KAISER PERMANENTE®

Kaiser Foundation Health Plan of Washington

Clinical Review Criteria
Intraoperative Radiation Therapy (IORT)

Criteria

For Medicare Members

Source	Policy
CMS Coverage Manuals	None
National Coverage Determinations (NCD)	None
Local Coverage Determinations (LCD)	4/01/2016 Noridian retired LCD Brachytherapy: Non-Intracoronary (L34065). These services still need to meet medical necessity as outlined in the LCD and will require review. LCDs are retired due to lack of evidence of current problems, or in some cases because the material is addressed by a National Coverage Decision (NCD), a coverage provision in a CMS interpretative manual or an LCD. Most LCDs are not retired because they are incorrect. The criteria should be still referenced when making an initial decision. However, if the decision is appealed, the retired LCD cannot be specifically referenced. Maximus instead looks for “medical judgment” which could be based on our commercial criteria or literature search.
Local Coverage Article	None

For Non-Medicare Members

Intraoperative radiation therapy (IORT) may be considered medically necessary in the following situation:

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

IORT is considered investigational when used for all other oncologic applications, including but not limited to:

- Breast cancer
- Fibromatosis
- Gastric cancer
- Glioma
- Gynecologic cancers
- Head and neck cancers
- Neuroblastoma
- Pancreatic cancer
- Renal cell cancer
- Soft tissue sarcoma

Some requests may be approved on a case-by-case basis by the Medical Director.

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If requesting this service, please send the following documentation to support medical necessity:

- Last 6 months of clinical notes from requesting provider &/or specialist

The following information was used in the development of this document and is provided as background only. It is provided for historical purposes and does not necessarily reflect the most current published literature. When significant new articles are published that impact treatment option, Kaiser Permanente will review as needed. This information is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage

Background

The usual method for delivering radiation is external beam with high-energy photons. However, the external beam doses required to achieve local tumor control can exceed the radiation tolerance of some normal organs and other structures of the body.

Intra-operative radiation therapy (IORT) is being investigated as a technique to deliver a high dose of radiation to a locally advanced tumor while attempting to protect adjacent normal tissues at the time of surgery. It is delivered with applicators and cones attached to the treatment head of high-energy medical linear accelerators. After all or most of the cancer is surgically removed, a large, single-dose of high-energy radiation is aimed directly at the tumor site. Nearby healthy tissue is protected with special shields.

The goal of IORT is to enhance local tumor control. Most patients receiving IORT are concurrently treated with high-dose external beam photon irradiation. The term “intraoperative radiation therapy” may also refer to intra-operative brachytherapy, the temporary or permanent implantation of radioactive seeds. Intra-operative radiation therapy is usually a component of a multi-disciplinary treatment approach for localized cancers that cannot be completely removed or that have a high risk of recurring in nearby tissues.

Medical Technology Assessment Committee (MTAC)

Intraoperative Radiation Therapy (IORT) for Breast Cancer

BACKGROUND

Breast cancer is the most common cancer in women of all races and ethnicities (not counting skin cancer), and the second most common cause of death from cancer among white, black, Asian/Pacific Islander, and American Indian/Alaska Native women. The American Cancer Society (ACS) estimated that in 2015, 231,840 new cases of invasive breast cancer and 62,570 breast carcinoma in-situ, will be diagnosed among women in the U.S. and that 40,290 will die from breast cancer. The reported five-year relative survival rate is 98.5% for women diagnosed with localized breast cancer. This drops to 84% among women with cancer that has spread to nearby lymph nodes (regional stage) and to 24% in those with metastases in distant lymph nodes and/or other organs (CDC and ACS web pages accessed October 27, 2015). The widespread screening programs and new developments in early detection of cancer have led to an increase in the incidence of early stage breast cancer. Surgical treatment has thus shifted from radical mastectomy to personalized local treatment that preserves the breast and axillary lymph nodes, together with adjuvant therapy. Breast conserving surgery (BCS) followed by postoperative whole breast external beam radiotherapy (EBRT or WBRT) is currently considered the standard treatment for patients with early-stage breast cancer. This approach has been shown to reduce local recurrence (LR) and improve the overall survival. Traditional whole breast EBRT is administered in the postoperative setting as 45-50 Gy in daily fractions for 5 consecutive weeks. An additional external beam boost of 10-16 Gy is often delivered to the tumor bed to improve local control and reduce local recurrence. It is reported that almost one third of the patients undergoing BCS in North America do not receive post-BCS breast radiation therapy and many others choose mastectomy instead, for several reasons including the long course of treatment, comorbidities, advanced age, distance from the radiation therapy facility, inconvenience, and cost (Vaidya, 2010, Esposito 2014, Abbott 2015, Zhang 2015). Accelerated partial breast irradiation (APBI), is a radiation technique that targets partial breast tissue around the tumor cavity with fewer fractions. APBI has emerged in the last 2 decades and is increasingly being accepted as an alternative to whole breast EBRT. It is based on the observation that more than 90% of local recurrences occur at /or near the tumor bed after BCS. There are several techniques for delivering APBI, including multi-catheter interstitial brachytherapy, balloon catheter brachytherapy, 3D- conformal radiation therapy, and intraoperative radiation therapy (IORT). These techniques differ widely in regard to the degree of invasiveness, radiation delivery, operator proficiency, acceptance between radiation oncologists, and length of treatment (Njeh 2010, Vaidya 2010, Abbott 2015, Esposito 2015, Zhang 2015). IORT is an APBI approach that delivers a single dose of irradiation directly to the tumor bed at the time of surgery. Unlike other APBI techniques

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that target the index quadrant, IORT specifically targets the tumor cavity. The index quadrant is not demarcated anatomically, whereas the tumor cavity is easily located by the operating surgeon. IORT can be delivered by using low-energy X-rays, electron beam radiation therapy, brachytherapy, high-dose-rate (HDR) after loaders, and other hybrid devices (Esposito 2015). The intrabeam® device (Carl Zeiss, Oberkochen, Germany) is a device used to deliver IORT during surgery after removal of the tumor. It comprises a miniature low-energy X -ray source (50 kVp) that delivers a dose of 20 Gy at the surface of the applicator and 5-5 Gy at 1 cm deep, in 20-40 minutes treatment time. Tungsten-impregnated sheets are used to shield the wound before treatment. Access to the operating room should be controlled and the medical personnel shielded during treatment. The intraoperative electron radiation therapy (IOERT) is another method for delivering IORT that involves the application of electron radiation directly to the tumor bed at the time of surgery. Compared to the X-ray beams, the electron beams have limited penetration into the tissue and faster delivery of the required radiation dose. The IOERT systems are designed to deliver radiation in non-shielded operating theaters. Currently there are three mobile linear accelerators that can be moved easily into an operating room and deliver IOERT (Novac 7®, Liac®, and the Mobetron®). The radiation procedure is completed in 2 minutes delivering a dose of 21 Gy with the depth of 90% isodose ranging from 13-24 mm (Esposito 2015). The advantages of IORT include the reduced treatment visits by delivering a single radiotherapy fraction during surgery, immediate visualization of the operative bed before delivering the radiotherapy, minimizing the possibility of missing the target, shielding the surrounding organs, avoiding treatment delay for patients who may also need to undergo chemotherapy, and reducing healthcare costs. Disadvantages of IORT on the other hand, include longer operating time, reported increased local recurrence compared to EBRT, and lack of final pathological results before delivering the IORT. In patients with positive margins that require re-excision, an IORT boost may be ineffective and may cause complications in re-excision of the margins and difficulty in interpreting the pathology. In addition, IORT requires training of staff, operating room equipment efforts, and expensive devices (Hanna 2014, Esposito 2015).

12/21/2015: MTAC REVIEW
IROT for breast cancer
Evidence Conclusion: There are two large published intraoperative radiation therapy (IORT) trials that investigated whether IORT is equivalent (ELIOT) or noninferior (TARGIT-A) to standard EBRT for the treatment of women with early stage breast cancer undergoing breast conservative surgery, The ELIOT trial used electron IORT (using 2 linear accelerators; NOVAC 7 and Liac) and the TARGIT-A trial used a point source low- energy x-rays (50kV maximum) using the Intrabeam device. TARGIT-A trial (Vaidya et al, 2010, 2014), Evidence Table 1 This was a large multicenter trial that examined the noninferiority of IORT to EBRT (within a specified margin of 2.5%) after breast conserving surgery (BCS). 2,232 women 48-75 years of age, with invasive ductal breast cancer undergoing BCS were randomly assigned to receive either a standard regimen of 25-25 fractions (40-56 Gy) EBRT or a single fraction low energy IORT. Randomization was performed either before surgery (pre-pathology entry) or after surgery (post-pathology entry). In the latter group IORT was given after surgery by reopening the wound. 15% of the patients in the IORT group received additional EBRT (the trial protocol allowed recipients of IORT to receive additional EBRT based on unfavorable features found in the pathology [risk adapted policy]). The primary outcome of the trial was pathologically confirmed ipsilateral breast tumor recurrence (IBTR). The initial results of the trial were published in 2010 when only less than one fifth of the participants were followed-up for at least 4 years (median 25 months for all subjects). These results showed that the IBTR rate was 1.2% in the IORT arm and 0.95% the EBRT arm (p=0.41). More recent results were published in 2014 after the addition of 1,219 participants, and longer follow-up for the initial cohort. The estimated 5-year risk of local recurrence was 3.3% in the IORT group and 1.3% in the EBRT group (p=0.042) (median follow-up was 29 months due to the short follow-up of the additional patients; only 18% of the patients had 5 years of follow-up). The results published in the first report indicate that rate of ipsilateral local recurrence in the IORT group IORT met the noninferiority margin of 2.5% (prespecified by the investigators) for the overall patient population, and for the pre-pathology subgroup, but not for the post-pathology group. However, the incidence of the local recurrence was significantly higher with IORT vs. EBRT. This higher rate was observed at a median follow-up of 29 months which is below the median time when local recurrences are expected, especially when 90% of the women had estrogen receptor positive tumors that tend to recur later. In addition, almost two thirds of the women received adjuvant hormonal therapy which delays recurrence in estrogen receptor positive cases (Silverstein 2014). The results also show that the women who received IORT alone had 3 times the recurrence rate vs. those who received IORT+EBRT (2.7 vs. 0.9%). The authors indicated that the difference was not statistically significant, but no p value was provided. The trial was multicenter, randomized, and controlled. However, it had several methodological limitations, mainly the inadequacy of follow-up duration needed to provide conclusive evidence on the noninferiority of IORT to EBRT. The prespecified non-inferiority margin of 2.5% required a 5-year follow-up for all patients, which was only fulfilled by 20% of the study cohort. Other limitations of the trial include the open-label design (due to the nature of the intervention), and the multiple amendments made to the protocol along the course of the study such as the addition of more participating countries, increasing the population size, changing the start and ending date of the trial, and changing the funding source. In addition, each center participating in the trial managed the EBRT group
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according to its institutional guidelines and determined its own criteria for treating patients with IORT given alone or as a boost therapy. ELIOT trial (Veronesi, et al 2013), Evidence Table 2 This was a prospective single-center trial that randomized 1,305 women 48-75 year of age with clinically invasive T1-T2, ≤2.5 cm breast cancer suitable for breast conservative surgery (BCS), to undergo whole breast EBRT delivered over 6 weeks, or receive a single dose of electron beam IORT. The primary outcome of the trial was ipsilateral breast tumor recurrence (IBTR). The results of the analysis show that after a median follow-up of 5.8 years the IBTR fell within the pre-defined equivalence margin of 4.5%, but the rate was significantly higher in the IORT group (4.4% vs. 0.4% in the EBRT group, p<0.0001, NNH of 25). The significantly higher rates of IBTR in the IORT group were observed for both the true local recurrence in the index quadrant, and for new ipsilateral breast tumors in other quadrants. The author indicated that the difference may be attributable to the very low recurrence rates in the EBRT group because of the high experience and quality of management. Some investigators raised the question on whether the 4-cm applicator size used in the trial might have been too small to adequately treat microscopic disease that extended beyond the existed tumor. Axillary or other regional lymph node metastasis and locoregional tumor recurrence were also significantly higher in the IORT group (NNH=143 and 22 and respectively). There were no significant differences between the two study arms in the development of contralateral breast metastasis, distant metastasis, or in the 5-year overall survival rate. Subgroup analysis according to patients' risk based on tumor size, grade, receptor status, and nodal positivity, showed that low risk women (69.4% of the study participants) had a 5-year IBTR rate of only 1.5% compared to 11.3% of those with one or more high-risk factors. A multivariate analysis showed that tumors size >2 cm, ≥4 positive lymph nodes, poorly differentiated tumors, and tumors with triple negative subtypes doubled the risk of IBTR. The rate of adverse skin effects (erythema, dryness and hyperpigmentation) was significantly higher in the EBRT group, and the rate of fat necrosis was significantly higher in the IORT group. There were no significant differences between the groups in mammary retraction, pain, or burning. Conclusion: The results of the two large published RCTs show that the rate of local recurrence with IORT was non-inferior (TARGIT-A trial) or equivalent (ELIOT trial) to EBRT. However, these results were based on margins prespecified by the investigators of the trials. The results of both TARGIT-A and ELIOT trials show that the risk of ipsilateral tumor recurrence was significantly higher with the IORT compared to EBRT. The published trials had relatively short follow-up duration and do not provide sufficient evidence to determine the long-term risk of delayed cancer recurrence inside or outside the index quadrant, as well as the long-term efficacy and safety of the therapy. There was significant heterogeneity between the published studies as regards to the study design, patients' ages, tumor size, threshold values, radiation sources and techniques used for delivering the IORT, as well as the follow-up duration. Multivariate analysis of the ELIOT trial results showed that the risk of ipsilateral local recurrence in women receiving IORT was almost double in patients with tumors size >2 cm, ≥4 positive lymph nodes, poorly differentiated tumors, or with triple negative subtypes.
Articles: The literature search revealed two large RCTs on IORT (TARGIT-A trial and ELIOT trial) as well a systematic review and meta-analysis of published studies, and a large number of single institution cohort studies. The two large RCTs and the meta-analysis were selected for critical appraisal. Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet*. 2010 Jul 10; 376 (9735):91-102. See Evidence Table 1**.** Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet.* 2014 Feb 15; 383 (9917):603-613. See Evidence Table 1**.** Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomized controlled equivalence trial. *Lancet Oncol*. 2013 Dec; 14 (13):1269-1277. See Evidence Table 2**.** Zhang L, Zhou Z, Mei X, et al. Intraoperative Radiotherapy versus Whole-Breast External Beam Radiotherapy in Early-Stage Breast Cancer: A Systematic Review and Meta-Analysis. *Medicine (Baltimore).* 2015 Jul; 94(27):e1143. See Evidence Table 3**.**

The use of IORT for breast cancer does not meet the *Kaiser Permanente Medical Technology Assessment Criteria.*

Applicable Codes

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

CPT® Codes	Description
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)
77424	Intraoperative radiation treatment delivery, x-ray, single treatment session

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77425	Intraoperative radiation treatment delivery, electrons, single treatment session
77469	Intraoperative radiation treatment management
HCPC Codes	**Description**
C9726	Placement and removal (if performed) of applicator into breast for intraoperative radiation therapy, add-on to primary breast procedure

***Note:** Codes may not be all-inclusive. Deleted codes and codes not in effect at the time of service may not be covered.

Date Created	Date Reviewed	Date Last Revised
12/01/2015	12/01/2015[MPC], 10/04/2016[MPC], 08/01/2017[MPC], 06/05/2018[MPC], 06/04/2019[MPC], 06/02/2020[MPC], 06/01/2021[MPC], 06/07/2022[MPC], 06/06/2023[MPC], 04/02/2024[MPC]	04/20/2016

[MPC] Medical Policy Committee

Revision History	Description
01/06/2016	MPC approved the MTAC recommendation of insufficient evidence for IORT for breast cancer
04/20/2016	Changed Medicare language as LCD 34065 was retired.

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