Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Intraoperative Radiotherapy

Description/Background

Intraoperative radiotherapy (IORT) increases the intensity of radiation directly delivered to tumors. The tumor and associated tissues at risk for micrometastatic spread are directly visualized during surgery. 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), low-energy x-ray IORT or high-dose rate brachytherapy.

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 also receive preoperative or postoperative external-beam radiotherapy (EBRT) in addition to surgical resection of the tumor. Therefore, IORT would be considered an adjunctive treatment to multimodal treatment that includes surgery plus EBRT. In recurrent tumors where EBRT has already been delivered and tissue is at risk for radiation toxicity (e.g., head and neck cancers), IORT is being evaluated in conjunction with surgery alone.

Regulatory Status

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. Xoft® Axxent® electronic brachytherapy system is also available and was approved to deliver high dose rate X-ray radiation for brachytherapy in 2008. FDA product codes: JAD, LHN.

Medical Policy Statement

The safety and effectiveness of intraoperative radiation therapy have been established for selected patients with specified cancers. It is a useful therapeutic option for patients meeting specific patient selection criteria.

Inclusionary and Exclusionary Guidelines

Inclusionary Guidelines (based on NCCN guidelines):

Established for the following recurrent and/or unresectable cancers without distant metastases, based on NCCN guidelines:

- Abdominal and retroperitoneal sarcoma-for surgery with or without IORT as primary treatment for tumors other than gastrointestinal stromal tumors (GIST) and desmoid sarcomas, provided that frozen section pathology can confidently demonstrate a non-GIST/non-desmoid pathology.
- Central pelvic recurrent cervical cancer after radiation therapy should be considered for pelvic exoneration with or without IORT.
- Colon cancer: For patients with T4 or recurrent cancers as an additional boost.
- Gynecological cancers, including recurrent cervical cancer, recurrent endometrial cancer and uterine sarcomas.
- Pancreatic cancer that in unresectable and resectable cases where resection may result in close or involved margins.
- Rectal cancer: For patients with T4 or recurrent cancers with very close or positive margins after resection, as an additional boost.
- Recurrent uterine endometrial adenocarcinoma in patients previously treated with external beam radiation at the site of recurrence.
- Soft tissue sarcomas.

Exclusionary Guidelines:

Experimental/investigational for all other indications.

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

Established codes:

77424 77425 77469

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

N/A

Rationale

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Intraoperative Radiotherapy for Various Cancers

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

The question addressed in this evidence review is: Does IORT improve the net health outcome when used as an adjunct to surgery and external-beam radiotherapy (EBRT) and when used to reduce radiation toxicity?

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

Populations

The relevant population of interest are patients undergoing tumor resection. The specific populations addressed in this evidence review are individuals with rectal cancer, gastric cancer, soft tissue sarcomas, gynecologic cancers, head and neck cancers, pancreatic cancer, renal cell carcinoma, glioblastoma, neuroblastoma, and fibromatosis.

Classification of surgical resection margins is listed in Table 1.

Table 1. General Surgical Resection Margin Classification

Classification	Definition
R0	Negative margins; no cancer cells detected in resected tissue
R1	Microscopic positive margin; cancer cells detected by microscope in resected tissue
R2	Macroscopic positive margin; tumor cells detected without microscope in resected tissue

Interventions

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the areas are exposed during surgery with the intent to minimize exposure to surrounding healthy tissues. Different IORT modalities are available that impact both the dose distribution and method of application. IORT techniques include electron beam IORT, high-dose rate brachytherapy based IORT, and low-energy x-ray IORT.
Most clinical experience involves intraoperative electron beam therapy.

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. IORT can be used alone but is more typically used in combination with other modalities such as surgical resection, EBRT, or chemotherapy.

Comparators

The following therapies and practices are currently being used to make decisions about patients with cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most patients receive preoperative or postoperative EBRT in addition to surgical resection of the tumor. Therefore, IORT would be considered an adjunctive treatment to multimodal treatment that includes surgery plus EBRT. For recurrent tumors already treated with EBRT, and tissue at risk for radiation toxicity (e.g., head and neck cancers), IORT is being evaluated in conjunction with surgery alone.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, and harms from treatment, specifically radiation toxicity.

Table 2. Outcomes of Interest

Outcomes	Details	Relevance
Overall survival	Survival rate or proportion dead [Timing: 1 year-10 years]	Considered the most reliable and preferred cancer endpoint
Disease-specific survival	Disease/recurrence-free survival [Timing: 1 year-10 years]	The most frequent use of this endpoint is in the adjuvant setting after definitive surgery or radiotherapy
Radiation toxicity	Can be divided into acute, subacute, and chronic effects [Timing: Weeks (acute effects) or months (subacute, chronic) after treatment]	Acute effects typically resolve within 2 weeks. Subacute and chronic effects include radiation pneumonitis, radiation-induced liver disease, fibrosis, and organ damage.

Study Selection Criteria

- Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.

- Studies with duplicative or overlapping populations were excluded

Review of Evidence

Randomized Controlled Trials

Locally Advanced Cancer

The available RCTs evaluating IORT for locally advanced rectal cancer are summarized in Table 3. No RCTs were identified that evaluated IORT for the management of locally recurrent rectal cancers.

Table 3. Summary of Key RCT Characteristics

Study	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Dubois (2011)[1]	France	7	1993 to 2001	142 patients with locally advanced rectal cancer (infiltrative rectal adenocarcinoma; T3 or T4 or N+, and M0) treated with preoperative radiotherapy	IORT plus surgical resection (n=73)	Surgical resection alone (n=69)
Masaki (2020)[2]	Japan	1	Not reported. Terminated in 2017	76 patients with locally advanced rectal cancer (M0)	IORT plus resection of rectum with total mesorectal excision (n=38)	Resection of rectum with total mesorectal excision alone (n=38)

IORT: intraoperative radiotherapy; RCT: randomzied controlled trial.

Health outcome results for RCTs are summarized in Table 4. Additionally, in the Dubois et al (2011) trial, postoperative complications were observed in the 29.6% of patients in the IORT group and 19.1% of patients in the control group(p=0.15).[1] Specific, radiation-specific complications were not reported. In the Masaki et al (2020) trial, the primary outcome of the study was to compare the pelvic sidewall recurrence rate between the groups.[2] The trial was prematurely stopped in July 2017 because distant metastasis-free survivals were found to be significantly worse in the IORT group compared to the control group. Therefore, the authors concluded that IORT should not be recommended as a standard therapy to compensate less radical resection for advanced lower rectal cancer.

The purpose of the limitations tables (see Tables 5 and 6) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 4. Summary of Key RCT Results

Study	Overall survival	Disease-free survival	Local relapse
Dubois (2011)[1]	*Median*	*Median*	*Local control at 5 years (%)*
N	140	140	140
IORT + surgical resection	88 months	80 months	91.8%
Surgical resection	106 months	89 months	92.8%

Difference	Not reported (p=0.2578)	Not reported (p=0.6037)	Not reported (p=0.6018)
Masaki (2020)[2,]	*5-year, 10-year, and 15-year overall survival*	*5-year, 10-year, and 15-year distant metastasis-free survival*	*5-year pelvic sidewall recurrence*
N	76	76	76
IORT + surgical resection	71.5%, 61.7%, and 61.7%	57.5%, 53%, and 53%	12.4%
Surgical resection	81.8%, 73.8%, and 64.6%	76.8%, 76.8%, and 76.8%	8.3%
Difference (95% CI)	OR=1.264 (0.523 to 3.051); p=0.603	OR=2.554 (1.041 to 6.269); p=0.041	OR=1.350 (0.302 to 6.034); p=0.694

CI: confidence interval; IORT: intraoperative radiotherapy; OR: odds ratio

Table 5. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Dubois (2011)[1,]					
Masaki (2020)[2,]	3. Staging of advanced rectal cancer not reported				

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4.Not the intervention of interest. c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 6. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Dubois (2011)[1,]		1. Patients and surgeons were not blinded to treatment assignment, though impractical for this study			3. Percent of local failures was smaller than expected, which may have reduced the power	
Masaki (2020)[2,]		1. Patients and surgeons were not blinded to treatment assignment, though impractical for this study			3. Trial was terminated early likely reducing power	

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

Systematic Reviews

Primary, Advanced, and Recurrent Cancer

Four systematic reviews were identified that evaluated IORT for either primary locally advanced rectal cancer or locally recurrent rectal cancer, or rectal cancer. Wiig et al (2014) reviewed 18 studies on primary rectal cancer (including 1 RCT, 5 comparative trials, 7 trials without IORT) and 18 studies on locally recurrent rectal cancer (including 5 studies without IORT).[3] Meta-analysis of the data was not performed due to heterogeneity in study designs and reporting. Mirnezami et al (2013) included 29 studies (14 prospective, 15 retrospective) published between 1965 and 2011 (N=3003 patients).[4] Indications for IORT were locally advanced disease in 1792 patients and locally recurrent disease in 1211 patients with colorectal cancer. Liu et al (2021) included 3 RCTs and 12 observational studies (N=1460) that evaluated IORT in both locally advanced and locally recurrent rectal cancer. [43] Fahy et al (2021) included 7 studies of patients with locally advanced and locally recurrent rectal cancer (N=833). [44]

Characteristics and results of these reviews are summarized in Tables 7 and 8.

Table 7. Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Wiig (2014)[3,]	1990-2013	Primary cancer: 15; Recurrent cancer: 18	Patients with locally advanced rectal cancer (either primary or recurrent)	Primary cancer: 4272; Recurrent cancer: 1174 (ranges not reported)	Randomized controlled trials (if available), comparative studies, non-comparative studies, non-IORT studies	Up to 5 years
Mirnezami (2013)[4,]	1991-2011	29	Patients with locally advanced colorectal cancer (either primary or recurrent) receiving IORT as part of a multimodal treatment	3003 (11-607)	Randomized controlled trials (if available), prospective and retrospective observational studies	Up to 5 years
Liu (2021)[43,]	1991-2020	15	Patients with rectal cancer	1460 (ranges not reported)	Randomized controlled trials (if available), prospective and retrospective observational studies	Up to 5 years

Fahy (2021)[44,]	2000 to 2020	7	Patients with locally advanced and locally recurrent rectal cancer	833 (ranges not reported)	Randomized controlled trials (if available), prospective and retrospective observational studies	Not reported

IORT: intraoperative radiotherapy

Table 8. Systematic Review Results [a]

Study	Overall survival	Disease-free survival	Local relapse
Wiig (2014)[3,]	*Overall survival*		*5-year local control*
Primary cancer			
Total N	Not reported (20 studies)		Not reported (18 studies)
IORT, mean (range)	60 (28-76)		13 (2-35)
non-IORT, mean (range)	72 (52-85)		8 (5-9)
Locally recurrent cancer			
Total N	NR (23 studies)		NR (12 studies)
IORT, mean (range)	25 (40-46)		49 (28-74)
non-IORT, mean (range)	19 (0-46)		81 (70-92)
Mirnezami (2013)[4,]	*5-year overall survival, IORT vs no IORT*	*5-year disease-free survival, IORT vs no IORT*	*5-year local control, IORT vs no IORT*
Total N	370	288	482
Pooled effect (95% CI)	HR=0.33 (0.2 to 0.54)	HR=0.51 (0.31 to 0.85)	OR=0.22 (0.05 to 0.86)
I^2 (p)	0 (.001)	42% (.009)	68% (.03)
Range of N	19 to 167	37 to 167	19 to 167
Range of effect sizes	0.13 to 0.36	0.32 to 1.54	0.04 to 1.88
Liu (2021)[43,]	*5-year overall survival, IORT vs no IORT*	*5-year disease-free survival, IORT vs no IORT*	*5-year local control, IORT vs no IORT*
Total N	NR (9 studies)	NR (6 studies)	NR (14 studies)
Pooled effect (95% CI)	HR=0.80 (0.60 to 1.06)	HR=0.94 (0.73 to 1.22)	HR=3.07 (1.66 to 5.66)
I^2 (p)	0 (.740)	0 (.503)	70.9 (.000)
Range of effect sizes	0.31 to 2.31	0.81 to 1.93	0.74 to 17.53
Fahy (2021[44,]			*Locoregional recurrence, IORT vs no IORT*
Total N			833
Pooled effect (95% CI)			OR=0.55 (0.27 to 1.14)
I^2 (p)			55 (.11)
Range of N			19 to 99
Range of effect sizes			0.10 to 1.45

[a]Formal meta-analysis not conducted in Wiig (2014), instead mean (range) for outcomes were presented for the publications included. CI: confidence interval; HR: hazard ratio; IORT: intraoperative radiotherapy; OR, odds ratio

Mirnezami et al (2013) demonstrated significant survival and local control benefits with IORT in a mixed population of patients with locally advanced colorectal cancer (either primary or recurrent). [4] More recently, however, Liu et al (2021) did not demonstrate a 5-year OS or disease-free survival (DFS) benefit with IORT in patients with rectal cancer. [43] IORT did, however, demonstrate benefit in 5-year local control. Fahy et al (2021) also did not find a benefit with IORT for locoregional recurrence in a mixed population of patients with locally advanced and locally recurrent rectal cancer. [44] Wiiget al (2014) results suggested IORT provided no OS benefit for primary completely resected rectal cancers, with a possible reduction in local recurrence in cases of incomplete tumor resection. [3] There was no evidence that IORT affected OS or local recurrence when used to treat locally recurrent rectal cancer.

Some analyses also reported outcomes for complications following IORT. Mirnezami et al (2013) did not demonstrate an increased risk in total (odds ratio [OR]=1.13; 95% confidence interval [CI], 0.77 to 1.65), urologic (OR=1.35; 95% CI, 0.84to 2.82), or anastomotic (OR=0.94; 95% CI, 0.42 to 2.1) complications with IORT; however, increased wound complications were noted after IORT (OR=1.86; 95% CI, 1.03 to 3.38; p =.049). Liu et al (2021) did not find an increase in the risk of complications with IORT, including fistulae (OR=0.79, 95% CI, 0.33 to 1.89), wound complication (OR=1.21,95% CI, 0.62 to 2.36), anastomotic leak (OR=1.09, 95% CI, 0.59 to 2.02), or neurogenic bladder dysfunction (OR=0.69,95% CI, 0.31 to1.55). [43] Likewise, Fahy et al (2021) did not find an increased risk of complications with IORT, including wound infections (OR, 1.13; 95% CI, 0.50 to 2.54), pelvic abscess (OR, 1.01; 95% CI, 0.54 to 1.87), or anastomotic leak(OR, 1.60; 95% CI, 0.51 to 2.81). [44] All reviews are limited by the risk of selection bias for IORT in nonrandomized studies, the variability in stages evaluated and IORT dosing, and high heterogeneity present for certain outcomes.

Section Summary: Rectal Cancer

The evidence for IORT as part of a multimodal treatment approach in patients who have locally advanced (colo-)rectal cancer includes RCTs, nonrandomized comparative studies, and systematic reviews with meta-analyses of these studies. Adjunctive use of IORT could permit an increase in radiation dose without increasing complications. Available meta-analyses on IORT, in addition to standard therapy, for rectal cancer have combined together studies on both locally advanced primary and recurrent disease. Of the 2 systematic reviews that quantitatively pooled results, there was no benefit with the addition of IORT in terms of survival, but there was conflicting results on local control with one demonstrating an improvement in 5-year local control, while the other found no benefit in locoregional reoccurrence. In individuals with locally advanced primary rectal cancer only, 2 RCTs failed to show benefit with the addition of IORT in terms of local control or survival. For individuals with locally advanced primary or recurrent colorectal disease, one meta-analysis evaluating these populations together showed a significant benefit with the addition of IORT on local control, DFS, and OS. More data are needed to determine the effect of adjunctive IORT in each specific population of locally advanced disease (ie, primary vs recurrent, rectal vs colorectal) with greater certainty.

GASTRIC CANCER

Systematic Reviews

A meta-analysis by Yu et al published in 2015 compiled studies that involved the use of IORT for resectable gastric cancer.[5] The literature search for this analysis encompassed the period January through July 2013. 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 four 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). In three studies that tested the efficacy of IORT for OS in a subgroup of patients with stage III disease, there was a significantly improved OS (HR=0.60; 95% CI, 0.40 to 0.89; p=0.011). 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, none of the 3 studies provided 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.

SOFT TISSUE SARCOMAS

Review of Evidence

Systematic Reviews

The 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.[6]

Randomized Controlled Trials

One randomized trial (N=35) reported by Sindelar et al (1993) compared IORT plus low-dose (35- to 40-gray [Gy]) postoperative EBRT with high-dose (50- to 55-Gy) EBRT alone.[7] 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, Lehnert et al (2000) reported that IORT patients had more surgical complications and significantly more infectious complications; however, the IORT-treated patients had a 40% lower rate of local recurrence.[8] IORT demonstrated effective tumor control in osteosarcoma.

A 2014 multicenter study by Calvo et al compared outcomes from 159 patients who had soft tissue sarcomas of the extremity treated using IORT plus multimodal therapy with 95 patients treated using 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 and IORT (n=37) or surgery only (n=26) between 1996 and 2011.[10] 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). OS 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 the use of 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 events 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

Review of Evidence
In a phase 2 trial, Giorda et al (2011) examined the use of radical surgery with IORT after chemotherapy in extracervical, locally advanced cancer patients.[11] Between 2000 and 2007, 42 locally advanced cervical cancer (stage IIA bulky-IVA) patients were treated. EBRT was administered to the whole pelvic region in combination with chemotherapy. After EBRT and chemotherapy, 35 of 42 patients (83%) underwent radical surgery and IORT treatment. Five-year DFS and OS rates were 46% and 49% respectively. DFS and OS were significantly longer when the 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).[12] 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 to 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 These findings suggest that IORT is a valuable boosting technique particularly in the management of advanced but resectable cervical cancer. Patients, especially those with recurrent disease, with positive lymph nodes, parametrial involvement, and/or incomplete resection have 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.[13] 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.

Chen et al (2022) evaluated the feasibility and safety of IORT as an adjuvant therapy for recurrent gynecological cancer in a case series of 5 women at a single center in Taiwan (cervical cancer, n=2;endometrial cancer, n=2; uterine leiomyosarcoma, n=1). [46]
Three women died during follow-up, 2 of which had local recurrence or progression of disease. The median recurrence-free survival was 13.8 months (95% CI, 1.6to not estimable) and the median OS was 16.4 months (95% CI, 4.7 months to not estimable).

HEAD AND NECK CANCERS

Review of Evidence

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.[14] 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, the OS rate was 34%, and the DFS rate was 46%. The only predictor of DFS was the 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).[15] There is a potential for overlap of patients with the 2008 study by Chen et al described above. 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 (2011, 2012) reported on 2 case series of head and neck cancers. In the 2011 publication, they reported on the use of IORT for patients with advanced cervical metastasis.[17] OS rates at 1, 3, and 5 were 58%, 34%, and 26%,respectively. Recurrence-free survival rates at 1, 3, and 5 years were 66%, 55%, and 49%, respectively. A second publication reviewed the use of IORT in 96 patients with primary or recurrent cancer of the parotid gland.[18] Recurrence-free survival 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 received IORT at another center were reported by Perry et al (2010).[19] 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 progression-free survival 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 patients (29%) 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 the use of 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.

PANCREATIC CANCER

Review of Evidence

Systematic Reviews

One recent systematic review by Jin et al (2020) was identified that evaluated clinical outcomes in patients with resectable pancreatic cancer with or without IORT.[20] The meta-analysis identified 15 pertinent articles for inclusion representing 401 patients undergoing pancreatic resection with IORT and 433 patients undergoing pancreatic resection only. Characteristics and results are summarized in Tables 9 and 10.

Table 9. Systematic Review Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Jin (2020)[20]	1990-2019	15	Patients with resectable pancreatic cancer (not metastatic or locally advanced) undergoing surgery with or without IORT	834 (11-203)	Non-randomized controlled trials	Not reported

IORT: intraoperative radiotherapy

Table 10. Systematic Review Results[a]

Study	Overall survival	Disease-free survival	Local relapse
Jin (2020)[20]			
Total N	Not reported (13 studies)		Not reported (8 studies)
Pooled effect (95% CI)	MSR: 1.20 (1.06 to 1.37)		RR: 0.70 (0.51 to 0.97)
I^2 (p)	65.3% (.005)		36.8% (p=0.135)
Range of N	Not reported		
Range of effect sizes	0.57-3.54		0.14-0.96

CI: confidence interval; MSR: median survival rate; RR: relative risk

Jin et al (2020) found that patients receiving IORT had an improved median survival rate and a reduced risk of local recurrence compared to those who did not receive adjuvant IORT with moderate heterogeneity.[20] The incidence of postoperative complications between the groups were not significantly different from each other (relative risk, 0.95; 95%CI 0.73-1.23). Results of the meta-analysis were limited by the small sample sizes of the included studies, substantial heterogeneity, and the mostly retrospective design of the studies.

Case Series

Other larger retrospective evaluations of IORT in pancreatic cancer that evaluated patients with unresectable disease are summarized in Tables 11 and 12 below.

Table 11. Summary of Case Series Characteristics - Unresectable Disease

Study	Country	Participants	Follow-Up
Chen (2016)[21,]	China	247 patients with nonmetastatic locally advanced pancreatic cancer	median, 10.1 months
Cai (2013)[22,]	United States	194 patients with unresectable locally advanced pancreatic cancer	median, 11.6 months
Harrison (2020)[23,]	United States	158 patients with borderline resectable/locally advanced pancreatic cancer (132 patients receiving FOLIRINOX were evaluated for survival analysis	not reported
Sekigami (2021) [45,]	United States	201 patients with borderline resectable/locally advanced pancreatic cancer who received total neoadjuvant therapy (FOLIRINOX with chemoradiation)and underwent resection between 2011and 2019. Of the 201 patients evaluated,88 received IORT following resection; of these, 69 underwent R0 and 19 underwentR1 resection.	not reported
Cho (2022) [47]	Korea	41 patients (men, 56%) with resectable pancreatic cancer	Median, 9

FOLIRINOX: folinic acid, fluorouracil, irinotecan, oxaliplatin

Table 12. Summary of Case Series Results - Unresectable Disease

Study	Treatment	Overall Survival	Progression-Free Survival
Chen (2016)[21,]	IORT delivered after palliative surgical procedures; postoperative adjuvant therapy (e.g., chemotherapy) was recommended for all patients	Overall, 1-, 2- and 3-year survival rates were 40%, 14%, and 7.2%. Median overall survival was 9 months.	1-, 2- and 3-year LPFS rates were 51.3%, 40.1%, and 34.6%. 1-, 2- and 3-year DMFS rates were 39.3%, 23.4%, and 11.9%.
Cai (2013)[22,]	IORT as part of multimodal approach including pre-IORT EBRT and chemotherapy	Overall, 1-, 2- and 3-year survival rates were 49%, 16%, and 6%. Median overall survival was 12 months.	1-, 2- and 3-year LPFS rates were 61%, 41%, and 38%. 1-, 2- and 3-year DMFS rates were 49%, 28%, and 19%.
Harrison (2020)[23,]	IORT as part of multimodal approach including neoadjuvant treatment prior to attempted resection with IORT	Overall, 1-, 2-, 4-year survival rates were 99%, 79%, and 47% for those receiving any form of resection plus IORT. Overall, 1-, 2-, 4-year survival rates were 98%, 49%, 13% for those receiving IORT only.	At time of study follow-up, 51% and 67% of patients had disease progression in the resection plus IORT and IORT only groups, respectively.

Sekigami (2021) [45,]	IORT following total neoadjuvant therapy(FOLIRINOX with chemoradiation) and resection	Among patients who received IORT, there was no difference in OS between patients who underwent R0 vs R1 resection:R0: 48 months, IQR 25-notreached vs R1: 37 months, IQR30-47; p =.307.	Among patients who received IORT, there was no difference in DFS between patients who underwent R0 vs R1resection: R0: 29 months, IQR 14-47 vsR1: 20 months, IQR 15-28; p =.114.
Cho (2022) [47]	IORT as part of multi modal approach including adjuvant gemcitabine-based chemotherapy	1 year OS: 94.1%	The 1-year local control and distant control rates were 76.4% and 55.7%,respectively.

DFS: disease-free survival; DMFS: distant metastasis-free survival; EBRT: external beam radiotherapy; FOLIRINOX: folinic acid, fluorouracil, irinotecan, oxaliplatin; IORT: intraoperative radiotherapy; IQR: interquartile range; LPFS: local progression-free survival; OS: overall survival.

Section Summary: Pancreatic Cancer

The evidence on IORT for pancreatic cancer includes large case series and a systematic review of nonrandomized comparative studies. The systematic review found that in patients with resectable pancreatic cancer the addition of IORT to standard therapy was associated with improved median survival and reduced local recurrence; the evidence was limited by mostly smaller retrospective designs contributing to the review. However, the vast majority of patients present at diagnosis with more advanced disease, such as borderline resectable, locally advanced, or with distant metastases. One-year and 2-year OS rates of patients with unresectable pancreatic cancer ranged from 40% to 98% and 14% to 49%, respectively, in the large case series. Lastly, 1 case series found IORT combined with surgical resection to be associated with increased survival compared to IORT alone in patients with positive or close margins, and another case series found that application of IORT following resection yields similar survival outcomes regardless of R0 (generally better prognosis) or R1 (generally worse prognosis) resection. RCTs in more diverse populations are needed to determine the effect of adjunctive IORT for resectable, locally advanced and metastatic pancreatic cancer with greater certainty.

RENAL CELL CANCER

Observational Studies

Paly et al (2014) reported on 98 advanced or locally recurrent renal cell carcinoma (RCC) patients treated with IORT during nephrectomy at 9 different institutions during the period of 1985 and 2010.[24] EBRT was given to 27% preoperatively and to 35% postoperatively. 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 treated with resection without IORT.

Calvo et al (2013) reported 20-year outcomes in 25 patients with locoregionally recurrent (n=10) RCC after radical nephrectomy or locoregionally advanced primary RCC (n=15) who were treated with IORT.[25] Fifteen patients (60%) received perioperative EBRT. Surgical resection resulted in negative margins (R0) in 6 patients (24%) and residual microscopic disease (R1) in 19 patients (76%). The median follow-up for surviving patients was 22.2 years (range, 3.6-26 years). OS and DFS 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. One patient died within 30 days of surgery (4%). Six patients (24%) experienced acute or late toxicities of grade 3 or higher according to the National Cancer Institute Common Toxicity Criteria version 4.

Hallemeier et al (2012) reported outcomes of a multimodality therapy combining maximal surgical resection and IORT for patients with locoregionally (LR) recurrent RCC after radical nephrectomy or LR advanced primary RCC.[26] (33) From 1989 through 2005, a total of 22 patients with LR recurrent (n=19) or LR advanced primary (n=3) RCC were treated with this multimodality approach. Twenty-one patients (95%) received perioperative EBRT with a median dose of 45 Gy (range, 41.4-55 Gy). Surgical resection was R0 (negative margins) in 5 patients (23%) and R1 (residual microscopic disease) in 17 patients (77%). The median IOERT dose delivered was 12.5 Gy (range, 10-20). The OS and DFS at 1, 5, and 10 years were 91%, 40%, and 35% and 64%, 31%, and 31%, respectively. Central recurrence (within the IOERT field), LR 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 a case series, grade 3 or higher toxicity was reported in 24% of patients after IORT.

Review of Evidence

GLIOBLASTOMA

Observational Studies
Nemoto et al (2002) reported results or treatment with IORT for 32 patients with previously untreated malignant gliomas over a 10-year period.[27] Patients also had postoperative radiotherapy. Eleven patients had histological 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 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 were also not significantly different between groups.

Sarria et al (2020) reported on an international, retrospective, pooled analysis of patients with suspected glioblastoma/high-grade glioma treated with low-energy IORT, in addition to standard of care, across 5 institutions in 3countries (Germany, Peru, and China).[40] All patients received standard of care therapy adjuvant therapy, which included EBRT and temozolomide chemotherapy. A total of 51 patients were evaluated and followed for a median of 18 months. The 1-, 2-, and 3-year OS rates were 79.5%, 38.7% and 25.6% respectively (median survival time, 18 months). The 1-,2-, and 3-year progression-free survival rates were 46.2%, 29.4%, and 5.9%. respectively (median progression-free survival, 11.4 months). The median local progression-free survival was 16 months. Radio necrosis was observed in 13 patients (25.5%).

Section Summary: Glioblastoma
Compared with historical controls, IORT for patients with previously untreated malignant gliomas had no survival benefit when given as an adjunct to surgery and EBRT. An international retrospective pooled analysis of patients treated with IORT in addition to standard of care reported 1- and 2-year OS rates of 79.5% and 38.7%.

NEUROBLASTOMA

Observational Study
Rich et al (2011) reported their experience using IORT after re-resection in patients with locally recurrent or persistent high-risk neuroblastomas.[28] They retrospectively reviewed 44 consecutive patients who received IORT at 1 institution between April 2000 and September 2009 after gross total resection of recurrent/persistent tumor. Median follow-up after IORT was 10.5 months. Each patient received prior chemotherapy and surgery, and 94.5% had previous 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

Observational Study
Roeder et al (2010) reviewed outcomes of 30 patients (31 lesions) with aggressive fibromatosis.[29] 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 patients received additional EBRT. After a median follow-up of 32 months (range, 3-139 months), no disease-related deaths occurred. A total of 5 local recurrences were seen, resulting in actuarial 3-year local control rates of 82% overall and 91% inside the IOERT areas. Trends to improved local control were seen for older age (>31 years) and negative margins, but none of these factors reached significance. Perioperative complications were found in 6 patients, in particular as wound healing disturbances in 5 patients and venous thrombosis in 1 patient. Late toxicity was seen in 5 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 that evaluated 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 adjunctive IORT, the evidence includes RCTs, nonrandomized comparative studies, and systematic reviews with meta-analyses of these studies. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Adjunctive use of IORT as part of a multimodal treatment could permit an increase in radiation dose without increasing complications. Available meta-analyses on IORT, in addition to standard therapy, for rectal cancer have combined together

studies on both locally advanced primary and recurrent disease. Of the 2 systematic reviews that quantitatively pooled results, there was no benefit with the addition of IORT in terms of survival, but there was conflicting results on local control with one demonstrating an improvement in 5-year local control, while the other found no benefit in locoregional reoccurrence. In individuals with locally advanced primary rectal cancer only, 2 RCTs failed to show benefit with the addition of IORT in terms of local control or survival. For individuals with locally advanced primary or recurrent colorectal disease, one meta-analysis evaluating these populations together showed a significant benefit with the addition of IORT on local control, DFS, and OS. More data are needed to determine the effect of adjunctive IORT in each specific population of locally advanced disease (ie, primary vs recurrent, rectal vs colorectal) with greater certainty. The evidence available is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have gastric cancer who receive adjunctive 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 whether IORT provides any benefit for overall survival in this patient population (gastric cancer patients) when used with EBRT. Further study is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have soft tissue sarcomas who receive adjunctive IORT, the evidence includes a systematic review, a small RCT, and several nonrandomized comparative studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Overall, the study quality is low. The limited data suggest that IORT may improve local control and overall survival, but adverse events may outweigh any treatment benefit. NCCN clinical practice guidelines on “soft tissue sarcoma” states that “advances in RT technology such as brachytherapy, intensity-modulated radiation therapy, and intraoperative radiation therapy have led to the improvement of treatment outcomes in patients with soft tissue sarcoma.” The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have gynecologic cancers who receive adjunctive 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 there may be severe complications related to the therapy. Although there is no evidence that IORT improves survival rates, NCCN guidelines for Oncology state: “intraoperative radiation therapy, if available, should be considered for patients with T4 or recurrent cancers as an additional boost.” The evidence is sufficient to determine some benefits of the technology on health outcomes.

For individuals who have head and neck cancers who receive adjunctive 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 adjunctive 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. Although no evidence was identified that evaluated outcomes when IORT was and was not added to multimodal therapy, NCCN practice guidelines on “Pancreatic Adenocarcinoma” states that “the role of IORT is controversial….Overall, there is no clear established role for IORT in patients with pancreatic cancer, and the panel believe it should only be performed at specialized centers”. NCCN found some improved patient results suggested that certain patients with well-controlled systemic disease may benefit from aggressive local therapy that includes IORT; prospective trials are ongoing The evidence is sufficient to determine the effects of the technology on health outcomes.

For individuals who have renal cell carcinoma who receive adjunctive 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 adjunctive IORT, the evidence includes case series. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Compared with other therapies, it is unclear whether IORT improves overall survival. However, compared with 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. 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

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

Clinical Input Received from Physician Specialty Societies/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 from Blue Cross Blue Shield Association (BCBSA), input was received through 1 physician specialty society and 2 academic medical centers (6 reviewers) while this policy was under review for October 2009. The input obtained 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

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

The American Brachytherapy Society

In 2019, the American Brachytherapy Society consensus statement on IORT provides recommendations for patient selection for IORT.[41] Table 12 summarizes their recommendations based on cancer type. The consensus statement did not rate evidence or strength of recommendations.

Table 13. Consensus statement on Use of IORT

Cancer site	Recommendation
Breast cancer	Monotherapy should not be offered unless in the context of a prospective clinical trial. Use as a boost technique can be considered in patients requiring a tumor bed boost.
CNS, brain metastases	Can be considered for selected patients
CNS, high-grade gliomas	Can be considered for selected patients
Colorectal	Consider in cases with concern for positive margins. "IORT can be considered at the time of surgical resection of locally advanced or recurrent colorectal cancer in cases with concern for a positive margin, particularly when pelvic EBRT has already been delivered. A dose of 15 Gy in a single treatment to 5 mm depth in tissue using IORT-HDR has been used"
Gynecologic	Consider in recurrent cases with concerns for close/positive margins. "IORT can be considered at the time of surgical resection for isolated recurrent gynecologic cancer in cases with concern for residual microscopic disease. IORT after chemoradiation and surgery for primary management of locally advanced cervical cancer should not be used off protocol."
Head and neck	Can consider in selected patients
Pancreas	Consider in cases with concerns for close/positive margins
Pediatric cancers	Consider for pediatric sarcomas upfront if concern for close/positive margins or in recurrent sarcomas
Sarcoma, extremity	Consider in situations with close/positive margins or recurrence with reirradiation
Sarcoma, retroperitoneal	Consider in conjunction with preoperative EBRT, especially if close/positive margins are expected
Thorax	Can be considered in selected patients. "IORT can be considered at the time of surgical resection in cases with concern for a positive margin. Intraoperative LDR brachytherapy may improve local control outcomes in patients undergoing sublobar resections for stage I NSCLC when there is a concern for a positive margin."

CNS: central nervous system; EBRT: external beam radiation therapy; Gy: gray; HDR: high dose radiation; IORT: intraoperative radiation therapy; LDR: low dose radiation; NSCLC: non-small cell lung cancer

National Comprehensive Cancer Network Guidelines (NCCN)

Table 14 lists NCCN recommendations on the use of IORT on the treatment of various cancers.

Table 14. Recommendations for the Use of IORT

Cancer Site	Version	Recommendation	COR
Cervical	v.1.2023[30]	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.	3
Colon	v.3.2022[31]	IORT "if available, should be considered for patients with T4 or recurrent cancers as an additional boost.	2A
Gastric	v.2.2022[32]	IORT is not addressed	N/A
Head/Neck	v.1.2023[33]	"In certain rare circumstances, reirradiation with IORT or brachytherapy may be considered in high-volume centers with expertise in these techniques."	N/A
Ovarian	v.1.2023[34]	IORT is not addressed	N/A
Pancreatic	v.2.2022[35]	"overall, there is no clear established role for IORT in patients with pancreatic cancer, and the panel believes it should only be performed at specialized centers"	N/A
Rectal	v.4.2022[36]	IORT if available may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers	2A
Kidney Cancer	v.4.2023[37]	IORT is not addressed	N/A
Soft tissue sarcoma	v.2.2022[38]	For patients with resectable disease, consider boost with IORT for known or suspected positive margins "10-12.5 Gy for microscopic residual disease" and "15 Gy for gross residual disease".	2A
Uterine	v.1.2023[39]	• For patients with local or regional recurrences and previously treated with brachytherapy only at the recurrence site, surgery with (or without) IORT is recommended. For those previously treated with EBRT, recommended therapy for isolated relapse includes: 1) surgery with (or without) IORT; and/or 2) systemic therapy with (or without) palliative RT." • For local recurrence in the vaginal/pelvis that is negative for distant metastatic disease surgical and RT treatment pathways are provided. Surgical options in patients without prior RT exposure includes the option for IORT. • For local recurrence in patients with previous RT exposure, treatment options include "1) surgery with the option of IORT and/or systemic therapy(category 3 for IORT); 2) systemic therapy; 3)selected reirradiation with EBRT and/or brachytherapy."	3

COR: category of recommendation; Gy: gray; IORT: intraoperative radiotherapy; N/A: not applicable; RT: radiotherapy

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05181488	A Prospective, Phase II Study Evaluating the Efficacy of Intraoperative Radiotherapy After Neoadjuvant Chemotherapy in Patients With Resectable Pancreatic Cancer	80	Apr 2026
NCT02685605	A Multicenter Randomized Phase III Trial on INTraoperative RAdiotherapy in Newly Diagnosed GliOblastoma Multiforme (INTRAGO II)	314	Mar 2023
NCT04681677	Recurrent GBM Treated With Neurosurgical Resection and IORT Using the Xoft Axxent eBx System and Bevacizumab (IORT)	100	Dec 2026
NCT04847284	Intraoperative Radiotherapy in Patients With Brain Metastases	25	Mar 2024

GBM:glioblastoma; IORT: intraoperative radiotherapy; NCT: national clinical trial.

Government Regulations National:

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers. Medicare reimburses 77424, 77425 and 77469.

Local:

There is no local Medicare policy on this topic.

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

Related Policies

- Accelerated Breast Irradiation after Breast Conserving Surgery for Early Stage Breast Cancer and Breast Brachytherapy as Boost with Whole Breast Irradiation

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/08	11/26/07	10/20/07	Joint policy established
3/1/09	1/22/09	12/9/08	Policy is now considered new as the policy is changing from E/I to established for rectal cancer and pelvic malignancies and E/I for all other indications.
12/1/1/2	9/27/12	9/27/12	Routine maintenance; code update effective 3/1/12. Policy reformatted on current template to mirror BCBSA policy.
1/1/14	10/15/13	10/25/13	Routine review. References and rationale updated. Added NCCN guideline covered indications to inclusionary section.
7/1/15	4/24/15	5/8/15	Routine maintenance. No change in policy status. References and rationale updated.
7/1/16	4/19/16	4/19/16	Routine maintenance
7/1/17	4/18/17	4/18/17	Routine maintenance
7/1/18	4/17/18	4/17/18	Routine policy maintenance. No change in status.
7/1/19	4/16/19		Routine policy maintenance, updated NCCN guidelines section, and the clinical trials section. No change in policy status.
7/1/20	4/14/20		Routine policy maintenance, no change in policy status.
7/1/21	4/20/21		Routine policy maintenance, updated NCCN guidelines section, and the clinical trials section. No change in policy status. Added references 2, 13, 20-23 and 40-41. Outdated references removed.

7/1/22	4/19/22		Routine policy maintenance, updated NCCN guidelines section, and the clinical trials section. No change in policy status.
7/1/23	4/18/23		Routine policy maintenance, updated NCCN guidelines section, and the clinical trials section. Vendor: eviCore. (ky)

Next Review Date: 2nd Qtr. 2024

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: INTRAOPERATIVE RADIOTHERAPY

I. Coverage Determination:

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

II. Administrative Guidelines:

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