table).
Reviewer 4 (TEP)	General Comment	The title states it is about local therapies for stage I lung cancer, yet it is really about therapy for stage I lung cancer where surgery is not recommended. The title should explicitly say this. Likewise, The "Conclusions" in the Structured Abstract talks about "insufficient evidence.....for inoperable or operable patients with stage I NSCLC", yet there is substantial evidence that surgery is effective for operable patients with stage I lung cancer. It is important in the title and throughout to make sure that this does not inadvertantly imply that there is not good data regarding surgery for stage I lung cancer.	The CER is about local, nonsurgical interventions for stage I NSCLC. We have revised the final report to reflect this concept by changing to the title to include the word "non-surgical" and referring to that term in the conclusions in the Key Questions, Structured Abstract, Executive Summary, and Conclusion sections. We therefore have changed the name of the CER to the following: "**Local Non-Surgical Therapies for Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors".**
Reviewer 4 (TEP)	General Comment	A common terminology used throughout is the term "local interventions", and seems to be implying that it is synonymous with non-surgical interventions. This is not a correct use of the term since surgery is also a "local intervention". I would strongly suggest changing the term "local intervention" to "non-surgical intervention" throughout.	We agree with the reviewer, and changed the name of the CER to the following: "**Local Non-Surgical Therapies for Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors".**

Commentator & Affiliation	Section	Comment	Response
Reviewer 4 (TEP)	General Comment	Clarity and Usability: Okay	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 5 (Peer)	General Comment	This report focuses on scientific evidence (review of 52 published articles) to support treatment of stage I NSCLC in the absence of surgery (medically inoperable, pt refuses). The studies were chosed to address 1 of 3 key questions. There is a lack of analysis for RFA of medically inoperable stage I NSCLC. Unfortunately, there are no RCT to address key question 1 and 2.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 5 (Peer)	General Comment	Clarity and Usability: 1. The report is cumbersome and in many areas redundant. I do like the tables in the results section. 2. The conclusions cannot be used to inform policy (by virtue of insufficient evidence) except to spawn the infusion of national health care dollars to cooperative groups to assemble some RCT's to answer comparative questions. 3. RFA is under-represented in this analysis and is more economically palatable than SBRT and PBRT.	1. The redundancy reflects the necessity to make the Executive Summary an essentially free-standing piece. As such, it must reproduce key elements of the main body of the CER. 2. We agree that a conclusion of insufficient evidence does not provide a strong basis to guide policy decisions. However, we are confident that the comprehensiveness of the report, and the transparent methods we used, illustrate the weakness of the available evidence on these interventions in the settings studied. This may be sufficient impetus for decision-makers to provide funding for rigorous study to address these issues. 3. We proposed strict, but reasonable, study selection criteria for the CER, including RFA. Unfortunately, we were able to identify only a few single arm studies of RFA that met those criteria. That points to a need for more rigorous comparative study designs. The relative economic palatability of RFA, compared to SBRT or PBRT, is beyond the scope of this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 6 (TEP)	General Comment	1. The findings indicate that for all 3 key questions there is no scientific information which allows a comparison of the effectiveness of the different methodologies, so the clinical value of the report is restricted. Unfortunately, there is no real incentive, and perhaps disincentive, in the United States market for performing comparison studies (with the possible exception of PBRT, where those who offer this treatment charge significantly more than what is charged for other radiotherapy, and are attempting to justify this difference in cost). 2. The targeted audience is primarily those who are involved in the care of patients who require radiation therapy. The document defines very clearly the absence of any information which would allow physicians and others to be able to correctly or adequately inform patients as to the most cost effective approach to a serious health problem. At a time when the patient is facing a life-threatening illness, and is least psychologically able to intelligently approach the question of what is the best therapy, this review defines clearly that the needed information is unavailable. 3. Inclusion of Key Question 3, while of some interest, is, from a patient standpoint, somewhat less useful. The presentation of this patient is usually semi-emergent at best, and the therapy chosen is essentially entirely in the hands of the physician(s) involved. This analysis should be helpful to physicians to allow more meaningful discussion about the lack of any good data informing correct therapy. As the authors found, it is unlikely that a comprehensive, multi-institutional study will ever be completed because of the variety of patient presentations and the difficulty inenlisting patients or physicians.	1. We agree, the clinical value of the report indeed may be restricted because of a lack of robust comparative evidence for any of the KQs. However, we are confident that the comprehensiveness of the report, and the transparent methods we used, illustrate the weakness of the available evidence on these interventions in the settings studied. This may be sufficient impetus for decision makers to provide funding for rigorous study to address these issues. The relative incentives and disincentives in the US market for comparative studies are outside the scope of the report, as are issues of cost. 2. Thank you. We appreciate your efforts in reviewing this report. 3. In the Background, we mention the dire status of the patients covered in KQ3 and that the choice of treatment is apt to be local, based on attending physician and institutional experience. We also agree a RCT is unlikely to materialize given these issues.
Reviewer 6 (TEP)	General Comment	Clarity and Usability: Clarity – good; Usability – Unfortunately, the results are essentially “negative”, i.e. there is no data to answer any of the 3 key questions. It is unlikely that the report will stimulate additional study (see “General Comments”).	We agree, the clinical value of the report indeed may be restricted because of a lack of robust comparative evidence for any of the KQs. However, we are confident that the comprehensiveness of the report, and the transparent methods we used, illustrate the weakness of the available evidence on these interventions in the settings studied. This may be sufficient impetus for decision-makers to provide funding for rigorous study to address these issues. The relative incentives and disincentives in the US market for comparative studies is outside the scope of the report, as are issues of cost.

Commentator & Affiliation	Section	Comment	Response
Reviewer 7 (Public/ ASTRO)	General Comment	1. In November, 2012, ASTRO provided substantive comments on the draft key questions citing our concerns about how the study was framed. We are very disappointed that our previous comments were largely ignored. Therefore, we believe this draft report significantly mischaracterizes the current state of radiotherapy, minimizes its established benefit, and fails to impartially balance the discussion of treatment options. 2. Moreover, the references cited in this draft do not reflect the current science regarding stereotactic body radiation therapy (SBRT). Specifically, we believe the absence of the following studies speaks to the incompleteness of this review: • Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75(3):677-682. • Senthi, S., Laggarward, F., Haasbeek, C., et al., Patterns of disease after stereotactic ablative rt for early non-small-cell lung cancer a retrospective analysis. Lancet Oncol 2012 (13): 802-09 • Timmerman R., Paulus R., Galvin J., et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303(11):1070-1076. 3. We value comparative effectiveness reviews and the prospects of CER to inform quality health care. However, this process seems flawed and non-responsive to a key stakeholder. It is unclear why AHRQ disregarded our offer to provide clinical expertise for drafting key questions and to serve as subject matter experts to the panel in the interest of reaching impartial and meaningful conclusions. We believe this failure has prevented us from contributing meaningfully to the benefit of patients and families that we serve daily.	1. The choice of key questions, the interventions, and clinical outcomes to be analyzed, were presented to the Key Informants (e.g. clinicians, payers, and patients) for their input. The Key Questions were then posted for public comment. Responses to the comments received were then discussed with the Technical Expert Pane (TEP) members. The input from those individuals was used in the context of our knowledge of the literature to select the outcomes we would examine, benefits and harms. With regard to harms, we did not limit the types of harms we collected, except the degree (e.g., grade 2 or higher according to NCI criteria). Moreover, we were very transparent in the PICOTS and analytical frameworks about what information we would seek to compile. Although ASTRO suggested comparison of surgical and non-surgical options for operable stage I disease, with input from the aforementioned Key Informants and TEP members, it was decided this would be outside the scope of the review . This CER is intended as an examination of the **comparative, relative clinical benefits and harms** of different interventions, based on evidence from clinical studies that are identified and selected for inclusion using pre-specified criteria and systematic review methods that are applied transparently across the evidence base. 2. Our reference librarian performed a thorough, deep search of the published literature, including NLM MEDLINE, EMBASE, Cochrane Controlled Trials databases. The search strings used accepted NLM MeSH terms and are are provided in the draft report for anyone who seeks to duplicate them.

Commentator & Affiliation	Section	Comment	Response
Reviewer 7 (Public/ ASTRO) (continued from previous page)	General Comment (contd)		We had the Fakiris 2009 and Timmerman 2010 papers in hand for the initial draft. We excluded both from the CER because our study selection criteria specified the use of a single, local (nonsurgical) intervention, not allowing combinations with systemic therapies. Both papers indicate stage I NSCLC patients received SBRT, and, from Fakiris, "No additional concomitant or adjuvant therapy was permitted during the protocol **except at disease progression**". Nearly the same language is used in Timmerman 2010. In Fakiris, 11 of 70 (16%) patients recurred or progressed whereas in Timmerman 14 of 55 (25%) recurred. Neither paper accounted for recurrent patients, nor their subsequent unspecified treatment(s), making it impossible to attribute overall survival or cancer-specific survival rates to SBRT alone in a substantial proportion of cases. No apparent adjustment was made to the data to account for those who received systemic therapies after failure. Thus, those studies were excluded as "not relevant intervention" and "unclear study design" exclusions. We identified the Senthi 2012 paper at our literature search update, prepared after the draft was posted for comment. This paper includes data on medically inoperable (69%) and potentially operable (31%) patients, but does not categorize results by operability. Thus, according to our study inclusion criteria, this study was excluded as we cannot discern whether it is relevant to KQ1 or KQ2.
Reviewer 7 (Public/ ASTRO) (continued from previous page)	General Comment (contd)		3. Thank you for the comment. In future systematic reviews we will be sure to include key stakeholders such as ASTRO.

Commentator & Affiliation	Section	Comment	Response
Reviewer 8 (TEP)	General Comment	Given the lack of alternatives for inoperable patients with stage 1 NSCLC the lack of comparative data between modalities in a randomized fashion does not indicate that the treatments are not worth performing. Further study is warranted. However given the current fee for service practice paradigm and competing specialties in US healthcare such a trial may never be successfully completed.	Our view is that further comparative study of local non-surgical interventions is warranted. We did not review issues related to the current fee for service paradigm in the US healthcare system and therefore cannot speculate on whether trials will be completed or not.
Reviewer 8 (TEP)	General Comment	Clarity and Usability: The main points are conveyed. Making practice decisions would be difficult given that the fall back position in patients who are not candidates for surgery is conventional 3D conformal therapy which most would agree is inferior to ablation and stereotactic body radiotherapy.	Our report concludes there is insufficient evidence to show that patients treated with SBRT have clinical outcomes that are superior to those achieved with IMRT or 3DRT. We are unsure what the reviewer is trying to convey in commenting that 3DRT is the "fall back" technique for inoperable patients. 3DRT is the minimum standard of care in the US, but it appears this technology is being supplanted by SBRT in patients for whom either may be used. We appreciate the positive comment on Clarity and Usability. In the Research Gaps section of the CER, we comment on "practice decisions" as follows: "The general dissemination of conformal radiotherapy technologies into community clinical practice, most lately and specifically SBRT is a potential impediment to comparative study of those technologies. Published survey results show that nearly 40 percent of solo practitioners treat patients with SBRT, which suggests that this technology is now widely accessible and accepted in the broader radiation oncology community. In addition, the shorter hypofractionated SBRT course is more "patient friendly" than those associated with conventionally fractionated conformal radiotherapy methods. This patient-specific advantage may represent a significant additional reason why SBRT has rapidly disseminated into clinical practice in the absence of direct comparative clinical trial evidence to support its reputation of clinical superiority over conventionally fractionated conformal techniques. We also recognize a number of significant – perhaps insurmountable - impediments to conducting adequate comparative studies among the most widely available conformal radiotherapy-based modalities and other interventions such as RFA."

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	ES	ES-9, it is curious that photodynamic therapy is not listed as a therapeutic option under KQ3. it is possible that the authors included PDT under the broad category of laser therapy. If so, this is confusing because by nd:yag laser therapy and PDT are used in the setting of endobronchial obstruction and could be considered laser therapies.	We did include photodynamic therapy within laser therapy. The text on page ES-9 was revised to read: o " Laser therapy, including photodynamic therapy"

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	ES	Pages ES-20 and ES-21 There may be some confusion regarding radiation therapy technique (3DCRT, and IMRT) versus fractionation scheme. SBRT refers to stereotactic radiation delivered in a hypofractionated fashion. IMRT, 3DCRT, or arc therapy are all techniques used to deliver SBRT to patients. This compares to conventionally fractionated radiotherapy which can also be delivered with IMRT or 3DCRT. It appears that the authors are referring to conventionally fractionated radiation regimens when they comment on IMRT or 3DCRT. The authors should clarify this in the manuscript. It is possible that this confusion arises from the wording of the key questions, where the interventions are listed as conformal radiation, proton therapy, and RFA.	1. We presume the reviewer is referring to Table ES5 in which we outlined differences between RT methods. To address this comment, we revised the bulleted text to read as follows. We have clarified that we are referring to conformal external beam photon-based methods, and noted the difference between hypofractionated SBRT and conventionally fractionated 3DRT or IMRT. • 3DRT, IMRT and SBRT represent different technological approaches to the delivery of conformal photon radiotherapy. The major advantage of each relative to traditional wide-field 2DRT is the ability to deliver tightly focused cytotoxic radiation to a tumor volume that is precisely delineated using a CT-based or other imaging planning system. • 3DRT represents a minimum technical standard for delivery of conformal conventionally fractionated radiotherapy. It involves static fields with a fixed shape, modified by compensators (wedges and segments). It is widely available. • Conventionally fractionated IMRT offers beam strength attenuation through a multileaf collimator (tungsten), with dynamic field shapes for each beam angle. IMRT is not as widely available as 3DRT, and requires a higher level of inverse planning and quality assurance. • SBRT is by definition a hypofractionated technique administered in 5 or fewer fractions; 3DRT and IMRT typically deliver radiation in many more fractions than SBRT. SBRT is not as widely available as 3DRT or IMRT, but our literature review suggests there has been growing interest in this technology in this setting, to the point that it may soon supplant the other technologies in the KQ1 and KQ2 settings. The institutional programmatic requirements for SBRT are similar to those of IMRT.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	ES (contd)	RCT of SBRT and IMRT/3DCRT would be problematic given the differences in biologically effective dose (BED). SBRT regimens are hypofractionated and deliver a BED of > 100 whereas it is unsafe to use such regimens with conventional radiotherapy whether the technique is IMRT or 3DCRT. The authors should clarify what is meant by comparative studies because significant confusion could result from this recommendation. This issue is a major problem with the current manuscript.	We acknowledge the concerns in calling for comparative studies, and have revised the text on pages ES-26 and 61 of the text as follows: "A key technical issue for comparing the RT-based interventions likely is the significant difference in the BED of radiation that can be safely delivered by SBRT, compared to IMRT or 3DRT delivered with conventional fractionation protocols. In brief, radiation therapy for NSCLC typically is delivered to a total dose of 60-70 Gray (Gy); SBRT delivers that dose in three to five fractions of 20 Gy each (estimated BED = 180 Gy_{10} using standard principles) whereas conventionally fractionated IMRT or 3DRT delivers 60-70 Gy in 30 fractions of 2 Gy each in 4 to 5 weeks, yielding an estimated BED of 72 Gy_{10}, a difference which is considered to have potential efficacy differences. The higher BED causes tumor ablation, rather than tumor cell kill, allowing for little to no tumor cell repopulation between doses of radiation. In this CER, we did not systematically investigate whether a higher BED delivered by any conformal RT modality can be associated with better clinical outcomes such as overall survival, compared to a lower BED. This has been reported in published single-arm studies reviewed in this CER, for example the large, multicenter, retrospective series on SBRT in Japan by Onishi and colleagues.[83] However, we are not aware of any direct comparative evidence on this topic among any of the conformal RT technologies, so it is not possible to make even indirect comparisons between the delivered BED and clinical outcomes in any case. Furthermore, we are aware of no published clinical trial evidence to ascertain whether a higher BED delivered by SBRT is associated with differences in patient outcomes compared to a lower BED delivered either by SBRT or by a conventionally fractionated conformal radiotherapy modality.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	ES (contd)	RCT of SBRT and IMRT/3DCRT would be problematic given the differences in biologically effective dose (BED). SBRT regimens are hypofractionated and deliver a BED of > 100 whereas it is unsafe to use such regimens with conventional radiotherapy whether the technique is IMRT or 3DCRT. The authors should clarify what is meant by comparative studies because significant confusion could result from this recommendation. This issue is a major problem with the current manuscript.	Further, we added the following text in this context: "We acknowledge the difference in delivered BED has biologically plausible clinical implications, and perhaps ethical implications, that would need to be addressed in designing a study of any type to compare conformal radiotherapy-based technologies. But, it is not clear to us that the BED issue under discussion here is settled. In summary, we acknowledge the views of some members of the radiation oncology and interventional radiology communities - that clinical trials of local nonsurgical modalities, including RFA, SBRT and other conformal radiotherapy modalities (e.g., 3DRT, IMRT, PBRT) in stage I NSCLC patients may be very difficult to recruit and conduct, based on technical and potential ethical issues related to perceptions of unequal clinical benefit among the interventions. However, we maintain that current evidence is insufficient to support the view that clinical outcomes with one technology are proved superior to those achieved with other modalities. Clinical evidence from rigorous studies as outlined above would establish the standard of care for local nonsurgical treatment of stage I NSCLC patients."

Commentator & Affiliation	Section	Comment	Response
Reviewer 4 (TEP)	ES	1. The Executive Summary continues by stating that "This report aims to compare the effectiveness and harms of local therapies for the first two indications above" relating to operable and potentially operable but locally advanced disease. However, that is NOT what this report is about. It is about non-surgical management of these stages of lung cancer. It is enormously confounding to not continue to make this explicit throughout the review, and this is an example of frequent inadvertant but misleading statements that don't clearly identify that surgery is not being evaluated here. 2. The Executive Summary emphasizes radiation over endobronchial interventions for endobronchial disease and incorrectly states that radiation can "quickly ameliorate symptoms", suggesting that endobronchial interventions are primarily considered when radiation is contraindicated. Both of these aspects are incorrect. Radiation can ameliorate symptoms quickly if one is measuring days or weeks as the time frame, while endobronchial debridement with or without stenting can relieve symptoms in a matter of minutes. These should be presented as complementary interventions, not as choices between one or the other. Endobronchial interventions should be considered for quick and effective palliation, and combined with subsequent radiation to extend the durability of the palliation, and to offer definitive therapy for local tumors. 3. Executive Summary Results on Key Question 3 does not address the local therapies of mechanical debridement or stenting.	1. We agree, and have changed the title of the CER to reflect this: "**Local Non-Surgical Therapies for Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors".** In addition, we added the following sentence to the Objectives section of the Structured Abstract: "The report does not include surgical resection as a comparator for any of the settings." **2.** We have removed the word "rapidly" from the second paragraph under the section **Local Non-Surgical Treatment Options for Symptomatic Malignant Endobronchial NSCLC** on page ES2. We revised the text in paragraph 5 of that section to read as follows: "Several interventional methods involve tumor debulking to palliate symptoms in patients with advanced endobronchial NSCLC. Interventional bronchoscopy with mechanical debulking and stent placement can **r**apidly re-establish airway patency and relieve dyspnea in patients with airway obstruction due to a malignant endoluminal tumor. Similarly, endobronchial stent placement can immediately reduce respiratory distress in patients with malignant airway obstruction. Debridement and stent placement may be complemented by subsequent application of radiotherapy to extend the durability of palliation, and offer definitive therapy for local tumors."
Reviewer 4 (TEP) (contd)	ES (contd)		3. The Results for KQ3 prioritize evidence from RCTs that met prespecified study selection criteria. We did not identify any RCTs that included mechanical debridement or stenting as comparators. We previously identified two single-arm studies and one arm of an otherwise comparative study (the other arms were not relevant to the CER) that reported on debridement and stenting but inadvertently did not highlight those in the first draft. In the revised draft, we highlight those single-arm studies a bit more, but they do not change the conclusions of the report. The strength of evidence from the single-arm reports is insufficient to draw conclusions.

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	ES	On page 40 [ES 1] line 15 and 16 I would suggest changing the order of the subtypes of non-small cell lung cancer to adenocarcinoma, squamous carcinoma and large cell carcinoma.	We changed the order to “adenocarcinoma, squamous cell carcinoma, and large cell carcinoma” as suggested.
Reviewer 9 (Peer)	ES	On page 42 [ES 2] line 41 the term long-term survival is used to should be defined.	In reviewing the sentence in question, we concluded that using the term “long-term” immediately before “survival rates” was confusing, and deleted it.
Reviewer 9 (Peer)	ES	The executive summary, background section online 16 page 13 of 284 the term bronchioalveolar cell carcinoma is used the new term is considered adenocarcinoma carcinoma in situ.	We reviewed the International Association for the Study of Lung Cancer, American Thoracic Society, and European Respiratory Society paper (J Thorac Oncol.2011;6(2):244) on re-classification of BAC and agree with the comment. We have revised the sentence to read as follows: “Adenocarcinoma and adenocarcinoma in situ (formerly bronchioalveolar carcinoma) usually arise in peripheral lung tissue.”
Reviewer 9 (Peer)	ES	On page 15 online [ES 3] we see the abbreviation BT is first seen. There is no definition until later in the article. It should be adjusted. Also, the term radical RT views and this page on the line 53 this should be defined.	We defined the term “BT” as brachytherapy in the sentence on line 33, ES-3. On line 42, ES-3, we deleted the term “radical” and added EBRT to appropriately differentiate the use of brachytherapy and EBRT.
Reviewer 1 (Peer)	Intro	Well written, clear, concise describes project and its importance very well.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 2 (TEP)	Intro	Excellent, well written	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 3 (Peer)	Intro	The introduction nicely and succinctly outlines the rationale for the report as well as the intended audience. The key questions and the background for the questions are presented clearly.	Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 4 (TEP)	Intro	1. In the section of Surgical Resection for Stage I NSCLC the paragraph on morbidity and mortality is misleading. Reference 50 should not be used to discuss mortality in this section since it is only a reference regarding a high risk subset of patients and does not fit with the normal data about morbidity immediately preceding. This should use general data about mortality that is approximately 2% for lobectomy and 5% for pneumonectomy. Reference 50 should only be used in the section identifying a prohibitive risk group of patients who should be considered for radiation instead of surgery, not as a general reference about surgery outcomes. 2. I am puzzled by the use of reference 25 that seems to repeatedly present a contradiction, i.e. that mechanical debridement in patients with severe central airway obstruction "relieves dyspnea effectively and rapidly" but that this "may not always translate into improvements in overall quality of life". Relief of severe dyspnea, by definition, improves overall quality of life so this does not make sense. 3. The "Scope of the Review" should note that this is for the NON_SURGICAL management of stage I lung cancer, not "local therapies for stage I" lung cancer as stated. Surgery is considered a local therapy. Every reference to "local therapy" should be changed to "non-surgical therapy".	1. We moved the text citing reference 50 from the background on surgery to the next section introducing non-surgical options for high-risk patients. We revised the text to further address this comment on page 3 of the Background section as follows: "A comprehensive preoperative assessment must be performed to assess the risk for morbidity and mortality in patient with stage I NSCLC being considered for curative-intent surgery. Surgical morbidity and mortality are typically low in most modern series in the stage I setting, with major complications reported in about 6 percent of lobectomy cases and 18 percent of pneumonectomy cases in a large study. It has been recommended that the risk of surgical mortality be estimated less than 4 percent for lobectomy and less than 9 percent for pneumonectomy in order to proceed." 2. In the citation, the authors state there was no reported improvement in "quality of life" following relief of dyspnea. This was their conclusion, which was why we made the statement. However, to avoid confusing readers with this statement, we revised the text on page 6 to reflect the reviewer's comment as follows: "Interventional bronchoscopy with mechanical tumor debridement and stent placement can rapidly re-establish airway patency and relieve dyspnea and respiratory distress in patients with airway obstruction due to a malignant endoluminal tumor". 3. We agree, and changed the title of the CER and text throughout to reflect this comment: "**Local Non-Surgical Therapies for Stage I Non-Small Cell Lung Cancer and Endobronchial Obstruction due to Advanced Lung Tumors**

Commentator & Affiliation	Section	Comment	Response
Reviewer 5 (Peer)	Intro	1. The introduction is adequate. 2. EBRT is an acronym that is not traditionally use for external beam radiation and may confuse readers. It will also be confused with endobronchial RT with is brachytherapy. 3. The key questions are clear. 4. There is mention of the 7th edition AJCC staging of lung cancer which is based on more than 5000 patients. It is now based on > 67,000 cases from 19 countries. This description is incorrect. 5. Definitions of Radiotherapy are useful.	1. Thank you. We appreciate your efforts in reviewing this report. 2. We acknowledge the reviewer's perspective on the term "EBRT"; however, we define it carefully and regularly in the draft to mean "external-beam radiotherapy". We use other acronyms to define specific types of EBRT, such as 2DRT, 3DRT, IMRT, SBRT and PBRT. We define "BT" to mean "brachytherapy, and carry that through the report. To reduce the potential for confusion, we have eliminated the use of the term "endobronchial" immediately prior to "brachytherapy" or "BT". 3. Thank you. We appreciate your efforts in reviewing this report. 4. We revised this number to reflect the current case load. 5. Thank you. We appreciate your efforts in reviewing this report.
Reviewer 6 (TEP)	Intro	The introduction identifies the issues involved, the necessary questions to be answered, and the methodology used to evaluate the data to arrive at the conclusions.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 8 (TEP)	Intro	Well written	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 9 (Peer)	Intro	1. The second chapter begins on page 40: overall, this is a good review of the current state-of-the-art radiation therapy and other interventional options. The method by which the authors dealt with conflict of interest is excellent. 2. As a note the term SBRT is currently under discussion to be replaced with SABR- (stereotactic ablative radiotherapy). The authors may choose to include this term under the section for radiation therapy on page 43. This is a relatively new term and I doubt would have any effect on the search strategies used for this article.	1. Thank you. We appreciate your efforts in reviewing this report. 2. We noted the alternative acronym (SABR) in the Executive Summary (page ES-2, line 44)) and Background (page 4, line 1), but given the number of times SBRT has been used in the draft and the Appendixes, we did not change terminology throughout the draft. The difference in terminology would not have affected the search strategies we used.
Reviewer 9 (Peer)	Intro	I would like to applaud the suggestion of the authors of the second chapter with reference to key question three specifically, the collection of all adverse events in a systematic method. This body of literature could significantly benefit from this approach.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 1 (Peer)	Methods	Very thorough, good detail, yet easy to follow and comprehend.	Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 2 (TEP)	Methods	1. Criteria are justifiable but limited. 2. Strategies are logical and well defined. 3. I don't like the word "poor" to describe the RCTs included in this study because the word is a value judgement which lacks precision. If used, the criteria that deems the study to be "poor" should be explicitly stated, in my opinion.	1. Thank you. We appreciate your efforts in reviewing this report. 2. Thank you. We appreciate your efforts in reviewing this report. 3. The term "poor" is a standard description used in validated study quality assessment tools such as that of the USPSTF for RCTs and the Carey and Boden convention for single-arm studies. The assignment of that word is not a value judgement but rests on defined criteria applied by independent raters. We spell out how we reached that assessment for each RCT in the results chapter (pages 36-41).
Reviewer 3 (Peer)	Methods	The methodology used in the report is sound and appropriate. The search strategies, definitions for outcome measures, and statistical methods are all explicitly stated and appropriate. The inclusion and exclusion criteria are justifiable.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 4 (TEP)	Methods	The evaluation of KQ 3 did not appear to evaluate any studies (at least none were reported) on endobronchial debridement, with or without stenting.	The Results present evidence from studies that met prespecified study selection criteria. We did not identify any RCTs that included mechanical debridement or stenting as comparators. However, we had two single-arm studies that included those techniques and have added them to the final report This addition does not change the conclusions of the CER.
Reviewer 5 (Peer)	Methods	1. The inclusion and exclusion criteria for study selection are relatively clear. 2. Search strategies are descriptive. Outcome measures are appropriate. 3. Statistical methods for this review are non-existent. 4. It is unclear to my why only 1 study was analyzed for RFA when there are large studies that focus on management of medically unresectable stage I NSCLC. Clearly, there are no RCT trials of RFA vs wedge vs SBRT ... although 1 is ongoing.	1. Thank you. We appreciate your efforts in reviewing this report. 2. Thank you. We appreciate your efforts in reviewing this report. 3. We did not perform any type of analysis that required the use of statistical combination (e.g., meta-analysis) because the nature of the evidence was not appropriate for such an approach. 4. We proposed specific study selection criteria for the CER, including RFA. Unfortunately, we were able to identify only a few single arm studies that met those criteria. That points to a need for more rigorous study designs.
Reviewer 6 (TEP)	Methods	The methodology is well defined, with inclusion criteria thoroughly stated, although exclusion criteria are less specific.	Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 8 (TEP)	Methods	The inclusion and exclusion criteria are very rigid which in the real world may be difficult to accomplish.	While it may be difficult to accomplish studies performed in alignment with our study selection criteria, we believe we adhered to a typical level of rigorousness for a systematic review of this type. Strict selection criteria are needed to parse out the effectiveness of interventions. If we allowed systemic therapy concurrent or subsequent to the intervention, it would be impossible to determine whether any effect observed on overall survival, for example, was due to the intervention, the systemic therapy, or the combination. Strict criteria for patient enrollment, for example stage I NSCLC only, or those with defined medical comorbidities, are needed to make interstudy comparisons and interpret findings in a similar clinical context. The information value of a study is a function of its internal validity, which is reflected by use of defined methods and protocols from patient enrollment procedures to statistical analyses. We used accepted means of assessing the internal validity of RCTs (USPSTF Study Quality Ratings) and the quality of single-arm studies (Carey and Boden convention) that take into account study design parameters in rating a study. The CER methods, which predefine the PICOTS and lock in the study selection criteria, were developed in consultation with Key Informants during the Topic Refinement phase of the project.
Reviewer 9 (Peer)	Methods	On page 15 online we see the abbreviation BT is first seen. There is no definition until later in the article. It should be adjusted. Also, the term radical RT views and this page on the line 53 this should be defined.	We defined the acronym “BT” as brachytherapy in that section. We removed the term “radical” and simply refer to radiotherapy (RT).
Reviewer 1 (Peer)	Results	This is a very inclusive report, I can not think of any important studies which were excluded. The text is again clear and concise for the volume of research which was performed. The tables are quite extensive, but clear and easy to follow. It is obvious that an extensive amount of work went into the data extraction presented.	Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 2 (TEP)	Results	These are complete and well done although as mentioned above, the lack of evidence does not necessarily translate to lack of effectiveness and this should be stressed.	Thank you. We appreciate your efforts in reviewing this report. As we state elsewhere in this document, the purpose of a CER is to assess the relative clinical benefits and harms of different interventions in patients with a specific disease. The purpose of a CER is not to define the level of effectiveness of an intervention versus a placebo. The latter is an issue for a technology assessment. That being said, we agree there is no question that the local, nonsurgical interventions addressed in this CER have clinical benefit and an established role in lung cancer treatment.
Reviewer 3 (Peer)	Results	The amount of detail presented is appropriate. The authors have nicely summarized the content of the current literature. The studies included are appropriate and there are no studies that have been overlooked	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 4 (TEP)	Results	The evaluation of KQ 3 did not appear to evaluate any studies (at least none were reported) on endobronchial debridement, with or without stenting.	The Results present evidence from RCTs that met prespecified study selection criteria. We did not identify any RCTs that included mechanical debridement or stenting as comparators. However, we had two single-arm studies that included those techniques and have added them to the final report This addition does not change the conclusions of the CER.

Commentator & Affiliation	Section	Comment	Response
Reviewer 5 (Peer)	Results	1. The authors indentify a research gap in all key questions. 2. The amount of detail in the results sections seems reasonable although analysis of RFA as a treatment modality is under-represented in answering Key question 1 and 2. 3. Studies that should be included: Beland et al Radiology 2010; 254:301-7, Lanuti et al, JTCVS 2009; 137:160-6. 4. Local control is poorly defined in the comparison of various radiation modalities and RFA. 5. Characteristics of the studies are described sufficiently. 6. The tables are clear. 7. The appendices are cumbersome but appear necessary. 8. All of the RCT's for local endobronchial therapies have limited value and are appropriately criticized in the results.	1. Thank you. We appreciate your efforts in reviewing this report. 2. We performed a thorough search of the published literature to identify all relevant studies. Based on our pre-specified study selection criteria, few RFA studies qualified for inclusion. 3. The Lanuti 2009 study was excluded based on our criterion of "unclear study description". The investigators stated in the Abstract that all patients were "deemed medically ineligible for resection", but in the Results they suggest some 35% may have been eligible but refused surgery. These were not discerned. Further, they stated that > 50% of patients had a history of resected NSCLC, who may have different prognosis than those with primary disease, but don't discern the different populations. Some patients received multiple RFA treatments, some received subsequent radiotherapy, and one went to salvage surgery at recurrence. None of these patients were identified or discerned in the survival results. The Beland 2010 study was not identified in our searches, likely because it contains the term "review" in the title and may have been inappropriately indexed in MEDLINE. We retrieved it and determined it would not meet inclusion criteria for numerous reasons: 13% of patients had stage IIB-IV NSCLC; 24% received EBRT in addition to RFA; 11% received BT in addition to RFA. None of these were distinguished in the Kaplan-Meier survival cure or Results section. 4. We defined "local control" on page 15 in the Methods as per NCI criteria. 5. Thank you. We appreciate your efforts in reviewing this report.
Reviewer 5 (Peer) (contd)	Results		6. Thank you. We appreciate your efforts in reviewing this report. 7. Thank you. We appreciate your efforts in reviewing this report. 8. Thank you. We appreciate your efforts in reviewing this report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 6 (TEP)	Results	The tables listing the articles reviewed, along with their findings, are most helpful, and the summary of all the results confirms the absence of any good outcome data for all 3 questions. I did not review each study that was included to determine if it should have been excluded. I did not recognize any English language studies which were not included.	Thank you. We appreciate your efforts in reviewing this report.
Reviewer 8 (TEP)	Results	1. Detail is sufficient. 2. ACOSOG Z4033 data will be forthcoming in the next few months, but this is a single arm trial looking at 2 year survival in patients with medically inoperable stage 1A NSCLC. A future trial comparing SBRT to RFA would be the next logical step if radiation oncologists want to be involved with such a study. 3. The political environment may make this trial hard to accomplish.	1. Thank you. We appreciate your efforts in reviewing this report. 2. Thank you. We appreciate your efforts in reviewing this report. We agree RFA versus SBRT may be logical, and mention that in the research gaps section of the report. 3. The political environment is beyond the scope of this CER.
Reviewer 9 (Peer)	Results	1. [P 27] In table 4 and table 7 the percentage refers to the percentage of studies that show the above mentioned toxicity. This is relevant and the percentages should be explained in the figure legends. 2. Also, in table 4 the mortality rate for RFA 100% however, no actual number was placed; it should be a one.	1. We agree, and altered the table to reflect that it shows percentages of studies, and revised the text on page 29 to read as follows: "As shown in Table 4 no relative difference in the proportion of studies reporting toxicities is evident among or across interventions, with the possible exception of rib fractures mentioned above." 2. The number was corrected as suggested.
Reviewer 9 (Peer)	Results	On page 79 [39] line 34 and 35 the word radiofrequency should be one word.	This has been corrected.
Reviewer 1 (Peer)	Discussion	The message presented is not complex, it is quite clear and very concise. There is currently insufficient data to recommend any one treatment over another in these populations. The studies that have been performed to date are grossly inadequate in their level of reporting to compare one modality of treatment to another.	Thank you. We appreciate your efforts in reviewing this report
Reviewer 2 (TEP)	Discussion	Yes. Well done	Thank you. We appreciate your efforts in reviewing this report
Reviewer 3 (Peer)	Discussion	Page 43, line 27, the term is Gray, grays. The authors should carefully review the document to correct this error	This term has been corrected throughout the report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	Discussion	Page 43, lines 27 & 28. Not all SBRT delivery involves continuous imaging during treatment. This should be corrected.	This was revised by removing the term “continuous” to reflect this comment. The text in the Background has been revised to read as follows: “**Stereotactic Body Radiation Therapy (SBRT)** SBRT delivers very high, conformal ablative doses of radiation in fewer treatment sessions than other conformal modalities, with the potential to cause less damage to surrounding normal tissue. SBRT regimens generally deliver a total dose of 60 Gy at greater than 10 Gy per fraction. Four-dimensional monitoring of tumor motion during the breathing cycle is accomplished using a number of imaging techiques (CT, X-ray, ultrasound) that depend on the platform, tracking on bony structures or implanted fiducials. SBRT can deliver very high biologically effective doses (BED) above 100 Gray equivalent (GyE) that are needed to ablate the tumor and sterilize the tumor margins, minimizing damage to adjacent normal tissue. Conventionally fractionated schemes, delivering a similar total dose in 25-40 fractions, typically do not reach a similar BED range.”
Reviewer 3 (Peer)	Discussion	The description of the studies, their weaknesses and strengths are well described and appropriate. The implications of the findings are stated.	Thank you. We appreciate your efforts in reviewing this report

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	Discussion	Page 43, lines 42-44, the authors state: The optimal definitive external RT modality is not defined for patients with medical contraindications (medically inoperable patients) or for those with stage I NSCLC who elect nonsurgical treatment (reference 14). While there are not level 1 data comparing conventionally fractionated radiotherapy with SBRT, the BED is significantly different and the Phase II data are compelling. This reviewer is concerned that the recommendation to compare in an RCT these approaches is not practical and would be considered by some unethical because of the differences in biologically effective dose. It is not clear that there is equipoise present with such a trial. These comments are also relevant for the overview of KQ1 and KQ2 provided on page 91.	This issue has been considered in a previous comment from another reviewer. We agree with the reviewer on the substance of this comment, that BED delivery differs between RT modalities. We acknowledge the concerns in calling for comparative studies, and have revised the text on pages ES-26 and 61 of the text as follows: "A key technical issue for comparing the RT-based interventions likely is the significant difference in the BED of radiation that can be safely delivered by SBRT, compared to IMRT or 3DRT delivered with conventional fractionation protocols. In brief, radiation therapy for NSCLC typically is delivered to a total dose of 60-70 Gray (Gy); SBRT delivers that dose in three to five fractions of 20 Gy each (estimated BED = 180 Gy_{10} using standard principles) whereas conventionally fractionated IMRT or 3DRT delivers 60-70 Gy in 30 fractions of 2 Gy each in 4 to 5 weeks, yielding an estimated BED of 72 Gy_{10}, a difference which is considered to have potential efficacy differences. The higher BED causes tumor ablation, rather than tumor cell kill, allowing for little to no tumor cell repopulation between doses of radiation. In this CER, we did not systematically investigate whether a higher BED delivered by any conformal RT modality can be associated with better clinical outcomes such as overall survival, compared to a lower BED. This has been reported in published single-arm studies reviewed in this CER, for example the large, multicenter, retrospective series on SBRT in Japan by Onishi and colleagues. However, we are not aware of any direct comparative evidence on this topic among any of the conformal RT technologies, so it is not possible to make even indirect comparisons between the delivered BED and clinical outcomes in any case. Furthermore, we are aware of no published clinical trial evidence to ascertain whether a higher BED delivered by SBRT is associated with differences in patient outcomes compared to a lower BED delivered either by SBRT or by a conventionally fractionated conformal radiotherapy modality.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3 (Peer)	Discussion	Continued from above.	We acknowledge the difference in delivered BED has biologically plausible clinical implications, and perhaps ethical implications, that would need to be addressed in designing a study of any type to compare conformal radiotherapy-based technologies. But, it is not clear to us that the BED issue under discussion here is settled. In summary, we acknowledge the views of some members of the radiation oncology and interventional radiology communities - that clinical trials of local nonsurgical modalities, including RFA, SBRT and other conformal radiotherapy modalities (e.g., 3DRT, IMRT, PBRT) in stage I NSCLC patients may be very difficult to recruit and conduct, based on technical and potential ethical issues related to perceptions of unequal clinical benefit among the interventions. However, we maintain that current evidence is insufficient to support the view that clinical outcomes with one technology are proved superior to those achieved with other modalities. Clinical evidence from rigorous studies as outlined above would establish the standard of care for local nonsurgical treatment of stage I NSCLC patients." The term "equipoise" has been deleted.
Reviewer 4 (TEP)	Discussion	Okay	Thank you. We appreciate your efforts in reviewing this report
Reviewer 5 (Peer)	Discussion	1. Discussion/ Conclusion: Unfortunately there is very little evidence to make sweeping treatment conclusions regarding optimal management of medically inoperable stage I NSCLC (key question 1 and 2). 2. Results of randomized studies looking at SBRT vs wedge or SBRT vs RFA are maturing and studies. Randomized trials for PBRT vs IMRT are also not currently organized to my knowledge. 3. The limitations of the review are obvious and stated to some degree.	1. Thank you. We appreciate your efforts in reviewing this report. 2. Thank you. We appreciate your efforts in reviewing this report. 3. Thank you. We appreciate your efforts in reviewing this report.
Reviewer 6 (TEP)	Discussion	The conclusion was brief, but well summarizes the lack of good information on the 3 key questions.	Thank you. We appreciate your efforts in reviewing this report