Intraoperative Radiation Therapy (IORT)

Number: 0721

Policy
*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

I. Aetna considers intraoperative radiation therapy (IORT) medically necessary for the treatment of cervical cancer, colorectal cancer, soft tissue sarcoma (including retroperitoneal sarcoma), and uterine cancer.

II. Aetna considers intraoperative radiation therapy experimental and investigational for the treatment of the following indications (not an all-inclusive list) because its effectiveness for these indications has not been established:

- Brain tumors (e.g., glioblastomas) and brain metastasis
- Breast cancer
- Cholangiocarcinoma
- Conjunctival neoplasms (e.g., lymphoma, sebaceous carcinoma, and squamous cell carcinoma)
- Gastric cancer
- Head and neck cancer (e.g., middle ear tumors)
- Osteosarcoma
- Pancreatic cancer

Policy History

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Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
Prostate cancer
Renal cell carcinoma
Spinal metastases
Vertebral metastases.

See also CPB 0083 - Stereotactic Radiosurgery (../1_99/0083.html); CPB 0270 - Proton Beam and Neutron Beam Radiotherapy (../200_299/0270.html); CPB 0371 - Brachytherapy (../300_399/0371.html); CPB 0590 - Intensity Modulated Radiation Therapy (../500_599/0590.html).

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

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

The goal of IORT is to enhance local tumor control. Most patients receiving IORT are concurrently treated with high-dose external beam photon irradiation. The term “intraoperative radiation therapy” may also refer to intra-operative brachytherapy, the temporary or permanent implantation of radioactive seeds.

Intra-operative radiation therapy is usually a component of a multi-disciplinary treatment approach for localized cancers that can not be completely removed or that have a high risk of
recurring in nearby tissues. For patients with colorectal cancer, IORT has been associated with improved local control. Several case series have demonstrated that adjuvant IORT has the potential to improve response rates with acceptable toxicities and improve survival with locally advanced colorectal cancer (Taylor et al, 2002; Ratto et al, 2003; Hashiguchi et al, 2003; Pacelli et al, 2004). Thus, the positive impact of IORT on local control of colorectal cancer appears to justify the inclusion of this therapeutic modality.

Pacelli et al (2004) reported early and long-term results of pre-operative radiotherapy plus IORT to total mesorectal excision of middle and lower T3 rectal cancer patients (n = 113). Five-year, disease-specific survival was 81.4 % for those patients receiving pre-operative radiotherapy plus IORT (n = 69) compared to 58.1 % for those patients in the mesorectal excision group (n = 44). The rates of local recurrence at 5 years were 6.6 % and 23.2 % in pre-operative radiotherapy plus IORT group and total mesorectal excision group, respectively. The authors concluded that pre-operative radiotherapy plus IORT associated with total mesorectal excision reduced local recurrence rate and improved survival in T3 rectal cancer compared with total mesorectal excision alone.

Persons from the American Society of Therapeutic Radiation and Oncology (ASTRO) have commented that “[c]urrently, it [IORT] is primarily used for treating rectal cancers, although in the near future it may be used for additional sites. Studies indicate that IORT might be used to treat head and neck, abdomen, and pelvic cancers, and cancers in the extremities. IORT can reduce the length of treatment. The Stanford Cancer Center states, 'In some cases, no further radiation treatment is required following IORT making it a much more convenient approach for delivering therapy. Furthermore, physicians are able to shield surrounding organs from radiation, limiting side effects to healthy tissue" (Demanes and Rieke, 2005).

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for Oncology recommends IORT for
colorectal cancers and uterine cancers. Regarding the use of IORT in colon cancer, NCCN guidelines state: “Intraoperative radiation therapy, if available, should be considered for patients with T4 or recurrent cancers as an additional boost. Preoperative radiation is preferred for these patients to aid resectability. If IORT is not available, low dose external beam radiation could be considered, prior to adjuvant chemotherapy” (NCCN, 2006).

NCCN guidelines also recommend the use of IORT in selected rectal cancers: “Intraoperative radiation therapy, 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. If IORT is not available, 10 to 20 Gy external beam radiation to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy” (NCCN, 2006).

Regarding the use of IORT for uterine cancers, NCCN guidelines state that: “For patients previously treated with external-beam RT, recommended salvage therapy includes pelvic exenteration with or without IORT, palliative radiotherapy, hormonal therapy, or chemotherapy. Radical surgery, such as pelvic exenteration, has been performed with reported survival rates approximating 20%. For patients without prior RT to the site of recurrence, or with previous brachytherapy only, surgical exploration of pelvis and abdomen should be performed with or without IORT” (NCCN, 2005).

NCCN guidelines also discuss the use of IORT in cervical cancers: “Patients with a localized recurrence of cervical cancer after surgery should be evaluated for salvage radiotherapy. Salvage rates of approximately 40% have been reported in such situations. For patients who experience pelvic recurrences with no prior radiation therapy or who experience recurrences outside of the previously treated field, salvage therapy includes definitive pelvic radiation with or without platinum-based chemotherapy with or without brachytherapy. Patients with central pelvic recurrent disease after radiation therapy should
be evaluated for pelvic exenteration, with or without IORT (or, in carefully selected patients with small lesions, radical hysterectomy or interstitial reirradiation). Surgical mortality is generally 5% or lower, with survival rates between 20% and 6%. Concomitant measures with such radical procedures include adequate rehabilitation programs dealing with the psychosocial and psychosexual consequences of the operation and reconstructive procedures. Recurrence after pelvic exenteration should be treated with platinum-based chemotherapy or best supportive care or be enrolled in a clinical trial. Those with non-central disease should be treated with pelvic exenteration/laterally extended endopelvic resection/IORT, platinum-based chemotherapy, best supportive care, or participation in a clinical trial” (NCCN, 2005).

A review of IORT in the management of locally advanced gynecological malignancies by del Carmen et al (2000) reported that IORT can be utilized to maximize local tumor control. According to del Carmen and colleagues, “[r]eview of the available literature indicates that IORT may improve long-term local control and overall survival in women with pelvic sidewall and/or para-aortic nodal recurrence. The most encouraging results have been reported in cases with microscopic residual disease, following surgical debulking.” According to a more recent review by del Carmen and colleagues (2003), “[h]igher 5-year disease-free and overall survival rates have been documented in women who have microscopic residual disease, compared with those who have gross residual disease.”

Orecchia et al (2006) stated that IORT has been used in the treatment of various malignancies, mostly in combination with external beam radiation therapy. The long-term results suggest a positive impact on local controls that appear to be associated with increased survival. Modern IORT can be performed either with electron beams or photons, and has been used recently in early-stage cancer as a boost or as an exclusive treatment, especially for breast tumors, with extremely promising results. The results of different clinical studies have shown the feasibility of the technique and it is expected that its application
will become more widespread in the immediate future. The authors noted that intraoperative electron radiotherapy in the treatment of initial-stage breast cancer may be an excellent alternative to external beam radiation therapy in an appropriate selected group of patients; however, intensive long-term follow-up is needed to better assess local control and possible side effects.

Sauer and colleagues (2007) stated that breast-conserving surgery followed by whole-breast radiotherapy (WBRT) has become the standard treatment for the majority of patients with early breast cancer. While the indications for systemic adjuvant treatment have continuously expanded, there is a tendency to restrict post-operative radiotherapy to accelerated partial breast irradiation (APBI) instead of WBRT. These investigators described various techniques of APBI; and their respective advantages or potential drawbacks. Moreover, they reviewed the scientific evidence in the literature, which forms the basis for the consensus statements and recommendations of the German Society of Radiation Oncology, the German Society of Senology, and the Working Group for Gynecological Oncology of the German Cancer Society. The methods mainly used for APBI are: interstitial radiotherapy with multi-catheter technique, IORT, the MammoSite, or 3-D conformal external beam radiotherapy. These techniques have marked differences in dose distribution and homogeneity. The published range of local recurrence rates varies between 0 % to 37 %, the median follow-up from 8 to 72 months. The authors concluded that to-date, follow-up times mostly do not yet permit a definite judgment concerning the long-term effectiveness and side effects of APBI. The relevant societies in Germany support randomized clinical studies comparing APBI with WBRT in a well-defined subset of low-risk patients. Moreover, the authors expressly discouraged the routine use of APBI outside clinical trials. Until definite results show that APBI neither impairs therapeutic outcome nor cosmetic results, WBRT remains the gold standard in the treatment of early breast cancer.

The conclusion by Sauer et al (2007) is in agreement with that
of Mitsumori and Hiraoka (2008) who noted that APBI is still an investigational treatment in Japan, and the optimal method of radiation delivery as well as its long-term safety and effectiveness should be ascertained in clinical trials. In this regard, Blohmer et al (2008) stated that ongoing prospective and randomized studies are investigating for which patients IORT is sufficient as the sole irradiation method after previous surgery.

Kalapurakal et al (2006) reported the findings of a phase I study in which IORT (first dose level of 10 Gy) with the photon radiosurgery system was used to treat children with recurrent brain tumors. A total of 14 children received IORT; 8 had been previously irradiated. Thirteen children had ependymoma. The median follow-up period was 16 months. Three patients (21%) developed radiation necrosis on follow-up MRI scans 6 to 12 months after IORT. They had not been previously irradiated and had received 10 Gy to a depth of 5 mm. One required surgery and the other 2 had resolution of their lesions without treatment. All 3 patients were asymptomatic at the last follow-up. No other late toxicity was observed at the last follow-up visit. Eight patients (57%) had tumor control within the surgical bed after IORT. The authors concluded that these findings demonstrated the safety and feasibility of IORT to a dose of 10 Gy to 2 mm in children with previously irradiated brain tumors, while IORT to a dose of 10 Gy at 5 mm was associated with a greater complication rate.

Bergenfeldt and Albertsson (2006) summarized the development of adjuvant therapy for pancreatic cancer over the last 20 years. Four randomized controlled trials compared long-term survival of different treatments. The small GITSG-study supported combined chemoradiation, but the EORTC-study found no significant effect. A Norwegian study of adjuvant chemotherapy found an increased median survival, but no effect beyond 2 years. The large ESPAC-1 study showed a benefit for 5-FU based chemotherapy, while chemoradiation had a negative effect. Thus, evidence favors adjuvant therapy, but 5-FU may not be the ultimate drug. Support for
gemcitabine is given by preliminary data from a German randomized trial, and further American and European studies are upcoming. However, post-operative therapy is problematic, as 20 to 30% of resected patients never undergo treatment because of slow recovery or other reasons. Pre-operative therapy has some theoretical advantages, and moreover, patients with rapidly progressive disease may be spared surgery. Randomized controlled trials are lacking, but published results compared well with post-operative, adjuvant therapy. The value of locally targeted therapy is difficult to assess. Reasonable results have been obtained with regional chemotherapy, whereas IORT does not seem to increase survival despite reducing local recurrences.

Ruano-Ravina et al (2008) evaluated the safety and effectiveness of IORT in pancreatic cancer. These investigators conducted a systematic review of scientific literature from January 1995 to February 2007, including Medline, Embase, ISI Web of Science and HTA (Health Technology Assessment). By applying a series of inclusion criteria, 2 independent reviewers selected those studies in which a minimum of 30 patients received IORT and which furnished survival results based on a minimum 3-month follow-up. A total of 14 papers were included, 1 was an IORT assessment report, 5 were cohort studies, and the remaining 8 were case series studies, 2 of which belonged to the same series. In general, these studies showed that IORT could slightly increase survival among patients with pancreatic cancer in localized stages. However, the results were not conclusively in favor of IORT in the case of pancreatic cancer in locally advanced and metastatic stages. There were no published studies that assessed quality of life. The authors concluded that there is no clear evidence to indicate that IORT is more effective than other therapies in treating pancreatic cancer in locally advanced and metastatic stages.

Showalter et al (2009) performed a retrospective analysis of patients who underwent pancreatoduodenectomy (PD) between 1995 and 2005 to identify patients who underwent
resection with and without IORT. Data collected included age, gender, complications, margin status, stage, survival, and recurrence. Unadjusted analyses of the IORT and non-IORT groups were performed using Fisher’s chi-square method for discrete variables and Wilcoxon rank sum test for continuous variables. To account for biases in patient selection for IORT, a propensity score was calculated for each patient and adjusted statistical analyses were performed for survival and recurrence outcomes. Between January 1995 and November 2005, a total of 122 patients underwent PD for peri-ampullary tumors, including 99 pancreatic cancers. Of this group, 37 patients were treated with IORT, and there was adequate follow-up information for a group of 46 patients who underwent PD without IORT. The IORT group contained a higher percentage of Stage IIB or higher tumors (65 %) than in the non-IORT group (39.1 %), though differences in stage did not reach significance (p = 0.16). There was a non-significant decrease in the rate of loco-regional recurrence in patients who had IORT (39 % non-IORT versus 23 % IORT, p = 0.19). 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 (p = 0.78). In the propensity analyses, IORT did not significantly influence survival or recurrence after PD. The authors concluded that IORT can be safely added to management approaches for resectable pancreatic cancer, with acceptable morbidity and mortality. However, IORT did not improve loco-regional control and did not alter survival for patients with resected pancreatic cancer. In the future, IORT may be combined with novel therapeutic agents in the setting of a clinical trial in order to attempt to improve outcomes for patients with pancreatic cancer.

Czito and colleagues (2006) stated that the prognosis of patients with biliary cancers is poor. Although surgery is potentially curative in selected patients, local recurrence is common. The use of adjuvant or neoadjuvant radiation therapy improves local control and possibly survival. In locally advanced patients, radiation therapy provides palliation and may prolong survival. Concurrently administered chemotherapy may further
enhance these results. Newer radiation therapy techniques, including intra-luminal transcatheter brachytherapy, IORT, intensity-modulated radiation therapy (IMRT), and 3- and 4-dimensional treatment planning, permit radiation dose escalation without significant increases in normal tissue toxicity, thus increasing the effective radiation dose. Preliminary results of studies employing hepatic transplantation with radiation therapy are encouraging. Although these new approaches hold promise, the prognosis in patients with biliary cancers remains poor, and the integration of novel therapeutic strategies is indicated.

Tzeng et al (2006) noted that retroperitoneal soft tissue sarcoma is an uncommon cancer that is difficult to treat because of its location and proximity to vital organs. Complete gross resection, often involving en bloc resection, is the standard of care as it represents the only treatment that improves overall survival. Unlike extremity sarcoma, retroperitoneal sarcoma tumor mortality is from local recurrence. Radiation therapy is the only adjuvant treatment that has improved local control in several institutional series. However, there remains no definitive prospective, randomized controlled study that establishes the role of adjuvant radiation versus no radiation. Owing to significant radiation morbidity with adjacent organs, especially the small intestine, there exists no consensus on radiation timing, delivery method or dosing. Recent and current protocols use pre-operative external-beam radiation with or without a method of focal boost dosing. Methods of boost dosing include brachytherapy, IORT and IMRT. Further studies are needed to definitively include radiation therapy in the standard treatment of retroperitoneal soft tissue sarcoma and to find the optimal balance between acceptable radiation toxicity and effective local control in treatment protocols.

Ballo and colleagues (2007) assessed the clinical outcomes of patients with localized retroperitoneal soft tissue sarcoma (STS) treated with complete surgical resection and radiation. The medical records of 83 patients were reviewed retrospectively;
60 patients presented with primary disease and the remaining 23 had recurrence after previous surgical resection. With a median follow-up of 47 months, the actuarial overall disease-specific survival (DSS), distant metastasis-free survival, and local control (LC) rates were 44 %, 67 %, and 40 %, respectively. Of the 38 patients dying of disease, local disease progression was the sole site of recurrence for 16 patients and was a component of progression for another 11 patients. Multi-variate analysis indicated that histological grade was associated with the 5-year rates of DSS (low-grade, 92 %; intermediate-grade, 51 %; and high-grade, 41 %, p = 0.006). Multi-variate analysis also indicated an inferior 5-year LC rate for patients presenting with recurrent disease, positive or uncertain resection margins, and age greater than 65 years. The data did not suggest an improved local control with higher doses of external-beam radiation therapy (EBRT) or with the specific use of IORT. Radiation-related complications (10 % at 5 years) developed in 5 patients; all had received their EBRT post-operatively. The authors concluded that although pre-operative radiation therapy and aggressive surgical resection is well-tolerated in patients, local disease progression continues to be a significant component of disease death. In this small cohort of patients, the use of higher doses of EBRT or IORT did not result in clinically apparent improvements in outcomes.

Patel and DeLaney (2008) noted that bone sarcomas are rare primary tumors. Radiation therapy (RT) can be useful in securing local control in cases where negative surgical margins can not be obtained or where tumors are not resected. Recent technical advances in RT offer the opportunity to deliver radiation to these tumors with higher precision, thus allowing higher doses to the tumor target with lower doses to critical normal tissues, which can improve local tumor control and/or reduce treatment-related morbidity. These researchers conducted a survey of recent technical developments that have been applied to RT for bone sarcomas. Radiation therapy techniques that show promise include intensity-modulated photon RT, 3-D conformal proton RT, intensity-modulated proton RT, heavy charged-particle RT, IORT, and brachytherapy.
All of these techniques permit the delivery of higher radiation doses to the target and less dose to normal tissue than had been possible with conventional 3-D conformal radiation techniques. Protons deliver substantially less dose to normal tissues than photons. The authors concluded that data from clinical studies using these advanced radiation techniques suggest that they can improve the therapeutic ratio (the ratio of local control efficacy to the risk of complications).

In a feasibility study, Marucci et al (2008) evaluated the acute toxicity of IORT delivered as an "early boost" after tumor resection in patients with locally advanced head and neck cancer. A total of 25 patients were enrolled in the study. All patients underwent surgery with radical intent, and 17 had microvascular flap reconstruction. The IORT was delivered in the operating room; 20 patients received adjuvant EBRT. Five patients experienced various degrees of complications in the post-operative period, all of which were treated conservatively. One patient had a partial flap necrosis after EBRT that was treated with flap removal. Six deaths were recorded during the mean follow-up period of 8 months; none of the deaths was related to radiation treatment. The authors concluded that these findings showed that the use of IORT as an early boost is feasible with no increase in acute toxicity directly attributable to radiation.

Perry et al (2010) reported the use of high-dose-rate IORT (HDR-IORT) for recurrent head-and-neck cancer (HNC) at a single institution. A total of 34 subjects with recurrent HNC received 38 HDR-IORT treatments using a Harrison-Anderson-Mick applicator with Iridium-192. A single fraction (median of 15 Gy; range of 10 to 20 Gy) was delivered intra-operatively after surgical resection to the region considered at risk for close or positive margins. In all patients, the target region was previously treated with EBRT (median dose of 63 Gy; range of 24 to 74 Gy). The 1- and 2-year estimates for in-field local progression-free survival (LPFS), loco-regional PFS (LRPFS), distant metastases-free survival (DMFS), and overall survival (OS) were calculated. With a median follow-up for surviving
patients of 23 months (range of 6 to 54 months), 8 patients (24 %) are alive and without evidence of disease. The 1- and 2-year LPFS rates are 66 % and 56 %, respectively, with 13 (34 %) in-field recurrences. The 1- and 2-year DMFS rates are 81 % and 62 %, respectively, with 10 patients (29 %) developing distant failure. The 1- and 2-year OS rates are 73 % and 55 %, respectively, with a median time to OS of 24 months. Severe complications included cellulitis (n = 5), fistula or wound complications (n = 3), osteo-radionecrosis (n = 1), and radiation-induced trigeminal neuralgia (n = 1). The authors concluded that HDR-IORT has shown encouraging local control outcomes in patients with recurrent HNC with acceptable rates of treatment-related morbidity. They stated that longer follow-up with a larger cohort of patients is needed to fully assess the benefit of this procedure.

Drognitz et al (2008) retrospectively analyzed the impact of IORT on long-term survival in patients with resectable gastric cancer. From 1991 to 2001, a total of 84 patients with gastric neoplasms underwent gastectomy or subtotal resection with IORT (23 Gy, 6 to 15 MeV; IORT-positive [IORT(+) group). Patients with a history of additional neoadjuvant chemotherapy, histologically confirmed R1 or R2 resection, or reoperation with curative intention after local recurrence were excluded from further analysis. The remaining 61 patients were retrospectively matched with 61 patients without IORT (IORT-negative [IORT(−)] group) for Union Internationale Contre le Cancer (UICC) stage, patient age, histologic grading, extent of surgery, and level of lymph node dissection. Subgroups included post-operative UICC stages I (n = 31), II (n = 11), III (n = 14), and IV (n = 5). Mean follow-up was 4.8 years in the IORT(+) group and 5.0 years in the IORT(−) group. The overall 5-year patient survival rate was 58 % in the IORT(+) group versus 59 % in the IORT(−) group (p = 0.99). Subgroup analysis showed no impact of IORT on 5-year patient survival for those with UICC stages I/II (76 % versus 80 %; p = 0.87) and III/IV (21 % versus 14 %, IORT(+) versus IORT(−) group; p = 0.30). Peri-operative mortality rates were 4.9 % and 4.9 % in the IORT(+) versus IORT(−) group. Total surgical complications were more common
in the IORT(+) than IORT(‐) group (44.3 % versus 19.7 %; p < 0.05). The loco-regional tumor recurrence rate was 9.8 % in the IORT(+) group. The authors concluded that use of IORT was associated with low loco-regional tumor recurrence, but had no benefit on long-term survival while significantly increasing surgical morbidity in patients with curable gastric cancer.

In a phase I-II study, Saracino et al (2008) examined the use of IORT following radical prostatectomy for prostate cancer. A total of 34 patients with localized prostate cancer with only 1 risk factor (Gleason score greater than or equal to 7, Clinical Stage [cT] greater than or equal to 2c, or prostate-specific antigen [PSA] of 11 to 20 ng/ml) and without clinical evidence of lymph node metastases were treated with radical prostatectomy (RP) and IORT on the tumor bed. A dose-finding procedure based on the Fibonacci method was employed. Dose levels of 16, 18, and 20 Gy were selected, which are biologically equivalent to total doses of about 60 to 80 Gy administered with conventional fractionation, using an alpha/beta ratio value of 3. At a median follow-up of 41 months, 24 (71 %) patients were alive with an undetectable PSA value. No patients died from disease, whereas 2 patients died from other malignancies. Loco-regional failures were detected in 3 (9 %) patients, 2 in the prostate bed and 1 in the common iliac node chain outside the radiation field. A PSA rise without local or distant disease was observed in 7 (21 %) cases. The overall 3-year biochemical progression-free survival rate was 77.3 %. The authors concluded that this dose-finding study showed the feasibility of IORT in prostate cancer also at the highest administered dose.

In a phase II clinical study, Lemanski et al (2010) examined the feasibility and the effectiveness of IORT as an alternative to conventional boost radiation after breast-conserving surgery in elderly patients. These investigators included 94 patients older than 65 years. Among them, 42 patients presented with all the inclusion criteria, i.e., stages pT0 to pT1 and pN0, ductal invasive unifocal carcinoma, and tumor-free margin of greater than 2 mm. Intra-operative radiation therapy was delivered
using a dedicated linear accelerator. One 21-Gy fraction was prescribed and specified at the 90% isodose, using electrons. In-vivo dosimetry was performed for all patients. The primary end point was the quality index. Secondary end points were quality-of-life, local recurrences, cosmetic results, and specific and overall rates of survival. The median follow-up was 30 months (range of 12 to 49 months), and median age was 72 years (range of 66 to 80 years). The median tumor diameter was 10 mm. All patients received the total prescribed dose. No acute grade 3 toxicities were observed. End points for all but 1 patient corresponded to acceptable quality index criteria. Pre-treatment quality-of-life scores were maximal, and no significant decrease was observed during follow-up. Cosmesis was good to excellent at 6 months. Two patients experienced recurrence but underwent salvage mastectomy. The authors concluded that these findings confirm that exclusive partial-breast IORT is feasible for treating early-stage breast cancer in the elderly. Intra-operative radiation therapy may be considered an alternative treatment for a selected population and offers a safe 1-step treatment.

In a prospective, randomized, non-inferiority trial, Vaidya et al (2010) compared targeted IORT versus whole breast radiotherapy for breast cancer. Women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 28 centers in 9 countries. Patients were randomly assigned in a 1:1 ratio to receive targeted IORT or whole breast EBRT, with blocks stratified by center and by timing of delivery of targeted IORT. Neither patients nor investigators or their teams were masked to treatment assignment. Post-operative discovery of pre-defined factors (e.g., lobular carcinoma) could trigger addition of EBRT to targeted IORT (in an expected 15% of patients). The primary outcome was local recurrence in the conserved breast. The pre-defined non-inferiority margin was an absolute difference of 2.5% in the primary endpoint. All randomized patients were included in the intention-to-treat analysis. A total of 1,113 patients were randomly allocated to targeted IORT and 1,119 were allocated to EBRT. Of 996
patients who received the allocated treatment in the targeted IORT group, 854 (86 %) received targeted IORT only and 142 (14 %) received targeted IORT plus EBRT. In the EBRT group, 1,025 (92 %) patients received the allocated treatment. At 4 years, there were 6 local recurrences in the IORT group and 5 in the EBRT group. The Kaplan-Meier estimate of local recurrence in the conserved breast at 4 years was 1.20 % (95 % confidence interval [CI]: 0.53 to 2.71) in the targeted IORT and 0.95 % (0.39 to 2.31) in the EBRT group (difference between groups 0.25 %, -1.04 to 1.54; p = 0.41). The frequency of any complications and major toxicity was similar in the 2 groups (for major toxicity, targeted IORT, 37 [3.3 %] of 1,113 versus EBRT, 44 [3.9 %] of 1,119; p = 0.44). Radiotherapy toxicity (Radiation Therapy Oncology Group grade 3) was lower in the targeted IORT group (6 patients [0.5 %]) than in the external EBRT group (23 patients [2.1 %]; p = 0.002). The authors concluded that for selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted IORT should be considered as an alternative to EBRT delivered over several weeks.

Wenz and associates (2010) developed a novel approach to deliver IORT during kyphoplasty and reported the first treated case, which dealt with a 60-year old patient with metastasizing breast cancer who under chemotherapy and later presented with a newly diagnosed painful metastasis in the 12th thoracic vertebra. Under general anesthesia, a bi-pedicular approach into the vertebra was chosen with insertion of specially designed metallic sleeves to guide the electron drift tube of the miniature X-ray generator. This was inserted with a novel sheet designed for this approach protecting the drift tube. A radiation dose of 8 Gy in 5-mm distance (50 kV X-rays) was delivered. The kyphoplasty balloons were inflated after IORT and polymethylmethacrylate cement was injected. The whole procedure lasted less than 90 minutes. The authors concluded that this novel, minimally invasive procedure can be performed in standard operating rooms and may become a valuable option for patients with vertebral metastases providing immediate stability and local control. They noted that a phase I/II study is
under way to establish the optimal dosage.

Marchioro et al (2012) noted that intra-operative electron beam radiotherapy (IOERT) for prostate cancer is a radiotherapeutic technique, giving high-doses of radiation during radical prostatectomy (RP). These investigators presented the published treatment approaches for IORT analyzing functional outcome, morbidity, and oncological outcome in patients with clinical intermediate-high-risk prostate cancer. A systematic review of the literature was performed, searching PubMed and Web of Science. A "free text" protocol using the term intraoperative radiotherapy and prostate cancer was applied. A total of 10 records were retrieved and analyzed including more than 150 prostate cancer patients treated with IOERT. The authors concluded that IOERT represents a feasible technique with acceptable surgical time and minimal toxicity. They stated that a greater number of cases and longer follow-up time are needed in order to assess the long-term side effects and oncological outcome.

Ruano-Ravina et al (2012) evaluated the safety and effectiveness of IORT for early breast cancer through a systematic review. A total of 15 studies met the inclusion criteria. Most studies assessed the combined treatment with IORT (10 to 24 Gy) and EBRT (45 to 50 Gy) on early stage breast cancer (T0-2). Local control was over 95 % for 1 and 4 years of follow-up and the 5-year OS was 99 %. The TARGIT-A study found a similar survival comparing IORT with standard treatment. The incidence of acute and chronic complications was scarce. IORT is well-tolerated by patients and acute and late toxicities are low. There are no differences in survival for IORT-treated patients versus standard treatment.

Zurrida et al (2012) stated that wide tumor resection plus post-operative whole breast irradiation is standard treatment for early breast cancer. Irradiation decreases recurrence rates, but may cause poor cosmesis, breast pain, and cardiac and lung toxicity. Accelerated partial breast irradiation is increasingly used in the hope of increasing convenience, decreasing
sequelae and maintaining cure rates. Intra-operative radiotherapy with electrons is an attractive accelerated partial breast irradiation technique because collimator placement is under the direct control of the surgeon who removes the tumor, the skin is spared, shielding protects the chest wall and complete irradiation can be given in a single intra-operative session (avoiding 5 to 7 weeks of whole breast irradiation). The authors concluded that IORT with electrons seems as safe as whole breast irradiation; however, long-term results on local control and survival are not available yet.

The American College of Radiology (ACR)'s Appropriateness Criteria® on "Conservative surgery and radiation -- stage I and II breast carcinoma" (Bellon et al, 2011) stated that "[t]here has also been interest in single-fraction intraoperative radiation therapy (using either electrons or low-energy photons). At present, however, there are very limited follow-up data, and this remains an experimental approach. Accrual is ongoing to a phase III trial cosponsored by the National Surgical Bowel and Breast Program and the Radiation Therapy Oncology Group (RTOG®) randomizing patients with stage 0-II cancer who have undergone lumpectomy to either whole-breast irradiation or PBI. There are other randomized trials ongoing in Canada and Europe examining this question, but their results are several years away".

Hershko et al (2012) described their experience with intra-operative electron radiotherapy (IOeRT) at the Rambam Health Care Campus in Haifa since they began utilizing this modality in 2006. From April 2006 to September 2010, 31 patients affected by unifocal invasive duct breast carcinoma less than or equal to 2 cm diameter received wide local resection followed by intra-operative radiotherapy with electrons. Patients were evaluated for early and late complications, and other events, 1 month after surgery and every 3 months thereafter for the duration of the first 2 years. After a mean follow-up of 36 months, 7 patients developed mild breast fibrosis and 3 suffered from mild post-operative infection. Rib fractures were observed in 4 patients before routine lead shielding was initiated. Additional
whole-breast irradiation was given to 4 patients. None of the patients developed local recurrences or other ipsilateral cancers. Similarly, no contralateral cancers or distant metastases were observed. The authors concluded that intra-operative electron radiotherapy may be an alternative to external beam radiation therapy in an appropriate selected group of early-stage breast cancer patients. Moreover, they stated that long-term results of clinical trials are required to better evaluate the indications and utility of this technique in the management of breast cancer.

Leonardi et al (2012) evaluated late toxicity and cosmetic outcome after intra-operative radiotherapy using electrons (ELIOT) as sole treatment modality in early breast cancer patients. A total of 119 patients selected randomly among 1,200 cases was analyzed. Late toxicities were documented using the LENT-SOMA scoring system, cosmesis was evaluated with the Harvard scale, and a numeric rating scale was used to assess symptoms. After a median follow-up of 71 months, grade II fibrosis was observed in 38 patients (31.9 %) and grade III fibrosis in 7 patients (5.9 %). Post-operative complications (12.6 %) did not correlate with late toxicity. Physicians and patients scored cosmesis as excellent or good in 84 % and 77.3 % of the cases, respectively. Patient satisfaction was higher than 90 %. The authors concluded that in the study, ELIOT gives low and acceptable long-term toxicity. They stated that a longer follow-up and a larger number of patients are needed to confirm these promising results.

Maluta et al (2012) reported the results of a single-institution, phase II trial of accelerated partial breast irradiation (APBI) using a single dose of intraoperative electron radiation therapy (IOERT) in patients with low-risk early stage breast cancer. A cohort of 226 patients with low-risk, early stage breast cancer were treated with local excision and axillary management (sentinel node biopsy with or without axillary node dissection). After the surgeon temporarily re-approximated the excision cavity, a dose of 21 Gy using IOERT was delivered to the tumor bed, with a margin of 2 cm laterally. With a mean follow-up of
46 months (range of 28 to 63 months), only 1 case of local recurrence was reported. The observed toxicity was considered acceptable. The authors concluded that APBI using a single dose of IOERT can be delivered safely in women with early, low-risk breast cancer in carefully selected patients. Moreover, they stated that a longer follow-up is needed to ascertain its efficacy compared to that of the current standard treatment of whole-breast irradiation.

Sawaki et al (2014) stated that IORT is under evaluation in breast-conserving surgery because the feasibility of the IORT procedure including transportation of the patient under general anesthesia is not well-established. Thus, this prospective single-center pilot study aimed to test the feasibility of IORT at a single dose of 21 Gy in Japanese breast cancer patients. The primary endpoint was early toxicity; the secondary endpoint was late toxicity. Patients with histologically or cytologically proven primary early breast cancer were eligible. Inclusion criteria were as follows: (i) T < 2.5 cm; (ii) desire for breast-conserving surgery; (iii) age greater than 50 years; (iv) surgical margin greater than 1 cm; (v) intra-operative pathologically free margins; and (vi) sentinel node negative. Exclusion criteria were (i) contraindications to radiation therapy; (ii) past radiation therapy for the same breast or chest; (iii) extensive intra-ductal component; and (iv) a tumor located in the axillary tail of the breast. All patients gave written informed consent. Partial resection was performed with at least a margin of 1 cm around the tumor. The patient was transported from the surgical suite to the radiation room. Radiation at 21 Gy was delivered directly to the mammary gland. Toxicity was evaluated with the Common Terminology Criteria for Adverse Events V4.0. A total of 5 patients were enrolled in this pilot study and received 21 Gy. Follow-up ranged from 7.8 to 11.0 months (median of 10.2). Intraoperative transportation to the radiation room during the surgical procedure under general anesthesia was performed safely in all patients. Treatment-related toxicities within 3 months were deep connective tissue fibrosis (grade 1, n = 3) and pain (grade 1, n = 3). There was no case of wound infection, wound dehiscence, or soft tissue
necrosis. Overall, there was no severe adverse event. The authors concluded that the procedure was tolerated very well in this first group of Japanese female patients treated with IORT, as was the case with European women. They stated that a longer follow-up is needed for the evaluation of any potential late side effects or recurrences; and a phase II study is now being conducted for the next group of patients.

Engel et al (2013) noted IORT with low-energy x-rays is increasingly used in breast-conserving therapy (BCT). Previous non-randomized studies have observed mammographic changes in the tumor bed to be more pronounced after IORT. The purpose of this study was to re-assess the post-operative changes in a randomized single-center subgroup of patients from a multi-center trial (TARGIT-A). In this subgroup (n = 48) 27 patients received BCT with IORT, 21 patients had BCT with standard whole-breast radiotherapy serving as controls. Overall 258 post-operative mammograms (median follow-up of 4.3 years, range of 3 to 8) were retrospectively evaluated by 2 radiologists in consensus focusing on changes in the tumor bed. Fat necroses showed to be significantly more frequent (56 % versus 24 %) and larger (8.7 versus 1.6 sq cm, median) after IORT than those in controls. Scar calcifications were also significantly more frequent after IORT (63 % versus 19 %). The authors stated that the high incidence of large fat necroses in this study confirmed previous study findings. However, the overall higher incidence of calcifications in the tumor bed after IORT represents a new finding, requiring further attention.

Vanderwalde et al (2013) performed a phase II study of pre-excision IORT for early-stage breast cancer. Patients greater than or equal to 48 years of age with invasive ductal carcinoma, less than or equal to 3 cm, and clinically node-negative were eligible for this study, which was approved by institutional review board. Ultrasound was used to select electron energy and cone size to cover the tumor plus 1.5 to 2.0 cm lateral margins and 1 cm deep margins (90 % isodose). Fifteen Gy was delivered with a Mobetron irradiator, and immediate needle-localized partial mastectomy followed. Local event results were
updated using the Kaplan-Meier method. A total of 53 patients received IORT alone. Median age was 63 years, and median tumor size was 1.2 cm. Of these, 81% were positive for estrogen receptor or progesterone receptor, 11% were positive for human epidermal growth factor receptor 2, and 15% were triple-negative. Also, 42%, 49%, and 9% would have fallen into the Suitable, Cautionary, and Unsuitable groups, respectively, of the American Society of Therapeutic Radiation Oncology consensus statement for accelerated partial breast irradiation. Median follow-up was 69 months. Ipsilateral events occurred in 8 of 53 patients. The 6-year actuarial rate of ipsilateral events was 15% (95% CI: 7% to 29%). The crude event rate for Suitable and Cautionary groups was 1 of 22 (5%) and 7 of 26 (27%), respectively. Overall survival was 94.4%, and breast cancer-specific survival was 100%. The authors concluded that the rate of local events in this study is a matter of concern, especially in the Cautionary group. On the basis of these findings, pre-excision IORT, as delivered in this study, may not provide adequate local control for less favorable early-stage breast cancers.

An UpToDate review on “Role of radiation therapy in breast conservation therapy” (Pierce and Sabel, 2013) does not mention the use of IORT as a management tool. Furthermore, the NCCN’s clinical practice guideline on “Breast cancer” (Version 3.2013) does not mention IORT as a management tool for breast conservation.

Zygogianni et al (2012) noted that pancreatic cancer is rarely curable, and the OS rate at 5 years is under 4%. This study aimed to assess the efficacy, effectiveness and safety of IORT as treatment in pancreatic cancer, by means of a systematic review of the literature. These investigators searched Pubmed from 1980 until 2010 by means of prospective randomized trials. The aim was to assess the potential impact of IORT on local control, quality of life and OS. The search was restricted to articles published in English. Intra-operative radiation therapy offers the opportunity to administer high-doses of irradiation to areas of neoplastic involvement while attempting
simultaneously to spare normal tissues in the region from potentially damaging radiation exposure. However, the results were not in favor of IORT in the case of pancreatic cancer in locally advanced and metastatic stages. The authors concluded that there is no clear evidence to indicate that IORT is more effective than other therapies in treating pancreatic cancer.

Niewald et al (2009) retrospectively evaluated the results after a regimen of surgery, IORT, and external beam radio-therapy (EBRT) for soft tissue sarcomas. A total of 38 consecutive patients underwent IORT for soft tissue sarcoma; 29 were treated for primary tumors, 9 for recurrences. There were 14 cases with liposarcomas, 8 with leiomyosarcomas, 7 with malignant fibrous histiocytomas; 27/38 tumors were located in the extremities, the remaining ones in the retro-peritoneum or the chest. Radical resection was attempted in all patients; a R0-resection was achieved in 15/38 patients, R1 in 12/38 pats and R2 in 4/38 pats. IORT was performed using a J-125 source and a HDR (high dose rate) after-loading machine after suturing silicone flaps to the tumor bed. The total dose applied ranged from 8-15 Gy/0.5 cm tissue depth measured from the flap surface. After wound healing, EBRT was applied in 31/38 patients with total doses of 23-56 Gy dependent on resection status and wound situation. The mean duration of follow-up was 2.3 years. A local recurrence was found in 10/36 patients, lymph node metastases in 2/35, and distant metastases in 6/35 patients. The actuarial local control rate was 63 %/5 years. The overall survival rate was 57 %/5 years. There was no statistically significant difference between the results after treatment for primaries or for recurrences. Late toxicity to the skin was found in 13/31 patients, wound healing problems in 5/31 patients. A neuropathy was never seen. The authors concluded that the combination of surgery, IORT, and EBRT yields favorable local control and survival data, which were well within the range of the results reported in the literature. The complication rates, however, are considerable although the complications are not severe, they should be taken into account when therapy decisions are made.
Call et al (2014) reviewed outcomes for patients who received IORT for upper-extremity sarcoma. These investigators identified patients with upper-extremity tumors who were treated with EBRT, surgery, and IORT, with or without chemotherapy. Kaplan-Meier estimates for overall survival (OS), central control (CC), local control (LC), and distant control (DC) were obtained. A total of 61 patients were identified. Median age was 50 years (range of 13 to 95 years). Median follow-up was 5.9 years. Eleven patients had gross (R2; n = 1) or microscopic (R1; n = 10) disease at the time of IORT. IORT doses ranged from 7.50 to 20.00 Gy. External beam radiotherapy doses ranged from 19.80 to 54.00 Gy. OS at 5 and 10 years was 72 % and 58 %, respectively. LC at 5 and 10 years was 91% and 88%, respectively. DC at 5 and 10 years was 80% and 77%, respectively. Patients treated for recurrent disease had inferior 5-year OS compared with patients with first diagnoses (63% vs. 74%; P=0.02) and lower 5-year LC (67 % versus 94 %; p < 0.01). For patients with R1 or R2 resections, LC at 5 and 10 years was 100 % and 86 %, respectively; for patients with R0 resections, LC was 89 % at both 5 and 10 years (p = 0.98). Severe toxicity attributable to treatment was noted for 4 patients (7 %). The authors concluded that for upper-extremity sarcoma, treatment including IORT was associated with excellent LC, limb preservation, and survival. LC rates were excellent for patients with positive margins after resection. Patients with recurrent disease had worse outcomes, but limb preservation was achievable for most patients.

An UpToDate review on “Local treatment for primary soft tissue sarcoma of the extremities and chest wall” (Delaney et al, 2013) states that “For patients treated preoperatively, 50 Gy is administered in 25 fractions over five weeks followed three to four weeks later by a conservative resection. A boost dose to 66 Gy may be given postoperatively or intraoperatively for microscopically positive margins and to 75 Gy if there is gross residual disease. In patients with frozen section evidence of close or positive margins, a boost can be delivered by placement of brachytherapy catheters or intraoperative electron beam radiation therapy”.
Also, NCCN’s clinical practice guideline on “Soft tissue sarcoma” (Version 1.2013) states that “Advances in RT technology such as brachytherapy, intensity-modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT) have led to the improvement of treatment outcomes in patients with STS”.

Sedmayer et al (2013) evaluated the outcome after partial breast re-irradiation for in-breast tumor recurrence (IBTR) following second breast conserving surgery (BCS) as alternative to salvage mastectomy. A survey of the literature was performed including publications between 2002 and 2012 (PubMed). Strategies comprised partial breast radiotherapy by external beam radiotherapy (EBRT), interstitial brachytherapy (BT) in low-, high- and pulse-dose rate technique, combined EBRT/BT, and IORT. Published evidence is scarce, with altogether 10 articles identified, in sum reporting about 310 patients. The vast majority (82 %) was treated by brachytherapy. Selection criteria for a second breast conservation attempt were comparable within all reports: all women presented with T0-2 recurrent lesions, late onset after primary treatment (70 months, mean of means) and no evidence of metastatic disease before undergoing gross tumor resection with free surgical margins. Treatment doses were in a similar range for brachytherapy (LDR 30 to 55 Gy, HDR 30 to 34 Gy; PDR 40 to 50 Gy), biologically comparable to the only series exclusively using EBRT (50 Gy). Follow-up times amounted 49 months (mean of the means, range of 21 to 89). Oncologic results were similar among the different methods with local control rates ranging between 76 % and 100 %, and disease free and overall survival rates comparable to mastectomy series. Acute toxicity was low in all cohorts. All authors reported cosmetic outcome, scoring results from excellent-to-good in 60 to 80 % of patients, mostly without using standardized evaluation schemes. Major late effects were fibrosis in re-irradiated parenchyma as a function of dose and volume, asymmetry (primarily due to double surgery), and breast pain. There were hardly any G3 and no G4 late reactions noted. The authors concluded that in a highly selected group of patients with IBTR, partial breast irradiation after second BCS is a viable
alternative to mastectomy, yielding high breast preservation rates without compromising oncologic safety. Whereas the evidence for brachytherapy is more solid, there is still little information about the effectiveness of PBI via EBRT or novel strategies like IORT, which therefore should preferably be investigated within trials.

Shah et al (2014) analyzed the cost-efficacy of IORT compared with whole-breast irradiation (WBI) and accelerated partial-breast irradiation (APBI) for early-stage breast cancer. Data for this analysis came from 2 phase III trials: the TARGIT (Targeted Intraoperative Radiotherapy) trial and the ELIOT (Electron Intraoperative Radiotherapy) trial. Cost analyses included a cost-minimization analysis and an incremental cost-effectiveness ratio analysis including a quality-adjusted life-year (QALY) analysis. Cost analyses were performed comparing IORT with WBI delivered using 3-dimensional conformal radiotherapy (3D-CRT), APBI 3D-CRT, APBI delivered with intensity-modulated radiotherapy (IMRT), APBI single-lumen (SL), APBI multi-lumen (ML), and APBI interstitial (I). Per 1,000 patients treated, the cost savings with IORT were $3.6 to $4.3 million, $1.6 to $2.4 million, $3.6 to $4.4 million, $7.5 to $8.2 million, and $2.8 to $3.6 million compared with WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I, respectively, with a cost decrement of $1.6 to $2.4 million compared with APBI 3D-CRT based on data from the TARGIT trial. The costs per QALY for WBI 3D-CRT, APBI IMRT, APBI SL, APBI ML, and APBI I compared with IORT were $47,990 to $60,002; $17,335 to $29,347; $49,019 to $61,031; $108,162 to $120,173; and $36,129 to $48,141, respectively, based on data from the ELIOT trial. These results were consistent with APBI and WBI being cost-effective compared with IORT. The authors concluded that based on cost-minimization analyses, IORT represents a potential cost savings in the management of early-stage breast cancer. However, absolute reimbursement is misleading, because when additional medical and non-medical costs associated with IORT are factored in, WBI and APBI represent cost-effective modalities based on cost-per-QALY analyses. They (WBI and APBI) remain the standard of care.
Vaidya et al (2014) stated that the TARGIT-A trial compared risk-adapted radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) versus fractionated EBRT for breast cancer. These investigators reported 5-year results for local recurrence and the first analysis of OS. TARGIT-A was a randomized, non-inferiority trial. Women aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned in a 1:1 ratio to receive TARGIT or whole-breast EBRT, with blocks stratified by center and by timing of delivery of targeted intraoperative radiotherapy: randomization occurred either before lumpectomy (pre-pathology stratum, TARGIT concurrent with lumpectomy) or after lumpectomy (post-pathology stratum, TARGIT given subsequently by reopening the wound). Patients in the TARGIT group received supplemental EBRT (excluding a boost) if unforeseen adverse features were detected on final pathology, thus radiotherapy was risk-adapted. The primary outcome was absolute difference in local recurrence in the conserved breast, with a pre-specified non-inferiority margin of 2.5 % at 5 years; pre-specified analyses included outcomes as per timing of randomization in relation to lumpectomy. Secondary outcomes included complications and mortality. Patients were enrolled at 33 centers in 11 countries, between March 24, 2000, and June 25, 2012. A total of 1,721 patients were randomized to TARGIT and 1,730 to EBRT. Supplemental EBRT after TARGIT was necessary in 15.2 % [239 of 1,571] of patients who received TARGIT (21.6 % pre-pathology, 3.6 % post-pathology). A total of 3,451 patients had a median follow-up of 2 years and 5 months (IQR 12 to 52 months), 2,020 of 4 years, and 1,222 of 5 years. The 5-year risk for local recurrence in the conserved breast was 3.3 % (95 % CI: 2.1 to 5.1) for TARGIT versus 1.3 % (0.7 to 2.5) for EBRT (p = 0.042). TARGIT concurrently with lumpectomy (pre-pathology, n = 2,298) had much the same results as EBRT: 2.1 % (1.1 to 4.2) versus 1.1 % (0.5 to 2.5; p = 0.31). With delayed TARGIT (post-pathology, n = 1,153) the between-group difference was larger than 2.5 % (TARGIT 5.4 % [3.0 to 9.7] versus EBRT 1.7 % [0.6 to 4.9]; p = 0.069). Overall, breast cancer mortality was much the same between groups (2.6 % [1.5 to 4.3] for TARGIT versus 1.9 % [1.1 to 3.2] for EBRT; p =
but there were significantly fewer non-breast-cancer deaths with TARGIT (1.4 % [0.8 to 2.5] versus 3.5 % [2.3 to 5.2]; p = 0.0086), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9 % (2.7 to 5.8) for TARGIT versus 5.3 % (3.9 to 7.3) for EBRT (p = 0.099). Wound-related complications were much the same between groups but grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1,720 versus 13 of 1,731, p = 0.029). The authors concluded that TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected as per the TARGIT-A trial protocol, as an alternative to post-operative EBRT.

Alvarado et al (2014) stated that the TARGIT-A Trial is an international randomized, prospective trial comparing IORT for equivalence to EBRT following lumpectomy for invasive breast cancer in selected low-risk patients; early results suggested that outcomes are similar. In addition to effectiveness data and cost considerations, the preferences of patients should help inform practice. This study was undertaken to explore and quantify preference in choosing between IORT and the current standard, EBRT. Eligible subjects were current or past candidates for breast-conserving surgery and radiation being seen at the University of California, San Francisco Breast Care Center. A trade-off technique varying the risk of local recurrence for IORT was used to quantify any additional accepted risk that these patients would accept to receive either treatment. Patients were first presented with a slideshow comparing EBRT with the experimental IORT option before being asked their preferences given hypothetical 10-year local recurrence risks. Patients were then given a questionnaire on demographic, social and clinical factors. Data from 81 patients were analyzed. The median additional accepted risk to have IORT was 2.3 % (-9 to 39 %), mean 3.2 %. Only 7 patients chose to accept additional risk for EBRT; 22 accepted IORT at no additional risk; and the remaining 52 chose IORT with some additional risk. Patients weigh trade-offs of risks and benefits when presented with medical treatment choices. The authors concluded that these findings
showed that the majority of breast cancer patients will accept a small increment of local risk for a simpler delivery of radiation. Moreover, they stated that further studies that incorporate outcome and side effect data from the TARGIT-A trial clarify the expected consequences of a local recurrence, and include an expanded range of radiation options that could help guide clinical decision making in this area.

UpToDate reviews on “Overview of the treatment of newly diagnosed, non-metastatic breast cancer” (Taghian et al, 2014) and “Treatment protocols for breast cancer” (Brenner et al, 2014) did not mention IORT as a management tool.

Furthermore, NCCN’s clinical practice guideline on “Breast cancer” (Version 3.2014) does not mention the use of IORT as a management tool.

Habl and colleagues (2013) analyzed their experience with IOERT followed by moderate doses of EBRT in patients with locally recurrent renal cell carcinoma. From 1992 to 2010, a total of 17 patients with histologically proven, locally recurrent renal cell carcinoma (median tumor size of 7 cm) were treated by surgery and IOERT with a median dose of 15 Gy. All patients met the premise of curative intent including 7 patients with oligo-metastases at the time of recurrent surgery, which were resected and/or irradiated. The median time interval from primary surgery to local recurrence was 26 months; 11 patients received additional 3D-conformal EBRT with a median dose of 40 Gy. Surgery resulted in free but close margins in 6 patients (R0), while 9 patients suffered from microscopic (R1) and 2 patients from macroscopic (R2) residual disease. After a median follow-up of 18 months, 2 local recurrences were observed, resulting in an actuarial 2-year local control rate of 91%. Eight patients developed distant failures, predominantly to liver and bone, resulting in an actuarial 2-year PFS of 32%. An improved PFS rate was found in patients with a larger time interval between initial surgery and recurrence (greater than 26 months). The actuarial 2-year OS rate was 73%. Lower histological grading (G1/2) was the only factor associated with
improved OS. Peri-operative complications were found in 4 patients; no IOERT specific late toxicities were observed. The authors concluded that combination of surgery, IOERT and EBRT resulted in high local control rates with low toxicity in patients with locally recurrent renal cell cancer despite an unfavorable surgical outcome in the majority of patients. However, PFS and OS were still limited due to a high distant failure rate, indicating the need for intensified systemic treatment especially in patients with high tumor grading and short interval to recurrence.

Also, NCCN’s clinical practice guideline on “Kidney cancer” (Version 3.2014) does not mention the use of IORT as a management tool.

Silverstein et al (2014a) reported that 2 randomized IORT trials for early-stage breast cancer were recently published. The ELIOT Trial used electrons (IOERT), and the TARGIT-A Trial Update used 50-kV X-rays (IORT). These studies were compared for similarities and differences. The results were analyzed and used to determine which patients might be suitable for single-dose treatment. The primary sources of data were the ELIOT Trial and TARGIT-A Trial, as well as a comprehensive analysis of the peer-reviewed literature of APBI using 50-kV X-rays or electrons. Studies published or presented prior to March 2014 were analyzed for efficacy, patient restrictions, complications, and outcome. With a median follow-up of 5.8 years, the 5-year recurrence rates for ELIOT versus EBRT patients were 4.4 % and 0.4 %, respectively, p = 0.0001. A low-risk ELIOT group was identified with a 5-year recurrence rate of 1.5 %. With a median follow-up of 29 months, the 5-year recurrence rates for the TARGIT-A versus EBRT patients were 3.3 % and 1.3 %, respectively, p = 0.042. The authors concluded that with 5.8 years of median follow-up, IOERT appears to have a subset of low-risk women for whom IOERT is acceptable. With 29 months of median follow-up the results of IORT with 50-kV devices are promising, but longer follow-up data are needed. They stated that at the current time, single-fraction IOERT or IORT patients should be treated under strict
institutional protocols.

Esposito et al (2015) noted that IORT constitutes a paradigm shift from the conventional 3 to 5 weeks of whole-breast EBRT. Intra-operative radiotherapy enables delivery of radiation at the time of excision of the breast tumor, targeting the area at highest risk of recurrence, while minimizing excessive radiation exposure to healthy breast tissue. The rationale for IORT is based on the observation that over 90% of local recurrences after breast-conserving surgery occur at or near the original operation site. These investigators reviewed trials of IORT delivered with different techniques and devices. Intra-operative radiotherapy is a very attractive option for delivering radiotherapy, reducing the traditional fractionated treatment to a single fraction administered at the time of surgery. It has been shown to be associated with reduced toxicity and has several potential benefits over EBRT. Only 2 randomized clinical trials (RCTs) have been published to-date. The TARGIT-A and ELIOT trials have demonstrated that IORT is associated with a low rate of local recurrence, although higher than that after EBRT (TARGIT-A: 3.3 versus 1.3 % respectively, p = 0.042; ELIOT: 4.4 versus 0.4 %, p < 0.001). However, the local recurrence rate for IORT fell within the predefined 2.5 % non-inferiority margin in TARGIT-A, and the 7.5 % equivalence margin in ELIOT. The authors concluded that longer follow-up data from existing trials, optimization of patient criteria and cost-effectiveness analyses are needed.

Giordano et al (2014) noted that glioblastoma multi-forme (GBM) is the most frequent primary malignant brain tumor in adults. Despite multi-modal therapies, almost all GBM recur within a narrow margin around the initial resected lesion. Thus, novel therapeutic intensification strategies must target both, the population of dispersed tumor cells around the cavity and the post-operative microenvironment. Intra-operative radiotherapy is a pragmatic and effective approach to sterilize the margins from persistent tumor cells, abrogate post-injury proliferative stimuli and to bridge the therapeutic gap between surgery and radio-chemotherapy. These researchers have set
up INTRAGO, a phase I/II dose-escalation study to evaluate the safety and tolerability of IORT added to standard therapy in newly diagnosed GBM. In contrast to previous approaches, the study involves the application of isotropic low-energy (kV) x-rays delivered by spherical applicators, providing optimal irradiation properties to the resection cavity. INTRAGO includes patients aged 50 years or older with a Karnofsky performance status of at least 50 % and a histologically confirmed (frozen sections) supra-tentorial GBM. Safety and tolerability (i.e., the maximum tolerated dose, MTD) will be assessed using a classical 3 + 3 dose-escalation design. Dose-limiting toxicities (DLT) are wound healing deficits or infections requiring surgical intervention, IORT-related cerebral bleeding or ischemia, symptomatic brain necrosis requiring surgical intervention and early termination of EBRT (before the envisaged dose of 60 Gy) due to radiotoxicity. Secondary end-points are PFS and OS. The study is registered with clinicaltrials.gov, number: NCT02104882 (Registration Date: 03/26/2014).

Wernicke et al (2014) noted that resected brain metastases (BrMs) have a high rate of local recurrence without adjuvant therapy. Adjuvant whole-brain radiotherapy remains the standard of care with a local control rate greater than 90 %. However, whole-brain radiotherapy is delivered over 10 to 15 days, which can delay other therapy and is associated with acute and long-term toxicities. Permanent cesium-131 ((131)Cs) implants can be used at the time of metastatic resection, thereby avoiding the need for any additional therapy. In a phase I/II clinical trial, these researchers evaluated the safety, feasibility, and efficacy of a novel therapeutic approach with permanent (131)Cs brachytherapy at the resection for brain metastases. After institutional review board approval was obtained, 24 patients with a newly diagnosed metastasis to the brain were accrued to a prospective protocol between 2010 and 2012. There were 10 frontal, 7 parietal, 4 cerebellar, 2 occipital, and 1 temporal BrMs. Histology included lung cancer (n = 16), breast cancer (n = 2), kidney cancer (n = 2), melanoma (n = 2), colon cancer (n = 1), and cervical cancer (n = 1). Stranded (131)Cs seeds were
placed as permanent volume implants. The prescription dose was 80 Gy at a 5-mm depth from the resection cavity surface. Distant metastases were treated with stereotactic radiosurgery (SRS) or whole-brain radiotherapy, depending on the number of lesions. The primary end-point was local (resection cavity) freedom from progression (FFP). Secondary end-points included regional FFP, distant FFP, median survival, OS, and toxicity. The median follow-up was 19.3 months (range of 12.89 to 29.57 months). The median age was 65 years (range of 45 to 84 years). The median size of resected tumor was 2.7 cm (range of 1.5 to 5.5 cm), and the median volume of resected tumor was 10.31 cm\(^3\) (range of 1.77 to 87.11 cm\(^3\)). The median number of seeds used was 12 (range of 4 to 35), with a median activity of 3.82 mCi per seed (range of 3.31 to 4.83 mCi) and total activity of 46.91 mCi (range of 15.31 to 130.70 mCi). Local FFP was 100 %. There was 1 adjacent leptomeningeal recurrence, resulting in a 1-year regional FFP of 93.8 % (95 % CI: 63.2 % to 99.1 %). One-year distant FFP was 48.4 % (95 % CI: 26.3 % to 67.4 %). Median OS was 9.9 months (95 % CI: 4.8 months, upper limit not estimated) and 1-year OS was 50.0 % (95 % CI: 29.1 % to 67.8 %). Complications included CSF leak (n = 1), seizure (n = 1), and infection (n = 1). There was no radiation necrosis. The authors concluded that the use of post-resection permanent (131)Cs brachytherapy implants resulted in no local recurrences and no radiation necrosis. This treatment was safe, well-tolerated, and convenient for patients, resulting in a short radiation treatment course, high response rate, and minimal toxicity. They stated that these findings merit further study with a multi-center trial.

In a non-randomized, prospective study, Weil et al (2015) examined the feasibility of IORT using a portable radiation source to treat newly diagnosed, surgically resected, solitary BrM. A total of 23 patients with histologically confirmed BrM were treated with an Intra-beam device that delivered 14 Gy to a 2-mm depth to the resection cavity during surgery. In a 5-year minimum follow-up period, PFS from the time of surgery with simultaneous IORT averaged (± SD) 22 ± 33 months (range of 1 to 96 months), with survival from the time of BrM
treatment with surgery+IORT of 30 ± 32 months (range of 1 to 96 months) and OS from the time of first cancer diagnosis of 71 ± 64 months (range of 4 to 197 months). For the Graded Prognostic Assessment (GPA), patients with a score of 1.5 to 2.0 (n = 12) had an average post-treatment survival of 21 ± 26 months (range of 1 to 96 months), those with a score of 2.5 to 3.1 (n = 7) had an average post-treatment survival of 52 ± 40 months (range of 5 to 94 months), and those with a score of 3.5 to 4.0 (n = 4) had an average post-treatment survival of 17 ± 12 months (range of 4 to 28 months). A BrM at the treatment site recurred in 7 patients 9 ± 6 months post-treatment, and 5 patients had new but distant BrM 17 ± 3 months after surgery+IORT. Six patients later received whole-brain radiation therapy, 7 patients received radiosurgery, and 2 patients received both treatments. The median Karnofsky Performance Scale scores before and 1 and 3 months after surgery were 80, 90, and 90, respectively; at the time of this writing, 3 patients remain alive with a central nervous system (CNS) progression-free survival of greater than 90 months without additional BrM treatment. The authors concluded that the findings of this study demonstrated the feasibility of resection combined with IORT at a dose of 14 Gy to a 2-mm peripheral margin to treat a solitary BrM. Local control, distant control, and long-term survival were comparable to those of other commonly used modalities. They stated that surgery combined with IORT seems to be a potential adjunct to patient treatment for CNS involvement by systemic cancer.

In a retrospective case-series study, Marr and colleagues (2015) described the results of patients with diffuse conjunctival neoplasms treated with radioactive phosphorus 32 (32P)-impregnated flexible film. This study was conducted between January 1, 2010, and January 1, 2013 at Memorial Sloan-Kettering Cancer Center. A total of 7 eyes (6 patients) were treated for diffuse conjunctival squamous cell carcinoma, sebaceous carcinoma, or lymphoma that had recurrent or residual disease after primary treatment. Patients underwent mapping biopsies and detailed conjunctival drawings to delineate the pathologic extent of the disease.
brachytherapy film used for treatment was the RIC Conformal Source Model 100 (RIC-100, RI Consultants). The RIC-100 is a flexible, thin (approximately 0.5-mm) film made of a polymer chemically bound to $^{32}$P. The radioactive $^{32}$P film was placed intra-operatively, allowed to stay in place until the prescription dose was reached, and then removed. The median dose at the prescription point (1 mm from the surface of the film) was 15 Gy (range of 5 to 17 Gy). Patients were tested for best-corrected visual acuity (BCVA), recurrence-free survival, and adverse events scored by using the Adult Comorbidity Evaluation-27 scale. Between 2010 and 2013, 7 eyes of 6 patients were treated. The median age of patients was 70 years. All patients had a recurrent or persistent neoplasm: 4 patients with squamous cell carcinoma, 1 with sebaceous carcinoma, and 1 with metachronous bilateral lymphomas were treated. The median treatment time was 19 minutes (range of 10 to 52 minutes). The median follow-up was 24.9 months (range of 3.1 to 38.2 months). Recurrence-free survival 24 months after brachytherapy was 75% (95% CI: 19 to 89.1). Two moderate adverse events and 1 severe adverse event occurred. Visual acuity was stable or improved in 5 of the 7 eyes (i.e., better than 20/70 in the 5 patients who retained their treated eye). The authors concluded that these findings showed the use of an intra-operative high-dose rate of $^{32}$P brachytherapy in selected cases of recalcitrant diffuse conjunctival neoplasms. They stated that this technique offers a novel adjunct in the treatment of these cancers; further follow-up and study are needed.

**Pancreatic Cancer:**

National Comprehensive Cancer Network’s clinical practice guideline on ”Pancreatic adenocarcinoma” (Version 1.2016) states that “The role of IORT is controversial .... Overall, there is no clear established role for IORT in patients with pancreatic cancer, and the panel believe it should only be performed at specialized centers”.

**Soft Tissue Sarcoma:**
National Comprehensive Cancer Network’s clinical practice guideline on “Soft tissue sarcoma” (Version 2.2016) states that “The use of IORT has provided encouraging results in patients with retroperitoneal STS .... IORT with or without EBRT has been effective in terms of local control and survival in patients with primary and recurrent retroperitoneal STS .... An ongoing study (NCT01566123) is examining preoperative RT, followed by surgery with IORT in patients with high-risk retroperitoneal sarcoma. Preliminary results suggest promising local control and OS rates”.

**Middle Ear Tumors:**

Cristalli and colleagues (2016) evaluated the safety, effectiveness and functional outcomes of IORT followed by IMRT in locally advanced stage tumors involving the middle ear. Data on 13 consecutive patients treated for malignant tumor of external auditory canal involving the middle ear were retrospectively reviewed. Median follow-up was 33 months (range of 6 to 133); 5 (38 %) patients were stage III and 8 (62 %) were Stage IV according to the University of Pittsburgh staging system. Lateral temporal bone resection (LTBR) was performed in all cases; LTBR was associated with parotidectomy in 5 (38 %) cases, and with neck dissection and parotidectomy in 6 (46 %) cases. No patients had gross residual tumor. Surgical treatment was followed by IORT (12 Gy) and IMRT (50 Gy). Adjuvant chemotherapy was used in 4 (30 %) cases.

Pre-operative and post-operative audiometric tests were performed to assess hearing loss; 5-year local-control (LC), 5-year distant-metastasis (DM), 5-year disease-free-survival (DFS) and 5-year OS were calculated with Kaplan-Meyer method. Significant changes in bone conduction were reported after treatment. Partial flap necrosis was the only early complication observed in 3 (23 %) cases, while meningeal fistula was seen in 1 (7.6 %) case as a late complication. The 5-year LC rate was 68 %; the 5-year DM rate was 90 %; the 5-year DFS rate was 61 %; and the 5-year OS rate was 69 %.

The authors concluded that IORT followed by IMRT for the treatment of advanced external auditory canal and middle ear
tumors appeared to be safe. No intra-operative death was reported; IORT may reduce the post-operative irradiation of remnant tissue obtaining the same full dose on the tumor bed. No complications of the residual external ear were observed; detriment of neurosensory hearing may be expected. They stated that future studies are needed to confirm the benefit of this procedure in the ear.

**Spinal Metastases:**

Bludau and associates (2015) stated that as a consequence of more effective systemic therapy, the survival of patients suffering from malignant tumors has been significantly improved but a longer life span is often associated with a higher incidence of osseous metastases. The majority of these metastases are localized in the spine causing pain, instability and neurological impairments. The inter-disciplinary management of spinal metastases previously consisted of stabilization followed by fractionated EBRT. A reduction in procedural severity and morbidity as well as consideration of self-sufficiency and hospitalization time are important target parameters for these palliative patients. Kyphoplasty combined with IORT (Kypho-IORT) is one of several modern treatment options, which involves a minimally invasive procedure with local high-dose trans-pedicular irradiation of the spine with low-energy (50 kV) X-rays. Immediately following irradiation, stabilization of the spine is carried out using kyphoplasty via the same access route so that a single stage procedure with excellent pain reduction and good local tumor control can be achieved. These researchers presented clinical data for this procedure and the different fields of indications were critically reviewed and compared to other therapeutic options. Methodological improvements and options for further individualization of therapy were demonstrated. The authors concluded that Kypho-IORT procedure is a safe, feasible and beneficial modern therapeutic option for instant stabilization and local tumor control in patients with spinal metastases. More than 100 operations have been successfully performed so that the method can be deemed suitable for inclusion in the
clinical routine. They noted that a phase II dose escalation study has now been completed and submitted for publication and a 2-arm non-inferiority trial (phase III study) for comparison with conventional irradiation is in progress.

**CPT Codes / HCPCS Codes / ICD-10 Codes**

*Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by "+":*

**ICD-10 codes will become effective as of October 1, 2015:**

**CPT codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>77424</td>
<td>Intraoperative radiation treatment delivery, x-ray, single treatment session</td>
</tr>
<tr>
<td>77425</td>
<td>Intraoperative radiation treatment delivery, electrons, single treatment session</td>
</tr>
<tr>
<td>77469</td>
<td>Intraoperative radiation treatment management</td>
</tr>
</tbody>
</table>

**Other CPT codes related to the CPB:**

<table>
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<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>77261 - 77299</td>
<td>Clinical treatment planning</td>
</tr>
<tr>
<td>77300 - 77399</td>
<td>Medical radiation physics, dosimetry, treatment devices, and special services</td>
</tr>
<tr>
<td>77401 - 77417</td>
<td>Radiation treatment delivery</td>
</tr>
<tr>
<td>77427 - 77499</td>
<td>Radiation treatment management</td>
</tr>
<tr>
<td>77750 - 77799</td>
<td>Clinical brachytherapy</td>
</tr>
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</table>

**ICD-10 codes covered if selection criteria are met:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>C18.0 - C21.8</td>
<td>Malignant neoplasm of colon, rectosigmoid junction, rectum, anus and anal canal</td>
</tr>
<tr>
<td>C46.1</td>
<td>Kaposi's sarcoma of soft tissue</td>
</tr>
<tr>
<td>C49.0</td>
<td>Malignant neoplasm of connective and soft tissue of head, face and neck</td>
</tr>
<tr>
<td>ICD-10 codes</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>C53.0 - C54.9</td>
<td>Malignant neoplasm of cervix uteri and of corpus uteri</td>
</tr>
<tr>
<td><strong>ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):</strong></td>
<td></td>
</tr>
<tr>
<td>C00.0 - C15.9</td>
<td>Malignant neoplasm of lip, oral cavity, pharynx and esophagus [head and neck cancer]</td>
</tr>
<tr>
<td>C16.0 - C16.9</td>
<td>Malignant neoplasm of stomach [gastric cancer]</td>
</tr>
<tr>
<td>C22.0 - C22.8</td>
<td>Malignant neoplasm of liver and intrahepatic bile ducts [cholangiocarcinoma]</td>
</tr>
<tr>
<td>C25.0 - C25.9</td>
<td>Malignant neoplasm of pancreas</td>
</tr>
<tr>
<td>C30.0 - C33</td>
<td>Malignant neoplasm of nasal cavity and middle ear, accessory sinuses, larynx and trachea [head and neck cancer]</td>
</tr>
<tr>
<td>C40.00 - C41.9</td>
<td>Malignant neoplasm of bone and articular cartilage [osteosarcoma]</td>
</tr>
<tr>
<td>C49.0</td>
<td>Malignant neoplasm of connective and soft tissue of head, face and neck [head and neck cancer]</td>
</tr>
<tr>
<td>C49.4 - C49.5</td>
<td>Malignant neoplasm of connective and soft tissue of abdomen and of pelvis [retroperitoneal sarcoma]</td>
</tr>
<tr>
<td>C50.011 - C50.929</td>
<td>Malignant neoplasm of breast</td>
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<tr>
<td>C61</td>
<td>Malignant neoplasm of prostate</td>
</tr>
<tr>
<td>C64.1 - C64.9</td>
<td>Malignant neoplasm of kidney, except renal pelvis</td>
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<tr>
<td>C69.00 - C71.9</td>
<td>Malignant neoplasm of eye and adnexa, meninges and brain [head and neck cancer and brain tumors] [conjunctival neoplasms (e.g., lymphoma, sebaceous carcinoma, and squamous cell carcinoma) and glioblastomas]</td>
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<tr>
<td>C72.20 - C72.59</td>
<td>Malignant neoplasm of cranial nerves [head and neck cancer and brain tumors]</td>
</tr>
</tbody>
</table>
The above policy is based on the following references:
7. Ratto C, Valentini V, Morganti AG, et al. Combined-


23. Letter from D. Jeffrey Demanes, M.D., Chair, American Society for Therapeutic Radiation Oncology (ASTRO) Regulatory Subcommittee and John W. Rieke, M.D., Chair, ASTRO Managed Care Workgroup to Aetna regarding IORT, December 9, 2005.


32. Agencia de Evaluacion de Tecnologias Sanitarias (AETS).


64. Ruano-Ravina A, Cantero-Muñoz P, Eraso Urién A. Efficacy


73. Engel D, Schnitzer A, Brade J, et al. Are mammographic changes in the tumor bed more pronounced after intraoperative radiotherapy for breast cancer? Subgroup


75. Pierce LJ, Sabel MS. Role of radiation therapy in breast conservation therapy. Last reviewed July 2013. UpToDate Inc. Waltham, MA.


77. Delaney TF, Harmon DC, Gebhardt MC. Local treatment for primary soft tissue sarcoma of the extremities and chest wall. Last reviewed July 2013. UpToDate Inc., Waltham, MA.


AETNA BETTER HEALTH® OF PENNSYLVANIA

Amendment to
Aetna Clinical Policy Bulletin Number: 0721
Intraoperative Radiation Therapy (IORT)

There are no amendments for Medicaid.

www.aetnabetterhealth.com/pennsylvania
Updated 03/2017