BlueCross BlueShield Federal Employee Program.

FEP 8.01.08 Intraoperative Radiotherapy

Effective Date: April 15, 2018

Related Policies:
8.01.13 Accelerated Breast Irradiation after Breast Conserving Surgery for Early Stage Breast Cancer and Breast Brachytherapy as Boost with Whole Breast Irradiation

Intraoperative Radiotherapy

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. It can be delivered by electron beams produced by linear accelerators or high-dose rate brachytherapy.

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 in the operating room, was cleared for marketing by the FDA through the 510(k) process.

This evidence review does not address the use of IORT for breast cancer (see review 8.01.13).

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.

BENEFIT APPLICATION

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

RATIONALE

Summary of Evidence

For individuals who have rectal cancer who receive adjunctive IORT, the evidence includes an RCT, nonrandomized comparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, disease-specific survival, change in disease status, and treatment-related morbidity. Adjunctive use of IORT as part of a multimodal treatment could allow an increase in radiation dose without increasing complications. However, a phase 3 RCT and meta-analysis of IORT for locally

advanced rectal cancer did not find improved outcomes with IORT in combination with EBRT and surgery. Nonrandomized comparative studies and a meta-analysis of these studies have shown some benefit in health outcomes with adjunctive IORT for recurrent rectal cancer, but these studies are limited by a high risk of selection bias, heterogeneous patient populations, and heterogeneous delivery of other treatments. Large RCTs are needed to determine the effect of IORT with greater certainty. The evidence is insufficient to determine the effects of the technology on health outcomes.

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

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

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

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

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

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

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

Table 1 lists National Comprehensive Cancer Network recommendations on the use of intraoperative radiotherapy on the treatment of various cancers.

Table 1 Recommendations for the Use of IORT

Cancer Site	Version	Recommendation	COR
Cervical	v.1.2018[30]	IORT "is particularly useful in patients with recurrent disease within a previously radiated volume. During IORT, overlying normal tissue (such as bowel or other viscera) can be manually displaced from the region at risk."	3
Colon	v.2.2017[31]	IORT "may be considered for patients with T4 or recurrent cancers as an additional boost."	2A
Gastric	v.5.2017[32]	IORT is currently not recommended	NA
Head/neck	v.2.2017[33]	IORT is not addressed	NA
Ovarian	v.3.2017[34]	IORT is not addressed	NA
Pancreatic	v.3.2017[35]	"The role of IORT for unresectable and resectable cases is controversial and should only be performed at specialized centers. It is sometimes used in cases where surgical resection may result in close or involved margins." The guidelines conclude: "Overall, there is no clear established role for IORT in patients with pancreatic cancer, and the panel believes it should only be performed at specialized centers."	NA
Rectal	v.3.2017[36]	IORT "if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers."	2A
Renal	v.1.2018[37]	IORT is not addressed	NA
Soft tissue sarcoma	v.1.2018[38]	For patients with resectable disease, surgery with or without IORT is the recommended primary treatment "10-12.5 Gy for microscopic residual disease" and "15 Gy for gross residual disease".	2A
Uterine	v.1.2018[39]	• For patients with "locoregional recurrence … [and] prior RT to site of recurrence … surgical exploration + resection ± IORT" may be considered. • For patients with "radiologically isolated vaginal/pelvic recurrence … surgical exploration + resection ± IORT ± systemic therapy" may be considered.	3

COR: category of recommendation; 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 (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY

Date	Action	Description
December 2011	New Policy	
December 2012	Update 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	Update Policy	Policy updated with literature search through July 2013; references 5, 7, 8, 20 and 26 added, policy statements unchanged.
December 2014	Update Policy	Policy updated with literature review, references 2, 9, 27 and 29 added, policy statements unchanged.
December 2015	Update Policy	Policy updated with literature review through July 8, 2015; references 8 and 10 added. Policy statements unchanged.
March 2108	Update 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 510k approval.