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

Policy Number: 8.01.48
Origination: 11/2009
Last Review: 11/2016
Next Review: 11/2017

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. The following table outlines radiation doses that are
generally considered tolerance thresholds for these normal structures in the area of the thyroid.

### Radiation tolerance doses for normal tissues

<table>
<thead>
<tr>
<th>Site</th>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
<th>1/3</th>
<th>2/3</th>
<th>3/3</th>
<th>Complication End Point</th>
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<tbody>
<tr>
<td>Esophagus</td>
<td>60</td>
<td>58</td>
<td>55</td>
<td>72</td>
<td>70</td>
<td>68</td>
<td>Stricture, perforation</td>
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<tr>
<td>Salivary glands</td>
<td>32</td>
<td>32</td>
<td>32</td>
<td>46</td>
<td>46</td>
<td>46</td>
<td>Xerostomia</td>
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<tr>
<td>Spinal cord</td>
<td>50 (5-10 cm)</td>
<td>NP</td>
<td>47 (20 cm)</td>
<td>70 (5-10 cm)</td>
<td>NP</td>
<td>NP</td>
<td>Myelitis, necrosis</td>
</tr>
</tbody>
</table>

aTD 5/5, the average dose that results in a 5% complication risk within 5 years
bTD 50/5, the average dose that results in a 50% complication risk within 5 years

NP: not provided
cm=centimeters

The tolerance doses in the table are a compilation from the following two sources:
Kehwar TS, Sharma SC. Use of normal tissue tolerance doses into linear quadratic equation to estimate normal tissue complication probability. [http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm](http://www.rooj.com/Radiation%20Tissue%20Tolerance.htm)

### Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations:</th>
<th>Interventions:</th>
<th>Comparators:</th>
<th>Outcomes:</th>
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<tr>
<td>With head and neck cancer</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td></td>
<td>• Intensity-modulated radiotherapy</td>
<td>• 3-dimensional conformal radiotherapy</td>
<td>▪ Overall survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 2-dimensional radiotherapy</td>
<td>▪ Functional outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Surgery</td>
<td>▪ Quality of life</td>
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<td></td>
<td></td>
<td></td>
<td>▪ Treatment-related morbidity</td>
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<th>Comparators of interest are:</th>
<th>Relevant outcomes include:</th>
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<tbody>
<tr>
<td>With thyroid cancer</td>
<td>• Intensity-modulated radiotherapy</td>
<td>• 3-dimensional conformal radiotherapy</td>
<td>▪ Overall survival</td>
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</tbody>
</table>

 Radiation therapy is an integral component in the treatment of head and neck cancers. Intensity-modulated radiation therapy (IMRT) has been proposed as a
method of radiation therapy that allows adequate radiation therapy to the tumor while minimizing the radiation dose to surrounding normal tissues and critical structures.

For individuals who have a head or neck cancer who receive IMRT, the evidence includes randomized controlled trials (RCTs), nonrandomized comparative studies, and meta-analyses of these studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. The single RCT that compared IMRT to 3-dimensional conformal radiotherapy (3D-CRT) found a significant benefit of IMRT on xerostomia that persisted through 5 years. Oncologic outcomes did not differ significantly between treatments. Other nonrandomized cohort studies have supported the findings that both short- and long-term xerostomia are reduced with IMRT. Overall, the body of 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 3D-CRT. The evidence permits no conclusions on tumor control or survival. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

For individuals who have thyroid cancer who receive IMRT, the evidence includes nonrandomized, retrospective studies. Relevant outcomes include overall survival, 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 for thyroid tumors may be appropriate in some circumstances, such as for 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. Thus, when possible 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. Limitations of published evidence include patient heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes (eg, overall survival vs progression-free survival or tumor control rates), and inconsistency in reporting or collecting outcomes. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

There was uniform consensus from clinical input that IMRT is appropriate for the treatment of head and neck cancers. There was near-uniform consensus from clinical input that IMRT is appropriate in select patients with thyroid cancer. Respondents noted that 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 the risks of adverse effects (eg, xerostomia, esophageal stricture).
Background

Radiation techniques

Conventional external beam radiation therapy. Over the past several decades, methods to plan and deliver radiation therapy have evolved in ways that permit more precise targeting of tumors with complex geometries. Most early trials used 2-dimensional treatment planning based on flat images and radiation beams with cross-sections of uniform intensity that were sequentially aimed at the tumor along 2 or 3 intersecting axes. Collectively, these methods are termed “conventional external beam radiation therapy”.

3-dimensional conformal radiation (3D-CRT). Treatment planning evolved by using 3-dimensional images, usually from computed tomography (CT) scans, to delineate the boundaries of the tumor and discriminate tumor tissue from adjacent normal tissue and nearby organs at risk for radiation damage. Computer algorithms were developed to estimate cumulative radiation dose delivered to each volume of interest by summing the contribution from each shaped beam. Methods also were developed to position the patient and the radiation portal reproducibly for each fraction and immobilize the patient, thus maintaining consistent beam axes across treatment sessions. Collectively, these methods are termed 3-dimensional conformal radiation therapy (3D-CRT).

Intensity-modulated radiation therapy (IMRT). IMRT, which uses computer software and CT images, offers better conformality than 3D-CRT as it is able to modulate the intensity of the overlapping radiation beams projected on the target and to use multiply-shaped treatment fields. It uses a device (a multileaf collimator, MLC) which, coupled to a computer algorithm, 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 and surrounding tissues and organs at risk, computer software optimizes the location, shape, and intensities of the beams’ ports, to achieve the treatment plan’s goals.

Increased conformality may permit escalated tumor doses without increasing normal tissue toxicity and thus may 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.

Technologic development has produced advanced techniques that may further improve RT treatment by improving dose distribution. These techniques are considered variations of IMRT. Volumetric modulated arc therapy (VMAT) delivers radiation from a continuous rotation of the radiation source. The principal advantage of VMAT 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.

IMRT methods to plan and deliver RT are not uniform. IMRT may use beams that remain on as MLCs move around the patient (dynamic MLC) or that are off during movement and turn on once the MLC reaches prespecified positions ("step and shoot" technique). A third alternative uses a very narrow single beam that moves spirally around the patient (tomotherapy). Each method uses different computer algorithms to plan treatment and yields somewhat different dose distributions in and outside the target. Patient position can alter target shape and thus affect treatment plans. Treatment plans are usually based on 1 imaging scan, a static 3D-CT image. Current methods seek to reduce positional uncertainty for tumors and adjacent normal tissues by various techniques. Patient immobilization cradles and skin or bony markers are used to minimize day-to-day variability in patient positioning. In addition, many tumors have irregular edges that preclude drawing tight margins on CT scan slices when radiation oncologists contour the tumor volume. It is unknown whether omitting some tumor cells or including some normal cells in the resulting target affects outcomes of IMRT.

**Head and Neck Tumors**
Head and neck cancers account for approximately 3% to 5% of cancer cases in the United States. The generally accepted definition of head and neck cancers includes 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. 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. Thyroid cancers are also addressed in this policy. External beam radiation therapy 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.

**Rationale**
This evidence review was originally created in April 2009 and has been regularly updated with searches of the MEDLINE database. The most recent literature update was performed through June 6, 2016. The following is a summary of the key findings to date.

Multiple-dose planning studies generate 3-dimensional conformal radiation (3D-CRT) and intensity-modulated radiotherapy (IMRT) treatment plans from the same scans, and then compare predicted dose distributions within the target area and adjacent organs. Results of such planning studies have shown that IMRT is better than 3D-CRT with respect to conformality to, and dose homogeneity within, the target. Results have also demonstrated that IMRT delivers less radiation to
nontarget areas. Dosimetry studies using stationary targets generally confirm these predictions. However, because patients move during treatment, dosimetry with stationary targets only approximate actual radiation doses received. Based on these dosimetry studies, radiation oncologists expect IMRT to improve treatment outcomes compared with those of 3D-CRT.

Comparative studies of radiation-induced adverse effects from IMRT versus alternative radiation delivery would constitute definitive evidence of establishing the benefit of IMRT. Single-arm series of IMRT can give some insights into the potential for benefit, particularly if an adverse effect that is expected to occur at high rates is shown to decrease by a large amount. Studies of treatment benefit are also important to establish that IMRT is at least as good as other types of delivery, but, absent such comparative trials, it is likely that benefit from IMRT is at least as good as with other types of delivery.

In general, when the indication for IMRT is to avoid radiation to sensitive areas, dosimetry studies have been considered sufficient evidence to demonstrate that harm would be avoided by using IMRT. For other indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

A proposed benefit of IMRT is to reduce toxicity to adjacent structures, allowing dose escalation to the target area and fewer breaks in treatment courses due to a reduction in side effects. However, this may come with a loss of locoregional control and overall survival (OS) due to factors discussed above. Thus, outcomes of interest are toxicity, quality of life (QOL), locoregional recurrence, and OS.

**Head and Neck Cancers**

**Systematic Reviews**

In 2014, Marta et al reported on a systematic review and meta-analysis of 5 prospective phase 3 randomized trials comparing IMRT with 2-dimensional radiotherapy (2D-RT) or 3D-CRT for head and neck cancer.¹ A total of 871 patients were randomized in these 5 studies to IMRT (n=434) versus 2D-RT or 3D-CRT (n=437). Xerostomia grade 2 to 4 was found to be significantly lower in patients treated with IMRT than with 2D-RT and 3D-CRT for all studies (hazard ratio, 0.76; 95% confidence interval, 0.66 to 0.87; p<0.001). Locoregional control and overall survival (OS) were similar between IMRT and 2D-RT or 3D-CRT.

A comparative effectiveness review (CER) on RT treatment for head and neck cancers was published in 2010 by the Agency for Healthcare Research and Quality.² This report noted that, based on moderate strength evidence, IMRT reduced late xerostomia and improved QOL domains related to xerostomia compared with 3D-CRT. The report also noted that no conclusions on tumor control or survival could be drawn from the evidence. An update of the report, published in 2014, was consistent with and strengthened the findings of the original CER on late xerostomia.³
Randomized Controlled Trials

Of the 5 phase 3 RCTs included in the Marta meta-analysis, only 1 trial (Gupta et al, 2012) compared IMRT to 3D-CRT. In 2016, long-term results from this trial were published. This trial included 60 patients with squamous cell carcinoma of the head and neck and was powered to detect a 35% difference in toxicity between treatments (85% vs 50%). The proportion of patients with salivary gland toxicity was lower in the IMRT group (59%) than in the 3D-CRT group (89%; p=0.009). The percentage of patients with substantial weight loss was significantly lower in the IMRT group at 1 and 2 years. There were no significant differences between the 2 groups for acute dysphagia, mucositis, dermatitis, or requirements for tube feeding. Xerostomia decreased over follow-up in both groups, but significant differences in late salivary toxicity persisted through 5 years. At 2 years posttreatment, grade 2 or worse xerostomia was 0% in the IMRT group compared with 28% following 3D-CRT (p=0.017). At 5 years, salivary toxicity was 0% in the IMRT group compared with 17% following 3D-CRT (p=0.041). Locoregional control and OS did not differ significantly between groups.

The other 4 RCTs reviewed by Marta et al compared IMRT to 2D-RT. An RCT by Pow et al on IMRT for nasopharyngeal carcinoma (NPC) was published in 2006; it included only 45 patients. In 2011, Nutting et al reported on the PARSPORT randomized phase 3 trial, which also compared conventional RT with parotid-sparing IMRT in 94 patients with tumor stage T1, T2, T3, or 4, nodal stage N0, N1, N2, or N3, and M0 pharyngeal squamous cell carcinoma. One year after treatment, grade 2 or worse xerostomia was reported in 38% of patients in the IMRT group, which was significantly lower than the reported 74% in the conventional RT group. Xerostomia continued to be significantly less prevalent 2 years posttreatment in the IMRT group (29% vs 83%, respectively). At 24 months, rates of locoregional control, nonxerostomia late toxicities, and OS did not differ significantly between treatment groups.

The largest RCT comparing IMRT to 2D-RT was by Peng et al in 2012. This trial included 616 patients with NPC. At a median follow-up of 42 months (range, 1-83 months), patients in the IMRT group had significantly lower radiation-induced toxicities. The 5-year OS rate was 80% in the IMRT group compared to 67% in the 2D-CRT group.

Nonrandomized Comparative Studies

Several nonrandomized comparative studies have evaluated late toxicities and quality of life for IMRT compared to 2D-RT and 3D-CRT.

A 2016 cross-sectional study by Huang et al included patients who had survived more than 5 years after treatment for NPC. 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 for > 5 years, completion of the self-reported questionnaire). Treatments were given from 1997 to 2007, with transition to the IMRT system in 2002. One hundred patients were treated with IMRT. Prior to the institution 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 and 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 QOL, cognitive functioning, social functioning, fatigue, and 11 scales of the head and neck module) outcomes with moderate effect sizes after adjusting for covariates (Cohen’s d range, 0.47-0.53). Late toxicities were less severe in the IMRT group, with adjusted odds 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.

In 2009, Vergeer et al compared IMRT and 3D-CRT for patient-rated acute and late xerostomia, and health-related quality of life (HRQOL) among patients with head and neck squamous cell carcinoma (HNSCC). The study included 241 patients with HNSCC (cancers arising from the oral cavity, oropharynx, hypopharynx, nasopharynx, or larynx and those with neck node metastases from squamous cell cancer of unknown primary) treated with bilateral irradiation with or without chemotherapy. All patients were included in a program that prospectively assessed acute and late morbidity and HRQOL at regular intervals. Before October 2004, all patients were treated with 3D-CRT (n=150); starting in October 2004, 91 patients received IMRT. The use of IMRT significantly reduced the mean dose to the parotid glands (27 gray [Gy] vs 43 Gy; p<0.001). During radiation, grade 3 or higher xerostomia at 6 weeks was significantly less common with IMRT (≈20%) than with 3D-CRT (≈45%). At 6 months, the prevalence of grade 2 or higher xerostomia was significantly lower after IMRT (32%) than with 3D-CRT (56%). Treatment with IMRT also had a positive effect on several general and head and neck cancer–specific HRQOL measures.

Rusthoven et al compared outcomes with use of IMRT and 3D-CRT in patients with oropharyngeal cancer. In this study, in which 32 patients were treated with IMRT and 23 with 3D-CRT, late xerostomia occurred in 15% of the IMRT patients and in 94% of the 3D-CRT patients.

Several earlier studies reported a reduction in late xerostomia with IMRT compared to 2D-RT in patients treated for oropharyngeal cancer. Braam et al, in a phase 2 study, found that at 6 months after treatment, 56% of IMRT patients and 81% of RT patients had parotid complications. Hodge et al compared outcomes for patients with oropharyngeal cancer treated with older technologies (pre-IMRT) to those treated with IMRT. In this study of 52 patients treated by IMRT, the late xerostomia rate was 56% in the IMRT patients compared with 63% in those who did not receive IMRT. Rades et al reported on 148 patients with oropharyngeal cancer treated with RT. Late xerostomia was noted in 17% of those treated with IMRT compared with 73% of those who received 3D-CRT and 63% of those who received standard RT.
**Section Summary: Head and Neck Cancer**

The literature on IMRT for head and neck cancer includes a health technology assessment and a meta-analysis of RCTs. Most RCTs compared IMRT to 2D-RT, which has been replaced by 3D-CRT. The single RCT that compared IMRT to 3D-CRT found a significant benefit of IMRT for xerostomia that persisted through 5 years. Oncologic outcomes did not differ significantly between treatments. Other nonrandomized cohort studies have compared IMRT to 3D-CRT or to 2D-RT plus 3D-CRT boost. These studies have supported findings of the RCT that both short- and long-term xerostomia is reduced with IMRT. HRQOL was also improved with IMRT compared to 3D-CRT or 2D-RT plus 3D-CRT boost. However, comparators in these nonrandomized studies were generally older technologies (eg, 2D-RT) with older treatment protocols, both of which limit interpretation of the results. Overall, the more recent evidence has supported the conclusions of the TEC Assessment that treatment of head and neck cancers with IMRT reduces xerostomia compared to other external-beam radiotherapy (EBRT) techniques.

**Thyroid Cancer**

In thyroid cancer, RT is generally used for 2 indications: treatment of anaplastic thyroid cancer and treatment for locoregional control in patients with incompletely resected high-risk or recurrent differentiated (papillary, follicular, or mixed papillary-follicular) thyroid cancer. Anaplastic thyroid cancer occurs in less than 5% of thyroid cancers.

The largest series comparing IMRT with 3D-CRT was published by Bhatia et al.\textsuperscript{15} This study reviewed institutional outcomes for anaplastic thyroid cancer treated with 3D-CRT or IMRT for 53 consecutive patients. Thirty-one (58%) patients were irradiated with curative intent. Median radiation dose was 55 gray (Gy; range, 4-70 Gy). Thirteen (25%) patients received IMRT to a median of 60 Gy (range, 39.9-69.0 Gy). 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 versus 3D-CRT did not influence toxicity.

Schwartz et al retrospectively reviewed single-institution outcomes for patients treated for differentiated thyroid cancer with postoperative conformal EBRT.\textsuperscript{16} One hundred thirty-one consecutive patients with differentiated thyroid cancer who underwent RT between January 1996 and December 2005. 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 spread 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, 38-72 Gy). Fifty-seven (44%) patients were treated with IMRT to a median dose of 60 Gy (range, 56-66 Gy). Median follow-up was 38 months (range, 0-134 months). 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. IMRT 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
For individuals who have thyroid cancer who receive IMRT alone or with chemotherapy, the evidence includes a few nonrandomized, retrospective studies. High-quality studies that differentiate the superiority of any type of EBRT technique to treat thyroid cancer are not available. 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 that are 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 possible 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. Limitations of published evidence include patient heterogeneity, variability in treatment protocols, short follow-up periods, inconsistency in reporting important health outcomes (eg, OS vs progression-free survival or tumor control rates), and inconsistency in reporting or collecting outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 1.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT02048254</td>
<td>A Randomized Control Trial (RCT) of Using Iodine-125 Brachytherapy Versus Intensity-modulated Radiation Therapy (IMRT) to Treat Inoperable Salivary Gland Cancer</td>
<td>90</td>
<td>Jun 2018</td>
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</table>

NCT: national clinical trial.

Summary of Evidence
For individuals who have a head or neck cancer who receive intensity-modulated radiotherapy (IMRT), the evidence includes randomized controlled trials (RCTs), nonrandomized comparative studies, and meta-analyses of these studies. Relevant outcomes are overall survival, functional outcomes, quality of life, and treatment-related morbidity. The single RCT that compared IMRT to 3-dimensional conformal radiotherapy (3D-CRT) found a significant benefit of IMRT on xerostomia that persisted through 5 years. Oncologic outcomes did not differ significantly between
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**Supplemental Information**

**Clinical Input Received 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.

In response to requests, input was received from 2 physician specialty societies (3 reviewers) and 4 academic medical centers while this review was under review in 2012. There was uniform consensus in responses that IMRT is appropriate for the treatment of head and neck cancers. There was near-uniform consensus in responses 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

National Comprehensive Cancer Network
The National Comprehensive Cancer Network (NCCN) guidelines (v.1.2016) on head and neck cancers comment that: “IMRT has been shown to be useful in reducing long-term toxicity in oropharyngeal, paranasal sinus, and nasopharyngeal cancers by reducing the dose to salivary glands, temporal lobes, auditory structures (including cochlea), and optic structures.” The guidelines also indicate: “The application of IMRT to other sites (eg, oral cavity, larynx, hypopharynx, salivary glands) is evolving and may be used at the discretion of treating physicians.”

NCCN guidelines for thyroid cancer (v.1.2016) state that external-beam radiotherapy (EBRT) and IMRT may be appropriate for locoregional recurrence “if radioiodine imaging [is] negative for select patients not responsive to other therapies.” Adjuvant EBRT/IMRT with or without chemotherapy is recommended for the treatment of anaplastic thyroid carcinoma.

American College of Radiology and American Society for Therapeutic Radiation and Oncology
The American College of Radiology and the American Society for Therapeutic Radiation and Oncology have noted that IMRT is a widely used treatment option for many indications including head and neck tumors. This guideline was last amended in 2014.

National Cancer Institute
The National Cancer Institute (NCI) has indicated that IMRT may be appropriate for head and neck cancers in several instances. For radiation of cervical lymph nodes (for primary cancer of unknown origin) and untreated primary occult metastatic squamous neck cancer, IMRT may have less short- and long-term toxicity than conventional radiotherapy in terms of xerostomia, acute dysphagia, and skin fibrosis. For nasopharyngeal cancer, NCI has indicated that IMRT results in a lower incidence of xerostomia and may provide a better quality of life than conventional 3- or 2-dimensional radiotherapy. IMRT may also be appropriate in select cases of recurrent nasopharyngeal cancer per NCI. Finally, to prevent or reduce the extent of salivary gland hypofunction and xerostomia, NCI has indicated that parotid-sparing IMRT is recommended as a standard approach in head and neck cancers, if oncologically feasible.

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

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.
References


**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.

Reference:

Billing Coding/Physician Documentation Information

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>77301</td>
<td>Intensity modulated radiotherapy plan, including dose-volume histograms for target and critical structure partial tolerance specifications</td>
</tr>
<tr>
<td>77338</td>
<td>Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan</td>
</tr>
<tr>
<td>77385</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; simple</td>
</tr>
<tr>
<td>77386</td>
<td>Intensity modulated radiation treatment delivery (IMRT), includes guidance and tracking, when performed; complex</td>
</tr>
<tr>
<td>77387</td>
<td>Guidance for localization of target volume for delivery of radiation treatment delivery, includes intrafraction tracking, when performed</td>
</tr>
<tr>
<td>G6001</td>
<td>Ultrasonic guidance for placement of radiation therapy fields</td>
</tr>
<tr>
<td>G6002</td>
<td>Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy</td>
</tr>
<tr>
<td>G6015</td>
<td>Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic MLC, per treatment session</td>
</tr>
<tr>
<td>G6016</td>
<td>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</td>
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ICD-10 Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>C00.0-</td>
<td>Malignant neoplasm of lip, oral cavity and pharynx code range</td>
</tr>
<tr>
<td>C14.8</td>
<td>Malignant neoplasm of nasal cavity</td>
</tr>
<tr>
<td>C30.0</td>
<td>Malignant neoplasm of accessory sinuses code range</td>
</tr>
<tr>
<td>C31.0-</td>
<td>Malignant neoplasm of larynx code range</td>
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<tr>
<td>C31.9</td>
<td>Malignant neoplasm of brain code range</td>
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Deleted Codes: (as of 1/1/2015) 0073T, 77418
Additional Policy Key Words

N/A

Policy Implementation/Update Information

<table>
<thead>
<tr>
<th>Date</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>11/1/09</td>
<td>New policy; may be considered medically necessary.</td>
</tr>
<tr>
<td>1/1/10</td>
<td>Coding updated.</td>
</tr>
<tr>
<td>11/1/10</td>
<td>Policy statement revised to include primary and malignant brain cancers as medically necessary.</td>
</tr>
<tr>
<td>1/1/11</td>
<td>Policy statement revised to include IMRT for thyroid cancer as investigational.</td>
</tr>
<tr>
<td>11/1/11</td>
<td>Policy statement on brain cancer corrected from “malignant” to “metastatic.”</td>
</tr>
<tr>
<td>11/1/12</td>
<td>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.</td>
</tr>
<tr>
<td>11/1/13</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>11/1/14</td>
<td>Added a not medically necessary policy statement for thyroid indications not included in the medically necessary statement.</td>
</tr>
<tr>
<td>1/1/15</td>
<td>Added HCPCS codes. No policy statement changes.</td>
</tr>
<tr>
<td>11/1/15</td>
<td>No policy statement changes.</td>
</tr>
<tr>
<td>11/1/16</td>
<td>No policy statement changes.</td>
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</table>

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