Name of Policy:
Intraoperative Radiation Therapy (IORT)

Policy #: 220
Category: Radiology

Latest Review Date: August 2014
Policy Grade: B

Background/Definitions:
As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. The technology must have final approval from the appropriate government regulatory bodies;
2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;
3. The technology must improve the net health outcome;
4. The technology must be as beneficial as any established alternatives;
5. The improvement must be attainable outside the investigational setting.

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. In accordance with generally accepted standards of medical practice; and
2. Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient’s illness, injury or disease; and
3. Not primarily for the convenience of the patient, physician or other health care provider; and
4. 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 that patient’s illness, injury or disease.
Description of Procedure or Service:
Intraoperative radiation therapy (IORT) is a technique in which unresectable or partially resectable tumors and cancerous regional lymph nodes are irradiated during surgical exposure. IORT allows direct visualization of the target volume, which results in a more precise mapping of the field to be irradiated. It also permits removal or shielding of normal structures from the radiation field. The objective is to permit a potentially cancericidal “boost” of radiation to the tumor, tumor bed, and nodes while sparing the surrounding radiosensitive organs.

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. Most patients are also treated with high dose external beam photon irradiation (EBRT).

Policy:
Intraoperative radiation therapy (IORT) meets Blue Cross and Blue Shield of Alabama’s medical criteria for coverage in patients with pancreatic cancer, pelvic malignancies, and locally advanced colorectal cancer.

Intraoperative radiation therapy that does not meet the medical indications listed above would not meet Blue Cross and Blue Shield of Alabama’s medical criteria for coverage and would be considered investigational.

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member’s contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:
Intraoperative therapy has been used most extensively in patients with pancreatic cancer, pelvic malignancies, and colorectal malignancies. The literature consists mainly of retrospective reports of small case series with historic controls from single institutions; systematic reviews and early phase trials have also been published. Evaluation of the effectiveness of intraoperative radiotherapy (IORT) is limited by the absence of randomized controlled trials (RCTs).

Skandarajah et al performed a systematic review of the literature to review indications, applications, and outcomes of IORT in nongynecologic solid tumors and concluded that “current studies in all common cancers show an additional benefit in local recurrence rates when intraoperative radiotherapy is included in the multimodal treatment. However, intraoperative radiotherapy may not improve overall survival (OS) and has significant morbidity depending on the site of the tumor.”
Colorectal Cancer
Several reviews have been published on IORT for colorectal cancer and have concluded IORT may confer some benefit in local control. One review by Wiig et al found no evidence IORT is beneficial. This review included 18 studies on primary rectal cancer (including one RCT and five comparative trials) and 18 studies on locally recurrent rectal cancer. Twelve additional studies on treatment of rectal cancer without IORT were also reviewed. A meta-analysis was not able to be performed due to heterogeneity in study design and reporting. The authors reported IORT provided no OS benefit for primary rectal cancers that were completely resected, but there was a possible reduction in local recurrence in cases of incomplete tumor resection. IORT did not affect OS or local recurrence when used to treat locally recurrent rectal cancer.

Cantero-Muñoz et al conducted a systematic review on the efficacy and safety of IORT in colorectal cancer. The scientific literature published between January 2000 and October 2009 was reviewed; study inclusion criteria included any study design, a minimum of 30 patients treated with IORT, adults diagnosed with any stage disease and a median follow-up period of greater than three months. Fifteen studies met the inclusion criteria and included one systematic review; most studies were case series, except for three, which had a comparative design. The median follow-up was over three years in only six studies and five years in two studies. Sample size was more than 100 patients in most studies and more than 200 patients in two studies. Study quality was judged to be low given the heterogeneous patient populations, lack of comparison groups, heterogeneous delivery of IORT doses, and the concomitant heterogeneous delivery of other treatments. Five-to-six-year local control was greater than 80% and five-year OS was close to 65%. For recurrences, the five-year OS was 30%. The main acute complications were gastrointestinal. The authors concluded that it was difficult to draw conclusions and to separate the attributing effects of IORT given the complexity of surgery, patient heterogeneity and because IORT was delivered as part of combined treatment but that adding IORT to conventional treatment approaches appeared to reduce the incidence of local recurrence within the radiation area by more than 10%.

The Skandarajah systematic review included large series (>100 patients) of IORT for locally advanced or recurrent colorectal cancer from Mayo clinic and Massachusetts General Hospital. In the Massachusetts General study of IORT for locally advanced colorectal cancer, for example, patients with negative tumor margins (R0) had local control of 89% and disease-free survival (DFS) at five years of 69%. Local control and DFS for patients with an R1 (microscopic involvement) margin were 68% and 40%, respectively, and for R2 (macroscopic involvement), 57% and 14%, respectively. These results were reported to be better than those for historical controls. In all of the studies, DFS was associated with complete surgical resection. Complete resection was also the most important prognostic factor in patients with recurrent rectal cancer for whom prior operation complicates surgery and extended resections may be required. Some, but not all, studies of multimodality treatment with IORT and preoperative external beam radiotherapy (EBRT) demonstrate improvement in local control in patients who received IORT. The authors note that the most extensive experience with IORT for recurrent rectal cancer is reported by the Mayo Clinic. Of 304 patients who underwent resection, 131 received IORT, 52% with palliative intent and 33% with curative intent. Mayo Clinic reported five-year survivals of 21% for the palliative group and 27% in the patients for whom the treatment was intended to be
curative. The possibility of selection bias prevents firm conclusions; good local control rates and good overall results suggest that combined therapy might be applied in selected patients.

Mirnezami et al conducted a systematic review and meta-analysis on the use of intraoperative radiotherapy in colorectal cancer. The review included studies that were published between 1965 and 2011 that reported outcomes after IORT for advanced or recurrent colorectal cancer (CRC). The review included 29 studies, 14 prospective and 15 retrospective, with a total of 3003 patients. Indications for IORT were locally advanced disease in 1792 patients and locally recurrent disease in 1211 patients. Comparative studies found a significant effect favoring IORT for improved local control (odds ratio [OR]=0.22; 95% confidence interval [CI], 0.05 to 0.86; p=0.03), DFS (hazard ratio [HR]=0.51; 95% CI, 0.31 to 0.85; p=0.009), and OS (HR=0.33; 95% CI, 0.2 to 0.54; p=0.001). With IORT, there was no increase in total (OR=1.13; 95% CI, 0.77 to 1.65; p=0.57), urologic (OR=1.35; 95% CI, 0.84 to 2.82; p=0.47), or anastomotic complications (OR=0.94; 95% CI, 0.42 to 2.1; p=0.98); however, increased wound complications were noted after IORT (OR=1.86; 95% CI, 1.03 to 3.38; p=0.049).

Investigators at Mayo Clinic describe a large series of patients treated from April 1981 through January 2008. Six hundred seven patients with recurrent CRC received IOERT (delivered by electron beams produced by linear accelerators) as a component of treatment. IOERT was preceded or followed by external radiation in 583 patients (96%). Resection was classified as R0 (negative margins) in 227 (37%) and R1 (residual microscopic disease) in 224 (37%). Median OS was 36 months. Five- and ten-year survival rates were 30% and 16%, respectively. Survival estimates at five years were 46% and 27% for R0 and R1 resection, respectively. Multivariate analysis revealed that R0 resection, no prior chemotherapy, and more recent treatment (in the second half of the series) were associated with improved survival. The three-year cumulative incidence of central (within the IOERT field), local, and distant relapse was 12%, 23%, and 49%, respectively. Toxicity Grade 3 or higher partially attributable to IOERT was observed in 66 patients (11%). The authors conclude that continued evaluation of curative-intent, combined-modality therapy is warranted for this high-risk population.

**Gastric Cancer**

Skandarajah et al observed that few studies of IORT for gastric cancer have been published in the last decade, suggesting that there is minimal efficacy for this indication and that is achieved only with potential toxicity to other organs. Three RCTs and case series with historic controls were reviewed; all demonstrate only a small survival benefit at any cancer stage and with high complication rates in the IORT-treated patients. Evaluation of IORT for pancreatic cancer is hampered by the small number of patients eligible for resection. In the single RCT reviewed by Skandarajah et al (12 patients and 12 controls), IORT decreased local recurrence rates (33% vs 100% in the control group) but had no impact on OS.

Calvo et al reported long-term outcomes in 32 patients with resectable locally advanced gastric adenocarcinoma treated with IORT. Between January 1995 and December 2010, 32 patients with primary gastric adenocarcinoma were treated with curative resection, either total gastrectomy (n=9; 28%), or subtotal gastrectomy (n=23; 72%) and lymphadenectomy, for disease confined to the locoregional area (stage: II [n=15; 47%], or stage III [n=17; 53%]). Patients were treated with IORT over the celiac axis and peripancreatic nodal areas. Sixteen (50%) patients also received
adjuvant treatment (EBRT (n=6), chemoradiation (n=9), or chemotherapy alone [n=1]). Median follow-up was 40 months (range, 2-60 months). Locoregional recurrence was observed in five (16%) patients. OS at five years was 54.6 % (95 % CI, 48.57 to 60.58). Postoperative mortality was 6% (n=2) and postoperative complications 19% (n=6).

Soft Tissue Sarcomas

Regarding soft tissue sarcomas, the systematic review by Skandarajah et al highlights the potential value of IORT in the multimodal treatment of retroperitoneal sarcoma because these tumors are often close to dose-limiting structures but the review notes that it is not without complications. One randomized study compared IORT combined with postoperative EBRT with EBRT alone. The local recurrence rate was 40% in the combined therapy group versus 80% in patients who received EBRT only, but there was no difference in OS. Patients who received IORT had fewer radiation enteritis events but more disabling peripheral neuropathies. In a nonrandomized study of 251 patients, 92 of whom received IORT, IORT patients had more surgical complications and significantly more infectious complications; however, the IORT-treated patients had a 40% lower rate of local recurrence. IORT has demonstrated effective tumor control in osteosarcoma, but fracture of irradiated bone can be significant.

Stucky et al reported on 63 consecutive patients with retroperitoneal sarcoma treated with preoperative EBRT, surgery and IORT (n=37) or surgery only (n=26) between 1996 and 2011. Median follow-up was 45 months. The five-year local control rate for patients receiving radiotherapy was 89% versus 46% for the surgery-only patients (p=0.03). OS did not differ as both groups had an actuarial five-year OS of 60%.

Call et al reported outcomes in 61 patients with upper-extremity soft tissue sarcomas treated with EBRT, surgery, and IORT, with or without chemotherapy. The median patient age was 50 years-old (median age, 13-95 years). The median follow-up was 5.9 years. Eleven patients had gross or microscopic disease at the time of IORT. IORT doses ranged from 7.50 Gy to 20.00 Gy and EBRT doses ranged from 19.80 Gy to 54.00 Gy. OS at five and ten years was 72% and 58%, respectively. Local control at five and ten years was 91% and 88%, respectively. Distant control at five and ten years was 80% and 77%, respectively. Patients who were treated for recurrent disease had inferior five-year OS compared with patients with a first diagnosis (63% vs 74%; p=0.02) and lower five-year local control rate (67% vs 94%; p<0.01). For patients with residual disease at the resection margin, local control at five and ten years was 100% and 86%, respectively, whereas for patients without residual tumor after resection, local control was 89% at both five and ten years (p=0.98). Limb preservation was achievable for most patients. Severe toxicity attributable to treatment was noted in 7% of patients.

Investigators in Japan reported on a series of 28 patients who received IORT after resection of large (median size 9.75cm) retroperitoneal sarcomas; resection of tumor and adjacent organs was performed to obtain a disease-free anterior margin and IORT was delivered to any close posterior margin. Margins were positive for disease in 15 patients, usually posterior. After median follow-up of 33 months, two patients with primary disease and three patients with recurrent disease experienced local recurrence. The authors conclude that IORT may deliver sufficient radiation dose to the posterior margin to control microscopic residual disease, especially in patients with primary disease. A retrospective analysis of a series of 38 patients treated at a German center.
with IORT and EBRT for soft tissue sarcoma found a local recurrence in ten of 36 patients, lymph node metastases in two of 35 patients, and distant metastases in six of 35 patients at a mean follow-up of 2.3 years. Actuarial local control was 63%, and OS rate was 57% at five years. Complications, though not severe, were frequent.

**Gynecologic Cancers**

No systematic reviews of IORT for gynecologic cancers were identified in the literature search. Reports of a sampling of case series are summarized here. A Phase 2 trial examined the use of radical surgery with intraoperative high-dose radiotherapy after chemotherapy in extra cervical locally advanced cervical cancer patients. Between 2000 and 2007, 42 locally advanced cervical cancer (stage IIA bulky-IVA) patients were treated. EBRT was administered to the whole pelvic region in combination with chemotherapy, and then radical surgery with IORT was performed six to eight weeks after the end of the EBRT and chemotherapy treatment. After EBRT and chemotherapy, 35/42 patients (83%) underwent radical surgery and IORT treatment. At pathologic examination 8/35 (23%) patients showed complete response, while the rest (27/35) had residual disease, either microscopic (17/27) or gross (10/27). The five-year DFS and the five-year OS were 46% and 49% respectively. There were significantly better DFS and OS when residual tumor was absent or limited to the cervix, respectively 78% versus 16% and 81% versus 20% (p<0.001). At the time of the analysis, 17/35 (48%) of patients were alive but developed a relapse with a median of 22 months, and 15/35 (43%) of patients died of disease with a median of 33 months. Three of 35 (9%) patients were alive and free of disease. The authors concluded that EBRT and chemotherapy followed by surgery and IORT in locally advanced cervical cancer patients was active in a subgroup of patients with pathologic complete response to treatment or partial response with residual tumor limited to the cervix.

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. Previously unirradiated patients received preoperative chemoradiation. The ten-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 to margin status, amount of residual disease, and pelvic lymph node involvement. The overall incidence of toxic events attributable to IORT was 13.9%. The ten-year survival rate for the entire group was 34%, 58% for patients with primary disease, and 14% for those with recurrent disease. The authors conclude that IORT is a valuable boosting technique particularly in the management of advanced but resectable cervical cancer. Patients, especially those with recurrent disease, with positive lymph nodes, parametrial involvement, and/or incomplete resection have poor local control, despite IORT at the doses used in the study.

Gemignani et al report on 17 patients with recurrent gynecologic cancers treated with radical resection and high-dose intraoperative radiation therapy (HDR-IORT) at the Sloan-Kettering Cancer Center. The site of the primary tumor was the cervix in nine, the uterus in seven, and the vagina in one patient. In patients with complete gross resection (n=13), the three-year local control rate was 83% versus 25% in patients with gross residual disease. The overall three-year survival rate was 54%. The overall distant metastasis-free rate was also 54%; seven patients, all of whom had microscopic residual disease, developed distant metastases. The authors conclude that radical surgical resection with IORT appears to provide a reasonable local control rate in
patients who have failed prior surgery and/or definitive radiation; however, only patients with complete gross resection at completion of surgery appear to benefit. Two of the authors state in a later review that for most patients with recurrent cervical cancer, pelvic exenteration is the only therapeutic option that offers the possibility of long-term survival, and patients for exenteration are those with central local recurrences that have not extended to the pelvic sidewalls. They suggest that HDR-IORT combined with radical resection makes this option available to more patients, and those with recurrences that extend close to the pelvic sidewalls should be referred to centers where HDR-IORT is available. Dowdy et al report on a series of 25 patients who received radical resection and IORT for recurrent endometrial cancer at Mayo Clinic; 56% received radiation, and 48% had either secondary surgery or chemotherapy before referral. Seven patients required exenteration with resection of the pelvic sidewall. Overall five-year survival was 47% versus 71% for those with a gross total resection but close margins. The most common complications were peripheral neuropathy, functional ureteral obstruction, and fistula formation. EBRT, tumor size after resection, grade, and patient age were associated with improved survival.

A retrospective study by Gao et al evaluated clinical outcomes and the toxicity of intraoperative, whole pelvic EBRT in advanced and recurrent ovarian carcinoma. Forty-five women with epithelial ovarian carcinoma were treated with IOERT; 25 had primary disease without distant metastasis at IOERT, and 20 patients had an isolated local recurrence after surgery. All 45 patients in this series underwent optimal cytoreductive surgery. Thirty-three patients received postoperative intraperitoneal chemotherapy, while seven received intravenous chemotherapy. Five patients refused concurrent chemotherapy. OS rates were analyzed using the Kaplan-Meier method. Tumor recurrence and metastasis were observed in 16 patients (35.6%). Of those, 14 patients (31.1%) relapsed and two patients (4.4%) had distant metastasis alone. Eight of 25 (32%) local failures were observed in the primary disease group, compared with 6/20 (30%) in the isolated local recurrence group (p=0.885). Actuarial local control at five-year follow-up was 31/45 (68.9%). Seventeen of the total 45 (37.8%) patients died; nine of 25 (36%) in the primary disease group, and eight of 20 (40%) in the isolated local recurrence group. The five-year OS and DFS rates were 28/45 (62.2%) and 25/45 (55.6%), respectively. In the primary disease group, the five-year OS and DFS rates were 16/25 (64%) and 14/25 (56%) (p>0.05, versus the isolated local recurrence group at 12/20 and 11/20, respectively). The OS and DFS in the IOERT plus intraperitoneal group were 25/33 (75.8%) and 23/33 (69.7%), respectively, which were superior to the rates achieved with IOERT plus intraoperative chemotherapy (p<0.05). The major complication of IOERT was neuropathy. Five (11.1%) patients developed peripheral neurotoxicity.

**Head and Neck Cancers**

Zeidan et al reported on two case series of head and neck cancers. In the first publication, they reported on the use of IORT for patients with advanced cervical metastasis. For this series, between August 1982 and July 2007, 231 patients underwent neck dissections as part of initial therapy or as salvage treatment for advanced cervical node metastases resulting from head and neck malignancies. IORT was administered as a single fraction to a dose of 15 Gy or 20 Gy in most patients. OS at one, three, and five years after surgery and IORT was 58%, 34%, and 26%, respectively. Recurrence-free survival (RFS) at one, three, and five years was 66%, 55%, and 49%, respectively. Disease recurrence was documented in 83 (42.8%) patients. The recurrences were regional in 38 patients, local in 20 patients, and distant failures in 25 patients. The authors
concluded that IORT results in effective local disease control at acceptable levels of toxicity. The authors indicate that these results support the initiation of a phase III trial comparing outcomes for patients with cervical metastasis treated with or without IORT. The second publication reviewed the authors’ experience with the use of IORT for primary or recurrent cancer of the parotid gland. For this study, conducted between 1982 and 2007, 96 patients were treated with gross total resection and IORT for primary or recurrent cancer of the parotid gland. Of the 96 patients, 33 had previously undergone EBRT as a component of definitive therapy. Also, 34 patients had positive margins after surgery, and 40 had perineural invasion. IORT was administered as a single fraction of 15 or 20 Gy. The median follow-up period was 5.6 years. In this series, one patient experienced local recurrence, 19 developed regional recurrence, and 12, distant recurrence. The RFS rate at one, three, and five years was 82%, 69%, and 65%, respectively. The one-, three-, and five-year OS rate after surgery and IORT was 88%, 66%, and 56%, respectively. Complications developed in 26 patients. The authors concluded that IORT results in local disease control at acceptable levels of toxicity and should be considered for patients with primary or recurrent cancer of the parotid gland.

Thirty-four patients with recurrent head and neck cancer received IORT at another U.S. center. At median follow-up of 23 months (range, 6-54 months), eight patients were alive and without evidence of disease. The one- and two-year estimates for in-field local progression-free survival rates were 66% and 56%, respectively, with 13 (34%) in-field recurrences. One- and two-year distant metastases-free survival rates were 81% and 62%, respectively, with ten patients (29%) developing distant failure. One- and two-year OS rates were 73% and 55%, respectively, with median time to OS of 24 months.

Pancreatic Cancer
Jingu et al reported 30-year experience with the use of IORT in pancreatic cancer. They retrospectively reviewed the records of 322 patients who received intraoperative radiotherapy with or without EBRT for localized pancreatic cancer. One hundred ninety-two patients had no distant organ metastases or dissemination at the time of laparotomy and were enrolled in the study. Eighty-three patients underwent gross total resection: 48 patients with all gross disease resected and margins microscopically free of disease (R0), and 35 patients with all gross disease resected with margins microscopically positive for disease (R1); 109 patients underwent only biopsy or palliative resection. Fifty-five patients underwent adjuvant EBRT, and 124 received adjuvant chemotherapy. The median follow-up was 37.5 months. At the time of the analysis, 166 patients had recurrent disease, and 35 had local failure. The two-year local control and OS rates were 71.0% and 16.9%, respectively. A multivariate analysis showed that the degree of resection (R0-1 vs R2 [partial resection with tumor left behind], HR=1.97, p=0.001) and adjuvant chemotherapy (yes vs no, HR=1.54, p=0.028) had significant impacts on OS. Late gastrointestinal morbidity of Common Terminology Criteria for Adverse Events grade 4 or 5 was observed in four of the patients.

Zygogianni et al conducted a systematic review of the literature on the effectiveness and safety of IORT in pancreatic cancer. The review assessed the potential impact of IORT on local control, quality of life, and OS. PubMed was searched from 1980 until 2010, and the search was restricted to articles published in English. Thirteen studies were included. The authors concluded
that the results of their review found no clear evidence to indicate that IORT was more effective than other therapies in treating pancreatic cancer.

A 2008 systematic review of the literature from 1995 to 2007 by Ruano-Ravina et al assessed the efficacy and safety of IORT in pancreatic cancer. Study inclusion criteria included a minimum of 30 patients and survival results based on a minimum three-month follow-up. Fourteen papers were included, one was an IORT technology assessment report, five were cohort studies, and eight were case series studies, two of which belonged to the same series. There were no published studies that assessed quality of life. The authors concluded that, in general, the studies showed that IORT could slightly increase survival among patients with pancreatic cancer in localized stages. However, there was no clear evidence to indicate that IORT was more effective than other therapies in treating pancreatic cancer in locally advanced and metastatic stages.

Reports of several series of patients treated with IORT for pancreatic cancer were identified. In some studies, IORT appeared to provide local control. Reports of a sampling of case series are summarized here. The largest series, a retrospective analysis of results in 201 patients treated with IORT after resection of pancreatic cancer (R0 [negative margins]: 147 patients; R1 [residual microscopic disease]: 63 patients), was performed by investigators in Japan. Fifty-four patients also had postoperative EBRT, and 114 patients had chemotherapy. Median follow-up of the surviving 62 patients was 26.3 months (range, 2.7-90.5 months). Fifteen percent of patients had positive margins, usually posterior. Median follow-up of surviving patients was 26.3 months (range, 2.7-90.5 months). At the time of analysis, 150 patients had disease recurrences, local failure was seen in 31 patients, and the two-year local control rate was 83.7%. The median survival time and the two-year actuarial OS in all 210 patients were 19.1 months and 42%, respectively. The authors concluded that IORT yields an excellent local control rate with infrequent severe late toxicity and that IORT combined with chemotherapy confers a survival benefit compared with IORT alone. Comparisons to other current management approaches are not made. A U.S. center reports a retrospective review of 23 patients treated between 1990 and 2001. Most tumors (83%) were located in the head of the pancreas. Most patients (83%) had IORT at the time of definitive surgery. Three patients had preoperative chemoradiation. Median and mean follow-up were 6.5 and 21 months, respectively. Kaplan-Meier two-year infield control, locoregional control, distant metastasis-free survival, and OS were 83%, 61%, 26%, and 27%, respectively. Cai et al reported on 194 consecutive patients treated with IORT for unresectable locally advanced pancreatic cancer between 1978 and 2010. The median OS was 12 months. Survival rates at one, two, three and five years were 49%, 16%, 6%, and 3% respectively. Favorable factors included IORT applicator diameter of 8cm or less, a Charlson age-comorbidity index of three or less and treatment with chemotherapy. The median OS increased to 21.2 months in patients with all three factors. Investigators at another U.S. center found that IORT did not improve locoregional control and did not alter survival in 37 patients who underwent pancreaticoduodenectomy for periampullary tumors including pancreatic cancers.

Renal Cell Cancer
Paly et al reported on 98 advanced or locally recurrent renal cell carcinoma (RCC) patients treated with IORT during nephrectomy at nine different institutions during the period of 1985 and 2010. EBRT was given to 27% preoperatively and to 35% postoperatively. Median follow-
up time was 3.5 years for surviving patients. For advanced disease, the five-year OS, disease-specific survival (DSS), and DFS were 37%, 41% and 39%, respectively. For locally recurrent disease, the five-year OS, DSS, and DFS were 55%, 60% and 52% and reported to be favorable to patients treated with resection without IOERT.

Calvo et al reported 20-year outcomes in 25 patients with locoregionally recurrent (n=10) RCC after radical nephrectomy or locoregionally advanced primary RCC (n=15) who were treated with IOERT. Fifteen patients (60%) received perioperative EBRT. Surgical resection resulted in negative margins (R0) in six patients (24%) and residual microscopic disease (R1) in 19 patients (76%). The median follow-up for surviving patients was 22.2 years (range, 3.6-26 years). OS and DFS at five and ten 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 five years were 80% and 22%, respectively. One patient died within 30 days of surgery (4%). Six patients (24%) experienced acute or late toxicities of Grade 3 or higher according to the National Cancer Institute Common Toxicity Criteria v4.

Hallemeier et al reported outcomes of a multimodality therapy combining maximal surgical resection and IOERT for patients with locoregionally (LR) recurrent RCC after radical nephrectomy or LR advanced primary RCC.31 From 1989 through 2005, a total of 22 patients with LR recurrent (n=19) or LR advanced primary (n= 3) RCC were treated with this multimodality approach. Twenty-one patients (95%) received perioperative EBRT with a median dose of 45 Gy (range, 41.4-55). Surgical resection was R0 (negative margins) in five patients (23%) and R1 (residual microscopic disease) in 17 patients (77%). The median IOERT dose delivered was 12.5 Gy (range, 10-20). The OS and DFS at one, five, and ten years were 91%, 40%, and 35% and 64%, 31%, and 31%, respectively. Central recurrence (within the IOERT field), LR relapse (tumor bed or regional lymph nodes), and distant metastases at five years were 9%, 27%, and 64%, respectively. The authors concluded that in patients with LR recurrent or LR advanced primary RCC, a multimodality approach of perioperative EBRT, maximal surgical resection, and IOERT yielded encouraging results, and this approach warrants further study.

Glioma

Nemoto et al reported results or treatment with IORT for 32 patients with previously untreated malignant gliomas over a ten-year period. Patients also had postoperative radiotherapy. Eleven patients had histological diagnoses of anaplastic astrocytoma (AA), and 21 had glioblastoma (GBM). Median survival time was 24.7 months in the AA group versus 33.6 months for matched historical controls. Differences in one-, two-, and five-year survival between IORT-treated patients and historical controls were also not significant. In the GBM group, median survival was 13.3 months in the IORT-treated patients versus 14.6 months in the matched controls. Data on one-, two-, and five-year survival were also not significantly different between groups.

The literature search also found recent reports of single institution case series of patients treated with IORT for head and neck tumors; however, comparisons with conventional treatment were not found. A large case series of patients was reported by Chen et al between 1991 and 2004; 137 patients underwent gross total resection and IORT for recurrence or persistence of locoregional cancer of the head and neck. 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, 3–122 months). One-, two-, and three-year estimates of in-field control after surgery and IORT 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. A series of Phase 2 clinical trials of three multimodal intensification regimens consisting of perioperative cisplatin chemoradiotherapy, surgical resection with intraoperative radiotherapy, and postoperative paclitaxel and cisplatin chemoradiotherapy for advanced, resectable, previously untreated squamous cell cancer of the oral cavity, oropharynx, or hypopharynx were conducted at Ohio State University,34 and 123 patients were treated. Compliance (patients receiving full doses of chemotherapy and radiation within the prescribed time without delay or dose reduction and receiving all courses of treatment in the protocol) was 61%. Overall five-year survival by Kaplan-Meier analysis was 57% (46% in the first regimen, 56% in the second, and 68% in the third). Overall disease-specific five-year survival was 73%, with 60% for the first regimen, 78% for the second and 80% for the third. The overall locoregional disease control rate was 91%, and the rate of distant metastases was 13.8%. The precise contribution of IORT cannot be established from these data.

**Neuroblastoma**
Rich et al reported their experience using IORT after reresection in patients with locally recurrent or persistent high-risk neuroblastomas. They retrospectively reviewed 44 consecutive patients who received IORT at one institution between April 2000 and September 2009 after gross total resection of recurrent/persistent tumor. Median follow-up after IORT was 10.5 months. Each patient received prior chemotherapy and surgery, and 94.5% had previous EBRT. There was a 50.4% probability of local control. Median OS was 18.7 months (95% CI, 11.7 to 25.6 months). The authors concluded that intraoperative radiotherapy after reresection of locally recurrent/persistent neuroblastoma results in a reasonable rate of local control with acceptable morbidity and survival and that this approach should be considered in this high-risk population.

**Fibromatosis**
Roeder et al reviewed outcomes of 30 patients (31 lesions) with aggressive fibromatosis. Treatment with IORT was undertaken to avoid mutilating surgical procedures when complete surgical removal seemed to be unlikely or impossible. Median age was 31 years (range, 13-59 years). Resection status was close margin in six lesions, microscopically positive in 13, and macroscopically positive in 12. Median tumor size was 9cm. Twenty-five patients received additional EBRT. After a median follow-up of 32 months (range, 3-139 months), no disease-related deaths occurred. A total of five local recurrences were seen, resulting in actuarial three-year local control rates of 82% overall and 91% inside the IOERT areas. Trends to improved local control were seen for older age (>31 years) and negative margins, but none of these factors reached significance. Perioperative complications were found in six patients, in particular as wound healing disturbances in six patients and venous thrombosis in one patient. Late toxicity was seen in five patients.

**Summary**
In summary, the evidence suggests that intraoperative radiation therapy (IORT), as part of multimodal treatment of solid tumors, provides a benefit in local recurrence rates for many tumors. However, the impact of its use on survival rates (and the development of distant disease)
is less clear and, for some tumors, is achieved at the price of significant treatment-related morbidity. In addition, the impact of this modality compared with some of the newer radiation therapy techniques (that allow better targeting of tumor) and chemotherapy regimens is not known. Finally, since standard radiation therapy is often administered following IORT, it is more difficult to determine the incremental value of IORT. Given the available evidence, the strength of the evidence, along with the clinical input obtained in 2009, IORT may be considered as a medically necessary treatment option in patients with rectal cancer with very close or positive margins after resection. For the purposes of this policy, IORT may be considered as a medical necessary treatment option in patients with pancreatic cancer, pelvic malignancies, and locally advanced colorectal cancer. All other uses are considered investigational given the limited evidence, especially the lack of comparative data, regarding the impact on net health outcomes.

**Key Words:**
Intraoperative radiation therapy (IORT), malignancy, INTRABEAM

**Approved by Governing Bodies:**
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. The 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 or intraoperative radiotherapy treatments. The Mobetron mobile election beam accelerator designed for use in the operating room received 510(k) marketing clearance in 1998.

**Benefit Application:**
Coverage is subject to member’s specific benefits. Group specific policy will supersede this policy when applicable.

ITS: Home Policy provisions apply
FEP contracts: Special benefit consideration may apply. Refer to member’s benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

**Current Coding:**
CPT codes: 77424 IORT delivery, x-ray, single treatment session
           77425 IORT delivery, electrons, single treatment session
           77469 IORT management
Previous Coding:
CPT codes: S8049 Intraoperative radiation therapy (single administration) (Deleted effective April 1, 2012)

References:

Policy History:
Medical Policy Group, February 2005 (1)
Medical Policy Administration Committee, April 2005
Available for comment April 12-May 26, 2005
Medical Policy Group, January 2007 (1)
Medical Policy Group, January 2009 (1)
Medical Policy Group, June 2011 (3): Updated Governing Bodies
Medical Policy Group, July 2011 (3): Updated Key Points, Key Words & References
Medical Policy Group, October 2011 (3): Added ‘non-coverage’ paragraph for clarity to Policy section
Medical Policy Group, November 2011 (3): Added 2012 CPT Codes; deleted code S8049
Medical Policy Group, July 2012 (4): Removed ICD-9 diagnosis codes from policy section, Updated Key Points and References. No policy changes were made
Medical Policy Group, March 2013 (3): Added information on IORT of the breast (accelerated partial-breast irradiation) – updated key points and references; no change in policy statement
Medical Policy Panel, August 2013
Medical Policy Group, August 2013 (3): August 2013 Updates to Key Points and References; no change in policy statement
Medical Policy Group, June 2014 (3): Updated policy with link to CareCore National© medical policies effective August 1, 2014
Medical Policy Administration Committee, June 2014
Available for comment June 16 through July 31, 2014
Medical Policy Group, July 2014: Removed CareCore link. Transfer to CareCore is on hold until further notice.
Medical Policy Panel, August 2014
Medical Policy Group, August 2014 (3): 2014 Updates to Key Points & References; no change in policy statement

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member’s plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield’s administration of plan contracts.