APPENDIX A. PROTON BEAM THERAPY COVERAGE POLICIES

Organization	Title	Last Review	Policy
Aetna	Clinical Policy Bulletin: Proton Beam and Neutron Beam Radiotherapy	8/8/2014	Aetna considers proton beam radiotherapy medically necessary in any of the following radiosensitive tumors: A. Chordomas or chondrosarcomas arising at the base of the skull or cervical spine without distant metastases; or B. Malignancies in children (21 years of age and younger); or C. Uveal melanomas confined to the globe (*ie*, not distant metastases) (the uvea is comprised of the iris, ciliary body, and choroid [the vascular middle coat of the eye]). Aetna considers proton beam radiotherapy for treatment of prostate cancer not medically necessary for individuals with localized prostate cancer because it has not been proven to be more effective than other radiotherapy modalities for this indication. Proton beam therapy for metastatic prostate cancer is considered experimental and investigational. Aetna considers proton beam radiotherapy experimental and investigational for all other indications.
American Society for Radiation Oncology (ASTRO)	Model Policy: Proton Beam Therapy	5/20/2014	The Model Policy lists the following disease sites that support the use of PBT: (1) Ocular tumors, including intraocular melanomas; (2) Tumors that approach or are located at the base of skull, including but not limited to chordoma and chondrosarcomas; (3) Primary or metastatic tumors of the spine where the spinal cord tolerance may be exceeded with conventional treatment or where the spinal cord has previously been irradiated; (4) Primary hepatocellular cancer treated in a hypofracitonated regimen; (5) Primary or benign solid tumors in children treated with curative intent and occasional palliative treatment of childhood tumors when at least one of the four criteria noted above apply; (6) Patients with genitive syndromes making total volume of radiation minimization crucial such as but not limited to NF-1 patients and retinoblastoma patients. All other indications…are suitable for Coverage with Evidence Development (CED). Radiation therapy for patients treated under the CED paradigm should be covered by the insurance carrier as long as the patient is enrolled in either an IRB-approved clinical trial or in a multi-institutional patient registry adhering to Medicare requirements for CED. At this time, no indications are deemed inappropriate for CED and therefore…includes various systems such as, but not limited to, the following: head and neck malignancies, thoracic malignancies, abdominal malignancies, pelvic malignancies including genitourinary, gynecologic, and gastrointestinal carcinomas.

Organization	Title	Last Review	Policy
Anthem	Proton Beam Radiation Therapy Medical Policy	5/15/2014	All Conditions other than Localized Prostate Cancer Proton beam radiation therapy, with or without stereotactic techniques, is considered medically necessary for the following conditions: (1) As primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) involving tumors of up to 24 mm in largest diameter and 14 mm in height, and with no evidence of metastasis or extrascleral extension; (2) As postoperative therapy for individuals who have undergone biopsy or partial resection of a chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (for example, skull-base chordoma or chondrosarcoma) or cervical spine and have residual, localized tumor without evidence of metastasis; (3) Pituitary adenoma when conventional stereotactic radiation is not an available option; (4) Intracranial arteriovenous malformation (AVM) not amenable to surgical excision or other conventional forms of treatment; (5) Central nervous system (CNS) lesions including but not limited to, primary or metastatic CNS malignancies or arteriovenous malformations, adjacent to critical structures such as the optic nerve, brain stem or spinal cord. Proton beam radiation therapy is considered not medically necessary for the treatment of choroidal neovascularization secondary to age-related macular degeneration (AMD). Proton beam radiation therapy is considered investigational and not medically necessary for all other indications not meeting the criteria above. Localized Prostate Cancer Proton beam radiation therapy is considered medically necessary for the initial monotherapy radiation treatment of localized prostate cancer. The use of proton beam radiation as dose escalation therapy, in conjunction with stereotactic radiosurgery, IMRT, three-dimensional conformal radiation therapy (3D CRT), or brachytherapy for the treatment of localized prostate cancer is considered investigational and not medically necessary. Proton beam radiation therapy is considered investigational and not medically necessary for the treatment of prostate cancer for all other indications not meeting the criteria above.

Organization	Title	Last Review	Policy
BlueCross BlueShield of North Carolina	Corporate Medical Policy Charged Particle Radiotherapy (Proton or Helium Ion)	6/2014	Charged particle irradiation with proton or helium ion beams may be considered medically necessary for the following clinical indications: (1) primary therapy for melanoma of the uveal tract (iris, choroid or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 millimeters in largest diameter and 14 millimeters in height; (2) post-operative therapy (with or without conventional high energy X-rays) in patients who have undergone biopsy or a partial resection of chordoma or low grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis; (3) In the treatment of pediatric central nervous system (CNS) tumors. Charged particle irradiation with proton beams using standard treatment doses is considered not medically necessary and therefore non -covered in patients with clinically localized prostate cancer, because the clinical outcomes with this treatment have not been shown to be superior to other approaches including intensity modulated radiation therapy (IMRT) or conformal radiation therapy. Charged particle irradiation is considered investigational for all other indications not addressed above under, When Charged Particle Radiotherapy is covered
BlueCross BlueShield of California	Charged-Particles (Proton or Helium) Radiation Therapy Medical Policy	10/28/2013	Charged-particle irradiation with proton or helium ion beams may be considered medically necessary and a covered benefit in any of the following clinical situations: (1) Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body) and both of the following: a. No evidence of metastasis or extrascleral extension, b. Tumor size up to 24 millimeters in largest diameter and 14 millimeters in height; (2) Postoperative therapy (with or without conventional high-energy x-rays) for residual localized tumor without metastasis in patients who have undergone biopsy or partial resection of one of the following: a. Chordoma, b. Low-grade (I or II) chondrosarcoma of the basisphenoid region (*eg*, skull-base chordoma or chondrosarcoma) or cervical spine; (3) Treatment of pediatric central nervous system tumors. Charged-particle irradiation with proton or helium beams is generally not a covered service for prostate cancer (clinically localized prostate cancer) because it is not cost-effective. Other applications of charged-particle irradiation with proton beams are considered investigational.

Organization	Title	Last Review	Policy
CIGNA	Proton Beam Therapy for Intracranial and Skull Base Tumors	Unknown	CIGNA HealthCare covers proton beam therapy as medically necessary for the treatment of intracranial and skull base tumors when radiation therapy is indicated and recommended by the treating physician.
CIGNA	Proton Beam Therapy for Ocular Melanoma, Ocular Hemangiomas and Macular Degeneration	Unknown	CIGNA HealthCare covers proton beam therapy as medically necessary for the treatment of melanoma of the uveal tract (*ie*, iris, ciliary body and choroid). CIGNA HealthCare does not cover proton beam therapy for choroidal hemangiomas or macular degeneration, because it is considered experimental, investigational or unproven.
CIGNA	Proton Beam Therapy for Prostate Cancer	Unknown	CIGNA HealthCare considers proton beam therapy to be clinically equivalent to conventional external beam radiation therapy for the treatment of localized prostate cancer (*ie*, cancer that is confined to the prostate), but does not consider it to be clinically superior to conventional external beam radiation therapy. Coverage for proton beam therapy for the treatment of localized prostate cancer may depend upon the applicable health benefit plan definition of medical necessity. Many health benefit plans administered by CIGNA HealthCare contain definitions of medical necessity which include a cost comparison component. Because proton beam therapy for the treatment of prostate cancer is significantly more expensive than conventional external beam radiation therapy but is not clinically superior, it is considered not medically necessary under those plans. For health benefit plans which contain definitions of medical necessity that do not include a cost comparison component, proton beam therapy may be covered as medically necessary for the treatment of localized prostate cancer (*ie*, cancer that is confined to the prostate).
CIGNA	Proton Beam Therapy for Lung Cancer	Unknown	Cigna does not cover proton beam therapy for the treatment of lung cancer because it is considered experimental, investigational or unproven.

Organization	Title	Last Review	Policy
HealthPartners	Proton Beam Radiation Therapy	7/2014	Indications that are covered: (1) Melanoma of the uveal tract that is not amenable to surgical excision or other conventional forms of treatment; (2) Chordomas or chondrosarcomas arising at the base of the skull or along the axial skeleton without distant metastases; (3) Pituitary neoplasms; (4) Other central nervous system tumors located near vital structures; (5) Salivary gland tumors. Indications not covered: (1) Prostate cancer; (2) Hepatocellular cancer; (3) Lung cancer; (4) Bladder cancer; (5) Breast cancer; (6) Esophageal cancer; (7) Cervical cancer; (8) Age-related maculardegeneration (AMD); (9) Chorical hemangiomas; (10) Non-uveal melanoma; (11) Parotid gland tumor; (12) Colon cancer; (13) Kidney cancer; (14) Pancreatic cancer; (15) Rectal cancer; (16) Soft tissue sarcomas.
Medica	Proton Beam Radiation Therapy	6/2013	Proton beam radiation therapy is indicated for individuals with conditions not amenable to surgical excision or other conventional forms of treatment AND have one of the following diagnoses: A. Chordomas or chondrosarcomas arising at the base of the skull or along the axial skeleton without distant metastasis; B. Pediatric central nervous system tumors adjacent to vital structures (*eg* optic nerve, spinal cord); C. Melanoma of the uveal tract (iris, choroid, ciliary body) without extrascleral extension and with no evidence of metastasis. Proton beam radiation therapy for hepatocellular cancer, prostate cancer or non-small cell lung cancer (NSCLC) is investigative and therefore not covered.

Organization	Title	Last Review	Policy
Regence	Charged-Particle (Proton or Helium Ion) Radiation Therapy	6/2014	Charged-particle irradiation with proton or helium ion beams may be considered medically necessary in the following clinical situations: A. Primary therapy for melanoma of the uveal tract (iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension, and with tumors up to 24 mm in largest diameter and 14 mm in height; B. Postoperative therapy (with or without conventional high-energy x-rays) in patients who have undergone biopsy or partial resection of the chordoma or low-grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis.; C. In the treatment of pediatric (less than 21 years of age) central nervous system tumors and retinoblastoma. Charged-particle irradiation with proton beams is considered not medically necessary in patients with clinically localized prostate cancer. Other applications of charged-particle irradiation are considered investigational.
United Healthcare	Medical Policy: Proton Beam Radiation Therapy	9/2014	Proton beam radiation therapy is proven and medically necessary for the following indications: (1) Intracranial arteriovenous malformations (AVMs); (2) Ocular tumors, including intraocular/uveal melanoma (includes the iris, ciliary body and choroid); (3) Skull-based tumors (*eg*, chordomas or chondrosarcomas). Proton beam radiation therapy is unproven and not medically necessary for treating ALL other indications.

Organization	Title	Last Review	Policy
Wellmark	Proton Beam Radiation Therapy	1/2014	Proton beam therapy may be considered medically necessary for the following conditions: (1) Primary therapy for melanoma of the uveal tract (*ie* iris, choroid, or ciliary body), with no evidence of metastasis or extrascleral extension and with tumors up to 24mm in largest diameter and 14mm in height; (2) Post operative therapy (with or without conventional high energy x-ray) in patients who have under gone biopsy or partial resection of the chordoma or low grade (I or II) chondrosarcoma of the basisphenoid region (skull-base chordoma or chondrosarcoma) or cervical spine. Patients eligible for this treatment have residual localized tumor without evidence of metastasis. (3) Osteosarcoma for patients with unresectable or incompletely resected osteosarcoma; (4) Central nervous system tumors (*ie* tumors within the skull, skull based tumors and spinal cord tumors); (5) Intracranial arteriovenous malformations, small lesions when surgery may be associated with increased risk based on anatomic location or feeding vessel anatomy; (6) Soft tissue sarcoma. Postoperative use in retroperitoneal soft tissue sarcoma not amenable to other radiotherapy (*eg*, IMRT, stereotactic body radiotherapy) in persons who have not received preoperative radiotherapy. Proton beam therapy as a treatment for prostate cancer is considered not medically necessary because the clinical outcomes with this treatment have not been shown to be superior or more effective than the other radiotherapy modalities for this indication. Proton beam radiation therapy is considered investigational for all other indications not meeting the criteria above.

APPENDIX B. CLINICAL PRACTICE GUIDELINES IN OTHER ORGANIZATIONS

Organization	Population	Title	Year	Statement
Alberta Health Services, Cancer Care	All diagnoses	Proton beam radiation therapy	2013	"Adult tumour sites that may be considered for referral for out-of-country proton beam radiotherapy include: a. The following CNS tumours or lesions: arteriovenous malformations, benign meningioma, neuromas, craniopharyngioma, CNS germ cell tumours, and low grade gliomas b. The following non-CNS tumours: sarcoma including chordoma and chondrosarcoma, lymphoma in patients under the age of 30 years, and paranasal sinus and nasal cavity tumours. Adult, pediatric, and adolescent patients with ocular melanomas requiring proton beam radiotherapy should be sent to the TRIUMF Proton Treatment Facility in Vancouver, British Columbia (BC) for treatment. Members of the working group do not currently recommend that patients with prostate cancer, non-small cell lung cancer, or most lymphomas be referred for proton beam radiotherapy, due to an insufficient evidence base. However, individual patient cases should be discussed by the multidisciplinary team during a Tumour Board meeting."
American College of Radiology	Stage T1 and T2 prostate cancer	ACR Appropriateness Criteria® definitive external-beam irradiation in stage T1 and T2 prostate cancer.	2013	"There are only limited data comparing proton beam therapy to other methods of irradiation or to radical prostatectomy for treating stage T1 and T2 prostate cancer. Further studies are needed to clearly define its role for such treatment."
American College of Radiology	N2 non-small cell lung cancer	ACR Appropriateness Criteria® induction and adjuvant therapy for N2 non–small-cell lung cancer.	2013	"The utility of intensity-modulated radiation therapy (IMRT) or protons to potentially further reduce normal tissue toxicity remains to be explored."

Organization	Population	Title	Year	Statement
American College of Radiology	Lymphoma	ACR Appropriateness Criteria® localized nodal indolent lymphoma.	2013	"Advanced radiation techniques, such as IMRT and proton therapy, may be considered depending on the clinical scenario and whether an improvement in the therapeutic ratio is expected."
American College of Radiology	Cervical cancer	ACR Appropriateness Criteria® advanced cervical cancer.	2012	"The combined use of imaging, advanced radiotherapeutic modalities, and chemotherapy has led to better treatment for cancer of the cervix." Particle therapy is included as one of the external beam radiotherapies.
American College of Radiology	Prostate cancer	ACR Appropriateness Criteria® external beam radiation therapy treatment planning for clinically localized prostate cancer.	2011	Proton beam therapy is "usually appropriate" (rating of 7) for treating prostate cancer.
American College of Radiology	Breast cancer	ACR Appropriateness Criteria® locally advanced breast cancer.	2011	"Maximal cardiac sparing achieved through proton therapy has the potential to decrease [common treatment-related toxicities]."
American College of Radiology	Brain cancer	ACR Appropriateness Criteria® pre-irradiation evaluation and management of brain metastases.	2011	Not mentioned

Organization	Population	Title	Year	Statement
American College of Radiology	Head/neck cancer	ACR Appropriateness Criteria® retreatment of recurrent head and neck cancer after prior definitive radiation.	2010	"Experience with nasopharyngeal retreatment has included combinations of nasopharyngectomy, chemotherapy, external beam radiation therapy (EBRT), brachytherapy, intraoperative radiotherapy, hyperthermia, radiosurgery, and proton therapy."
BlueCross BlueShield	Prostate cancer	Proton Beam Therapy for Prostate Cancer	2014	"Based on the above, proton beam therapy as a boost to photon external-beam radiotherapy or proton beam therapy without photon external-beam radiotherapy in the treatment of prostate cancer does not meet the TEC criteria."
BlueCross BlueShield	Non-small cell lung cancer	Proton Beam Therapy for Prostate Cancer	2014	"Proton beam radiotherapy for treatment of non-small cell lung cancer at any stage or for recurrent non-small cell lung cancer does not meet the TEC criteria."
National Comprehensive Cancer Network	Prostate Cancer	NCCN Guidelines Version 1.2015 Prostate Cancer	2014	"An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise."

APPENDIX C. SEARCH STRATEGIES

MEDLINE® via PubMed® searched on December 10, 2014

Concept	Search Terms	Comments
All Cancers	neoplasm* OR cancer* OR carcinom*	Key words in title/abstract
Proton Beam Therapy	proton OR "proton beam" OR "proton beam therapy" OR proton* OR proton* therap* OR protontherap*	Key words in title/abstract
	"Protons"[Mesh] OR "Proton Therapy"[Mesh]	MeSH terms
Limits	AND Humans[Mesh] AND English[lang]	Removes non-English language articles and animal studies
	NOT (Comment[ptyp] OR Letter[ptyp] OR Review[ptyp])	Removes publication types that are not studies. (this is more sensitive than restricting the search to RCTs)
	NOT ("Proton Pump Inhibitors"[Mesh] OR "Proton Pump Inhibitors" [Pharmacological Action])	Removes Proton Pump Inhibitor Studies
	NOT AND (infant[MeSH] OR child[MeSH] OR adolescent[MeSH])	Removes Children from search (safer than limiting to adults only)
Total Results = 1,964		

Cochrane Central Register of Controlled Trials via OVID searched on December 10, 2014

Step	Term	Results
1	exp Protons/	106
2	proton.mp.	2,172
3	proton beam.mp.	37
4	proton beam therapy.mp.	7
5	exp Proton Therapy/	3
6	proton*.mp.	2,239
7	proton$ therap$.mp.	19
8	protontherap$.mp.	0
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	2,239
10	(neoplasm* or cancer* or carcinoma*).mp.	68,072
11	9 and 10	169
12	limit 11 to english language	146
13	Proton Pump Inhibitors/	811
14	12 not 13	111
15	limit 14 to (editorial or letter or "review")	0
16	14 not 15	111

ClinicalTrials.gov searched on December 10, 2014

Term	Results
neoplasm* or cancer* or carcinoma* | proton therapy | Adult, Senior	50

MEDLINE® via PubMed® searched on December 10, 2014 with special emphasis on selected journals without any limitations for cancer type for proton beam therapy

Concept	Search Terms	Comments
Proton Beam Therapy	proton[tiab] AND irradiation OR radiation OR radiotherap* OR therap* OR beam[tiab]	Keywords in title or abstract
	OR "Proton Therapy"[Mesh] OR "Protons/therapeutic use"[Mesh]	Medical Subject terms
Selected Journals	"Acta oncologica (Stockholm, Sweden)"[Journal] OR "American journal of clinical oncology"[Journal] OR "BMC cancer"[Journal]) OR "Cancer"[Journal] OR "Cancer journal (Sudbury, Mass.)"[Journal] OR "International journal of radiation oncology, biology, physics"[Journal] OR "J Clin Oncol"[Journal] OR "J Surg Oncol"[Journal] OR "JAMA : the journal of the American Medical Association"[Journal] OR "J Thorac Oncol"[Journal] OR "Jpn J Clin Oncol"[Journal] OR "Radiat Oncol"[Journal] OR “Radiother Oncol” [Journal] OR "Strahlenther Onkol"[Journal] OR "Urology"[Journal]	Top journals from previous search
Total Results = 927		

APPENDIX D. ICER COMPARATIVE STUDIES EXCLUDED AT FULL-TEXT LEVEL

Citation	Reason for Exclusion
Demizu Y, Murakami M, Miyawaki D, et al. Analysis of Vision loss caused by radiation-induced optic neuropathy after particle therapy for head-and-neck and skull-base tumors adjacent to optic nerves. *Int J Radiat Oncol Biol Phys.* Dec 1 2009;75(5):1487-1492.	Ineligible comparator: carbon ion therapy
Desjardins L, Lumbroso-Le Rouic L, Levy-Gabriel C, et al. Combined proton beam radiotherapy and transpupillary thermotherapy for large uveal melanomas: a randomized study of 151 patients. *Ophthalmic Res.* 2006;38(5):255-260.	Ineligible population: uveal melanoma patients
Fujii O, Demizu Y, Hashimoto N, et al. A retrospective comparison of proton therapy and carbon ion therapy for stage I non-small cell lung cancer. *Radiother Oncol.* Oct 2013;109(1):32-37.	Ineligible comparator: carbon ion therapy
Gragoudas ES, Lane AM, Regan S, et al. A randomized controlled trial of varying radiation doses in the treatment of choroidal melanoma. *Arch Ophthalmol.* Jun 2000;118(6):773-778.	Ineligible population: uveal melanoma patients
Jabbari S, Weinberg VK, Shinohara K, et al. Equivalent biochemical control and improved prostate-specific antigen nadir after permanent prostate seed implant brachytherapy versus high-dose three-dimensional conformal radiotherapy and high-dose conformal proton beam radiotherapy boost. *Int J Radiat Oncol Biol Phys.* Jan 1 2010;76(1):36-42.	Ineligible outcomes: interval to reach PSA nadir, PSA level, biological no evidence of disease
Komatsu S, Fukumoto T, Demizu Y, et al. Clinical results and risk factors of proton and carbon ion therapy for hepatocellular carcinoma. *Cancer.* Nov 1 2011;117(21):4890-4904.	Ineligible comparator: carbon ion therapy
Lopez Guerra JL, Gomez DR, Zhuang Y, et al. Changes in pulmonary function after three-dimensional conformal radiotherapy, intensity-modulated radiotherapy, or proton beam therapy for non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* Jul 15 2012;83(4):e537-543.	Ineligible outcome: decline in lung diffusing capacity for carbon monoxide
Matsuzaki Y, Osuga T, Chiba T, et al. New, effective treatment using proton irradiation for unresectable hepatocellular carcinoma. *Intern Med.* Apr 1995;34(4):302-304.	Ineligible comparator: proton beam therapy plus chemotherapy
Miyawaki D, Murakami M, Demizu Y, et al. Brain injury after proton therapy or carbon ion therapy for head-and-neck cancer and skull base tumors. *Int J Radiat Oncol Biol Phys.* Oct 1 2009;75(2):378-384.	Ineligible comparator: carbon ion therapy
Park L, Delaney TF, Liebsch NJ, et al. Sacral chordomas: Impact of high-dose proton/photon-beam radiation therapy combined with or without surgery for primary versus recurrent tumor. *Int J Radiat Oncol Biol Phys.* Aug 1 2006;65(5):1514-1521.	Ineligible comparator: proton beam therapy plus photon therapy and surgery
Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer.* Jan 1 2014;120(1):126-133.	Ineligible population: pediatric and retinoblastoma
Tokuuye K, Akine Y, Kagei K, et al. Proton therapy for head and neck malignancies at Tsukuba. *Strahlenther Onkol.* Feb 2004;180(2):96-101.	Ineligible comparator: proton beam therapy plus photon therapy

APPENDIX E. QUALITY ASSESSMENT OF PRIMARY STUDIES

Observational Studies

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Arvold 2009 US	"The decision to treat patients with photons versus protons versus a combination of both was made by the treating radiation oncologist and was based primarily on treatment machine availability."	No. 12% (3/25) loss to follow-up.	Yes.	Yes.	Yes.	No. Differences in tumor size at baseline (2.25 mL, 3.63 mL, and 4.15 mL).	No. 42 months for photon therapy, 78 months for combination therapy, and 12.5 months for proton therapy.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Brown 2013 US	Unclear how patients were selected for each group.	Unclear.	Yes.	Yes.	Yes. Unknown whether outcome ascertainers were blinded, outcomes are not subjective.	Not adequate. Only performed for hematologic toxicity endpoints.	No. 26.3 months (PBT) vs 57.1 months (photon)	Poor.
Chakravarti 1999 US	Unclear how patients were selected for each group.	N/A	Yes.	Yes.	Yes.	No. Differences in age at baseline (23.5 yrs vs 52.5 yrs for combined and photon only groups, respectively).	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Chung 2013 US	Yes. Patients compared with historical results, but matched.	Yes. 27% excluded from proton cohort because they were lost to follow-up and it is plausible that their loss is associated with second cancer events.	Yes.	Yes.	No. Method of data collection differed between groups. PBT: "data abstracted from pathology reports, operative notes and clinic visit notes ... Patients were also contacted by mail and scripted telephone calls to obtain data." Photon group: based on diagnosis codes from SEER database.	Age at treatment, sex, primary tumor site, and year of treatment. No information on dose of RT or chemotherapy in either group.	No.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Coen 2012 US	Yes. Patients compared with historical results, but matched.	N/A	Yes.	Yes.	Unclear.	No, but matched on T stage, Gleason score, PSA level, and age.	Yes.	Fair.
Duttenhaver 1983 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes. While outcome ascertainers were apparently not blinded, outcomes are not subjective.	No. Did not control for potentially confounding effects of differentiation which could lead to better survival, but had an unknown effect on local control. XRT: 55% had poorly differentiated tumors XRT+PBT: 35% had poorly differentiated tumors	Yes.	Local control: Fair. Other outcomes: Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Fang 2014 US	Allocation to PBT or IMRT was based on suitability for PBT as determined by triage committee, patient desire, machine availability, and insurance coverage.	N/A	Yes.	Yes.	Unknown whether outcome assessors were blinded	Yes. Matched on prostate cancer risk group, age at diagnosis, prior GI or GU disorders. Potential confounders included ADT, hypertension, hemorrhoids, diabetes, Eastern Cooperative Oncology Group performance status, IPSS score and Bowel Symptom Score.	No. Shorted F/U time for the PBT group compared with IMRT group (29 months vs 47 months)	Fair.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Galbraith 2001 US	Yes.	No. 17% attrition at 18 months.	Yes.	Yes.	Yes.	No. Age and stage assessed as covariates, but were not significant.	Yes.	Fair.
Galland-Girodet 2014 US	Unclear how patients were selected for each group.	No. 2% loss to follow-up	Yes.	Yes.	Yes. While outcome ascertainers were apparently not blinded, outcomes are not subjective.	No. No significant differences in patient or tumor characteristics between the two groups.	Yes.	Fair.
Gomez 2012 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Yes.	Yes. Age, gender, smoking status, stage, and histology did not predict severe esophagitis.	Yes.	Fair.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Gray 2013 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Unclear.	No. Did not control for time or site-specific variables.	Yes.	Poor.
Hocht 2006 Germany	Patients received protons once they were made available in Germany in 1998.	N/A	Yes.	No.	Unclear.	Controlled for differential follow-up time, tumor characteristics differed at baseline.	Yes.	Fair.
Hoppe 2014 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Unclear.	Yes. Controlled for age, prostate size, ADT use, baseline QOL, but not for time or site-specific variables.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Hug 2000 US	"Patients were selected for protons or photons based on the specific dose conformity advantages of protons for certain anatomic locations and for high degrees of target irregularity."	No.	Yes.	Yes.	Yes.	Unknown. No baseline patient characteristics were given by treatment group.	Yes.	Poor.
Kahn 2011 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes. Unknown whether outcome ascertainers were blinded, outcomes are not subjective.	Performed for survival but not local control outcome.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Kim 2011 US	Yes.	N/A	Yes.	Yes.	Yes.	Yes. Controlled for diagnosis year, comorbidity, age group, clinical stage, SEER region, race, marital status, poverty, cancer grade.	Yes.	Fair.
McCurdy 2013 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes.	No.	Yes.	Fair.
Mizumoto 2013 Japan	Treatment modality was chosen based on the location, distribution, and size of recurrent tumor.	No.	Yes.	Yes.	Yes.	No. Initial radiation dose, age, tumor volume differed between the reirradiation treatment groups.	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Otsuka 2003 Japan	Patients were selected for each group based on availability of PBT system.	No.	No.	No.	Unclear.	No. X-ray group older (60 vs 56 years) and had larger tumors (3.6 vs 2.7 cm) at baseline.	Yes.	Poor.
Sejpal 2011 US	No. PBT patients compared with historical results.	No.	Yes.	Yes.	Yes.	Performed stratification of harms, but not multivariate regression. Didn't control for temporal trends or differences at baseline (age, race, disease stage, tumor volume, adjuvant chemotherapy, time since treatment)	Yes.	Poor.

Author Year Country	Non-biased selection?	High overall loss to follow-up or differential loss to follow-up?	Outcomes pre-specified and defined?	Ascertainment techniques adequately described?	Non-biased and adequate ascertainment methods?	Statistical analysis of potential confounders?	Adequate duration of follow-up?	Overall quality rating
Sheets 2012 US	Yes.	N/A	Yes.	Yes.	Yes.	Yes. Propensity score weighting.	Yes.	Fair.
Solares 2005 US	Unclear how patients were selected for each group.	No.	Yes.	No.	Unclear.	No. No baseline demographic information given by patient group.	Yes.	Poor.
Wang 2013 US	Unclear how patients were selected for each group.	No.	Yes.	Yes.	Yes.	Yes.	Yes.	Fair.
Yu 2013 US	Yes.	N/A	Yes.	Yes.	Yes.	No, but matched on age, race, residence, comorbidity, receipt of ADT, prior influenza vaccination, or prior visit to a primary care physician.	Yes.	Fair.

Randomized Controlled Trial

Author Year	Adequate sequence generation?	Adequate allocation concealment?	Blinding of participants, personnel and outcome assessors?	Incomplete outcome data adequately addressed?	Study reports free of suggestion of outcome reporting bias?	Study free of other sources of bias?	Risk of bias?
Shipley 1995 US	Unknown.	Unknown.	Unknown. Outcomes are not subjective.	No. 6.4% (13/202) did not complete planned protocol, excluded from analysis.	Yes.	Yes.	Medium.

APPENDIX F. ONGOING CLINICAL TRIALS

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
A Bayesian Randomized Trial of Image-Guided Adaptive Conformal Photon vs Proton Therapy, With Concurrent Chemotherapy, for Locally Advanced Non-Small Cell Lung Carcinoma: Treatment Related Pneumonitis and Locoregional Recurrence MD Anderson Cancer Center MD Anderson Cancer Center, Massachusetts General Hospital USA NCT00915005	RCT	PBT (74 Gy) PBT (66 Gy) Photon therapy	N=250 18-85 years Unresected, locoregionally advanced NSCLC (stage II-IIIb) w/out evidence of hematogenous metastases Suitable for concurrent chemoradiation therapy FEV1 ≥ 1 liter	Time to treatment failure	June 2015

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Prostate Advanced Radiation Technologies Investigating Quality of Life (PARTIQoL): A Phase III Randomized Clinical Trial of Proton Therapy vs IMRT for Low or Intermediate Risk Prostate Cancer Massachusetts General Hospital Massachusetts General Hospital, University of Pennsylvania USA NCT01617161	RCT	PBT IMRT	N=400 ≥18 years Histologically confirmed adenocarcinoma of the prostate Clinical stages T1c-T2b	Efficacy of PBT vs IMRT QOL Long-term survival	January 2016
Randomized Comparison of Proton and Carbon Ion Radiotherapy With Advanced Photon Radiotherapy in Skull Base Meningiomas: The PINOCCHIO Trial University Hospital Heidelberg University Hospital of Heidelberg Germany NCT01795300	RCT	PBT Carbon ion therapy Hypo- fractionated photon therapy Conventional photon therapy	N=80 ≥18 years Histologically or imaging confirmed skull base meningioma Macroscopic tumor, Simpson grade 4 or 5 Karnofsky score ≥60	Toxicity (graded after one year) Overall survival Progression-free survival QOL	February 2016

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Randomized Phase II Study Comparing Stereotactic Body Radiotherapy (SBRT) With Stereotactic Body Proton Therapy (SBPT) for Centrally Located Stage I, Selected Stage II and Recurrent Non-Small Cell Lung Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA NCT01511081	RCT	SBPT SBRT	N=120 ≥18 years Histological confirmation or clinically diagnosed primary NSCLC Centrally located stage I or selective stage II primary tumors Isolated recurrent disease Zubrod status = 0-2	SBRT and SBPT related toxicity Treatment response	August 2016
A Prospective Phase II Randomized Trial to Compare Intensity Modulated Proton Radiotherapy (IMPT) vs Intensity Modulated Radiotherapy (IMRT) for Newly Diagnosed Glioblastoma (WHO Grade IV) MD Anderson Cancer Center MD Anderson Cancer Center USA NCT01854554	RCT	IMPT IMRT	N=80 ≥18 years Histological diagnosis of glioblastoma or gliosarcoma (WHO grade IV) adapted RPA class III, IV or V Mini Mental Status Exam score ≥21 Karnofsky score ≥70	Time to cognitive failure	May 2017

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Phase III Randomized Trial of Proton Beam Therapy Versus Intensity-Modulated Radiation Therapy for the Treatment of Esophageal Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA NCT01512589	RCT	PBT IMRT	N=180 ≥18 years Histologically confirmed adenocarcinoma or squamous cell carcinoma of the cervical or thoracic esophagus or gastroesophageal junction or cardia of stomach Karnofsky score ≥60 ECOG criteria = 0, 1, or 2	Progression-free survival Total toxicity burden (TTB)	April 2018
Phase III Randomized Trial Comparing Overall Survival After Photon Versus Proton Chemoradiotherapy for Inoperable Stage II-IIIB NSCLC Radiation Therapy Oncology Group University of Florida, MD Anderson Cancer Center USA NCT01993810	RCT	PBT + chemotherapy Photon therapy + chemotherapy	N=560 ≥18 years Histologically or cytologically proven NSCLC Patients w/non-operable disease or refuse surgery Clinical stage TII, TIIIA, TIIIB Zubrod status = 0-1 FEV1 ≥ 1 liter	Overall survival Progression-free survival Adverse events QOL Changes in pulmonary function	December 2020

Title Trial Sponsor Location(s) Identifier	Design	Treatment/ Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Phase II/III Randomized Trial of Intensity-Modulated Proton Beam Therapy (IMPT) Versus Intensity-Modulated Photon Therapy (IMRT) for the Treatment of Oropharyngeal Cancer of the Head and Neck Cancer MD Anderson Cancer Center MD Anderson Cancer Center USA NCT01893307	RCT	IMPT IMRT	N=360 ≥18 years Histologically documented squamous cell carcinoma of the oropharynx ECOG criteria = 0, 1, or 2	Rates and severity of late grade 3-5 toxicity between IMRT and IMPT	August 2023
Randomized Phase II Trial of Hypofractionated Dose-Escalated Photon IMRT or Proton Beam Therapy Versus Conventional Photon Irradiation With Concomitant and Adjuvant Temozolomide in Patients With Newly Diagnosed Glioblastoma NRG Oncology NRG Oncology, Cadence Cancer Center USA NCT02179086	RCT	3-D conformal radiation therapy IMRT Photon beam radiation therapy Proton beam radiation therapy Temozolomide	N=576 ≥18 years MRI of the brain performed postoperatively within 72 hours of resection; enhancing tumor must have a maximal diameter of 5 cm GBM tumor located in the supratentorial compartment only Histologically proven diagnosis of glioblastoma (WHO grade IV) Karnofsky performance status ≥70	Overall survival Progression-free survival Incidence of treatment-related toxicity Change in cognitive and neurocognitive function	May 2019

APPENDIX G. QUALITY ASSESSMENT OF SYSTEMATIC REVIEWS

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Amichetti 2010	Can't answer. *No protocol number noted.*	Can't answer. *Duplicate study selection, but unknown data abstraction.*	No. *Only PubMed® was searched.*	Yes. *Restricted to English language.*	No.	Yes.	No.	No.	Not applicable.	No.	No.
De Ruysscher 2012	Can't answer.	Can't answer.	Yes.	No.	No.	Yes.	Assessed but not documented.	No.	Not applicable.	No.	Yes.
Cianchetti 2012	Can't answer.	Can't answer.	Yes.	Yes. *Restricted to English language.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Not applicable.	No.	No.
Grimm 2012	Can't answer.	Can't answer.	Yes.	Can't answer.	A list of included, but not excluded, studies was provided.	Yes.	No.	No.	No. Did not control for confounding between non-comparative studies.	No.	Yes.

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Grutters 2010	Can't answer. *Duplicate data abstraction, but unknown study selection.*	Can't answer.	Yes.	Yes. *Restricted to English language.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Yes.	No.	No.
Ollendorf 2014 (ICER)	Can't answer. *No protocol number noted.*	No.	Yes. *"The electronic databases we searched… included MEDLINE, EMBASE, and The Cochrane Library… for health technology assessments, systematic reviews, and primary studies."*	Yes. *Restricted to English language, but didn't tell us whether they included grey lit.*	Yes. *Did not provide a list of excluded studies, gave PRISMA flow chart*	Yes.	Assessed but not documented.	Yes.	Not applicable.	Yes.	Yes. No statement on author conflict of interest.

Author Year	Was an 'a priori' design provided?	Was there duplicate study selection and data extraction?	Was a comprehensive literature search performed?	Was the status of publication (*ie* grey literature) used as an inclusion criterion?	Was a list of studies (included and excluded) provided?	Were the characteristics of the included studies provided?	Was the scientific quality of the included studies assessed and documented?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the likelihood of publication bias assessed?	Was the conflict of interest stated?
Patel 2014	Yes.	Yes.	Yes.	Can't answer.	Yes. *Did not provide a list of excluded studies, gave PRISMA flow chart*	Yes.	Yes.	No.	Yes.	No.	Yes.
Ramaekers 2011	Can't answer.	Can't answer. *Duplicate data abstraction, but unknown study selection.*	No. *Only PubMed® was searched.*	Yes. *Restricted to English language.*	Yes.	Yes.	No.	No.	Yes.	No.	Yes.
Walsh 2012 (CTAF)	Can't answer.	Can't answer.	Yes.	Yes. *Restricted to English language, no grey literature search.*	No. *Did not provide a list of excluded studies.*	Yes.	No.	No.	Not applicable.	No.	No.

APPENDIX H. DATA ABSTRACTION OF COMPARATIVE STUDIES NOT INCLUDED IN THE ICER REVIEW

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Duttenhaver 1983 Prospective cohort Massachusetts General Hospital	XRT plus PBT XRT only 5 years	<u>XRT plus PBT</u> N=64 Age: 67.7 (mean) Race: unknown Clinical stage: T1: 3%, T2: 25%, T3: 59%, T4: 13% <u>XRT only</u> N=116 Age: 67.7 (mean) Race: unknown Clinical stage: T1: 4%, T2: 30%, T3: 56%, T4: 10%	<u>XRT plus PBT</u> Initial 50 Gy given using standard external beam Total dose: 70-76.5 CGE (mean: 74 CGE) <u>XRT only</u> Pelvis treated to 50 Gy in 5 ½ weeks, 5 fractions per week, 1.8 Gy fractions, initial dose followed by a boost to prostatic tumor volume Total dose: 60-68.4 Gy (mean: 67 Gy)	<u>Survival</u> Did not differ between XRT plus PBT and XRT groups <u>Disease-free survival</u> Did not differ between XRT plus PBT and XRT groups <u>Clinical local recurrence-free survival</u> "As yet there is no observed improvement in local control in the XRT plus PRT group despite an 8-10% increase in radiation dose, when compared to the XRT group."	<u>Mild dysuria/increased frequency</u> XRT plus PBT: 11% XRT: 10% <u>Hematuria</u> XRT plus PBT: 8% XRT: 10% <u>Benign structure</u> XRT plus PBT: 5% XRT: 4% <u>Mild proctitis</u> XRT plus PBT: 8% XRT: 11% <u>Moderate proctitis</u> XRT plus PBT: 13% XRT: 5% <u>Severe proctitis</u> XRT plus PBT: 0% XRT: 1%	Poor

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Fang 2014 Retrospective cohort University of Pennsylvania (PBT: 01/10-12/12; IMRT: 07/09-12/12)	PBT IMRT PBT median: 47 months (5-65) IMRT median: 29 months (5-50)	PBT N=94 IMRT N=94	PBT and IMRT: 79.2 Gy delivered in 44 fractions		Clinician-reported grade ≥ 2 GI toxicity: 4.3% (PBT) vs 13.8% (IMRT); OR (PBT vs IMRT): 0.27 (95% CI, 0.06-1.24) Clinician-reported grade ≥ 2 GU toxicity:21.3% (PBT) vs 28.7% (IMRT); OR (PBT vs IMRT): 0.69 (95% CI, 0.32-1.51)	Fair
Galland-Grirodet 2014 Prospective phase 1 nonrandomized trial Massachusetts General Hospital (10/03—04/06)	PBT Photon-based 3D-APBI Median: 82.5 months Range: 1.6—103.8 months	PBT N=19 Age: 63 (median) Race: unknown Grade: 1: 53%, 2: 32%, 3: 15% Photon-based 3D-APBI N=79 Age: 60 (median) Race: unknown Grade: 1: 46%, 2: 46%, 3: 8%	PBT Dose: 32 Gy in 8 fractions Photon-based 3D-APBI Dose: 32 Gy in 8 fractions	7-year cumulative incidence of local failure rate PBT: 11% Photon: 4% (P=.22)	5-year skin color change PBT: 44% Photon: 2% ($P \leq 0.0001$) Patchy atrophy PBT: 50% Photon: 5% ($P \leq 0.0001$) "At 7 years, physician assessments of skin color change (P=.02) and late skin toxicity (P=.029) were significantly worse in the PBT group. Telangiectasia >4 cm^2 was observed for 38.5% of the PBT group as compared with 4% of the photon-based group (P=.0013)." "There was no difference between the treatment groups in noncutaneous toxicities, including breast pain, breast edema, and rib tenderness, at either 5 or 7 years."	Fair

Author Year Study Design Study Site	Intervention Comparator Follow-up	Sample Size Patient characteristics	Treatment protocol	Outcomes assessed Main findings	Harms	Quality
Mizumoto 2013 Retrospective cohort University of Tsukuba (01/05-09/10)	PBT Traditional radiotherapy and stereotactic radiotherapy Median follow-up for survivors: 19.4 months	PBT N=8 Age: 51 (median) Initial dose: 64.1 Gy Tumor volume: 70.4 cc RT N=8 Age: 41 (median) Initial dose: 57.1 Gy Tumor volume: 70.9 cc SRT N=10 Age: 64.5 (median) Initial dose: 58.9 Gy Tumor volume: 11.5 cc	PBT Mean reirradiation dose: 39.5 Gy RT Mean reirradiation dose: 43.7 Gy SRT Mean reirradaition dose: 41.7 Gy	Overall survival PBT: 19.4 months RT: 5.15 months SRT:11.6 months Mortality after a median of 11.6 months:62.5% (conventional photon), 50% (SRT), 62.5% (PBT); P>.99 Local recurrence:25% (conventional photon), 30% (SRT), 25% (PBT); P>.99		Poor

APPENDIX I. PEER REVIEW COMMENT DISPOSITION TABLE

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
1.	**Are the objectives, scope, and methods for this review clearly described?**		
1	1	Yes (*no comments*)	
2	2	Yes (*no comments*)	
3	3	Yes (*no comments*)	
4	4	Yes (*no comments*)	
5	5	Yes (*no comments*)	
6	6	Yes (*no comments*)	
7	7	Yes (*no comments*)	
8	8	Yes (no comments)	
2.	**Is there any indication of bias in our synthesis of the evidence?**		
1	1	No (*no comments*)	
2	2	No (*no comments*)	
3	3	No (*no comments*)	
4	4	No (*no comments*)	
5	5	No (*no comments*)	
6	6	No (*no comments*)	
7	7	No (*no comments*)	
8	8	Yes: The actual title, "Effectiveness and Harms of proton irradiation treatment" seems to imply there is something bad with proton beam RT vs other forms of radiation therapy. While there have been studies reported with possibly worse than expected toxicities, these are entirely related to technique vs proton beam itself. For example, the partial breast proton beam series toxicity was related to the use of a single-beam, not protons itself. The more contemporary series from Loma Linda	We changed the title of our review to “Comparative Effectiveness of Proton Irradiation Treatment”

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		published earlier this year (D. Bush, IJROBP 2014) showed this quite nicely and was supported by the accompanying editorial from E. Strom. This theme continues with prostate, where the series from Shipley, published in the 1990's, used single perineal fields, an outdated technique. I think re-titling this, "Proton Beam Therapy: An Updated Review" would be more appropriate and less inflammatory.	
3.	**Are there any published or unpublished studies that we may have overlooked?**		
1	1	No (*no comments*)	
2	2	No (*no comments*)	
3	3	Yes: Systematic reviews of the past 5 years were included. Although it will not add value to the data and will not influence the overall conclusion, below three more reviews to add: • van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.Review. • Pijls-Johannesma M, Grutters JP, Verhaegen F, Lambin P, De Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A systematic literature review. Oncologist. 2010;15(1). Review. • Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. Semin Radiat Oncol 2013r;23(2):120-6. Review.	Thank you for suggesting these additional systematic reviews. We excluded the 2011 van de Water et al. publication because, as a review of in silico planning studies, it did not include any outcomes of interest for our review. We excluded the 2010 Pijls-Johannesma et al. publication because none of the included PBT studies included comparison groups. We excluded the 2013 Combs et al. publication because this systematic review included non-comparative studies and did not perform any pooling of studies or meta-analysis.
4	4	Yes - Grimm et al., 2012, mentioned in my review	Thank you for bringing this study to our attention. We added a discussion of Grimm et al. 2012 in the Prostate Cancer section.
5	5	Yes: Talcott JA et al, JAMA 303(11):1046-53, 2010. Fang P, et al. Cancer 2014 Epub, PMID: 25423899	Thank you for these suggestions. We excluded the 2010 Talcott et al publication because we could not isolate the effect of PBT since it compared two different doses of combined proton beam and photon

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
			therapies. Fang: Added
6	6	No (*no comments*)	N/A
7	7	Yes: Please see my written report	N/A
8	8	Yes: Receny partial breast RT series (Bush et al, PMID: 25084608)(Strom et al, PMID: 25304946)	Bush 2014 is already included. Strom 2014 is an editorial that provides interpretation of the differences between Galland-Girodet 2014 and Bush 2014; which are consistent with ours.
4.	**Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.**		
1	4	Pg. 1 line 10 “Dosimetric advantages are not theoretical. I would rephrase: "because of the physical properties of the proton beam, which can translate into dosimetric advantages for certain clinical situation..."	Changed to “appealing dosimetric characteristics”
2	4	Pg. 2 line 14 “It is critical to note that this trial was only for the partial-breast irradiation, which means only patients with Stage I cancer were eligible, and the partial breast concept is to eliminate the dose to lungs and heart. Therefore there is not much advantage for protons in the partial breast RT. HOWEVER, proton beam is a very interesting concept for patients with LEFT breast locally advanced cancer (Stages II and III), where the entire left chest wall needs to be irradiates. A regular 3D photon treatment exposes too much heart, with a 7.5% risk of coronary events for each Gray of RT to the heart. Protons can significantly spare the dose to the heart in these clinical scenarios. For patients with Left locally advanced breast cancer, proton beam therapy should be considered, if a regular 3D plan cannot achieve a heart mean dose of less than 5 Gy.”	We clarified that the patients in this trial were being treated for stage I breast cancer.
3	4	Pg. 2 line 38 “This dose (54.6 vs 52.9) is to the primary disease in the brain. Yes, protons allow for a very modest dose escalation to the primary disease, and it is not yet clear whether 1.7 Gy of difference leads to improved survival. However,	We thank the reviewer for these insights. No change needed.

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		protons allow for much less dose to the healthy brain parenchyma, and to Right and Left cochleas. This could lead to improved hearing and cognitive function with a long follow-up. In terms of esophagitis and nausea/vomiting - this comes from the toxicity of the spinal cord irradiation for medulloblastoma. The dose is the same with photons and with protons, but there is much less exit dose into the body cavity with all internal organs, which leads to better acute tolerance of treatment, and theoretically decreased risk of secondary malignancies in these organs, when patients are followed for longer than 15 years."	
4	4	Pg. 3 line 4 "Rephrase this: There is also insufficient evidence to draw conclusions of proton beam -based stereotactic ablative therapy for early stage lung cancer, in comparison to photon-based stereotactic ablative therapy."	We rephrased this sentence: "There is also insufficient evidence to draw conclusions about proton-based stereotactic ablative therapy for early-stage lung cancer compared with photon-based stereotactic ablative therapy."
5	4	Pg. 3 line 23 "Survival difference is known - there is NO survival difference. In prostate cancer, one cannot find a difference in survival between two treatment modalities - it takes over decades for prostate cancer failure to translate into survival difference. All studies of IMRT vs protons have used the same radiation dose, therefore the only question that was ever asked in these studies - is the quality of life and toxicity."	Deleted "but unknown survival" for IMRT and 3D-CRT comparisons. We take your point that calling out the lack of evidence on survival may lack relevance here given that finding a difference in survival at 5 years may not be plausible given the natural history of the disease.
6	4	Pg. 3 line 58 "It is critical to mention that the main disadvantage of this study was a very low number of patients analyzed, therefore any outcome is likely to be influenced by chance alone. Moreover, proton beam was not associated on a univariate analysis (table 4), therefore it is more likely that selection of patients for proton beam was influenced more by worse pathology and size of the tumor, inability to resect the tumor, etc, rather than the choice of therapy itself."	We agree with the reviewer that the strength of the evidence is low due to the mentioned methodological limitations and have described these in the full results section. No change needed to the Executive Summary.
7	4	Pg. 4 line 7 "Why you have not included a special section on chordoma and chondrosarcoma of the spine and base of skull? These are pathologies that SHOULD only be treated with	We did not identify any comparative studies in chordoma or chondrosarcoma patients so did not include a separate section for these conditions. In our

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		protons at this moment, as there is no data that photon-based therapy is equivalent to results achieved with protons."	introduction we cite a VA Memorandum that acknowledges the improved safety of radiation delivery to sacral and base of skull chordomas.
8	4	Pg. 4 line 13 "Evaluation of recurrent tumors is very patient-specific. If patient has a locally recurrent tumor with no evidence of metastatic disease, and re-irradiation offers a second chance of cure, then attention should be drawn to the cumulative dose to the organs, when previous and present treatment plans are combined. If dosimetrically, the physician cannot achieve a dose high enough for tumor control, without damaging normal structures, based on their radiation tolerance, and a physician can show that a proton beam therapy can improve this, then there is an indication for proton beam therapy."	We appreciate the reviewer's rationale for the role of proton beam therapy in recurrent tumors. We do not think that Mizumoto 2013 and Otsuka 2003 are the last word on proton beam for recurrent tumors and would strongly encourage this as an area for future research efforts.
9	4	Pg. 4 line 39 "This is not true. A SEER-based publication showed fewer secondary malignancies for kids treated with proton vs photons (Chung et al., 2013). Therefore when one applies the same criterias for young adults (young men with seminoma, young women with breast cancer or lymphoma), the same principle applies to this population - less normal tissue exposed to overall radiation translates into fewer secondary malignancies. This cannot be applied to elderly population, as it takes at least 15 to 20 years to develop secondary malignancy after RT, but for young adults this is very applicable."	Yes, Chung 2013 is included in our review. But it is retrospective, not prospective, so this statement is correct and relevant. But, we have added a section about its findings to the Executive Summary.
10	4	Pg. 9 line 32 "you mean genetic?"	We rephrased this sentence to more clearly reflect ASTRO's model policy: "The American Society for Radiation Oncology supports the use of PBT for ocular tumors, tumors that approach or are located at the base of the skull, certain tumors of the spine, primary hepatocellular cancer treated in a hypofractionated regimen, solid tumors in children treated with curative intent, and in patients with genetic syndromes for whom minimizing the total volume of radiation is
11	4	Pg. 9 line 33 "Hepatocellular carcinoma has nothing to do with the genetic syndromes. It is all about how much of normal liver receives radiation therapy. At least 700 cc of normal liver should be completely spared of any radiation dose in order for treatment to be safe and for patients not to develop radiation-induced liver disease (RILD). This means that with proton beams, larger tumors can be safely irradiated, in comparison to	

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
		photon-based treatment."	crucial."
12	4	Pg. 10 line 19 "An additional expense that comes with proton beam therapy is the need to create brass apertures for each beam used on an individual patient. This requires special facilities, specially trained personnel. The cost of brass material is very high."	Thank you for this information. We added the following sentence: "Additional expenses associated with PBT is the creation of individual brass apertures for each beam, requiring special facilities and personnel."
13	4	Pg. 15 line 53 "Massachusetts General Hospital and MD Anderson. The prostate randomized trial was started at Mass General Hospital, the second institution that joined the trial is UPenn. Lung Cancer was a collaborative work between MGH and MDACC."	We altered Appendix G and updated this sentence: "These ongoing studies are being conducted at the University of Texas MD Anderson Cancer Center, Massachusetts General Hospital and the University of Pennsylvania as well as other centers in the US and abroad."
14	4	Pg. 26 line 4 "partial breast treatment for early stage breast cancer. It is very crucial to distinguish whole breast treatment or chest wall treatment with radiation therapy for advanced breast cancer vs partial breast treatment for patients with Stage I breast cancer."	We altered the title of table 4: "Strength of evidence (SOE) for comparative benefits and harms of PBT or photons or mixed photons/electrons in partial breast treatment for early-stage breast cancer"
15	4	Pg. 27 line 16 "Exactly! The effectiveness of both treatments was the same. When patients die from the spinal cord glioma, they die from the local disease progression. The fact that the local recurrence rates were the same puts the multi-variable analysis under suspicion, that it inappropriately adjusted for large difference in age and made proton beam therapy look horrible, whereas on univariate analysis there was no difference. I am worried that this inappropriate analysis will make proton beam look so much worse for the spinal cord gliomas, where in reality the effectiveness dose per dose is the same."	Yes, we also have low confidence in the stability of this estimate for the reasons you've mentioned, including the insufficient sample size and the inconsistency between the univariate and multivariate analyses. For these reasons, we have rated the strength of this evidence as low.
16	4	Pg. 28 line 48 "Poorly worded. Effectiveness of combination of protons with photons vs photons alone?"	We rephrased this sentence: "We identified one poor-quality retrospective comparative cohort that evaluated the clinical effectiveness of combination proton and photon treatment versus photon-only treatment in giant cell tumor of bone."

Comment #	Reviewer #	REVIEWER COMMENT	RESPONSE
17	4	Pg. 31 line 41 “Proton-based Ablative RT vs photon-based ablative RT for early stage NSCLC.”	We rephrased this heading: “Proton-based Ablative RT versus photon-based ablative RT for early stage NSCLC”
18	4	Pg. 32 line 30 “for locally advanced NSCLC”	Added to this heading: “PBT versus IMRT or 3D-CRT for locally advanced NSCLC”
19	4	Pg. 39 line 38 “I am not sure this is relevant now. Almost everyone agrees that IMRT is superior to 3D-CRT for high-dose RT to prostate (over 70 Gy), therefore no one is treating patients with localized disease without IMRT.”	Thank you for this comment. As the scope of our review includes both conventional and state-of-the art therapies, we included this evidence for the sake of completeness
20	4	Pg. 41 line 18 “There is a meta-analysis of various treatment modalities for prostate cancer which indicates that brachytherapy is superior to all forms of external beam RT, including proton beam therapy. Grimm et al., BJUI 2012. If you look at the names of co-authors, you will see that these are all leaders of the prostate cancer treatment in radiation oncology. I think it is important to incorporate this study.”	Thank you for bringing this study to our attention. We added a discussion of Grimm et al. 2012 in the Prostate Cancer section.
21	4	Pg. 41 line 38 “The "boost" was only a few fractions at the very end of the treatment. The main question of this randomized trial at MGH was to determine whether increasing the dose beyond 70 Gy, what was considered standard back then with 3D-CRT would improve the outcomes, not the protons. But since the trail was done at MGH where protons are available, the study used protons for the last five fractions. So this study is really about 79.2 Gy vs 70 Gy of radiation therapy, not about photons alone vs photons + protons.”	We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a “boost” of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
22	4	Pg. 44 line 32 “$p<0.01$”	Added.
23	4	Pg. 44 line 41 “These patients were treated for non-metastatic disease, using standard treatments doses, therefore we can be sure that the doses were comparable, if not exactly the same, diagnosis for diagnosis.”	We disagree. Although patients were matched by treatment site and histology in an attempt to control for irradiation volume, we still cannot be completely sure radiation dose and field size were comparable.
24	4	Pg. 44 line 60 “Yes!!! This is the MAIN criticism and argument against this article. We do not anticipate to see 2nd malignancy	Agreed.

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		during the RT within the first 5 years, more likely to develop these malignancies in 15 years or longer."	
25	4	Pg. 45 line 37 "This is a situation where there will be no data. It is similar to taking very difficult surgical cases and trying to determine which technique led to improved outcomes. Based on the amount of disease, prior radiation therapy plan, patient's anatomy, physician should be able to decide how best to approach the treatment - and if proton beam allows for less dose to previously irradiated organs, then protons will be superior. Similar to open vs laparoscopic surgery - surgeon decides at the time of surgery which technique is necessary for best visualization/access, etc, and that in theory should be left to the physician to decide and will never be analyzed in literature."	It is precisely because this is a particularly difficult to treat population that this is a worthwhile question to ask. Knowing whether patients with recurrences are more or less likely to benefit from proton therapy compared with other alternatives could be particularly useful when, in general, recurrent tumors may be less sensitive to all treatments. And, in fact, there are already studies that have evaluated the comparative effectiveness of proton therapy in recurrent tumors.
26	4	Pg. 46 line 53 "It is incorrect to say that proton therapy is less beneficial in patients with recurrent tumors. The correct statement is: 'Any treatment form is less effective in the setting of disease recurrence.' This is primarily driven by two factors: often patients have metastatic disease at the time of recurrence, and if the tumor comes back, it is more likely to be less sensitive to treatment effect. Therefore physicians always tell patients that the effectiveness of treatment is lower in the setting of disease recurrence. Don't state that this is specific to proton beam therapy."	Thank you for this information. We replaced this sentence with: "Any treatment form is less effective in the setting of disease recurrence, including proton therapy."
27	4	Pg. 47 line 7 "Have all the confidence in the world with this statement! It has absolutely nothing to do with protons! The same can be shown for brachytherapy, surgery, external beam RT, chemotherapy, you name it! Cancer at the time of recurrence is always worse than at the time of the new diagnosis."	Agreed, our point is not about protons. It is that the reduced benefit of protons for recurrent vs primary tumors seen in these studies is likely not entirely due to the inherently worse prognosis for recurrences, given the potential for confounding due to differences in radiation dosage, years of treatment and patient age.
28	4	Pg. 47 line 20 "What this means is that experience with proton beam is more important than the experience with photon therapy. A fresh proton beam facility with minimal experience	We thank the reviewer for this insight. No change needed.

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		is likely to have initially worse outcomes than a proton beam facility with 20 years of experience. It is similar to neurosurgeons who are fresh out of residency programs, vs experienced surgeons."	
29	4	Pg. 51 line 13 "again, chordoma and chondrosarcoma have only successfully been treated with protons, so it is up to IMRT-based treatment studies to prove IMRT is just as good. Uveal melanoma is also can be treated with brachytherapy or proton beam therapy, IMRT-based therapy is not used for uveal melanoma."	We did not identify any comparative studies in chordoma or chondrosarcoma patients so did not include a separate section for these conditions. In our introduction we cite a VA Memorandum that acknowledges the improved safety of radiation delivery to sacral and base of skull chordomas. We altered this sentence: "For all cancer sites and types, except for ocular and pediatric cancers which were not reviewed here…"
30	4	Pg. 51 line 40 "again, only in the setting of PARTIAL BREAST IRRADIATION. This should be stated very clearly, that this does not apply to whole breast RT situations."	We rephrased the beginning of this sentence: "Increased harms include that (1) for partial breast irradiation, various skin toxicities are more common with PBT than with 3D-CRT when PBT is delivered in single-fields…"
31	4	Pg. 51 line 46 "again, would not use this study to claim that proton beam causes more death."	Agree that Kahn 2011 has major deficiencies and provides only low-strength evidence. We added the low-strength evidence qualifier to our statement about Kahn's 2011 findings.
32	4	Pg. 53 line 53 "Not true."	We altered Appendix G and updated this sentence: "Many of these ongoing studies are multi-site and are being conducted at MD Anderson Cancer Center, Massachusetts General Hospital, and the University of Pennsylvania as well as other centers in the US and abroad."
33	4	Pg. 54 line 19 "I think the conclusion is pretty nihilistic. A current randomized study of protons vs IMRT for prostate cancer as done at MGH and UPenn is actually a very good study, well designed, with all biases controlled, that will show	Changed to: "Although numerous randomized controlled trials are underway that carry the promise of improved toxicity measurement, it is unclear whether they will fully address gaps in evidence on other

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		whether there is any difference in rectal toxicity."	important outcomes including recurrence, ability to deliver planned chemotherapy and radiation regimens, functional capacity, overall severe late toxicity, and secondary malignancies"
34	1	Table 1, page 3, Harms column. For each entry, make explicit which is the reference arm. For IMRT on lines 23-27, it appears proton beam is compared to IMRT (in that order, so PB is the reference) and proton beam has higher GI toxicity with HR = 3.32. However, in lines 29-35, the order appears to be reversed (IMRT vs PB) with IMRT now the reference and with RR of less than 1, so proton beam is again more toxicity. This change in reference is prone to confusion. This is repeated in Table 2, page 5.	Thank you for this suggestion. We clarified the reference group for every measure of association listed in a table.
35	2	Conclusions stated within the tables, such as Table 15, are occasionally unclear. Though the accompanying text clearly attributes relative benefits or harms to the appropriate radiation modality, table entries are less clear.	We labeled all outcomes by treatment group in tables throughout the report.
36	3	This report represents a review on the clinical evidence of proton therapy as compared to conventional/state of the art photon therapy. This systematic review was very well performed, including a risk of bias analysis. Methodological I have nothing to add. Systematic reviews of the past 5 years were included. Although it will not add value to the data and will not influence the overall conclusion, below three more reviews to add: • van de Water TA, Bijl HP, Schilstra C, Pijls-Johannesma M, Langendijk JA. The potential benefit of radiotherapy with protons in head and neck cancer with respect to normal tissue sparing: a systematic review of literature. Oncologist. 2011;16(3):366-77.Review. • Pijls-Johannesma M, Grutters JP, Verhaegen F, Lambin P, De Ruysscher D. Do we have enough evidence to implement particle therapy as standard treatment in lung cancer? A	Thank you for suggesting these additional systematic reviews. We excluded the 2011 van de Water et al. publication because, as a review of in silico planning studies, it did not include any outcomes of interest for our review. We excluded the 2010 Pijls-Johannesma et al. publication because none of the included PBT studies included comparison groups. We excluded the 2013 Combs et al. publication because this systematic review included non-comparative studies and did not perform any pooling of studies or meta-analyses.

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		systematic literature review. Oncologist. 2010;15(1). Review. • Combs SE, Laperriere N, Brada M. Clinical controversies: proton radiation therapy for brain and skull base tumors. Semin Radiat Oncol 2013r;23(2):120-6. Review. Although disappointedly, mainly due to lack of evidence, I fully agree with the overall conclusions that was drawn by the authors. I have no additional comments.	
37	5	Overall, this is an outstanding article and demonstrates that the authors have an impressive insight into radiation treatment and outcomes.	Thank you.
38	5	Please see two suggested articles (Talcott, Fang), which add to the literature (and perhaps level of overall evidence) on comparative patient-reported outcomes of proton vs photon for prostate cancer.	We excluded the 2010 Talcott et al publication because we could not isolate the effect of PBT since it compared two different doses of combined proton beam and photon therapies. Added Fang 2014
39	5	In the lung sections, it may be worthwhile for the authors to examine whether IMRT is deemed "standard of care" for this disease. I think many insurers do not cover IMRT routinely for lung cancer radiation treatment. This consideration provides important practical insight to the reader of this review, in terms of the proton vs 3DCRT (standard) and proton vs IMRT (not standard) comparisons.	Defining the standard of care is outside of the scope of this review as it may vary across health systems and over time and may incorporate other information (*eg*, clinical expert input, cost, adherence)
40	5	For prostate cancer, it is important to note that the randomized trial of PBT+photon vs photon alone used different doses in the 2 arms. This is an important detail that was left out of the review. Some would interpret the data from this trial to suggest that proton can be used to safely increase dose of prostate cancer radiation without increasing toxicity. It is also important to note that the photon used in this trial was not IMRT. So this trial does not directly provide evidence on the toxicity outcomes of PBT vs IMRT for prostate cancer.	We amended the discussion of PBT+photon versus photon alone in the prostate cancer section to include information on the delivered dose in each treatment group of the three included studies.
41	5	Table 4 and other tables: it would be helpful to label the outcomes. For example "7-year cumulative local recurrence:	Thank you for the suggestion. We labeled all outcomes by treatment group in tables throughout the report.

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		11% vs 4%" – which is PBT and which is photon? I can give a good guess based on the data, but labeling this in the Tables would be even better.	
42	5	Page 38, the significant space used for criticisms of the Sheets et al study seems way out of proportion with the rest of the document, and suggests bias by the authors. As the authors note, all of the literature comparing PBT to photons have significant flaws – but the criticisms of this one study took up almost an entire page of space and seems unusual. The language of "widely criticized" to describe this study seems especially harsh, especially given the context that the 3 cited letters-to-the editor all came from physicians from proton centers, who may have inherent bias and financial conflicts of interest. To provide full disclosure, I am one of the authors of that study and am able to provide further insight on the limitations of the study. The reason that critiques were not all fully answered was because of the significant JAMA word count limitations for author responses. The criticism of using surrogate measures and data from few proton institutions – apply to all SEER-Medicare studies (include Kim et al, and Yu et al), not just the Sheets study. Frankly, until 2006, there were only 2-3 proton centers treating prostate cancer in total. I believe it is inappropriate to directly translate results from the Sheets study to institutional series. The institutional series reported % of patients with toxicity attributed to radiation treatment. The Sheets (and Yu and Kim) studies examined % of patients who had a diagnosed GI or GU morbidity, or had GI or GU procedures after radiation treatment. These are very different outcomes, and one cannot be calculated to compare to the other. Patients can have GI or GU diagnosed morbidity or procedures not related to radiation treatment, which are counted	We streamlined our discussion of the Kim 2011 and Sheets 2012 weaknesses to focus on the similar and well-accepted problems in both with exposure and outcome assessment methods: "*GI toxicity at 4-5 years.* Two fair-quality, population-based retrospective cohort studies of Medicare claims data linked to the Surveillance Epidemiology and End Results (SEER) database provide low-strength evidence of an increased risk of late GI toxicity at 4-5 years (Table 16).[9,10] The first of the SEER-database studies, by Kim et al, included patients diagnosed with early-stage localized prostate cancer between 1992 and 2005 and used ICD-9 or CPT procedure codes to assess grade 3 to 4 bleeding, ulceration, fistula, stricture, and colostomy that developed at least 6 months after diagnosis and required intervention.[9] The second of the SEER-database studies, by Sheets et al, assessed risk of unspecified GI morbidity-related procedures (including colonoscopy) and diagnoses that occurred at least 12 months after diagnosis in patients diagnosed with early-stage prostate cancer between 2000 and 2007.[10] The main limitations of both studies include their high potential for exposure and outcome misclassification biases.[67-69] Regarding exposure ascertainment, risk of bias was high because dose and field size specifics were unknown; therefore, the increased risk of late GI toxicity with PBT may have been entirely due to higher doses. Regarding outcome ascertainment, risk of bias was high because of the questionable reliability of using surrogate procedure (including colonoscopy) and

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		as events in the SEER/Medicare studies – with unclear attribution to radiation treatment, but with the assumption that underlying events unrelated to treatment should be similar between PBT and IMRT patients. There is an underlying "baseline" event rate in these elderly patients (many elderly patients have GI or GU problems anyway). But differences found in event rates between PBT and IMRT patients are possibly due to treatment outcome differences. If there is bias, the bias should favor PBT patients who are usually younger, healthier, and can travel longer distances to receive treatment – and therefore may have lower baseline event rates than photon patients. The criticism about photon with lower dose than PBT: this applies to all 3 SEER/Medicare studies. Further, the Sheets study directly addresses the common claim by proton center physicians that proton treatment can deliver a higher dose to the prostate safely, therefore increase cure rate compared to IMRT. In fact, if indeed PBT patients received a modestly higher dose than IMRT in the Sheets study, the results do not support these claims – there was no higher cure rate, and morbidity was higher.	diagnosis code-based measures to detect the actual clinical events of interest. Also, both studies may suffer from potential confounding by study site since likely a high majority of proton patients were treated at the single Loma Linda study site, whereas IMRT patients were likely treated at a variety of sites."
43	5	Applicability section, page 52: "more or less experience." It is unlikely that newer proton facilities would have "more" experience compared to the facilities that have been treating patients for many years/decades.	We changed this sentence to read: "First, the majority of the proton beam treatment groups came from one of 3 proton facilities that are among the oldest in operation (Loma Linda, MD Anderson, or Massachusetts General). It is unclear whether the patient outcomes of these centers would generalize to other facilities with less experience treating patients and that may have difference standards of care."
44	5	Page 53: It is worth noting that some dosimetric comparison studies show that PBT can have worse dose distribution compared to IMRT. For example, in prostate cancer, PBT vs IMRT delivers higher doses to the femoral heads, and more	Changed to: "Other clinicians and experts in radiation oncology question whether PBT's dosimetric characteristics translate into measurable clinical benefits or increased survival for patients."

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		high dose to the bladder. The statement of "obvious superior dose distribution" is not always true.	
45	6	This was a well written review of the evidence for the treatment of adult cancers with proton radiotherapy. The authors have done an outstanding job collecting all the comparative studies.	Thank you.
46	6	Page 3, Table 1. "IMRT" Comparator: "Harms" column: The Yu et al. (ref 11) did not find increased late GI toxicity. Also, in the "Benefits" column for the "IMRT" Comparator: the Yu et al. (ref 11) paper found transiently lower GU toxicity for 0-6 months after treatment.	Moved Yu 2013 citation to statement about similar acute toxicity at beginning of sentence; added evidence on transient GU advantage at 6 months.
47	6	Page 4: Rather than simply saying "hemangiomas", which can occur anywhere, I would specify "uveal hemangiomas", which given their location in the eye there is much more impetus to use proton beam radiotherapy. I would replace "hemangiomas" throughout the whole review with "uveal hemangiomas."	We made this change throughout the report.
48	6	Page 5: Table 2: Prostate row "-vs IMRT": the Yu et al. study found a transiently lower GU toxicity for 0-6 months after treatment but no long term differences. This is a potential advantage. For the disadvantage row "-PBT + photon vs photon alone:" the comparison is a little difficult to make as the "PBT+photon" was a higher dose than the photon alone. The study cited (Shipley et al) was testing PBT as a boost therapy. This would be clearer if the row reads "-PBT Boost + Photon vs photon alone". Furthermore, the Shipley et al study used much older radiotherapy techniques, and so should not be indicative of current outcomes and is of limited relevance. The same can be said for Duttenhaver et al.	Added evidence on transient GU advantage at 6 months We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a "boost" of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
49	6	Page 9 – line 60: "with 9 additional centers under construction." I believe 10 centers are under construction (Mayo is constructing 2 centers in different locations).	We changed the number of centers under construction to 10.
50	6	Page 22: Row "Esophageal". The Wang paper seems to indicate	It is difficult to compare these two studies because they

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		that pulmonary complications are improved with PBT, but the McCurdy reports the opposite – that PBT is associated with greater complications – specifically pneumonitis. Given this conflicting data – should not the evidence considered inadequate?	report very different outcomes: Wang reports a 30-day broad composite outcome of any pulmonary complication and McCurdy reports a 3-month specific outcome of pneumonitis. We evaluated them separately for this reason.
51	6	Page 23: Line 28: GI toxicity was not worse in the Yu 2013 study, but in the Kim 2011 study. Also, the Yu 2013 study showed transient genitourinary benefits for proton beam (as noted above in comments 1 and 3)	Moved Yu 2013 citation to statement about similar acute toxicity at beginning of sentence; added evidence on transient GU advantage at 6 months.
52	6	Page 24: Line 11: again, the "PBT + Photon" would be clearer if it was "PBT boost + photon". Though there were higher rectal bleeding with PBT boost, it was a higher dose of radiation (75.6 CGE vs 67.2 Gy). Duttenhaver et al also used a higher dose for the proton arm. This is also noted above in comment 3.	We altered our discussion of both Shipley et al. 1995 and Duttenhaver et al 1983 to emphasize that these studies used a "boost" of protons in addition to photon therapy and that this combined group received a larger overall dose compared with the group that received photon treatment only.
53	6	Page 26: General comment re: CNS cancers. There is some evidence / consensus in the medulloblastoma literature that for pediatric cancers there is long term benefit in terms of IQ, etc. I'm not sure whether this is important for the VA ESP.	Thank you for this information, but reviewer is right that pediatric outcomes are not relevant to this review.
54	6	Page 28: "Giant cell tumor" – would be better to entitle this section "Giant cell tumor of the bone."	We made this change throughout the report.
55	6	Page 30: "Hemangioma" – would be better to entitle this section "uveal hemangioma."	We made this change throughout the report.
56	6	Page 41: Line 34: Again, it should be emphasized that PBT and photon therapy was to a greater dose than photon therapy alone in the Shipley study. It also used older technique and is so dated that the findings are not helpful to the technology assessment of PBT in current practice.	We amended the discussion of PBT+photon versus photon alone in the prostate cancer section to include information on the delivered dose in each treatment group as well as noting that the radiotherapy techniques used in Duttenhaver 1983 and Shipley 1995 are outdated.
57	6	Page 49: Line 31: "Giant cell tumor" again would be better to write as "Giant cell tumor of the bone"	We made this change throughout the report.
58	6	Page 49: Line 37: "Hemangioma" again would be better as	We made this change throughout the report.

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		"Uveal Hemangioma"	
59	7	Overall this is a very well-researched and written summary report and reasonably current. As the report outlines, 4 key strategies were utilized, a literature review, a summary of clinical trials, review of coverage policies by various insurance companies, and review of prior summary reports, and this report clearly highlights one major limitation of any such exercise, that this field is extremely dynamic and fluid, and therefore, obsolence is a very rapid phenomenon, rendering most prior reports significantly out-of-date.	Thank you.
60	7	As key examples of this rapid obsolence, while the report was being commissioned, several new pieces of data were presented at the PTCOG-NA meeting in October 2014, and most of these have not made it into the current report.	We thank the reviewer for this information. We reviewed the abstract book from the October 2014 PTCOG-NA meeting and identified one comparative study on head and neck cancer which we now include in that section of the report (Abstract #33, P.B. Romesser, O. Cahlon, E. Scher, Y. Zhou, T. Leven, R. Wong, N. Riaz, S. McBride, N.Y. Lee).
61	7	A second important example of the rapidly shifting field, is the update to the NCCN guidelines; for example, the 2015 Prostate Cancer NCCN guidelines now include the following phrase: "conventionally fractionated prostate proton therapy can be considered a reasonable alternative to x-ray based regimens at clinics with appropriate technology, physics, and clinical expertise." (The 2014 version provided as follows: "proton therapy is not recommended for routine use at this time. Research hasn't shown proton beams to be the same or better for treating prostate cancer than conventional external beams.") This is a very clear example of how within 1 year, there is a dramatic change even in NCCN coverage language relative to protons. Further examples of this significant and rapid change in recommendations will be highlighted in disease-specific categories.	Thank you for this information. We added the most recent guidelines issues by the NCCN regarding PBT for prostate cancer: "An ongoing prospective randomized trial is accruing patients and comparing prostate proton therapy to prostate IMRT. The NCCN panel believes there is no clear evidence supporting a benefit or decrement to proton therapy over IMRT for either treatment efficacy or long-term toxicity. Conventionally fractionated prostate proton therapy can be considered a reasonable alternative to X-ray based regimens at clinics with appropriate technology, physics, and clinical expertise."
62	7	Pencil Beam Scanning (PBS) Intensity Modulated Proton	We discuss PBS in the Introduction, but added a

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		Therapy (IMPT): In the last 3+ years, a dramatic technological change has occurred in this field, *ie* the rapid and almost immediate adaptation of PBS IMPT over the historic spread-out Bragg peak (SOBP) approach; this is widely, and almost universally recognized as having multiple advantages such as superior dosimetry, and more importantly the robust ability to expand the reach of proton therapy into various organ sites and disease categories, not historically treated with SOBP because of technical limitations; this major technological advance potentially has huge clinical implications and the development and consequences of this aspect have largely been ignored in this report; going forward, significant data are expected to emerge for PBS, and therefore, a focus on this technology is crucial for any such report.	mention of the lack of studies on the newer PBT delivery systems and methods (*ie*, pencil beam scanning) to the 'Gaps in Evidence' section of the Discussion
63	7	Breast Cancer: This disease has historically not been the focus of proton therapy, primarily because prior to approximately 3+ years ago, the technology did not permit easy delivery of whole breast and regional nodal irradiation, a scenario that has changed dramatically with the advent of PBS IMPT. Therefore, it is now technically feasible to expand the role of proton therapy to much beyond partial breast irradiation, which is what was primarily discussed in the VA report. Two key clinical facts have also created a "perfect storm". There are now 2 randomized clinical trials that underscore the fact that in several subcategories, regional nodal irradiation, especially internal mammary (IM) irradiation improves overall survival, making this an integral component of future therapeutic approaches (Budach, 2013). An unfortunate consequence of this is the guaranteed increase in cardiac dose, relative to treatment planning that avoids the internal mammary nodal chain. A seminal long-term cohort study published in the NEJM in 2013 by Darby et al, very convincingly established that the adverse cardiac outcome risk level is directly proportional to the mean heart radiation dose, and therefore, although IM irradiation is	Added: "With the advent of intensity-modulated proton therapy (IMPT), it may now be more feasible to expand the role of PBT beyond partial breast irradiation. However, we found no IMPT for whole breast or nodal irradiation. It will be important to consider whether IMPT can improve on the 7.4%-per-gray rate for major coronary events within the first 5 years observed in a population-based case-control study of 2168 women who underwent external radiotherapy for breast cancer between 1958 and 2001 in Sweden and Denmark. [56]"

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		now the new standard, women receiving this will be expected to have a categorical increase in late adverse cardiac events, some delayed by 10+ years, as a consequence of increased mean heart dose. Numerous dosimetric studies in the literature have demonstrated the categorical, and unquestioned superiority of proton beam therapy over photon therapy (something that is analogous to an in-silico randomized trial) in terms of decreasing cardiac dose. Further, as more and more cardiotoxic systemic therapies, such as Adriamycin, and anti-her2 agents are combined in the management of non-metastatic breast cancer, the risk to these women of developing late cardiac toxicities should not be underestimated; in this context, relying on the low level evidence regarding the MGH partial breast irradiation papers is not an appropriate approach to making a determination regarding the development of VA recommendations for whole breast and nodal irradiation, especially because a short-sighted approach could result in subjecting a large number of women with breast cancer to late cardiotoxicity which may not become apparent for a decade or more, and in addition to the negative clinical consequences of this approach, the global cost of managing these cardiac toxicities would most likely exceed the up-front investment in treating such women with proton therapy. The VA should therefore seriously consider either launching its own trial, or whole-heartedly supporting the randomized and non-randomized efforts currently in development to test proton vs photon therapy for breast cancer, at least for women who need whole breast and/or chest wall irradiation, especially in the event that they also need IM irradiation, and also for those women who have other underlying cardiac risk factors. This is an absolutely key healthcare consideration, and a major focus of the future VA effort, in cognizance of the dramatic increase of women as a proportion of our veterans.	
64	7	Prostate Cancer: The biochemical progression free survival	Yes, we agree that dose considerations are key and we

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		improves as function of dose, and modern conventionally fractionated approaches requires doses in the order of 78+ Gy.	are hopeful they are being better addressed in ongoing studies. The dose in the new Fang 2014 study, for example, was 79.2 Gy.
	7	Prostate Cancer: Retrospective comparisons of databases, most notably the SEER database suggests that the disease-related clinical outcomes are comparable for photon versus proton treated patients, and some toxicities might in fact be higher in frequency in the proton cohort. These retrospective comparisons, in fact, are seriously flawed; radiation toxicities are a function, among other things, of total dose. In the comparative studies that have been referenced, no dose-correction was applied; in fact most proton patients were treated to higher doses. Further, most of the proton patients received a combination of photons and protons, and the reported toxicities are largely artefactual because of the fact that the photon treated patients were not on any trials, whereas several of the proton treated patients were, with the trial requiring a more intense level of scrutiny, including the use of endoscopies, one of the endpoints reported on by the Shelby study.	Yes we fully agree with this reviewer's criticism and have discussed in detail their high potential for exposure and outcome misclassification biases
65	7	Prostate Cancer: The very large University of Florida experience with protons which reports (in a non-randomized context, and therefore subject to bias) some of the best clinical outcomes for prostate cancer following radiotherapy, ever reported (Hoppe et al, IJROBP, 2014).	We clarified with the reviewer that he is referencing: Mendenhall NP, Hoppe BS, Romaine NC, et al. Five-year outcomes from 3 prospective trials of image-guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(3):596-602. This is a noncomparative study in which all patients received proton beam therapy. We had already been aware of this study, but did not discuss its findings because it did not compare outcomes with any other radiation modality. Although its results are promising, as the study authors themselves admit, it does not address remaining concerns about comparative effectiveness.
66	7	Prostate Cancer: The elegant very recently reported case-matched study of protons versus photons for prostate cancer	Thank you for this information. We added Fang 2014 to our analysis.

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		from the University of Pennsylvania, which does not show the increase in rectal/GI toxicities and colonoscopies attributed to the SEER study (Fang 2014).	
67	7	Prostate Cancer: The very significant comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer (Hoppe et al, cancer 2014) which compared patient-reported quality-of-life (QOL) outcomes after proton therapy (PT) and intensity-modulated radiation therapy (IMRT) for prostate cancer, performed on prospectively collected QOL data using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. PT was delivered to 1243 men at doses from 76 to 82 Gy. IMRT was delivered to 204 men who were included in the Prostate Cancer Outcomes and Satisfaction with Treatment Quality Assessment (PROSTQA) study in doses from 75.6 Gy to 79.4 Gy. No differences were observed in summary score changes for bowel, urinary incontinence, urinary irritative/obstructive, and sexual domains between the 2 cohorts. However, more men who received IMRT reported moderate/big problems with rectal urgency (P = 0.02) and frequent bowel movements (P = 0.05) than men who received PT. These outcomes highlight the need for further comparative studies of PT and IMRT.	We agree that the Hoppe et al study published in Cancer in 2014 provides important information on QOL outcomes for prostate cancer patients treated with IMRT or PBT. This study has already been included in our discussion of IMRT vs PBT for prostate cancer.
68	7	Prostate Cancer: Proton therapy has become widely accepted as a key standard of care by thousands of men with prostate cancer, especially when it comes to assessing patient satisfaction, and reporting patient-based outcomes; in fact the quality of data for proton therapy far exceeds anything that is available for photon therapy in this context, especially when one recognizes the “power of numbers”. As an example, at the National proton Conference in April 2014, the National Association of Proton Therapy (NAPT) released a patient-centered report on the outcomes following proton therapy for	Thank you for this information. Since we did not include patient satisfaction as an outcome and the report that you reference did not compare prostate cancer patients that received photon modalities, this study does not meet our inclusion criteria.

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		prostate cancer in almost 4000 men treated at 12 different proton centers, with the following key observations: 1. 96% have recommended proton therapy to others 2. 98% rated their proton therapy experience as “excellent” or “good” 3. 98% believed they made the best treatment decision for themselves 4. 96% were “satisfied” or “extremely satisfied” with their proton therapy treatment 5. 85% reported that their quality of life was “better than” or “the same as” before their treatment. Collectively, these data very strongly suggest that modern proton therapy, especially PBS, deserves to be seriously incorporated and evaluated as an option for men with prostate cancer, either in the context of a prospective longitudinal multi-institutional cohort study, or a randomized trial, with the VA being a key player in either or both efforts, given the extremely high patient satisfaction ratings for this therapy.	
69	7	Lung Cancer: For NSCLC, the factual elements in play are a categorical dose-response relationship favoring higher dose radiotherapy in terms of improved loco-regional control, but the review also categorically demonstrates that the major US trial seeking a survival benefit from this dose-escalation strategy failed; however, there are several important observations that are missed in this top-line conclusion: a. There is already a previous, randomized phase III trial from China that shows a categorical survival improvement with higher doses (Chen et al., 2013). b. More detailed analysis of the RTOG trial demonstrates that the likely cause of “endpoint failure” was excess toxicities associated with higher doses, especially higher cardiac and pulmonary doses (Cox et al., 2012). c. An analysis of technique in the RTOG trial shows that when “tissue-sparing” IMRT techniques were employed (in	We agree that these studies do not provide conclusive evidence on the comparative effectiveness of PBT and look forward to evidence from additional ongoing RCTs

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		comparison to 3-D techniques), patient reported QOL (using the FACT-L TOI tool) was superior, and translated to a survival benefit, underscoring the enormous significance of decreasing cardiac and lung dose, something that PBS has been shown in several dosimetric studies to achieve readily. At this point, several randomized trials are evaluating the photon versus proton question in various stages and clinical presentation of NSCLC, and the VA would be ideally positioned to contribute to this in a major way.	
70	7	Esophageal Cancer: The review appropriately summarizes the data, in particular highlighting the key observation of decreased mortality in the context of trimodality therapy, in favor of proton therapy, underscoring the need and value in supporting such an approach, ideally in a prospective multi-institutional registry trial, or perhaps even through a prospective randomized trial.	Thank you for confirming our findings.
71	7	Medulloblastoma: This is an uncommon disease in the adult context; however, the data that exist show a very dramatic reduction in several toxicities, and given the very dramatic toxicities from photon therapy for large field irradiation, especially craniospinal, this should be considered as a default indication in favor of proton therapy.	Thank you for confirming our findings.
72	7	Head and Neck Cancer: Emerging data from the ongoing randomized MDACC trial very strongly favor consideration of PBS IMPT in several forms of H/N cancer. The extent of reduction in radiation dose to several H/N substructures is very dramatic, and emerging data regarding acute toxicities and cost effectiveness lean toward IMPT. Given the relatively high incidence of this diagnosis in the VA patient population, a major opportunity exists to support the ongoing trials and categorically establish the value in this disease.	We look forward to the final results of the MDACC trial.
73	7	Ocular Tumors: Although not reviewed, PBT is an obvious choice for these tumors.	Agreed. It was not reviewed because the VA already covers PBT for ocular melanomas.

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74	7	Skull base and Brain Tumors: For several tumors in this category, such as chordoma, chondrosarcoma, and possibly craniopharyngioma, low grade glioma, meningioma, etc., PBS IMPT is the logical therapy; for example, the high radiation doses necessary to control chordoma simply cannot be delivered with photon therapy; meningiomas represented a logical target for PBS IMPT, given that radiation the the meningeal surface is one of the few known causes of this condition, and photons would irradiate a dramatically larger volume of meninges, etc.	Agreed. At least some of these tumors are already covered by the VA.
75	7	Combination therapy approaches: Increasingly, in several malignancies, combination chemoradiotherapy is becoming the defacto standard. This combination is frequently associated with profound myelotoxicity and two pieces of data have recently become very clear: a. Proton therapy decrease myelotoxicity in comparison to photon therapy. b. Treatment-induced lymphopenia is associated with inferior survival in several disease types, and inadvertent irradiation of the circulating lymphocyte compartment is a major causative factor in this. PBT would very likely diminish this. The additional recognition in the last 2+ years that up-regulation of effector T cells can dramatically improve cancer outcomes in several malignancies underscores the major need to use therapies with the lowest likelihood of treatment-associated lymphopenia, and PBS would be much better suited for this purpose, compared to IMRT.	We confirmed with the reviewer that the data sources supporting his statement (a) about decreased myelotoxicity with proton vs photon are: Komaki R. Reduction of bone marrow suppression for patients with stage III NSCLC treated by protons and chemotherapy compared with IMRT and chemotherapy. The Particle Therapy Cooperative Group (PTCOG) 47 Conference; May 19-24 2008; Jacksonville, FL and Krause M, Baumann M. [Reduced acute toxicity for adults with medulloblastoma treated with proton beam craniospinal irradiation]. *Strahlenther Onkol.* 2014;190(1):111-112. As a conference abstract, Komaki 2008 lacks adequate detail about methodology to fully assess its internal validity (*eg*, patient selection and outcome ascertainment methods, baseline characteristics, statistical methods, N analyzed). Krause 2014 is in German and our methods do not include translation of non-English articles.
76	7	Conclusion: The purpose of this report is to synthesize the evidence supporting the role/value of proton therapy, specifically in terms of assisting the VA in making further recommendations as to how to approach this modality. My summary comments should provide strong rationale for	Thank you.

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		pursuing this in a logical, organized, and structured manner, and if done smartly, without a dramatic escalation in cost-of-care.	
77	8	Overall, I think there is confusion in what is toxicity due to proton beam itself vs proton beam techniques. Proton beam is a relatively young technology. Although centers have been using this technology for 2+ decades, the overall number is low (just 2 - Loma Linda and MGH). Of the 14 currently operating proton centers, 12 have been treating for less than 10 years. As a result, techiques are still evolving. In contrast, there are probably ~3000 RT centers in operation today. If you look at the metric of "proton years" vs "IMRT years", it's probably 150 years vs 30,000 years. This is not meant to be a soapbox defense of proton beam, but rather an explanation of what should be considered by the reviewers.	Added to conclusion: "Because this is still a rapidly evolving field, with ongoing efforts to improve techniques and reduce costs, this review may need more frequent updating to keep up-to-date with emerging research"
78	8	I think in lung cancer, the Sejpal MDA manuscript, along with other manuscripts from MDA, indicate that much higher doses of RT can be delivered with proton beam vs either 3D conformal RT or IMRT and result in much lower complication rates.	Yes, we agree that Sejpal found lower Grade 3 esophagitis for PBT vs 3D-CRT and IMRT in a subgroup of 202 patients treated with concurrent chemotherapy.
79	8	For prostate cancer, there are now 6 dose escalation studies. All 6 showed that higher doses lead to higher biochemical control rates. But 5 of 6 studies showed increased GI complication risks with dose escalation. The 6th study used proton beam for the final RT boost (PROG 9509, Zietman JCO 2010) and showed the same complication rates in the low and high dose arms. In looking at these 6 studies together, it is very reasonable to conclude that the only method in which dose escalation in prostate cancer has been shown to feasible WITHOUT an increase in GI toxicity is with the use of proton beam.	Yes, this is a reasonable inference to make based on comparing findings from high vs low dose comparisons of proton beam to high vs low dose comparisons of non-proton beam modalities; yet, that didn't translate into an actual GI toxicity advantage based on direct evidence from a head-to-head comparison of proton beam vs IMRT in the newest Fang 2014 study. Added dose escalation studies to the report.
80	8	If the Sheets article is to be used, then the comparison of the 6 dose-escalation studies should also be used. The Sheets article has multiple flaws, not the least of which was the use of a	Yes, we agree that the Sheets article has multiple flaws which we have described in detail and have cited the JAMA letters to the editor.

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		surrogate marker (colonoscopcies) to quantify GI morbidity. No one knows the indications for ordering the colonoscopies. The letter to the editor from Mendenhall, Shields, and Slater in JAMA outlined the flaws in the Sheets article.	Also added comparison of dose escalation studies: "Some dose-escalation studies have found increased GI complication risks with increased dose of photons,[65] but not with protons.[66] But when compared head-to-head in prostate cancer, proton beam has only transiently reduced risk of 6-month acute GU toxicity versus IMRT, but may increase risk of late GI toxicity after 4-5 years."
81	8	Finally, secondary malignancies may well be lower with the use of proton beam RT. The article from Chung et al only examined one side, if protons had a higher rate of radiation induced malignanices than X-rays. They found a lower rate of second cancers in the matched populations.	Yes, Chung's finding can seem promising, but it provided insufficient evidence to draw any conclusions at this time due to its high potential for unmeasured confounding due to higher missing data but superior outcome ascertainment methods in the proton group and unknown radiation dose.