Washington State Health Care Authority

Intensity-modulated Radiation Therapy for Selected Indications

Assessing Signals for Update

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Health Technology Assessment Program (HTA)

Washington State Health Care Authority

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Contents

List of Appendices

List of Tables

List of Abbreviations

CRT conventional radiotherapy

CMS Centers for Medicare & Medicaid Services

COE certainty of evidence

EBRT external beam radiation therapy

GI gastrointestinal

GU genitourinary

HCA Health Care Authority

HT helical tomotherapy

HTA health technology assessment

HTCC Health Technology Clinical Committee

IMRT intensity-modulated radiation therapy

KQ key question

NRSI nonrandomized studies of interventions

OAR organs at risk

PBT proton beam therapy

QOL quality of life

RCT randomized controlled trial

SBRT stereotactic body radiation therapy

SR systematic review

VMAT volumetric modulated arc therapy

Executive Summary

Background

In 2012, the Washington State Health Technology Clinical Committee voted to cover intensity-modulated radiation therapy (IMRT) for head and neck cancers and prostate cancer, as well as for other cancers when used to spare critical structures adjacent to treatment sites to prevent toxicities or when used in the context of outcome data collection.[1] The objective of this report was to determine whether there is new evidence that will change the conclusions of the 2012 Health Technology Assessment (HTA) used to inform the Committee's decision.[2]

Methods

We searched MEDLINE® (via PubMed) for relevant English-language systematic reviews (SRs) published between January 1, 2013, and April 24, 2025, as well as ClinicalTrials.gov to identify ongoing trials. Using a modified Ottawa approach, we evaluated the identified information to determine whether a signal suggesting a need for an updated HTA was present.

Results

We identified 68 SRs for inclusion in the signal search. Head and neck and prostate cancer yielded the largest number of SRs, but SRs were also identified for other cancers (see table). Harms were the most common outcome reported followed by survival. For prostate cancer and head and neck cancers, we did not identify any signal suggesting new harms of IMRT compared to conventional external beam radiation (EBRT). For other cancer types, the signal search identified SRs with a larger number of studies with comparative study designs than was available for the 2012 HTA. Evidence from these SRs suggest more certainty about larger benefits, fewer harms, or both for IMRT compared to EBRT. For some cancer types, new evidence is also available comparing IMRT to proton beam therapy, a type of EBRT that the HTCC voted to cover with conditions in 2019.

Cancer Types	Signal
Head & Neck, Prostate	None
Brain/craniospinal Breast Female Pelvic Cancers GI: Anal, Esophageal, Gastric, Liver, Pancreatic, Rectal Lung Sarcoma Urologic	New evidence available with findings that fill previous evidence gaps or increase certainty of the conclusions in the 2012 HTA.

Abbreviations: GI = gastrointestinal; HTA = health technology assessment

Conclusions

A signal search of IMRT for cancer treatment identified new and potentially more robust evidence from comparative studies across multiple cancer types. This new evidence suggests an updated HTA may find a higher certainty of evidence for a direction of effect favoring IMRT (larger benefit, fewer harms, or both) compared to conventional EBRT, which may influence the 2012 coverage conditions that currently apply for cancers other than head and neck and prostate.

1. Introduction

In 2012, the Washington State Health Technology Clinical Committee (HTCC) voted to cover intensity-modulated radiation therapy (IMR) based on findings from a 2012 Health Technology Assessment (HTA).[1,2] Specifically, IMRT is covered for head and neck and prostate cancers, as well as additional cancers under certain conditions.

1.1 Epidemiology and Burden of Disease

Despite recent diagnostic and treatment advances, cancer remains a leading cause of death in the United States, second only to heart diseases. The most common cancers among women in the United States include breast, lung, and colorectal cancers, which accounted for 51% of new cases in 2024. For men, the most common cancers include prostate, lung, and colorectal cancers (48% of new cases).[3] Though cancer incidence and mortality rates have declined overall, mortality remains significant, with an estimated 611,720 deaths in the United States in 2024 (approximately 1,680 deaths/day), and the incidence of breast and colorectal cancers is increasing in some populations.[3]

1.2 Treatments

Cancer treatments vary by disease location and characteristics but can include surgery, chemotherapy, hormone therapy, immunotherapy, stem cell transplant, targeted cancer cell therapies, thermal and photodynamic therapies, and radiation therapy.[4]

1.3 Radiation Therapy

Radiation therapy kills cancer cells by damaging DNA, exploiting differences in the rate of repair and repopulation between normal and cancerous cells to preferentially eradicate the latter. Treatment is fractionated to mitigate adverse effects and allow time for normal cells to repair.[5] Radiation therapy commonly uses photons or electrons to deliver charged particles to cancer sites.[5] Radiation therapy may be employed as a singular therapy or as adjuvant, neoadjuvant, or concurrent treatment with surgery, chemotherapy, hormonal therapy, or immunotherapy, depending on the cancer type and therapeutic goals (e.g., curative, palliative).

Radiation therapy can be delivered within the body via internal modalities, such as brachytherapy, or with external beam modalities. Conformal external beam radiation therapy (EBRT) approaches include 2-D or 3-D conformal radiation therapy (2DCRT or 3DCRT). EBRT uses imaging to map and shape multiple radiation beams (beamlets) to conform to the shape and size of the tumor using small, leaf-shaped metal structures (multileaf collimators). More precise EBRT radiation delivery techniques include IMRT and stereotactic body radiation therapy (SBRT), or stereotactic radiosurgery.[6] Although most EBRT uses photons, protons (proton beam therapy, PBT) or heavy ions can also be used because of potential to more precisely treat malignant tissue with higher doses of radiation and expose surrounding healthy tissues to lower doses.[7] IMRT is the intervention of interest for this signal search.

Intensity-Modulated Radiation Therapy (IMRT)

IMRT uses radiation conformed to the tumor shape, but the delivered radiation dose is modulated by varying intensity of each beamlet. This approach allows for higher radiation doses directed to cancerous tissue while minimizing damage to surrounding tissues and organs at risk (OAR).[8,9] IMRT itself comprises multiple planning and delivery techniques that reflect differences in delivery technology.[8,9] IMRT modalities include volumetric modulated arc therapy (VMAT)**,** a technique that varies the speed of rotation, the shape of the radiation beams, and the dose rate to deliver radiation from multiple angles; helical tomotherapy (HT), which combines the use of computed tomography in radiation beam delivery; and Image-Guided Radiation Therapy (IGRT), which incorporates imaging prior to and during IMRT to verify and adapt treatment delivery.[10]

Regardless of the specific technique used, IMRT requires precise planning to define tumor borders and shape and dosimetric calculations that factor in the varied intensities of the radiation to be delivered. Treatment also requires quality assurance processes to maximize safety.[9] Treatment typically involves immobilizing the patient in order to deliver highly conformed radiation doses per the treatment plan and to minimize effects on OAR. IMRT may result in greater overall exposure to radiation of normal tissues (i.e., increased low-dose bath) and development of second cancers compared to conventional EBRT.[11,12]

The State of Washington's 2012 HTA on this topic evaluated the effectiveness and safety of IMRT for any malignancies, effects in subpopulations defined by patient, tumor, and treatment characteristics, and cost and cost effectiveness compared with conventional EBRT.[2]

1.4 Policy Context

In 2012, the Washington State Health Technology Clinical Committee (HTCC) voted to cover IMRT with conditions based on evidence presented from Health Technology Assessment (HTA) commissioned for the committee.[1,2] } Specifically, IMRT is covered for head and neck cancers and prostate cancer. IMRT is also covered for other cancers but only when needed to spare critical structures adjacent to treatment sites to prevent toxicities within the expected life span, or for treatment in the context of evidence collection or submission of outcome data. We also note that the HTCC voted to cover PBT in 2019 (for children and for selected cancer types in adults) and voted to cover SBRT with conditions for selected cancers in 2024.

We did not identify a Centers for Medicare & Medicaid Services (CMS) national coverage determination for IMRT. Now retired local coverage determinations from CMS contractors First Coast Service Options and Novitas Solutions note that IMRT is considered covered, if the tumor can be precisely targeted, radiation doses are in excess of those commonly used for similar tumors with conventional treatment, if the tumor is in close proximity to OAR, if the patient can tolerate immobilization, and if IMRT offers an advantage over conventional EBRT.[13,14]

The American Society of Radiation Oncologist's model policy provides guidance for coverage of IMRT and indicates that coverage decisions must include considerations of the clinical scenario and medical necessity. IMRT is considered medically necessary in cases for which sparing normal tissue surrounding the cancer is of added clinical benefit or, in the case of metastasis, if the patient's status justifies aggressive local therapy. The policy includes a non-exhaustive list of

indications for which IMRT is usually of clinical benefit including dose escalation for inoperable cancers; re-irradiation; primary bone tumors; and cancers including the central nervous system tumors, head and neck, breast, thorax, gastrointestinal (GI) system, pelvic or gynecological systems, genitourinary (GU) system, and sarcomas.[8]

1.5 Scope and Key Questions of the 2012 HTA

Key questions for the 2012 HTA listed below served as the basis for the signal search. The prior report specified conventional EBRT as the comparator, however, radiation therapies have advanced since 2012 and recent literature indicates the use of newer radiation modalities, specifically PBT and heavy ion therapy. We have expanded the list of comparators for this signal search to account for these advances. We note adaptations to the key questions in italics.

KQ 1: What is the evidence of effectiveness for intensity modulated radiation therapy compared to conventional EBRT (2D- or 3D-CRT), *proton beam therapy, or heavy ion radiation therapy* for patients with cancer by site and type of cancer?

KQ 2: What are the potential harms of IMRT compared to conventional EBRT, *proton beam therapy, or heavy ion radiation therapy*? What is the incidence of these harms? Include consideration of progression of treatment in unnecessary or inappropriate ways.

KQ 3: What is the evidence that IMRT has differential efficacy or safety issues in subpopulations? Including consideration of:

a. Gender;

b. Age;

c. Site and type of cancer;

d. Stage and grade of cancer; and

e. Setting; provider; *or treatment* characteristics *including treatment goal (e.g., palliative, curative) or timing;* equipment; quality assurance standards and procedures.

KQ 4: What is the evidence of cost and cost-effectiveness of IMRT compared to conventional EBRT, *proton beam therapy, or heavy ion radiation therapy?*

1.6 Objectives

The primary aim of this signal search was to determine whether there is new evidence that will change the conclusions of the most recent HTA on IMRT, which was published in September 2012.[2]

2. Methods

We used a **modified** Ottawa approach (see **Appendix A**) and examined full texts of systematic reviews (SRs) published since the prior HTA. Because the 2012 coverage decision specified coverage of IMRT for head and neck cancers and prostate cancer only, we focused primarily on new evidence on harms for these cancers. For other cancers, we focused on identifying new evidence for efficacy, harms, and cost.

We examined SRs published since 2013 and abstracted data on relevant study characteristics and outcomes. We identified at least one SR for nearly all cancers evaluated in the prior HTA. As a result, we did not search for primary studies for those cancers if an SR was not available as these additional data would not have significantly influenced the overall signal assessment.

2.1. Literature Search

We searched MEDLINE® (via PubMed) for relevant English-language systematic reviews published between January 1, 2013, and April 24, 2025. The search strategy is described in **Appendix B**. In addition to PubMed, we searched ClinicalTrials.gov for ongoing studies on June 11, 2025.

2.2. Study Selection

Table 1 lists detailed inclusion and exclusion criteria from the 2012 HTA. Eligible comparators have been revised to reflect newer radiation therapy modalities (noted in italics).

Table 1. Inclusion and exclusion criteria for signal search

Study Component	Inclusion	Exclusion
Population	Adults and children with malignancies where treatment by radiation therapy is appropriate	Individuals with malignancies not appropriate for radiation therapy
Intervention	IMRT including VMAT, HT, IGRT with or without cotreatment	Internally delivered radiation therapy (e.g. brachytherapy) only Studies focused on treatment planning, including different dosing regimens SBRT*
Comparator	Conventional (conformal) external beam therapy*: *proton beam therapy, Other, None*	Non-EBRT modalities (i.e. brachytherapy) Other treatment modalities (e.g., chemotherapy) SBRT**
Outcomes	KQs 1,3: Survival rate (including disease-free survival, progression-free survival, recurrence-free survival, biochemical disease-free survival, symptom-free survival, overall survival); tumor control (including recurrence, metastases); duration of symptom-free remission; quality of life KQs 2,3: Harms including radiation exposure and complications KQ 4: Cost, cost-effectiveness	Other outcomes not specified Difference in doses
Study Design	KQs 1,3, 4: SRs, TAs, RCTs, and observational comparative study designs (prospective, retrospective, and controlled clinical trials) Studies of breast, head and neck, and prostate cancers: minimum sample size of 50 Studies of less prevalent malignancies: case series; studies with minimum sample size of 20 KQ 2: All study designs with a minimum sample size of 50 participants	Commentaries, letters, editorials, narrative reviews, and news articles Studies not meeting sample size criteria as appropriate

Study Component	Inclusion	Exclusion
	Pediatric populations and/or reports of serious harms (i.e., surgery, hospitalization, mortality): all study designs with a sample size of 20	
Other	English language publications	Non-English publications

*For the purposes of this signal search, the term conventional EBRT includes 2D-CRT and 3D-CRT.
**An HTA was conducted, and the HTCC issued a coverage determination for SBRT in 2023[15]; thus, SBRT was excluded from this signal search.
Abbreviations: CRT = conformal radiotherapy; EBRT = external beam radiation therapy; HT = helical tomotherapy; HTA = health technology assessment; IGRT=image-guided radiation therapy; IMRT = intensity-modulated radiation therapy; RCT = randomized controlled trial; SBRT=stereotactic body radiation therapy; SR=systematic review; VMAT = volumetric modulated arc therapy.

2.3. Data Abstraction and Signal Assessment

One reviewer evaluated titles and abstracts retrieved by our search and reviewed the full text SRs to determine if they met selection criteria. One reviewer abstracted data and a second reviewer confirmed that the abstracted data were accurate. We abstracted study characteristics such as included study designs, number of studies, and cumulative sample size of the SR. For each SR, we also abstracted the type of cancer, comparator intervention, and a summary of eligible outcomes. Results were summarized in narrative format as benefit, harm, or no difference in the use of IMRT compared with the study-specific comparator (if present). This was evaluated against the findings from the 2012 HTA to determine whether a signal for update was present.

3. Results

3.1. Search Yield and Overview of Studies

Using the search strategy from the 2012 HTA, we identified 326 SRs which underwent title and abstract screening, resulting in 179 records for full text review. Ultimately, 68 SRs were reviewed for the signal search. The cancers with the largest number of SRs were head and neck cancers (k = 20), prostate cancer (k = 10), GI cancers (k = 11), cancers of the brain (k = 5), female pelvic cancers (k = 4), and lung cancer (k = 4). The remaining cancer types had 3 or fewer SRs that were evaluated.

3.2. Study Characteristics

The systematic reviews we identified included studies conducted in adults (k = 22) or both adults and children (k = 4) or did not report age criteria. One SR was conducted solely in individuals younger than 18 years.[16] Eleven studies analyzed results by subgroups: age (k = 2)[17,18]; cancer stage (k = 9)[19-27]; and by grade, primary cancer site, and prior treatment (k = 1).[22]

Nearly all SRs compared IMRT to conventional EBRT. Eight studies compared IMRT to PBT,[22,28-34] and 1 study had a carbon ion comparator.[22] The majority of SRs included studies with a comparative study design (randomized controlled trial [RCT] or comparative nonrandomized study of interventions [NRSI]); 7 SRs included only non-comparative NRSIs.[35-41] The majority of SRs reported harms outcomes, followed by survival outcomes. Few SRs included outcomes of

quality of life (QOL) or pain. ***Table 2*** provides an overview of the yield of SRs for each outcome.

Table 2. Yield of SRs by Outcome Category

Outcome Category	Number of SRs
Survival	18
Tumor control	7
QOL	2
Pain	1
Harms	58
Cost	1

Abbreviations: QOL=quality of life, SR=systematic review

3.3 Findings

We present the findings of the signal search by cancer type. Each section reviews the 2012 HTA findings by outcome category with certainty of evidence, compares these findings to that of the signal search and reports if a signal for an update of the HTA on this topic is present. In the tables that follow, we focus on the SRs that included comparative research designs (RCTs or NRSIs); additional SRs were identified but may have only included single-arm studies.

Brain and Craniospinal Cancers

The 2012 HTA reported on several brain tumors that were not identified in the signal search: astrocytoma, high-grade glioma, meningioma, and pituitary adenoma. We report findings from the signal search for 3 tumor types: glioblastoma,[29,42] craniospinal tumors (including chordomas),[30,43] and meningioma (specifically of the optic nerve sheath).[32]

For the 2012 HTA, no comparative study designs were found among SRs and primary studies and all COE grades were *Very Low* for survival, tumor control, and harms. In contrast, all 5 SRs from the signal search included comparative designs.[29,30,32,42,43] Survival outcomes comparing IMRT to conventional EBRT favored IMRT (**Table 3**). Concerning harms, there were mixed results; in 1 review,[32] IMRT had fewer harms than conventional EBRT, and in another, there were inconsistent results with regards to secondary malignancy risk[30]; in the remaining review, harms were similar between therapies.[42] Compared to PBT or carbon ion, survival and tumor control outcomes for IMRT were similar or worse.[30,43] Results for harms were mixed: no difference in unspecified harms for IMRT compared with PBT but worse OAR sparing for IMRT.[30,32] The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 3. Signals for Update Search: Brain and Craniospinal Cancers

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	No comparative studies/ *Very low* for all tumors	Compared to EBRT, survival outcomes for IMRT were similar or better. (k=3) *Glioblastoma (k=2)* *Craniospinal tumor (k=1)*	Yes, for an update to conditions for coverage

		Compared to PBT or carbon ion, survival outcomes for IMRT were similar or worse. (k=2) *Craniospinal Tumor (k=2)*	
Tumor control	NR	Compared to PBT or carbon ion, tumor control outcomes for IMRT were similar or worse. (k=2) *Craniospinal Tumor (k=2)*	
Harms	No comparative studies/ *Very low* for all tumors	IMRT mixed results compared to EBRT (k=2) *Craniospinal tumors (k=1)* *Meningioma (k=1)* IMRT mixed results compared to PBT (k=2) *Craniospinal tumors (k=1)* *Meningioma (k=1)*	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews, NR = not reported; PBT=proton beam therapy.

Breast Cancer

In the 2012 HTA, both whole and partial breast radiation were included. Survival, tumor control, QOL, and harm outcomes were no different between IMRT and comparator groups; cost of IMRT was higher than EBRT. With the exception of QOL, COE was *Low*. The 2012 HTA was based on 2 SRs, which included RCTs, comparative and non-comparative NRSIs, the latter being the majority.

In our signal search, we identified 3 SRs (cumulative sample size range 408 to 8,211), which all included comparative study designs and reported harms.[44-46] Harms reported included sparing of OAR,[44], radiation dermatitis,[45] and additional toxicities such as edema and fat necrosis.[46] Lower harm to OARs and radiation dermatitis were associated with IMRT compared with EBRT; there was no difference for other harm outcomes. Of note, the largest SR (k = 27), cumulative sample size 8,211) evaluating the outcome of radiation of dermatitis included only RCTs.[45] The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 4. Signals for Update Search: Breast Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	No difference/*Low*	None	Yes, for an update to conditions for coverage
Tumor Control	No difference/ *Low*	None	
QOL	No difference/*Moderate*	None	
Harms	No difference/ *Low*	Fewer harms IMRT (k = 3)	
Cost	IMRT higher cost/ *Low*	None	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Female Pelvic Cancers

The 2012 HTA reported improved survival outcomes and fewer harms for IMRT compared to EBRT for cervical cancer based on 1 SR with 1 comparative NRSI (COE *Low*). Endometrial cancer, vaginal cancer, and paraaortic lymph node metastases were not identified as tumor types in the signal search.

The 4 SRs from our signal search included studies with comparative study designs and reported outcomes of radiation treatment for cervical cancer [47] or combined gynecologic cancers including cervical, endometrial, and vaginal cancers (**Table 5**).[48-50] Cumulative sample sizes ranged from 229 to 1,008. For cervical cancer, there were no significant differences in survival outcomes between IMRT and conventional IMRT.[47] IMRT had more favorable survival outcomes compared with EBRT for general gynecologic cancers,[48,49] and no difference in locoregional recurrence between treatment groups.[48] There were fewer pelvic insufficiency fractures in patients with cervical cancer receiving IMRT compared to non-IMRT.[49] GI and GU toxicities for patients with multiple gynecologic cancers were lower for patients receiving IMRT.[47,49,50] The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 5. Signals for Update Search: Female Pelvic Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	*Cervical Cancer* Favor IMRT/ *Low*	*Cervical cancer* No difference (k=1) *Multiple cancers* Longer survival IMRT (k=2)	Yes, for an update to conditions for coverage
Tumor Control	NR	*Multiple cancers* No difference (k=2)	
Harms	*Cervical Cancer* Fewer harms IMRT/ *Low*	*Cervical cancer* Fewer harms IMRT (k=1) *Multiple cancers* Fewer harms IMRT (k=3)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews; NR = not reported.

Gastrointestinal Cancers

Anal Cancer

In the 2012 HTA, IMRT was associated with improved survival outcomes with regards to overall survival, progression-free survival, and locoregional control compared to EBRT and IMRT had fewer harms with regards to GI events. The COE for each outcome was *Very Low*. Studies of small comparative NRSIs and case-series served as the basis of the COE assessment

We identified 2 SRs (cumulative sample size range 1,265 to 3,178) reporting on survival outcomes and harms of IMRT,[28,51] both which included comparative study designs (**Table 6**). Overall survival results were mixed for IMRT compared with EBRT and no different for metastases-free survival. Compared to PBT, there was no difference for IMRT with regards to overall survival, progression-free survival, and local recurrence. Toxicities for IMRT compared to PBT were not different. This signal search identified several differences in outcomes from the 2012 HTA, including change in direction of effect, new comparative studies, and a new comparator. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 6. Signals for Update HTA: Anal Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal

Survival	Favor IMRT/*Very Low*	Mixed results or no difference for IMRT compared with EBRT (k=2) No difference for IMRT compared to PBT (k=1)	Yes, for an update to conditions for coverage
Tumor control	Favor IMRT/ *Very Low*	No difference IMRT compared to PBT (k=1)	
Harms	Fewer harms IMRT/ *Very Low*	No difference IMRT compared to PBT (k=1)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews, PBT=proton beam therapy.

Esophageal Cancer

In the 2012 HTA, no conclusions could be reached for IMRT regarding overall survival and harms due to lack of comparative data. The COE was *Very Low*. We identified 2 SRs (cumulative sample size range 567 to 1,755) reporting on the survival rate and harms of IMRT.[52,53] Both SRs included comparative study designs. For IMRT, overall survival was either better than or similar to EBRT, whereas disease-free survival was better than EBRT (**Table 7**). Adverse events and toxicities were either lower for IMRT compared to EBRT or no different. No other outcomes were reported. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 7. Signals for Update HTA: Esophageal Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	No conclusions IMRT/*Very Low*	Longer or similar survival outcomes (k=2)	Yes, for an update to conditions for coverage
Harms	No conclusions IMRT/ *Very Low*	Fewer harms or no difference IMRT (k=2)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Gastric Cancer

In the 2012 HTA, IMRT was found to have fewer harms than EBRT based on two small comparative NRSIs. The COE was *Very Low*. The signal search identified 1 SR that included comparative study designs (cumulative sample size 2,115) reporting on the harms of IMRT.[54] Harm findings from the signal search were consistent with 2012 HTA (**Table 8**). No other outcomes were reported. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 8. Signals for Update HTA: Gastric Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Harms	Fewer harms IMRT/ *Very Low*	Fewer harms IMRT (k=1)	Yes, for an update to conditions for coverage

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Liver Cancer

In the 2012 HTA, no conclusions could be reached for IMRT regarding survival and harms due to lack of comparative data in patients with liver cancer. The COE was *Very Low*. We identified

3 SRs (cumulative sample size range 516 to 874) reporting on the survival rate and harms of IMRT,[55-57] all of which included studies with comparative study designs. Overall survival and tumor control were better for IMRT compared to EBRT (**Table 9**). There was no difference in disease-free survival between IMRT and EBRT. Toxicities were either lower or no different for IMRT compared to EBRT. No other outcomes were reported. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 9. Signals for Update HTA: Liver Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	No conclusions IMRT/ *Very low*	Longer survival IMRT (k=1)	Yes, for an update to conditions for coverage
Tumor control	None	Greater tumor control IMRT (k=1)	
Harms	No conclusions IMRT/ *Very low*	Fewer harms or no difference IMRT (k=3)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Pancreatic Cancer

In the 2012 HTA, no conclusions could be reached for IMRT regarding harms due to lack of comparative data. The COE was *Very Low*. We identified 1 SR that included comparative study designs (cumulative sample size 859) reporting on the harms of IMRT.[58] In contrast to the 2012 HTA, SRs identified in the signal search reported that GI adverse events were lower for IMRT compared to EBRT (**Table 10**). No other outcomes were reported. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 10. Signals for Update HTA: Pancreatic Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
GI adverse events	No conclusions IMRT/ *Very low*	Fewer harms IMRT (k=1)	Yes, for an update to conditions for coverage

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, GI = gastrointestinal; IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Rectal Cancer

In the 2012 HTA, no conclusions could be reached for IMRT regarding survival and harms due to lack of comparative data. The COE was *Very Low*. We identified 2 SRs reporting on the survival rate and harms of IMRT for rectal cancer,[18,59] both included comparative study designs (cumulative sample size 13 to 451). Overall survival was either better or no different for IMRT compared to EBRT (**Table 11**). There was no difference regarding progression-free survival. Toxicities were either lower or not different for IMRT compared to EBRT. No other outcomes were reported. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 11. Signals for Update HTA: Rectal Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal

Survival	No conclusions IMRT/ *Very Low*	Longer survival or no difference IMRT (k=2)	Yes, for an update to conditions for coverage
Harms	No conclusions IMRT/ *Very Low*	Fewer harms or no difference IMRT (k=2)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Head and Neck Cancers

The 2012 HTA graded COE only for the following 3 harm outcomes: xerostomia, osteonecrosis of the jaw, and hearing loss. IMRT was associated with fewer of these harms than conventional EBRT. COE ranged from *Moderate* to *Very Low*. Other outcomes were reported in a limited number of studies and included nausea, vomiting, fatigue, dermatitis, mucositis, dysphagia, laryngeal symptoms. In this signal search, 20 SRs (cumulative sample size range 213 to 13,304) reported harm outcomes for comparisons of IMRT and conventional EBRT or PBT.[20,22,24-26,41,60-71] All but 2 SRs included comparative study designs.

Our signal search found the same direction of effect for the 3 harm outcomes with COE graded in the 2012 HTA (**Table 12**). New SRs have included outcomes of death and any adverse events. There was no difference in mortality between treatments.[62,69] Any adverse events were lower in the IMRT group compared to conventional EBRT[22-24,62,67,69]; however, any adverse events were higher for the IMRT group compared to PBT.[22] We identified various other harm outcomes with limited data.

IMRT is considered the standard of care[72] for head and neck cancers and is already covered based on the 2012 HTCC coverage decision. We did not identify any signal suggesting a change in the harms associated with IMRT compared to EBRT. New evidence comparing IMRT to PBT is available; however, it is unclear how this evidence would impact the existing coverage decision.

Table 12. Signals for Update Search on Harms: Head and Neck Cancers

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Xerostomia	Fewer harms IMRT/*Moderate*	Fewer harms IMRT (k=10)	No
Osteonecrosis of the jaw	Fewer harms IMRT/*Very Low*	Fewer harms IMRT (k=4)	
Hearing loss	Fewer harms IMRT/*Very Low*	Fewer harms of IMRT or no difference between groups (k=2)	
Various Harms	NR	Fewer harms IMRT compared to EBRT More harm of IMRT compared to PBT (n=4)	
Mortality	NR	No difference between groups (k=2)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews, NR = not reported; PBT=proton beam therapy.

Lung Cancer

In the 2012 HTA, the COE was *Low* for better overall survival with IMRT compared to 3D-CRT for non-small cell lung cancer (NSCLC) and low for no differences in distant metastasis-free survival or locoregional progression-free survival. The 2012 HTA also found *Low* COE for fewer

harms (Grade 3 pneumonitis) for IMRT. The COE for all other outcomes and for malignant mesothelioma was *Very Low*.

We identified 4 SRs evaluating IMRT for lung cancer: 2 in NSCLC[73,74] and 2 in malignant mesothelioma (**Tables 13 and 14**).[75,76] All but 1 SR included comparative NRSIs.[76] For both lung cancer types, treatment with IMRT was associated with improved survival outcomes compared with conventional EBRT.[73-75] Radiation pneumonitis and radiation esophagitis were less frequent for IMRT compared to EBRT in the 2 SRs of malignant mesothelioma.[73,74] The signal search did not identify any SRs reporting tumor control, QOL, or cost outcomes.

Results of the signal search were consistent with most findings from the 2012 HTA. SRs reporting harms of IMRT used for treatment of malignant mesothelioma showed fewer harms for IMRT versus no difference in 2012. The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 13. Signals for Update Search: NSCLC

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	Improved survival IMRT/*Low*	Longer survival/IMRT (k=2)	Yes, for an update to conditions for coverage
Tumor Control	No difference/*Low*	NR	
Harms	No difference/*Low*	NR	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews, NR = not reported; NSCLC=non-small cell lung cancer, PBT=proton beam therapy.

Table 14. Signals for Update Search: Malignant Mesothelioma

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Survival	Improved survival IMRT/*Low*	Improved survival outcomes (k=1)	Yes, for an update to conditions for coverage
Tumor Control	No difference/*Low*	NR	
Harms	No difference/*Low*	Fewer harms IMRT (k=2)	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews; NR = not reported.

Prostate Cancer

In the 2012 HTA, IMRT was found to have fewer harms with regards to GI harms, GU harms, erectile dysfunction, and hip fracture. The COE for each outcome was *Low*, with the exception of GI adverse events, which was evaluated as *Moderate* COE.

In this signal search, we identified 10 SRs (cumulative sample size range 723 to 19,898) reporting on the harms of IMRT,[17,27,37-39,77-81], including 6 SRs that included comparative study designs (**Table 15**).[17,27,38,39,77-81] Findings from SRs with comparative study designs identified by the signal search were consistent with the 2012 HTA for GI adverse events. In contrast to the 2012 assessment, GU adverse events were either higher in the IMRT compared to EBRT or no different. No studies reported on outcomes of hip fracture or erectile dysfunction.

With the exception of GU adverse events, there is no signal for an update of other IMRT harms. With respect to GU harms, though some SRs report more harms of IMRT compared with EBRT,

the current standard radiation technique for prostate cancer is IMRT,[82] and an updated HTA would likely not change the current HTCC coverage determination.

Table 15. Signals for Update HTA: Prostate Cancer

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
GI adverse events	Fewer harms IMRT/*Moderate*	Fewer harms IMRT (k=6)	No
GU adverse events	Fewer harms IMRT/ *Low*	Mixed results: More harm IMRT or no difference (k=5)	
Hip fracture	Fewer harms IMRT/ *Low*	None	
Erectile dysfunction	Fewer harms IMRT/ *Low*	None	

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, GI=gastrointestinal, GU=genitourinary, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Sarcoma

In the 2012 HTA, IMRT was reported to have harms of nausea, fatigue, dry mouth, pharyngitis or esophagitis, and pain. However, there were no comparative studies. The COE for IMRT harms was rated as *Very Low.*

For this signal search, we identified 2 SRs (cumulative sample size range 227 to 2,796) reporting on the harms of IMRT,[40,83] 1 of which included comparative study designs (**Table 16**).[83] The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 16. Signals for Update Search: Sarcoma

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
Harms	Unable to determine/*Very low*	Fewer harms IMRT (k=1)	Yes, for an update to conditions for coverage

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Urologic Cancers

Urologic cancers were not included in the 2012 HTA. For the signal search, we identified 1 Cochrane SR assessing GI toxicities of treatment of primary pelvic cancers including urological cancers (sample size 215).[50] There were fewer GI adverse events for patients with urological cancers treated with IMRT compared to EBRT (**Table 17**). The new evidence could inform an update to the conditions for coverage in the existing coverage decision.

Table 17. Signals for Update Search: Urologic Cancers

Outcome	2012 Findings/COE	2025 Signal Search Findings*	Signal
GI adverse events	Not included	Fewer harms IMRT (k=1)	Yes, for an update to conditions for coverage

*Findings from comparative studies only are summarized; comparator is EBRT unless otherwise specified.
Abbreviations: COE=certainty of evidence, EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, k=number of comparative systematic reviews.

Multiple Cancers

Two SRs included multiple types of cancer, including one focused on evaluating toxicities of IMRT in children.[16] Only 1 included study in this review was comparative; it evaluated IMRT

compared with EBRT (2D-CRT) for a head and neck cancer. Xerostomia and hearing loss were found to occur more frequently for EBRT compared to IMRT. The remaining studies in this SR were single arm studies for range of cancers for pediatric patients. Reported harms lacked precise and valid estimate of the frequency of late toxicities. The other SR evaluated cost-effectiveness; IMRT was more cost-effective than EBRT but inconsistencies between studies limited conclusions.[84]

Ongoing Studies

We searched ClinicalTrials.gov for ongoing Phase 3 trials of IMRT and found 6 relevant trials, all in the recruitment phase **(Table 18).**[85-90]

Table 18. Ongoing Phase 3 Clinical Trials of IMRT

Registration Number	Cancer Site	Title	Comparator	Status
NCT01893307	Head and Neck	Intensity-Modulated Proton Beam Therapy or Intensity-Modulated Photon Therapy in Treating Patients With Stage III-IVB Oropharyngeal Cancer	PBT	Recruiting
NCT07000643	Head and Neck	Phase III Non-Inferiority Trial of Proton Versus Photon Therapy for Nasopharyngeal Carcinoma	PBT	Recruiting
NCT06846450	Head and Neck	Phase 3 Trial Comparing IMRT or IMPT Plus CIRT for Patients With Locally Advanced NPC	PBT with EBRT	Recruiting
NCT03801876	Esophagus	Comparing Proton Therapy to Photon Radiation Therapy for Esophageal Cancer	PBT	Recruiting
NCT06509724	Cervical Cancer	Comparison of Conventional and Hypofractionated IMRT in High-Risk Cervical Cancer Post-Radical Hysterectomy (POHIM-P3)	EBRT	Recruiting
NCT01185132	Breast Cancer	Intensity Modulated Radiotherapy (IMRT) vs. 3D-conformal Accelerated Partial Breast Irradiation (APBI) for Early-Stage Breast Cancer After Lumpectomy (2009-APBI)	EBRT	Recruiting

Abbreviations: CIRT=carbon ion radiation therapy; EBRT=external beam radiation therapy, IMRT=intensity-modulated radiation therapy, PBT=proton beam therapy.

4. Discussion and Conclusions

This signal search reviewed SRs published after the 2012 HTA on IMRT. The prior coverage determination specified coverage of IMRT for head and neck and prostate cancer as well as for other cancers under the condition that it was being used to spare adjacent critical structures to prevent toxicities or was being used within the context of a registry or cohort with outcome data collection. Our signal search identified new evidence since the 2012 HTA. In this new evidence, we did not identify any signal for new harms from IMRT when compared to conventional EBRT. We identified 8 SRs which compared IMRT with PBT (a newer form of EBRT).[22,28-34] Further, our search of ClinicalTrials.gov yielded 4 ongoing trials comparing IMRT to PBT, which was not included as a comparator in the 2012 HTA. However, its not clear that updating the 2012 HTA with data from these PBT comparisons would influence the existing coverage decision given that IMRT is already covered (albeit with some conditions for most cancers), and PBT is also a covered therapy for some cancers.

In the 2012 HTA, the certainty of evidence for benefit or harms of IMRT for many cancer types was judged as *Low* or *Very low*, sometimes with inconclusive direction of effect, often related to limited or no comparative data for IMRT. In the 2012 HTA, SRs and primary studies often only included case series or small cohorts. In contrast, across several cancer types in the signal search, many SRs included studies with RCT or comparative NRSI study designs. With the availability of more comparative studies, it is likely that intervention-comparator-outcome combinations would be graded with a higher COE in a future HTA update. An updated HTA with this new evidence could influence the conditions currently in place for the existing coverage decision for cancers other than head/neck and prostate (**Table 19**).

Table 19. Summary of Signals for Update Search

Cancer Types	Signal
Head & Neck Prostate	None
Brain/craniospinal Breast Female Pelvic Cancers GI: Anal GI: Esophageal GI: Gastric GI: Liver GI: Pancreatic GI: Rectal Lung Sarcoma Urologic	New evidence available with findings that fill previous evidence gaps or increase certainty of conclusions in the 2012 HTA. This new evidence may influence the existing coverage conditions in the 2012 coverage decision which requires the need to spare critical structures adjacent to treatment sites to prevent toxicities within the expected life span or for treatment in the context of evidence collection or submission of outcome data.

4.1 Limitations

This signal search has several limitations. First, we searched a single electronic database (PubMed); therefore, we may have missed relevant SRs published in journals not indexed in PubMed. Second, we conducted a limited data abstraction, and we did not conduct risk-of-bias assessments. We also did not perform GRADE COE assessments. Due to the volume of SRs, the signal search evaluation did not include primary studies. We also did not perform an exhaustive review of clinical practice guidelines for each cancer type.

The majority of SRs in this signal search reported harms outcomes, followed by survival outcomes. Tumor control, QOL, and pain were not frequently reported outcomes. However, the limited amount of data on these outcomes may be related to the inclusion criteria of the specific SR rather than the availability of data on those outcomes, particularly in the context of a larger number of comparative studies identified since 2012. For example, 1 SR evaluating radiation dermatitis from treatment of breast cancer included only RCTs.[45] Twenty-seven RCTs were included in the SR and there likely may be additional relevant outcomes that the primary trials reported that were not included for an SR on a specific harm.

4.2 Conclusions

A signal search of IMRT for cancer treatment identified new and potentially more robust evidence from comparative studies across multiple cancer types. This new evidence suggests an

updated HTA may find a higher certainty of evidence for a direction of effect favoring IMRT (larger benefit, fewer harms, or both) compared to conventional EBRT, which may influence the 2012 coverage conditions that currently apply for cancers other than head and neck and prostate.

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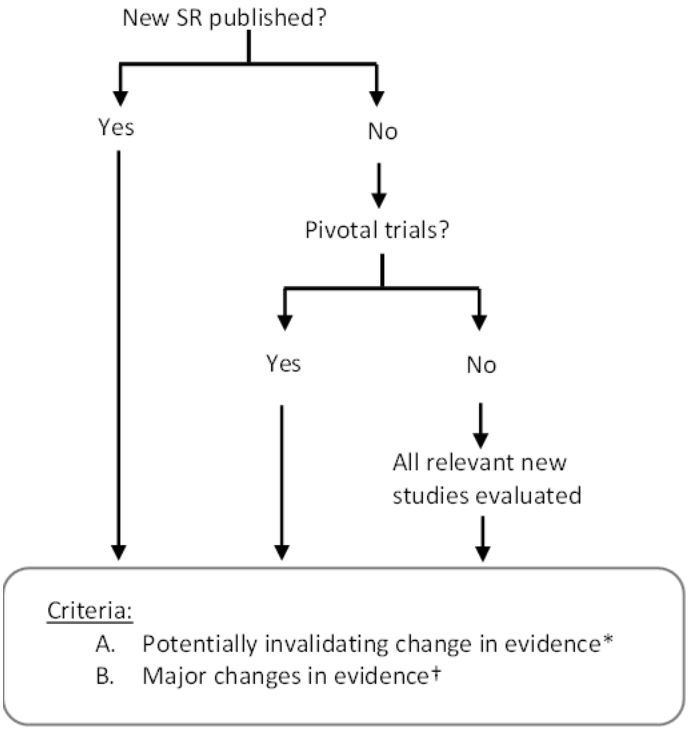
Appendix A. Algorithm of the Modified Ottawa Method of Identifying Signals for SR Update



**A-1. Opposing findings: Pivotal trial or SR including at least one new trial that characterized the treatment in terms opposite to those used earlier*
A-2. Substantial harm: Pivotal trial or SR whose results called into question the use of the treatment based on evidence of harm or that did not proscribe use entirely but did potentially affect clinical decision making
A-3. Superior new treatment: Pivotal trial or SR whose results identified another treatment as significantly superior to the one evaluated in the original review, based on efficacy or harm.
†B-1. Important changes in effectiveness short of "opposing findings"
B-2. Clinically important expansion of treatment
B-3. Clinically important caveat
B-4. Opposing findings from discordant meta-analysis or nonpivotal trial

Appendix B. Search Strategy

Below is the search strategy for the signal search. These terms were combined with search terms for the cancer types evaluated in the 2012 HTA.

Table B-1. PubMed Search Strategy, January 1, 2013 to April 24, 2015

Search number	Query	Results
1	Radiotherapy, Intensity-Modulated[mh]	14,422
2	(radiother* OR therap* OR treat* OR regimen* OR session*) AND ("intensity modulat*")	22,180
3	imrt [tiab] OR "Volumetric Modulated Arc Therapy" OR VMAT OR tomotherapy	25,011
4	"intensity modulated radiotherapy" OR "intensity modulated radiation therapy"	13,053
5	rt [sh]	217,946
6	radiotherapy [mh]	214,095
7	#5 OR #6	322,358
8	#7 AND #4	10,149
9	#8 OR #1 OR #2 OR #3	25,735
10	("systematic review" OR "systematic literature review" OR systematic review [pt] OR cochrane OR systematic [sb] OR meta-analysis [pt] OR "meta-analysis")	551,848
11	#9 AND #10	370
12	#11 AND eng [la]	358
13	#12 AND 2012:2025 [dp]	327

Note: Search adapted from terminology and strategy used in 2012 report; the 2012 report search was conducted in April 2012.

Appendix C. Results for Individual Systematic Reviews

Table C-1. Gastrointestinal Cancers

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Troester, 2024[28]	GI, Anal	NRSI comparative	2000 to 2024 k = 3 n = 3,178	Adults	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT, Proton therapy	Overall Survival: Conflicting evidence for IMRT vs. CRT Disease free survival: No difference for IMRT vs. CRT Metasases free survival: No difference for IMRT vs. CRT Progression-free survival: No difference for IMRT vs. proton therapy Tumor control: None Local recurrence: No difference for IMRT vs. proton therapy QOL: None Pain: None Harms: Acute and late overall toxicity: No difference for IMRT vs. proton therapy Cost:None
Yang, 2024[55]	GI, Liver	RCT, NRSI comparative	NR k = 9 n = 516	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Surgery	Conventional EBRT	Overall survival rate higher for IMRT vs. 3D-CRT (not significant) No significant difference in disease-free survival rate between IMRT and 3D-CRT Tumor control: None Local control rate significantly higher for IMRT vs. 3D-CRT QOL: None Pain: None Harms: Grade 2-4 toxicities were similar between IMRT and 3D-CRT Cost:None
Jang, 2023[56]	GI, Liver	NRSI comparative, NRSI non-comparative	Inception to 2017 k = 19 n = 874	Not reported	Intervention: Unspecified IMRT, Volumetric	None	Survival: None Tumor control: None QOL: None Pain: None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
					modulated arc therapy (VMAT) Co-treatment Yes, Chemotherapy		Harms: Grade IV or V radiation pneumonitis after radiochemotherapy with IMRT for esophageal cancer was lower than 3D-CRT for GRADE 1 and 2; No Grade 3 or higher cases. Cost: None
Wu, 2021[57]	GI, Liver	NRSI comparative, NRSI non-comparative	1980 to 2018 k = 130 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL: None Pain: None Harms: lower incidence of fecal incontinence, including severe (Grade 2 or 3) fecal incontinence in the IMRT group compared to 3D-EBRT Cost: None
Sipaviciute, 2020[18]	GI, Rectal	NRSI comparative	Inception to 2016 k = 7 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: Meta-analysis showed that the 3D-CRT group had a lower survival chance than the IMRT group (OR: 0.68 [95% CI, 0.52 to 0.90], *P*=.007). Tumor control: None QOL: None Pain: None Harms: No difference in harms for radiation pneumonitis or radiation esophagitis. Cost: None
Ren, 2019[54]	GI, Gastric	NRSI comparative	1995 to 2019 k = 9 n = 2115	Adults	Intervention: VMAT Co-treatment Yes, Surgery	Conventional EBRT	Survival: None Tumor control: None QOL: None Pain: None Harms: Late toxicity lower for IMRT compared to 3D-CRT -Adverse events were proctitis and enteritis Cost: None
Tonison, 2018[52]	GI, Esophagus	NRSI comparative	1998 to 2023 k = 29 n = 1755	Adults	Intervention: Unspecified IMRT, Helical	None	Survival with IMRT for HCC similar to that of 3D-CRT Tumor control: None QOL: None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
					tomotherapy, VMAT Co-treatment Yes, Chemotherapy		Pain: None Harms:Hepatic toxicity after IMRT is lower than that after 3D-CRT Cost:None
Pan, 2018[51]	GI, Anal	RCT, NRSI comparative	2014 to 2023 k = 12 n = 1265	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Surgery	Conventional EBRT	Overall survival: Patients who underwent IMRT after surgery had a better overall survival than those who underwent 3D-CRT Disease-free survival: Patients who underwent 3D-CRT after surgery experienced less recurrence than did patients who underwent IMRT Tumor control: None QOL: None Pain: None Harms:None Cost:None
Wee, 2018[59]	GI, Rectal	RCT, NRSI comparative	Inception to 2014 k = 13 n = IMRT range 13 to 71; 3D-CRT 30-451	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: No differences in overall survival or progression-free survival Tumor control: None QOL: None Pain: None Harms:Nausea and vomiting. diarrhea, gastrointestinal late toxicities lower in the IMRT group compared with 3D-CRT group Cost:None
Xu, 2017[53]	GI, Esophagus	RCT	2005 to 2021 k = 5 n = 567	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Surgery	Conventional EBRT	Overall survival and disease-free survival higher for IMRT+Surgery compared with 3D-CRT+Surgery Tumor control: None QOL: None Pain: None Harms:Fewer adverse events IMRT vs. 3D-CRT; No difference in grade 3-4 toxicities Cost:None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Bittner, 2015[58]	GI, Pancreas	RCT, NRSI comparative	Inception to 2017 k = 6 n = 859	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival:None Tumor control: None QOL: None Pain: None Harms:IMRT, compared to 3D-CRT, significantly reduced overall GI, diarrhea and proctitis with a pooled ORs of 0.38 (95% CI, 0.26 to 0.54; *P*<0.01), 0.32 (95% CI, 0.20 to 0.50; *P*<0.01) and 0.60 (95% CI, 0.42 to 0.86; *P*<0.01), respectively Cost:None

Abbreviations: CRT = conformal radiation therapy; CI = confidence interval; EBRT = external beam radiation therapy; GI = gastrointestinal; IMRT = intensity-modulated radiation therapy; NR = not reported; NRSI = nonrandomized studies of interventions; OR = odds ratio; QOL = quality of life; RCT = randomized controlled trial; SR = systematic review.

Table C-2. Breast Cancer

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Protopapa, 2022[44]	NRSI comparative, NRSI non-comparative	1998 to 2021 k = 32 n = 408	Adults	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	In general, IMRT had lower target volumes than 3D-CRT, but 3D-CRT had lower OAR sparing
Yee, 2018[45]	RCT	Inception to 2017 k = 27 n = 8211	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy, surgery	Conventional EBRT	Patients who underwent IMRT in all studies experienced significantly less radiation dermatitis compared with those receiving conventional radiation therapy
Jensen, 2017[46]	RCT, NRSI comparative	Inception to 2015 k = 11 n = 2956	Adults	Intervention: Unspecified IMRT Co-treatment Yes, Surgery	Conventional EBRT	Harms: No difference in odds of developing edema, hyperpigmentation, fat necrosis, pain, induration, late toxicity for IMRT vs. standard wedge radiation therapy; Potential protective associations for dermatitis and moist desquamation side effects for IMRT vs. standard wedge radiation therapy

Abbreviations: CRT = conformal radiation therapy; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; NRSI = nonrandomized studies of interventions; OAR = organs at risk; RCT = randomized controlled trial; SR=systematic review.

Table C-3. Female Pelvic Cancers

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Sapienza, 2020[49]	Female Pelvis, Multiple	NRSI comparative, NRSI non-comparative	1980 to 2018 k = 21 n = 392	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Unspecified, None	Survival: None Tumor control: None QOL: None Pain: None Harms: Sites include cervix, endometrium, vagina Pelvic insufficiency fractures lower in the IMRT group compared to other RT techniques Cost: None
Lin, 2018[47]	Female Pelvis, Cervix	RCT, NRSI comparative	Inception up to 2018 k = 6 n = 1,008	Adults	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: No significant difference in overall survival and disease-free survival for IMRT vs. 3D-CRT or 2D-CRT Tumor control: None QOL:None Pain:None Harms: Significantly lower incidence of acute GI toxicity and GU toxicity for IMRT vs. 3D-CRT or 2D-CRT Fewer incidences of chronic genitourinary toxicity for IMRT vs. 3D-CRT or 2D-CRT Cost:None
Lawrie, 2018[50]	Pelvis, mulitple	RCT, NRSI comparative	Inception to 2017 k = 4 n = 444	Adults	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: Reduced acute GI toxicity (grade 1+) for IMRT vs. 3D-CRT No difference in acute or late GI toxicity (grade 1+) No difference in acute or late GI toxicity (grade 2+) Diarrhea and vomiting worse for IMRT vs. 3D-CRT Cost: None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
D'Souza, 2012[48]	Female Pelvis, Multiple	NRSI comparative	NR k = 4 n = 619	Adults	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT, Unspecified	Survival:Overall survival higher in IMRT vs. non-IMRT Recurrence-free survival no difference Tumor control: None Locoregional recurrence no difference QOL: None Pain: None Harms: Fewer acute GI and GU harms for IMRT vs. 3D-CRT Fewer late GI harms for IMRT vs. 3D-CRT No difference in late GU harms Cost: None

Abbreviations: CRT = conformal radiation therapy; GI = gastrointestinal; GU = genitourinary; IMRT = intensity-modulated radiation therapy; NRSI = nonrandomized studies of interventions; QOL = quality of life; RCT = randomized controlled trial; SR=systematic review.

Table C-4. Head and Neck Cancers

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Chen, 2024[91]	Head & Neck, Nasopharynx	RCT, NRSI comparative	Inception to 2022 k = 9 n = 1,659	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Not reported	Survival: None Tumor control: None QOL:Results are mixed for the IMRT subgroup for different QOL measures; Some measures or measure components show improvement that is greater in the IMRT group compared with comparator, while others show no difference or worsening in the IMRT group Pain:None Harms: None Cost:None
deAlameida, 2024[36]	Head & Neck, Oropharynx	NRSI non-comparative	Inception to 2023 k = 11 n = 1,434	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy and Surgery	None	Survival: None Tumor control: None QOL:None Pain:None Harms: Incidence of osteoradionecrosis: 8% (95% CI, 6% to 11%) Cost:None
Razavian, 2023[19]	Head & Neck, Larynx	NRSI comparative, NRSI non-comparative	2000 to 2022 k = 15 n = 2,083	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	None	Survival: None Tumor control: None QOL:None Pain:None Harms: IMRT had fewer acute and late toxicities compared with CRT Study reports post-IMRT toxicity frequencies by adverse event Most common: Acute dysphagia, acute dermatitis, and late hoarseness (severity: 57%, 35%, and 14%, respectively). CVD events: 1.5% Late toxicity (feeding tube, edema): 0.4% to 2.2%

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
							The most commonly reported toxicities post IMRT were acute dysphagia, acute dermatitis, and late hoarseness; these were most frequently reported as grade 1 in severity (57%, 35%, and 14%, respectively) Carotid and cerebrovascular events post IMRT were reported in 2 of 130 patients (1.5%) from 3 studies; Using random effects models, the pooled rates of late (6 months or longer) feed tube use (n = 402), late grade 3 or more laryngeal edema (n = 397), and any late grade 3 or more toxicity (n = 330) were 0.4% (95% CI, 0.0% to 1.0%), 1.8% (95% CI, 0.4% to 3.1%), and 2.2% (95% CI, 0.0% to 5.1%), respectively Cost:None
Xue, 2023[20]	Head & Neck, Nasopharynx	RCT, NRSI comparative	Inception to July 2022 k = 7 n = 1,558	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: Chemoradiation with IMRT compared to chemoradiation with CCRT had elevated risk of leukopenia and thrombocytopenia; No difference with regard to anemia, hepatotoxicity, nephrotoxicity Cost:None
Wang, 2022[69]	Head & Neck, Nasopharynx	RCT, NRSI comparative, NRSI non-comparative	1990 to 2022 k = 89 n = 6,807	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Rate of radiation-induced toxicity (grade 3 or higher) was higher for IMRT vs. EBRT (CRT)

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
							No difference in treatment related mortality across treatments Cost:None
Céspedes-Ajún, 2022[65]	Head & Neck, Multiple	RCT, NRSI comparative	Inception to 2021 k = 8 n = 2,045	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: Mandibular osteoradionecrosis incidence was lower for IMRT vs. 3D-CRT (13.2% vs. 5.4%) Cost:None
Newton, 2021[21]	Head & Neck, Nasopharynx	RCT, NRSI comparative, NRSI non-comparative	1990 to 2021 k = 66 n = 4,468	Adults	Intervention: Unspecified IMRT Co-treatment Not reported	None	Survival: For early-stage or late-stage recurrent cancers (rT1-rT2), the 5-year overall survival rate was higher for IMRT and CRT Tumor control: None QOL:None Pain:None Harms: Death from treatment with IMRT was 23% Grade 3 toxicity or higher with IMRT was 39% (Single arm studies) Cost:None
Alterio, 2020[62]	Head & Neck, Oropharynx	RCT, NRSI comparative	Inception up to 2020 k = 8 n = 1,229	Adults	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Lower frequencies of acute and late toxicities for IMRT vs. 2D/3D-CRT; These toxicities included xerostomia, dysphagia, PEG tube, mucositis, skin and hematologic toxicities of grade 2 or higher No difference for death for IMRT vs. 2D/3D-RT Cost:None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Zhang, 2020[22]	Head & Neck, Sinonasal	NRSI comparative	1991 to 2019 k = 44 n = 2,282	Adults	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT, Proton therapy, Carbon ion	Survival: None Tumor control: None QOL:None Pain:None Harms: Acute grade 3-5 adverse event rate higher for IMRT vs. PRT and lower for IMRT vs. CIRT Specific adverse events were not specified. Overall adverse event rate lower for IMRT vs. CIRT Late toxic reactions were similar among IMRT, CIRT, and PRT Cost:None
Ge, 2020[64]	Head & Neck, Not specified	RCT, NRSI comparative	Inception to 2019 k = 7 n = 1,939	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Surgery	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: IMRT significantly lower scores for xerostomia than conventional radiation therapy Cost:None
Felice, 2020[66]	Head & Neck, Multiple	RCT	Inception to 2019 k = 3 n = 213	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Xerostomia grade ≥2 toxicity analysis demonstrated a benefit in favor of IMRT vs. 3D-CRT, acutely and at 1 and 2 years Cost:None
Du, 2019[23]	Head & Neck, Nasopharynx	RCT, NRSI comparative, NRSI non-comparative	Inception to 2018 k = 10 n = 13,304	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: Risk of toxicity reduced for IMRT vs. 2D-CRT, including

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
							xerostomia, trismus, and temporal lobe neuropathy induced by radiation -No significant difference in hearing loss for IMRT vs. 2D-CRT Cost:None
Gupta, 2018[61]	Head & Neck, Multiple	RCT	1995 to 2017 k = 7 n = 1,155	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Brachytherapy, chemotherapy	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Significant reduction in risk of ≥grade 2 acute and late xerostomia for IMRT vs. 2D/3D-CRT Cost:None
Leong, 2017[24]	Head & Neck, Nasopharynx	RCT, NRSI comparative, NRSI non-comparative	2005 to 2016 k = 12 n = 1,768	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	None	Survival: None Tumor control: None QOL:None Pain:None Harms:Overall rate of grade 5 toxicities was 33% Cost:None
Ursino, 2017[60]	Head & Neck, Multiple	NRSI comparative, NRSI non-comparative	2000 to 2016 k = 22 n = 1311	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT, None	Survival: None Tumor control: None QOL:None Pain:None Harms: Improved swallowing outcomes for IMRT vs. 3D-CRT Cost:None
Co, Mejia, 2014[25]	Head & Neck, Nasopharynx	RCT	NR k = 3 n = NR	Adults	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Less acute xerostomia and improvement of xerostomia at follow-up for IMRT vs. 2D-CRT using objective and physician-rated measures Cost:None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Zhang, 2015[67]	Head & Neck, Nasopharynx	RCT, NRSI comparative	Inception to 2014 k = 8 n = 3,570	Adults	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy, surgery	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Significantly lower incidence of late xerostomia for IMRT vs. 2D-CRT or 3D-CRT Significantly lower radiation-induced chronic toxicities rate (trismus and temporal lobe necrosis for IMRT vs. 2D-CRT or 3D-CRT) Cost:None
Ratko, 2014[63]	Head & Neck, Multiple	RCT, NRSI comparative	2009 to 2014 k = 15 n = 1,781	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Significantly lower risk of grade 2 or higher late xerostomia for IMRT vs. 3D-CRT Insufficient evidence on adverse events other than late xerostomia and overall radiotherapy-associated toxicities for IMRT vs. 3D-CRT Cost: None
de Almeida, 2014[41]	Head & Neck, Oropharynx	NRSI non-comparative	Inception to 2012 k = 8 n = 1,337	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	None	Survival: None Tumor control: None QOL:None Pain:None Harms:Osteoradionecrosis of the mandible was 2.6% Esophageal stenosis was 4.8% Gastrostomy tubes was 43% Cost:None
Marta, 2014[70]	Head & Neck, Not specified	RCT	Inception to 2012 k = 5 n = 871	Not reported	Intervention: Unspecified IMRT	Conventional EBRT	Survival: None Tumor control: None QOL:None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
					Co-treatment Yes, Chemotherapy, Surgery		Pain:None Harms:Significant reduced incidence of grade 2-4 xerostomia for IMRT vs. 2D-CRT or 3D-CRT Cost:None
Mujica-Mota, 2012[71]	Head & Neck, Not specified	NRSI comparative, NRSI non-comparative	1970 to 2011 k = 14 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Lower incidence of sensorineural hearing loss for IMRT vs. 2D-CRT or 3D-CRT Cost: None
Kouloulias, 2013[68]	Head & Neck, Not specified	RCT, NRSI comparative, NRSI non-comparative	2000-2013 k = 38 n = 4,587	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Reduced late xerostomia for IMRT vs. 2D-CRT and 3D-CRT No significant difference in acute mucositis for IMRT vs. 2D-CRT and 3D-CRT Cost:None
O'Sullivan, 2012[26]	Head & Neck, Multiple	RCT, NRSI comparative	Inception to 2009 k = 15 n = 1,555	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Less xerostomia and osteonecrosis in IMRT group vs. 3D-CRT/2D-CRT Improved optic nerve preservation in IMRT vs. 3D-CRT/2D-CRT group Cost:None

Abbreviations: CRT = conformal radiation therapy; CCRT = conventional cancer radiotherapy; CI = confidence interval; CIRT = carbon ion radiotherapy; CVD = cardiovascular; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; NR = not reported; NRSI = nonrandomized studies of interventions; PEG = percutaneous endoscopic gastrostomy; QOL = quality of life; RCT = randomized controlled trial; SR=systematic review.

Table C-5. Lung Cancer

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Patel, 2020[76]	Lung, malignant mesothelioma	NRSI comparative, NRSI non-comparative	Inception to 2019 k = 10 n = 780	Not reported	Intervention: Unspecified IMRT, Helical tomotherapy, Volumetric modulated arc therapy (VMAT) Co-treatment Not reported	None	Survival: Overall survival ranged from 19 to 28 months or 2 year survival 35% to 65%. Progression free survival, 12-16 months, or 2 year PFS 19 to 50%; Authors consider these results "reasonable" Tumor control: None QOL:None Pain:None Harms: IMRT produced relatively few higher-grade toxicities (grade 3 pneumonitis ranging from 0%-16%, and grades 4 and 5 pneumonitis in <1.5%); Authors consider these results "reasonable" Cost:None
Ashton, 2017[75]	Lung, malignant mesothelioma	NRSI comparative, NRSI non-comparative	1946 to 2018 k = 249 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy, surgery	Conventional EBRT, None	Survival:Improved overall survival in patients treated with modern trimodality therapy with IMRT as the radiation technique compared with conventional radiotherapy (median overall survival: 20.2 months and 12.3 months, respectively; *P*<0.001) Tumor control: None QOL:None Pain:None Harms: None Cost:None
Hu, 2016[73]	Lung, non-small cell lung cancer	NRSI comparative	Inception to 2015 k = 5 n = 12,896	Not reported	Intervention: Unspecified IMRT Co-treatment	Conventional EBRT	Survival:Overall survival was similar between IMRT and 3D-CRT Tumor control: None QOL:None Pain:None

Author, Year	Cancer Type	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
					Yes, Chemotherapy		Harms:Radiation pneumonitis: IMRT had lower incidence compared with 3D-CRT Radiation esophagitis: IMRT had higher incidence compared with 3D-CRT Cost:None
Bezjak, 2012[74]	Lung, non-small cell lung cancer	NRSI comparative	NR k = 2 n = 699	Not reported	Intervention: Unspecified IMRT Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival:Overall survival higher for IMRT vs. CRT Tumor control: None QOL:None Pain:None Harms:Pneumonitis lower for IMRT vs. CRT Cost:None

Abbreviations: CRT = conformal radiation therapy; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; NR = not reported; NRSI = nonrandomized studies of interventions; QOL = quality of life; SR=systematic review.

Table C-6. Metastatic Cancer

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Bilski, 2024[35]	NRSI non-comparative	Inception to Feb 2024 k = 4 n = 70	Adults	Intervention: Helical tomotherapy, Volumetric modulated arc therapy (VMAT) Co-treatment Yes, Chemotherapy	Conventional EBRT	Survival: None Tumor control: None QOL:Tomotherapy study: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30, global health status better in 66% Pain:None Harms: VMAT study acute toxicity (RTOG scale): G3-1 toxicity: 5.26% Tomotherapy acute toxicity (CTCAE): G1/2-5 toxicity: 39%, G3 toxicity: 23% Cost:None

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; EBRT = external beam radiation therapy; NRSI = nonrandomized studies of interventions; QOL = quality of life; RTOG = Radiation Therapy Oncology Group; SR=systematic review.

Table C-7. Multiple Cancer Types

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Alipour, 2023[84]	Cost	2000 to 2019 k = 12 n = NA	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: None Cost:IMRT likely more cost-effective than 3D-CRT but inconsistencies between studies
Beijer, 2022[16]	NRSI comparative, NRSI non-comparative	2000 to 2019 k = 13 n = NR	Both	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: For the one comparative study of IMRT vs. 2D-CRT for nsopharyngeal cancer, xerostomia and hearing loss were found to occur more frequently for 2D-CRT vs. IMRT The remaining studies in this SR are single-arm studies on use of radiation therapy for range of cancers for pediatric patients; Reported harms lack precise and valid estimate of the frequency of late toxicities Cost:None

Abbreviations: CRT = conformal radiation therapy; EBRT = external beam radiation therapy; IMRT = intensity-modulated radiation therapy; NA = not applicable; NR = not reported; NRSI = nonrandomized studies of interventions; QOL = quality of life; SR=systematic review.

Table C-8. Prostate Cancer

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Dornisch, 2024[37]	NRSI non-comparative	Inception to 2023 k = 7 n = 723	Not reported	Intervention: Unspecified IMRT, Volumetric modulated arc therapy (VMAT) Co-treatment Not reported	Unspecified, None	Survival: 5-year biochemical recurrence-free survival rates range = 69.7–100% Tumor control: None QOL:None Pain:None Harms: Acute/late grade 3+gastrointestinal toxicities range = 0%/1–10%. Acute/late grade 3+genitourinary toxicities range= 0–13%/0–5.6% Cost:None
Guo, 2023[77]	RCT, NRSI comparative	Inception to 2022 k = 20 n = 8,645	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: Conflicting results on harms: IMRT was associated with lower rate of acute and late GI adverse events compared to 3D-CRT IMRT was associated with higher rate of acute and late GU adverse events compared to 3D-CRT Cost:None
David, 2023[38]	NRSI non-comparative	2008-2021 k = 6 n = 5,840	Adults	Intervention: Unspecified IMRT Co-treatment No	None	Survival: None Tumor control: None QOL:None Pain:None Harms:The 60-month incidence of genitourinary toxicity following IMRT provided in the current study exceeds traditional expectations and is likely a conservative estimate Cost:None
Marotte, 2022[17]	NRSI comparative, NRSI non-comparative	2000 to 2021 k = 24 n = 19,898	Adults	Intervention: Unspecified IMRT Co-treatment	None	Survival: None Tumor control: None QOL:None Pain:None Harms:

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
				Yes, Brachytherapy		Late toxicity rates for elderly (>70 years) are low and most often comparable to younger populations Cost:None
Butala, 2022[31]	Cost	2000 to 2018 k = 37 n = NR	Adults	Intervention: Unspecified IMRT Co-treatment No	Proton therapy	Survival: None Tumor control: None QOL:None Pain:None Harms: None Cost:IMRT was less costly and more effective than proton therapy
Hunt, 2021[39]	NRSI non-comparative	2002 to 2018 k = 24 n = 2,714	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	None	Survival: None Tumor control: None QOL:None Pain:None Harms: Harms from comparison of pooled data from single arm studies for each radiation therapy type: Median increase in erectile dysfunction slightly higher for IMRT vs. 3D-CRT (25% vs. 17%), similar to proton therapy (25% vs. 22%) at 5 years Cost:None
Zaorsky, 2018[78]	RCT	NR k = 12 n = 6,884	Adults	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Significantly fewer late GI toxicities for IMRT vs. 3D-CRT; No difference for acute GI and GU toxicities or late GU toxicities Cost:None
Schroeck, 2017[33]	Cost	2001 to 2016 k = 49 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT, Proton therapy	Survival: None Tumor control: None QOL:None Pain:None Harms: None Cost:IMRT is more expensive from a payer's perspective compared with 3D-CRT, but also more cost effective when defined by an incremental cost

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
						effectiveness ratio <$50 000 per quality-adjusted life year -Proton beam therapy is costlier than IMRT, and its cost effectiveness remains unclear given the limited comparative data on outcomes
Di Franco, 2017[79]	RCT, NRSI comparative	NR k = 32 n = NR	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:For conventional IMRT vs. conventional 3D-CRT: Acute GI and late GU toxicities lower for IMRT vs. 3D-CRT; No difference for Late GI toxicity; Acute GU worse for IMRT vs. 3D-CRT For hypofractionated IMRT vs hypofractionated 3D-CRT: Acute and late GU and GI toxicities higher for IMRT vs. 3D-RCT Cost:None
Yu, 2016[80]	RCT, NRSI comparative	NR k = 23 n = 9,l556	Not reported	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Significant decrease in acute and late (1year, 5-10 years) gastrointestinal toxicity and late rectal toxicity for IMRT vs. 3D-CRT No difference in acute rectal toxicity, acute or late genitourinary toxicity for IMRT vs. 3D-CRT Cost:None
Amin, 2014[34]	Cost	2003-2013 k = 14 n = NR	Adults	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT, Proton therapy	Survival: None Tumor control: None QOL:None Pain:None Harms:None Cost:IMRT was more cost effective than 3D-CRT; Proton beam therapy was found not to be cost effective compared with IMRT

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Bauman, 2012[27]	RCT, NRSI comparative	2000 to 2009 k = 11 n = 4,559	Adults	Intervention: Unspecified IMRT Co-treatment No	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:Lower acute GU and late GI side effects for IMRT vs. 3D-CRT Cost:None
Ohri, 2012[81]	RCT, NRSI comparative, NRSI non-comparative	NR k = 20 n = 11,835	Not reported	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms:GI toxicity rates were lower in series employing IMRT or proton beam therapy vs. 3D-CRT Cost:None

Abbreviations: CRT = conformal radiation therapy; EBRT = external beam radiation therapy; GI = gastrointestinal; GU = genitourinary; IMRT = intensity-modulated radiation therapy; NR = not reported; NRSI = nonrandomized studies of interventions; QOL = quality of life; SR = systematic review.

Table C-9. Urological Cancer

Author, Year	Study Designs Included in SR	Years conducted No. of studies (k) Total sample size (n)	Population	Intervention(s) Cotreatment(s)	Comparator(s)	Results
Lawrie, 2018[50]	RCT, NRSI comparative	Inception to 2017 k = 4 n = 444	Adults	Intervention: Unspecified IMRT Co-treatment Not reported	Conventional EBRT	Survival: None Tumor control: None QOL:None Pain:None Harms: -Reduced acute GI toxicity (any grade) for IMRT vs. 3D-CRT -Reduced acute GI toxicity (grade 1+) for IMRT vs. 3D-CRT -Reduced acute GI toxicity (grade 2+) for IMRT vs. 3D-CRT -No difference in acute or late GI toxicity (grade 2+) -Reduced late GI toxicity (grade 2+) for IMRT vs. 3D-CRT -No difference in vomiting Cost:None

Abbreviations: CRT = conformal radiation therapy; EBRT = external beam radiation therapy; GI = gastrointestinal; IMRT = intensity-modulated radiation therapy; NRSI = nonrandomized studies of interventions; QOL.