# FEP Medical Policy Manual

## FEP 8.01.08 Intraoperative Radiotherapy

**Effective Policy Date: October 1, 2023**

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**Related Policies:**

None

# Intraoperative Radiotherapy

## Description

## 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.

## OBJECTIVE

The objectives of this evidence review are 2-fold: (1) to determine whether intraoperative radiotherapy (IORT) improves the net health outcome when used in conjunction with surgery and external-beam radiotherapy; and (2) to determine whether the use of IORT improves the net health outcome in individuals who cannot be treated with external-beam radiotherapy due to radiation toxicity.

# POLICY STATEMENT

Use of intraoperative radiotherapy may be considered **medically necessary** in the following situation:

- Rectal cancer with positive or close margins with T4 lesions or recurrent disease.

Use of intraoperative radiotherapy is considered **investigational** for all other oncologic applications.

# POLICY GUIDELINES

None

# BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

# FDA 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

## Summary of Evidence

For individuals who have rectal cancer who receive adjunctive intraoperative radiotherapy (IORT) , the evidence includes randomized controlled trials (RCTs) , nonrandomized comparative studies, and systematic reviews with meta-analyses of these studies. Relevant outcomes are overall survival (OS) , disease-specific survival, change in disease status, and treatment-related morbidity. Adjunctive use of IORT as part of a multimodal treatment could permit an increase in radiation dose without increasing complications. 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, disease-free survival (DFS) , and OS. More data are needed to determine the effect of adjunctive IORT in each specific population of locally advanced disease (ie, primary vs recurrent, rectal vs colorectal) with greater certainty. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have gastric cancer who receive adjunctive IORT, the evidence includes RCTs and a systematic review of RCTs. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. A meta-analysis of 8 RCTs found a benefit of IORT in locoregional control (but not OS) when used with external-beam radiotherapy (EBRT). When IORT was administered without adjuvant EBRT in

patients with stage III disease, OS improved. Thus, IORT might be considered an alternative to EBRT in patients undergoing surgery for stage III gastric cancer. Randomized studies comparing the benefits and harms of the 2 treatments are needed to determine the efficacy of IORT with greater certainty. It cannot be determined whether IORT provides any benefit for OS in this patient population (gastric cancer patients) when used with EBRT. Further study is needed. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have gynecologic cancers who receive adjunctive IORT, the evidence includes a nonrandomized trial and case series. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. The contribution of adjuvant IORT cannot be determined from the available literature. There is no evidence that IORT improves survival rates, and there may be severe complications related to the therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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

For individuals who have pancreatic cancer who receive adjunctive IORT, the evidence includes large case series, cohort studies, and systematic reviews of these studies. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. The systematic review found that in patients with resectable pancreatic cancer the addition of IORT to standard therapy was associated with improved median survival and reduced local recurrence; the evidence was limited by mostly smaller retrospective designs contributing to the review. However, the vast majority of patients present at diagnosis with more advanced disease, such as borderline resectable, locally advanced, or with distant metastases. More data are needed to determine the effect of adjunctive IORT for resectable, locally advanced, and metastatic pancreatic cancer with greater certainty. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have renal cell carcinoma (RCC) who receive adjunctive IORT, the evidence includes case series. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. No controlled trials were identified to determine whether adjunctive IORT improves health outcomes when added to multimodal therapy with surgical resection and EBRT. Grade 3 or higher toxicity after IORT has been reported in a substantial percentage of patients. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have glioblastoma or neuroblastoma or fibromatosis who receive adjunctive IORT, the evidence includes case series. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Compared with other therapies, it is unclear whether IORT improves OS. However, compared with historical controls, IORT for patients with previously untreated malignant gliomas had no survival benefit when given in conjunction with multimodal therapy. In addition, complication rates may be high. Comparative trials are needed to evaluate the safety and efficacy of this treatment modality. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

# SUPPLEMENTAL INFORMATION

## 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 1 summarizes their recommendations based on cancer type. The consensus statement did not rate evidence or strength of recommendations.

**Table 1. 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 2 lists the National Comprehensive Cancer Network guidelines on the use of IORT for the treatment of various cancers relevant to this evidence review.

**Table 2. Recommendations for the Use of IORT**

| Cancer Site | Version | Recommendation | COR |
|---|---|---|---|
| Central Nervous System | v.1.2023[36], | IORT is not addressed for the management of glioblastoma. | NA |
| Cervical | v.1.2023[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.2.2023 [38], | IORT "if available, may be considered for patients with T4 or recurrent cancers as an additional boost." | 2A |
| Gastric | v.1.2023 [39], | IORT is not addressed. | NA |
| Head/neck | v.2.2023 [40], | "In certain rare circumstances, reirradiation with IORT or brachytherapy may be considered in high-volume centers with expertise in these techniques." | 2A |
| Ovarian | v.1.2023 [41], | IORT is not addressed. | NA |
| Pancreatic | v.1.2023 [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.3.2023 [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.4.2023 [44], | IORT is not addressed. | NA |
| Soft tissue sarcoma | v.2.2023 [45], | For patients with resectable disease, consider boost with IORT for known or suspected positive margins at the time of surgery "10-12.5 Gy for microscopic positive disease" and "15 Gy for gross disease". | 2A |
| Uterine | v.2.2023[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: 1) 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 for IORT |

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.

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## POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

| Date | Action | Description |
|---|---|---|
| December 2011 | New policy | |
| December 2012 | Replace policy | Policy updated with literature search, references 2, 8, 13, 17-18 added, FDA approved device-"investigational, changed to "not medically necessary, in policy statement. |
| December 2013 | Replace policy | Policy updated with literature search through July 2013; references 5, 7, 8, 20 and 26 added, policy statements unchanged. |
| December 2014 | Replace policy | Policy updated with literature review, references 2, 9, 27 and 29 added, policy statements unchanged. |
| December 2015 | Replace policy | Policy updated with literature review through July 8, 2015; references 8 and 10 added. Policy statements unchanged. |
| March 2018 | Replace policy | Policy updated with literature review through October 25, 2017; references 1, 4, 8-9, 14 and 30-39 added/updated. Policy statements unchanged except statement regarding other applications corrected from "not medically necessary, to "investigational, based on FDA 510(k) approval. |
| September 2018 | Replace policy | Policy updated with literature review through May 7, 2018; references 30-39 updated. Policy statements unchanged. |
| September 2019 | Replace policy | Policy updated with literature review through May 6, 2019; references on NCCN updated. Policy statements unchanged. |
| September 2020 | Replace policy | Policy updated with literature review through May 19, 2020; references added. Policy statements unchanged. |
| September 2021 | Replace policy | Policy updated with literature review through May 31, 2021; references added. Policy statements unchanged. |
| September 2022 | Replace Policy | Policy updated with literature review through May 31, 2022; references added. Policy statements unchanged. |
| September 2023 | Replace policy | Policy updated with literature review through May 31, 2023; reference added. Policy statements unchanged. |