Medical Policy

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Title: Intensity-Modulated Radiation Therapy (IMRT): Abdomen, Pelvis, and Chest

Description/Background

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 in ways that 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 evolved to use 3-dimensional images, usually from computed tomography (CT) scans, to more precisely delineate the boundaries of the tumor and 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

IMRT 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, Tempe, AZ), cleared in 2006, and the Decimal Tissue Compensator (Southeastern Radiation Products, Sanford, FL), cleared in 2004. FDA product code: IXI. Intensity modulators may be added to standard linear accelerators to deliver IMRT when used with proper treatment planning systems.

RT planning systems have also been cleared for marketing by FDA through the 510(k) process. They include the FOCUS Radiation Treatment Planning System (Computerized Medical Systems) cleared in 2002, Prowess Panther™ (Prowess) cleared in 2003, TiGRT (LinaTech) cleared in 2009, the Ray Dose (RaySearch Laboratories) cleared in 2008, and the Eclipse Treatment Planning System (Varian Medical Systems) cleared in 2017. 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. Varian Medical Systems has several 510(k) marketing clearances for high-

energy linear accelerator systems that can be used to deliver precision RT such as IMRT. FDA product code: IYE.

Medical Policy Statement

Intensity-modulated radiation therapy (IMRT) may be considered established as an approach to delivering radiation therapy for patients with cancer of the anus and anal canal.

Intensity-modulated radiation therapy (IMRT) may be considered established for the treatment of cancers of the abdomen, pelvis, and chest based on analysis of dosimetric data including comparative models, if necessary.

Inclusionary and Exclusionary Guidelines

Refer to medical policy statements.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes:

77301	77338	77385	77386	77387
G6015	G6016			

Other codes (investigational, not medically necessary, etc.):

N/A

Rationale

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, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs are rarely large enough 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.

Note that the evidence for the following abdominal and pelvic cancers has not yet been reviewed and is beyond the scope of this review: bladder, kidney, and ureter cancer and sarcoma.

INTENSITY-MODULATED RADIOTHERAPY FOR CANCERS OF THE ABDOMEN, PELVIS, AND CHEST

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 insights into the potential for benefit, particularly if an adverse event expected to occur at high rates is shown to decrease significantly. 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 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.

GASTROINTESTINAL TRACT CANCERS

Clinical Context and Therapy Purpose

The purpose of IMRT in individuals who have gastrointestinal (GI) tract 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 gastrointestinal cancers (eg, stomach, hepatobiliary, and pancreatic cancers) who are recommended for radiotherapy (RT).

Interventions

The therapy being considered is IMRT. This therapy uses computer software and magnetic resonance imaging for increased conformality, permitting the delivery of higher doses of radiation to the tumor while limiting the exposure of surrounding normal tissues.

Comparators

The following therapy is currently being used: 3D-CRT. This therapy uses 3-dimensional images typically from computed tomography to discriminate tumor tissue from adjacent normal tissue and nearby organs. Computer algorithms are used to estimate radiation doses being delivered to each treatment segment.

Outcomes

The general outcomes of interest are overall survival (OS), recurrence (locoregional control), quality of life, and treatment-related adverse events (eg, toxicity). Toxicity can be assessed using U.S. Department of Health and Human Services grading criteria for adverse events (1=mild, 2=moderate, 3=severe or medically significant, 4=life-threatening, and 5=death).

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

Stomach

Systematic Review

Ren et al (2019) completed a systematic review and meta-analysis evaluating the efficacy and safety of IMRT versus 3D-CRT that included 9 controlled clinical trials enrolling 516 patients with gastric cancer.[2] Results revealed a slightly improved 3-year OS rate (risk ratio [RR], 1.16; 95% confidence interval [CI], 0.98 to 1.36) and a significantly better 2-year OS rate with IMRT (RR, 2.49; 95% CI, 1.18 to 5.25; p=0.02) as compared to 3D-CRT. Additionally, the 3-year rate of locoregional recurrence was improved with IMRT versus 3D-CRT (RR, 0.62; 95% CI, 0.39 to 0.98; p<.05). Similar 3-year disease-free survival rates were noted between the techniques (RR, 1.16; 95% CI, 0.95 to 1.43; p>.05). No significant differences in liver, GI, and kidney toxicity were observed among patients receiving IMRT compared with 3D-CRT. Limitations of this analysis included the small number of enrolled subjects (ie, the majority of studies had < 100 subjects), retrospective nature of includes studies, which increased the risk of selective reporting bias, and the heterogeneity of IMRT or 3D-CRT techniques in studies. Additionally, the detail and radiation fields of RT varied considerably among the studies, impacting the efficacy and toxicity seen by investigators.

Nonrandomized Comparative Studies

Boda-Heggemann et al (2009) evaluated the efficacy and safety of 2 different adjuvant chemoradiotherapy regimens using 3D-CRT or IMRT in 2 consecutive cohorts who underwent primarily D2 resection for gastric cancer.[3] A subsequent report (2013) from this group included 27 3D-CRT patients and 38 IMRT patients.[4] The cohorts were generally well-matched, with American Joint Committee on Cancer (AJCC) advanced stage (II-IV) disease. Most (96%) who received 3D-CRT were treated with 5-fluorouracil plus folinic acid (FA). Patients in the IMRT cohort received capecitabine plus oxaliplatin (70%) or 5-fluorouracil plus folinic acid (30%). Radiation was delivered to a total prescribed dose of 45 gray (Gy) at 1.8 Gy per fraction. In the 3D-CRT cohort, 5 patients received less than 45 Gy because of treatment intolerance. Two patients in the IMRT cohort did not tolerate the full course, and 1 patient received 47 Gy. Overall, the IMRT plus chemotherapy regimen decreased renal toxicity with a trend toward improved survival (Table 1). However, interpretation of the safety and efficacy of IMRT in this study is limited by differences in the chemotherapy regimens.

Table 1. Outcomes for IMRT With Capecitabine Plus Oxaliplatin versus - 3-Dimensional Conformal Radiotherapy With 5-Fluorouracil Plus Folinic Acid for Stomach Cancer

Outcomes	3D-CRT	intensity-modulated radiotherapy	p
Sample	27	38	
Renal toxicity, n (%)	2 (8)	0	0.021
Median disease-free survival, mo	14	35	0.069
Median overall survival, mo	18	43	0.060
Actutimes 2-y overall survival, %	37	67	
Actutimes 5-y overall survival, %	22	44	

Adapted from Boda-Heggemann et al (2009, 2013).[3,4]
3D-CRT: 3-dimensional conformal radiotherapy.

Hepatobiliary

Fuller et al (2009) compared a retrospective series with a historical control cohort. Clinical results using image-guided IMRT (n=24) were compared with results with CRT (n=24) in patients with primary adenocarcinoma of the biliary tract.[5] Most patients underwent postsurgical chemoradiotherapy with concurrent fluoropyrimidine-based regimens. Treatment plans prescribed 46 to 56 Gy to the planning target volume that included the tumor and involved lymph nodes, in daily fractions of 1.8 to 2 Gy. Both groups received boost doses of 4 to 18 Gy as needed. The IMRT cohort had median OS of 17.6 months (range, 10.3-32.3 months), while the 3D-CRT cohort had a median OS of 9.0 months (range, 6.6-17.3 months). There were no significant differences between patient cohorts in acute gastrointestinal (GI) toxicity. Generalization of results is limited by the small numbers of patients, use of retrospective chart review data, nonrepresentative case spectrum (mostly advanced/metastatic disease), and comparison to a nonconcurrent control RT cohort.

Pancreatic

Literature searches have identified a few comparative studies and case series on IMRT for pancreatic cancer. For example, Lee et al (2016) reported a prospective comparative study of GI toxicity in patients treated with concurrent chemoradiotherapy with IMRT or 3D-CRT for treatment of borderline resectable pancreatic cancer.[6] Treatment selection was by patient choice after consultation with a radiation oncologist. Symptoms of dyspepsia, nausea/vomiting, and diarrhea did not differ between the groups. Upper endoscopy revealed more patients with gastroduodenal ulcers in the 3D-CRT group than in patients treated with IMRT (Table 2). OS was longer in the IMRT group than in the 3D-CRT group, but interpretation of this result is limited by risk of bias in this nonrandomized study.

Prasad et al (2016) retrospectively reviewed charts of patients with locally advanced pancreatic cancer who were treated with IMRT (n=134) or 3D-CRT (n=71).[7] Propensity score analysis was performed to account for potential confounding variables, including age, sex, radiation dose, RT field size, and concurrent RT. Grade 2 GI toxicity occurred in significantly more patients treated with 3D-CRT than IMRT patients (propensity score odds ratio, 1.26; 95% confidence interval [CI], 1.08 to 1.45; p=.001; see Table 2). Hematologic toxicity and median survival were similar in the 2 groups.

Table 2. Outcomes for IMRT versus 3-Dimensional Conformal Radiotherapy for Pancreatic Cancer

Comparison	**3D-CRT**	IMRT	**p**
Lee et al (2016)[6]	n=40	n=44	
Grade 1-2 gastroduodenal ulcers, n (%)	11 (42.3)	3 (9.1)	0.003
Overall survival, mo	15.8	22.6	0.006
Prasad et al (2016)[7]	n=71	n=134	
Grade 2+ gastrointestinal toxicity, n (%)	24 (33.8)	21 (15.7)	0.001
Overall survival whole population, mo	NR	NR	NS

3D-CRT: 3-dimensional conformal radiotherapy; IMRT: intensity-modulated radiotherapy; NR: not reported; NS: not significant.

Section Summary: Gastrointestinal Tract Cancers

The evidence on IMRT for GI tract cancers includes nonrandomized comparative studies, retrospective series and a systematic review. Intensity-modulated radiotherapy has been compared to 3D-CRT for the treatment of stomach, hepatobiliary, and pancreatic cancers, with some studies reporting longer OS and decreased toxicity with IMRT. For the treatment of stomach cancer, IMRT improved survival compared with 3D-CRT, with a comparable or improved safety profile. The evidence on hepatobiliary cancer includes a series of historical controls that found an increase in median survival with no difference in toxicity. Two comparative studies (1 prospective, 1 retrospective) were identified on IMRT for pancreatic cancer. The prospective comparative study found an increase in survival with a reduction in GI toxicity, while the retrospective study found a decrease in GI toxicity. Although most studies were limited by their retrospective designs and changes in practice patterns over time, the available evidence would suggest that IMRT improves survival and decreases toxicity better than 3D-CRT in patients with GI cancers.

GYNECOLOGIC CANCERS

Clinical Context and Therapy Purpose

The purpose of IMRT in individuals who have gynecologic 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 gynecologic cancers (ie, cervical and endometrial cancers) who are recommended for radiotherapy (RT).

Interventions
The therapy being considered is IMRT. This therapy uses computer software and magnetic resonance imaging for increased conformality, permitting the delivery of higher doses of radiation to the tumor while limiting the exposure of surrounding normal tissues.

Comparators
The following therapy is currently being used: 3D-CRT. This therapy uses 3-dimensional images typically from computed tomography to discriminate tumor tissue from adjacent normal tissue and nearby organs. Computer algorithms are used to estimate radiation doses being delivered to each treatment segment.

Outcomes
The general outcomes of interest are OS, recurrence (locoregional control), quality of life, and treatment-related adverse events (eg, toxicity). Toxicity can be assessed using the U.S. Department of Health and Human Services grading criteria for adverse events (1=mild, 2=moderate, 3=severe or medically significant, 4=life-threatening, and 5=death).

Study Selection Criteria
See information under the first indication.

Review of Evidence

Systematic Review
Lin et al (2018) completed a meta-analysis of 6 studies enrolling 1008 subjects in order to compare the efficacy and safety of IMRT with 3D-CRT or 2D-RT for definitive treatment of cervical cancer.[8] Results revealed a nonsignificant difference in 3-year OS (OR, 2.41; 95% CI, 0.62 to 9.39; p=.21) and disease-free survival rates (OR, 1.44; 95% CI, 0.69 to 3.01; p=.33) between IMRT and 3D-CRT or 2D-RT. However, IMRT was associated with a significantly reduced rate of acute GI and genitourinary (GU) toxicity: Grade 2 GI: OR, 0.5; 95% CI, 0.28 to 0.89; p=.02; Grade 3 or higher GI: OR, 0.55; 95% CI, 0.32 to 0.95; p=.03; Grade 2 GU: OR, 0.41; 95% CI, 0.2 to 0.84; p=.01; Grade 3 or higher GU: OR, 0.31; 95% CI, 0.14 to 0.67; p=.003. Some chronic GU toxicity also occurred less frequently with IMRT (Grade 3: OR, 0.09; 95% CI, 0.01 to 0.67; p=.02). This analysis had several limitations including the fact that most included studies had relatively small sample sizes and were retrospective and nonrandomized in nature. Additionally, some of the included studies did not compare clinical outcomes between the RT techniques.

Randomized Controlled Trials

Kapoor et al (2023) conducted a prospective, randomized, single-center, phase 3 trial that compared hematologic and GI toxicities in patients with cervical cancer (Stage IB to IVA) treated with IMRT and 3D-CRT.[9,] A total of 80 patients were randomized 1:1 to receive either IMRT (n=40) or 3D-CRT (n=40). The median patient age was 56.5 years (range, 36 to 67) and 59.5 years (range, 37 to 68) in the IMRT and 3D-CRT groups, respectively. The median dose of external radiation was 50 Gy in 25 fractions, and of brachytherapy was 24 Gy in 3 fractions in both groups. All patients received concurrent chemotherapy with cisplatin; the median number of cycles was 5 (range, 3 to 5) in both groups. All 5 cycles of concurrent chemotherapy could be completed in 25 (62.5%) patients and 24 (60%) patients in the IMRT and 3D-CRT groups, respectively. The median overall treatment time was 57 days (range, 56 to 85) and 57.5 days (range, 49 to 88) in patients receiving IMRT and 3D-CRT, respectively. The incidence of neutropenia (grade 2 or higher) was 15% and 42.5% in the IMRT and 3D-CRT groups, respectively (p<.001). Diarrhea (grade 2 or higher) was observed in 42.5% of patients in the IMRT group compared to 90% of patients in the 3D-CRT group. The study found that IMRT also had a better dosimetry profile compared to 3D-CRT.

Chopra et al (2021) conducted the open-label, parallel-group, randomized, phase 3, Postoperative Adjuvant Radiation in Cervical Cancer (PARCER) trial in order to evaluate whether postoperative image-guided IMRT was associated with an improvement in late GI toxicity compared to 3D-CRT.[10] In PARCER, 300 patients with cervical cancer and an indication for adjuvant postoperative RT were randomly assigned to image-guided IMRT (n=151) or 3D-CRT (n=149), with a median follow-up of 46 months (interquartile range, 20 to 72 months). Results revealed significantly fewer primary endpoint events (ie, grade late GI toxicity of grade 2 or higher) in the image-guided IMRT arm versus the 3D-CRT arm (29 vs. 54). The 3-year cumulative incidence of grade late GI toxicity of grade 2 or higher was significantly reduced in the IMRT arm (21.1% vs. 42.4%; hazard ratio [HR], 0.46; 95% CI, 0.29 to 0.73; p<.001) as was the cumulative incidence of 3-year grade late GI toxicity of grade 3 or higher (2.9% vs. 15.5%; HR, 0.22; 95% CI, 0.08 to 0.59; p<.003). The cumulative incidence of any late toxicity of grade 2 or higher was also significantly reduced with IMRT (28.1% vs. 48.9%; HR, 0.50; 95% CI, 0.33 to 0.76; p<.001). Patients administered IMRT reported less diarrhea (p=.04), improvement in appetite (p=.008), and fewer bowel symptoms (p=.002) compared to those administered 3D-CRT. No differences in disease outcomes were noted between the RT techniques including 3-year pelvic relapse-free survival (p=.55) and disease-free survival (p=.89).

In the international, randomized, Adjuvant Chemoradiotherapy Versus Radiotherapy Alone in Women With High-Risk Endometrial Cancer (PORTEC-3) trial, Wortman et al (2021) evaluated whether IMRT compared to 3D-CRT resulted in fewer adverse events and patient-reported symptoms among 658 patients with high-risk endometrial cancer.[11] Of these patients, 559 received 3D-CRT and 99 received IMRT; median follow-up at the time of analysis was 74.6 months. Results revealed no significant differences in frequency and grades of adverse events between the RT techniques. There was an increase in grade adverse events of grade 3 or higher (mainly GI and hematologic) with 3D-CRT (37.7% vs. 26.3%; p=.03). During follow-up, significantly more diarrhea of grade 2 or higher (15.4% vs. 4%; p<.01) and hematologic adverse events of grade 2 or higher (26.1% vs. 13.1%; p<.01) were observed in patients administered 3D-CRT as compared to IMRT. More patients reported diarrhea (37.5% vs. 28.6%; p=0.125), bowel urgency (22.1% vs. 10%; p=.0039), and abdominal cramps (18.2% vs. 8.6%; p=.058) following 3D-CRT as compared to IMRT.

Klopp et al (2018) designed a randomized trial that measured the impact of pelvic IMRT versus standard 4-field RT on patient-reported toxicity and quality of life in 278 women with cervical and endometrial cancer.[12] Results revealed that the mean Expanded Prostate Cancer Index Composite (EPIC) bowel score decreased significantly less in the IMRT as compared to the standard RT group from baseline to end of RT (18.6 versus 23.6 points; p=.048). Additionally, both the mean EPIC urinary score (5.6 versus 10.4 points; p=.03) and Trial Outcome Index score (8.8 versus 12.8 points; p=.06) declined significantly less with IMRT compared to standard RT. Frequent or almost constant diarrhea was also reported more frequently among women receiving standard RT versus IMRT at the end of RT (51.9% versus 33.7%; p=0.01) and significantly more women administered standard RT were taking antidiarrheal medications 4 or more times daily (20.4% versus 7.8%; p=.04).

A trial by Naik et al (2016) randomized 40 patients with cervical cancer to IMRT or to 3D-CRT.[13] Both arms received concurrent chemotherapy (cisplatin) plus RT at 50 Gy in 25 fractions. Dosimetric planning showed higher conformality and lower doses to organs at risk with IMRT. With follow-up through 90 days after treatment, vomiting and acute GI and genitourinary (GU) toxicity were significantly higher in the 3D-CRT group (Table 3).

Ghandi et al (2013) reported on a prospective randomized study that compared whole-pelvis IMRT with whole-pelvis 2-dimensional RT in 44 patients with locally advanced cervical cancer.[14] Each treatment arm had 22 patients. The OS rate at 27 months was 88% with IMRT and 76% with 2-dimensional RT (p=0.645). However, fewer grade 2, 3, or 4 GI toxicities were experienced in the IMRT group than in the conventional RT group (Table 3).

Table 3. Acute Toxicity of Grade 2, 3 or 4 With 3-Dimensional Conformal Radiotherapy versus Intensity-Modulated Radiotherapy for Cervical Cancer

Toxicity	3D-CRT, n (%)	IMRT, n (%)	95% CI for the Difference	p
Naik et al (2016)[13]				
Hematologic	8 (40)	7 (35)	-0.219 to 0.119	.644
Leucopenia	3 (15)	2 (10)	-0.1479 to 0.479	.424
Vomiting	7 (35)	3 (15)	0.338 to 0.061	.007
Acute gastrointestinal toxicity	9 (45)	4 (20)	-0.408 to -0.091	.003
Acute genitourinary toxicity	7 (35)	4 (20)	-0.295 to -0.004	.058
Gandhi et al (2013)[14]				
Gastrointestinal, grade ≥2	14 (64)	7 (32)	0.002 to 0.604	.034
Gastrointestinal, grade ≥3	6 (27)	1 (5)	0.003 to 0.447	.047
Genitourinary, grade ≥2	7 (32)	5 (24)	-0.202 to 0.361	.404
Genitourinary, grade ≥3	3 (14)	0 (0)	-0.019 to 0.291	.125

CI: confidence interval; IMRT: intensity-modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy.

Nonrandomized Comparative Studies

Shih et al (2016) reported a retrospective comparison of bowel obstruction following IMRT (n=120) or 3D-CRT (n=104) after hysterectomy for endometrial or cervical cancer.[15] Groups were generally comparable, except more patients in the 3D-CRT group had open

hysterectomy (81% vs 47%, p<.001). Patients received regular examinations throughout a median follow-up of 67 months, and the 5-year rate of bowel obstruction was 0.9% in the IMRT group compared with 9.3% for 3D-CRT (p=0.006). A body mass index of 30 kg/m2 or more was also associated with less bowel obstruction. However, on multivariate analysis the only significant predictor of less bowel obstruction was IMRT (p=.022).

Chen et al (2014) reported on 101 patients with endometrial cancer treated with hysterectomy and adjuvant RT.[16] No significant differences between IMRT (n=65) and CRT (n=36) were found in 5-year OS (82.9% vs 93.5%; p=.26), local failure-free survival (93.7% vs 89.3%; p=.68), and disease-free survival (88.0% vs 82.8%; p=.83). However, IMRT patients experienced fewer acute and late toxicities.

Section Summary: Gynecologic Cancers
The evidence on IMRT for gynecologic cancers includes a systematic review, 6 RCTs and nonrandomized comparative studies. There is limited comparative evidence on survival outcomes following IMRT or 3D-CRT. However, available results have generally been consistent that IMRT reduces GI and GU toxicity. Based on evidence with other cancers of the pelvis and abdomen in close proximity to organs at risk, it is expected that OS with IMRT would be at least as good as 3D-CRT, with a decrease in toxicity.

ANORECTAL CANCER

Clinical Context and Therapy Purpose
The purpose of IMRT in individuals who have anorectal 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 anorectal cancer who are recommended for radiotherapy (RT).

Interventions
The therapy being considered is IMRT. This therapy uses computer software and magnetic resonance imaging for increased conformality, permitting the delivery of higher doses of radiation to the tumor while limiting the exposure of surrounding normal tissues.

Comparators
The following therapy is currently being used: 3D-CRT. This therapy uses 3-dimensional images typically from computed tomography to discriminate tumor tissue from adjacent normal tissue and nearby organs. Computer algorithms are used to estimate radiation doses being delivered to each treatment segment.

Outcomes
The general outcomes of interest are OS, recurrence (locoregional control), quality of life, and treatment-related adverse events (eg, toxicity). Toxicity can be assessed using the U.S. Department of Health and Human Services grading criteria for adverse events (1=mild, 2=moderate, 3=severe or medically significant, 4=life-threatening, and 5=death).

Study Selection Criteria
See information under the first indication.

Review of Evidence

Randomized Controlled Trials

Rattan et al (2016) conducted a small (N=20) RCT assessing IMRT for the treatment of anal canal cancer.[17] Grade 3 GI toxicity during treatment was not observed in any patients in the IMRT group but was seen in 60% of patients treated with 3D-CRT (p=.010). Hematologic grade 3 toxicity was not seen in any patients treated with IMRT but was noted in 20% of patients treated with 3D-CRT (p=.228). Other parameters indicating better tolerance to treatment with IMRT were reduced need for parenteral fluid (10% vs 60%; p=.019) and blood transfusion (0% vs 20%; p=.060).

Nonrandomized Comparative Studies

Sun et al (2017) reported on a comparative analysis of the National Cancer Database of IMRT with 3D-CRT for the treatment of rectal adenocarcinoma.[18] A total of 7386 patients with locally advanced rectal carcinoma were treated with neoadjuvant chemoradiotherapy (45 to 54 Gy) from 2006 to 2013; 3330 (45%) received IMRT and 4065 (55%) received 3D-CRT. Use of IMRT increased from 24% in 2006 to 50% in 2013. Patient age, race, insurance status, Charlson-Deyo comorbidity score, hospital type, income and educations status, and clinical disease stage were not predictive of which RT was used. The mean radiation dose was higher with IMRT (4735 centigray vs 4608 centigray, p<.001) and the occurrence of sphincter loss surgery was higher in the IMRT group (Table 4). However, patients treated with IMRT had a higher risk of positive margins. Multivariate analysis found no significant differences between the treatments for pathologic downstaging, unplanned readmission, 30-day mortality, or long-term survival. This study used unplanned readmission as a surrogate measure of adverse events but could not assess acute or late toxicity.

Table 4. Outcomes Following Radiochemotherapy with 3-Dimensional Conformal Radiotherapy or Intensity-Modulated Radiotherapy for Rectal Cancer

Outcome	3D-CRT, %	IMRT, %	Adjusted Odds Ratio	95% CI	p
Pathologic downstaging	57.0	55.0	0.89	0.79 to 1.01	.051
Sphincter loss surgery	28.3	34.7	1.32	1.14 to 1.52	<.001
Positive resection margin	5.6	8.0	1.57	1.21 to 2.03	<.001
Unplanned readmission	7.9	6.4	0.79	0.61 to 1.02	.07
30-d mortality	0.8	0.6	0.61	0.24 to 1.57	.31
Survival at 5 y	64	64	1.06	0.89 to 1.28	.47

Adapted from Sun et al (2017).[18]
CI: confidence interval; IMRT: intensity-modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy. OR: odds ratio.

Huang et al (2017) reported on a retrospective comparison of outcomes and toxicity for preoperative image-guided IMRT and 3D-CRT in locally advanced rectal cancer.[19] A total of 144 consecutive patients treated between 2006 and 2015 were analyzed. The 3D-CRT group was treated with 45 Gy in 25 fractions while the IMRT group was treated with 45 Gy in 25 fractions with a simultaneous integrated boost of 0.2 Gy per day for the primary tumor up to a total dose of 50 Gy. Statistical analysis was performed for grade 0, 1, 2, 3, or 4 toxicity and was significant only for acute GI toxicity (p=.039; Table 5). Four-year OS and disease-free survival did not differ between the 2 groups. Multivariate analysis found IMRT to be an

independent predictor of local failure-free survival (hazard ratio, 0.35; 95% CI, 0.11 to 0.95; p=.042).

Table 5. Grade 3 or Greater Toxicity Following Chemoradiotherapy for Rectal Cancer

Comparison	3D-CRT (n=99), n (%)	IMRT (n=45), n (%)
Skin	3 (3)	1 (2.2)
Acute gastrointestinal	14 (14.1)	3 (6.7)
Acute genitourinary	3 (3)	0 (0)
Hematologic	2 (2.0)	0 (0)
Late gastrointestinal	10 (10.1)	2 (4.4)
Late genitourinary	3 (3.1)	0 (0)

Adapted from Huang et al (2017).[19]
IMRT: intensity-modulated radiotherapy; 3D-CRT: 3-dimensional conformal radiotherapy.

In a retrospective review of 89 consecutive patients (52 IMRT, 37 3D-CRT), Chuong et al (2013) found 3-year OS, progression-free survival (PFS), locoregional control, and colostomy-free survival did not differ significantly between patients treated with IMRT and with 3D-CRT (p>.1).[20] Adverse events with 3D-CRT were more frequent and severe, and required more treatment breaks than IMRT (11 days vs 4 days; p=.006) even though the median duration of treatment breaks did not differ significantly (12.2 days vs 8.0 days; p=.35). IMRT patients had fewer acute grade 3 or 4 nonhematologic toxicity (p<.001), improved late grade 3 or 4 GI toxicity (p=.012), and fewer acute grade 3 or 4 skin toxicity (p<.001) than 3D-CRT patients.

Dasgupta et al (2013) retrospectively reviewed 223 patients (45 IMRT, 178 CRT) to compare outcomes for anal cancer.[21] They reported that 2-year OS, distant metastases-free survival, and locoregional recurrence-free survival did not differ significantly between patients in the IMRT and CRT groups.

Dewas et al (2012) retrospectively reviewed 51 patients with anal cancer treated with IMRT (n=24) or 3D-CRT (n=27).[22] Outcomes also did not differ significantly between patients in the IMRT and 3D-CRT groups in 2-year OS, locoregional relapse-free survival, and colostomy-free survival. Grade 3 acute toxicity occurred in 11 IMRT patients and in 10 3D-CRT patients.

Case Series

A GI toxicity study by Devisetty et al (2009) reported on 45 patients who received concurrent chemotherapy plus IMRT for anal cancer.[23] Intensity-modulated radiotherapy was administered to a dose of 45 Gy in 1.8-Gy fractions, with areas of gross disease subsequently boosted with 9 to 14.4 Gy. Acute GU toxicity was grade 0 in 25 (56%) cases, grade 1 in 10 (22%) patients, and grade 2 in 5 (11%) patients, with no grade 3 or 4 toxicities reported; 5 (11%) patients reported no GU tract toxicities. Grades 3 and 4 leukopenia was reported in 26 (56%) cases, neutropenia in 14 (31%), and anemia in 4 (9%). Acute GI toxicity included grade 0 in 2 (4%) patients, grade 1 in 11 (24%), grade 2A in 25 (56%), grade 2B in 4 (9%), grade 3 in 3 (7%), and no grade 4 toxicities. Univariate analysis of data from these patients suggested a statistical correlation between the volume of bowel that received 30 Gy or more of radiation and the risk for clinically significant (grade ≥2) GI toxicities.

Pepek et al (2010) conducted a retrospective analysis of toxicity and disease outcomes associated with IMRT in 47 patients with anal cancer.[24] Thirty-one patients had squamous cell

carcinoma. IMRT was prescribed to a dose of at least 54 Gy to areas of gross disease at 1.8 Gy per fraction. Forty (89%) patients received concurrent chemotherapy with various agents and combinations. The 2-year OS for all patients was 85%. Eight (18%) patients required treatment breaks. Toxicities included grade 4 leukopenia (7%) and thrombocytopenia (2%); grade 3 leukopenia (18%) and anemia (4%); and grade 2 skin toxicity (93%). These rates were lower than those reported in previous trials of chemoradiation, where grade 3 or 4 skin toxicity was noted in about 50% of patients and grade 3 or 4 GI toxicity noted in about 35%. In addition, the rate of treatment breaks was lower than in many studies; and some studies of chemoradiation included a break from RT.

Section Summary: Anorectal Cancer
The evidence on IMRT for anorectal cancer includes a small RCT with 20 patients, nonrandomized comparative studies, and case series. Survival outcomes have not differed significantly between IMRT and 3D-CRT. Studies have found that patients receiving IMRT plus chemotherapy for the treatment of anal cancer experience fewer acute and late adverse events than patients receiving 3D-CRT plus chemotherapy, primarily in GI toxicity.

ESOPHAGEAL CANCER

Clinical Context and Therapy Purpose
The purpose of IMRT in individuals who have esophageal 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 esophageal cancer who are recommended for radiotherapy (RT).

Interventions
The therapy being considered is IMRT. This therapy uses computer software and magnetic resonance imaging for increased conformality, permitting the delivery of higher doses of radiation to the tumor while limiting the exposure of surrounding normal tissues.

Comparators
The following therapy is currently being used: 3D-CRT. This therapy uses 3-dimensional images typically from computed tomography to discriminate tumor tissue from adjacent normal tissue and nearby organs. Computer algorithms are used to estimate radiation doses being delivered to each treatment segment.

Outcomes
The general outcomes of interest are OS, recurrence (locoregional control), quality of life, and treatment-related adverse events (eg, toxicity). Toxicity can be assessed using the U.S. Department of Health and Human Services grading criteria for adverse events (1=mild, 2=moderate, 3=severe or medically significant, 4=life-threatening, and 5=death).

Study Selection Criteria
See information under the first indication.

Review of Evidence

Systematic Reviews

Xu et al (2017) performed a systematic review and meta-analysis to compare IMRT and 3D-CRT in the treatment of esophageal cancer with regard to dosimetry and clinical outcomes (n=7 studies).[25] For the dosimetric comparison of organs at risk, 5 studies were included. Results revealed that the mean dose of 3D-CRT was significantly higher as compared to IMRT for the lung (mean difference dose: 2.18; 95% CI, 0.83 to 3.53; p=.002), with patients treated with 20 Gy or more having significantly higher irradiated volumes for 3D-CRT than for IMRT. For the heart, the mean dose was not significantly different between 3D-CRT and IMRT (mean difference dose: 0.17; 95% CI, -3.73 to 4.07; p=.93); however, the heart in patients treated with 50 Gy had significantly higher irradiated volumes for 3D-CRT. The maximum dose in the spinal cord revealed no difference between the 2 RT techniques (p=.33). Evaluated clinical outcomes included OS (n=3 studies; 871 patients) and toxicity (n=2 studies; 205 patients). The 3-year OS was significantly improved with IMRT as compared to 3D-CRT (OR, 0.68; 95% CI, 0.52 to 0.90; p=.007). No difference between the 2 RT techniques was seen with regard to the incidence of radiation pneumonitis or radiation esophagitis, regardless of grade. Limitations of the review were the small number of studies available for OS and toxicity outcome analyses and the retrospective nature of clinical outcomes studies.

Nonrandomized Comparative Studies

Lan et al (2020) retrospectively compared survival outcomes and symptomatic radiation pneumonitis in patients with esophageal cancer who received either IMRT (n=297) or 3D-CRT (n=91) from 2010 through 2017.[26] The median age of patients was 60 years and the median radiation dose for the entire cohort was 60 Gy. Results revealed significantly improved OS (p=.001), PFS (p=.008), and distant-metastases free survival (p=.011) with IMRT versus 3D-CRT; locoregional failure-free survival was not significantly different between the groups (p=.721). Intensity-modulated radiotherapy was also associated with significantly less radiation pneumonitis of grade 2 or higher as compared to 3D-CRT (5.4% vs. 23.1%; p<.001).

Ito et al (2017) retrospectively compared failure patterns and toxicities between IMRT (n=32) and 3D-CRT (n=48) in patients with esophageal cancer.[27] All patients were administered systemic chemotherapy consisting of either induction chemotherapy or concurrent chemoradiotherapy, with or without adjuvant chemotherapy. The median follow-up of the entire cohort was 24.6 months and the median follow-up time for survivors was 35.9 months. Results revealed a 3-year OS of 81.6%, 57.2% (p=.037 vs. IMRT), and 66.6% for the IMRT, 3D-CRT, and total groups, respectively. However, there was no significant difference between IMRT and 3D-CRT in complete response rate (75% vs. 68.9%; p=.62). Rates of locoregional control or PFS were not different between the groups as well. Overall, 47 patients developed recurrence of any type; there was no apparent difference in the failure pattern between the 2 RT techniques. The incidence of late toxicities was also not significantly different between IMRT and 3D-CRT. Ten patients in the IMRT groups were salvaged, and 60% survived without recurrence compared to 20% of the 3D-CRT group.

Haefner et al (2017) reported a retrospective analysis of 93 patients with esophageal cancer and compared outcomes and acute toxicity among patients receiving definitive CRT with either 3D-CRT (n=49) or IMRT (n=44).[28]he median follow-up for all patients was 20.1 months. The 1- and 3-year local relapse rates were 20.4% and 28.6% in the 3D-CRT group and 15.9% and 22.7% in the IMRT group, respectively (p=.62 for the 3-year rate). Median PFS and OS were

not significantly different between the groups; 13.8 months 3D-CRT versus 16.6 months IMRT (p=.448) and 18.4 months 3D-CRT versus 42 months IMRT (p=.198), respectively. The incidence of acute toxicities (dysphasia, radio dermatitis, nausea/vomiting, mucositis, bleeding, pneumonitis) was also not significantly different between the 2 RT techniques.

Section Summary: Esophageal Cancer
The evidence on IMRT for esophageal cancer includes a systematic review and nonrandomized comparative studies. Survival outcomes from studies have been mixed with some concluding improved survival with IMRT and others demonstrating no difference from 3D-CRT. Similarly, some studies have concluded that IMRT is associated with a reduced dose for organs at risk and potentially less radiation-related toxicity as compared to 3D-CRT.

SUMMARY OF EVIDENCE

For individuals who have gastrointestinal (GI) tract cancers who receive intensity-modulated radiotherapy (IMRT), the evidence includes nonrandomized comparative studies, retrospective series, and a systematic review. Relevant outcomes are OS, disease-specific survival, recurrence, quality of life, and treatment-related morbidity. IMRT has been compared with 3-dimensional conformal radiotherapy (3D-CRT) for the treatment of stomach, hepatobiliary, and pancreatic cancers. Evidence has been inconsistent with the outcome of survival, with some studies reporting increased survival among patients receiving IMRT compared with patients receiving 3D-CRT, and other studies reporting no difference between groups. However, most studies found that patients receiving IMRT experienced significantly less GI toxicity compared with patients receiving 3D-CRT. The available comparative evidence, together with dosimetry studies of organs at risk, would suggest that IMRT decreases toxicity compared with 3D-CRT in patients with GI cancers. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have gynecologic cancers who receive IMRT, the evidence includes a systematic review, 6 randomized controlled trials (RCTs) , and nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, recurrence, quality of life, and treatment-related morbidity. There is limited comparative evidence on survival outcomes following IMRT or 3D-CRT. However, results are generally consistent that IMRT reduces GI and genitourinary toxicity. Based on evidence with other cancers of the pelvis and abdomen that are proximate to organs at risk, it is expected that overall survival with IMRT would be at least as good as 3D-CRT, with a decrease in toxicity. A reduction in GI toxicity is likely to improve the quality of life in patients with gynecologic cancer. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have anorectal cancer who receive IMRT, the evidence includes a small RCT (N=20), nonrandomized comparative studies, and case series. Relevant outcomes are OS, disease-specific survival, recurrence, quality of life, and treatment-related morbidity. Survival outcomes have not differed significantly between patients receiving IMRT and 3D-CRT. However, studies have found that patients receiving IMRT with chemotherapy for the treatment of anal cancer experience fewer acute and late adverse events than patients receiving 3D-CRT plus chemotherapy, primarily in GI toxicity. A reduction in GI toxicity is likely to improve the quality of life in patients with anorectal cancer. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have esophageal cancer who receive IMRT, the evidence includes a systematic review and nonrandomized comparative studies. Relevant outcomes are OS, disease-specific survival, recurrence, quality of life, and treatment-related morbidity. Survival outcomes have been mixed with some studies concluding that IMRT is associated with a significant improvement in OS, progression-free survival , or distant-metastases free survival versus 3D-CRT and others reporting no difference between the radiotherapy techniques. Intensity-modulated radiotherapy appears to be associated with a reduced dose for organs at risk and may result in less radiation-induced toxicity. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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 Received From Physician Specialty Societies and Academic Medical Centers

2012 Input

In response to requests, the Blue Cross Blue Shield Association received input from 1 physician specialty society (4 reviewers) and 3 academic medical centers while their policy was under review in 2012. Input was mixed, but there was support for use of IMRT in a number of cancers discussed herein. In general, this support was based on normal tissue constraints for radiation doses and whether these dose constraints could not be met without the use of IMRT.

2010 Input

In response to requests, the Blue Cross Blue Shield Association received input from 1 physician specialty society (2 reviewers) and 3 academic medical centers while their policy was under review in 2010. There was support for use of IMRT in a number of cancers discussed herein. In general, this support was based on normal tissue constraints for radiation doses and whether these dose constraints could not be met without the use of IMRT.

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 Guidelines

Gastrointestinal Tract Cancers

The NCCN guideline for gastric cancer (v3.2024) indicates that "CT simulation and conformal treatment planning should be used with either 3D-CRT or IMRT."[29] In addition, target volumes need to be carefully defined and encompassed while taking into account variations in stomach filling and respiratory motion.

The NCCN guideline for hepatobiliary cancers (v.2.2024) states that “All tumors irrespective of the location may be amenable to RT [radiation therapy] (3D conformal RT, intensity-modulated radiation therapy [IMRT], or stereotactic body radiation therapy [SBRT]).”[30] The NCCN

guideline (v.2.2024) on biliary tract cancers also states that "all tumors irrespective of the location may be amenable to RT (3D-CRT, IMRT, or SBRT)."[31]

Intensity-modulated radiotherapy is mentioned as an option in NCCN guideline for pancreatic adenocarcinoma (v.3.2024), stating that IMRT "is increasingly being applied for the therapy of locally advanced pancreatic adenocarcinoma and in the adjuvant setting with the aim of increasing radiation dose to the gross tumor while minimizing toxicity to surrounding tissues."[32] In addition, the guideline states that "there is no clear consensus on the appropriate maximum dose of radiation when IMRT is used."

Gynecologic Cancers
For cervical cancer, the NCCN guideline (v3.2024) indicates IMRT “is preferred to minimize toxicities in definitive treatment of the pelvis with or without the para-aortic region" and is helpful in minimizing the dose to the bowel and other critical structures in the post-hysterectomy setting and in treating the para-aortic nodes when necessary.” This technique can also be useful “when high doses are required to treat gross disease in regional lymph nodes.”[33] Intensity-modulated radiotherapy “should not be used as a routine alternative to brachytherapy for treatment of central disease in patients with an intact cervix.” The guideline also mentions that “very careful attention to detail and reproducibility (including consideration of target and normal tissue definitions, patient and internal organ motion, soft tissue deformation, and rigorous dosimetric and physics quality assurance) is required for proper delivery of IMRT and related highly conformal technologies.”

The NCCN guideline (v.2.2024) on uterine neoplasms states that radiotherapy for uterine neoplasms includes external-beam radiotherapy and/or brachytherapy, but states that IMRT may be considered “for normal tissue sparing.”[34]

The NCCN guideline (v.3.2024) on ovarian cancer does not mention IMRT.[35]

Anorectal Cancers
The NCCN guideline (v.1.2024) for anal carcinoma states that IMRT “is preferred over 3D conformal RT [radiotherapy] in the treatment of anal carcinoma”; and that its use “requires expertise and careful target design to avoid reduction in local control by so-called ‘marginal-miss’.”[36]

The NCCN guideline (v.3.2024) on rectal cancer indicates that “IMRT is preferred for reirradiation of previously treated patients with recurrent disease, patients treated postoperatively due to increased acute of later toxicity, or unique anatomical situations.”[37]

Esophageal Cancer
The NCCN guideline (v.4.2024) for esophageal and esophagogastric junction cancers states that "CT simulation and conformal treatment planning should be used with either 3D conformal radiation or IMRT."[38]

American Society for Radiation Oncology
In 2020, the American Society for Radiation Oncology published a clinical practice guideline on RT for cervical cancer.[39] One key question within the guideline asked when it was appropriate to deliver IMRT for women administered definitive or postoperative RT for cervical cancer. Recommendations regarding this clinical scenario included:

- "In women with cervical cancer treated with postoperative RT with or without chemotherapy, IMRT is recommended to decrease acute and chronic toxicity." This was a strong recommendation based on moderate quality evidence for acute toxicity and low quality evidence for chronic toxicity.
- "In women with cervical cancer treated with definitive RT with or without chemotherapy, IMRT is conditionally recommended to decrease acute and chronic toxicity." This was a conditional recommendation based on moderate quality evidence for acute and chronic toxicity.

The guideline also notes that there are "no data that IMRT improves disease-specific survival or OS over 2D/3D techniques."

In 2021, the American Society for Radiation Oncology published a clinical practice guideline on RT for rectal cancer.[40] Within this guideline, IMRT-specific recommendations include:

> "For patients with rectal cancer treated with RT, an IMRT/volumetric modulated arc therapy (VMAT) technique is conditionally recommended (low quality of evidence). IMRT/VMAT may be beneficial when the external iliac nodes and/or the inguinal nodes require treatment or when 3-D conformal techniques may confer a higher risk for toxicity."

In 2022, the American Society for Radiation Oncology published a clinical practice guideline on RT for liver cancers including hepatocellular carcinomas [HCC].[41.] Their recommendations include, "For patients with HCC receiving dose-escalated ultra- or moderately hypofractionated EBRT [external beam radiation therapy], IMRT or proton therapy is recommended, with choice of regimen based on tumor location, underlying liver function, and available technology." They also conditionally recommended IMRT or proton therapy for unresectable IHC receiving dose-escalated ultra- or moderately hypofractionated EBRT.

In 2023, the American Society for Radiation Oncology published a clinical practice guideline on RT for endometrial cancer.[42.] These guidelines recommend use of IMRT to reduce acute and late toxicity in patients with endometrial carcinoma undergoing adjuvant EBRT.

The American Society for Radiation Oncology also published guidelines on multimodality therapy for locally advanced cancer of the esophagus or gastroesophageal junction.[43.] The authors note that IMRT is being increasingly used compared to other 3D-CRT techniques and recommend IMRT when other techniques cannot sufficiently reduce the dose to organs at risk to meet required dose objectives.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			

NCT03239626	Postoperative Hypofractionated Intensity-Modulated Radiation Therapy in Cervical Cancer: A Prospective Exploratory Trial (POHIM_RT Trial)	120	Apr 2025
NCT03239613	Postoperative Hypofractionated Intensity-Modulated Radiation Therapy with Concurrent Chemotherapy in Cervical Cancer: A Prospective Exploratory Trial (POHIM_CCRT Trial)	84	Apr 2024

Unpublished			
NCT02964468	Multicenter Dose-escalation Trial of Radiotherapy in Patients with Locally Advanced Rectal Cancer	525	May 2020

NCT: national clinical trial

Government Regulations

National:

There is no national coverage determination on this topic.

Local:

Wisconsin Physicians Service Insurance Corporation – LCD for Radiation Oncology Including Intensity Modulated Radiation Therapy (IMRT) (L34652)
Original Effective Date 10/01/2015
Retirement Date 04/01/2016

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Intensity-Modulated Radiation Therapy (IMRT): Cancer of the Head and Neck or Thyroid
Intensity Modulated Radiation Therapy (IMRT): Central Nervous System Tumors
Intensity Modulated Radiation Therapy (IMRT) of the Breast and Lung
Intensity-Modulated Radiation Therapy (IMRT) of the Prostate

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/5/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/13	8/20/13	9/10/13	Joint policy established
1/1/15	10/21/14	11/3/14	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	8/21/18	8/21/18	Routine maintenance
1/1/19	10/16/18	10/16/18	Routine maintenance: revised MPS to be more general, no exclusions; diverge from BCBSA with broader scope.
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance
1/1/22	10/19/21		Routine maintenance Ref 22,23,24,25,34,36 added
1/1/23	10/18/22		Routine maintenance (ls) Ref 9,10 added “Chest” added to title
1/1/24	10/17/23		Routine maintenance (jf) Vendor Managed: eviCore Added ref 9
1/1/25	10/15/24		Routine maintenance (jf) Vendor Managed: eviCore Ref added: 31,41,42,43

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTENSITY-MODULATED RADIATION THERAPY (IMRT): ABDOMEN, PELVIS, AND CHEST

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered; criteria apply
BCNA (Medicare Advantage)	See Governmental Regulations Section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.

Attachment A
ICD10 Codes for IMRT of the Abdomen and Pelvis

ICD10 Codes	Code Description
C16.0	Malignant neoplasm of cardia
C16.1	Malignant neoplasm of fundus of stomach
C16.2	Malignant neoplasm of body of stomach
C16.3	Malignant neoplasm of pyloric antrum
C16.4	Malignant neoplasm of pylorus
C16.5	Malignant neoplasm of lesser curvature of stomach, unspecified
C16.6	Malignant neoplasm of greater curvature of stomach, unspecified
C16.8	Malignant neoplasm of overlapping sites of stomach
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0	Malignant neoplasm of anus, unspecified
C21.1	Malignant neoplasm of anal canal
C21.2	Malignant neoplasm of cloacogenic zone
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.2	Hepatoblastoma
C22.3	Angiosarcoma of liver
C22.4	Other sarcomas of liver
C22.7	Other specified carcinomas of liver
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder

Attachment A
ICD10 Codes for IMRT of the Abdomen and Pelvis

ICD10 Codes	Code Description
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C25.0	Malignant neoplasm of head of pancreas
C25.1	Malignant neoplasm of body of pancreas
C25.2	Malignant neoplasm of tail of pancreas
C25.3	Malignant neoplasm of pancreatic duct
C25.4	Malignant neoplasm of endocrine pancreas
C25.7	Malignant neoplasm of other parts of pancreas
C25.8	Malignant neoplasm of overlapping sites of pancreas
C25.9	Malignant neoplasm of pancreas, unspecified
C26.0	Malignant neoplasm of intestinal tract, part unspecified
C26.1	Malignant neoplasm of spleen
C26.9	Malignant neoplasm of ill-defined sites within the digestive system
C45.1	Mesothelioma of peritoneum
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C51.0	Malignant neoplasm of labium majus
C51.1	Malignant neoplasm of labium minus
C51.2	Malignant neoplasm of clitoris
C51.8	Malignant neoplasm of overlapping sites of vulva
C51.9	Malignant neoplasm of vulva, unspecified
C52	Malignant neoplasm of vagina
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C53.8	Malignant neoplasm of overlapping sites of cervix uteri
C53.9	Malignant neoplasm of cervix uteri, unspecified
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified
C56.1	Malignant neoplasm of right ovary
C56.2	Malignant neoplasm of left ovary
C56.9	Malignant neoplasm of unspecified ovary

Attachment A
ICD10 Codes for IMRT of the Abdomen and Pelvis

ICD10 Codes	Code Description
C57.00	Malignant neoplasm of unspecified fallopian tube
C57.01	Malignant neoplasm of right fallopian tube
C57.02	Malignant neoplasm of left fallopian tube
C57.10	Malignant neoplasm of unspecified broad ligament
C57.11	Malignant neoplasm of right broad ligament
C57.12	Malignant neoplasm of left broad ligament
C57.20	Malignant neoplasm of unspecified round ligament
C57.21	Malignant neoplasm of right round ligament
C57.22	Malignant neoplasm of left round ligament
C57.3	Malignant neoplasm of parametrium
C57.4	Malignant neoplasm of uterine adnexa, unspecified
C57.7	Malignant neoplasm of other specified female genital organs
C57.8	Malignant neoplasm of overlapping sites of female genital organs
C57.9	Malignant neoplasm of female genital organ, unspecified