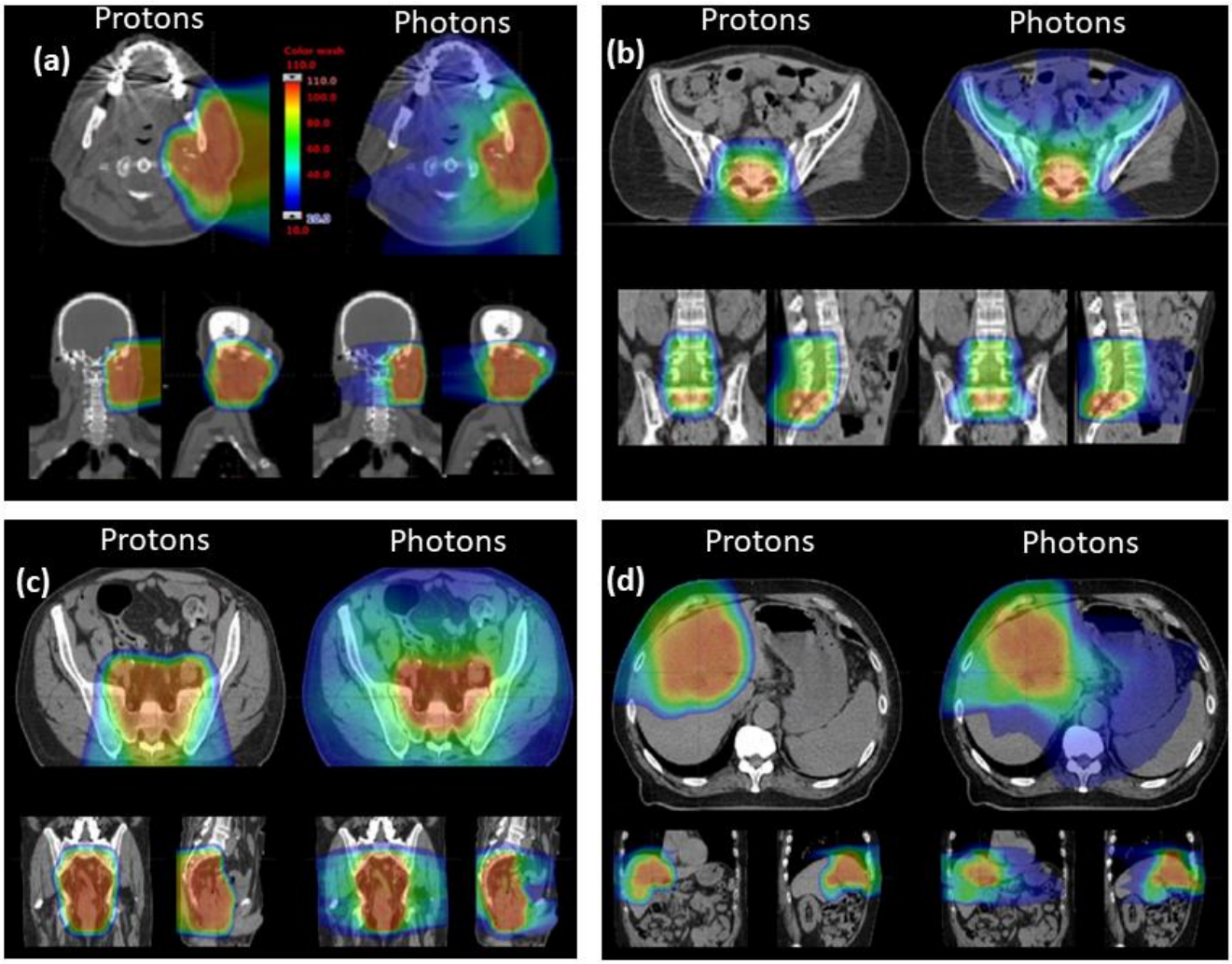
Supplementary Online Content

Baumann BC, Mitra N, Harton JG, et al. Comparative effectiveness of proton vs photon therapy as part of concurrent chemoradiotherapy for locally advanced cancer. *JAMA Oncol.* Published online December 26, 2019. doi:10.1001/jamaoncol.2019.4889

This supplementary material has been provided by the authors to give readers additional information about their work.

I. Supplemental Figure



eFigure. Representative Proton and Photon Treatment Plans With Radiation Dose Represented as a Color Wash

Part II. **Supplemental Methods**

eMethods 1. Prospective Analysis Plan (2017)

Title: Comparative Effectiveness of Concurrent Chemotherapy and Radiation therapy using Proton versus Photon Radiation in the Treatment of Non-metastatic Cancer

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Project abstract:

Concurrent chemotherapy and radiation therapy (CRT) is the standard-of-care curative therapy for many cancers, including lung cancer, glioma, head and neck cancer, esophagus cancer, and pancreas cancer. However, concurrent chemo-radiotherapy is associated with substantial morbidity, including oral mucositis, esophagitis, nausea, vomiting, significant weight loss, and radiation-induced lung injury that can lead to unplanned hospitalizations, ER visits, treatment interruptions that can diminish the effectiveness of radiation therapy, and decreased patient performance status. We hypothesize that reducing radiation dose to normal tissues with proton radiation in the setting of combined modality treatment with concurrent chemo-radiotherapy will reduce treatment-related morbidity. The primary outcome will be incidence of severe adverse events during concurrent chemo-radiotherapy for patients treated with proton versus photon radiation. Severe adverse events are those that require medical intervention and/or hospitalization and will be defined using the Common Terminology Criteria for Adverse Events (CTCAE) version 4 as toxicities that are grade ≥3. Grade ≥3 toxicities are common in patients treated with concurrent chemo-radiotherapy with photons, occurring in 76% of patients with locally advanced lung cancer (1), 74% of head and neck cancer patients treated post-operatively (2), and 20% of esophageal cancer patients treated pre-operatively (3). Secondary outcomes will be CTCAE grade ≥2 toxicities, changes in patient performance status, overall survival, disease-free survival, and total cost of care for the 6 month episode beginning with the start of concurrent chemo-radiotherapy. We will conduct an observational comparative effectiveness research study to compare proton versus photon concurrent chemo-radiotherapy.

Specific Aims:

The overarching aim of this study is to examine the comparative effectiveness of proton versus photon concurrent chemo-radiation therapy for non-metastatic cancer patients ≥18 years of age. We propose the following specific aims:

Aim 1: To compare rates of adverse events after proton versus photon chemo-radiotherapy, after adjustment for measured confounders and assessing the potential effect of unmeasured confounders. Adverse events will be defined as CTCAE v4 grade ≥3 toxicities that would prompt medical intervention or hospitalization. We will also compare secondary outcomes, including CTCAE v4 grade ≥2 toxicities and changes in patient performance status as measured using the ECOG performance status metric, disease-free survival, and overall survival,

> Aim 1 Hypothesis: We hypothesize that proton therapy is associated with fewer Grade ≥ 3 acute toxicities compared to photon therapy for patients receiving concurrent chemo-radiotherapy.

Aim 2: To compare the total cost of care for a 6-month episode beginning from the start of concurrent chemo-radiotherapy for proton versus photon patients using insurance claims data from one of our largest insurers (Independence Blue Cross), after adjustment for confounders.

> Aim 2 Hypothesis: We hypothesize that the total cost of care during the 6-month episode will be lower for proton therapy compared to photon therapy (the higher upfront cost of proton therapy will be offset by cost savings realized due to reductions in costs related to acute toxicities).

2. Significance: This is the first observational study, to our knowledge, to evaluate the comparative effectiveness of concurrent chemo-radiotherapy for patients treated with proton versus photon radiotherapy. Regardless of whether the study results support or do not support the use of protons for concurrent chemo-radiotherapy, the findings will inform decision-making for stakeholders in the oncology community (patients, payers, providers, manufacturers, researchers and policy makers). Even as proton therapy gains in popularity and more treatment centers are opening around the world, the central tenet justifying proton therapy, i.e., that it reduces toxicity, remains largely unproven in terms of whether the dosimetric benefits seen with protons translate to real improvements in clinical outcome and whether this more expensive treatment is cost-effective. If protons are not found to reduce toxicity, then there would be less justification for their continued use in the marketplace. This study will drive research efforts into the comparative effectiveness of proton versus photon therapy, is of great interest to the University of Pennsylvania Health System as it addresses questions of the value in the marketplace, and could inform insurer coverage policy of proton therapy

3. Innovation: This study is novel in three ways. First, we construct a unique registry-administrative claims linked dataset to analyze the comparative effectiveness of proton versus photon chemo-radiotherapy by linking clinical data from Epic (the Penn electronic medical record), the Penn Tumor Registry, the Penn DataStore, Aria and Eclipse (the radiation oncology-

specific electronic information systems) to the insurance claims data provided by Independence Blue Cross. Second, this study will use advanced comparative effectiveness methods, including time-varying confounding and informative censoring to produce doubly-robust estimators based on propensity scores and an ensemble machine learning approach for both parametric and non-parametric approaches to propensity score and cost estimation, all to account for measured and unmeasured confounding. Third, this study evaluates both the clinical and cost effectiveness of proton therapy in the commercial population.

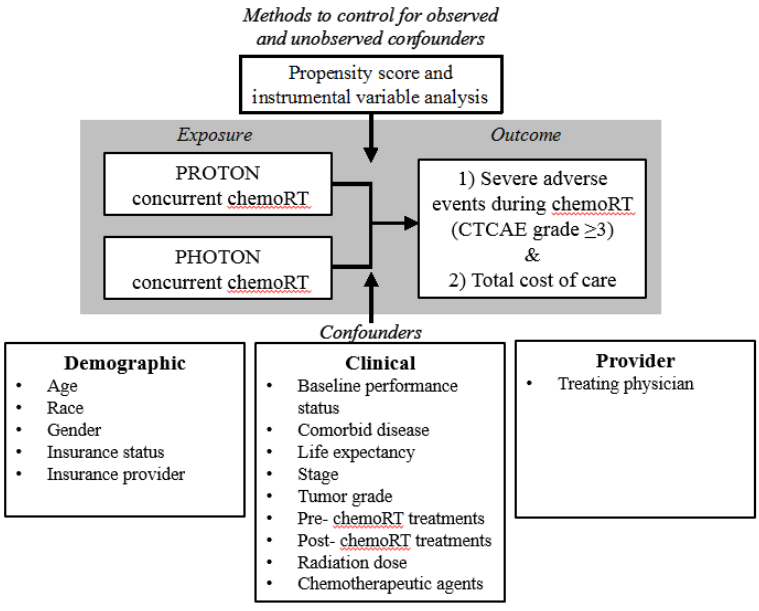
4. Approach

4.1a Prior work: Concurrent chemotherapy and radiation therapy (CRT) is the standard curative treatment for many different cancers, but this combined approach is associated with significant morbidity and 1-5% treatment-related mortality (1, 4). For decades, concurrent chemo-radiotherapy has been administered using photon (i.e. x-ray) radiation. Photon therapy, delivered as either intensity-modulated radiotherapy (IMRT) or 3D conformal radiotherapy, uses multiple x-ray beams to irradiate a tumor target but unavoidably deposits radiation in normal tissues beyond the tumor. Proton radiation therapy has emerged as an alternative radiation treatment that directs multiple beams of protons (positively charged subatomic particles) at the tumor target where they deposit the bulk of their energy to a finite depth in tissue with essentially no residual radiation beyond the tumor target (5). Figure 1 illustrates a comparative plan to treat the brain and entire spinal cord using proton versus photon radiation. In the proton plan, the chest, abdomen, and pelvic tissues anterior to the spine (e.g. heart, lungs, and bowel) receive no radiation whereas the photon plan exposes those normal structures to moderate-to-high doses of radiation that can lead to significant GI and cardio-pulmonary toxicities. Concurrent chemo-radiation with protons may be able to significantly reduce treatment toxicity, but there is limited data available on its effectiveness compared to conventional photon radiation, which is less costly (6).This application extends also work that Dr. Baumann has conducted to evaluate the dosimetric differences between proton versus photon radiation for patients treated with adjuvant radiation therapy for bladder cancer (7) and for chordoma/chondrosarcoma patients (8).

4.1.b. Mentorship and Research Environment: The mentorship available to me at Penn extends across a spectrum of clinicians, clinical researchers, and full-time research faculty. I have established close mentorship relationships with Dr. Justin Bekelman, MD (9), Associate Professor in Radiation Oncology at Penn. I am also mentored by Dr. James Metz, MD (10), Chairman of Radiation Oncology, and an expert on proton radiation therapy. Dr. Bekelman and Dr. Metz have provided mentorship about study design, data analysis, effective dissemination of policy-relevant research findings, career counseling, and grant writing. Both have outstanding mentorship track records, and my research project aligns closely with their own interests. Dr. Bekelman is my primary mentor and is dedicated to my project and career success. Dr. Bekelman is a senior fellow at the Leonard Davis Institute of Health Economics and an NIH-funded health services researcher. I will meet with Dr. Bekelman and Dr. Metz on a bimonthly basis to review our progress on the project. We are also collaborating Dr. Peter Gabriel, Chief Oncology Information Officer, to acquire the data needed to perform the analysis.

We also are collaborating with Dr. Nandita Mitra, PhD(11), a professor of biostatistics and senior LDI fellow with expertise in the development and application of doubly robust propensity score and instrumental variable methods for comparative effectiveness and cost-effectiveness estimation. Dr. Mitra and her master's level statistician, Weiwei Feng, will provide the statistical support for this project.

Figure 2: Conceptual Model



4.2. Conceptual Model: As shown in Figure 2, we hypothesize that concurrent chemo-radiotherapy with

protons will be associated with lower acute grade ≥3 adverse events and lower total cost of care compared to concurrent chemo-radiotherapy with photon radiation.

4.3. Data Sources: We will generate a linked registry-administrative claims database of patients with information drawn from the Penn Tumor Registry List, the EPIC electronic medical record, the Penn DataStore, radiation-oncology specific data from Aria and Eclipse, and claims data from Independence Blue Cross.

4.4. Patient cohort: Our preliminary work has identified 1,839 patients who were treated with concurrent chemo-radiotherapy with curative intent for non-metastatic disease from 2010 – 2016. 470 were treated with proton therapy and 1,369 were treated with photon therapy. Cases of re-irradiation of patients who recurred after prior curative radiation will be excluded. The most common disease sites are lung cancer (proton=153, photon=264), followed by brain cancer (proton=89, photon=219), head and neck cancer (proton=52, photon=364), and esophageal cancer (proton=46, photon=100).

4.5. Variables: Our analysis includes four categories of variables: exposure (proton versus photon chemo-radiotherapy); outcome (toxicity measures and survival outcomes); confounder (patient and physician characteristics), and candidate instrumental variables.

4.5.a. Exposure: *Photon or Proton chemo-radiotherapy*. Patients will be classified as receiving concurrent chemo-radiation therapy with photon versus proton radiation based on the Penn Tumor Registry and Aria (the Penn radiation oncology electronic medical record).

4.5.b. Aim 1: Primary Outcome: *Acute CTCAE grade ≥3 toxicities*. Acute grade ≥3 toxicities are common in patients treated with concurrent chemo-radiotherapy with photons, occurring in 76% of patients with locally advanced lung cancer (1), 74% of head and neck cancer patients treated post-operatively (2), and 20% of esophageal cancer patients treated pre-operatively (3). All non-hematologic acute toxicities are scored on a weekly basis by radiation oncology clinicians while patients are undergoing treatment using the standard toxicity scoring system [Common Terminology Criteria Adverse Events (CTCAE) version 4] and recorded in the electronic medical record. Hematologic toxicities were not scored prospectively and so will not be included in the analysis.

4.5.b. Aim 1: Secondary outcomes: *Acute CTCAE grade ≥2 toxicities, Changes in ECOG performance status, disease-free survival, and overall survival.* The patient's global functional status, defined as the ECOG performance status, is recorded on a weekly basis by radiation oncology clinicians in the Penn electronic medical record. Disease-free survival will be defined as the interval from the start date of chemo-radiotherapy to the date of progression of cancer or death, whichever happens first. Overall survival will be determined as the interval from the start date of chemo-radiotherapy to the date of death. Patients will be censored at the time of last follow-up if they are still alive. Data on disease-free survival and overall survival will be obtained from the Penn Tumor Registry.

4.5.b. Aim 2: Primary Outcome: *Total cost of care for the 6 month episode beginning with the start of concurrent chemo-radiotherapy.* Total cost of care for the 6 month period from the start of chemo-radiotherapy will be calculated for patients with Independence Blue Cross (IBC) insurance based on claims data that has already been provided by IBC to the University of Pennsylvania Health System in October, 2016.

4.5.c. Confounder Variables: *Patient and Physician Characteristics.* We will adjust for variables that may be associated with bias treatment assignment and outcomes. Patient variables will include age, sex, race, tumor stage, tumor grade, comorbid disease, BMI, baseline ECOG performance status, oncologic treatments given before concurrent chemoRT (e.g. surgery or upfront chemotherapy), oncologic treatments given after concurrent chemoRT (e.g. surgery or chemotherapy), and specifics of radiation and chemotherapy treatments (12). Physician characteristics will include comparison based on the treating physician.

4.5.d. Candidate Instrumental Variables: A valid instrument influences the probability of receiving treatment and has no independent effect on outcome (except through correlation with treatment status). We will evaluate the strength and validity of a range of candidate instrumental variables (e.g. insurance status, insurance carrier, age).

4.6. Statistical Methods for Specific Aims 1 and 2: Comparative effectiveness of proton versus photon chemo-radiotherapy. We will use propensity score and instrumental variable analysis (IVA) to compare the primary and secondary endpoints of interest between proton versus photon chemo-radiotherapy. These methods will allow us to adjust for

confounding due to biased treatment assignment (13). Propensity scores will be estimated by logistic regression as the probability (between 0 and 1) that a patient would be assigned to the proton group given pretreatment patient and physician characteristics (14). The estimated propensity scores will be used in inverse probability weighting (IPTW) in the Cox model. In the IVA, we will develop and test several candidate instrumental variables. Instrumental variables serve as partly random varying factors by which to assign patients to "treatment" groups. In contrast to propensity adjusted analysis, IVA estimates the average treatment effect on the marginal subject (patients whose treatment was determined by the instrument). We will compare results from the propensity score and instrumental variable analyses to a traditional multilevel, multivariable Cox proportional hazards model adjusted for patient and physician level characteristics. For disease-free and overall survival, we will compute adjusted survival curves and present estimates of 1- and 3-year survival with 95% confidence intervals. Total cost of care will be compared for the subset of patients with Independence Blue Cross insurance for whom claims data is available. We will also estimate the cost-effectiveness of proton versus photon therapy by estimating common measures such as the incremental cost-effectiveness ratio and the net monetary benefit. We will use newly developed methods by Dr. Mitra and her team that account for time-varying confounding and informative censoring that produce doubly-robust estimators based on propensity scores. An ensemble machine learning approach will be used for both parametric and non-parametric approaches to propensity score and cost estimation (15). We have enlisted Dr. Nandita Mitra, Senior LDI Fellow and Professor of Biostatistics and Epidemiology, to lead the statistical analysis.

eMethods 2. List of the 131 Variables in the Database

Demographic variables:

Age

Race

Hispanic (yes or no)

Gender

Insurance provider

Status of insurance provider with respect to proton insurance approval

Type of insurance (Medicare, Private insurance, MediCaid, other)

ECOG performance status at start of RT

Date for ECOG performance status

Charlson-Deyo comorbidity data (20 separate variables regarding presence or absence of diseases used in the Charlson-Deyo comorbidity calculation)

Charlson-Deyo unadjusted score

Charlson-Deyo adjusted score

Body mass index

Clinical variables

Site of cancer

Subsite of cancer

Histology

Histology subcategory

Sequence of the primary (prior or subsequent cancers)

AJCC version

Clinical T-stage

Clinical N-stage

Clinical M-stage

Overall clinical stage

Pathologic variables

pT stage

pN stage

pM stage

pathologic overall stage

Overall stage

Tumor size

Grade

LVI invasion

Date of surgery

Type of surgery performed

Number of nodes removed

Number of involved nodes

Surgical margins

Site-specific variables (14 in total, including FIGO stage, HPV status for H&N cancer, extent of resection for brain tumors, and tumor markers for primary brain cancer)

Chemotherapy-related variables

Chemotherapy start date

Sequence of surgery and chemotherapy

Elapsed days from first surgery to chemo

Elapsed days from chemo to first surgery

Elapsed days from chemo to RT

Concurrent systemic therapy agents

Concurrent chemo agents (grouped together) (5-FU based, platinum-based, temozolomide, other)

Chemo-RT timing (pre-operative, definitive, post-operative)

Radiation-specific variables

Radiation course ID and course number

Treatment intent of RT

Diagnosis code for RT

Treatment modality (proton vs. photon)

Type of Photon RT (IMRT, Rapid Arc, 3-D conformal, electrons)

Type of proton therapy (double-scatter, pencil beam)

Combination of proton and photon

Start date for radiation

End date for radiation

Elapsed days for radiation

Interruptions in RT >7 days

Delivered radiation dose

Delivered fractions of radiation

Mean dose

Patient volume

External integral dose

Planning target volume (PTV) integral dose

Body – PTV integral dose

Attending radiation oncologist

Re-irradiation case?

Re-irradiation for recurrence?

Re-irradiation for a different cancer?

Radiation for a different cancer that overlaps with the prior RT?

Treatment at the main site vs. satellite facility

Outcome variables

ECOG performance status at start of RT

Date for ECOG performance status at start of RT

Ending ECOG performance status at end of RT

Date for ECOG performance status at end of RT

Change in ECOG performance status

Toxicity date for first grade 2 toxicity

Presence of grade 2 toxicity?

Number of grade 2 toxicities

Time to grade 2 toxicity

90-day grade 2 toxicity

Toxicity date for first grade 3 toxicity

Presence of grade 3 toxicity?

Number of grade 3 toxicities

Time to grade 3 toxicity

90-day grade 3 toxicity

Date of last contact

Status at last contact

Date of recurrence and type of recurrence

Disease-free survival duration

Disease-free survival event indicator

Alive or dead?

Overall survival duration

Local recurrence event indicator

Local-recurrence free survival duration

Distant metastasis event indicator

Distant metastasis-free survival duration

Part III. **Supplemental Table**

eTable. Unmeasured Confounding Sensitivity Analysis for Acute Toxicity of Grade ≥3

Boldfaced type indicates scenarios in which the statistical significance for reduced acute grade ≥3 toxicity for protons is lost. We assumed physical frailty was the unmeasured confounder (UC), but the analysis could apply to smoking status or socioeconomic status.

Original Treatment RR	Original Treatment 95% CI LB	Original Treatment 95% CI UB
0.3137	0.1483	0.6638

Prevalence UC Photon Group	Prevalence UC Proton Group	UC Relative Risk	New Treatment Relative Risk	New Treatment 95% CI LB	New Treatment 95% CI UB
0.3	0.25	1.25	0.338	0.16	0.712
0.3	0.2	1.25	0.366	0.174	0.771
0.3	0.15	1.25	0.399	0.189	0.841
0.3	0.1	1.25	0.439	0.208	0.925
0.3	**0.05**	**1.25**	**0.487**	**0.231**	**1.027**
0.3	0.25	1.5	0.343	0.163	0.723
0.3	0.2	1.5	0.378	0.179	0.797
0.3	0.15	1.5	0.421	0.2	0.888
0.3	**0.1**	**1.5**	**0.476**	**0.226**	**1.003**
0.3	**0.05**	**1.5**	**0.546**	**0.259**	**1.151**
0.3	0.25	1.75	0.348	0.165	0.733
0.3	0.2	1.75	0.39	0.185	0.822
0.3	0.15	1.75	0.444	0.211	0.937
0.3	**0.1**	**1.75**	**0.516**	**0.245**	**1.087**
0.3	**0.05**	**1.75**	**0.615**	**0.292**	**1.296**
0.3	0.25	2	0.352	0.167	0.743
0.3	0.2	2	0.402	0.191	0.847
0.3	0.15	2	0.467	0.222	0.985
0.3	**0.1**	**2**	**0.558**	**0.265**	**1.177**
0.3	**0.05**	**2**	**0.693**	**0.329**	**1.462**
0.3	0.25	2.25	0.356	0.169	0.751
0.3	0.2	2.25	0.412	0.196	0.869
0.3	**0.15**	**2.25**	**0.489**	**0.232**	**1.032**
0.3	**0.1**	**2.25**	**0.602**	**0.285**	**1.268**
0.3	**0.05**	**2.25**	**0.781**	**0.371**	**1.646**
0.3	0.25	2.5	0.36	0.171	0.759
0.3	0.2	2.5	0.422	0.2	0.89
0.3	**0.15**	**2.5**	**0.51**	**0.242**	**1.076**
0.3	**0.1**	**2.5**	**0.645**	**0.306**	**1.359**
0.3	**0.05**	**2.5**	**0.876**	**0.416**	**1.847**

Prevalence UC Photon Group	Prevalence UC Proton Group	UC Relative Risk	New Treatment Relative Risk	New Treatment 95% CI LB	New Treatment 95% CI UB
0.4	0.35	1.25	0.335	0.159	0.705
0.4	0.3	1.25	0.358	0.17	0.755
0.4	0.25	1.25	0.386	0.183	0.813
0.4	0.2	1.25	0.418	0.198	0.881
0.4	0.15	1.25	0.456	0.216	0.961
0.4	**0.1**	**1.25**	**0.501**	**0.238**	**1.057**
0.4	**0.05**	**1.25**	**0.557**	**0.264**	**1.174**
0.4	0.35	1.5	0.338	0.161	0.713
0.4	0.3	1.5	0.367	0.174	0.774
0.4	0.25	1.5	0.401	0.19	0.846
0.4	0.2	1.5	0.442	0.21	0.933
0.4	**0.15**	**1.5**	**0.493**	**0.234**	**1.039**
0.4	**0.1**	**1.5**	**0.557**	**0.264**	**1.174**
0.4	**0.05**	**1.5**	**0.639**	**0.303**	**1.348**
0.4	0.35	1.75	0.342	0.162	0.72
0.4	0.3	1.75	0.375	0.178	0.791
0.4	0.25	1.75	0.416	0.197	0.877
0.4	0.2	1.75	0.467	0.221	0.984
0.4	**0.15**	**1.75**	**0.531**	**0.252**	**1.12**
0.4	**0.1**	**1.75**	**0.617**	**0.293**	**1.3**
0.4	**0.05**	**1.75**	**0.735**	**0.349**	**1.55**
0.4	0.35	2	0.345	0.164	0.727
0.4	0.3	2	0.382	0.181	0.806
0.4	0.25	2	0.429	0.204	0.905
0.4	**0.2**	**2**	**0.49**	**0.232**	**1.032**
0.4	**0.15**	**2**	**0.57**	**0.27**	**1.201**
0.4	**0.1**	**2**	**0.681**	**0.323**	**1.435**
0.4	**0.05**	**2**	**0.845**	**0.401**	**1.782**
0.4	0.35	2.25	0.347	0.165	0.732
0.4	0.3	2.25	0.389	0.184	0.82
0.4	0.25	2.25	0.442	0.21	0.931
0.4	**0.2**	**2.25**	**0.511**	**0.242**	**1.077**
0.4	**0.15**	**2.25**	**0.607**	**0.288**	**1.278**
0.4	**0.1**	**2.25**	**0.746**	**0.354**	**1.572**
0.4	**0.05**	**2.25**	**0.968**	**0.459**	**2.04**
0.4	0.35	2.5	0.349	0.166	0.736
0.4	0.3	2.5	0.394	0.187	0.831
0.4	0.25	2.5	0.452	0.215	0.953
0.4	**0.2**	**2.5**	**0.53**	**0.252**	**1.118**
0.4	**0.15**	**2.5**	**0.641**	**0.304**	**1.352**
0.4	**0.1**	**2.5**	**0.811**	**0.385**	**1.708**
0.4	**0.05**	**2.5**	**1.101**	**0.522**	**2.321**

Part IV. Supplemental References

eReferences

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