



CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

Subject Intraoperative Radiation Therapy

Effective Date 8/15/2010
Next Review Date 8/15/2012
Coverage Policy Number 0452

Table of Contents

| | |
|----------------------------------|---|
| Coverage Policy | 1 |
| General Background | 1 |
| Coding/Billing Information | 5 |
| References | 5 |
| Policy History | 9 |

Hyperlink to Related Coverage Policies

Brachytherapy for Gynecological Cancers
 Brachytherapy for Breast Cancer
 Inpatient Admission for Radiation Therapy
 Intensity-Modulated Radiation Therapy (IMRT)
 Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiation Therapy (SBRT)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

CIGNA covers intraoperative radiation therapy as medically necessary at the time of surgical excision to treat radiosensitive cancers that cannot be completely removed or that have a high risk of recurring in nearby tissues.

General Background

Intraoperative radiation therapy, or intraoperative radiotherapy (IORT), refers to the delivery of radiation at the time of surgery. In IORT, high radiation dosage is delivered to the target area with minimal exposure of surrounding tissues, which are displaced and shielded during the procedure. IORT can be delivered with or without other therapies such as external beam radiation therapy (EBRT) and/or chemotherapy.

Proponents of IORT suggest patient selection criteria for IORT include:

- surgery alone does not achieve acceptable local control (i.e., microscopic residual disease or greater after maximal resection);
- EBRT doses needed for adequate local control after subtotal resection or no resection would exceed normal tissue tolerance;
- using IORT together with EBRT would result in improved benefit versus risk ration;

- when there is no evidence of distant metastases or peritoneal seeding (rare exception are single-organ metastasis, good chemotherapy options, slow progression of systemic disease);
- when IORT as well as other treatment modalities of partial breast irradiation may be an alternative to the traditional postoperative radiotherapy after conservative surgery in some selected cases, or used as a boost technique in the treatment of initial-stage breast cancer.

U.S. Food and Drug Administration (FDA)

Radiation delivery systems and devices are regulated by the FDA as Class II devices. Numerous devices have received approval via the 510(k) and premarket approval (PMA) processes.

Literature Review

Comparative studies demonstrating survival outcomes that can be directly tied to the use of IORT are lacking. While IORT-specific impact to health outcomes remains unknown, there are numerous published studies evaluating IORT performed in conjunction with other therapies (adjuvant). Study populations include patients who also underwent chemotherapy and/or other radiation therapy; these small heterogeneous populations precluded the ability to generalize clear findings regarding whether the added use of IORT impacts meaningful patient outcomes, such as survival. Additionally, the efficacy of IORT used as a palliative measure has not been well-delineated in the published, peer-reviewed scientific literature. Optimal patient selection criteria have not yet been established through well-designed trials. Although varied, the overall body of evidence suggests that IORT, when used as part of a multimodal regimen, may aid in locoregional and distant metastatic disease control with acceptable side effects. This does not consistently translate into increased survival rates.

Brain, Head and Neck Cancers: Studies are small and primarily retrospective; evaluating patients with locally advanced and/or previously irradiated brain, head and neck cancers:

Nag et al. (2005) retrospectively studied 65 patients with locally advanced tumors arising in the head and neck. Most had tumors arising in the paranasal sinuses. The predominant histopathology was squamous cell carcinoma. A total of 53 had new primaries (of those, 46 received post-operative EBRT) and 12 had recurrent previously irradiated disease (of those one had follow-up permanent brachytherapy). Nag et al. utilized brachytherapy to deliver IORT, citing its usefulness in selected locally advanced head and neck tumors arising at sites inaccessible to conventionally delivered IORT. The median follow-up was 65 months. There were no major intraoperative or acute postoperative complications. The 1-, 3-, and 5-year local control rates for the entire group were 77%, 69%, and 59%, respectively. The 1-, 3-, and 5-year overall survival rates were 83%, 63%, and 42%, respectively. Patients who received IORT plus EBRT and had microscopic margins (versus gross) demonstrated significantly increased local control rates. The addition of EBRT to IORT significantly increased overall survival (48% and 28%).

In a prospective observational trial, Pinheiro et al. (2003) performed IORT on 44 patients with advanced head and neck cancers (34 patients with advanced squamous cell carcinoma [SCCA] and ten patients with advanced non-SCCA). Most patients had been previously treated with combinations of surgery, EBRT, and chemotherapy. The median follow-up for the 12 living patients was 6.3 years. Tumor control rates at 2 years in the IORT field were 46% for the SCCA patients and 52% for the non-SCCA patients. The 2-year overall survivals were 32% and 50% respectively, for SCCA and non-SCCA patients.

In a retrospective case-control study, 32 patients with malignant gliomas who had received IORT and postoperative EBRT were randomly matched with a cohort of 32 patients who had been treated with postoperative EBRT alone (Nemoto, et al., 2002). Patients were matched according to histological grade, age, extent of tumor removal, and tumor location; however, they were not able to be matched by performance status. There was no significant difference in survival rates between the treatment groups.

Schleicher et al. (2001) reported in a retrospective study, the results of 84 patients with previously irradiated head and neck cancers who underwent IORT. Palliation of symptoms was achieved in all patients with ulcerating tumors, tumor swelling, bleeding, fistula, dyspnea and dysphagia. Pain relief was achieved in 70.7% of patients, resulting in an overall palliative effect in 88% of symptomatic patients. The complication rate did not exceed that expected after surgery alone. The median actuarial overall survival time was 6.8 months, with a median time to local tumor recurrence or progression of 3.7 months.

Breast Cancer: Studies published to date have been primarily in the form of small case series, and include IORT as part of a multimodal treatment plan (Reitsamer, et al., 2006; Lemanski, et al., 2006; Kraus-Tiefenbacher, et al., 2006; Intra, et al., 2005; Veronesi, et al., 2005). Reitsamer et al. (2006) conducted a prospective comparison of postoperative whole-breast radiation therapy (WBRT) with postoperative external beam boost radiation (EBRT) to the tumor bed (n=188, group 1) compared to postoperative WBRT with IORT (n=190, group 2). All 378 patients were treated with breast conserving surgery primarily for stage I and II invasive breast cancer. Additionally included were patients with invasive breast cancers who were eligible for breast conserving surgery with histologically clear margins of at least 3– 5 mm. Although not randomized, the groups were comparable with regard to age, menopausal status, tumor size, histological type, grading and axillary lymph node status. The median follow up period was 81.0 months in group 1 and 51.1 months in group 2. Subsets of patients in both groups received chemotherapy and/or hormonal therapy. The 5-year actuarial rates of ipsilateral breast tumor recurrence (IBTR) were 4.3% and 0.0%, respectively; this difference was statistically significant. The 5-year disease-free survival rates of 90.9% in group 1 and 95.8% in group 2 were not statistically significant.

Colorectal Cancer: Small retrospective case series involve IORT as an adjuvant treatment in patients with locally recurrent or advanced primary colorectal cancer. In general, studies did not specify the surgery as curative or palliative, but spoke generally to the poor prognosis of the recurrent colorectal cancer patient (Dresen, et al., 2008; Pacelli, et al., 2004; Lindel, et al., 2001; Harrison, et al., 1998; Bussieres, et al., 1996). Dresen et al. (2008) retrospectively reported on one of the largest populations (n=147) with locally recurrent rectal cancer. Patients received EBRT then extended resection surgery with IORT and a subset also received chemotherapy. Median follow-up time for survivors was 34.0 months. Dresen et al. reported 5-year overall, disease-free, and metastasis-free survival and local control of 31.5%, 34.1%, 49.5% and 54.1% respectively. Local control rates and survival rates specific to IORT only (compared to adjuvant IORT) remain unknown.

Gastric Cancer: Evidence in the published, peer-reviewed scientific literature is conflicting and includes IORT as part of a multimodal treatment plan:

Fu et al (2008) conducted a prospective, observational trial. A total of 97 consecutive patients with locally advanced, non-metastatic adenocarcinoma of the stomach underwent gastrectomy with lymph node dissection; 46 were treated with surgery followed by adjuvant IORT and combined chemotherapy and EBRT. The remaining 51 patients were treated with surgery followed by adjuvant chemotherapy and EBRT using the same regimen, but without IORT. The use of IORT was determined by patient preference and the availability of the facility at surgery without randomization. No significant differences in the patient characteristics between the two groups of patients were observed. Results showed four patients experienced Grade 3 or 4 late complications, but no significant difference was observed between the two groups. After a median follow-up of 24 months, the 3-year locoregional control rate was 77% and 63% in the two groups with or without IORT, respectively (statistically significant). The 3-year overall survival and disease-free survival rate was 47% and 36% in the EBRT group and 56% and 44% in the EBRT+IORT group, respectively (not statistically significant). The authors noted that a limitation of this study is it may have been underpowered; a calculation of the number of patients required for a set level of statistical power was not performed.

Drognitz et al. (2008) retrospectively compared a cohort of 61 patients with gastric neoplasms who had undergone gastrectomy or subtotal resection with IORT, to a matching cohort of 61 patients without IORT. Matches were selected on the basis of postoperative stage, postoperative histologic grading, extent of surgery, sex, and similarity of age at the time of diagnosis and date of surgery (both within 4 years). Mean follow-up was 4.8 years in the IORT group and 5.0 years in the non-IORT group. The authors reported no significant difference in overall survival with IORT. The locoregional tumor recurrence rate was 9.8% in the IORT group and unknown in the non-IORT group. Although not reaching the level of significance in every category, surgical complications such as pancreatitis were more common in the IORT than non-IORT group.

In a prospective two-cohort, non-randomized trial, Qin et al. (2006) studied 547 patients. A total of 106 patients with stages I-IV gastric carcinoma were treated by radical resection and IORT; and 441 patients were treated by surgery alone. The 5-year survival rate (YSR) for patients treated by operation alone was 92.8% for stage I, 80.6% for stage II, 45.1% for stage III, and 10% for stage IV. The 5-YSR for patients treated by IORT was 100% for stage I and stage II, 60.4% for stage III, and 14.3% for stage IV. IORT made a statistically significant difference in survival in patients with stage II and III gastric cancers. Neither significant late complications nor deviation from the usual postoperative course was observed.

Sindelar et al. (1993) performed a randomized, controlled trial. A total of 41 patients with adenocarcinoma of the stomach underwent gastrectomy; 16 patients followed surgery with IORT. The remaining 25 patients underwent surgery alone or postoperative EBRT. Results showed seven patients (17%) died of complications. The median survival for patients with tumors of all stages was 25 months for the IORT group and 21 months for the control group (not statistically significant). Locoregional disease failures occurred in 44% of IORT patients and 92% of control patients (statistically significant). Complication rates were similar between IORT and control patients.

Gynecological Cancer: Evidence involving the use of IORT in gynecological cancers consists of small retrospective case series evaluating adjuvant IORT in patients with locally advanced and recurrent gynecological cancers (Tran, et al., 2007; Dowdy, et al., 2006; Yap, et al., 2005; Martinez-Monge, et al., 2001; Gemignani, et al., 2001). Martinez-Monge et al. (2001) retrospectively reported on one of the largest gynecologic populations (n=67). Patients with advanced cervical cancer included 36 recurrent and 31 primary disease patients. Patients underwent IORT in addition to EBRT and chemotherapy. Median follow-up was 58 months for patients with primary tumors and 18.9 months for patients with recurrent disease. The 10-year survival results were significantly better for primary disease, 58.1%, than for recurrent disease, 14.1%. Local control rates and survival rates specific to IORT only (versus adjuvant IORT) have not been established.

Pancreatic Cancer: Evidence in the published, peer-reviewed scientific literature includes IORT as part of a multimodal treatment plan and present conflicting study findings. Some authors spoke to using IORT for palliative indications, and those findings were also conflicting (Showalter, et al., 2009; Valentini, et al., 2009a; Nakagohri, et al., 2007; Ihse, et al., 2005; O'Connor, et al., 2005; Ma, et al., 2004; Reni, et al., 2001). In a retrospective study, Showalter et al. (2009) reported on 83 patients and found the median survival time of patients who received IORT was 19.2 months, which was not significantly different than patients managed without IORT, 21.0 months. Nakagohri et al. (2007) retrospectively studied 105 patients, noting the 1-, 3-, and 5-year survival rates for patients with and without IORT were 43%, 11% 5%, and 61% 18% 18% respectively. These results were not statistically significant. Reni et al. (2001) retrospectively evaluated 203 patients (IORT, n=127; surgery only n=76). In 49 patients with locally limited disease (Stage I-II; LLD), IORT (n = 30) reduced the local failure rate and significantly prolonged time to local failure, time to failure, and overall survival with respect to surgery alone (n = 19). Because of conflicting study findings, it remains unknown if IORT provides clinical value such as long-term survival. Ma et al. (2004) (n=81) noted adjuvant IORT supported a pain remission rate of 92%. Ihse et al. (2005) (n=55) did not observe any obvious ameliorating effects on pain, with 63% of the unresectable patients requiring opioids within three months following the treatment. The author noted "As there are other less invasive alternatives available today, IORT is not indicated exclusively for pain control."

Sarcoma: Data are primarily small retrospective case series, involving patients with soft tissue sarcomas or osteosarcomas of the extremities, and soft tissue sarcoma of the retroperitoneum. Most authors did not specify surgery as curative or palliative, but spoke to poor prognosis or high risk of metastases (Tran, et al., 2006; Kretzler, et al., 2004; Sindelar, et al., 2003; Sakayama, et al., 2003; Oya, et al., 2001; Alektiar, et al., 2000). Sindelar et al. (2003) conducted a small randomized controlled trial with a median follow-up of 8 years. A total of 35 patients with surgically resected sarcomas of the retroperitoneum were included; 15 underwent IORT plus EBRT, 20 underwent EBRT only. Some subsets of both groups received chemotherapy. Patients who received IORT had fewer complications of disabling radiation-related enteritis (two of 15) than control patients (10 of 20), but radiation-related peripheral neuropathy was more frequent among those who received IORT (nine of 15) than among control patients (one of 20). The number of locoregional recurrences was statistically significantly lower among those who received IORT (six of 15) than control patients (16 of 20). Median survival times were similar for the group that received IORT (45 months) and the control group (52 months).

Professional Societies/Organizations

National Comprehensive Cancer Network® (NCCN®): The NCCN addresses IORT in several of their Clinical Practice Guidelines in Oncology™. NCCN Guidelines™ include algorithmic and narrative recommendations. NCCN recommendations include the following:

- Breast Cancer (v.1.2010): Under partial breast radiation therapy, "IORT with photons or electrons with a single fraction (targeted IORT) can be used in institutions with that experience and expertise."
- Cervical Cancer (v.1.2010): Under therapy for relapse, "patients with central pelvic recurrent disease after RT should be evaluated for pelvic exenteration with or without IORT."

- Colon Cancer (v.2.2010): "IORT, if available, should be considered for patients with T4 or recurrent cancers as an additional boost."
- Esophageal Cancer (v.1.2010): "Experience of IORT as an alternative to external-beam radiation is limited."
- Rectal Cancer (v.2.2010): "IORT, if available, should be considered for very close or positive margins after resections as an additional boost, especially for patients with T4 or recurrent cancers."
- Soft Tissue Sarcoma (v.1.2010): IORT as a treatment option is discussed frequently throughout the guideline.
- Uterine Cancers (v.1.2010): Under treatment of relapsed or metastatic disease, "for patients previously treated with external-beam radiation at the recurrence site, surgical exploration of the pelvis and resection with or without IORT is recommended."

American Cancer Society (ACS): The ACS states that "IORT is the delivery of radiation to the cancer during surgery. The radiation may be given externally or internally, and is often combined with a course of external radiation given before or after the operation. IORT is useful for abdominal or pelvic cancers (especially those that have grown close to vital areas) and in cancers that have a tendency to grow back after treatment. Normal tissues can be moved out of the way and protected during surgery, so IORT reduces the amount of tissue that is exposed to radiation. This allows a higher dose of radiation to reach the cancer. IORT is delivered in a special operating room lined with radiation-shielding walls" (ACS, 2009).

Summary

The independent incremental clinical value of IORT has not yet been demonstrated, as published studies evaluate IORT performed in conjunction with other radiotherapies and/or chemotherapies. Although IORT-specific impact to health outcomes remains unknown, the overall body of evidence suggests that IORT, when used as part of a multimodal regimen, may aid in locoregional and distant metastatic disease control with acceptable side effects. This does not consistently translate into increased survival rates.

Coding/Billing Information

Note: This list of codes may not be all-inclusive.

Covered when medically necessary:

| CPT ^{®*} Codes | Description |
|----------------------------|---|
| 77470 | Special treatment procedure (eg, total body irradiation, hemibody radiation, per oral, endocavitary or intraoperative cone irradiation) |

| HCPCS Codes | Description |
|----------------|--|
| S8049 | Intraoperative radiation therapy (single administration) |

| ICD-9-CM Diagnosis Codes | Description |
|--------------------------------|-------------------|
| | Multiple / varied |

*Current Procedural Terminology (CPT[®]) © 2010 American Medical Association: Chicago, IL.

References

1. Alektiar KM, Hu K, Anderson L, Brennan MF, Harrison LB. High-dose-rate intraoperative radiation therapy (HDR-IORT) for retroperitoneal sarcomas. *Int J Radiat Oncol Biol Phys.* 2000 Apr 1;47(1):157-63.

2. American Cancer Society. What's New in Radiation Therapy? Revised: 07/17/2009. Accessed March 2010. Available at URL address: http://www.cancer.org/docroot/ETO/content/ETO_1_4X_Whats_new_in_radiation_therapy.asp?sitearea=ETO
3. Bussieres E, Gilly FN, Rouanet P, Mahe MA, Roussel A, Delannes M, et al. Recurrences of rectal cancers: results of a multimodal approach with intraoperative radiation therapy. French Group of IORT. Intraoperative Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 1996 Jan 1;34(1):49-56.
4. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy first part: rationale and techniques. *Crit Rev Oncol Hematol*. 2006a Aug;59(2):106-15.
5. Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy part 2. Clinical results. *Crit Rev Oncol Hematol*. 2006b Aug;59(2):116-27.
6. Dowdy SC, Mariani A, Cliby WA, Haddock MG, Petersen IA, Sim FH, et al. Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: technique and analysis of outcomes. *Gynecol Oncol*. 2006 May;101(2):280-6.
7. Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol*. 2008 Jul;15(7):1937-47. Epub 2008 Apr 4.
8. Drognitz O, Henne K, Weissenberger C, Bruggmoser G, Göbel H, Hopt UT, et al. Long-term results after intraoperative radiation therapy for gastric cancer. *Int J Radiat Oncol Biol Phys*. 2008 Mar 1;70(3):715-21. Epub 2007 Dec 31.
9. Fu S, Lu JJ, Zhang Q, Yang Z, Peng L, Xiong F. Intraoperative radiotherapy combined with adjuvant chemoradiotherapy for locally advanced gastric adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2008 Dec 1;72(5):1488-94. Epub 2008 Jun 4.
10. Harrison LB, Minsky BD, Enker WE, Mychalczak B, Guillem J, Paty PB, et al. High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. *Int J Radiat Oncol Biol Phys*. 1998 Sep 1;42(2):325-30.
11. Holmes DR, Baum M, Joseph D. The TARGIT trial: targeted intraoperative radiation therapy versus conventional postoperative whole-breast radiotherapy after breast-conserving surgery for the management of early-stage invasive breast cancer (a trial update). *Am J Surg*. 2007 Oct;194(4):507-10.
12. Ihse I, Andersson R, Ask A, Ewers SB, Lindell G, Tranberg KG. Intraoperative radiotherapy for patients with carcinoma of the pancreas. *Pancreatol*. 2005;5(4-5):438-42. Epub 2005 Jun 28.
13. Intra M, Leonardi C, Luini A, Veronesi P, Gennari R, Gatti G, et al. Full-dose intraoperative radiotherapy with electrons in breast surgery: broadening the indications. *Arch Surg*. 2005 Oct;140(10):936-9.
14. Kraus-Tiefenbacher U, Bauer L, Kehrer T, Hermann B, Melchert F, Wenz F. Intraoperative Radiotherapy (IORT) as a Boost in Patients with Early-Stage Breast Cancer - Acute Toxicity. *Onkologie*. 2006 Mar;29(3):77-82. Epub 2006 Mar 3.
15. Kretzler A, Molls M, Gradinger R, Lukas P, Steinau HU, Wurschmidt F. Intraoperative radiotherapy of soft tissue sarcoma of the extremity. *Strahlenther Onkol*. 2004 Jun;180(6):365-70
16. Lemanski C, Azria D, Thezenas S, Gutowski M, Saint-Aubert B, Rouanet P, et al. Intraoperative radiotherapy given as a boost for early breast cancer: Long-term clinical and cosmetic results. *Int J Radiat Oncol Biol Phys*. 2006 Apr 1;64(5):1410-5. Epub 2006 Jan 25.

17. Lindel K, Willett CG, Shellito PC, Ott MJ, Clark J, Grossbard M, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. *Radiother Oncol*. 2001 Jan;58(1):83-7.
18. Ma HB, Di ZL, Wang XJ, Kang HF, Deng HC, Bai MH. Effect of intraoperative radiotherapy combined with EBRT following internal drainage for advanced pancreatic carcinoma. *World J Gastroenterol*. 2004 Jun 1;10(11):1669-771.
19. Martinez-Monge R, Jurado M, Aristu JJ, Moreno M, Cambeiro M, Perez-Ochoa A, et al. Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. *Gynecol Oncol*. 2001 Sep;82(3):538-43.
20. Nag S, Koc M, Schuller DE, Tippin D, Grecula JC. Intraoperative single fraction high-dose-rate brachytherapy for head and neck cancers. *Brachytherapy*. 2005;4(3):217-23.
21. Nakagohri T, Kinoshita T, Konishi M, Takahashi S, Tanizawa Y. Clinical results of extended lymphadenectomy and intraoperative radiotherapy for pancreatic adenocarcinoma. *Hepatogastroenterology*. 2007 Mar;54(74):564-9.
22. National Comprehensive Cancer Network[®] (NCCN). NCCN GUIDELINES[™] Clinical Guidelines in Oncology[™]. © National Comprehensive Cancer Network, Inc 2010, All Rights Reserved. Accessed March 2010. Available at URL address:
http://www.nccn.org/professionals/physician_gls/f_guidelines.asp?button=I+Agree#site
23. Nemoto K, Ogawa Y, Matsushita H, Takeda K, Takai Y, Yamada S, et al. Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas. *BMC Cancer*. 2002;2:1. Epub 2002 Jan 15.
24. O'Connor JK, Sause WT, Hazard LJ, Belnap LP, Noyes RD. Survival after attempted surgical resection and intraoperative radiation therapy for pancreatic and periampullary adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2005 Nov 15;63(4):1060-6. Epub 2005 Jun 22.
25. Oya N, Kokubo M, Mizowaki T, Shibamoto Y, Nagata Y, Sasai K, et al. Definitive intraoperative very high-dose radiotherapy for localized osteosarcoma in the extremities. *Int J Radiat Oncol Biol Phys*. 2001 Sep 1;51(1):87-93
26. Pacelli F, Di Giorgio A, Papa V, Tortorelli AP, Covino M, Ratto C, et al. Preoperative radiotherapy combined with intraoperative radiotherapy improve results of total mesorectal excision in patients with T3 rectal cancer. *Dis Colon Rectum*. 2004 Feb;47(2):170-9.
27. Pinheiro AD, Foote RL, McCaffrey TV, Kasperbauer JL, Bonner JA, Olsen KD, et al. Intraoperative radiotherapy for head and neck and skull base cancer. *Head Neck*. 2003 Mar;25(3):217-25; discussion 225-6
28. Qin HL, Lin CH, Zhang XL. Evaluation of intraoperative radiotherapy for gastric carcinoma with D2 and D3 surgical resection. *World J Gastroenterol*. 2006 Nov 21;12(43):7033-7
29. Reitsamer R, Sedlmayer F, Kopp M, Kametrise G, Menzel C, Deutschmann et al. The Salzburg concept of intraoperative radiotherapy for breast cancer: results and considerations. *Int J Cancer*. 2006 Jun 1;118(11):2882-7
30. Reni M, Panucci MG, Ferreri AJ, Balzano G, Passoni P, Cattaneo GM, et al. Effect on local control and survival of electron beam intraoperative irradiation for resectable pancreatic adenocarcinoma. *Int J Radiat Oncol Biol Phys*. 2001 Jul 1;50(3):651-8.
31. Sakayama K, Kidani T, Fujibuchi T, Yamamoto H, Shibata T, Fujii T, Ochi T, Kawamura M. Definitive intraoperative radiotherapy for musculoskeletal sarcomas and malignant lymphoma in combination with surgical excision. *Int J Clin Oncol*. 2003 Jun;8(3):174-9.

32. Schleicher UM, Phonias C, Spaeth J, Schlondorff G, Ammon J, Andreopoulos D. Intraoperative radiotherapy for pre-irradiated head and neck cancer. *Radiother Oncol.* 2001 Jan;58(1):77-81.
33. Showalter TN, Rao AS, Rani Anne P, Rosato FE, Rosato EL, Andrel J, et al. Does intraoperative radiation therapy improve local tumor control in patients undergoing pancreaticoduodenectomy for pancreatic adenocarcinoma? A propensity score analysis. *Ann Surg Oncol.* 2009 Aug;16(8):2116-22. Epub 2009 May 13.
34. Sindelar WF, Kinsella TJ, Chen PW, DeLaney TF, Tepper JE, Rosenberg SA, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. *Arch Surg.* 1993 Apr;128(4):402-10.
35. Sindelar WF, Kinsella TJ, Tepper JE, DeLaney TF, Maher MM, Smith R, et al. Randomized trial of intraoperative radiotherapy in carcinoma of the stomach. *Am J Surg.* 1993 Jan;165(1):178-86; discussion 186-7.
36. Skandarajah AR, Lynch AC, Mackay JR, Ngan S, Heriot AG. The role of intraoperative radiotherapy in solid tumors. *Ann Surg Oncol.* 2009 Mar;16(3):735-44. Epub 2009 Jan 14. Review.
37. Tran QN, Kim AC, Gottschalk AR, et al. Clinical outcomes of intraoperative radiation therapy for extremity sarcomas. *Sarcoma.* 2006; 2006(1):91671.
38. Tran PT, Su Z, Hara W, Husain A, Teng N, Kapp DS. Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. *Int J Radiat Oncol Biol Phys.* 2007 Oct 1;69(2):504-11.
39. Valentini V, Calvo F, Reni M, Krempien R, Sedlmayer F, Buchler MW, et al. Intra-operative radiotherapy (IORT) in pancreatic cancer: joint analysis of the ISIORT-Europe experience. *Radiother Oncol.* 2009a Apr;91(1):54-9. Epub 2008 Aug 30.
40. Valentini V, Coco C, Rizzo G, Manno A, Crucitti A, Mattana C, et al. Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. *Surgery.* 2009b May;145(5):486-94. Epub 2009 Mar 21.
41. Veronesi U, Orecchia R, Luini A, Galimberti V, Gatti G, Intra M, et al. Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery: experience with 590 cases. *Ann Surg.* 2005 Jul;242(1):101-6.
42. Yap OW, Kapp DS, Teng NN, Husain A. Intraoperative radiation therapy in recurrent ovarian cancer. *Int J Radiat Oncol Biol Phys.* 2005 Nov 15;63(4):1114-21. Epub 2005 Jun 20.

Policy History

| Pre-Merger Organizations | Last Review Date | Policy Number | Title |
|-------------------------------------|-----------------------------|--------------------------|----------------------------------|
| CIGNA HealthCare | 4/15/2008 | 0452 | Intraoperative Radiation Therapy |

“CIGNA”, “CIGNA HealthCare” and the “Tree of Life” logo are registered service marks of CIGNA Intellectual Property, Inc., licensed for use by CIGNA Corporation and its operating subsidiaries. All products and services are provided by such operating subsidiaries and not by CIGNA Corporation. Such operating subsidiaries include Connecticut General Life Insurance Company, CIGNA Health and Life Insurance Company, CIGNA Behavioral Health, Inc., CIGNA Health Management, Inc., and HMO or service company subsidiaries of CIGNA Health Corporation and CIGNA Dental Health, Inc. In Arizona, HMO plans are offered by CIGNA HealthCare of Arizona, Inc. In California, HMO plans are offered by CIGNA HealthCare of California, Inc. In Connecticut, HMO plans are offered by CIGNA HealthCare of Connecticut, Inc. In North Carolina, HMO plans are offered by CIGNA HealthCare of North Carolina, Inc. In Virginia, HMO plans are offered by CIGNA HealthCare Mid-Atlantic, Inc. All other medical plans in these states are insured or administered by Connecticut General Life Insurance Company or CIGNA Health and Life Insurance Company.