Kansas City

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Intensity-Modulated Radiotherapy (IMRT): Head, Neck, Thyroid and Brain Cancers

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Blue KC has developed medical policies that serve as one of the sets of guidelines for coverage decisions. Benefit plans vary in coverage and some plans may not provide coverage for certain services discussed in the medical policies. Coverage decisions are subject to all terms and conditions of the applicable benefit plan, including specific exclusions and limitations, and to applicable state and/or federal law. Medical policy does not constitute plan authorization, nor is it an explanation of benefits.

When reviewing for a Medicare beneficiary, guidance from National Coverage Determinations (NCD) and Local Coverage Determinations (LCD) supersede the Medical Policies of Blue KC. Blue KC Medical Policies are used in the absence of guidance from an NCD or LCD.

NCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=NCD&contractOption=all

LCDs
https://www.cms.gov/medicare-coverage-database/search-results.aspx?keyword=&keywordType=starts&areaId=s29&docType=F,P&contractOption=all

Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for intensity-modulated radiation therapy (IMRT) for head, neck and brain cancers when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered

Intensity-modulated radiation therapy may be considered **medically necessary** for the treatment of head and neck cancers.

Intensity-modulated radiation therapy may be considered **medically necessary** for the treatment of primary and metastatic brain cancers.

Intensity-modulated radiation therapy may be considered **medically necessary** for the treatment of thyroid cancers in close proximity to organs at risk (esophagus, salivary glands, and spinal cord) and 3-D CRT planning is not able to meet dose volume constraints for normal tissue tolerance. (see Considerations)

When Policy Topic is not covered

Intensity-modulated radiation therapy is **not medically necessary** for the treatment of thyroid cancers for all indications not meeting the criteria above.

Considerations

For this policy, head and neck cancers are cancers arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and occult primaries in the head and neck region.

Organs at risk are defined as normal tissues whose radiation sensitivity may significantly influence treatment planning and/or prescribed radiation dose. These organs at risk may be particularly vulnerable to clinically important complications from radiation toxicity. Table PG1 outlines radiation doses that are generally considered tolerance thresholds for these normal structures in the area of the thyroid. Clinical documentation based on dosimetry plans may be used to demonstrate that radiation by 3-dimensional conformal radiotherapy without intensity-modulated radiotherapy would exceed tolerance doses to structures at risk.

Radiation tolerance doses for normal tissues

	TD 5/5 (Gy)[a]			**TD 50/5 (Gy)[b]**			
	Portion of organ involved			**Portion of organ involved**			
Site	**1/3**	**2/3**	**3/3**	**1/3**	**2/3**	**3/3**	**Complication End Point**
Esophagus	60	58	55	72	70	68	Stricture, perforation
Salivary glands	32	32	32	46	46	46	Xerostomia
Spinal cord	50 (5-10 cm)	NP	47 (20 cm)	70 (5-10 cm)	NP	NP	Myelitis, necrosis

Compiled from 2 sources: (1) Morgan MA, Ten Taken RK, Lawrence TS. Essentials of Radiation Therapy. In: DeVita, Helman, and Rosenberg, *Cancer: Principles and Practice of Oncology.* Philadelphia: Lippincott Williams and Wilkins. 2019; and (2) Emami B, Lyman J, Brown A, et al.

Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109-122.
NP: not provided; TD: tolerance dose.
a TD 5/5 is the average dose that results in a 5% complication risk within 5 years.
b TD 50/5 is the average dose that results in a 50% complication risk within 5 years.

Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: • With head and neck cancer	Interventions of interest are: • Intensity-modulated radiotherapy	Comparators of interest are: • 3-dimensional conformal radiotherapy • 2-dimensional radiotherapy	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity
Individuals: • With thyroid cancer in close proximity to organs at risk	Interventions of interest are: • Intensity-modulated radiotherapy	Comparators of interest are: • 3-dimensional conformal radiotherapy • 2-dimensional radiotherapy	Relevant outcomes include: • Overall survival • Functional outcomes • Quality of life • Treatment-related morbidity

Radiotherapy is an integral component in the treatment of head and neck cancers. Intensity-modulated radiotherapy has been proposed as a method to allow adequate radiation to the tumor, minimizing the radiation dose to surrounding normal tissues and critical structures.

For individuals who have head and neck cancer who receive intensity-modulated radiotherapy (IMRT), the evidence includes systematic reviews, randomized controlled trials (RCTs), and nonrandomized comparative studies. Relevant outcomes are overall survival (OS), functional outcomes, quality of life, and treatment-related morbidity. Recently published systematic reviews compared IMRT to 2-dimensional radiotherapy (2D-RT) and 3-dimensional conformal radiotherapy (3D-CRT) in patients with nasopharyngeal carcinoma. Results revealed a significant improvement in clinical oncologic outcomes (eg, OS, progression-free survival, locoregional control/survival) and toxicities such as xerostomia with IMRT in this patient population. A 2014 systematic review concluded that IMRT, when compared with 2D-RT or 3D-CRT, had no significant impact on OS or locoregional control in previously untreated patients with non-metastatic head and neck cancers; however, IMRT was associated with a significant improvement in xerostomia. A 2023 systematic review concluded that local and regional control are similar for patients with early stage glottic cancer treated with IMRT and 2D-RT or 3D-CRT. One RCT compared 2 fractionation schedules of IMRT for locally advanced head and neck cancer and found a survival benefit in using simultaneous modulated accelerated radiotherapy boost over simultaneous integrated boost-IMRT. Nonrandomized cohort studies have supported the findings that both short- and long-term xerostomia are reduced with IMRT. Overall, evidence has shown that IMRT significantly and consistently reduces both early and late xerostomia and improves quality of life domains

related to xerostomia compared with 2D-RT or 3D-CRT. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have thyroid cancer in close proximity to organs at risk who receive IMRT, the evidence includes case series data. Relevant outcomes include OS, functional outcomes, quality of life, and treatment-related morbidity. High-quality studies that differentiate the superiority of any type of external beam radiotherapy to treat thyroid cancer are not available. However, the published evidence plus additional dosimetry considerations together suggest IMRT may be appropriate for thyroid tumors in some circumstances, such as for anaplastic thyroid carcinoma or thyroid tumors located near critical structures (eg, salivary glands, spinal cord), similar to the situation for head and neck cancers. Thus, when adverse events could result if nearby critical structures receive toxic radiation doses, the ability to improve dosimetry with IMRT might be accepted as meaningful evidence for its benefit. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Additional Information
Clinical input obtained in 2012 provided a uniform consensus that IMRT is appropriate for the treatment of head and neck cancers. There was a near-uniform consensus that IMRT is appropriate in select patients with thyroid cancer. Respondents noted that IMRT for the head, neck, and thyroid tumors may reduce the risk of exposure to radiation in critical nearby structures (eg, spinal cord, salivary glands), thus decreasing the risks of adverse events (eg, xerostomia, esophageal stricture).

Background
Head and Neck Cancers
This evidence review focuses on cancers affecting the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and occult primaries in the head and neck region.

Radiotherapy Techniques
Radiation therapy may be administered externally (ie, a beam of radiation is directed into the body) or internally (ie, a radioactive source is placed inside the body, near a tumor).[1,] External radiotherapy (RT) techniques include "conventional" or 2-dimensional (2D) RT, 3-dimensional (3D) conformal RT, and intensity-modulated radiation therapy (IMRT).

Conventional External-Beam Radiotherapy
Methods to plan and deliver RT have evolved to permit more precise targeting of tumors with complex geometries. Conventional 2D treatment planning utilizes X-ray films to guide and position radiation beams.[1,] Bony landmarks visualized on X-ray are used to locate a tumor and direct the radiation beams. The radiation is typically of uniform intensity.

Three-Dimensional Conformal Radiotherapy

Radiation treatment planning has evolved to use 3D images, usually from computed tomography (CT) scans, to more precisely delineate the boundaries of the tumor and to discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Three-dimensional conformal RT (3D-CRT) involves initially scanning the patient in the position that will be used for the radiation treatment.[1,] The tumor target and surrounding normal organs are then outlined in 3D on the scan. Computer software assists in determining the orientation of radiation beams and the amount of radiation the tumor and normal tissues receive to ensure coverage of the entire tumor in order to minimize radiation exposure for at risk normal tissue and nearby organs. Other imaging techniques and devices such as multileaf collimators may be used to "shape" the radiation beams. Methods have also been developed to position the patient and the radiation portal reproducibly for each fraction and to immobilize the patient, thus maintaining consistent beam axes across treatment sessions.

Intensity-Modulated Radiotherapy

Intensity-modulated radiotherapy is the more recent development in external radiation. Treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. Similar to 3D-CRT, the tumor and surrounding normal organs are outlined in 3D by a scan and multiple radiation beams are positioned around the patient for radiation delivery.[1,] In IMRT, radiation beams are divided into a grid-like pattern, separating a single beam into many smaller "beamlets". Specialized computer software allows for “inverse” treatment planning. The radiation oncologist delineates the target on each slice of a CT scan and specifies the target's prescribed radiation dose, acceptable limits of dose heterogeneity within the target volume, adjacent normal tissue volumes to avoid, and acceptable dose limits within the normal tissues. Based on these parameters and a digitally reconstructed radiographic image of the tumor, surrounding tissues, and organs at risk, computer software optimizes the location, shape, and intensities of the beam ports to achieve the treatment plan's goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and is proposed to improve local tumor control, with decreased exposure to surrounding, normal tissues, potentially reducing acute and late radiation toxicities. Better dose homogeneity within the target may also improve local tumor control by avoiding underdosing within the tumor and may decrease toxicity by avoiding overdosing.

Other advanced techniques may further improve RT treatment by improving dose distribution. These techniques are considered variations of IMRT. Volumetric modulated arc therapy delivers radiation from a continuous rotation of the radiation source. The principal advantage of volumetric modulated arc therapy is greater efficiency in treatment delivery time, reducing radiation exposure, and improving target radiation delivery due to less patient motion. Image-guided RT involves the incorporation of imaging before and/or during treatment to more precisely deliver RT to the target volume.

Regulatory Status

In general, IMRT systems include intensity modulators, which control, block, or filter the intensity of radiation, and RT planning systems, which plan the radiation dose to be delivered.

A number of intensity modulators have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. Intensity modulators include the Innocure Intensity Modulating Radiation Therapy Compensators (Innocure) and Decimal Tissue Compensator (Southeastern Radiation Products), cleared in 2006 and 2004, respectively. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

Radiotherapy treatment planning systems have also been cleared for marketing by the FDA through the 510(k) process. They include the Prowess Panther (Prowess) cleared in 2003, TiGRT (LinaTech) cleared in 2009, and the Ray Dose (RaySearch Laboratories) cleared in 2008. FDA product code: MUJ.

Fully integrated IMRT systems also are available. These devices are customizable and support all stages of IMRT delivery, including planning, treatment delivery, and health record management. One such device cleared for marketing by the FDA through the 510(k) process is the Varian IMRT system (Varian Medical Systems). FDA product code: IYE.

Rationale

This evidence review was created in April 2009 and has been regularly updated with searches of the PubMed database. The most recent literature update was performed through May 16, 2024.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large or long

enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Head and Neck Cancers

Clinical Context and Therapy Purpose

The purpose of intensity-modulated radiotherapy (IMRT) in individuals who have head and neck cancers is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with head and neck cancers. Head and neck cancers account for about 4% of all cancer cases in the U.S.[2,] The generally accepted definition of head and neck cancers includes those arising from the oral cavity and lip, larynx, hypopharynx, oropharynx, nasopharynx, paranasal sinuses and nasal cavity, salivary glands, and occult primaries in the head and neck region. Cancers generally not considered as head and neck cancers include uveal and choroidal melanoma, cutaneous tumors of the head and neck, esophageal cancer, and tracheal cancer.

Interventions

The test being considered is IMRT. A proposed benefit of IMRT is to reduce toxicity to adjacent structures, allowing dose escalation to the target area and fewer breaks during treatment to reduce side effects.

Comparators

The following practices are currently being used to treat cancer of the head and neck: 3-dimensional conformal radiotherapy (3D-CRT) and 2-dimensional radiotherapy (2D-RT).

Outcomes

The general outcomes of interest are overall survival (OS), functional outcomes, and treatment-related morbidity (eg, xerostomia). Evaluation of patient-reported outcomes and quality of life measures are also of interest.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews
Systematic reviews have evaluated IMRT compared to 2D-RT or 3D-CRT in patients with head and neck cancers. A comparison of the trials in more recent systematic reviews that included outcomes of interest is shown in Table 1. These systematic reviews included a total of 22 articles published between 2006 and 2018. Characteristics and results of these reviews are summarized in Tables 2 and 3. Overall, Du et al (2019)[3,] and Luo et al (2019)[4,] reported significantly improved OS, locoregional free survival/control, and progression- or disease-free survival (PFS or DFS) with IMRT versus 2D-RT or 3D-CRT among patients with nasopharyngeal carcinoma (NPC). Marta et al (2014)[5,] concluded that IMRT, when compared with 2D-RT or 3D-CRT, had no significant impact on OS or loco-regional control in previously untreated patients with non-metastatic head and neck cancers. The incidence of xerostomia was significantly reduced with IMRT as compared to patients undergoing 2D-RT or 3D-CRT.[5,3,]

There are inherent limitations to the data within some of these systematic reviews, including the prevalence of retrospective and nonrandomized study designs. Some studies had small sample sizes of 20 to 50 subjects. Studies also varied considerably with regard to tumor stage, length of follow-up, and radiological dose. All of these variations contributed to heterogeneity of the data. Additionally, 1 of the reviews specifically noted the existence of publication bias for the OS outcome.[3,]

Table 1. Trials Included in Systematic Reviews of IMRT Versus 2D-RT or 3D-CRT

Trials	**Systematic Reviews**		
	Marta et al (2014)[5,]	Luo et al (2019)[4,]	Du et al (2019)[3,]
Kam et al (2007)[6,]	●		●
Lai et al (2011)[7,]		●	●
Peng et al (2012) [8,]	●	●	●
Zhou et al (2013)[9,]			●
Moon et al (2016)[10,]		●	●

Zhang et al (2015)[11,]		●	●
Qiu et al (2017)[12,]		●	●
Tang et al (2015)[13,]			●
Lee et al (2014)[14,]			●
Zhong et al (2013)[15,]			●
OuYang et al (2016)[16,]		●	
Jiang et al (2015)[17,]		●	
Fang et al (2008)[18,]		●	
Kuang et al (2012)[19,]		●	
Huang et al (2013)[20,]		●	
Chen et al (2014)[21,]		●	
Zou et al (2015)[22,]		●	
Bisof et al (2018)[23,]		●	
Pow et al (2006)[24,]	●		
Nutting et al (2011)[25,]	●		
Gupta et al (2011)[26,]	●		
Gupta et al (2012)[27,]	●		

2D-RT: 2-dimensional radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy.

Table 2. Summary of Systematic Reviews of IMRT versus 2D-RT or 3D-CRT

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Du et al (2019)[3,]	To December 1, 2018	10	Patients with nasopharyngeal carcinoma who underwent IMRT or 2D-RT	13,304 (56 to 7081)	2 RCTs; 8 nonrandomized trials	Follow-up data evaluated up to 5 years for certain outcomes
Luo et al (2019)[4,]	To November 20, 2018	13	Patients with nasopharyngeal carcinoma who underwent IMRT or CRT	14,745 (24 to 7081)	1 RCT; 1 prospective study; 11 retrospective studies	Mean follow-up: 42 to ≥ 60 months
Marta et al (2014)[5,]	To December 20, 2012	5 (6 publications corresponding to 5 trials)	Previously untreated patients with non-metastatic head and neck cancers treated with RT either primarily or combined with	871 (45 to 616)	Prospective RCTs; 4 studies compared 2D-RT with IMRT	Follow-up data evaluated up to 5 years for certain outcomes

			surgery or chemotherapy with or without brachytherapy boost			

2D-RT: two-dimensional radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; CRT: conformal radiotherapy; IMRT: intensity-modulated radiotherapy; RCT: randomized controlled trial; RT: radiotherapy.

Table 3. Results of Systematic Reviews of IMRT versus 2D-RT or 3D-CRT

Study	Overall survival	Locoregional free survival/ control rate	Progression- or disease-free survival	Metastasis-free survival	Xerostomia
Du et al (2019)[3,]		Local-regional free survival			
Total N	10,851	13,003	9380	10,432	1764
Pooled effect OR (95% CI)	1.70 (1.36 to 2.21) at 5 years	2.08 (1.82 to 2.37) at 5 years	1.40 (1.26 to 1.56) at 5 years	1.11 (0.99 to 1.24)	0.21 (0.09 to 0.51)
I^2; p value	68.7%;.007	20.7%;.272	0%;.446	17.9%;.301	87.3%;.00
Luo et al (2019)[4,]		Locoregional control			
Total N	13,018	13,899	2464	4171	
Pooled effect OR (95% CI); p value	0.51 (0.41 to 0.65); <.00001	0.59 (0.52 to 0.67); <.00001	0.77 (0.65 to 0.91);.002	0.71 (0.54 to 0.94);.01	
I^2; p value	63%;.002	44%;.06	38%;.15	54%;.03	
Marta et al (2014)[5,]		Locoregional control			
Total N	770	770			826
Pooled effect HR (95% CI); p value	1.12 (0.97 to 1.29);.11	1.07 (0.93 to 1.23);.35			0.76 (0.66 to 0.87); <.0001
I^2; p value		0%; NR			0%; NR

2D-RT: two-dimensional radiotherapy; 3D-CRT: three-dimensional conformal radiotherapy; CI: confidence interval; HR: hazard ratio; NR: not reported; OR: odds ratio.

In addition, to the systematic reviews summarized in Tables 1 to 3, Ursino et al (2017) published a systematic review of 22 studies (N=1311) that focused specifically on swallowing outcomes in patients treated with 3D-CRT or IMRT for head and neck cancer.[28,] The heterogeneity of the population limited analysis, but reviewers concluded that IMRT produced markedly better results than 3D-CRT in terms of swallowing impairments, aspiration, pharyngeal residue, and functional parameters, especially when swallowing-related organs at risk were specifically taken into account during IMRT treatment planning. The analysis was limited by a

lack of standardized evaluation questionnaires, objective instrumental parameter scores, amount and consistency of bolus administration, and timing of evaluations.

Ge et al (2020) recently evaluated the effects of IMRT as compared to conventional RT with regard to quality of life and xerostomia severity in 761 patients with head and neck cancer.[29,] This meta-analysis included data from 7 studies: 3 RCTs, 2 prospective studies, 1 prospective case control study, and 1 retrospective study. Overall, patients who underwent IMRT had a better global health status (pooled standardized mean difference [SMD], 0.80; 95% confidence interval [CI], 0.26 to 1.35; p=.004) and improved cognitive function (pooled SMD, 0.30; 95% CI, 0.06 to 0.54; p=.013) as compared to patients who underwent conventional radiotherapy (RT). Intensity-modulated radiotherapy was also associated with significantly lower scores for xerostomia than conventional RT (pooled SMD, -0.60; 95% CI, -0.97 to -0.24; p=.001). There were no differences between the groups with regard to emotional function (p=.531) and social function (p=.348). The analysis was limited by a small number of included studies, heterogeneity of data, and relatively small sample sizes.

Razavian et al (2023) performed a systematic review and meta-analysis that compared IMRT to 2D-RT or 3D-CRT in patients with early stage squamous cell carcinoma of the glottic larynx.[30,] A total of 15 studies (14 retrospective, 1 prospective) consisting of 2083 patients were included. Among the studies (n=5) that reported outcomes of both treatment modalities (IMRT and 2D-RT/3D-CRT), no significant difference was found in the rate of local failure between the 2 modalities (log odds ratio, -0.48; 95% CI, -1.09 to 0.14; p=.12). Similarly, no significant difference was found in the rate of regional failure between the 2 modalities (log odds ratio, 0.25; 95% CI, -0.66 to 1.16; p=.58). Notably, all 5 studies used for the direct comparison between the 2 treatment techniques were retrospective, and employed different IMRT techniques and heterogeneous methods for treatment volume delineation. Despite these limitations, authors state that pooled outcomes data found that IMRT for early glottis larynx cancer is associated with low rates of local and regional failure, which are in line with historic outcomes of 2D-RT/3D-CRT.

Randomized Controlled Trials

Beyond the trials included in the systematic reviews, Tandon et al (2018) published a non-blinded RCT, which compared 2 fractionation schedules of IMRT for locally advanced head and neck cancer— simultaneous integrated boost (SIB-IMRT) and simultaneous modulated accelerated radiotherapy (SMART)— with the endpoint measures of toxicity, PFS, and OS.[31,] Characteristics and results of this RCT are summarized in Tables 4 and 5. The SIB-IMRT group received 70, 63, and 56 gray (Gy) in 35 fractions to clinical target volumes 1, 2, and 3, respectively. The SMART group received 60 and 50 Gy to clinical target volumes 1 and clinical target volumes 3, respectively. No statistically significant differences in acute or late toxicities were found between the groups except in fatigue, which was experienced by 66.7% of the control group and 40.0% of the study group (p=.038). At 2 years post-treatment, PFS and OS were improved for the SMART versus SIB-IMRT group (Table 5). The small sample sizes within subgroups, which

result in greater standard errors and less power, may have prevented any meaningful interpretation of subgroup analysis. Also, due to cost, human papillomavirus (HPV) status was not part of the pre-treatment workup; the treatment response and prognosis for HPV-positive tumors are considerably different compared to HPV-negative tumors, but this factor could not be included in the analysis. Relevance, study design, and conduct limitations of the RCT are detailed in Tables 6 and 7.

Table 4. Characteristics of an RCT Comparing SIB-IMRT versus SMART

Study	Countries	Sites	Dates	Participants	Interventions
Tandon et al (2018)[31,]	India	1	June 2014 to March 2016	Adults (18 to 65 years) with Stage III or non-metastatic Stage IV locally advanced head and neck cancer	RT using standard SIB-IMRT fractionation RT using SMART boost technique

RCT: randomized controlled trial; RT: radiotherapy; SIB-IMRT: simultaneous integrated boost-intensity-modulated radiotherapy; SMART: simultaneous modulated accelerated radiotherapy.

Table 5. Results of the SIB-IMRT versus SMART RCT

Study	Overall survival (2 years)	Progression-free survival (2 years)
Tandon et al (2018)[31,]		
N	NR	NR
SIB-IMRT	60%	53.3%
SMART	86.7%	80%
p value	.02	.28

NR: not reported; RCT: randomized controlled trial; SIB-IMRT: simultaneous integrated boost-intensity-modulated radiotherapy; SMART: simultaneous modulated accelerated radiotherapy.

Table 6. Study Relevance Limitations of the SIB-IMRT versus SMART RCT

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of follow-up[e]
Tandon et al (2018)[31,]	4. Small sample sizes within each subgroup			1. Locoregional control not addressed	

RCT: randomized controlled trial; SIB-IMRT: simultaneous integrated boost-intensity-modulated radiotherapy; SMART: simultaneous modulated accelerated radiotherapy.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a]Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
[b]Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest.
[c]Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d]Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5.

Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e]Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 7. Study Design and Conduct Limitations of the SIB-IMRT versus SMART RCT

Study	Allocation[a]	Blinding[b]	Selective reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Tandon et al (2018)[31,]	3. Allocation using "chit method"	1, 2		1. During follow-up, there were 11 disease-related deaths (7 SIB-IMRT; 4 SMART) and 4 non-disease-related deaths each in both arms	3. Sample size calculated based on historical trials; power analysis done to detect a difference in incidence of toxicity not survival	1. Survival statistics required still median follow-up for deriving clinically meaningful results

RCT: randomized controlled trial; SIB-IMRT: simultaneous integrated boost-intensity-modulated radiotherapy; SMART: simultaneous modulated accelerated radiotherapy.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Nonrandomized Comparative Studies

Nonrandomized comparative studies have evaluated late toxicities and quality-of-life after treatment with IMRT, 2D-RT, and 3D-CRT.

Qiu et al (2017) published a retrospective, single-center study comparing 2D-CRT and IMRT as treatments for NPC in children and adolescents.[12,] All 176 patients (74 treated with 2D-CRT, 102 with IMRT) identified for the study were between 7 and 20 years of age and treated at a single institution. The OS rate at 5 years was significantly higher for IMRT than 2D-CRT (90.4% vs. 76.1%, respectively; hazard ratio [HR], 0.30; 95% CI, 0.12 to 0.78; p=.007), as well as the 5-year DFS rate (85.7% vs. 71.2%, respectively; HR, 0.47; 95% CI, 0.23 to 0.94; p=.029). Grade 2, 3, and 4 xerostomia (52.7% vs. 34%, respectively; p=.015) and hearing loss (40.5% vs. 22.5%, respectively; p=.01) were also significantly lower with IMRT

than with 2D-CRT. The duration of follow-up for late-onset radiation-induced toxicity and small sample size are limitations of the report.

A cross-sectional study by Huang et al (2016) assessed patients who had survived more than 5 years after treatment for NPC.[32,] Of 585 NPC survivors, data were collected on 242 patients who met study selection criteria (no history of tumor relapse or second primary cancers, cancer-free survival >5 years, completion of the self-reported questionnaire). Treatments were given from 1997 to 2007, with the transition to the IMRT system in 2002. One hundred patients were treated with IMRT. Prior to use of IMRT, treatments included 2D-RT (n=39), 3D-CRT (n=24), and 2D-RT plus 3D-CRT boost (n=79). Patients had scheduled follow-ups at 3- to 4-month intervals until 5 years posttreatment; then, at 6-month intervals thereafter. Late toxicities (eg, neuropathy, hearing loss, dysphagia, xerostomia, neck fibrosis) were routinely assessed at clinical visits. At the time of the study, the mean follow-up was 8.5 years after 2D-RT or 3D-CRT, and 6.4 years after IMRT. The IMRT group had statistically and clinically superior results for both clinician-assessed and patient-assessed (global quality-of-life, cognitive functioning, social functioning, fatigue, and 11 scales of a head and neck module) outcomes with moderate effect sizes after adjusting for covariates (Cohen *d* range, 0.47 to 0.53). Late toxicities were less severe in the IMRT group, with adjusted odd ratios (ORs) of 3.2, 4.8, 3.8, 4.1, and 5.3 for neuropathy, hearing loss, dysphagia, xerostomia, and neck fibrosis, respectively. No significant differences in late toxicities were observed between the 2D-RT and the 3D-CRT groups.

Section Summary: Head and Neck Cancer

The literature on IMRT for head and neck cancer includes systematic reviews as well as RCTs and nonrandomized comparative studies. Some of the most recently published systematic reviews compared IMRT to 2D-RT and 3D-CRT in patients with NPC. Results revealed a significant improvement in clinical oncologic outcomes (eg, OS, PFS, locoregional control/survival) and toxicities such as xerostomia with IMRT in this patient population. A 2014 systematic review concluded that IMRT, when compared with 2D-RT or 3D-CRT, had no significant impact on OS or locoregional control in previously untreated patients with non-metastatic head and neck cancers; however, a significant improvement in xerostomia was observed with IMRT. A 2023 systematic review concluded that retrospective data suggest that local and regional control are similar for patients with early stage glottic cancer treated with IMRT and 2D-RT or 3D-CRT. Nonrandomized comparative studies have compared IMRT with 3D-CRT or with 2D-RT plus 3D-CRT boost. These studies support the findings that both short- and long-term xerostomia is reduced with IMRT. Health-related quality of life was also improved with IMRT compared with 3D-CRT or with 2D-RT plus 3D-CRT boost. Comparators in these nonrandomized studies were generally older technologies (eg, 2D-RT) with older treatment protocols, both of which limit interpretation of the results. For the outcomes of PFS and OS, another RCT compared 2 fractionation schedules of IMRT and found SMART superior to SIB-IMRT in the areas of 2-year PFS and OS.

Thyroid Cancer

Clinical Context and Therapy Purpose

The purpose of IMRT in individuals who have thyroid cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with thyroid cancer in close proximity to organs at risk. Anaplastic thyroid cancer occurs in less than 2% of patients with thyroid cancer.[33,]

Interventions

The test being considered is IMRT. A proposed benefit of IMRT is to reduce toxicity to adjacent structures, allowing dose escalation to the target area and fewer breaks during treatment to reduce side effects.

Comparators

The following practices are currently being used to treat cancer of the thyroid: 3D-CRT and 2D-RT. Conventional external-beam radiotherapy is uncommonly used in the treatment of thyroid cancers, but may be considered in patients with anaplastic thyroid cancer and for locoregional control in patients with incompletely resected high-risk or recurrent differentiated (papillary, follicular, or mixed papillary-follicular) thyroid cancer. In particular, for patients with anaplastic thyroid cancer variants, which are uncommon but have often demonstrated local invasion at the time of diagnosis, RT is a critical part of locoregional therapy.

Outcomes

The general outcomes of interest are OS, functional outcomes, and treatment-related morbidity. Evaluation of patient-reported outcomes and quality of life measures are also of interest. Locoregional control and OS should be assessed at 1 and 5 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Case Series

The best available evidence for this indication consists of case series. For example, Bhatia et al (2010) published a series that reviewed institutional outcomes for anaplastic thyroid cancer treated with 3D-CRT or IMRT in 53 consecutive patients.[34,] Thirty-one (58%) patients were irradiated with curative intent. Median radiation dose was 55 Gy (range, 4 to 70). Thirteen (25%) patients received IMRT to a median of 60 Gy (range, 39.9 to 69.0). The Kaplan-Meier estimate of OS at 1 year for definitively irradiated patients was 29%. Patients without distant metastases receiving 50 Gy or more had superior survival outcomes; in this series, use of IMRT or 3D-CRT did not influence toxicity.

Schwartz et al (2009) retrospectively reviewed single-institution outcomes for patients treated for differentiated thyroid cancer with postoperative conformal external-beam RT.[35,] One hundred thirty-one consecutive patients with differentiated thyroid cancer who underwent RT between 1996 and 2005 were included. Histologic diagnoses included 104 papillary, 21 follicular, and 6 mixed papillary-follicular types. Thirty-four (26%) patients had high-risk histologic types, and 76 (58%) had recurrent disease. Extraglandular disease progression was seen in 126 (96%) patients, microscopically positive surgical margins were seen in 62 (47%) patients, and gross residual disease was seen in 15 (11%) patients. Median RT dose was 60 Gy (range, 38 to 72). Fifty-seven (44%) patients were treated with IMRT to a median dose of 60 Gy (range, 56 to 66). Median follow-up was 38 months (range, 0 to 134). Kaplan-Meier estimates of locoregional relapse-free survival, disease-specific survival, and OS at 4 years were 79%, 76%, and 73%, respectively. On multivariate analysis, high-risk histologic features, M1 (metastatic) disease, and gross residual disease were predictors for inferior disease-specific survival and OS. Intensity-modulated radiotherapy did not impact survival outcomes, but was associated with less frequent severe late morbidity (12% vs. 2%, respectively), primarily esophageal stricture.

Section Summary: Thyroid Cancer
The evidence on IMRT in individuals who have thyroid cancer includes case series data. High-quality studies that differentiate the superiority of any type of external-beam RT technique to treat thyroid cancer are not available. Limitations of published evidence include patient heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes (eg, OS vs. PFS or tumor control rates), and inconsistency in reporting or collecting outcomes. However, the published evidence plus additional dosimetry considerations together suggest IMRT for thyroid tumors may be appropriate in some circumstances (eg, anaplastic thyroid carcinoma) or for thyroid tumors located near critical structures (eg, salivary glands, spinal cord), similar to the situation for head and neck cancers. Given the rarity of both anaplastic thyroid cancer and papillary thyroid cancers that are not treatable by other methods, high-quality trials are unlikely. Thus, when adverse events could result if nearby critical structures receive toxic radiation doses, the ability to improve dosimetry with IMRT may be accepted as meaningful evidence for its benefit.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

2012 Input

In response to requests, input was received from 2 physician specialty societies (3 reviewers) and 4 academic medical centers while this policy was under review in 2012. There was a uniform consensus that intensity-modulated radiotherapy (IMRT) is appropriate for the treatment of head and neck cancers. There was a near uniform consensus that IMRT is appropriate in select patients with thyroid cancer. Respondents noted IMRT for head, neck, and thyroid tumors may reduce the risk of exposure to radiation in critical nearby structures (eg, spinal cord, salivary glands), thus decreasing risks of adverse effects (eg, xerostomia, esophageal stricture).

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN; v4.2024) guideline on head and neck cancers notes that: "Advanced RT [radiation therapy] technologies such as IMRT (preferred), tomotherapy, VMAT [volumetric modulated arc therapy], image-guided RT (IGRT), and PBT [proton beam therapy] may offer clinically relevant advantages in specific instances to spare important organs at risk (OARs)...and decrease the risk for late, normal tissue damage while still achieving the primary goal of local tumor control.[36,] The demonstration of clinically significant dose-sparing of these OARS reflects best clinical practice." The NCCN guideline also notes that "randomized studies to test [advanced radiation therapy technologies] are unlikely to be done since specific clinical scenarios represent complex combinations of multiple variables. In light of that, the modalities and techniques that are found best to reduce the doses to the clinically relevant OARs without compromising target coverage should be considered."

The NCCN (v2.2024) guideline for thyroid cancer states, "The multidisciplinary team should carefully weigh the potential for benefit and the expected acute and chronic toxicity from EBRT [external-beam radiotherapy] when deciding when to

incorporate EBRT into an individual patient's treatment plan." They also recommend, "Conformal radiotherapy techniques including (IMRT) with simultaneous integrated boost (SIB) and image guidance are strongly encouraged in the adjuvant/definitive setting given the potential for reduced toxicity."[37,]

American Thyroid Association
The American Thyroid Association published a guideline for the management of patients with anaplastic thyroid cancer in 2021.[38,] These guidelines contain the following recommendations regarding use of IMRT:

- "Following R0 or R1 resection, we recommend that good performance status patients with no evidence of metastatic disease who wish an aggressive approach should be offered standard fractionation IMRT with concurrent systemic therapy.
  Strength of recommendation: strong; Quality of evidence: low.
- We recommend that patients who have undergone R2 resection or have unresectable but nonmetastatic disease with good performance status and who wish an aggressive approach be offered standard fractionation IMRT with systemic therapy.
  Strength of recommendation: strong; Quality of evidence: low.
- Among patients who are to receive radiotherapy for unresectable thyroid cancer or in the postoperative setting, IMRT is recommended.
  Strength of recommendation: strong; Quality of evidence: low."

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 8.

Table 8. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT06282497	Xerostomia-optimised Intensity-modulated Radiotherapy Versus Standard Intensity-modulated Radiotherapy in Nasopharyngeal Carcinoma Patients:a Multicenter Non-inferior Randomized Controlled Phase III Clinical Trial	524	Oct 2029
NCT06136962	A Comprehensive Prospective Study on the 10-Year Outcome and Late Toxicity, Quality of Life of Reduced Volume Intensity Modulated Radiation Therapy in Nasopharyngeal Carcinoma	500	Dec 2024

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT01220583	A Randomized Phase II/Phase III Study of Adjuvant Concurrent Radiation and Chemotherapy Versus Radiation Alone in Resected High-Risk Malignant Salivary Gland Tumors	252	Oct 2028
NCT04448522	A Multicenter Randomized Controlled Trial Comparing Reduced Dose With Regular Dose Intensity-modulated Radiotherapy for Chemotherapy Sensitive Stage II-III Nasopharyngeal Carcinoma	508	Aug 2028
NCT05187091	The SWOAR Trial: A Phase III Trial Evaluating Sparing of Swallowing and Aspiration Related Organs at Risk & Submandibular Gland With Intensity Modulated Radiotherapy Versus Standard IMRT in Head and Neck Squamous Cell Carcinomas	136	Jun 2025
NCT03669432	Phase II Randomized Controlled Trial Of Postoperative Intensity Modulated Radiotherapy (IMRT) in Locally Advanced Thyroid Cancers	72	Jul 2026
NCT03164460	Phase II Randomized Trial of Stereotactic Onco-Ablative Reirradiation Versus Conventionally Fractionated Conformal Radiotherapy for Patients With Small Inoperable Head and Neck Tumors (SOAR-HN)	100	May 2025

NCT: national clinical trial.

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Rationale for Brain Cancers

The published evidence is limited mainly to feasibility studies of IMRT for malignant glioma including 1 open, nonrandomized comparison of 25 patients who received IMRT and 60 patients who received EBI, and 8 case series (n=10 to 58). The results of the comparative study showed a benefit of IMRT compared with conventional EBI (progression-free survival at 2 years, 53.6% versus 17.6%; and overall survival at 2 years, 56% versus 19%). IMRT was associated with a higher failure rate due to CSF dissemination although the difference from the EBI group was not statistically significant. However, in the uncontrolled case series, the survival times (median 7 to 14.4 months) were similar to those achieved historically with conventional EBI (median 8 to 14 months). In most of the case series studies, the majority of patients had local tumor recurrence by the end of

the study. IMRT did not improve time to disease progression compared with conventional EBI. In both the case series and the comparative study, IMRT was generally well tolerated with few major adverse effects reported. No late toxicity was reported; however, such effects can be missed when survival times are relatively short.

Based on an analysis of the limited available evidence, it is difficult to determine whether IMRT improves survival compared with EBI despite the fact that the comparative study showed a positive effect since in all of the case series, IMRT displayed similar efficacy as EBI. No definitive conclusions can be drawn about the efficacy and safety of the IMRT for malignant gliomas in the absence of data from well-designed randomized controlled trials. However, the shorter treatment duration for hypofractionated regimens (2 or 4 weeks versus 6 weeks or longer) and the possible reduction in toxicity of IMRT compared with EBI may provide some palliative benefits for these patients who have a limited life expectancy. There are no published standards regarding its use (optimal technique, fraction size, dose, duration, etc.), which are also needed for a rigorous assessment of the value of IMRT for malignant glioma.

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Billing Coding/Physician Documentation Information

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by federal, state, or contractual requirements and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member. Other Policies and Guidelines may apply.

77301 Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications
77338 Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan
77385 Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple
77386 Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex
77387 Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed

G6001 Ultrasonic guidance for placement of radiation therapy fields
G6002 Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
G6015 Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session
G6016 Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

ICD-10 Codes

C00.0-C14.8 Malignant neoplasm of lip, oral cavity and pharynx code range
C30.0 Malignant neoplasm of nasal cavity
C31.0-C31.9 Malignant neoplasm of accessory sinuses code range
C32.0-C32.9 Malignant neoplasm of larynx code range
C71.9-C71.0 Malignant neoplasm of brain code range
C73 Malignant neoplasm of thyroid gland

Additional Policy Key Words

N/A

Policy Implementation/Update Information

11/1/09 New policy; may be considered medically necessary.
1/1/10 Coding updated.
11/1/10 Policy statement revised to include primary and malignant brain cancers as medically necessary.
1/1/11 Policy statement revised to include IMRT for thyroid cancer as investigational.
11/1/11 Policy statement on brain cancer corrected from "malignant" to "metastatic."
11/1/12 Policy statement on thyroid tumors changed - may be medically necessary for the treatment of thyroid cancers in close proximity to organs at risk (esophagus, salivary glands and spinal cord) and 3-D CRT planning is not able to meet dose volume constraints for normal tissue tolerance.
11/1/13 No policy statement changes.
11/1/14 Added a not medically necessary policy statement for thyroid indications not included in the medically necessary statement.
1/1/15 Added HCPCS codes. No policy statement changes.
11/1/15 No policy statement changes.
11/1/16 No policy statement changes.
11/1/17 No policy statement changes.

11/1/18 No policy statement changes.
11/1/19 No policy statement changes.
11/1/20 No policy statement changes.
11/1/21 No policy statement changes.
11/1/22 No policy statement changes.
11/1/23 No policy statement changes.
11/1/24 No policy statement changes.
