Intraoperative Radiotherapy

Policy Number: 8.01.08  
Last Review: 10/2017  
Origination: 10/1988  
Next Review: 10/2018

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for intraoperative radiation therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Use of intraoperative radiation therapy may be considered medically necessary in the following situation:
- Rectal cancer with positive or close margins with T4 lesions or recurrent disease.

When Policy Topic is not covered
Use of intraoperative radiation therapy is considered investigational for all other oncologic applications.

Description of Procedure or Service

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Multimodality therapy (external-beam radiotherapy plus surgery or chemotherapy) without IORT | Overall survival  
Disease-specific survival  
Change in disease status  
Treatment-related morbidity |
| Individuals: With gastric cancer | Adjunctive intraoperative radiotherapy | Surgery without intraoperative radiotherapy  
Multimodality therapy (external-beam radiotherapy plus surgery or chemotherapy) without IORT | Overall survival  
Disease-specific survival  
Change in disease status  
Treatment-related morbidity |
| Individuals: With soft tissue sarcomas | Adjunctive intraoperative radiotherapy | Surgery without intraoperative radiotherapy  
Multimodality therapy | Overall survival  
Disease-specific survival |
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| With fibromatosis | • Adjunctive intraoperative radiotherapy | • Surgery without intraoperative radiotherapy  
|              |                               | • Multimodality therapy (external-beam radiotherapy plus surgery or chemotherapy) without IORT | • Overall survival  
|              |                               |                               | • Disease-specific survival  
|              |                               |                               | • Change in disease status  
|              |                               |                               | • Treatment-related morbidity |

Intraoperative radiation therapy is delivered directly to exposed tissues during surgery. It can be delivered by electron beams produced by linear accelerators (also called IOERT) or high-dose rate brachytherapy (HDR-IORT).

For individuals who have rectal cancer who receive IORT, the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Adjunctive use of IORT as part of a multimodal treatment could allow an increase in radiation dose without increasing complications. However, a phase 3 RCT and meta-analysis of IORT for locally advanced rectal cancer did not find improved outcomes with IORT in combination with external-beam radiotherapy (EBRT) and surgery. Nonrandomized comparative studies and a meta-analysis of these studies have shown some benefit in health outcomes with adjunctive IORT for recurrent rectal cancer, however, these studies are limited by a high risk of selection bias, heterogeneous patient populations, and heterogeneous delivery of other treatments. Large RCTs are needed to determine the effect of IORT with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

National Comprehensive Cancer Network guidelines and clinical input from 2009 supported the use of IORT for rectal tumors.

For individuals who have gastric cancer who receive IORT, the evidence includes RCTs and a systematic review of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. A meta-analysis of 8 RCTs found a benefit of IORT in locoregional control but not overall survival when used with EBRT. When IORT was administered without adjuvant EBRT in patients with stage III disease, overall survival improved. Thus, IORT might be considered an alternative to EBRT in patients undergoing surgery for stage III gastric cancer. Randomized studies comparing benefits and harms of the 2 treatments are needed to determine the efficacy of IORT with greater certainty. It cannot be determined if IORT provides any benefit for overall survival in this patient population when used in with EBRT. Further study is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have soft tissue sarcomas who receive IORT, the evidence includes a systematic review, small RCT, and several nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Overall, study quality is low. The limited data suggest that IORT may improve local control and overall survival, but adverse effects may outweigh any treatment benefit. RCTs are needed to determine the risks and benefits of IORT for soft tissue sarcomas with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have gynecologic cancers who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The contribution of adjuvant IORT cannot be determined from the available literature. There is no evidence that IORT improves survival rates, and complications may be severe. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck cancers who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The strongest evidence is from a retrospective analysis of patients who had recurrent salivary gland carcinomas and were at risk of radiation toxicity due to prior treatment with EBRT. Some patients received IORT plus salvage surgery, and multivariate analysis found that use of IORT was a significant predictor of improved outcomes. Although these findings suggested an improvement in health outcomes for head and neck cancers that cannot be treated with EBRT due to toxicity, there was a high risk of selection bias in this study. Comparative trials are needed to determine the efficacy of IORT with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pancreatic cancer who receive IORT, the evidence includes large case series, cohort studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The systematic reviews found no evidence that IORT was more effective than other therapies in treating pancreatic cancer. No evidence was identified that evaluated outcomes when IORT was and was not added to multimodal therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have renal cell carcinoma who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. No controlled trials were identified to determine whether adjunctive IORT improves health outcomes when added to multimodal therapy with surgical resection and EBRT. Grade 3 or higher toxicity after IORT has been reported in a substantial percentage of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have glioblastoma or neuroblastoma or fibromatosis who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. In general, whether IORT improves overall survival compared to other therapies is unclear. Compared to historical controls, IORT for patients with previously untreated malignant gliomas had no survival benefit when given in conjunction with multimodal therapy. In addition, complication rates may be high. It cannot be determined from available data whether IORT improves outcomes when used as an alternative to EBRT in previously treated patients. Comparative trials are needed to evaluate the safety and efficacy of this treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input on use of IORT for other solid tumors was mixed.

**Background**

Intraoperative radiation therapy (IORT) is designed to increase the intensity of radiation directly delivered to tumors. The tumor and associated tissues at risk for micrometastatic spread are directly visualized at operation. IORT is delivered directly to the tumor, and normal or uninvolved tissues are not exposed to radiation because they are removed or shielded from the treatment field. It can be delivered by electron beams produced by linear accelerators (also called IOERT), or high-dose rate brachytherapy (HDR-IORT). Most clinical experience involves IOERT. (1)

IORT is performed with applicators and cones that attach to the treatment head of high-energy medical linear accelerators that are designed to direct radiation to defined surface structures. Most patients are subsequently treated with external beam photon irradiation (EBRT).

The INTRABEAM® system was first approved for use by the U.S. Food and Drug Administration (FDA) for intracranial tumors in 1999 and was subsequently approved for whole body use in 2005. The INTRABEAM® spherical applicators are indicated for use with the INTRABEAM® system to deliver a prescribed dose of radiation to the treatment margin or tumor bed during intracavity or intraoperative radiotherapy treatments. The Mobetron mobile electron beam accelerator designed for use in the operating room received 510(k) marketing clearance in 1998.

**Rationale**

This evidence review was initially developed in March 1996 and has been updated periodically using the MEDLINE database. The most recent literature update was performed through October 10, 2016. No new studies were identified that would change the conclusions of the review.

**RECTAL CANCER**
**Randomized Controlled Trials**
The only randomized controlled trial (RCT) identified was a 2011 multicenter study on intraoperative radiotherapy (IORT) for locally advanced rectal cancer by Dubois et al. (1) It was included in the meta-analyses described next. Patients (N=142) with locally advanced rectal cancer were treated with preoperative radiotherapy and randomized to surgical resection alone or surgical resection plus IORT. Mean duration without local relapse, based on Kaplan-Meier analysis, was 107 months with surgery plus IORT and 126 months with surgery alone (p=NS). There was no significant difference between groups in the incidence of local control or overall survival (OS).

**Systematic Reviews**
Several reviews have evaluated IORT for colorectal cancer. Wiig et al (2014) found no evidence that IORT is beneficial for primary rectal cancer. (2) This review included 18 studies on primary rectal cancer (including 1 RCT, 5 comparative trials, and 5 trials without IORT) and 18 studies on locally recurrent rectal cancer (including 5 studies without IORT). The indications for IORT varied, and meta-analysis was not performed due to heterogeneity in study designs and reporting. Results suggested IORT provided no OS benefit for primary rectal cancers that were completely resected, with a possible reduction in local recurrence in cases of incomplete tumor resection. There was no evidence that IORT affected OS or local recurrence when used to treat locally recurrent rectal cancer. These results are limited by risk of selection bias for IORT in nonrandomized studies as well as variability in stages and IORT dosing.

In 2013, Mirnezami et al conducted a systematic review and meta-analysis on the use of IORT for advanced or recurrent colorectal cancer (CRC). (3) The review included 29 studies (14 prospective, 15 retrospective) published between 1965 and 2011 (total N=3003 patients). Indications for IORT were locally advanced disease in 1792 patients and locally recurrent disease in 1211 patients. Comparative studies found a significant effect favoring IORT for improved local control (odds ratio [OR], 0.22; 95% confidence interval [CI], 0.05 to 0.86; p=0.03), disease-free survival (DFS; hazard ratio [HR], 0.51; 95% CI, 0.31 to 0.85; p=0.009), and OS (HR=0.33; 95% CI, 0.2 to 0.54; p=0.001). With IORT, no increase was observed in total (OR=1.13; 95% CI, 0.77 to 1.65; p=0.57), urologic (OR=1.35; 95% CI, 0.84 to 2.82; p=0.47), or anastomotic (OR=0.94; 95% CI, 0.42 to 2.1; p=0.98) complications; however, increased wound complications were noted after IORT (OR=1.86; 95% CI, 1.03 to 3.38; p=0.049).

**Nonrandomized Comparative Studies**
In 2015, Zhang et al reported on a nonrandomized comparative study with 148 patients who had primary locally advanced rectal cancer treated with IORT plus external-beam radiotherapy (EBRT) or EBRT alone. (4) Use of IORT was based on patient preference and technology availability. Thus, there was a high risk of selection bias. Five-year local control was 89.7% for IORT plus EBRT compared to 79.2% for EBRT alone (p=0.032). DFS was also increased in the IORT group (69%) compared to IORT alone (58.5%; p=0.049). However, OS rates did not differ significantly between groups. Multivariate analysis found a significant impact
of tumor size classification and staging, with a trend (p=0.079) for improved locoregional control with IORT, and no significant differences between groups in acute and late toxicity.

Observational Studies
The largest series was reported in 2011 by Haddock et al for patients treated from 1981 through early 2008. (5) Six hundred seven patients with recurrent CRC received IORT as a component of treatment. IORT was preceded or followed by EBRT in 583 (96%) patients. Resection was classified as R0 (negative margins) in 227 (37%) and R1 (residual microscopic disease) in 224 (37%). Median OS was 36 months. Five- and 10-year survival rates were 30% and 16%, respectively. Survival estimates at 5 years were 46% and 27% for R0 and R1 resection, respectively. Multivariate analysis revealed that R0 resection, no prior chemotherapy, and more recent treatment (in the second half of the series) were associated with improved survival. Three-year cumulative incidence rates of central (within the IORT field), local, and distant relapse were 12%, 23%, and 49%, respectively. Toxicity grade 3 or higher partially attributable to IORT was observed in 66 (11%) patients.

Section Summary: Rectal Cancer
The evidence for IORT as part of a multimodal treatment approach in patients who have CRC includes an RCT, nonrandomized comparative studies, and systematic reviews of these studies. Adjunctive use of IORT could allow an increase in radiation dose without increasing complications. However, a phase 3 RCT and meta-analysis of locally advanced CRC did not find improved outcomes with IORT in combination with preoperative EBRT and surgery. Nonrandomized comparative studies have shown some benefit in health outcomes with adjunctive IORT, however, these studies were limited by a high risk of selection bias, heterogeneous patient populations, and heterogeneous delivery of other treatments.

RCTs are needed to determine the effect of adjunctive IORT for locally advanced or recurrent rectal tumors with greater certainty.

GASTRIC CANCER

Systematic Reviews
A meta-analysis published in 2015 compiled 8 RCTs that used IORT for resectable gastric cancer. (6) The literature search encompassed 1990 through mid 2013, and included trials that assigned patients to surgery plus IORT or to surgery without IORT. Three studies also gave EBRT to both arms. Hazard ratios to describe the impact of adjuvant IORT on OS and locoregional control were extracted directly from the original studies or calculated from survival curves. Compiled data from 4 studies that reported OS revealed that IORT had no significant impact on OS (HR=0.97; 95% CI, 0.75 to 1.26; p=0.837). Notably, 3 of the 4 studies provided adjuvant EBRT. In 3 studies that tested the efficacy of IORT for OS in patients with stage III disease, there was significantly improved OS (HR=0.60; 95% CI, 0.40 to 0.89; p=0.011). However, all 3 of these studies did not administer EBRT, and used
a higher dose of IORT than the other studies. The largest study in the meta-analysis included 292 patients with stage III disease. The hazard ratio for OS in this study was 0.54 (95% CI, 0.35 to 0.83). Significant improvement in locoregional control was observed in 4 studies that provided such data (HR=0.40; 95% CI, 0.26 to 0.62; p<0.001).

**Section Summary: Gastric Cancer**
A meta-analysis of 8 RCTs found a benefit of IORT in locoregional control but not OS when used in combination with EBRT. Three studies found improved OS in patients with stage III disease. However, all 3 studies did not provide EBRT. Randomized studies comparing the benefits and harms of IORT and EBRT are needed to determine the efficacy of IORT with greater certainty. It cannot be determined from this literature whether IORT in patients with stage III disease provides any benefit for OS when used with EBRT. Further study is needed.

**SOFT TISSUE SARCOMAS**

**Systematic Reviews**
A systematic review by Skandarajah et al (2009) highlights the potential value of IORT in the multimodal treatment of retroperitoneal sarcoma because these tumors are often close to dose-limiting structures, but the review notes that it is not without complications (see next). (7)

**Randomized Controlled Trials**
One small randomized trial (N=35) from 1993 compared IORT plus low-dose (35- to 40-gray [Gy]) postoperative EBRT to high-dose (50- to 55-Gy) EBRT alone. (8) The local recurrence rate was lower (40%) in the combined therapy group than in the EBRT-only group (80%), with no difference in OS. Patients who received IORT had fewer radiation enteritis events but had more disabling peripheral neuropathies.

**Nonrandomized Comparative Studies**
In a nonrandomized comparative study of 251 patients, 92 of whom received IORT, IORT patients had more surgical complications and significantly more infectious complications; however, the IORT-treated patients had a 40% lower rate of local recurrence. IORT demonstrated effective tumor control in osteosarcoma.

A 2014 multicenter study by Calvo et al compared outcomes from 159 patients with soft tissue sarcomas of the extremity treated with IORT plus multimodal therapy to 95 patients treated with multimodal therapy without IORT. (9) IORT was administered to patients who had close (<1 cm) or positive surgical margins while patients with margins of 1 cm or greater were treated only with multimodal therapy. Use of IORT in the high-risk patients led to 5-year local control (82%) and OS rates (72%) that were similar to lower risk sarcoma patients treated without IORT. DFS (62%) remained modest due to the high risk of distant metastases. In multivariate analysis, only surgical margin resection was significantly associated with local control.
Stucky et al (2014) reported on 63 consecutive patients with retroperitoneal sarcoma treated with preoperative EBRT, surgery plus IORT (n=37), or surgery only (n=26) between 1996 and 2011. Median follow-up was 45 months. The 5-year local control rate for patients receiving radiotherapy was 89% versus 46% for the surgery-only patients (p=0.03). Survival did not differ as both groups had an actuarial 5-year OS of 60%. The contribution of IORT cannot be determined from this study.

Section Summary: Soft Tissue Sarcomas
The evidence on adjunctive IORT for the treatment of soft tissue sarcomas includes a systematic review, a small RCT, and several nonrandomized comparative studies. Overall, study quality was low. The limited data available suggest that IORT may improve local control and OS, but adverse effects may outweigh any treatment benefit. RCTs are needed to determine the risks and benefits of IORT for soft tissue sarcomas with greater certainty.

GYNECOLOGIC CANCERS
The literature on IORT for gynecologic cancers consists primarily of case series. A phase 2 trial examined the use of radical surgery with IORT after chemotherapy in extracervical, locally advanced cancer patients. Between 2000 and 2007, 42 locally advanced cervical cancer patients were treated. EBRT was administered to the whole pelvic region in combination with chemotherapy. After EBRT and chemotherapy, 35 (83%) of 42 patients underwent radical surgery and IORT treatment. Five-year DFS and OS rates were 46% and 49%, respectively. There were significantly better DFS and OS when residual tumor was absent or limited to the cervix. At follow-up, only 3 (9%) of 35 patients were alive and free of disease.

A case series of 67 patients with locally advanced (n=31) and recurrent cervical cancer (n=36) treated with IORT at a Spanish center was reported by Martinez-Monge et al (2001). Previously unirradiated patients received preoperative chemoradiation. The 10-year control rate within the area treated with IORT was 69.4% for the entire group, 98.2% for the primary group, and 46.4% for the recurrent group. Control in the treated area correlated with margin status, amount of residual disease, and pelvic lymph node involvement. The overall incidence of toxic events attributable to IORT was 13.9%. The 10-year survival rate for the entire group was 34%, 58% for patients with primary disease, and 14% for those with recurrent disease. Patients, especially those with recurrent disease, with positive lymph nodes, parametrial involvement, and/or incomplete resection had poor local control, despite IORT at the doses used in the study.

Gao et al (2011) evaluated clinical outcomes and toxicity of IORT plus EBRT in advanced and recurrent ovarian carcinoma. All 45 patients in this series underwent optimal cytoreductive surgery. At 5-year follow-up, local control was observed in 68.9%, with OS and DFS rates of 64% and 56%, respectively. The major complication was peripheral neuropathy, affecting 5 (11%) of patients.
Section Summary: Gynecologic Cancers
The literature on IORT for gynecologic cancers consists primarily of case series. The contribution of adjuvant IORT cannot be determined from these studies. While OS rates in patients with locally advanced or recurrent disease are low, complications may be severe.

HEAD AND NECK CANCERS

Observational Studies
In 2008, Chen et al reported on a retrospective study of 99 patients with locally recurrent salivary gland carcinomas treated surgically with or without IORT. All patients had previously been treated with surgery and 82% had received postoperative EBRT. Median time from the initial surgery to local recurrence was 3.1 years. After salvage surgery, 37 (37%) patients received IORT. Reasons for IORT use were not clearly described in the report. For the entire patient population, the 1-, 3-, and 5-year estimates of local control were 88%, 75%, and 69%, respectively. Univariate analysis revealed predictors of local recurrence to be positive surgical margins, tumor size greater than 4 cm, and lack of IORT. Six of 37 patients treated with IORT experienced a local recurrence compared with 26 of 32 treated without IORT. At 5 years, OS was 34% and DFS was 46%. The only predictor of DFS was use of IORT, with a 5-year DFS rate of 61% in patients treated with IORT and 44% in patients without IORT. Complications were not analyzed.

A case series of 137 patients with persistent or recurrent salivary gland tumors who were treated with IORT after surgical resection was reported by Chen et al in 2007. Eighty-three percent had previously received EBRT. Surgical margins were microscopically positive in 56 patients. Median follow-up among surviving patients was 41 months (range, 3-122 months). One-, 2-, and 3-year estimates of in-field control after surgery and IORT were 70%, 64%, and 61%, respectively, and positive margins at the time of IORT predicted in-field failure. Three-year rates of locoregional control, distant metastasis-free survival, and OS were 51%, 46%, and 36%, respectively.

Zeidan et al reported on 2 case series of head and neck cancers. In a 2011 publication, they reported on the use of IORT for 231 patients with advanced cervical metastasis. OS at 1, 3, and 5 was 58%, 34%, and 26%, respectively. Recurrence-free survival (RFS) at 1, 3, and 5 years was 66%, 55%, and 49%, respectively. A second publication (2012) reviewed use of IORT in 96 patients with primary or recurrent cancer of the parotid gland. RFS rates at 1, 3, and 5 years were 82%, 69%, and 65%, respectively. One-, 3-, and 5-year OS rates after surgery and IORT were 88%, 66%, and 56%, respectively. Complications developed in 26 patients.

Thirty-four patients with recurrent head and neck cancer treated with IORT at another center was reported by Perry et al in 2010. At median follow-up of 23 months (range, 6-54 months), 8 patients were alive and without evidence of
disease. The 1- and 2-year estimates for in-field local PFS rates were 66% and 56%, respectively, with 13 (34%) in-field recurrences. One- and 2-year distant metastases-free survival rates were 81% and 62%, respectively, with 10 (29%) patients developing distant failure. One- and 2-year OS rates were 73% and 55%, respectively, with median time to OS of 24 months.

Section Summary: Head and Neck Cancers
The evidence on IORT for head and neck cancers includes case series. The strongest evidence is from a retrospective study of patients who had recurrent salivary gland carcinomas and were at risk of radiation toxicity due to prior treatment with EBRT. In this study, multivariate analysis found that use of IORT was a significant predictor of improved outcomes. However, the reasons for using or not using IORT were not clearly described, and there was a risk of selection bias in this retrospective study.

PANCREATIC CANCER

Systematic Reviews
Zygogianni et al (2011) conducted a review of the literature on the effectiveness and safety of IORT in pancreatic cancer.(19) Reviewers assessed the potential impact of IORT on local control, quality of life, and OS. PubMed was searched from 1980 until 2010, and the search restricted to articles published in English. Thirteen studies were included. Results provided no clear evidence to indicate that IORT was more effective than other therapies in treating pancreatic cancer.

A 2008 systematic review of the literature from 1995 to 2007 by Ruano-Ravina et al assessed the efficacy and safety of IORT in pancreatic cancer.(20) Inclusion criteria were studies with a minimum of 30 patients and survival results based on a minimum 3-month follow-up. Fourteen articles were selected: 1 was an IORT technology assessment report, 5 were cohort studies, and 8 were case series studies, 2 of which belonged to the same series. None assessed quality of life. In general, the studies showed that IORT was associated with slightly increased survival among patients with pancreatic cancer in localized stages. However, no clear evidence indicated that IORT was more effective than other therapies in treating pancreatic cancer in locally advanced and metastatic stages.

Case Series
Jingu et al reported 30-year experience with use of IORT for pancreatic cancer.(21) One hundred ninety-two patients who had no distant organ metastases or dissemination at the time of laparotomy were enrolled. Fifty-five patients underwent adjuvant EBRT plus IORT, and 124 received adjuvant chemotherapy. Median follow-up was 37.5 months. At the time of the analysis, 166 patients had recurrent disease and 35 had local failure. Two-year local control and OS rates were 71.0% and 16.9%, respectively. A multivariate analysis showed that the degree of resection (R0 [negative margins] to R1 [residual microscopic disease] vs R2 [partial resection with tumor left behind]) and adjuvant chemotherapy both had a significant impact on OS. Late gastrointestinal morbidity
of Common Terminology Criteria for Adverse Events grade 4 or 5 was observed in
4 patients.

Another large series (2010) retrospectively analyzed 210 patients treated with
IORT after resection of pancreatic cancer (R0 [negative margins], 147 patients; R1
[residual microscopic disease], 63 patients), performed by investigators in
Japan. (22) Fifty-four patients also had postoperative EBRT, and 114 patients had
chemotherapy. Median follow-up for the surviving 62 patients was 26.3 months
(range, 2.7-90.5 months). At the time of analysis, 150 patients had disease
recurrences, and the 2-year local control rate was 83.7%. Median survival time
and the 2-year actuarial OS in all 210 patients were 19.1 months and 42%,
respectively.

**Section Summary: Pancreatic Cancer**
The evidence on IORT for pancreatic cancer includes large case series and
systematic reviews of cohorts and case series. The systematic reviews found no
evidence that IORT was more effective than other therapies in treating pancreatic
cancer. No evidence was identified that evaluated outcomes when IORT was and
was not added to multimodal therapy. Two-year OS rates in the large case series
ranged from 16.9% to 42%.

**RENAL CELL CARCINOMA**
The evidence on IORT for renal cell carcinoma (RCC) includes case series. Paly et
al (2014) reported on 98 advanced or locally recurrent RCC patients treated with
IORT during nephrectomy at 9 different institutions during the period of 1985 and
2010. (23) Pre- or postoperative EBRT was given to 62% of patients. Median
follow-up time was 3.5 years for surviving patients. For advanced disease, the 5-
year OS, disease-specific survival (DSS), and DFS were 37%, 41% and 39%,
respectively. For locally recurrent disease, the 5-year OS, DSS, and DFS were
55%, 60% and 52%, and reported to be favorable to patients who had resection
without IORT.

Calvo et al (2013) reported 20-year outcomes in 25 patients with advanced
(n=15) or recurrent (n=10) RCC treated with IORT. (24) Fifteen (60%) patients
received perioperative EBRT. Surgical resection resulted in negative margins (R0)
in 6 (24%) patients and residual microscopic disease (R1) in 19 (76%) patients.
Median follow-up for surviving patients was 22.2 years (range, 3.6-26 years). OS
and DFS rates at 5 and 10 years were 38% and 18% and 19% and 14%,
respectively. Locoregional control (tumor bed or regional lymph nodes) and distant
metastases-free survival rates at 5 years were 80% and 22%, respectively. Six
(24%) patients experienced acute or late toxicities of grade 3 or higher using
National Cancer Institute Common Toxicity Criteria version 4.

Hallemeier et al (2012) reported outcomes of a multimodality therapy combining
maximal surgical resection, EBRT, and IORT for 22 patients with advanced or
recurrent RCC. (25) Surgical resection was R0 (negative margins) in 5 patients
(23%) and R1 (residual microscopic disease) in 17 patients (77%). OS rates at 1,
5, and 10 years were 91%, 40%, and 35% and DFS rates at 1, 5, and 10 years
were 64%, 31%, and 31%, respectively. Central recurrence (within the IORT field), locoregional relapse (tumor bed or regional lymph nodes), and distant metastases at 5 years were 9%, 27%, and 64%, respectively.

**Section Summary: Renal Cell Carcinoma**
The evidence on IORT for RCC includes case series. No controlled trials were identified to determine whether adjunctive IORT improves health outcomes when added to multimodal therapy with surgical resection and EBRT. In 1 case series, grade 3 or higher toxicity was reported in 24% of patients after IORT.

**GLIOBLASTOMA**
Nemoto et al (2002) reported on treatment with IORT for 32 patients with previously untreated malignant gliomas over a 10-year period.(26) Patients also had postoperative radiotherapy. Eleven patients had histologic diagnoses of anaplastic astrocytoma (AA) and 21 had glioblastoma (GBM). Median survival time was 24.7 months in the AA group versus 33.6 months for matched historical controls. Differences in 1-, 2-, and 5-year survival rates between IORT-treated patients and historical controls were also not significant. In the GBM group, median survival was 13.3 months in the IORT-treated patients versus 14.6 months in the matched controls. Data on 1-, 2-, and 5-year survival rates also did not differ significantly between groups.

**Section Summary: Glioblastoma**
Compared to historical controls, IORT for patients with previously untreated malignant gliomas had no survival benefit when given as an adjunct to surgery and EBRT.

**NEUROBLASTOMA**
Rich et al (2011) reported their experience using IORT after re-resection in patients with locally recurrent or persistent high-risk neuroblastomas.(27) They retrospectively reviewed 44 consecutive patients who received IORT at 1 institution between 2000 and 2009 after gross total resection of recurrent or persistent tumor. Median follow-up after IORT was 10.5 months. Each patient had received prior chemotherapy and surgery and 94.5% had received EBRT. Median OS was 18.7 months (95% CI, 11.7 to 25.6 months), with 50.4% probability of local control.

**Section Summary: Neuroblastoma**
No controlled trials were identified. There is insufficient evidence to evaluate the efficacy of IORT as an adjunct to multimodal therapy for neuroblastomas.

**FIBROMATOSIS**
Roeder et al (2010) reviewed outcomes of 30 patients (31 lesions) with aggressive fibromatosis who were treated with IORT after surgery.(28) Treatment with IORT was undertaken to avoid mutilating surgical procedures when complete surgical removal seemed to be unlikely or impossible. Median age was 31 years (range, 13-59 years). Resection status was close margin in 6 lesions, microscopically positive in 13, and macroscopically positive in 12. Median tumor size was 9 cm.
Twenty-five (83%) patients received additional EBRT. After a median follow-up of 32 months (range, 3-139 months), no disease-related deaths occurred. Five local recurrences were seen, resulting in actuarial 3-year local control rates of 82% overall and 91% inside the IORT areas. Trends to improved local control were seen for age (>31 years) and negative surgical margins, but none of these factors was statistically significant. Perioperative complications were found in 6 patients (wound healing disturbances in 5 patients, venous thrombosis in 1 patient). Late toxicity was seen in 5 (17%) patients.

Section Summary: Fibromatosis
Although the local control rate for aggressive fibromatosis is high in patients who have had incomplete surgery and EBRT, no controlled trials were identified to evaluate whether IORT improves survival. Late toxicity was observed with the combined treatment in 17% of patients.

SUMMARY OF EVIDENCE
For individuals who have rectal cancer who receive intraoperative radiotherapy (IORT), the evidence includes a randomized controlled trial (RCT), nonrandomized comparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Adjunctive use of IORT as part of a multimodal treatment could allow an increase in radiation dose without increasing complications. However, a phase 3 RCT and meta-analysis of IORT for locally advanced rectal cancer did not find improved outcomes with IORT in combination with external-beam radiotherapy (EBRT) and surgery. Nonrandomized comparative studies and a meta-analysis of these studies have shown some benefit in health outcomes with adjunctive IORT for recurrent rectal cancer, however, these studies are limited by a high risk of selection bias, heterogeneous patient populations, and heterogeneous delivery of other treatments. Large RCTs are needed to determine the effect of IORT with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have gastric cancer who receive IORT, the evidence includes RCTs and a systematic review of RCTs. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. A meta-analysis of 8 RCTs found a benefit of IORT in locoregional control but not overall survival when used with EBRT. When IORT was administered without adjuvant EBRT in patients with stage III disease, overall survival improved. Thus, IORT might be considered an alternative to EBRT in patients undergoing surgery for stage III gastric cancer. Randomized studies comparing benefits and harms of the 2 treatments are needed to determine the efficacy of IORT with greater certainty. It cannot be determined if IORT provides any benefit for overall survival in this patient population when used in with EBRT. Further study is needed. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have soft tissue sarcomas who receive IORT, the evidence includes a systematic review, small RCT, and several nonrandomized comparative...
studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Overall, study quality is low. The limited data suggest that IORT may improve local control and overall survival, but adverse effects may outweigh any treatment benefit. RCTs are needed to determine the risks and benefits of IORT for soft tissue sarcomas with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have gynecologic cancers who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The contribution of adjuvant IORT cannot be determined from the available literature. There is no evidence that IORT improves survival rates, and complications may be severe. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have head and neck cancers who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The strongest evidence is from a retrospective analysis of patients who had recurrent salivary gland carcinomas and were at risk of radiation toxicity due to prior treatment with EBRT. Some patients received IORT plus salvage surgery, and multivariate analysis found that use of IORT was a significant predictor of improved outcomes. Although these findings suggested an improvement in health outcomes for head and neck cancers that cannot be treated with EBRT due to toxicity, there was a high risk of selection bias in this study. Comparative trials are needed to determine the efficacy of IORT with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have pancreatic cancer who receive IORT, the evidence includes large case series, cohort studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. The systematic reviews found no evidence that IORT was more effective than other therapies in treating pancreatic cancer. No evidence was identified that evaluated outcomes when IORT was and was not added to multimodal therapy. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have renal cell carcinoma who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. No controlled trials were identified to determine whether adjunctive IORT improves health outcomes when added to multimodal therapy with surgical resection and EBRT. Grade 3 or higher toxicity after IORT has been reported in a substantial percentage of patients. The evidence is insufficient to determine the effects of the technology on health outcomes.
For individuals who have glioblastoma or neuroblastoma or fibromatosis who receive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. In general, whether IORT improves overall survival compared to other therapies is unclear. Compared to historical controls, IORT for patients with previously untreated malignant gliomas had no survival benefit when given in conjunction with multimodal therapy. In addition, complication rates may be high. It cannot be determined from available data whether IORT improves outcomes when used as an alternative to EBRT in previously treated patients. Comparative trials are needed to evaluate the safety and efficacy of this treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

CLINICAL INPUT FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests, input was received from 1 physician specialty society and 2 academic medical centers (6 reviewers) while this policy was under review in 2009. The input was quite variable, with some supporting use of IORT for multiple indications and others considering it investigational. The strongest support was for rectal cancer.

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network
Table 1 provides a lists National Comprehensive Cancer Network recommendations for the use of IORT in the treatment of various cancers.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Recommendation</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>v.1.2017: IORT “is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk.”</td>
<td>3</td>
</tr>
<tr>
<td>Colon</td>
<td>v.2.2016: “Intraoperative radiotherapy (IORT) should be considered for patients with T4 or recurrent cancers as an additional boost.”</td>
<td>2A</td>
</tr>
<tr>
<td>Gastric</td>
<td>v.3.2016: IORT is currently not recommended.</td>
<td>NA</td>
</tr>
<tr>
<td>Head and neck</td>
<td>v.2.2016: IORT is not addressed</td>
<td>NA</td>
</tr>
<tr>
<td>Ovarian</td>
<td>v.1.2016: IORT is not addressed</td>
<td>NA</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>v.2.2016: “The role of IORT for unresectable and resectable cases is controversial and should only be</td>
<td>NA</td>
</tr>
</tbody>
</table>
performed at specialized centers. It is sometimes used in cases where surgical resection may result in close or involved margins.” The guidelines conclude: “Overall there is no clear established role for IORT in patients with pancreatic cancer.”

Rectal  
v.2.2016\textsuperscript{35}: “IORT, if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers.”  
2A

Renal  
v.2.2.2017\textsuperscript{36}: IORT is not addressed  
NA

Soft tissue sarcoma  
v.2.2016\textsuperscript{37}: For patients with resectable disease, surgery with or without IORT is the recommended primary treatment (10-12.5 Gy for microscopic residual disease and 15 Gy for gross residual disease).  
2A

Uterine  
v.2.2016\textsuperscript{38}:  
- For patients with "local/regional recurrence ... [and] prior RT to site of recurrence ... surgical exploration + resection ± IORT" may be considered.  
- For patients with "radiologically isolated vaginal/pelvic recurrence ... surgical exploration + resection + IORT" may be considered.  
3


U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS
Not applicable.

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

ONGOING AND UNPUBLISHED CLINICAL TRIALS
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>A Multicenter Randomized Phase III Trial on INTraoperative RAdiotherapy in Newly Diagnosed GliOblastoma Multiforme (INTRAGO II)</td>
<td>314</td>
<td>Feb 2021</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

References


Billing Coding/Physician Documentation Information

19294 Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with partial mastectomy (List separately in addition to code for primary procedure)

77424 Intraoperative radiation treatment delivery, x-ray, single treatment session

77425 Intraoperative radiation treatment delivery, electrons, single treatment session

77469 Intraoperative radiation treatment management

ICD-10 Codes

C20 Malignant neoplasm of rectum
C49.4 Malignant neoplasm of connective and soft tissue of abdomen
C49.8 Malignant neoplasm of overlapping sites of connective and soft tissue

Additional Policy Key Words

N/A

Policy Implementation/Update Information

10/1/88 New policy added to the Radiology section, considered investigational.
9/1/00 No policy statement changes.
9/1/01 No policy statement changes.
9/1/02 Policy statement revised to indicate IORT may be medically necessary when there are no metastases and the outcome of treatment (surgical resection plus IORT) is expected to be curative (five or more years survival). Intraoperative radiation therapy (IORT) is considered not medically necessary as palliative treatment.
9/1/03 No policy statement changes.
9/1/04 Policy statement reversed to indicate all indications of IORT are considered investigational.
9/1/05 No policy statement changes.
9/1/06 No policy statement changes.
3/1/07 No policy statement changes.
9/1/07 No policy statement changes.
3/1/08 No policy statement changes.
9/1/08 No policy statement changes.
3/1/09 No policy statement changes.
9/1/09 No policy statement changes.
11/1/09 Policy statement revised. May be considered medically necessary for some cases of rectal cancer and sarcomas. Other applications remain investigational. This change is effective 10/6/2009.
9/1/10 No policy statement changes.
9/1/11 No policy statement changes.
1/1/12 Coding updated.
9/1/12 No policy statement changes.
10/1/13 No policy statement changes.
10/1/14  No policy statement changes.
10/1/15  Updated title to say Radiotherapy. No policy statement changes.
10/1/16  No policy statement changes.
10/1/17  No policy statement changes.

State and Federal mandates and health plan contract language, including specific provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The medical policies contained herein are for informational purposes. The medical policies do not constitute medical advice or medical care. Treating health care providers are independent contractors and are neither employees nor agents Blue KC and are solely responsible for diagnosis, treatment and medical advice. No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, photocopying, or otherwise, without permission from Blue KC.