| 8.01.08 | Intraoperative Radiotherapy | | |
|---|---|---|---|
| **Original Policy Date:** | October 5, 2012 | **Effective Date:** | September 1, 2024 |
| **Section:** | 8.0 Therapy | **Page:** | Page 1 of 38 |

## Policy Statement

I. Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation:
   A. Rectal cancer with positive or close margins with T4 lesions
   B. Recurrent rectal cancer

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

See Policy Guidelines for allowable codes/number of units.

**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.

### Coding

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)

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

### Allowable Codes and Frequencies for Intraoperative Radiotherapy

| Description | Code | Maximum per course of treatment | Notes |
|---|---|---|---|
| Clinical Treatment Planning | 77261, 77262 or 77263 | 1 | |

| Description | Code | Maximum per course of treatment | Notes |
|---|---|---|---|
| Simulations | 77280, 77285, 77290 | 1 | May not be billed with 77301 |
| Verification Simulation | 77280 | 1 | May not be billed with 77301 |
| Respiratory Motion Management | 77293 | 0 for Brachytherapy<br><br>1 for EBRT | For breast, lung, and upper abdominal or thoracic cancer areas |
| 3D CRT plan | 77295 | 1 | May not be billed with 77301 |
| Basic Dosimetry | 77300 | 4 + 1 boost; up to a max of 10 with documentation | 0 if billed with 77306, 77307, 77321, 0394T or 0395T |
| Special Radiation Physics Consult | 77370 | 0 | May allow x 1; documentation of medical necessity required |
| 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 |
| Intraoperative Radiation Treatment Management | 77469 | 1 | |
| Special MD Consultation (Special Tx Procedure) | 77470 | 0 | May allow x 1; documentation of medical necessity required |
| Supervision, Handling, Loading of Radiation Source | 77790 | 0 | May not be billed with 77761, 77762, 77763, 77770, 77771, 77772 or 77778 |
| High Dose Rate Electronic Brachytherapy, per fraction | 0395T | 1 | Investigational for the treatment of skin lesions. The following services are bundled with 0395T and should not be reported separately: 77300, 77261–77263, 77306–77307, 77316–77318, 77332–77334, 77336, 77427, 77431, 77432, 77435, 77469, 77470, 77499, 77761–77763, 77767–77768, 77770–77772, 77778, 77789 |

See the Codes table for details.

## 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.

In the United States, certain racial/ethnic groups continue to be at an increased risk of developing or dying from particular cancers. Notably, Black men have the highest rate of new cancer diagnoses and Black men and women experience the highest rate of cancer-related death. Additionally, American Indians/Alaska Natives are disproportionally affected by kidney cancer and also have higher death rates from this cancer when compared to other racial/ethnic groups.

### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of a 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 a technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 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. Randomized controlled trials 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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

## Intraoperative Radiotherapy for Rectal Cancer

### Clinical Context and Therapy Purpose

The purpose of intraoperative radiotherapy (IORT) is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with rectal cancer.

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

#### *Populations*

The relevant population of interest is individuals with rectal cancer undergoing tumor resection. Classification of surgical resection margins is listed in Table 1.

**Table 1. General Surgical Resection Margin Classification**

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

#### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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, external-beam radiotherapy (EBRT) , or chemotherapy.

#### *Comparators*

The following therapies and practices are currently being used for individuals with rectal cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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).

**Table 2. Outcomes of Interest**

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

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

## Systematic Reviews

### Primary, Advanced, and Recurrent Cancer

Four systematic reviews were identified that evaluated IORT for either primary locally advanced rectal cancer or locally recurrent colorectal or rectal cancer. Wiig et al (2014) reviewed 18 studies on primary rectal cancer (including 1 RCT, 5 comparative trials, 7 trials without IORT) and 18 studies on locally recurrent rectal cancer (including 5 studies without IORT).[1,] 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).[2,] Indications for IORT were locally advanced disease in 1792 patients and locally recurrent disease in 1211 patients with colorectal cancer. Liu et al (2021) included 3 RCTs and 12 observational studies (N=1460) that evaluated IORT in both locally advanced and locally recurrent rectal cancer.[3,] Fahy et al (2021) included 7 studies of patients with locally advanced and locally recurrent rectal cancer (N=833).[4,]

A comparison of the studies included in the systematic reviews is included in Table A-1. Characteristics and results of these reviews are summarized in Tables 3 and 4.

**Table 3. Systematic Review Characteristics**

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| **Wiig (2014)[1,]** | 1990 to 2013 | Primary cancer: 15; Recurrent cancer: 18 | Patients with locally advanced rectal cancer (either primary or recurrent) | Primary cancer: 4272; Recurrent cancer: 1174 | RCTs (if available), comparative studies, non-comparative | Up to 5 years |

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| | | | | (ranges not reported) | studies, non-IORT studies | |
| **Mirnezami (2013)[2,]** | 1991 to 2011 | 29 | Patients with locally advanced colorectal cancer (either primary or recurrent) | 3003 (11 to 607) | RCTs (if available), prospective and retrospective observational studies | Up to 5 years |
| **Liu (2021)[3,]** | 1991 to 2020 | 15 | Patients with rectal cancer | 1460 (ranges not reported) | RCTs (if available), prospective and retrospective observational studies | Up to 5 years |
| **Fahy (2021)[4,]** | 2000 to 2020 | 7 | Patients with locally advanced and locally recurrent rectal cancer | 833 (ranges not reported) | RCTs (if available), prospective and retrospective observational studies | Not reported |

IORT: intraoperative radiotherapy; RCT: randomized controlled trial.

**Table 4. Systematic Review Results[a]**

| Study | OS | DFS | Local relapse |
|---|---|---|---|
| **Wiig (2014)[1,]** | *OS* | | *5-year local control* |
| ***Primary cancer*** | | | |
| **Total N** | NR (20 studies) | | NR (18 studies) |
| **IORT, mean (range)** | 60 (28 to 76) | | 13 (2 to 35) |
| **non-IORT, mean (range)** | 72 (52 to 85) | | 8 (5 to 9) |
| ***Locally recurrent cancer*** | | | |
| **Total N** | NR (23 studies) | | NR (12 studies) |
| **IORT, mean (range)** | 25 (40 to 46) | | 49 (28 to 74) |
| **non-IORT, mean (range)** | 19 (0 to 46) | | 81 (70 to 92) |
| **Mirnezami (2013)[2,]** | *5-year OS, IORT vs no IORT* | *5-year DFS, IORT vs no IORT* | *5-year local control, IORT vs no IORT* |
| **Total N** | 370 | 288 | 482 |
| **Pooled effect (95% CI)** | HR=0.33 (0.2 to 0.54) | HR=0.51 (0.31 to 0.85) | OR=0.22 (0.05 to 0.86) |
| **$I^2$ (p)** | 0 (.001) | 42% (.009) | 68% (.03) |
| **Range of N** | 19 to 167 | 37 to 167 | 19 to 167 |
| **Range of effect sizes** | 0.13 to 0.36 | 0.32 to 1.54 | 0.04 to 1.88 |
| **Liu (2021)[3,]** | *5-year OS, IORT vs no IORT* | *5-year DFS, IORT vs no IORT* | *5-year local control, IORT vs no IORT* |
| **Total N** | NR (9 studies) | NR (6 studies) | NR (14 studies) |
| **Pooled effect (95% CI)** | HR=0.80 (0.60 to 1.06) | HR=0.94 (0.73 to 1.22) | HR=3.07 (1.66 to 5.66) |
| **$I^2$ (p)** | 0 (.740) | 0 (.503) | 70.9 (.000) |
| **Range of effect sizes** | 0.31 to 2.31 | 0.81 to 1.93 | 0.74 to 17.53 |
| **Fahy (2021)[4,]** | | | *Locoregional recurrence, IORT vs no IORT* |
| **Total N** | | | 833 |
| **Pooled effect (95% CI)** | | | OR=0.55 (0.27 to 1.14) |
| **$I^2$ (p)** | | | 55 (.11) |
| **Range of N** | | | 19 to 99 |
| **Range of effect sizes** | | | 0.10 to 1.45 |

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

Mirnezami et al (2013) demonstrated significant survival and local control benefits with IORT in a mixed population of patients with locally advanced colorectal cancer (either primary or recurrent).[2,] More recently, however, Liu et al (2021) did not demonstrate a 5-year OS or disease-free survival (DFS) benefit with IORT in patients with rectal cancer.[3,] IORT did, however, demonstrate benefit in 5-year local control. Fahy et al (2021) also did not find a benefit with IORT for locoregional recurrence in a mixed population of patients with locally advanced and locally recurrent rectal cancer.[4,] Wiig et al (2014) results suggested IORT provided no OS benefit for primary completely resected rectal cancers, with a possible reduction in local recurrence in cases of incomplete tumor resection.[1,] There was no evidence that IORT affected OS or local recurrence when used to treat locally recurrent rectal cancer.

Some analyses also reported outcomes for complications following IORT. Mirnezami et al (2013) did not demonstrate an increased risk in total (odds ratio [OR]=1.13; 95% confidence interval [CI], 0.77 to 1.65), urologic (OR=1.35; 95% CI, 0.84 to 2.82), or anastomotic (OR=0.94; 95% CI, 0.42 to 2.1) complications with IORT; however, increased wound complications were noted after IORT (OR=1.86; 95% CI, 1.03 to 3.38; p =.049).[2,] Liu et al (2021) did not find an increase in the risk of complications with IORT, including fistulae (OR=0.79; 95% CI, 0.33 to 1.89), wound complication (OR=1.21; 95% CI, 0.62 to 2.36), anastomotic leak (OR=1.09; 95% CI, 0.59 to 2.02), or neurogenic bladder dysfunction (OR=0.69; 95% CI, 0.31 to 1.55).[3,] Likewise, Fahy et al (2021) did not find an increased risk of complications with IORT, including wound infections (OR=1.13; 95% CI, 0.50 to 2.54), pelvic abscess (OR=1.01; 95% CI, 0.54 to 1.87), or anastomotic leak (OR=1.60; 95% CI, 0.51 to 2.81).[4,] All reviews are limited by the risk of selection bias for IORT in nonrandomized studies, the variability in stages evaluated and IORT dosing, and high heterogeneity present for certain outcomes.

### Randomized Controlled Trials

#### Locally Advanced Cancer

The available RCTs evaluating IORT for locally advanced rectal cancer are summarized in Table 5. No RCTs were identified that evaluated IORT for the management of locally recurrent rectal cancers.

**Table 5. Summary of Key RCT Characteristics**

| Study | Countries | Sites | Dates | Participants | Interventions | |
|---|---|---|---|---|---|---|
| | | | | | Active | Comparator |
| **Dubois (2011)[5,]** | 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)[6,]** | Japan | 1 | Not reported. Terminated in 2017 | 76 patients with locally advanced rectal cancer (M0) | IORT plus resection of the rectum with total mesorectal excision (n=38) | Resection of the rectum with total mesorectal excision alone (n=38) |

IORT: intraoperative radiotherapy; RCT: randomzied controlled trial.

Health outcome results for RCTs are summarized in Table 6. Additionally, in the Dubois et al (2011) trial, postoperative complications were observed in 29.6% of patients in the IORT group and 19.1% of patients in the control group (p=.15).[5,] 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.[6,] 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 for less radical resection for advanced lower rectal cancer.

Table 6. Summary of Key RCT Results

| Study | OS | DFS | Local relapse |
|---|---|---|---|
| **Dubois (2011)[5,]** | *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 =.2578) | Not reported (p =.6037) | Not reported (p =.6018) |
| **Masaki (2020)[6,]** | *5-year, 10-year, and 15-year OS* | *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 =.603 | OR=2.554 (1.041 to 6.269); p =.041 | OR=1.350 (0.302 to 6.034); p =.694 |

CI: confidence interval; DFS: disease-free survival; IORT: intraoperative radiotherapy; OR: odds ratio; OS: overall survival; RCT: randomzied controlled trial.

The purpose of the limitations tables (see Tables 7 and 8) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence and provides conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations

| Study | Population[a] | Intervention[b] | Comparator[c] | Outcomes[d] | Follow-Up[e] |
|---|---|---|---|---|---|
| **Dubois (2011)[5,]** | | | | | |
| **Masaki (2020)[6,]** | 2. 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. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest (e.g., proposed as an adjunct but not tested as such); 5: Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively; 5. Other.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. Incomplete reporting of harms; 4. Not establish and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported; 7. Other.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms; 3. Other.

Table 8. Study Design and Conduct Limitations

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| **Dubois (2011)[5,]** | | 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)[6,]** | | 1. Patients and surgeons were not blinded to treatment assignment, | | | 3. Trial was terminated early likely reducing power | |

| Study | Allocation[a] | Blinding[b] | Selective Reporting[c] | Data Completeness[d] | Power[e] | Statistical[f] |
|---|---|---|---|---|---|---|
| | | though impractical for this study | | | | |

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; 5. Other.
[b] Blinding key: 1. Participants or study staff not blinded; 2. Outcome assessors not blinded; 3. Outcome assessed by treating physician; 4. Other.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication; 4. Other.
[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); 7. Other.
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference; 4. Other.
[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; 5. Other.

### Section Summary: Rectal Cancer

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

## Intraoperative Radiotherapy for Gastric Cancer

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with gastric cancer.

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

#### *Populations*

The relevant population of interest is individuals with gastric cancer undergoing tumor resection. Classification of surgical resection margins is listed in Table 9.

**Table 9. General Surgical Resection Margin Classification**

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

*Interventions*
The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with gastric cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 10).

Table 10. Outcomes of Interest

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

## Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### Review of Evidence

### Systematic Review

A meta-analysis by Yu et al (2015) assessed 8 RCTs that used IORT for resectable gastric cancer.[7,] 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. Hazard ratios (HR) 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 =.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 =.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 <.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.

## Intraoperative Radiotherapy for Soft Tissue Sarcomas

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with soft tissue sarcoma.

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

#### *Populations*

The relevant population of interest is individuals with soft tissue sarcoma undergoing tumor resection.

Classification of surgical resection margins is listed in Table 11.

**Table 11. General Surgical Resection Margin Classification**

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

#### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with soft tissue sarcoma: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 12).

**Table 12. Outcomes of Interest**

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

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Systematic Review

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.[8,]

### Randomized Controlled Trial

One 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.[9,] 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.[10,] 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.[11,] 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.[12,] Median follow-up was 45 months. The 5-year local control rate for patients receiving surgery plus IORT was 89% versus 46% for the surgery-only patients (p =.03). Survival did not differ as both groups had a 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.

## Intraoperative Radiotherapy for Gynecologic Cancers

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with gynecologic cancer.

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

#### *Populations*

The relevant population of interest is individuals with gynecologic cancer undergoing tumor resection.

Classification of surgical resection margins is listed in Table 13.

**Table 13. General Surgical Resection Margin Classification**

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

#### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with gynecologic cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 14).

**Table 14. Outcomes of Interest**

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

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Observational Studies

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.[13,] Between 2000 and 2007, 42 locally advanced cervical cancer patients were treated at a single center in Italy. 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).[14,] 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.[15,] All 45 patients in this series underwent optimal cytoreductive surgery at a single center in China. 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%) patients.

Chen et al (2022) evaluated the feasibility and safety of IORT as an adjuvant therapy for recurrent gynecological cancer in a case series of 5 women at a single center in Taiwan (cervical cancer, n=2; endometrial cancer, n=2; uterine leiomyosarcoma, n=1).[16,] Three women died during follow-up, 2 of which had local recurrence or progression of disease. The median recurrence-free survival was 13.8 months (95% CI, 1.6 to not estimable) and the median OS was 16.4 months (95% CI, 4.7 months to not estimable).

### 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.

## Intraoperative Radiotherapy for Head and Neck Cancers

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with head and neck cancer.

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

#### *Populations*

The relevant population of interest is individuals with head and neck cancer undergoing tumor resection.

Classification of surgical resection margins is listed in Table 15.

**Table 15. General Surgical Resection Margin Classification**

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

#### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with head and neck cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 16).

**Table 16. Outcomes of Interest**

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

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Observational Studies

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.[17,] OS rates at 1, 3, and 5 years were 58%, 34%, and 26%, respectively. Recurrence-free survival rates at 1, 3, and 5 years were 66%, 55%, and 49%, respectively. A second publication reviewed the use of IORT in 96 patients with primary or recurrent cancer of the parotid gland.[18,] Recurrence-free survival rates at 1, 3, and 5

years were 82%, 69%, and 65%, respectively. Rates of OS 1, 3, and 5 years 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).[19] At a median follow-up of 23 months (range, 6 to 54 months), 8 patients were alive and without evidence of disease. The 1- and 2-year estimates for in-field local progression-free survival (PFS) rates were 66% and 56%, respectively, with 13 (34%) in-field recurrences. Distant metastases-free survival rates were 81% and 62%, respectively, with 10 (29%) patients developing distant failure. Rates of OS at 1 and 2 years 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.[20] All patients had previously been treated with surgery, and 82% had received postoperative EBRT. The 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).[21] 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 to 122 months). Estimates of in-field control after surgery and IORT at 1, 2, and 3 years 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.

## Intraoperative Radiotherapy for Pancreatic Cancer

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with pancreatic cancer.

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

#### *Populations*

The relevant population of interest is individuals with pancreatic cancer undergoing tumor resection.

Classification of surgical resection margins is listed in Table 17.

**Table 17. General Surgical Resection Margin Classification**

| Classification | Definition |
|---|---|
| R0 | Negative margins; no cancer cells detected in resected tissue |

| Classification | Definition |
|---|---|
| R1 | Microscopic positive margin; cancer cells detected by microscope in resected tissue |
| R2 | Macroscopic positive margin; tumor cells detected without microscope in resected tissue |

*Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with pancreatic cancer: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 18).

Table 18. Outcomes of Interest

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

## Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Systematic Review

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.[22,] 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 19 and 20.

**Table 19. Systematic Review Characteristics**

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| **Jin (2020)[22,]** | 1990-2019 | 15 | Patients with resectable pancreatic cancer (not metastatic or locally advanced) undergoing surgery with or without IORT | 834 (11 to 203) | Non-randomized controlled trials | Not reported |

IORT: intraoperative radiotherapy

**Table 20. Systematic Review Results**

| Study | OS | Local relapse |
|---|---|---|
| **Jin (2020)[22,]** | | |
| **Total N** | Not reported (13 studies) | Not reported (8 studies) |
| **Pooled effect (95% CI)** | MSR=1.20 (1.06 to 1.37) | RR=0.70 (0.51 to 0.97) |
| **$I^2$ (p)** | 65.3% (.005) | 36.8%(.03) |
| **Range of N** | Not reported | Not reported |
| **Range of effect sizes** | 0.57 to 3.54 | 0.14 to 0.96 |

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

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.[22,] The incidence of postoperative complications between the groups were not significantly different from each other (relative risk=0.95; 95% CI, 0.73 to 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 21 and 22 below.

**Table 21. Summary of Case Series Characteristics - Unresectable Disease**

| Study | Country | Participants | Follow-Up, months |
|---|---|---|---|
| **Chen (2016)[23,]** | China | 247 patients with nonmetastatic locally advanced pancreatic cancer; the male to female ratio was 1.4 | median, 10.1 |
| **Cai (2013)[24,]** | United States | 194 patients (men, 53%; racial/ethnic composition not specified) with unresectable locally advanced pancreatic cancer | median, 11.6 |
| **Harrison (2020)[25,]** | United States | 158 patients (men, 56%; racial/ethnic composition not specified) with borderline resectable/locally advanced pancreatic cancer (132 patients receiving | NR |

| Study | Country | Participants | Follow-Up, months |
|---|---|---|---|
| | | FOLIRINOX were evaluated for survival analysis | |
| **Sekigami (2021)[26,]** | United States | 201 patients (men, 51%; White race, >90%) with borderline resectable/locally advanced pancreatic cancer who received total neoadjuvant therapy (FOLIRINOX with chemoradiation) and underwent resection between 2011 and 2019. Of the 201 patients evaluated, 88 received IORT following resection; of these, 69 underwent R0 and 19 underwent R1 resection. | NR |
| **Cho (2022)[27,]** | Korea | 41 patients (men, 56%) with resectable pancreatic cancer | median, 9 |

FOLIRINOX: folinic acid, fluorouracil, irinotecan, oxaliplatin; IORT: intraoperative radiotherapy; NR: not reported.

**Table 22. Summary of Case Series Results - Unresectable Disease**

| Study | Treatment | OS | PFS |
|---|---|---|---|
| **Chen (2016)[23,]** | 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 OS 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)[24,]** | 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 OS 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)[25,]** | IORT as part of multimodal approach including neoadjuvant treatment prior to attempted resection with IORT | Overall 1-, 2-, 4-year survival rates were 99%, 79%, and 47% for those receiving any form of resection plus IORT. Overall 1-, 2-, 4-year survival rates were 98%, 49%, 13% for those receiving IORT only. | At time of study follow-up, 51% and 67% of patients had disease progression in the resection plus IORT and IORT only groups, respectively. |
| **Sekigami (2021)[26,]** | IORT following total neoadjuvant therapy (FOLIRINOX with chemoradiation) and resection | Among patients who received IORT, there was no difference in OS between patients who underwent R0 vs R1 resection: R0: 48 months, IQR 25 to not reached vs R1: 37 months, IQR 30 to 47; p =.307. | Among patients who received IORT, there was no difference in DFS between patients who underwent R0 vs R1 resection: R0: 29 months, IQR 14 to 47 vs R1: 20 months, IQR 15 to 28; p =.114. |
| **Cho (2022)[27,]** | IORT as part of multimodal approach including adjuvant gemcitabine-based chemotherapy | 1 year OS: 94.1% | The 1-year local control and distant control rates were 76.4% and 55.7%, respectively. |

DFS: disease-free survival; DMFS: distant metastasis-free survival; EBRT: external beam radiotherapy; FOLIRINOX: folinic acid, fluorouracil, irinotecan, oxaliplatin; IORT: intraoperative radiotherapy; IQR: interquartile range; LPFS: local progression-free survival; NR: not reported; OS: overall survival; PFS: 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 large case series. Lastly, 1 case series found IORT combined with surgical resection to be associated with increased survival compared to IORT alone in patients with positive or close margins, and another case series found that application of IORT following resection yields similar survival outcomes regardless of R0 (generally better prognosis) or R1 (generally worse prognosis) resection. RCTs in more diverse populations are needed to determine the effect of adjunctive IORT for resectable, locally advanced and metastatic pancreatic cancer with greater certainty.

### Intraoperative Radiotherapy for Renal Cell Carcinoma

#### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with renal cell carcinoma (RCC).

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

##### *Populations*

The relevant population of interest is individuals with RCC undergoing tumor resection.

Classification of surgical resection margins is listed in Table 23.

**Table 23. General Surgical Resection Margin Classification**

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

##### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with RCC: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 24).

**Table 24. Outcomes of Interest**

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

## Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence
### Observational Studies
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 to 2010.[28,] 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.[29,]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 to 26). 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.[30,] 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.

### Intraoperative Radiotherapy for Glioblastoma or Neuroblastoma or Fibromatosis

### Clinical Context and Therapy Purpose

The purpose of IORT is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with glioblastoma or neuroblastoma or fibromatosis.

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

#### *Populations*

The relevant population of interest is individuals with glioblastoma or neuroblastoma or fibromatosis undergoing tumor resection.

Classification of surgical resection margins is listed in Table 25.

**Table 25. General Surgical Resection Margin Classification**

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

#### *Interventions*

The therapy being considered is IORT. IORT delivers a fractional dose of radiation directly to the tumor/tumor bed while the area 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 electron beam IORT.

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 individuals with glioblastoma or neuroblastoma or fibromatosis: surgery alone, multimodal therapies (EBRT plus surgery or chemotherapy).

Most individuals 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 OS, disease-specific survival, and harms from treatment, specifically radiation toxicity (Table 26).

Table 26. Outcomes of Interest

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

### Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

### Review of Evidence
### Glioblastoma

#### Observational Studies

Nemoto et al (2002) reported on treatment with IORT for 32 patients with previously untreated malignant gliomas over a 10-year period.[31,] 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).[32,] All patients received standard of care therapy and adjuvant therapies that 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 PFS rates were 46.2%, 29.4%, and 5.9%, respectively (median PFS, 11.4 months). The median local PFS 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

#### Observational Study

Rich et al (2011) reported on their experience using IORT after re-resection in patients with locally recurrent or persistent high-risk neuroblastomas.[33,] 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), 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

#### Observational Study

Roeder et al (2010) reviewed the outcomes of 30 patients (31 lesions) with aggressive fibromatosis who were treated with IORT after surgery.[34,] Treatment with IORT was undertaken to avoid mutilating surgical procedures when complete surgical removal seemed to be unlikely or impossible. The median age was 31 years (range, 13 to 59). Resection status was a close margin in 6 lesions, microscopically positive in 13, and macroscopically positive in 12. The median tumor size was 9 cm. Twenty-five (83%) patients received additional EBRT. After a median follow-up of 32 months (range, 3 to 139), 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 toward 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.

### Supplemental Information

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

### Clinical Input 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.

#### 2009 Input

In response to requests, input was received from 1 physician specialty society and 2 academic medical centers (6 reviewers) while this policy was under review in 2009. 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

Guidelines or position statements will be considered for inclusion in ‘Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to

guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

### American Brachytherapy Society

In 2019, the American Brachytherapy Society consensus statement on intraoperative radiotherapy (IORT) provides recommendations for patient selection for IORT.[35,] Table 27 summarizes their recommendations based on cancer type. The consensus statement did not rate evidence or strength of recommendations.

**Table 27. 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 28 lists the National Comprehensive Cancer Network guidelines on the use of IORT for the treatment of various cancers relevant to this evidence review.

**Table 28. Recommendations for the Use of IORT**

| Cancer Site | Version | Recommendation | COR |
|---|---|---|---|
| **Central Nervous System** | v.1.2024 [36,] | IORT is not addressed for the management of glioblastoma. | NA |
| **Cervical** | v.3.2024 [37,] | IORT "is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk." | 3 |
| **Colon** | v.3.2024 [38,] | IORT "if available, may be considered for patients with T4 or recurrent cancers as an additional boost." | 2A |
| **Gastric** | v.2.2024 [39,] | IORT is not addressed. | NA |
| **Head/neck** | v.4.2024 [40,] | "In certain rare circumstances, reirradiation with IORT or brachytherapy may be considered in high-volume centers with expertise in these techniques." | 2A |

| Cancer Site | Version | Recommendation | COR |
|---|---|---|---|
| **Ovarian** | v.2.2024 [41] | IORT is not addressed. | NA |
| **Pancreatic** | v.2.2024 [42] | "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.2.2024 [43] | 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.4.2024 [44] | IORT is not addressed. | NA |
| **Soft tissue sarcoma** | v.1.2024 [45] | For patients with resectable disease, consider boost with IORT for known or suspected positive margins at the time of surgery "10 to 12.5 Gy for microscopic positive disease" and "15 Gy for gross disease". | 2A |
| **Uterine** | v.2.2024 [46] | Treatment of recurrent or metastatic disease:<br><br>"For patients previously treated with brachytherapy only at the recurrence site, surgery with (or without) IORT is recommended."<br><br>"For patients previously treated with EBRT at the recurrence site, recommended therapy for isolated relapse includes surgery with (or without) IORT plus or minus systemic therapy."<br><br>For local recurrence in the vaginal/pelvis that is negative for distant metastatic disease:<br><br>"Surgical and RT treatment pathways are provided. The surgical pathway for treating local recurrence in patients without prior RT exposure includes the option for IORT."<br><br>"Patients with local recurrence who have had prior RT exposure can be treated with 1) surgery with the option of IORT with (or without) systemic therapy; 2) systemic therapy; or 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 29.

**Table 29. Summary of Key Trials**

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|
| *Ongoing* | | | |
| **NCT05181488** | A Prospective, Phase II Study Evaluating the Efficacy of Intraoperative Radiotherapy After Neoadjuvant Chemotherapy in Patients With Resectable Pancreatic Cancer | 80 | Apr 2026 |
| **NCT02685605** | A Multicenter Randomized Phase III Trial on INTraoperative RAdiotherapy in Newly Diagnosed GliOblastoma Multiforme (INTRAGO II) | 314 | Mar 2024 |
| **NCT04847284** | Intraoperative Radiotherapy in Patients With Brain Metastases | 25 | Mar 2024 |

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

# Appendix 1

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

| | Wiig (2014)[a1,] | Mirnezami (2013)[2,] | Liu (2021)[3,] | Fahy (2021)[4,] |
|---|---|---|---|---|
| *Primary (locally advanced) rectal cancer* | | | | |
| Alberda (2014)[47,] | | | O | O |
| Bosset (2006)[48,] | O | | | |
| Diaz-Gonzales (2006)[49,] | O | O | | |
| Dubois (2011)[5,] | O | O | O | O |
| Ferenschild (2006)[50,] | O | O | O | |
| Gerard (2006)[51,] | O | | | |
| Harris (2002)[52,] | O | | | |
| Huber (1996)[53,] | O | O | O | |
| Krempien (2006)[54,] | | O | | |
| Kusters (2010)[55,] | O | O | | |
| Kusters (2009)[56,] | O | | | |
| Klink (2014)[57,] | | | O | |
| Larsen (2008)[58,] | O | | | |
| Lim (2012)[59,] | O | | | |
| Mannaerts (2000)[60,] | | O | | |
| Masaki (2008)[61,] | | O | O | O |
| Masaki (2020)[6,] | | | O | |
| Mathis (2012)[62,] | O | | | |
| Nakfoor (1998)[63,] | O | O | | |
| Nuyttens (2004)[64,] | | O | | |
| Pacelli (2004)[65,] | O | | | |
| Palmer (2007)[66,] | O | | | |
| Park (2011)[67,] | O | | | |
| Ratto (2003)[68,] | O | O | O | |
| Roeder (2007)[69,] | O | O | | |
| Sadahiro (2004)[70,] | O | O | O | O |
| Sanfilippo (2001)[71,] | O | | | |
| Sauer (2004)[72,] | O | | | |
| Valentini (2009)[73,] | O | O | O | O |
| Willet (1991)[74,] | | O | O | |
| Zhang (2014)[75,] | | | O | |
| Zhang (2015)[76,] | | | O | O |
| *Locally recurrent rectal cancer* | | | | |
| Abuchiabe (1993)[77,] | O | | | |
| Bedrosian (2006)[78,] | O | | | |
| Dresen (2008)[79,] | | O | | |
| Eble (1998)[80,] | | O | | |
| Haddock (2011)[81,] | O | O | | |
| Hansen (2009)[82,] | O | | | |
| Hashiguchi (1999)[83,] | O | | | |
| Hashiguchi (2003)[84,] | | O | | |
| Kanemitsu (2010)[85,] | O | | | |
| Kusters (2009)[56,] | O | | | |
| Lee (2011)[86,] | O | | | |
| Lindel (2001)[87,] | O | O | | |
| Mannaerts (2001)[88,] | O | | | |
| Martinez-Monge (1999)[89,] | O | O | | |
| Mohiuddin (1993)[90,] | O | | | |
| Nuyttens (2004)[64,] | | O | | |
| Palmer (2007)[66,] | O | | | |
| Park (2009)[91,] | O | | | |
| Pezner (2002)[92,] | | O | | |

| | Wiig (2014)[a1,] | Mirnezami (2013)[2,] | Liu (2021)[3,] | Fahy (2021)[4,] |
|---|---|---|---|---|
| Rahbari (2011)[93,] | O | | | |
| Roeder (2007)[69,] | O | | | |
| Salo (1999)[94,] | O | | | |
| Shoup (2002)[95,] | O | O | | |
| Suzuki (1995)[96,] | O | O | O | |
| Valentini (1999)[97,] | | O | | |
| Vermas (2008)[98,] | | O | | |
| Wells (2007)[99,] | O | | | |
| Wiig (2000)[100,] | | | | O |
| Wiig (2002)[101,] | O | O | O | |
| Wiig (2008)[1,] | O | | | |
| Willett (1991)[74,] | | O | | |

[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.

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## Documentation for Clinical Review

**Please provide the following documentation:**

- (click here >>>) Radiation Oncology – Prior Authorization fax form
- (click here >>>) Radiation Oncology – Post Service fax form

## 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® | 0735T | Preparation of tumor cavity, with placement of a radiation therapy applicator for intraoperative radiation therapy (IORT) concurrent with primary craniotomy (List separately in addition to code for primary procedure) |
| | 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 |

| Type | Code | Description |
|---|---|---|
| | 77425 | Intraoperative radiation treatment delivery, electrons, single treatment session |
| | 77469 | Intraoperative radiation treatment management |
| | 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<br>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. |
| 08/01/2021 | Annual review. Policy statement and guidelines updated. |
| 09/01/2021 | Administrative update. No change to policy statement.<br>Literature review updated. |
| 12/01/2021 | Administrative update. No change to policy statement. Policy guidelines updated. |
| 08/01/2022 | Annual review. No change to policy statement. Coding update. |
| 09/01/2022 | Administrative update. No change to policy statement. Literature review updated. |
| 09/01/2023 | Annual review. No change to policy statement. Literature review updated. |
| 09/01/2024 | Annual review. No change to policy statement. Literature review updated. |

## 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 and Feedback (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.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

*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 (No changes) | |
|---|---|
| **BEFORE** | **AFTER** |
| **Intraoperative Radiotherapy 8.01.08**<br><br>**Policy Statement:**<br>I. Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation:<br>A. Rectal cancer with positive or close margins with T4 lesions<br>B. Recurrent rectal cancer<br><br>II. Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications, including but not limited to breast cancer.<br><br>See Policy Guidelines for allowable codes/number of units. | **Intraoperative Radiotherapy 8.01.08**<br><br>**Policy Statement:**<br>I. Use of intraoperative radiotherapy (IORT) may be considered **medically necessary** in **either** of the following situation:<br>A. Rectal cancer with positive or close margins with T4 lesions<br>B. Recurrent rectal cancer<br><br>II. Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications, including but not limited to breast cancer.<br><br>See Policy Guidelines for allowable codes/number of units. |