8.01.08	Intraoperative Radiotherapy		
Original Policy Date:	October 5, 2012	**Effective Date:**	April 1, 2021
Section:	8.0 Therapy	**Page:**	Page 1 of 29

Policy Statement

Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation:

I. Rectal cancer with positive or close margins with T4 lesions
II. Recurrent rectal cancer

Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications, including but not limited to breast cancer.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not address the use of other types of hypofractionation or other approaches such as Accelerated Irradiation, Brachytherapy Boost, etc.

The following codes may be used for this application:

- **77261**: Therapeutic radiology treatment planning; simple
- **77262**: Therapeutic radiology treatment planning; intermediate
- **77263**: Therapeutic radiology treatment planning; complex
- **77280**: Therapeutic radiology simulation-aided field setting; simple
- **77285**: Therapeutic radiology simulation-aided field setting; intermediate
- **77290**: Therapeutic radiology simulation-aided field setting; complex
- **77295**: 3-dimensional radiotherapy plan, including dose-volume histograms
- **77316**: Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)
- **77317**: Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)
- **77318**: Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
- **77370**: Special medical radiation physics consultation
- **77470**: Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)

Coding

There are specific CPT codes for intraoperative radiotherapy:

- **77424**: Intraoperative radiation treatment delivery, x-ray, single treatment session
- **77425**: Intraoperative radiation treatment delivery, electrons, single treatment session
- **77469**: Intraoperative radiation treatment management

Description	Code	Maximum per course of treatment	Notes
Treatment Planning	77261, 77262 or 77263	1	.
Treatment simulations	77280, 77285, 77290	1	
Radiotherapy plan	77295	1	Only one plan is allowed per course of treatment
Special radiation physics consult	77370	0	May allow x 1; documentation of

Description	Code	Maximum per course of treatment	Notes
			medical necessity required
Special physician consult	77470	0	May allow x 1; documentation of medical necessity required
Supervision, handling, loading of radiation source	77790	0	May not be billed with 77770, 77771, 77772 or 77778
Intraoperative radiation treatment management	77469	1	
Intraoperative radiation treatment delivery, x-ray, single treatment session	77424	1	May not be billed with 77425
Intraoperative radiation treatment delivery, electrons, single treatment session	77425	1	May not be billed with 77424

Description

Intraoperative radiotherapy (IORT) is delivered directly to exposed tissues during surgery and may allow higher radiation doses by excluding nearby radiation dose-sensitive 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.

Related Policies

- Radiation Oncology

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity 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. 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 radiotherapy or IORT treatments. In 1998, the Mobetron® mobile electron beam accelerator, designed for use during surgery, was cleared for marketing by the FDA through the 510(k)

process. 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.

Rationale

Background

Intraoperative radiotherapy (IORT) increases the intensity of radiation delivered directly 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.

Literature Review

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and 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

Clinical Context and Therapy Purpose

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.

Patients

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

Classification of surgical resection margins are 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

Classification	Definition
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 is 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 for 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
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.

Rectal Cancer
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

Study	Countries	Sites	Dates	Participants	Interventions	
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

Health outcome results for RCTs are summarized in Table 3. 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 4 and 5) 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

Two systematic reviews were identified that evaluated IORT for either primary rectal cancer, locally recurrent rectal cancer, or advanced or recurrent colorectal 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. A comparison of the studies

included in the systematic reviews are included in Table A-1. 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

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	Not reported (23 studies)		Not reported (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 (0.85)	42% (0.161)	68% (0.007)
Range of N	19-167	37-167	19-167
Range of effect sizes	0.13-0.36	0.32-1.54	0.04-1.88

[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

Wiig et al (2014) results suggested ORT provided no OS benefit for primary completely resected rectal cancers, 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. Mirnezami et al (2013) also reported outcomes for complications following IORT.[4] With IORT, no increase was observed in total (odds ratio [OR]=1.13; 95% confidence interval [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). Both 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 of these studies. Adjunctive use of IORT could permit an increase in radiation dose without increasing complications. For individuals with locally advanced rectal cancer who received IORT in addition to standard therapy, the evidence includes 2 RCTs and 1 meta-analysis, which all failed to show any benefit with addition of IORT in terms of local control or survival. For individuals with locally recurrent rectal disease, evidence is more limited. One systematic review evaluating locally advanced and recurrent rectal cancers together, has shown a significant benefit with addition of IORT on local control, disease-free survival and OS. More data are needed to determine the effect of adjunctive IORT for locally advanced rectal tumors with greater certainty.

Breast Cancer
Review of Evidence

Intraoperative Brachytherapy
Randomized Controlled Trials
One RCT, reported by Vaidya et al (2010, 2014) compared intraoperative radiotherapy (IORT) with WBI in 2232 women.[96,97,] Radiotherapy was delivered to the tumor bed using the Intrabeam device, which provides a point source of 50 kV energy x-rays at the center of a spherical applicator, for 20 to 45 minutes. It was specifically developed for IORT. The Risk-adapted **Targeted Intraoperative Radiotherapy (TARGIT-A) trial** was a noninferiority study at 28 centers in 9 countries and a sample size of 3451. (In 2010, the trial was extended for 2 more years to allow accrual in subprotocols.) An intention-to-treat approach was used. Patients were not blinded to treatment choice. As anticipated, 14% of those in the IORT arm received external-beam radiotherapy (EBRT) as well, because of unfavorable pathologic features determined after surgery (e.g., lobular carcinoma). The predefined noninferiority margin was an absolute difference of 2.5% between groups for pathologically confirmed, ipsilateral local recurrence. The most recent report (2013) provided 5-year results, defined as results for patients with 5 years of follow-up or "if they were seen the year before database lock."[97,] Median follow-up for all patients was 2 years and 5 months (interquartile range, 12-52 months), and 1222 (35%) patients had a median follow-up of 5 years. Estimated 5-year risks for ipsilateral local recurrence were 3.3% (95% CI, 2.1% to 5.1%) in the TARGIT group and 1.3% (95% CI, 0.7% to 2.5%; p=0.042) in the WBI group. Mortality was similar between the 2 groups (2.6% with TARGIT vs 1.9% with WBI; p=0.56). However, there were significantly fewer non-breast cancer deaths in the TARGIT group (1.4%; 95% CI, 0.8% to 2.5%) than in the WBI group (3.5%; 95% CI, 2.3% to 5.2%; p<0.001), with fewer deaths from cardiovascular causes and other cancers in the TARGIT group. In the group that received IORT plus WBI, the mortality rate was higher at 8% (95% CI, 3.7% to 17.5%), but the percentage of women with local recurrences (0.9%; 95% CI, 0.1% to 6.1%) was similar for those who only received IORT. Noninferiority was established for the whole intraoperative cohort and for those who received IORT alone but not for patients who underwent both types of radiotherapy. There was no significant difference between the IORT and WBI groups in predefined six-month wound-related complications. However, grade 3 or 4 radiotherapy-related skin complications were more common in the WBI group (13/1730 vs 4/1731; p=0.029). Five- and 10-year follow-ups for the entire TARGIT-A cohort have yet to be accrued.

Another form of IORT, called electron intraoperative radiotherapy (ELIOT), uses electrons.[98,]The ELIOT trial, reported by Veronesi et al (2013), compared IORT plus ELIOT with WBI.[99,] With a sample size of 1305 patients and median follow-up of 5.8 years (interquartile range, 4.1-7.7 years), 35 (4.4%) patients in the intraoperative group and 4 (0.4%) patients in the WBI group developed ipsilateral breast tumor recurrences (hazard ratio, 9.3; 95% CI, 3.3 to 26.3; p<0.001). There was no statistically significant difference in five-year OS. For women with data on adverse skin events (IORT=464, WBI=412), there were significantly fewer events among women who received IORT

(p<0.001). This was an equivalence trial with a prespecified limit of 7.5% for local recurrence in the IORT group only. Therefore, although the criterion for equivalence was satisfied, the ipsilateral breast recurrence rate was significantly higher in the IORT group. A subsequent review of ELIOT trial data by Silverstein et al (2014) noted that, of 69 women who had 4 or more positive lymph nodes, those randomized to WBI (n=38) received concurrent axillary radiation; for those randomized to ELIOT (n=31), axillary irradiation was delayed 6 to 12 weeks.[95,] These reviewers also characterized ELIOT data as premature and noted that long-term results are needed to assess net health benefit.

Section Summary: Intraoperative Brachytherapy
RCTs have not demonstrated that outcomes after intraoperative brachytherapy are noninferior to WBI. Five-year results from the **TARGIT-A RCT** showed increased ipsilateral local recurrence with APBI compared with WBI. In another RCT that used a related but different technology (ELIOT), the recurrence rate with IORT was statistically greater than that with WBI.

Gastric Cancer
Review of Evidence

Systematic Reviews
A meta-analysis by Yu et al (2015) assessed 8 RCTs that used IORT for resectable gastric cancer.[5,] The literature search from 1990 through mid-2013 identified trials that assigned patients to surgery plus IORT or to surgery without IORT. Three studies also gave EBRT to both arms. HRs to describe the impact of adjuvant IORT on OS and locoregional control were obtained 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 another 3 studies that tested the efficacy of IORT for OS in patients with stage III disease, OS significantly improved (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 HR 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, 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 the current 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
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 reviewers noted that it is not without complications.[6,]

Randomized Controlled Trials
One small randomized trial (n=35), reported by Sindelar et al (1993), compared IORT plus low-dose (35- to 40-gray) postoperative EBRT with high-dose (50- to 55-gray) 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 multicenter study by Calvo et al (2014) 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 surgery plus 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 surgery plus IORT was 89% and 46% for the surgery-only patients (p=0.03). Survival did not differ as both groups had an actutimes 5-year OS rate 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 would suggest that IORT might improve local control and OS but adverse events might 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

The literature on IORT for gynecologic cancers consists primarily of case series.

In a phase 2 trial, Giorda et al (2011) examined the use of radical surgery with IORT after chemo-therapy in extracervical, locally advanced cancer patients.[11] 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. 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 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.[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.

Section Summary: Gynecologic Cancer
The literature on IORT for gynecologic cancers consists of a nonrandomized trial and case series. The contribution of adjuvant IORT cannot be determined from these studies. OS rates in patients with locally advanced or recurrent disease are low and reported complications can be severe.

Head and Neck Cancers
Review of Evidence
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 231 patients with advanced cervical metastasis.[14] 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.[15] 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 treated with IORT at another center were reported by Perry et al (2010).[16] At a 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 (29%) patients developing distant failure. One- and 2-year OS rates were 73% and 55%, respectively, with a median time to OS of 24 months.

Chen et al (2008) reported on a retrospective study of 99 patients with locally recurrent salivary gland carcinomas treated surgically with or without IORT.[17] 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 treated with IORT after surgical resection was also reported by Chen et al (2007).[18] There is a potential for overlap of patients with the Chen et al (2008) study 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.

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 the 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.[19] 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)[19]	1990-2019	15	Patients with resectable pancreatic cancer (not metastatic or locally advanced) undergoing surgery	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)[19]			
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% (p=0.00)		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

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.[19] 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)[20]	China	247 patients with nonmetastatic locally advanced pancreatic cancer	median, 10.1 months
Cai (2013)[21]	United States	194 patients with unresectable locally advanced pancreatic cancer	median, 11.6 months
Harrison (2020)[22]	United States	158 patients with borderline resectable/locally advanced pancreatic cancer (132 patients receiving FOLIRINOX were evaluated for survival analysis	not reported

FOLIRINOX: folinic acid, fluorouracil, irinotecan, oxaliplatin

Table 12. Summary of Case Series Results - Unresectable Disease

Study	Treatment	Overall Survival	Progression-Free Survival
Chen (2016)[20]	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)[21]	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)[22]	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.

DMFS: distant metastasis-free survival; EBRT: external beam radiotherapy; IORT: intraoperative radiotherapy; LPFS: local progression-free survival

Section Summary: Pancreatic Cancer
The evidence on the use of IORT for pancreatic cancer includes large case series and a systematic review of non-randomized 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. RCTs are needed to determine the effect of adjunctive IORT for resectable, locally advanced and metastatic pancreatic cancer with greater certainty.

Renal Cell Carcinoma
Review of Evidence
The evidence on IORT for 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, and DFS rates were 37%, 41%, and 39%, respectively. For locally recurrent disease, the 5-year OS, disease-specific survival, and DFS rates were 55%, 60%, and 52%, and reported to be favorable to patients who had resection without IORT.

Calvo et al (2013) reported on 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 on 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 rates at 5 years were 9%, 27%, and 64%, respectively.

Section Summary: Renal Cell Carcinoma
The evidence on the use of 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.

Glioblastoma
Review of Evidence
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, and 21 had glioblastoma. Median survival time was 24.7 months in the anaplastic astrocytoma group and 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 statistically significant. In the glioblastoma group, median survival was 13.3 months for IORT-treated patients and 14.6 months for matched controls. Data on 1-, 2-, and 5-year survival rates also did not differ significantly 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 3 countries (Germany, Peru, and China).[27] 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. Radionecrosis 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
Review of Evidence
Rich et al (2011) reported on 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 a single institution between 2000 and 2009 after gross total resection of the 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 a 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

Review of Evidence

Roeder et al (2010) reviewed outcomes of 30 patients (31 lesions) with aggressive fibromatosis who were treated with IORT after surgery.[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 a 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 reported, resulting in actutimes 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 were 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 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 randomized controlled trials (RCTs), nonrandomized comparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival (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. 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. One systematic review evaluating locally advanced and recurrent rectal cancers together, has shown a significant benefit with addition of IORT on local control, disease-free survival and OS. Additional data are needed to determine the effect of adjunctive IORT for locally advanced rectal tumors with greater certainty. National Comprehensive Cancer Network guidelines suggest use of IORT in patients with T4 or recurrent cancers as an additional boost. Outside of those parameters, the evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have gastric cancer who receive adjunctive IORT, the evidence includes RCTs and a systematic review of RCTs. Relevant outcomes are OS, 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 OS) when used with EBRT. When IORT was administered without adjuvant EBRT in patients with stage III disease, OS improved. Thus, IORT might be considered an alternative to EBRT in patients undergoing surgery for stage III gastric cancer. Randomized studies comparing the 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 OS in this patient population (gastric cancer patients) when used 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 adjunctive IORT, the evidence includes a systematic review, a small RCT, and several nonrandomized comparative studies. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Overall, the study quality is low. The limited data suggest that IORT might improve local control and OS but adverse events might 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 adjunctive IORT, the evidence includes a nonrandomized trial and case series. Relevant outcomes are OS, 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. The evidence is insufficient to determine the effects 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 OS, 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 the 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 OS, disease-specific survival, change in disease status, and treatment-related morbidity. 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, where comparative evidence is limited to case series. More data are needed to determine the effect of adjunctive IORT for resectable, locally advanced and metastatic pancreatic cancer with greater certainty. The evidence is insufficient 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 OS, 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 OS, disease-specific survival, change in disease status, and treatment-related morbidity. Compared with other therapies, it is unclear whether IORT improves OS. 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 modality. 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 from Blue Cross Blue Shield Association, input was received from 1 physician specialty society and 2 academic medical centers (6 reviewers) in 2009. Input was quite variable, with some supporting use of intraoperative radiotherapy for multiple indications and others considering it investigational. The strongest support was for rectal cancer.

Practice Guidelines and Position Statements

The American Brachytherapy Society

In 2019, the American Brachytherapy Society consensus statement on IORT provides recommendations for patient selection for IORT.[30] Table 13 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

Table 14 lists the National Comprehensive Cancer Network guidelines on the use of intraoperative radiotherapy for the treatment of various cancers relevant to this evidence review.

Table 14. Recommendations for the Use of IORT

Cancer Site	Version	Recommendation	COR
Cervical	v.1.2020[31]	IORT "is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such	3

Cancer Site	Version	Recommendation	COR
		as bowel or other viscera) can be manually displaced from the region at risk."	
Colon	v.3.2020[32]	IORT "if available, should be considered for patients with T4 or recurrent cancers as an additional boost."	2A
Gastric	v.2.2020[33]	I IORT is not addressed	NA
Head/neck	v.1.2020[34]	"In certain rare circumstances, reirradiation with IORT or brachytherapy may be considered in high-volume centers with expertise in these techniques."	2A
Ovarian	v.1.2020[35]	IORT is not addressed	NA
Pancreatic	v.1.2020[36]	"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."	NA
Rectal	v.3.2020[37]	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
Renal	v.2.2020[38]	IORT is not addressed	NA
Soft tissue sarcoma	v.1.2020[39]	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.1.2020[40]	"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 (category 3 for 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; EBRT: external beam radiation therapy; Gy: gray; IORT: intraoperative radiotherapy; NA: not applicable; RT: radiotherapy.

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

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, 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 15.

Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02685605	A Multicenter Randomized Phase III Trial on INTraoperative RAdiotherapy in Newly Diagnosed GliOblastoma Multiforme (INTRAGO II)	314	Mar 2023

NCT: national clinical trial.

Appendix 1

Table A1. Comparison of Studies Included in the Systematic Reviews for Rectal Cancer.

	Wiig (2014)[a,3]	Mirnezami (2013)[4]
Primary (locally advanced) rectal cancer		
Bosset (2006)[41]	○	
Diaz-Gonzales (2006)[42]	○	○
Dubois (2011)[1]	○	○
Ferenschild (2006)[43]	○	○
Gerard (2006)[44]	○	
Harris (2002)[45]	○	
Huber (1996)[46]	○	○
Krempien (2006)[47]		○
Kusters (2010)[48]	○	○
Kusters (2009)[49]	○	
Larsen (2008)[50]	○	
Lim (2012)[51]	○	
Mannaerts (2000)[52]		○
Masaki (2008)[53]		○
Mathis (2012)[54]	○	
Nakfoor (1998)[55]	○	○
Nuyttens (2004)[56]		○
Pacelli (2004)[57]	○	
Palmer (2007)[58]	○	
Park (2011)[59]	○	
Ratto (2003)[60]	○	○
Roeder (2007)[61]	○	○
Sadahiro (2004)[62]	○	○
Sanfilippo (2001)[63]	○	
Sauer (2004)[64]	○	
Valentini (2009)[65]	○	○
Willet (1991)[66]		○
Locally recurrent rectal cancer		
Abuchiabe (1993)[67]	○	
Bedrosian (2006)[68]	○	
Dresen (2008)[69]		○
Eble (1998)[70]		○
Haddock (2011)[71]	○	○
Hansen (2009)[72]	○	
Hashiguchi (1999)[73]	○	
Hashiguchi (2003)[74]		○
Kanemitsu (2010)[75]	○	
Kusters (2009)[49]	○	
Lee (2011)[76]	○	
Lindel (2001)[77]	○	○
Mannaerts (2001)[78]	○	
Martinez-Monge (1999)[79]	○	○
Mohiuddin (1993)[80]	○	
Nuyttens (2004)[56]		○
Palmer (2007)[58]	○	
Park (2009)[81]	○	
Pezner (2002)[82]		○
Rahbari (2011)[83]	○	
Roeder (2007)[61]	○	
Salo (1999)[84]	○	
Shoup (2002)[85]	○	○
Suzuki (1995)[86]	○	○
Valentini (1999)[87]		○
Vermas (2008)[88]		○
Wells (2007)[89]	○	
Wiig (2002)[90]	○	○

	Wiig (2014)[a][3]	Mirnezami (2013)[4]
Wiig (2008)[3]	○	
Willett (1991)[66]		○

[a]Authors indicated that only the most recent paper from a single center was evaluated, but the article did not indicate which studies were excluded due to this criteria. Thus, there are more studies listed than included in the final evaluation.

References

1. Dubois JB, Bussieres E, Richaud P, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol. Mar 2011; 98(3): 298-303. PMID 21339010
2. Masaki T, Matsuoka H, Kishiki T, et al. Intraoperative radiotherapy for resectable advanced lower rectal cancer-final results of a randomized controlled trial (UMIN000021353). Langenbecks Arch Surg. May 2020; 405(3): 247-254. PMID 32347365
3. Wiig JN, Giercksky KE, Tveit KM. Intraoperative radiotherapy for locally advanced or locally recurrent rectal cancer: Does it work at all?. Acta Oncol. Jul 2014; 53(7): 865-76. PMID 24678823
4. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol. Mar 2013; 22(1): 22-35. PMID 23270946
5. Yu WW, Guo YM, Zhang Q, et al. Benefits from adjuvant intraoperative radiotherapy treatment for gastric cancer: A meta-analysis. Mol Clin Oncol. Jan 2015; 3(1): 185-189. PMID 25469292
6. Skandarajah AR, Lynch AC, Mackay JR, et al. The role of intraoperative radiotherapy in solid tumors. Ann Surg Oncol. Mar 2009; 16(3): 735-44. PMID 19142683
7. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Arch Surg. Apr 1993; 128(4): 402-10. PMID 8457152
8. Lehnert T, Schwarzbach M, Willeke F, et al. Intraoperative radiotherapy for primary and locally recurrent soft tissue sarcoma: morbidity and long-term prognosis. Eur J Surg Oncol. Nov 2000; 26 Suppl A: S21-4. PMID 11130875
9. Calvo FA, Sole CV, Polo A, et al. Limb-sparing management with surgical resection, external-beam and intraoperative electron-beam radiation therapy boost for patients with primary soft tissue sarcoma of the extremity: a multicentric pooled analysis of long-term outcomes. Strahlenther Onkol. Oct 2014; 190(10): 891-8. PMID 24715241
10. Stucky CC, Wasif N, Ashman JB, et al. Excellent local control with preoperative radiation therapy, surgical resection, and intra-operative electron radiation therapy for retroperitoneal sarcoma. J Surg Oncol. Jun 2014; 109(8): 798-803. PMID 24862926
11. Giorda G, Boz G, Gadducci A, et al. Multimodality approach in extra cervical locally advanced cervical cancer: chemoradiation, surgery and intra-operative radiation therapy. A phase II trial. Eur J Surg Oncol. May 2011; 37(5): 442-7. PMID 21492777
12. Martinez-Monge R, Jurado M, Aristu JJ, et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol. Sep 2001; 82(3): 538-43. PMID 11520152
13. Gao Y, Liu Z, Chen X, et al. Intraoperative radiotherapy electron boost in advanced and recurrent epithelial ovarian carcinoma: a retrospective study. BMC Cancer. Oct 11 2011; 11: 439. PMID 21989202
14. Zeidan YH, Yeh A, Weed D, et al. Intraoperative radiation therapy for advanced cervical metastasis: a single institution experience. Radiat Oncol. Jun 15 2011; 6: 72. PMID 21676211
15. Zeidan YH, Shiue K, Weed D, et al. Intraoperative radiotherapy for parotid cancer: a single-institution experience. Int J Radiat Oncol Biol Phys. Apr 01 2012; 82(5): 1831-6. PMID 21514074

16. Perry DJ, Chan K, Wolden S, et al. High-dose-rate intraoperative radiation therapy for recurrent head-and-neck cancer. Int J Radiat Oncol Biol Phys. Mar 15 2010; 76(4): 1140-6. PMID 19560882
17. Chen AM, Garcia J, Bucci MK, et al. Recurrent salivary gland carcinomas treated by surgery with or without intraoperative radiation therapy. Head Neck. Jan 2008; 30(1): 2-9. PMID 17828788
18. Chen AM, Bucci MK, Singer MI, et al. Intraoperative radiation therapy for recurrent head-and-neck cancer: the UCSF experience. Int J Radiat Oncol Biol Phys. Jan 01 2007; 67(1): 122-9. PMID 17084543
19. Jin L, Shi N, Ruan S, et al. The role of intraoperative radiation therapy in resectable pancreatic cancer: a systematic review and meta-analysis. Radiat Oncol. Apr 09 2020; 15(1): 76. PMID 32272945
20. Chen Y, Che X, Zhang J, et al. Long-term results of intraoperative electron beam radiation therapy for nonmetastatic locally advanced pancreatic cancer: Retrospective cohort study, 7-year experience with 247 patients at the National Cancer Center in China. Medicine (Baltimore). Sep 2016; 95(38): e4861. PMID 27661028
21. Cai S, Hong TS, Goldberg SI, et al. Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer. Dec 01 2013; 119(23): 4196-204. PMID 24006012
22. Harrison JM, Wo JY, Ferrone CR, et al. Intraoperative Radiation Therapy (IORT) for Borderline Resectable and Locally Advanced Pancreatic Ductal Adenocarcinoma (BR/LA PDAC) in the Era of Modern Neoadjuvant Treatment: Short-Term and Long-Term Outcomes. Ann Surg Oncol. May 2020; 27(5): 1400-1406. PMID 31758284
23. Paly JJ, Hallemeier CL, Biggs PJ, et al. Outcomes in a multi-institutional cohort of patients treated with intraoperative radiation therapy for advanced or recurrent renal cell carcinoma. Int J Radiat Oncol Biol Phys. Mar 01 2014; 88(3): 618-23. PMID 24411190
24. Calvo FA, Sole CV, Martinez-Monge R, et al. Intraoperative EBRT and resection for renal cell carcinoma : twenty-year outcomes. Strahlenther Onkol. Feb 2013; 189(2): 129-36. PMID 23223810
25. Hallemeier CL, Choo R, Davis BJ, et al. Long-term outcomes after maximal surgical resection and intraoperative electron radiotherapy for locoregionally recurrent or locoregionally advanced primary renal cell carcinoma. Int J Radiat Oncol Biol Phys. Apr 01 2012; 82(5): 1938-43. PMID 21514065
26. Nemoto K, Ogawa Y, Matsushita H, et al. Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas. BMC Cancer. 2002; 2: 1. PMID 11818027
27. Sarria GR, Sperk E, Han X, et al. Intraoperative radiotherapy for glioblastoma: an international pooled analysis. Radiother Oncol. Jan 2020; 142: 162-167. PMID 31629553
28. Rich BS, McEvoy MP, LaQuaglia MP, et al. Local control, survival, and operative morbidity and mortality after re-resection, and intraoperative radiation therapy for recurrent or persistent primary high-risk neuroblastoma. J Pediatr Surg. Jan 2011; 46(1): 97-102. PMID 21238648
29. Roeder F, Timke C, Oertel S, et al. Intraoperative electron radiotherapy for the management of aggressive fibromatosis. Int J Radiat Oncol Biol Phys. Mar 15 2010; 76(4): 1154-60. PMID 19647952
30. Tom MC, Joshi N, Vicini F, et al. The American Brachytherapy Society consensus statement on intraoperative radiation therapy. Brachytherapy. May 2019; 18(3): 242-257. PMID 31084904
31. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Cervical cancer. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed May 22, 2020.
32. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Colon cancer. Version 3.2020. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed May 20, 2020.

33. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Gastric cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf. Accessed May 22, 2020.
34. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Head and neck cancers. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed May 20, 2020.
35. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Ovarian cancer. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed May 20, 2020.
36. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Pancreatic adenocarcinoma. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf. Accessed May 21, 2020.
37. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Rectal cancer. Version 3.2020 http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed May 20, 2020.
38. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Kidney cancer. Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf. Accessed May 20, 2020.
39. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Soft tissue sarcoma. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed May 20, 2020.
40. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Uterine neoplasms. Version 1.2020. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed May 20, 2020.
41. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. Sep 14 2006; 355(11): 1114-23. PMID 16971718
42. Diaz-Gonzalez JA, Calvo FA, Cortes J, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. Int J Radiat Oncol Biol Phys. Mar 15 2006; 64(4): 1122-8. PMID 16406393
43. Ferenschild FT, Vermaas M, Nuyttens JJ, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. Dis Colon Rectum. Sep 2006; 49(9): 1257-65. PMID 16912909
44. Gerard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. Oct 01 2006; 24(28): 4620-5. PMID 17008704
45. Harris GJ, Senagore AJ, Lavery IC, et al. Factors affecting survival after palliative resection of colorectal carcinoma. Colorectal Dis. Jan 2002; 4(1): 31-35. PMID 12780652
46. Huber FT, Stepan R, Zimmermann F, et al. Locally advanced rectal cancer: resection and intraoperative radiotherapy using the flab method combined with preoperative or postoperative radiochemotherapy. Dis Colon Rectum. Jul 1996; 39(7): 774-9. PMID 8674370
47. Krempien R, Roeder F, Oertel S, et al. Long-term results of intraoperative presacral electron boost radiotherapy (IOERT) in combination with total mesorectal excision (TME) and chemoradiation in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. Nov 15 2006; 66(4): 1143-51. PMID 16979835
48. Kusters M, Valentini V, Calvo FA, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant

chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol. Jun 2010; 21(6): 1279-84. PMID 19889621
49. Kusters M, Holman FA, Martijn H, et al. Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment. Radiother Oncol. Aug 2009; 92(2): 221-5. PMID 19339070
50. Larsen SG, Wiig JN, Dueland S, et al. Prognostic factors after preoperative irradiation and surgery for locally advanced rectal cancer. Eur J Surg Oncol. Apr 2008; 34(4): 410-7. PMID 17614249
51. Lim SB, Yu CS, Hong YS, et al. Long-term outcomes in patients with locally advanced rectal cancer treated with preoperative chemoradiation followed by curative surgical resection. J Surg Oncol. Nov 2012; 106(6): 659-66. PMID 22674581
52. Mannaerts GH, Martijn H, Crommelin MA, et al. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer. Int J Radiat Oncol Biol Phys. May 01 2000; 47(2): 425-33. PMID 10802370
53. Masaki T, Takayama M, Matsuoka H, et al. Intraoperative radiotherapy for oncological and function-preserving surgery in patients with advanced lower rectal cancer. Langenbecks Arch Surg. Mar 2008; 393(2): 173-80. PMID 18172677
54. Mathis KL, Larson DW, Dozois EJ, et al. Outcomes following surgery without radiotherapy for rectal cancer. Br J Surg. Jan 2012; 99(1): 137-43. PMID 22052336
55. Nakfoor BM, Willett CG, Shellito PC, et al. The impact of 5-fluorouracil and intraoperative electron beam radiation therapy on the outcome of patients with locally advanced primary rectal and rectosigmoid cancer. Ann Surg. Aug 1998; 228(2): 194-200. PMID 9712564
56. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. Int J Radiat Oncol Biol Phys. Jan 01 2004; 58(1): 106-12. PMID 14697427
57. Pacelli F, Di Giorgio A, Papa V, et al. Preoperative radiotherapy combined with intraoperative radiotherapy improve results of total mesorectal excision in patients with T3 rectal cancer. Dis Colon Rectum. Feb 2004; 47(2): 170-9. PMID 15043286
58. Palmer G, Martling A, Cedermark B, et al. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. Feb 2007; 14(2): 447-54. PMID 17139457
59. Park JH, Yoon SM, Yu CS, et al. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. Cancer. Aug 15 2011; 117(16): 3703-12. PMID 21328328
60. Ratto C, Valentini V, Morganti AG, et al. Combined-modality therapy in locally advanced primary rectal cancer. Dis Colon Rectum. Jan 2003; 46(1): 59-67. PMID 12544523
61. Roeder F, Treiber M, Oertel S, et al. Patterns of failure and local control after intraoperative electron boost radiotherapy to the presacral space in combination with total mesorectal excision in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys. Apr 01 2007; 67(5): 1381-8. PMID 17275208
62. Sadahiro S, Suzuki T, Ishikawa K, et al. Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer. Eur J Surg Oncol. Sep 2004; 30(7): 750-8. PMID 15296989
63. Sanfilippo NJ, Crane CH, Skibber J, et al. T4 rectal cancer treated with preoperative chemoradiation to the posterior pelvis followed by multivisceral resection: patterns of failure and limitations of treatment. Int J Radiat Oncol Biol Phys. Sep 01 2001; 51(1): 176-83. PMID 11516868
64. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. Oct 21 2004; 351(17): 1731-40. PMID 15496622
65. Valentini V, Coco C, Rizzo G, et al. Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. Surgery. May 2009; 145(5): 486-94. PMID 19375606

66. Willett CG, Shellito PC, Tepper JE, et al. Intraoperative electron beam radiation therapy for recurrent locally advanced rectal or rectosigmoid carcinoma. Cancer. Mar 15 1991; 67(6): 1504-8. PMID 2001537
67. Abuchaibe O, Calvo FA, Azinovic I, et al. Intraoperative radiotherapy in locally advanced recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. Aug 01 1993; 26(5): 859-67. PMID 8344855
68. Bedrosian I, Giacco G, Pederson L, et al. Outcome after curative resection for locally recurrent rectal cancer. Dis Colon Rectum. Feb 2006; 49(2): 175-82. PMID 16392024
69. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. Jul 2008; 15(7): 1937-47. PMID 18389321
70. Eble MJ, Lehnert T, Treiber M, et al. Moderate dose intraoperative and external beam radiotherapy for locally recurrent rectal carcinoma. Radiother Oncol. Nov 1998; 49(2): 169-74. PMID 10052883
71. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. Jan 01 2011; 79(1): 143-50. PMID 20395067
72. Hansen MH, Balteskard L, Dorum LM, et al. Locally recurrent rectal cancer in Norway. Br J Surg. Oct 2009; 96(10): 1176-82. PMID 19787766
73. Hashiguchi Y, Sekine T, Sakamoto H, et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. Dis Colon Rectum. Jul 1999; 42(7): 886-93; discussion 893-5. PMID 10411435
74. Hashiguchi Y, Sekine T, Kato S, et al. Indicators for surgical resection and intraoperative radiation therapy for pelvic recurrence of colorectal cancer. Dis Colon Rectum. Jan 2003; 46(1): 31-9. PMID 12544519
75. Kanemitsu Y, Hirai T, Komori K, et al. Prediction of residual disease or distant metastasis after resection of locally recurrent rectal cancer. Dis Colon Rectum. May 2010; 53(5): 779-89. PMID 20389212
76. Lee JH, Kim DY, Kim SY, et al. Clinical outcomes of chemoradiotherapy for locally recurrent rectal cancer. Radiat Oncol. May 20 2011; 6: 51. PMID 21595980
77. Lindel K, Willett CG, Shellito PC, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. Radiother Oncol. Jan 2001; 58(1): 83-7. PMID 11165686
78. Mannaerts GH, Rutten HJ, Martijn H, et al. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. Dis Colon Rectum. Dec 2001; 44(12): 1749-58. PMID 11742155
79. Martinez-Monge R, Nag S, Martin EW. Three different intraoperative radiation modalities (electron beam, high-dose-rate brachytherapy, and iodine-125 brachytherapy) in the adjuvant treatment of patients with recurrent colorectal adenocarcinoma. Cancer. Jul 15 1999; 86(2): 236-47. PMID 10421259
80. Mohiuddin M, Lingareddy V, Rakinic J, et al. Reirradiation for rectal cancer and surgical resection after ultra high doses. Int J Radiat Oncol Biol Phys. Dec 01 1993; 27(5): 1159-63. PMID 8262842
81. Park JK, Kim YW, Hur H, et al. Prognostic factors affecting oncologic outcomes in patients with locally recurrent rectal cancer: impact of patterns of pelvic recurrence on curative resection. Langenbecks Arch Surg. Jan 2009; 394(1): 71-7. PMID 18663464
82. Pezner RD, Chu DZ, Ellenhorn JD. Intraoperative radiation therapy for patients with recurrent rectal and sigmoid colon cancer in previously irradiated fields. Radiother Oncol. Jul 2002; 64(1): 47-52. PMID 12208575
83. Rahbari NN, Ulrich AB, Bruckner T, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure?. Ann Surg. Mar 2011; 253(3): 522-33. PMID 21209587

84. Salo JC, Paty PB, Guillem J, et al. Surgical salvage of recurrent rectal carcinoma after curative resection: a 10-year experience. Ann Surg Oncol. Mar 1999; 6(2): 171-7. PMID 10082043
85. Shoup M, Guillem JG, Alektiar KM, et al. Predictors of survival in recurrent rectal cancer after resection and intraoperative radiotherapy. Dis Colon Rectum. May 2002; 45(5): 585-92. PMID 12004205
86. Suzuki K, Gunderson LL, Devine RM, et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer. Feb 15 1995; 75(4): 939-52. PMID 7531113
87. Valentini V, Morganti AG, De Franco A, et al. Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma: prognostic factors and long term outcome. Cancer. Dec 15 1999; 86(12): 2612-24. PMID 10594856
88. Vermaas M, Nuyttens JJ, Ferenschild FT, et al. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. Radiother Oncol. Jun 2008; 87(3): 357-60. PMID 18353474
89. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. Ann Surg Oncol. Feb 2007; 14(2): 390-5. PMID 17063304
90. Wiig JN, Larsen SG, Dueland S, et al. Preoperative irradiation and surgery for local recurrence of rectal and rectosigmoid cancer. Prognostic factors with regard to survival and further local recurrence. Colorectal Dis. Jan 2008; 10(1): 48-57. PMID 18028472
91. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 8.01.08 (July 2020).
92. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Accelerated radiotherapy after breast-conserving surgery for early stage breast cancer. TEC Assessments. 2013;Volume 27:Tab 6.
93. Kaidar-Person O, Yarnold J, Offersen BV, et al. Is current evidence about intraoperative partial breast irradiation sufficient for broad implementation in clinical practice? Eur J Surg Oncol. Jul 2014;40(7):791-793. PMID 24721228
94. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 2-TARGIT. Ann Surg Oncol. Nov 2014;21(12):3793-3799. PMID 25138079
95. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: a critical analysis of the ELIOT and TARGIT trials. Part 1-ELIOT. Ann Surg Oncol. Nov 2014;21(12):3787-3792. PMID 25160734
96. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. Lancet. Jul 10 2010;376(9735):91-102. PMID 20570343
97. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet. Feb 15 2014;383(9917):603-613. PMID 24224997
98. Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. Breast Cancer Res Treat. Nov 2010;124(1):141-151. PMID 20711810
99. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol. Dec 2013;14(13):1269-1277. PMID 24225155

Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Cancer description, location and tumor staging
  - Previous treatment(s) and response(s)
  - Radiology report(s)

  - Pathology report(s)
- Intraoperative radiation treatment report(s)/note(s)
  - Operative report(s) including: Description and location of cancer

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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)
	77014	Computed tomography guidance for placement of radiation therapy fields
	77261	Therapeutic radiology treatment planning; simple
	77262	Therapeutic radiology treatment planning; intermediate
	77263	Therapeutic radiology treatment planning; complex
	77280	Therapeutic radiology simulation-aided field setting; simple
	77285	Therapeutic radiology simulation-aided field setting; intermediate
	77290	Therapeutic radiology simulation-aided field setting; complex
	77295	3-dimensional radiotherapy plan, including dose-volume histograms
	77316	Brachytherapy isodose plan; simple (calculation[s] made from 1 to 4 sources, or remote afterloading brachytherapy, 1 channel), includes basic dosimetry calculation(s)
	77317	Brachytherapy isodose plan; intermediate (calculation[s] made from 5 to 10 sources, or remote afterloading brachytherapy, 2-12 channels), includes basic dosimetry calculation(s)
	77318	Brachytherapy isodose plan; complex (calculation[s] made from over 10 sources, or remote afterloading brachytherapy, over 12 channels), includes basic dosimetry calculation(s)
	77370	Special medical radiation physics consultation
	77387	Guidance for localization of target volume for delivery of radiation treatment, includes intrafraction tracking, when performed
	77417	Therapeutic radiology port image(s
	77424	Intraoperative radiation treatment delivery, x-ray, single treatment session
	77425	Intraoperative radiation treatment delivery, electrons, single treatment session
	77469	Intraoperative radiation treatment management

Type	Code	Description
	77470	Special treatment procedure (e.g., total body irradiation, hemibody radiation, per oral or endocavitary irradiation)
	77790	Supervision, handling, loading of radiation source
HCPCS	C9726	Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure
	G6001	Ultrasonic guidance for placement of radiation therapy fields
	G6002	Stereoscopic x-ray guidance for localization of target volume for the delivery of radiation therapy
	G6017	Intra-fraction localization and tracking of target or patient motion during delivery of radiation therapy (e.g., 3D positional tracking, gating, 3D surface tracking), each fraction of treatment

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/05/2012	New Policy Adoption BCBSA Medically necessary criteria revised
07/31/2015	Coding update
01/01/2016	Policy title change from Intraoperative Radiation Therapy (IORT) with External Beam Policy revision with position change effective 3/01/2016
03/01/2016	Policy revision with position change
02/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
09/01/2018	Policy revision without position change
09/01/2019	Policy revision without position change
09/01/2020	Annual review. No change to policy statement. Literature review updated. Coding update.
11/20/2020	No change to policy statement. Policy guidelines updated.
04/01/2021	Administrative update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment,

procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE **Red font: Verbiage removed**	**AFTER** **Blue font: Verbiage Changes/Additions**
Intraoperative Radiotherapy 8.01.08 **Policy Statement:** Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation (see Policy Guidelines section related to breast cancer): I. Rectal cancer with positive or close margins with T4 lesions II. Recurrent rectal cancer Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications, including but not limited to breast cancer.	**Intraoperative Radiotherapy 8.01.08** **Policy Statement:** Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation: I. Rectal cancer with positive or close margins with T4 lesions II. Recurrent rectal cancer Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications, including but not limited to breast cancer.