Intraoperative Radiation Therapy

Policy Number: 8.01.08  Last Review: 10/2014

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for intraoperative radiation therapy when it is determined to be medically necessary because the criteria shown below are met.

When Policy Topic is covered
Use of intraoperative radiation therapy may be considered medically necessary in the following situation:
- Rectal cancer with positive or close margins with T4 lesions or recurrent disease.

When Policy Topic is not covered
Use of intraoperative radiation therapy is considered investigational for all other oncologic applications.

Description of Procedure or Service
Intraoperative radiation therapy is delivered directly to exposed tissues during surgery. It can be delivered by electron beams produced by linear accelerators (also called IOERT) or high-dose rate brachytherapy (HDR-IORT).

The evidence suggests that intraoperative radiotherapy (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 radiotherapy techniques (that allow better targeting of tumor) and chemotherapy regimens is not known. Finally, because standard radiotherapy 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. All other uses are considered investigational given the limited evidence, especially the lack of comparative data, regarding the impact on net health outcome.

Intraoperative radiation therapy (IORT) is designed to increase the intensity of radiation directly delivered to tumors. The tumor and associated tissues at risk for micrometastatic spread are directly visualized at operation. IORT is delivered directly to the tumor, and normal or uninvolved tissues are not exposed to radiation because they are removed or shielded from the treatment field. It can be delivered by electron beams produced by linear accelerators (also called IOERT), or high-dose rate brachytherapy (HDR-IORT). Most clinical experience involves IOERT. (1)

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 subsequently treated with external beam photon irradiation (EBRT).
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 electron beam accelerator designed for use in the operating room received 510(k) marketing clearance in 1998.

Rationale
This policy was initially developed in 1996; it was extensively updated in 2009 based on a MEDLINE search through May 2009. The most recent MEDLINE review is for the period of July 2013 through July 20, 2014. 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 radiation therapy (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 non-gynecological 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 1 randomized and 5 comparative) and 18 studies on locally recurrent rectal cancer. Twelve additional studies on treatment of rectal cancer without IORT were also reviewed. A meta-analysis wasn’t 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 3 months. Fifteen studies met the inclusion criteria and included one systematic review; the majority of studies were case series, except for 3, which had a comparative design. The median follow-up was over 3 years in only 6 studies and 5 years in 2 studies. Sample size was more than 100 patients in the majority of studies and more than 200 patients in 2 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 5-year OS was close to 65%. For recurrences, the 5-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 the 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 5 years of
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. The Mayo Clinic reported 5-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 and 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 3,003 patients. Indications for IORT were locally advanced disease in 1,792 patients and locally recurrent disease in 1,211 patients. Comparative studies found a significant effect favoring IORT for improved local control (odds ratio [OR]: 0.22; 95% confidence interval [CI]: 0.05-0.86; p=0.03), DFS (hazard ratio [HR]: 0.51; 95% CI: 0.31-0.85; p=0.009), and OS (HR 0.33; 95% CI: 0.2-0.54; p<0.001). With IORT, there was no increase in total (OR: 1.13; 95% CI: 0.77-1.65; p=0.57), urologic (OR: 1.35; 95% CI: 0.84-2.82; p=0.47), or anastomotic complications (OR: 0.94; 95% CI: 0.42-2.1; p=0.98); however, increased wound complications were noted after IORT (OR: 1.86; 95% CI: 1.03-3.38; p=0.049).

Investigators at the Mayo Clinic describe a large series of patients treated from April 1981 through January 2008. Six hundred seven patients with recurrent colorectal cancer 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 10-year survival rates were 30% and 16%, respectively. Survival estimates at 5 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 3-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 (external-beam radiotherapy (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 5 (16%) patients. OS at 5 years was 54.6 % (95 % CI: 48.57-60.58). 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 notes that it is not without complications. One randomized study compared IORT combined with postoperative external-beam radiation therapy (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 5-year local control rate for patients receiving radiation therapy was 89% versus 46% for the surgery only patients (p=0.03). OS did not differ as both groups had an actuarial 5-year OS of 60%.

Call et al reported outcomes in 61 patients with upper-extremity soft tissue sarcomas treated with external-beam radiotherapy, surgery, and IORT, with or without chemotherapy. The median patient age was 50 years old (median age 13 to 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 external-beam radiotherapy doses ranged from 19.80 Gy to 54.00 Gy. OS at 5 and 10 years was 72% and 58%, respectively. Local control at 5 and 10 years was 91% and 88%, respectively. Distant control at 5 and 10 years was 80% and 77%, respectively. Patients who were treated for recurrent disease had inferior 5-year OS compared with patients with a first diagnosis (63% vs. 74%; p=0.02) and lower 5-year local control rate (67% vs. 94%; p<0.01). For patients with residual disease at the resection margin, local control at 5 and 10 years was 100% and 86%, respectively, whereas for patients without residual tumor after resection, local control was 89% at both 5 and 10 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 9.75 cm) 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, 2 patients with primary disease and 3 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 10 of 36 patients, lymph node metastases in 2 of 35 patients, and distant metastases in 6 of 35 patients at a mean follow-up of 2.3 years. Actuarial local control was 63% and OS rate was 57% at 5 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. External-beam radiation was administered to the whole pelvic region in combination with chemotherapy, and then radical surgery with IORT was performed 6-8 weeks after the end of the external-beam radiation and chemotherapy treatment. After external-beam radiation 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 5-year DFS and the 5-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 external-beam radiation and chemotherapy followed by surgery and IORT in locally advanced cervical cancer patients was active in a subgroup of patients with pathological 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 10-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 10-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. 15 The site of the primary tumor was the cervix in 9, the uterus in 7, and the vagina in 1 patient. In patients with complete gross resection (n=13), the 3-year local control rate was 83% versus 25% in patients with gross residual disease. The overall 3-year survival rate was 54%.The overall distant metastasis-free rate was also 54%; 7 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 and colleagues report on a series of 25 patients who received radical resection and IORT for recurrent endometrial cancer at the 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 5-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 electron-beam radiation therapy 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 7 received intravenous chemotherapy. Five patients refused concurrent chemotherapy. Overall survival 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 2 patients (4.4%) had distant metastasis alone. Eight of 25 (32%) local failures were observed in the primary disease group, as compared to 6/20 (30%) in the isolated local recurrence group (p=0.885). Actuarial local control at 5-year follow-up was 31/45 (68.9%). Seventeen of the total 45 (37.8%) patients died; 9 of 25 (36%) in the primary disease group, and 8 of 20 (40%) in the isolated local recurrence group. The 5-year OS and DFS rates were 28/45 (62.2%) and 25/45 (55.6%), respectively. In the primary disease group, the 5-year OS and DFS rates were 16/25 (64%) and 14/25 (56%) (p>0.05, vs. 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 2 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. Overall survival at 1, 3, and 5 years after surgery and IORT was 58%, 34%, and 26%, respectively. Recurrence-free survival (RFS) at 1, 3, and 5 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 external-beam radiotherapy 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, 1 patient experienced local recurrence, 19 developed regional recurrence, and 12, distant recurrence. The RFS rate at 1, 3, and 5 years was 82%, 69%, and 65%, respectively. The 1-, 3-, and 5-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), 8 patients were alive and without evidence of disease. The 1- and 2-year estimates for in-field local progression-free survival rates were 66% and 56%, respectively, with 13 (34%) in-field recurrences. One- and 2-year distant metastases-free survival rates were 81% and 62%, respectively, with 10 patients (29%) developing distant failure. One- and 2-year OS rates were 73% and 55%, respectively, with median time to OS of 24 months.

**Pancreatic Cancer**

Jingu et al reviewed 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 external-beam radiotherapy 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 2-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], hazard ratio: 1.97, p=0.001) and adjuvant chemotherapy (yes vs. no, hazard ratio: 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 4 of the patients.

Zygogianni et al conducted a systematic review of the literature on the effectiveness and safety of IORT in pancreatic cancer. 23 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 and colleagues assessed the efficacy and safety of IORT in pancreatic cancer. 24 Study inclusion criteria included a minimum of 30 patients and survival results based on a minimum 3-month follow-up. Fourteen papers were included, one was an IORT technology assessment report, 5 were cohort studies, and 8 were case series studies, 2 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. 25 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 2-year local control rate was 83.7%. The median survival time and the 2-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. 26 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 2-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. 27 The median OS was 12 months. Survival rates at 1-, 2-, 3- and 5-years were 49%, 16%, 6%, and 3% respectively. Favorable factors included IORT applicator diameter ≤ 8 cm, a Charlson age-comorbiditity index ≤ 3 and treatment with chemotherapy. The median OS increased to 21.2 months in patients with all 3 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. 28

Renal Cell Cancer
Paly et al reported on 98 advanced or locally recurrent renal cell carcinoma (RCC) patients treated with IORT during nephrectomy at 9 different institutions during the period of 1985 and 2010. 29 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 5-year OS, disease-specific survival (DSS) and DFS were 37%, 41% and 39%, respectively. For locally recurrent disease, the 5-year OS, DSS and DFS were 55%, 60% and 52% and reported to be favorable to patients treated with resection without IORT.

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. 30 Fifteen patients (60%) received perioperative EBRT. Surgical resection resulted in negative margins (R0) in 6 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 5 and 10 years were 38% and 19% and 19% and 14%, respectively. Locoregional control (tumor bed or regional lymph nodes) and distant metastases-free survival rates at 5 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 external-beam radiotherapy (EBRT) with a median dose of 45 Gy (range, 41.4-55). Surgical resection was R0 (negative margins) in 5 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 1, 5, and 10 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 5 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 10-year period. 32 Patients also had postoperative radiation therapy. 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 1-, 2-, and 5-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 1-, 2-, and 5-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. 33 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 of them 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-, 2-, and 3-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 overall survival were 51%, 46%, and 36%, respectively. A series of Phase 2 clinical trials of 3 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, 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 5-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 5-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 re-resection 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 overall survival was 18.7 months (95% CI: 11.7-25.6 months). The authors concluded that intraoperative radiation therapy after re-resection 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 6 lesions, microscopically positive in 13, and macroscopically positive in 12. Median tumor size was 9 cm. 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 5 local recurrences were seen, resulting in actuarial 3-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 6 patients, in particular as wound healing disturbances in 5 patients and venous thrombosis in 1 patient. Late toxicity was seen in 5 patients.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov on July 20, 2014 identified no phase 3 trials on the use of IORT for the tumors addressed in this policy.

Clinical Input Received from Physician Specialty Societies and Academic Medical Centers

In response to requests, input was received through 1 physician specialty society and 2 academic medical centers (6 reviewers) while this policy was under review for October 2009. While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted. The input obtained was quite variable with some supporting use of IORT for multiple indications and others considering it investigational. The strongest support was for rectal cancer.

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. All other uses are considered investigational given the limited evidence, especially the lack of comparative data, regarding the impact on net health outcome.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network Guidelines**

NCCN guidelines for treatment of rectal cancer (v3.2014) indicate that “IORT, if available, should be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers.”

For colon cancer (v3.2014), NCCN guidelines state that “Intraoperative radiotherapy (IORT) should be considered for patients with T4 or recurrent cancers as an additional boost”.

For gynecological cancers, NCCN guidelines indicate that IORT is an option for patients with:

- **Cervical cancer (v1.2014):** Central pelvic recurrent cervical cancer after radiation therapy should be considered for pelvic exenteration with or without IORT. (category 3 for IORT). Non-central recurrent cervical cancer after radiation therapy- resection with IORT for close or positive margins (category 3). Distant metastases, amenable to local treatment, consider resection + RT or local ablative therapies + RT or TR + concurrent chemotherapy.
- **Uterine endometrial adenocarcinoma (v1.2014):** Recurrent endometrial cancer, for patients previously treated with external-beam radiation at the site of recurrence, resection +/- IORT.

NCCN guidelines do not address the use of IORT in ovarian cancer (v3.2014)

NCCN guidelines indicate that newer techniques such as brachytherapy, intraoperative RT (IORT), and intensity- modulated RT (IMRT) have led to improvement of treatment outcomes in patients with soft tissue sarcomas (v2.2014).

For pancreatic cancer, NCCN guidelines (v2.2014) state that “the role of IORT for unresectable and resectable cases is controversial and should only be performed at specialized centers in well selected cases. It is ideally used in cases where surgical resection may result in close or involved margins.

**U.S. Preventive Services Task Force Recommendations**

Intraoperative Radiation Therapy is not a preventive service.

**Medicare National Coverage**

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

**References**


**Billing Coding/Physician Documentation Information**

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**Additional Policy Key Words**
Policy Implementation/Update Information

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<tr>
<td>10/1/88</td>
<td>New policy added to the Radiology section, considered investigational.</td>
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<td>9/1/00</td>
<td>No policy statement changes.</td>
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<td>9/1/01</td>
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<td>9/1/02</td>
<td>Policy statement revised to indicate IORT may be medically necessary when there are no metastases and the outcome of treatment (surgical resection plus IORT) is expected to be curative (<em>five or more years survival</em>). Intraoperative radiation therapy (IORT) is considered not medically necessary as palliative treatment.</td>
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<td>Policy statement revised. May be considered medically necessary for some cases of rectal cancer and sarcomas. Other applications remain investigational. This change is effective 10/6/2009.</td>
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