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Medical Policy Manual Medicine, Policy No. 165

Intensity Modulated Radiotherapy (IMRT) of the Thorax, Abdomen, and Pelvis

Effective: August 1, 2019

Next Review: July 2020
Last Review: July 2019

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Intensity modulated radiotherapy (IMRT) is a form of radiation therapy that conforms closely to the targeted tumor shape and allows higher doses of radiation to be delivered while minimizing toxicity to surrounding healthy tissues.

MEDICAL POLICY CRITERIA

I. Intensity modulated radiotherapy (IMRT) of the thorax, abdomen, and pelvis may be considered **medically necessary** when any of the following criteria are met (Note: This policy addresses specific indications only. Please see Medicine, Policy No. 166 for IMRT for breast cancer and Medicine, Policy No. 167 for requests where only through IMRT can published dose/volume constraints be met for organs at risk):

   A. There is documented prior radiation treatment to the planned target volume; or

   B. To deliver irradiation to the thorax when one or more of the following criteria are met:

      1. Documented significant pulmonary function impairment, meeting either of the following criteria:

a. FEV_1/FVC <0.70; or

b. FVC greater than or equal to 80% of predicted; or

2. Documented curative treatment for any of the following indications:

a. Esophageal and gastroesophageal junction cancers

b. Lung cancer including non-small cell or small cell

c. Pleural mesothelioma

d. Thymic carcinoma

e. Thymoma

C. Primary, adjuvant, or salvage treatment of pancreatic cancer; or

D. For the treatment of prostate cancer when any of the following criteria are met:

1. Primary treatment of local (clinical or pathological T1, T2, N0, M0) or locally advanced (clinical or pathological T3, T4, N0, N1, M0) prostate cancer; or

2. Low metastatic burden prostate cancer (defined as 3 or fewer bone metastases and no metastases outside the vertebral bodies or pelvis, or visceral metastases) when planned target volume includes all oligometastatic foci; or

3. Post radical prostatectomy as either adjuvant or salvage treatment when any of the following are met:

a. Documentation includes evidence of adverse pathologic findings post-prostatectomy, defined as capsular penetration, seminal vesicle involvement, or positive surgical margins; or

b. There is clinical documentation of persistence of detectable PSA post-surgery; or

c. Increase in PSA after non-detectability, post-surgery; or

E. As an approach to delivering radiotherapy for patients with cancer of the anus/anal canal.

II. Intensity-modulated radiotherapy (IMRT) is considered **not medically necessary** for the treatment of tumors of the abdomen, pelvis, and thorax not meeting the criteria above (Please see Medicine, Policy No. 167 for requests where only through IMRT can published dose/volume constraints be met for organs at risk).

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

ORGANS AT RISK

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. At-risk organs may include the lungs, heart, and esophagus.

CANCERS OF THE ABDOMEN AND PELVIS

Cancers of the abdomen and pelvis include, but are not limited to, tumors of the lumbar and sacral spine and pelvic bones, sarcomas, and anal, gastric, pancreatic, hepatobiliary, rectal, prostate, and gynecologic tumors.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome. Quality assurance for 3D and IMRT submitted plans are not required with a preauthorization request.

- Clinical history
- Physical/chart notes
- Relevant imaging reports documenting that the policy criteria are met for medical necessity.

CROSS REFERENCES

1. Charged-Particle (Proton) Radiotherapy, Medicine, Policy No. 49
2. Intensity Modulated Radiotherapy (IMRT) of the Central Nervous System (CNS), Head, Neck, and Thyroid, Medicine, Policy No. 164
3. Intensity Modulated Radiotherapy (IMRT) for Breast Cancer, Medicine, Policy No. 166
4. Intensity Modulated Radiotherapy (IMRT) for Tumors in Close Proximity to Organs at Risk, Medicine, Policy No. 167
5. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Intracranial, Skull Base, and Orbital Sites, Surgery, Policy No. 213
6. Stereotactic Radiosurgery and Stereotactic Body Radiation Therapy for Tumors Outside of Intracranial, Skull Base, or Orbital Sites, Surgery, Policy No. 214

BACKGROUND

RADIATION TECHNIQUES

Conventional External Beam Radiotherapy

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

Three-Dimensional Conformal Radiation

Treatment planning evolved by using three 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 three-dimensional conformal radiation therapy (3D-CRT).

Intensity-Modulated Radiotherapy

IMRT, which uses computer software, CT images, and magnetic resonance imaging (MRI), 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 multiple-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 adjoining organs at risk (OAR). 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. Alternatively, IMRT provides the opportunity to construct heterogenous dose deposition within the target volume thus tailoring differential dose in keeping with physician assessment of differential cancer cell density, etc. This may diminish local failure within the overall target volume.

Because most tumors move as patients breathe, dosimetry with stationary targets may not accurately reflect doses delivered within target volumes and adjacent tissues in patients. Furthermore, treatment planning and delivery are more complex, time-consuming, and labor-intensive for IMRT than for 3D-CRT. Thus, clinical studies must test whether IMRT improves tumor control or reduces acute and late toxicities when compared with 3D-CRT.

EVIDENCE SUMMARY

Multiple-dose planning studies generate three-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 IRMT 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 in 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 IMRT indications, such as using IMRT to provide better tumor control, comparative studies of health outcomes are needed to demonstrate such a benefit.

The focus of the evidence review below is on the indications identified as investigational in the policy criteria.

LUNG CANCER

Systematic Reviews

In 2012, Bezjak published a systematic review that examined the evidence for the use of IMRT in the treatment of lung cancer to quantify its potential benefits and make recommendations for RT programs considering adopting this technique within Ontario, Canada.[1] This review consisted of two retrospective cohort studies (through March 2010) reporting on cancer outcomes, which was considered insufficient evidence on which to make evidence-based recommendations. These two cohort studies reported on data from the same institution (M.D. Anderson Cancer Center); the study by Liao (2010, reported next)[2] acknowledged that patients included in their cohort (N=409) were previously reported on in the earlier cohort by Yom (2007, N=290), but it is not clear exactly how many patients were added in the second report.[3] However, due to the known dosimetric properties of IMRT and extrapolating from clinical outcomes from other disease sites, the review authors recommended that IMRT should be considered for lung cancer patients where the tumor is in close proximity to an organ at risk, where the target volume includes a large volume of an organ at risk, or in scenarios where dose escalation would be potentially beneficial while minimizing normal tissue toxicity.[1]

Nonrandomized Comparative Studies

Koshy (2017) published a retrospective cohort analysis of patients with stage III NSCLC, comparing those treated with IMRT and with non-IMRT.[4] Using the National Cancer Database, 7493 patients treated between 2004 and 2011 were assessed. Main outcomes were OS and the likelihood and effects of radiation treatment interruption, defined as a break in the treatment of 4 or more days. OS for non-IMRT and IMRT patients, respectively, were 18.2 months and 20 months ($p<0.001$). Median survival with and without a radiation treatment interruption was 16.1 and 19.8 months, respectively ($p<0.001$), and IMRT significantly reduced the likelihood of a radiation treatment interruption (odds ratio, 0.84; $p=0.04$). The study was limited by unavailable information regarding radiation treatment planning and potential mechanisms affecting survival, and by a possible prescription, bias causing patients with better performance status to be given IMRT.

In 2017, Chun reported a secondary analysis of trial that assessed the addition of cetuximab to a standard chemotherapy regimen and radiation dose escalation.[5] Use of IMRT or 3D-CRT was a stratification factor in the 2×2 design. Patients were not randomized to IMRT or 3D-CRT. Of 482 patients in the trial, 53% were treated with 3D-CRT, and 47% were treated with IMRT. Compared with the 3D-CRT group, the IMRT group had larger planning treatment volumes (486 mL vs 427 mL, $p=0.005$), larger planning treatment volume/volume of lung ratio (median,

0.15 vs 0.13; p=0. 13), and more Stage IIIB disease (38.6% vs 30.3%, p=0.056). Even though there was an increase in treatment volume, IMRT was associated with less grade three or greater pneumonitis (3.5% vs 7.9%, p=0.039) and a reduced risk (odds ratio [OR], 0.41; 95% confidence interval [CI], 0.171 to 0.986; p=0.046), with no significant differences between the groups in two-year overall survival, progression-free survival, local failure, or distant metastasis-free survival.

Ling (2016) compared IMRT and 3D-CRT in patients with stage III NSCLC treated with definitive RT.[6] In this study of 145 consecutive patients treated between 1994 and 2014, the choice of treatment was at the treating physician's discretion, but all IMRT treatments were performed in the last five years. Ling found no significant differences between the groups for any measure of acute toxicity (grade ≥2 esophagitis, grade ≥2 pneumonitis, percutaneous endoscopic gastrostomy, narcotics, hospitalization, or weight loss). There were no significant differences in oncologic and survival outcomes.

Harris (2014) compared the effectiveness of IMRT, 3D-CRT, or 2D-RT in treating stage III non-small-cell lung cancer (NSCLC) using a cohort of patients from the Surveillance, Epidemiology, and End Results–Medicare database treated between 2002 and 2009.[7] OS was better with IMRT and 3D-CRT than with 2D-CRT. In univariate analysis, improvements in OS (HR=0.90, p=0.02) and cancer-specific survival (HR=0.89, p=0.02) were associated with IMRT. However, IMRT was similar to 3D-CRT after controlling for confounders in OS and cancer-specific survival (HR=0.94, p=0.23; HR=0.94, p=0.28, respectively). On multivariate analysis, toxicity risks with IMRT and 3D-CRT were also similar. Results were similar for the propensity score–matched models and the adjusted models.

In 2013, Shirvani reported on an M.D. Anderson Cancer Center study on the use of definitive IMRT in limited-stage small cell lung cancer treated with definitive RT.[8] In this study of 223 patients treated from 2000 to 2009, 104 received IMRT and 119 received 3D-CRT. Median follow-up times were 22 months (range, 4-83 months) for IMRT and 27 months (range, 2-147 months) for 3D-CRT. In either multivariable or propensity score–matched analyses, OS and disease-free survival did not differ between IMRT and 3D-CRT. However, rates of esophagitis-related percutaneous feeding tube placements were lower with IMRT (5%) than 3D-CRT (17%; p=0.005).

The 2010 nonrandomized comparative study by Liao compared patients who received one of three forms of RT, along with chemotherapy, for inoperable NSCLC at one institution.[2] This study retrospectively compared 318 patients who received CT plus 3D-CRT and chemotherapy from 1999 to 2004 (mean follow-up, 2.1 years) to 91 patients who received four-dimensional CT plus IMRT and chemotherapy from 2004 to 2006 (mean follow-up, 1.3 years). Both groups received a median dose of 63 Gy. Disease end points were locoregional progression, distant metastasis, and OS. Disease covariates were gross tumor volume (GTV), nodal status, and histology. The toxicity end point was grade three, four, or five radiation pneumonitis; toxicity covariates were GTV, smoking status, and dosimetric factors. Using Cox proportional hazards models, the hazard ratios (HRs) for IMRT were less than one for all disease end points; the difference was significant only for OS. The median (SD) survival was 1.40 (1.36) years for the IMRT group and 0.85 (0.53) years for the 3D-CRT group. The toxicity rate was significantly lower in the IMRT group than in the 3D-CRT group. The V20 (volume of the lung receiving 20 Gy) was higher in the 3D-CRT group and was a factor in determining toxicity. Freedom from distant metastasis was nearly identical in both groups. The authors concluded that treatment with 4D-CT plus IMRT was at least as good as that with 3D-CRT in terms of the rates of

freedom from locoregional progression and metastasis. This retrospective study found a significant reduction in toxicity and improvement in survival. The nonrandomized, retrospective aspects of this study from one center limit the ability to draw definitive treatment conclusions about IMRT.

Summary

For the treatment of lung cancer, no RCTs were identified that compared IMRT with 3D-CRT. Dosimetry studies have reported that IMRT can reduce radiation exposure to critical surrounding structures, especially in large lung cancers. Based on nonrandomized comparative studies, IMRT appears to produce survival outcomes comparable with those of 3D-CRT with a reduction in adverse events. Interpretation of these studies is limited by the potential for bias in treatment assignment and/or change in treatments over time.

ESOPHAGUS

The esophagus is considered to be an organ at risk as it may be particularly vulnerable to clinically important complications from radiation toxicity. In addition, the thoracic esophagus is in close proximity to vital structures including the heart and lungs. Therefore, conformal radiation therapy is an appropriate delivery method for radiation therapy for esophageal cancer.

In 2017, Ito retrospectively analyzed 80 patients with esophageal cancer treated with chemoradiotherapy and compared outcomes of those receiving IMRT and 3D-CRT.[9] IMRT and 3D-CRT were reported to have three-year OS of 81.6% and 57.2%, respectively. In a univariate analysis, IMRT patients had significantly better three-year OS but groups were not different in locoregional control or PFS. A multivariate analysis indicated IMRT as the only independent favorable factor for OS (p=0.045). Of the 62 cases with nodal involvement, 9.6% developed upper cervical node recurrence outside the prophylactic region. Salvage was successful in 10 of the IMRT patients and 20% of the 3D-CRT patients. Survival without recurrence was reported in 60% of the IMRT group.

Haefner (2017) retrospectively analyzed 49 3D-CRT and 44 IMRT patients who received definitive radiation for locally advanced esophageal cancer.[10] Patients were followed up for a mean of 34.7 months. The three-year local relapse rate was 28.6% and 22.7% for the 3D-CRT and IMRT group, respectively. Median progression-free and overall survival in the 3D-CRT group were 13.8 and 18.4 months, respectively. Survival was not significantly different in the IMRT group, where progression-free and overall survival were 16.6 and 42 months, respectively.

In 2017, Xu performed a systematic review and meta-analysis of studies using IMRT and 3D-CRT to treat esophageal cancer.[11] Dose-volume histograms, overall survival (OS), and toxicity were analyzed in 80, 871, and 205 patients, respectively. Patients had lower average irradiated volumes in heart and lung from IMRT compared to 3D-CRT. Higher OS was observed in IMRT-treated patients, although there was no significant difference in the incidence of radiation pneumonitis or radiation esophagitis.

Yang (2017) evaluated the effectiveness and toxicities of 3D-CRT, IMRT, and volumetric modulated arc therapy (VMAT) in treating cervical esophageal cancer in a prospective comparative study.[12] The two-year OS was 53.6, 55.6, and 60.6% (P = 0.965) and the two-year failure free survival was 49.5, 56.7, and 60.1% (P = 0.998) for the 3DCRT, IMRT, and

VMAT groups, respectively. There was an advantage of treatment modality with respect to OS ($P < 0.001$), as determined by a univariate analysis of the complete response to treatment. There were significantly fewer occurrences of Grade one radiation pneumonitis in patients treated with IMRT and VMAT as compared to 3D-CRT.

In addition, case series and retrospective studies have reported superior dose conformity and homogeneity, as well as superior survival outcomes and reduced radiation dose to the heart and lungs with IMRT compared with 3D-CRT for esophageal cancer.[13-17]

MALIGNANT PLEURAL MESOTHELIOMA

Systematic Reviews

Chi (2011) report on a systematic review of IMRT as part of trimodal therapy (surgery, chemotherapy and radiation) for treatment of malignant pleural mesothelioma (MPM).[18] However, search criteria were not expressed a priori and the quality of studies was not critically appraised; therefore, interpretation of results from this review is limited.

Another systematic review of radiotherapy in general and IMRT specifically was published in 2011 by Price.[19] No randomized controlled trials were identified involving use of these therapies after surgical resection. Available evidence for IMRT consisted of case series, and reports of pulmonary toxicity with IMRT lead the author to conclude that additional studies are needed to establish the factors which differentiate those pre-disposed to adverse effects from radiation therapy from those not at risk. Based upon the available state of evidence, the review stated, "Much work has gone into exploring methods of radical treatment in the few thought suitable for this treatment, again without any evidence that such treatment is of any value, and very little into the palliation of symptoms for what remains an incurable disease in all who present with it." Therefore, the review concluded that, "There is currently no evidence to support the routine role of radiotherapy in patients with mesothelioma."

In 2006, Chapman conducted a systematic review on the use of any radiation therapy in the treatment of MPM.[20] The authors were unable to find any literature that met the prespecified inclusion criteria (randomized controlled trial comparing patients treated with radiation therapy with a control group).

Nonrandomized Studies

Since the above systematic reviews, two nonrandomized comparative studies were identified that reported on comparisons of primary health outcomes (e.g., overall-, disease-, or progression-free survival).

Foroudi (2017) reported survival, progression, and toxicity from a retrospective study of high-dose hemithorax radiotherapy for MPM patients.[21] A total of 71 patients received doses of 45-60 Gy delivered by 3D-CRT in 17 patients and IMRT in 54 patients. Median overall survival of patients treated with 3D-CRT was 8.1 months (95%CI 5.2-19.4) and of patients treated with IMRT was 10.0 months (95% CI 7.2 to 14.0). Median progression free survival of patients treated with 3D-CRT and IMRT was 4.4 months (95% CI 3.3 to 5.5) and 5.4 months, respectively. Grade 3-5 toxicities were reported in 53% of 3D-CRT and 78% of IMRT patients. The authors concluded that high-dose radiotherapy to the hemothorax in MPM patients does not improve survival but does cause significant toxicity.

Shaikh (2017) retrospectively analyzed outcomes in MPM patients who received adjuvant chemotherapy and hemithoracic intensity-modulated pleural RT or adjuvant conventional RT following lung-sparing pleurectomy/decortication.[22] The IMRT group had significantly higher OS (median 20.2 (95% CI 13.5 to 28.2) versus 12.3 months (95% CI 10 to 15.3), p=0.0001). This group also had significantly higher rates of epithelioid histological type, which was significantly associated with longer OS in multivariate analysis, advanced pathological stage, and chemotherapy treatment. Grade 2 or higher esophagitis was reported in 23% and 47% of IMRT and conventional RT patients, respectively. The one-year incidences of local failure were 42% and 47% for IMRT and conventional RT, respectively, which were not significantly different.

Section Summary

In summary, there is limited evidence regarding the role of IMRT in the treatment of MPM. Well-designed comparative studies are needed to isolate the treatment effect of radiation therapy from other components of care, and to firmly establish treatment timing and dosing guidelines.

THYMUS TUMORS

Published literature on IMRT for the treatment of thymomas and thymic carcinoma was summarized in a 2013 systematic review.[23] Giannopoulou reported that the treatment of choice is tumor resection in patients who are surgical candidates. Postoperative radiotherapy is recommended based upon a five-year survival of 50-60%. For unresectable disease concurrent chemotherapy and radiation therapy is recommended. The optimal tumor target definition was found with 3D RT, 4D RT, IMRT, image-guided RT, and computed tomography fusion with PET scan.

No new randomized controlled trials or comparative studies have been published since the systematic review.

MULTIPLE INDICATIONS

Two systematic reviews, published in 2008 and 2010, summarized evidence on the use of IMRT for a number of cancers, including head and neck, prostate, gynecologic, breast, lung, and gastrointestinal.[24,25] The authors presented the reviews as an analysis of comparative clinical studies; however, these reviews really categorized several small case series using historical cohorts as controls. Many of the included studies in the systematic reviews are summarized below by indication.

STOMACH

Nonrandomized Studies

In a small (n=7) case series, Milano (2006) reported clinical outcomes of patients with stage III gastric cancer receiving postoperative chemoradiotherapy with 5-fluorouracil (5-FU) and leucovorin and IMRT delivered to a dose of 50.4 Gy in 1.8 Gy fractions.[26] Chemoradiotherapy with IMRT was well tolerated, with no acute gastrointestinal (GI) tract toxicities (nausea, diarrhea, esophagitis) greater than grade 2.

Boda-Heggemann (2006) evaluated the efficacy and safety of two different adjuvant chemoradiotherapy regimens using 3D-CRT (n = 27) or IMRT (n = 33) in two consecutive

cohorts of patients who underwent primarily D2 resection for gastric cancer.[27] The cohorts in this study were generally well-matched, with American Joint Committee on Cancer (AJCC) advanced stage (II-IV) disease. The majority (n = 26, 96%) of those who received 3D-CRT were treated with 5-fluorouracil plus folinic acid (5FU/FA); the other patient received oxaliplatin plus capecitabine (XELOX). In the 3D-CRT cohort, 13 (50%) patients completed the 5FU/FA regimen, 13 halted early because of acute toxicity or progression, and received a median 60% of planned cycles. Patients in the IMRT cohort received XELOX (n = 23, 70%) or 5FU/FA (n = 10, 30%). Five of 10 (50%) patients completed all planned 5FU/FA cycles; the other five received only a median 60% of cycles because of acute toxicity. Thirteen (56%) treated with XELOX completed all planned cycles; the other 10 received a median of 70% planned cycles because of toxicity. Radiation was delivered to a total prescribed dose of 45 Gy/1.8 Gy/fraction in 21 (81%) of the 3D-CRT cohort patients; five received < 45 Gy because of intolerance to treatment. Thirty (91%) patients in the IMRT cohort received the planned 45 Gy dosage; two (6%) were unable to tolerate the full course, and one case planned for 50.4 Gy was halted at 47 Gy. Overall, the IMRT chemotherapy regimen decreased renal toxicity with a trend toward improving survival (see Table 1). However, interpretation of this study regarding the safety and efficacy of IMRT is limited by differences in the chemotherapy regimens.

Table 1. Outcomes for Intensity-Modulated Radiotherapy With Capecitabine Plus Oxaliplatin vs Three-Dimensional Conformal Radiation With 5-FU/FA for Stomach Cancer

Comparison	3-Dimensional Conformal Radiation	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
Actuarial 2-yr overall survival, %	37%	67%	
Actuarial 5-yr overall survival, %	22%	44%	

5-FU/FA: 5-fluorouracil plus folinic acid.

The median OS was 18 months in the 3D-CRT cohort, and more than 70 months in the IMRT cohort (p = 0.0492). The actuarial two-year OS rates were 67% in the IMRT cohort and 37% in the 3D-CRT group (p not reported). Acute renal toxicity based on creatinine levels was generally lower in the IMRT cohort compared to the 3D-CRT group, with a significant difference observed at six weeks (p=0.0210). In the 3D-CRT group, LENT-SOMA grade 2 renal toxicity was observed in two patients (8%) whereas no grade 2 toxicity was reported in the IMRT group.

In a recent update of this study, which included 27 3D-CRT patients and 38 IMRT patients, authors reported the actuarial five-year OS rates were 47% in the IMRT group and 26% in the 3D-CRT group.[28] The median disease free survival (DFS) times were 35 months in the IMRT group and 14 months in the 3D-CRT group, (p=0.0693). Actuarial five-year DFS survival rates were 44% in the IMRT group and 22% in the 3D-CRT group. Interpretation of this study is limited by differences in the chemotherapy regimens for the 3D-CRT and IMRT groups.

At the two-year follow-up point, the authors of this study assert that adjuvant IMRT with XELOX is more efficacious and associated with less renal toxicity than 3D-CRT with 5FU/FA in patients with advanced gastric cancer. However, a statistically significant difference in

chemotherapy regimens was not observed within the IMRT cohort at the five-year follow-up point.[28] Among patients receiving 5-FU/FA, DFS tended to be better in the IMRT group, but this was also not a statistically significant observation. In addition, the nonconcurrent cohorts study design precludes direct comparison of outcomes data and conclusions about the relative efficacy of these radiotherapy modalities in this setting.

A small non-randomized study compared the clinical outcomes and toxicity in patients with gastric or gastroesophageal junction cancer who postoperatively received concurrent chemotherapy and either IMRT (n= 31) or 3D-CRT (n=26).[29] Dose volume histogram parameters for kidney and liver were compared between treatment groups. The two-year OS rates were not significantly different between the groups (51% for 3D CRT and 65% for IMRT). The groups experienced similar rates of locoregional failures (15% 3D CRT vs. 13% IMRT) and Grade ≥2 acute gastrointestinal toxicity (61.5 3D CRT vs. 61.2% IMRT); however, the 3D CRT group needed more treatment breaks (three vs. zero). IMRT was found to provide sparing to the liver and possibly renal function.

Additional publications of IMRT for gastric cancer consist of case series.[30-37]

HEPATOBILIARY

Nonrandomized Studies

In a retrospective series with a historical control cohort, Fuller (2009) reported that clinical results achieved with image-guided IMRT (n=24) were compared to results with CRT (n=24) in patients with primary adenocarcinoma of the biliary tract.[38] The majority of patients underwent postsurgical chemoradiotherapy with concurrent fluoropyrimidine-based regimens. IMRT treatment plans prescribed 46 to 56 Gy to the planning target volume (PTV) that includes the tumor and involved lymph nodes, in daily fractions of 1.8–2 Gy. CRT involved 3-D planning that delivered 46–50 Gy in 1.8–2 Gy daily fractions. Both groups received boost doses of 4–18 Gy as needed. The median estimated OS for all patients who completed treatment was 13.9 months (range: 9.0–17.6); the IMRT cohort had median OS of 17.6 months (range: 10.3–32.3), while the CRT cohort had a median OS of 9.0 months (range: 6.6–17.3). Acute GI toxicities were mild to moderate, with no significant differences between patient cohorts. These results suggest that moderate dose escalation via conformal radiotherapy is technically and clinically feasible for treatment of biliary tract adenocarcinoma. However, while this series represents the largest group of patients with this disease treated with IMRT, generalization of its 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 radiotherapy cohort.

Two single arm studies reported outcome with IMRT in patients with hepatobiliary cancers. The first study, from Jang (2009), included 42 patients with advanced (33% AJCC stage IIIC, 67% stage IV) hepatocellular carcinoma (HCC) with multiple extrahepatic metastases.[39] Among the 42 cases, 33 (79%) had intrahepatic HCC with extrahepatic metastases, 9 (21%) had only extrahepatic lesions. The extrahepatic locations of HCC metastatic lesions included lung (n = 19), lymph node and adrenal (n = 20), other soft tissues (n = 6), and bone (n = 5). Helical tomotherapy was performed simultaneously for all lesions in each patient, with a total radiation dose of 50 and 40 Gy to 95% of the GTV and PTV in 10 fractions divided over two weeks. All received capecitabine during the course of IMRT as a radiosensitizer. After completion of tomotherapy, additional transarterial or systemic chemotherapy was administered to patients eligible for it according to tumor location. Among 31 patients who

underwent hepatic IMRT, a mean of three courses (range one to six) transarterial chemolipiodolization was performed in 23. Among nine patients with extrahepatic lesions only, three received an additional three-seven cycles of systemic chemotherapy consisting of epirubicin, cisplatin, and 5FU. Median follow-up was 9.4 months (range, 1.9-25.3 months). Tumor response was reported separately for each organ treated with IMRT. The overall objective tumor response rate was 45% for intrahepatic HCC, 68% for pulmonary lesions, 60% for lymph node and adrenal cases, and 67% for soft-tissue metastases. Three cases of local tumor progression occurred within the target radiation area, including two intrahepatic HCC and one abdominal lymph node metastasis. Median OS was 12.3 months, with 15% OS at 24 months. The most common acute adverse events were mild anorexia and constitutional symptoms that occurred one-two weeks after start of IMRT, regressed spontaneously or subsided with symptomatic care, and did not interfere with the scheduled delivery of IMRT. However, it is not possible to discern the impact of IMRT on adverse events because almost all occurred in patients who received chemotherapy following IMRT. Most patients were reported to have tolerated therapy well, with no treatment-related mortality.

A second retrospective single-arm study (McIntosh 2009) involved 20 patients with primary, unresectable HCC who were treated with IMRT and concurrent capecitabine.[40] Patients had AJCC grade T1 (n = 7) and T3 (n = 13) HCC. IMRT was prescribed to a minimum tumor dose of 50 Gy in 20 fractions over four weeks, with the optimization goal of delivering the prescription dose to 95% of the PTV. Capecitabine was administered as radiosensitizer on the days of IMRT delivery. Eleven (55%) patients underwent at least one transarterial chemoembolization (range one-three procedures) before radiotherapy planning. Eighteen of 20 (90%) patients completed the full course of IMRT, two died before follow-up imaging was obtained. The mean survival of 18 patients who completed IMRT was 9.6 months after its conclusion. Disease progression occurred in-field in three patients, two failed elsewhere in the liver. Four patients (25%) required hospitalization during therapy, due to encephalopathy (n = 1), gastric ulcer (n = 1), acute hepatitis (n = 1) and sepsis (n = 1). Four required a break from chemotherapy because of peripheral neuropathy (n = 2), acute hepatitis (n = 1), and sepsis (n = 1). Grade 1 acute abdominal pain was observed in 15%, 30% reported grade 1 nausea, 5% experienced grade 2 nausea. No acute or late toxicity greater than grade two was reported.

In a small case series (n=40), Ren (2011) reported the outcomes of irradiation dose escalation in patients with locally advanced hepatocellular carcinoma treated with a combination of 3D CRT/IMRT and transcatheter arterial chemoembolization.[41] The authors report that irradiation dose was safely escalated by using 3D/IMRT with an active breathing coordinator to a maximum tolerated dose of 62 Gy for patients with tumor diameters of <10 cm and 52 Gy for ≥10 cm. However, the findings are not reported for each radiation type separately.

Additional publications of IMRT for hepatobiliary cancer consist of similar case series.[42] However, similar to the limitations found in IMRT for gastric cancers, evidence regarding IMRT for hepatobiliary cancers is limited by a lack of concurrent comparison groups, small sample sizes and nonrepresentative patient samples. Therefore, it is not possible to draw conclusions about the relative clinical efficacy or toxicities of IMRT in patients with hepatobiliary cancer versus any other radiotherapy method.

PANCREATIC

Nonrandomized Studies

In 2016, Lee reported a prospective comparative study of GI toxicity in patients treated with concurrent chemoradiotherapy with IMRT (n=44) or 3D-CRT (n=40) for treatment of borderline resectable pancreatic cancer.[43] Selection of treatment was by patient choice after explanation by 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 (42.3%) than in patients treated with IMRT (9.1%; p=0.003; see Table 2). OS was longer in the IMRT group (22.6 months) compared to the 3D-CRT group (15.8 months; p=0.006), but interpretation of this result is limited by risk of bias in this nonrandomized study.

Table 2. Outcomes for Intensity-Modulated Radiotherapy vs Three-Dimensional Conformal Radiation for Pancreatic Cancer

Comparison	3-Dimensional Conformal Radiation	Intensity-Modulated Radiotherapy	p
Sample	40	44	
Gastroduodenal ulcers	42.3%	9.1%	0.003
Overall survival, mo	22.6	15.8	0.006

Prasad (2016) conducted a retrospective study of IMRT (n=134) versus 3D-CRT (n=71) in patients with locally advanced pancreatic cancer.[44] The institutional transition from 3D-CRT to IMRT for pancreatic cancer occurred in 2007. Propensity score analysis was performed to account for potential confounding variables, including age, gender, radiation dose, RT field size, and concurrent radiotherapy. Grade II GI toxicity occurred in 34% of patients treated with 3D-CRT compared to 16% of IMRT patients (propensity score odds ratio, 1.26; 95% confidence interval [CI], 1.08 to 1.45; p=0.001). Hematologic toxicity and median survival (15.3 months) was similar in the 2 groups.

In 2007 Fuss reported the largest series, which involved a retrospective analysis of 41 patients who received image-guided IMRT alone, postsurgically (41%), or with a number of concurrent primarily fluoropyrimidine-based chemotherapy regimens (88%).[45] The prescribed radiation dose to the PTV ranged from 41.4–60.4 Gy in daily fractions of 1.8–2 Gy. For all patients diagnosed with adenocarcinoma (85%), one- and two-year actuarial OS were 38% and 25%, respectively; median OS in resected patients was 10.8 months (range: 6.2–55.1), as compared to 10.0 months (range: 3.4–28.0) in inoperable cases. Four patients (9.7%) were unable to complete radiotherapy as prescribed. Any upper GI acute toxicity (none grade 4) was reported in 29 (70%) patients, most commonly nausea, vomiting, and abdominal pain; any lower GI acute toxicity (less than 5% grade 4) was reported in 17 (42%) cases, primarily diarrhea.

In a series of 25 patients with pancreatic and bile duct cancers (68% unresectable), Milano (2004) reported that 24 were treated with IMRT and concurrent 5-FU, one refused chemotherapy.[46] Resected patients received 45–50.4 Gy to the PTV, whereas unresectable patients received 50.4–59.4 Gy. For all cancers, the median OS was 13.4 months, with one- and 2-year OS of 55% and 22%, respectively. One- and two-year median OS were 83% and 50%, respectively, among resected cases, and 40% and 8%, respectively, among unresected cases. IMRT was well tolerated, with grade 2 or less acute upper GI toxicity in 80% of patients; grade 4 late liver toxicity was reported in one patient who survived more than five years.

Ben-Joseph (2004) reported on a retrospective series that described the experience of 15 patients with pancreatic adenocarcinoma (seven resected, eight unresectable) who underwent IMRT plus concurrent capecitabine.[47] Resected cases received 45–54 Gy to the gross tumor volume, unresected cases received 54–55 Gy to the gross tumor volume; all cases received 45 Gy to the draining lymph node basin. At a median follow-up of 8.5 months, no deaths were

reported among the resected patients, compared to two deaths in the unresected cases, yielding a one-year OS rate of 69% among the latter. No grade 4 toxicities were reported, with the vast majority of acute toxicities reported at grade 1 (nausea, vomiting, diarrhea, neutropenia, anemia).

A small nonrandomized comparative study reported the difference in the rates of acute GI toxicity between pancreatic/ampullary cancer patients treated with concurrent chemotherapy and either IMRT or 3D CRT.[48] The design relied on historical controls. There was a significant decrease in upper and lower GI toxicity (nausea, vomiting, diarrhea) in the IMRT-treated group. There was no significant difference in grade 3-4 weight loss among two groups of patients.

Additional, small case series studies continue to be published[49,50]; however, large comparative studies are needed in order to draw conclusions about the efficacy and safety of IMRT for the treatment of pancreatic tumors.

GYNECOLOGIC CANCERS

Randomized Controlled Trials

A 2016 trial by Naik randomized 40 patients with cervical cancer to IMRT or to 3D-CRT.[51] Both arms received concurrent radiation with cisplatin and 50 Gy at 25 fractions of RT. 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 (see Table 3).

Table 3. Acute Toxicity Grade 2 or Greater

Toxicity	3D-CRT, n (%)	IMRT, n (%)	95% CI for the Difference	p
Hematologic	8 (40%)	7 (35%)	-0.219 to 0.119	0.644
Leucopenia	3 (15%)	2 (10%)	-0.1479 to 0.479	0.424
Vomiting	7 (35%)	3 (15%)	0.338 to 0.061	0.007
Acute gastrointestinal toxicity	9 (45%)	4 (20%)	-0.408 to -0.091	0.003
Acute genitourinary toxicity	7 (35%)	4 (20%)	-0.295 to -0.004	0.058

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

Nonrandomized Studies

In 2016, Shih reported a retrospective comparison of bowel obstruction following IMRT (n=120) or 3D-CRT (n=104) after hysterectomy for endometrial or cervical cancer.[52] Groups were generally comparable, except more patients in the 3D-CRT group had open hysterectomy (81% vs 47%, p<0.001). Patients received regular examinations throughout a median follow-up of 67 months, and the five-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=0.022).

A series of reports from a single institution provided data on clinical outcomes achieved with IMRT in women with gynecologic malignancies. Patients from an initial series[53] were included in a subsequent report that comprised 40 patients who underwent IMRT to treat cancers of the cervix, endometrium, and other sites.[54] Patients in this series underwent postsurgical IMRT (70%), with (58%) or without (42%) cisplatin chemotherapy, with a majority (60%) also undergoing postradiotherapy intracavitary brachytherapy (ICB). IMRT was prescribed to the PTV at a dose of 45 Gy, delivered in 1.8 Gy daily fractions; ICB delivered an additional 30–40 Gy to cervical cancer patients and 20–25 Gy to those with endometrial cancer. A well-matched nonconcurrent cohort of patients who underwent four-field CRT (45 Gy to the PTV, 1.8 Gy daily fractions) using 3D planning and received cisplatin chemotherapy was used to compare acute GI and genitourinary (GU) toxicities between radiotherapy modalities. No grade 3 acute GI or GU toxicities were reported in IMRT or CRT recipients. Grade two GI toxicity was noted in 60% of the IMRT cohort versus 91% of the CRT group (p=0.002). No significant differences were noted in the incidence of grade 2 GU toxicity in IMRT recipients (10%) compared to the CRT cohort (20%).

Three other reports from the same group provide data on acute hematologic toxicity[55], chronic GI toxicities[56], and acute GI toxicities[57] among patients who underwent IMRT with or without chemotherapy. It is unclear whether or not the patients in these reports are those from the initial studies or are new patients.

These and other studies[58,59] suggest that the use of IMRT is associated with a low incidence of severe toxicities, although mild-to-moderate adverse effects were reported. However, no tumor control or survival data are available for comparison to CRT. Furthermore, generalization of these findings to current practice is limited by the small numbers of cases involved, the lack of concurrent controls, patient and treatment heterogeneities, and the relatively distant (1994-2002) timeframe during which they were accrued.

Two subsequent studies examined the use of post-hysterectomy radiotherapy in women with high-risk cervical cancer. In the first study, 68 patients were treated with adjuvant pelvic radiotherapy, high dose-rate ICB, and concurrent chemotherapy.[60] The initial 35 cases received four-field box CRT delivered to the whole pelvis; a subsequent 33 patients underwent IMRT. All patients received 50.4 Gy of radiation in 28 fractions and six Gy of high dose-rate vaginal cuff ICB in three insertions; cisplatin was administered concurrently to all patients. All patients completed the planned course of treatment. At median follow-up of 34.6 months (range: 12–52 months) in CRT recipients and 14 months (range: 6–25 months) in IMRT recipients, the one-year locoregional control rate was 94% for CRT and 93% for IMRT. Grades 1 to 2 acute GI toxicities were noted in 36% and 80% of IMRT and CRT recipients, respectively (p=0.00012), while acute grade 1 to 2 GU toxicities occurred in 30% versus 60%, respectively (p=0.022). There was no significant difference between IMRT and CRT in the incidence of acute hematologic toxicities. Overall, the IMRT patients had lower rates of chronic GI (p=0.002) toxicities than the CRT patients.

A subsequent report from the same group included the initial 33 patients in that experience with an additional 21 cases.[61] At a median follow-up of 20 months, this study showed a three-year disease-free survival rate of 78% and an OS rate of 98% in IMRT recipients.

Ghandi reported on a prospective randomized study that compared whole-pelvic IMRT with whole pelvic CRT in 44 patients with locally advanced cervical cancer.[62] Each treatment arm had 22 patients. OS at 27 months was 87.7% with IMRT versus 76% with CRT (p=0.645). However, fewer grade ≥2 and ≥3 GI toxicities were experienced in the IMRT group than the CRT group.

In 2014, Chen reported on 101 patients with endometrial cancer treated with hysterectomy and adjuvant radiotherapy.[63] No significant differences between IMRT patients (n=65) and CRT patients (n=36) were found in five-year OS, local failure-free survival, and DFS (82.9% vs 93.5% [p=0.26]; 93.7% vs 89.3% [p=0.68]; 88.0% vs 82.8% [p=0.83], respectively). However, the IMRT patients experienced less acute and late toxicities.

Shih (2013) reported the results on 46 patients who received IMRT after hysterectomy and bilateral salpingo-oophorectomy for endometrial cancer, 78% of whom had stage III disease.[64] At a median of 52 months of follow-up, five-year OS was 90% while toxicities were minimal.

Beriwal (2013) reported on 42 patients treated for locally advanced vulvar carcinoma with IMRT and chemotherapy.[65] Sixteen (48.5%) patients had complete pathologic response and 15 remained progression-free at a median of 26.5 months. Eight patients developed recurrence at the surgical site of the vulva. Chronic grade 3 or higher GI or GU toxicity did not occur.

A small case series (Hsieh 2009) involved 10 patients who underwent IMRT with intracavitary brachytherapy boost for locally advanced (FIGO stage IIB and IIIB) cervical cancer.[66] During radiotherapy, all patients received cisplatin. Whole pelvic IMRT was administered to a dose of 50.4 Gy in 28 fractions, and intracavitary brachytherapy was delivered to a dose of 30 Gy in six fractions. The mean OS was 25 months (range three-27 months), with actuarial OS of 67%. Acute toxicities included one patient with grade 3 diarrhea, one with grade 3 thrombocytopenia, and three with grade 3 leukopenia. One case of subacute grade 3 thrombocytopenia was noted.

Additional publications of IMRT for gynecologic cancer consist of small case series[62,67-78] and non-randomized comparative studies[76,77,79-82] that continue to report favorable outcomes with IMRT treatment in patients with different types of gynecologic cancers (cervical, ovarian, endometrial).

ANORECTAL CANCER

Recent studies have found IMRT with chemotherapy for the treatment of anal cancer reduces acute and late adverse events compared with 3D-CRT with chemotherapy. This raises the possibility of increasing dose to the target tissue without increasing adverse events. However, survival outcomes have not differed significantly between IMRT and CRT, and concerns exist over increases in locoregional recurrence with IMRT.

Systematic Reviews

Wee (2018) performed a systematic review of the literature comparing acute GI and GU toxicity profiles between IMRT and 3D-CRT in rectal cancer patients treated with neoadjuvant chemoradiation.[83] No significant heterogeneity or publication bias was detected in the six studies that met inclusion criteria. A subset of these studies were used in meta-analyses of grade ≥ 2 acute overall GI toxicity, diarrhea, proctitis, and overall GU toxicity. GI toxicity, diarrhea, and proctitis were significantly reduced in the IMRT group. In the meta-analysis of ≥ 3

overall GI toxicity, diarrhea, proctitis, and overall GU toxicity, only acute proctitis was found to be significantly reduced in the IMRT group. In the pooled analysis, the IMRT group was found to have significantly lower rates of every toxicity endpoint except for grade ≥ 3 overall GU toxicity.

Randomized Controlled Trials

One small (N=20) RCT on IMRT for the treatment of anal canal cancer was identified. In this publication from Rattan (2016), grade III GI toxicity during treatment was observed in 0% of patients in the IMRT group compared with 60% of patients treated with 3D-CRT (p=0.010).[84] Hematologic grade III toxicity was seen in 0% of patients treated with IMRT compared to 20% of patients treated with 3D-CRT (p=NS). Other parameters indicating better tolerance of treatment were reduced need for parenteral fluid (10% vs 60%, p=0.019) and blood transfusion (0% vs 20%, p=0.060).

Nonrandomized Comparative Studies

In 2017, Sun reported an analysis of the National Cancer Data Base to compare IMRT with 3D-CRT for the treatment of rectal adenocarcinoma.[85] A total of 7386 patients with locally advanced rectal carcinoma were treated with neoadjuvant chemoradiotherapy (45-54 Gy) during the period 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 stage of disease were not predictive of which RT was used. The mean radiation dose was higher with IMRT (4735 centigray vs 4608 centigray, p<0.001) and the occurrence of sphincter loss surgery was higher (see Table 4). However, patients treated with IMRT had 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 3D-CRT or IMRT for Rectal Cancer

Outcome	3D-CRT	IMRT	Adjusted OR	95% CI	p
Pathologic downstaging	57.0%	55.0%	0.89	0.79 to 1.01	0.051
Sphincter loss surgery	28.3%	34.7%	1.32	1.14 to 1.52	<0.001
Positive resection margin	5.6%	8.0%	1.57	1.21 to 2.03	<0.001
Unplanned readmission	7.9%	6.4%	0.79	0.61 to 1.02	0.07
30-d mortality	0.8%	0.6%	0.61	0.24 to 1.57	0.31
Survival at 5 y	64%	64%	1.06	0.89 to 1.28	0.47

CI: confidence interval; IMRT: intensity-modulated radiotherapy; OR: odds ratio; 3D-CRT: three-dimensional conformal radiation.

In 2017, Huang reported a retrospective comparison of outcomes and toxicity for preoperative image-guided IMRT versus 3D-CRT in locally advanced rectal cancer.[86] A total of 144 consecutive patients who were treated between 2006 and 2015 were included in the analysis. 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 or greater toxicity and was significant only for acute GI toxicity (p=0.039; see Table 5). Four-year OS and disease-free survival did not differ between the two 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=0.042).

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

Comparison	3-Dimensional Conformal Radiation (n=99)	Intensity-Modulated Radiotherapy (n=45)
Skin	3 (3%)	1 (2.2%)
Acute GI	14 (14.1%)	3 (6.7%)
Acute GU	3 (3%)	0 (0%)
Hematologic	2 (2.0%)	0 (0%)
Late GI	10 (10.1%)	2 (4.4%)
Late GU	3 (3.1%)	0 (0%)

Values are n (%). GI: gastrointestinal; GU: genitourinary.

In a retrospective review of 89 consecutive patients (52 IMRT, 37 3D-CRT), Chuong (2013) found three-year OS, progression free survival, locoregional control, and colostomy-free survival did not differ significantly in patients treated with IMRT compared with 3D-CRT (p>0.1).[87] Adverse events with 3D-CRT were more frequent and severe, and required more treatment breaks than IMRT (11 vs 4; p=0.006) even though the median duration of treatment breaks did not differ significantly (12.2 days vs 8.0 days; p=0.35). IMRT patients had fewer acute grade 3 or higher nonhematologic toxicity (p=0.012), and fewer acute grade 3 or higher skin toxicity.

Dewas (2012) retrospectively reviewed 51 patients with anal cancer treated with IMRT or 3D-CRT (24 IMRT, 27 3D-CRT).[88] Outcomes also did not differ significantly between IMRT and 3D-CRT for 2-year OS, locoregional relapse-free survival, and colostomy-free survival. Grade 3 acute toxicity occurred in 11 IMRT patients versus 10 3D-CRT patients.

Dasgupta (2013) retrospectively reviewed 223 patients (45 IMRT, 178 CRT) to compare outcomes in patients treated for anal cancer.[89] The authors reported that 2- year OS, distant metastases-free survival, and locoregional recurrence-free survival did not differ significantly between IMRT and CRT. Milano (2005) published a single-institution series included 17 patients with stage I/II cancer who underwent IMRT alone (n=3) or concurrent with 5FU alone (n=1) or 5FU with mitomycin C (MMC, n=13).[90] Patients generally received 45 Gy to the PTV at 1.8 Gy per fraction, followed by a 9 Gy boost to the GTV. Thirteen (76%) of 17 patients completed treatment as planned. None experienced acute or late grade 3 or above nonhematologic (GI or GU) toxicity. Grade 4 acute hematologic toxicity (leukopenia,

neutropenia, thrombocytopenia) was reported in five (38%) of 13 patients who received concurrent chemoradiotherapy. At a median follow-up of 20.3 months, the two-year OS rate was 91%.

Noncomparative Studies

Foster (2018) reported on 52 anal squamous cell carcinoma patients treated with IMRT and concurrent chemotherapy.[91] Patients were followed to a median of 33 months. Three-year freedom from locoregional failure, freedom from distant metastasis, freedom from colostomy, and OS were reported in 94, 85, 91, and 90% of patients, respectively. Acute grade 2+ toxicities occurred in 83% (skin), 71% (GI), and 19% (GU) of evaluable patients. Late grade 2 toxicities occurred in 28% (GI) and 9% (GU) of evaluable patients, respectively. HPV genotypes were also evaluated and HPV status was not significantly associated with any clinical outcome.

De Bari (2018) reported outcomes of anal cancer patients treated with image-guided IMRT.[92] A total of 155 patients were analyzed and median follow-up was 38 months. A subset of patients (138) were also administered chemotherapy. Of the 143 patients with toxicity data available, 22% presented a G3+ acute toxicity. No grade 4 acute or late toxicities were reported. Actuarial four-year local control was 83%.

In a multicenter series, Salama (2007) included a cohort of 53 consecutive patients who received concurrent chemotherapy and IMRT.[93] Forty-eight (91%) received 5FU plus MMC; the rest received other regimens not including MMC. Radiation was delivered at 45 Gy to the PTV. Thirty-one (58%) patients completed therapy as planned, with breaks in the others because of grade 4 hematologic toxicities (40% of patients), painful moist desquamation, or severe GI toxicities. At the18-month follow-up, the local tumor control rate was 83.9% (range, 69.9%-91.6%), with an OS rate of 93.4% (range, 80.6%-97.8%). Univariate analyses did not reveal any factors significantly associated with tumor control or survival rates, whereas a multivariate analysis showed patients with stage IIIB disease experienced a significantly lower colostomy-free survival (hazard ratio, 4.18; 95% confidence interval, 1.062 to 16.417; p=0.041).

A GI toxicity study was reported in 45 patients who received concurrent chemotherapy and IMRT for anal cancer.[94] Chemoradiotherapy is becoming the standard treatment for anal cancer, in part due to preservation of sphincter function. Patients had T1 (n=1), T2 (n=24), T3 (n=16), and T4 (n=2) tumors; N stages included Nx (n=1), N0 (n=31), N1 (n=8), N2 (n=3), and N3 (n=2). Concurrent chemotherapy primarily comprised 5-FU plus MMC. IMRT 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 genitourinary toxicity was grade 0 in 25 (56%) cases, grade 1 in 10 (22%) patients, grade 2 in five (11%) patients, with no grade 3 or 4 toxicities reported; five (11%) patients had no GU tract toxicities reported. Grades three and four leukopenia were reported in 26 (56%) cases, neutropenia in 14 (31%), and anemia in four (9%). Acute GI toxicity included grade 0 in two (4%) patients, grade one in 11 (24%), grade 2A in 25 (56%), grade 2B in four (9%), grade 3 in three (7%), and no grade 4 toxicities. Univariate analysis of data from these patients suggests a statistical correlation between the volume of bowel that received 30 Gy or more of radiation and the risk for clinically significant (grade 2 or higher) GI toxicities.

In 2010, Pepek performed a retrospective analysis of toxicity and disease outcomes associated with IMRT in 47 patients with anal cancer.[95] Thirty-one patients had squamous cell

carcinoma (SCC). Patients had AJCC stage I (n=6 [13%]), stage II (n=16 [36%]), stage III (n=14 [31%]), stage IV (n=6 [13%]), or recurrent disease (n=3 [7%]). 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 a variety of agents including MMC, 5FU, capecitabine, oxaliplatin, etoposide, vincristine, doxorubicin, cyclophosphamide, and ifosfamide in various combinations. The two-year actuarial OS for all patients was 85%. Eight patients (18%) 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 much lower than previous trials of chemoradiation, where grade 3 to 4 skin toxicity was noted in about 50% of patients and grade 3 to 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 include a break from radiotherapy. Some investigators believe that treatment breaks reduce the efficacy of this combined approach.

Zhu (2013) reported on a phase two trial of neoadjuvant IMRT with chemotherapy for 42 patients with stage II or III rectal adenocarcinoma.[96] Surgical resection was performed in 38 patients and pathologic complete response occurred in six patients. Skin, GI tract, and hematologic grade 3 toxicities were 26.2%, 14.3%, and 4.7%, respectively. No grade 4 toxicity was seen. Patients who responded well (defined as tumor regression grade [TRG] 3 to 4) had OS of 83.9% versus 40.7% in patients who were poor responders (defined as TRG one to two; p=0.007).

Zhu (2013) also reported on a phase two trial of IMRT with chemotherapy for 32 patients with rectal adenocarcinoma and unresectable distant metastases.[97] IMRT was delivered to the pelvis at 45 Gy with a concomitant 10 Gy boost to the gross tumor. Surgical resection of the rectal tumor was also performed in 14 patients. Dermatitis from the IMRT around the anal verge occurred most commonly in 18.8% of patients. OS was 17.5 months and PFS was 12 months at a median follow-up of 12 months (range, 4-23 months). Local failure occurred in two patients.

EVIDENCE SUMMARY

For individuals who have cancer of the abdomen or pelvis who receive IMRT, the evidence includes small randomized controlled trials (RCTs), nonrandomized comparative studies, and case series. Relevant outcomes are OS, change in disease status, quality of life, and treatment-related morbidity.

For individuals who have gastrointestinal tract cancer who receive IMRT, the evidence includes nonrandomized comparative studies and retrospective series. IMRT has been compared with three-dimensional conformal radiation (3D-CRT) for the treatment of stomach, hepatobiliary, and pancreatic cancers, with some studies reporting longer OS and decreased toxicity with IMRT. The evidence on hepatobiliary cancer includes a series with historical controls that found an increase in median survival with no difference in toxicity. Two comparative studies (one prospective, one retrospective were identified on IMRT for pancreatic cancer. The prospective comparative study found an increase in survival with a reduction in gastrointestinal (GI) toxicity, while the retrospective study found a decrease in GI toxicity. The available comparative evidence, together with dosimetry studies of organs at risk, suggests that IMRT may improve survival and decrease toxicity compared to 3D-CRT in patients with GI cancers. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have gynecologic cancer who receive IMRT, the evidence includes two randomized controlled trials (RCTs) and several nonrandomized comparative studies. There is limited comparative evidence on survival outcomes following IMRT or 3D-CRT. However, available results are generally consistent that IMRT leads to a reduction in GI and GU toxicity. Based on evidence with other cancers of the pelvis and abdomen that are 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 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 a meaningful improvement in the net health outcome.

For individuals who have anorectal cancer who receive IMRT, the evidence includes a small RCT with 20 patients, nonrandomized comparative studies, and case series. Relevant outcomes are overall survival, disease-specific survival, quality of life, and treatment-related morbidity. Survival outcomes have not differed significantly between IMRT and CRT. Recent studies have found IMRT with chemotherapy for the treatment of anal cancer reduces acute and late adverse events better than 3D-CRT with chemotherapy. The comparative data on use of IMRT versus 3D-CRT in chemoradiotherapy for anal cancer has shown reductions 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 a meaningful improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

Prostate Cancer

The National Comprehensive Cancer Network (NCCN) guidelines (v.2.2019) for prostate cancer indicate, in the principles of radiotherapy (RT) for primary external beam radiation therapy, highly conformal radiotherapy (CRT) should be used in conventional fraction doses of 75.6 to 79.2 Gy for low-risk prostate cancer and up to 81 Gy for intermediate- and high-risk prostate cancer.[43] A reference in the discussion section indicates IMRT is preferred over 3D-CRT because it seems to decrease salvage therapy rates while the risk of adverse effects such as gastrointestinal toxicities are reduced with IMRT.

NCCN states that evidence supports offering adjuvant/salvage RT in most men with adverse pathologic features or detectable PSA and no evidence of disseminated disease. Indications for adjuvant RT include pT3 disease, positive margins, or seminal vesicle involvement. Indications for salvage RT include an undetectable PSA that becomes detectable and then increases on two subsequent measurements. The recommended prescribed doses for adjuvant/salvage post-prostatectomy RT are 64-72 Gy in standard fractionation. NCCN guidelines also indicate 3D-CRT or IMRT may be considered as initial treatment options in all prostate cancer patients except for patients with a very low risk of recurrence and less than 20 years' expected survival.

Pancreatic Cancer

NCCN guidelines (v.3.2019) for Pancreatic Adenocarcinoma state that "3D conformal RT (3D-CRT), intensity-modulated RT (IMRT), and SBRT with breathholding/gating techniques can result in improved planning target volume (PTV) coverage with decreased dose to OARs."

Lung Cancer

NCCN guidelines (v.5.2019) for non-small-cell lung cancer indicate that “More advanced technologies are appropriate when needed to deliver curative RT safely.” These technologies include (but are not limited to) IMRT/VMAT. “Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.”[100]

NCCN guidelines (v.1.2019) for small cell lung cancer indicate “Use of more advanced technologies is appropriate when needed to deliver adequate tumor dose while respecting normal tissue dose constraints.” IMRT is included in the technologies listed and “is preferred over 3D conformal external-beam RT (CRT) on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.”

Esophageal and Esophagogastric Junction Cancer

The NCCN guidelines for esophageal and esophagogastric junction cancers (v. 2.2019) state that IMRT “is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3-D techniques.”

Malignant Pleural Mesothelioma

Guidelines from NCCN on treatment of malignant pleural mesothelioma (v.2.2019) state “Use of conformal radiation technology [IMRT] is the preferred choice based on comprehensive consideration of target coverage and clinically relevant normal tissue tolerance. CT simulation-guided planning using either intensity-modulated radiation therapy (IMRT) or conventional photon/electron radiation therapy is acceptable. When IMRT is used, the NCI and ASTRO/ACR IMRT guidelines should be strictly followed.

Thymus Tumors

The NCCN guidelines for thymomas and thymic carcinomas (v.2.2019) state that “RT should be given by 3-D conformal technique to reduce surrounding normal tissue damage (e.g., heart, lungs, esophagus, spinal cord). Intensity modulated RT (IMRT) may further improve the dose distribution and decrease the dose to the normal tissue as indicated. If IMRT is applied, the ASTRO/ACR IMRT guidelines should be strictly followed.”

AMERICAN SOCIETY FOR RADIATION ONCOLOGY

The American Society for Radiation Oncology (ASTRO) task force’s 2011 consensus-based guideline recommended that radiation doses to the lung and heart during WBRT should be minimized, provided the coverage of the breast is not compromised. [105,106] IMRT was included in the ASTRO summary of techniques for WBRT following breast conserving therapy (BCT) or mastectomy, irrespective of margin width. There was no reference to IMRT in the 2018 updated guideline.[107]

The American Society of Clinical Oncology (ASCO) published a guideline on the treatment of malignant pleural mesothelioma in 2018.[108] For palliative radiation therapy, the guideline includes a strong, evidence-based recommendation stating “electrons, 2D, 3D, and IMRT may be considered appropriate techniques depending on location of the treatment target and organs at risk.” For adjuvant or neoadjuvant hemithoracic radiation therapy, the guideline includes the strong, evidence-based recommendation, “3D or IMRT may be offered, respecting guidelines of organs at risk.”

SUMMARY

The available research on intensity modulated radiotherapy (IMRT) suggests that for certain cancers of the thorax, abdomen, and pelvis, IMRT may lead to clinical outcomes comparable with 3D-conformal radiation therapy (CRT) and may reduce radiation exposure to surrounding critical structures such as the heart. Therefore, IMRT may be considered medically necessary for the treatment of cancers of the thorax, abdomen, and pelvis when policy criteria are met.

For all other indications within the thorax, abdomen, and pelvis, intensity-modulated radiotherapy (IMRT) has not been shown to improve net health outcomes compared to other treatment modalities. Therefore, except in the select group of patients identified in the policy criteria, IMRT is not medically necessary for the treatment of all other cancers of the thorax, abdomen, and pelvis.

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CODES

NOTE: The correct code to use for image fusion performed to provide enhanced delineation of target and normal critical structures is CPT code 77399 (Unlisted procedure, medical radiation physics, dosimetry and treatment devices, and special services); however, it is considered part of the treatment planning.

Codes	Number	Description
CPT	77301	Intensity modulated radiotherapy plan, including dose volume histograms for target and critical structure partial tolerance specification
	77338	Multi-leaf collimator (MLC) device(s) for intensity modulated radiation therapy (IMRT), design and construction per IMRT plan (new code 1/1/10)
	77385	Intensity modulated radiation treatment deliver (IMRT), includes guidance and tracking, when performed; simple
	77386	;complex
HCPCS	G6015	Intensity modulated treatment delivery, single or multiple fields/arcs, via narrow spatially and temporally modulated beams, binary, dynamic mlc, per treatment session
	G6016	Compensator-based beam modulation treatment delivery of inverse planned treatment using 3 or more high resolution (milled or cast) compensator, convergent beam modulated fields, per treatment session

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