Intraoperative Radiation Therapy

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Intraoperative radiation therapy (IORT) delivers a high dose of radiation at the time of surgery in 1 fraction vs a standard course of treatment over several weeks. This article discusses the types of IORT, clinical investigation of the effectiveness of IORT, and the future of IORT as a treatment option. Current research findings regarding IORT for breast, cervical, prostate, brain, spine, skin, soft tissue, gastrointestinal, head and neck, and pediatric cancers are presented, with a focus on comparing outcomes for IORT vs standard treatment.

Intraoperative radiation therapy (IORT) was first used in the treatment of endometrial cancer in 1905 by Comas and Prio. IORT administers a high dose of ionizing radiation to a targeted region of interest during surgery to intensify the radiation dose and potentially improve therapeutic response. Using radiation at the time of surgery offers several advantages, including:

- Exposure of the tumor bed while shielding or displacing adjacent critical normal structures.
- Ability to see the treatment field, which limits setup uncertainties.
- Greater biologic effectiveness when delivered in a single fraction.
- Convenience of fewer visits to complete radiation therapy.
- Potentially increased radiosensitivity of oxygenated intact tumors or tumor beds.

IORT can be used as a stand-alone treatment or with external-beam radiation therapy (EBRT) and chemotherapy as part of a multimodality approach. The technique has been added to the treatment of many tumor sites, including the breast, cervix, prostate, brain, spine, skin, soft tissue, stomach, esophagus, gallbladder, pancreas, rectum, and head and neck.

Equipment

Equipment used for IORT procedures includes linear accelerators, which deliver treatment from outside the body, and a brachytherapy system, which administers treatment from inside the body (see Table 1). In general, the equipment delivers photon or electron radiation in a large, single fraction. Applicators in a variety of shapes and sizes are used to administer the treatment directly to the surgical site. Other accessory equipment includes beam modifiers such as a bolus, which is placed at the end of the applicator or on the surface of the patient to increase surface dose. Beam absorbers, such as lead shielding, are used to protect critical structures or for field matching. Many IORT systems are mobile and...
self-shielded so they can be used in nondedicated surgical settings. All equipment in clinical use is approved by the U.S. Food and Drug Administration (FDA). The following information concerning specific IORT equipment is current as of publication.

The Intrabeam linear accelerator (Carl Zeiss Meditec AG) delivers low-energy photons at a high dose rate of about 2.5 Gy per minute (see Figure 1). The reusable spherical applicators are made of biocompatible polyetherimide and range in diameter from 2.5 cm to 5 cm in 0.5-cm increments. Because of the shape of the applicator, the dose distribution is spherical, and the radical dose attenuation decrease is $1/r^3$ (where $r =$ distance). The pretreatment physics check covers the probe adjuster (mechanical), dynamic offsets (electrical), photodiode array source, and probe adjuster ion chamber holder output. The medical physicist, physician, and anesthesiologist remain in the operating room behind a glass shield for the duration of the treatment. Figure 2 shows the applicators used with the Intrabeam system.

Like Intrabeam, the Axxent electronic brachytherapy system (Xoft) also delivers 50 kV of energy at a similar high dose rate (see Figure 3). The equipment uses a proprietary miniature x-ray source that targets cancer cells while sparing healthy tissue. The source is inserted into different applicators for the treatment of early-stage breast cancer, gynecological cancer, and nonmelanoma skin cancer. The brachytherapy applicators are shaped to treat specific types of cancer. For example, the system offers balloon-shaped applicators for breast cancer treatment, cone-shaped surface applicators for nonmelanoma skin cancer, cylindrical

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**Table 1**

<table>
<thead>
<tr>
<th>Treatment Unit</th>
<th>Manufacturer</th>
<th>Radiation Source</th>
<th>Energy Range</th>
<th>Dose Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intrabeam</td>
<td>Carl Zeiss Meditec</td>
<td>Linear accelerator, photons</td>
<td>40-50 kV</td>
<td>3-10 Gy/min</td>
</tr>
<tr>
<td>LIAC 10</td>
<td>Sordina IORT Technologies</td>
<td>Linear accelerator, electrons</td>
<td>4, 6, 8, 10 MeV</td>
<td>3-20 Gy/min</td>
</tr>
<tr>
<td>LIAC 12</td>
<td>Sordina IORT Technologies</td>
<td>Linear accelerator, electrons</td>
<td>6, 8, 10, 12 MeV</td>
<td>3-20 Gy/min</td>
</tr>
<tr>
<td>Novac 7</td>
<td>Sordina IORT Technologies</td>
<td>Linear accelerator, electrons</td>
<td>4-10 MeV</td>
<td>10 Gy in &lt; 20 s</td>
</tr>
<tr>
<td>Mobetron</td>
<td>IntraOp</td>
<td>Linear accelerator, electrons</td>
<td>4, 6, 9, 12 MeV</td>
<td>2.5-10 Gy/min</td>
</tr>
<tr>
<td>Axxent</td>
<td>Xoft</td>
<td>Brachytherapy system, photons</td>
<td>50 kV</td>
<td>Nominal rate of 0.7 Gy/min</td>
</tr>
</tbody>
</table>

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**Figure 1.** Zeiss Intrabeam. Image courtesy of ©Carl Zeiss Meditec AG.
applicators for gynecological cancers, and a special applicator for cervical cancer treatment. Figure 4 shows the Xoft Axxent system source and applicators.

The Novac 7 and LIAC units (Sordina IORT Technologies) are electron accelerators, and the Novac 7 was the first electron linear accelerator used for IORT. The Novac 7 produces a range of energies and can deliver 10 Gy to a 6-cm field in less than 20 seconds. The radiation is emitted along the beam axis, and the staff in the operating room are exposed to a dose of 1 µSv per 10 Gy administered to the patient. There are 2 models of LIAC machines, LIAC 10 and LIAC 12; they differ primarily in energy capability. In addition to energies of 6, 8, and 10 MeV common to both units, the LIAC 10 can generate 4 MeV and the LIAC 12 can generate 12 MeV.

The Mobetron system (IntraOp Medical Corporation) was introduced in 1997. Mobetron uses flat applicators that range in size from 3 cm to 10 cm and 30° beveled applicators that range from 3 cm to 6 cm in diameter. At a source-to-skin distance of 50 cm and using an applicator 10 cm in diameter, the dose rate ranges from 2.5 Gy to 10 Gy per
measures. This section focuses on the Intrabeam QA procedures. The Intrabeam QA should be completed within 36 hours before each patient’s treatment. The radiation therapist conducts the QA procedure with a lead-shielded photodiode array and ion chamber specifically designed for the Intrabeam system.

Quality Assurance

Before performing any procedures using IORT, staff must complete appropriate quality assurance (QA) measures. This section focuses on the Intrabeam QA procedures. The Intrabeam QA should be completed within 36 hours before each patient’s treatment. The radiation therapist conducts the QA procedure with a lead-shielded photodiode array and ion chamber specifically designed for the Intrabeam system.

minute. Personnel in the operating room during treatment are exposed to less than 6 µSv at a distance of 3 m.

Figure 4. A. The Xoft System’s proprietary miniaturized x-ray source (shown lying on the tip of a finger) delivers a precise dose of radiation directly to cancerous cells, while sparing healthy tissue. B. Axxent vaginal applicators with source channel. C. Axxent spherical balloons ranging in size from 3-6 cm. The system’s balloon-shaped catheter is placed temporarily inside the lumpectomy cavity and used to deliver the single dose of radiation directly to the tumor bed, killing cancer cells while reducing risk to nearby healthy tissue such as the heart, lung, and ribs. D. The cervical applicator has multiple channels to deliver a precise dose of radiation to target areas of the cervix, uterus, endometrium, and vagina while minimizing exposure to healthy tissue. E. Skin electronic brachytherapy cone applicators are used to treat nonmelanoma skin cancer. Images courtesy of iCAD Inc.

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The first QA step is evaluating probe alignment. The probe directs the electron beam to strike a gold target and generate 50-kV photons. If the probe is not aligned properly, the electron beam does not hit the target accurately, resulting in asymmetric dose distribution. The alignment is measured with a photodiode array by determining the central axis alignment of the electron beam and the resulting symmetry of photons generated from the gold target. If the alignment is off by more than 0.1 mm, an adjustment is needed. The probe adjuster contains a light beam, light-emitting diode (LED), photo detector, and plunger. The light beam, LED, and photo detector measure probe offset. The plunger can push the probe back into alignment. The realignment process of pushing the plunger, rotating the adjuster, and pushing the plunger again until the 0.1 mm tolerance is satisfied is an essential task, but somewhat tedious. After the probe is aligned correctly, the offset and isotropy are measured.

If the electron beam alignment is off, the system adjusts the beam steering within the beam deflector. After adjustments, the photon symmetry is evaluated by comparing the photodiode voltage readings from the +X, –X, +Y, –Y, and +Z to ensure they are similar.

The final QA check involves measuring the dose rate with an ion chamber that has been calibrated by an accredited dosimetry calibration laboratory. The QA measurement is compared with the calibration dose rate measurement. The treatment time then is corrected to account for the difference between the measured and calibrated data. The difference usually is less than 2%, but time should be adjusted to ensure each patient receives 20 Gy to the applicator surface. Facilities also should have in place an emergency shutdown procedure (see Box).

**Emergency Shutdown of IORT Equipment**

In case of an emergency during an IORT treatment, a physicist or radiation oncologist present during the treatment should perform an emergency shutdown. Shutdown steps are as follows:

1. The physicist or radiation oncologist depresses the emergency off button located on the console.
2. The surgeon removes the applicator from the patient to outside the sterile field and prepares the patient for possible transfer out of the operating room (OR).
3. The physicist moves the stand away from the OR table, and moves the console and the lead glass shield away from the OR door to clear a path in case the patient needs to be moved out of the OR.
4. Once the patient is transported out of the room, the physicist removes the radiation source from the stand, places it in the storage tray, and completes the patient treatment documentation form.

**Treatment Planning**

When delivering IORT, it is difficult to plan treatment before the surgical procedure. The surgeon and radiation oncologist must rely on their experience and information gathered during the procedure to choose the applicator size and its positioning, the bevel angle, and the treatment parameters for the linear accelerator. In addition, it is difficult to calculate dosimetry before surgery because the patient’s geometry changes with removal of tissue. Before IORT-specific planning software was developed, water-measured doses were distributed as a basis for manual dosimetry.

Radiance (GMV), an IORT-specific planning software, has helped overcome several IORT planning limitations. Currently, Radiance is the sole FDA-approved treatment planning software that can be used for contouring, image display, dose calculation algorithms, dose volume histogram calculations, and reporting. Using the patient’s simulation computed tomography (CT) scan, the planning software can simulate the IORT delivery before, during, and after treatment with 3-D images. Table 2 describes the 11 treatment planning steps.

Several studies have evaluated the effectiveness of the Radiance software. For example, in a study of 14 patients conducted by 3 radiation oncologists, the ability to simulate treatment had a positive effect on the quality and accuracy of the IORT procedures. The 14 patients in the study represented a variety of cases, including those treated for breast, rectal, and pancreatic cancers; retroperitoneal and Ewing sarcomas; and rectal and ovarian relapses. In addition to simulating parameters for treatment planning accurately, the software improved presurgical preparation because clinicians could view multiple treatment plans. Specialists also could exchange
Medicare pays for IORT in hospital and freestanding environments. As a commercial example, a payer might require evidence-based guidelines that indicate a treatment is considered effective. For example, as of 2016, a national payer stated that it only covers IORT treatment for rectal cancer when the patient has a positive surgical margin or a margin that is considered close, recurrent lesions, or tumors staged T4. If a lesion does not meet these specific conditions, IORT is considered an investigational treatment. Investigational technology has not been proven to improve health outcomes, such as length of life, quality of life, or functional ability.

**Table 2**

<table>
<thead>
<tr>
<th>Radiance (GMV) Treatment Planning Steps</th>
<th>Defined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beam modeling and CT calibration</td>
<td>User inputs type of linear accelerator and all possible applicators to be used. Input data are obtained from scanning a phantom and using the Hounsfield units to determine the material density. These data are then used to create the CT calibration model.</td>
</tr>
<tr>
<td>Loading of 3-D images in DICOM format (typically CT scans)</td>
<td>Software assumes that the entire medium is water unless images are from a CT scan that can depict tissue density.</td>
</tr>
<tr>
<td>Navigation on the patient to determine course of action</td>
<td>MPR and VR. Patients can be viewed in either supine or prone positions to show lesions. Measurement tools help choose applicator size and their angles.</td>
</tr>
<tr>
<td>Identification of regions of interest including gross tumor volume</td>
<td>Contouring the region of interest helps the software assign a specific density value to the contoured region identified.</td>
</tr>
<tr>
<td>CTV and organs at risk</td>
<td>Contouring the organs to be protected allows dose simulation and the ability to remove an image to simulate the resected tumor. Helps determine applicator position, orientations, and anatomical restrictions.</td>
</tr>
<tr>
<td>Determination of surgical frame</td>
<td>Simulation of the incision area as seen by the surgeon.</td>
</tr>
<tr>
<td>Definition of resection STV</td>
<td>“Resected area” can be filled with air.</td>
</tr>
<tr>
<td>PTV removing the STV from the CTV</td>
<td>Tumor bed.</td>
</tr>
<tr>
<td>Simulation bolus, protections, air, etc</td>
<td>User can place these contours to change the effect of radiation attenuation when applied to dose calculation.</td>
</tr>
<tr>
<td>Optimization of IORT parameters with the help of the DVH</td>
<td>Electron devices use pencil-beam and Monte Carlo algorithms. Intrabeam only dose painting algorithm. Dose is prescribed at desired reference isodose percentage and at desired depth in clinical axis. DVH computed over all regions, and treatment parameters can be optimized at any time. Modification during planning automatically is recalculated for the DVH.</td>
</tr>
<tr>
<td>Report</td>
<td>Stores all generated information during the simulation including applicator parameters, dose volumes, DVH snapshots, linear accelerator configuration, and regions information. Documentation can be stored before, during, and after treatment.</td>
</tr>
</tbody>
</table>

Abbreviations: CT, computed tomography; CTV, clinical target volume; DICOM, Digital Imaging and Communications in Medicine; DVH, dose volume histogram; MPR, multiplanar reconstruction; PTV, planning target volume; STV, surgical target volume; VR, volumetric rendering.

Information about specific IORT cases to decide the best treatment approach, and the software could be used as a training tool to demonstrate the outcomes of different treatment modifications. Examples of dosimetry treatment planning for the brain and skin are shown in Figure 5.

**Reimbursement**

Although IORT can provide beneficial cancer treatment, the patient’s insurance carrier often dictates an individual’s treatment options. Insurance companies have differing views on the benefit of IORT, and reimbursement for the treatment can vary widely.
Other insurers cover IORT when the technology is deemed medically necessary for boost treatment. This can include IORT reimbursement for several cancers when the tumor cannot be removed completely or the lesion is considered to have a high risk of recurring. Some U.S. payers cover IORT under certain clinical conditions for specific sites and will not reimburse treatment of other cancers until the benefit is properly established. An example of evidence is the National Comprehensive Cancer Network guidelines, and some payers only cover IORT treatment when the network recommends the procedure or when the treatment is part of a clinical trial. The network is a not-for-profit alliance of 27 leading cancer centers that develops standards of care for cancer treatment.

**Treatment Sites**

Use of IORT has been shown to improve morbidity and mortality for many types of cancer. However, as a relatively new technology, IORT has not yet been studied extensively for use in some cancer sites and is not always the most favorable approach.

**Breast**

Breast cancer is the most common cancer diagnosis in women and the second leading cause of cancer death.

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**Figure 5.** Dosimetry plans for brain (A) and skin (B) treatments. Images of Radiance software screen captures courtesy of GMV, Spain.
following lung cancer.\textsuperscript{18,19} Breast cancer that has not spread to the lymph nodes or other sites outside the breast is considered early-stage disease and accounts for 61% of breast cancer cases.\textsuperscript{20} Although radical mastectomy was once the standard breast cancer treatment, therapeutic approaches now have shifted to localized treatment that preserves the axillary lymph nodes and breast.\textsuperscript{21} Today, patients with early-stage breast cancer typically are treated with breast-conserving surgery followed by whole-breast EBRT.\textsuperscript{21}

Whole-breast EBRT is required after a lumpectomy because of the risk of local recurrence and subsequent mortality.\textsuperscript{22} After breast-conserving surgery, more than 90% of local recurrences are found in the index quadrant (ie, the breast quadrant with the primary tumor at its center) even though multicentric disease is found elsewhere in the breast.\textsuperscript{22} For this reason, the site of the primary tumor must be irradiated to achieve local control of the cancer. IORT is a treatment option designed to replace whole-breast EBRT in women eligible for breast-conserving therapy.\textsuperscript{23}

A growing body of research supports the use of IORT for the treatment of early-stage breast cancer; recurrence rates for IORT are similar to EBRT recurrence rates, but IORT is associated with a lower mortality rate and fewer adverse effects, such as radiation burns and fatigue.\textsuperscript{21,22}

**TARGIT-A**

The TARGIT-A trial was a randomized, noninferiority trial to compare IORT and conventional whole-breast EBRT.\textsuperscript{21} Noninferiority trials are designed to show that a new treatment is not inferior to a standard treatment; that is, any difference between the 2 treatments is small enough for researchers to conclude the new treatment is no worse than the established standard. The goal of the study was to evaluate the outcome of a single dose of radiation applied to the tumor bed at the time of lumpectomy vs standard EBRT delivered over several weeks following surgery.\textsuperscript{21}

Many patients have limited access to radiation therapy for different reasons and therefore find it difficult to undergo 6 weeks of EBRT after breast-conserving surgery.\textsuperscript{21} Extended treatment regimens are burdensome especially for working and elderly women. If IORT at the time of surgery proved to be at least as adequate as EBRT, women could be spared postsurgery radiation treatment and unnecessary mastectomies.\textsuperscript{22}

Targeted IORT involves placing an applicator from 1.5 cm to 5 cm in diameter, depending on the surgical cavity, inside the surgical bed after tumor removal.\textsuperscript{1,21} The applicator tip delivers low-energy radiation at a distance of at least 5 mm from the surface of the applicator to the skin. The beam is on for 20 to 45 minutes, depending on the size of the applicator used, and typically delivers 20 Gy.\textsuperscript{21} For treatment safety and to minimize healthy tissue exposure, the radiation attenuates to 5 Gy to 7 Gy at a depth of 1 cm.\textsuperscript{22} The TARGIT-A trial used Intrabeam equipment. Figure 6 shows an example of targeted IORT.

The TARGIT-A trial was conducted at 33 centers in 11 countries between March 2000 and June 2012.\textsuperscript{22} To qualify for the study, patients had to be 45 years or older with an early-stage breast cancer diagnosis of invasive ductal breast carcinoma and eligible for wide local excision. The primary tumors had to be 3.5 cm or smaller and staged N0-1, M0, or lower.\textsuperscript{21,25} Patients were assigned randomly to receive targeted IORT or standard whole-breast EBRT in a 1:1 ratio, with the research blocks stratified by treatment center and timing of treatment delivery. Because postsurgery pathology results could indicate unexpected adverse conditions (eg, lobular carcinoma), researchers implemented a risk-adapted approach.\textsuperscript{21} An additional 5 weeks of EBRT was added to targeted IORT to serve as a tumor-bed boost.\textsuperscript{22,25}

TARGIT-A was a large randomized study with nearly equal groups of women who had excision of the cancer plus concurrent TARGIT (risk-adapted) and those who underwent excision of the cancer plus conventional EBRT. TARGIT-A researchers amended the study protocol in 2004 to include patients who had undergone wide local excision of the primary tumor and therefore for whom postsurgical pathology results were available. These patients were randomized at least 30 days after the lumpectomy and assigned to a delayed targeted IORT group or a conventional EBRT group.\textsuperscript{25} Researchers analyzed the prepathology and postpathology groups separately to account for the timing of IORT delivery.\textsuperscript{22} Of the 3451 patients included in the study, 1721 were randomized to receive targeted IORT and the other 1730 to receive EBRT.\textsuperscript{22}
The primary outcome measured by the study was local recurrence of breast cancer in the conserved breast. Secondary outcomes included measures of toxicity and overall survival. Complications assessed included hematoma, seroma, wound infection, skin breakdown, and delayed wound healing. Follow-up assessments were scheduled at 3 months, 6 months, and then every 6 months for up to 5 years. When the 5-year results were reported in 2014, the median follow-up for the entire study group was 2 years and 5
months, which is the most likely time period for local breast cancer recurrence.22

The TARGIT-A results showed that local recurrence of breast cancer in the conserved breast at 5 years was 3.3% in the targeted IORT group vs 1.3% in the EBRT group.22 Toxicity and overall survival results were similar, with a breast cancer mortality of 2.6% in the targeted IORT treatment group vs 1.9% in the EBRT group; overall mortality was 3.9% for targeted IORT patients vs 5.3% for patients receiving EBRT.21,22 With regard to the timing of treatment delivery, the IORT group who received treatment immediately following lumpectomy but before final pathology results were available had the same outcome as the patients in the EBRT group; in this case, local recurrence rates were 2.1% for the IORT group vs 1.1% in the EBRT group.22 However, the postpathology IORT group had a much higher local recurrence rate of 5.4% vs a 1.7% local recurrence rate in the EBRT group.22

Overall, TARGIT-A researchers concluded that when the appropriate candidates are selected, targeted IORT is safe, is associated with lower mortality rates than standard EBRT treatment, and has similar overall complications. They added that patients who are eligible to receive targeted IORT should consider the benefits of this treatment option. Because radiation is administered as a single treatment, IORT alleviates the stress for patients of daily treatment over 6 weeks and reduces the cost of treatment.22 IORT’s low toxicity results and timing of treatment delivery also can have a positive effect on a woman’s choice between a radical mastectomy and breast conserving surgery.21,22

ELIOT

The ELIOT trial was conducted from November 2000 to December 2007.26 The purpose of the trial was to compare a single dose of intraoperative electron radiation therapy (IOERT) to conventional whole-breast EBRT followed by a 10-Gy boost in 5 fractions.27 Unlike the TARGIT-A trial, which used low-energy photons, equipment in the ELIOT study delivered electron energies in a single IORT treatment of 21 Gy to the tumor bed.27,28 The effective energy used to treat the tumors was 12 MeV.29 The ELIOT trial used Novac 7 and LIAC linear accelerators.29

IOERT must be delivered from outside the breast and is administered by separating the breast tissue from the chest wall and underlying pectoralis muscle.28 A 4-cm to 10-cm diameter applicator was used to deliver the treatment at the 90% isodose depth while a beam stopper and lead shields were used for protection.24 The entire procedure took no more than 15 minutes.30

The ELIOT trial studied 1305 women aged 48 to 75 years with early-stage breast cancer who were eligible for standard breast-conserving surgery. The study group included only perimenopausal or postmenopausal women who had not undergone previous breast therapy.28-30 Tumors were either ductal or lobular carcinoma no larger than 2.5 cm. Patients were randomized after undergoing lumpectomy.28 At the 5-year follow-up, results were reported for 1186 patients, 601 in the whole-breast EBRT group and 585 in the IOERT group. The recurrence rate was 4.4% for the IOERT group vs 0.4% in the EBRT group.30 However, when study participants were categorized as low risk or high risk based on tumor size, receptor status, nodal positivity, and grade, recurrence rates were lower for low-risk patients. At 5 years, the low-risk IOERT group had a recurrence rate of 1.5%, which indicated IOERT could be considered an acceptable alternative to EBRT postsurgery in these patients. High-risk patients should compare the advantages and disadvantages of treatment options to receive the “minimum effective treatment.”25,29,31

TARGIT-B

The objective of the TARGIT-B study is to determine whether targeted IORT delivered to the tumor bed as a boost is superior to standard EBRT boosts in women with a high risk of local breast cancer recurrence.24 Both the TARGIT-A and ELIOT trials demonstrated the benefit of patients receiving a boost to the tumor bed following breast-conserving surgery; researchers hope the TARGIT-B trial will indicate which treatment boost option is best.24 The TARGIT-B trial is ongoing with a completion year of 2022.32

To be eligible for the trial, participants must be at high risk of local recurrence. This group includes women younger than 45 years of age, those with invasive lobular carcinoma, and patients who received neoadjuvant
systemic therapy. Other high-risk factors for women 45 years and older are a grade 3 tumor histology, tumors that are estrogen-receptor or progesterone-receptor negative, and positive axillary nodes. All patients are randomized before surgical excision of the tumor, and all patients receive whole-breast EBRT. Tumor size cannot exceed 4 cm because the largest applicator size is 5 cm.

Patients assigned to the IORT group receive the boost intraoperatively after surgical excision. The Intrabeam system delivers the targeted dose of 20 Gy in about 30 minutes, depending on the applicator size. To administer the dose safely, the skin is kept at least 1 cm from the applicator, and surgical sutures are used to prevent the skin from touching the applicator. A purse-string suture brings the targeted breast tissue together and keeps it in place during treatment. The IORT group then undergoes a standard course of EBRT. Patients who are assigned to the EBRT boost group receive whole-breast EBRT treatment followed by an appropriate electron boost delivered as 16 Gy in 8 fractions over 1.5 weeks.

**Cervix**

Intraoperative radiation therapy is not often a part of cervical cancer treatment. Only a few studies on its use for cervical cancer care have been completed, but 1 study evaluated IOERT for the treatment of locally advanced or recurrent cervical cancer. The authors retrospectively studied 86 women who had surgery followed by IOERT between 1983 and 2010. The authors concluded that IOERT as part of a multimodality approach to advanced or recurrent cervical cancer care improves chance of long-term survival despite poor prognostic factors and severe treatment morbidity from IOERT.

Electronic brachytherapy has been used for the treatment of cervical and other gynecological cancers. A study comparing iridium 192 and cobalt 60 treatment with electronic brachytherapy (Xoft) concluded that electronic brachytherapy could be a viable replacement for 192Ir and 60Co in tandem and ovoid brachytherapy. Another study revealed no difference between 192Ir and 60Co plans and treatment with electronic brachytherapy. Use of electronic brachytherapy resulted in similar-to-better sparing of organs at risk. Because of the higher dwell times needed at the tip of the applicator with 192Ir, dose can bulge at the tip of the tandem. Electronic brachytherapy with the Xoft System has a more forward-directed dose, which reduces dwell times at the tip; the system delivers a more uniform dose at the tip and a lower surface dose along the tandem.

**Prostate**

Radical prostatectomy or definitive radiation therapy are the most commonly accepted standards of treatment for localized prostate cancer. Kyoto University and the Saitama Cancer Center in Japan first reported more than 20 years ago use of IOERT as a single treatment or in combination with pelvic lymphadenectomy or EBRT. Early treatment methods involved a perineal approach without radical prostatectomy and used electron energies that ranged from 10 MeV to 14 MeV. The treatment then shifted away from the perineal approach to the retropubic method, delivering a single dose of 20 Gy to 25 Gy.

The retropubic approach has become the standard for prostate treatment with IORT. The approach requires the patient to be in the supine position under spinal anesthesia. An extraperitoneal incision is made in the lower abdomen. A sterile cone then is inserted and placed adjacent or attached to the tumor. A spacer can be placed in the rectum to reduce rectal dose, and if necessary, rectal dose can be measured using radiochromic film placed on the surface of the rectal spacer. The use of IORT and IOERT for treatment of high-risk prostate cancer with metastases also has been studied. A potential advantage of IOERT in treating high-risk prostate cancer patients is that IOERT optimizes identification of and targeted treatment to the prostate. No early or late toxicities have been observed in patients who received IORT for high-risk prostate cancer. Some patients with high-risk prostate cancer have IORT for a boost treatment in a single-fraction dose of 10 Gy to 12 Gy delivered with 9 MeV to 12 MeV to the 90% isodose line. The boost treatment is followed by EBRT.

For patients with metastatic prostate disease, the benefit of IORT is control of local symptoms caused by disease progression. The data also suggest there
is improved survival with the use of IORT instead of treating only with androgen deprivation therapy.39

Prostate cancer patients also benefit from IORT when there is no evidence of severe bone and non-regional lymph node metastatic involvement.40 Radiobiological studies suggest the use of single-fraction delivery might improve treatment results in terms of higher tumor cell destruction.41 The safety of IOERT and feasibility of the technology as a treatment option combined with a radical prostatectomy for patients with high-risk cancer has been demonstrated in early research. However, long-term studies need to be conducted before IOERT could replace standard treatment for these patients.39,42

**Brain**

Studies can be found dating back 20 or more years in which IORT was used for multiple types of brain lesions; the first reported IOERT treatment of the brain took place in the early 1980s.43 More recently, IORT has been used to treat the most aggressive and deadly type of primary brain tumor: glioblastoma multiforme (GBM). GBM is associated with a median survival time of 14 months. More than 12 000 new cases were projected in the United States in 2016.43,44 Because of the aggressive nature of GBM, at least 98% of the tumor must be removed during surgery for improved patient survival.43 Resection of nearly the entire GBM is only possible in about 20% of patients. Even when removed, local recurrence of GBM within 2 cm to 3 cm of the primary lesion is a main cause of clinical deterioration.43

Intraoperative radiation therapy is not yet recommended for treatment of GBM outside of clinical trials.43 TARGIT trials are using IORT (Intrabeam, Zeiss International) for brain metastases with interstitial radiation therapy and a dose between 10 Gy and 20 Gy at a 2-mm depth.43 IORT with Intrabeam has shown some success in local control of up to 80% of cases. Delayed necrosis has occurred in less than 5% of all cases.43 Interstitial radiation can be delivered before surgical resection of a mass. The IORT needle-shaped applicator is mounted to the stereotactic frame and advanced into the center of the mass to deliver treatment.43

The IORT method of delivery can be more desirable than forward beaming electron cones because of the complexity of port-resection cavities and spherical irradiation from the kV-based IORT devices. The primary focus of intraoperative treatment is to destroy remaining tumor cells at the cavity border during surgical resection to afford the patient the best chance of preventing local recurrence.47

Clinical trials continue to evaluate use of IORT in the treatment of brain lesions. INTRAGO, a phase 1 and 2 trial, is being conducted to evaluate the safety and dose-limiting toxicities associated with IORT dose escalation for GBM. The INTRAGO study should provide a maximum tolerable dose that can be used as the basis for a future randomized low-kV IORT phase 3 study of GBM treatments.43

Patients who could benefit the most from IORT have treatable tumors and have carefully selected population characteristics, including being younger than 70 years and with tumors that are at least partially resectable. IORT might not improve overall survival, but it could be considered superior to EBRT or chemotherapy alone in improving quality of life for brain cancer patients.43

**Spine**

Vertebral metastasis is one of the leading causes of reduced quality of life, and the vertebrae are the third-most frequent site for metastatic disease following lung and liver metastases.45,46 Thirty percent to 40% of all cancer patients develop bone metastases, and 85% of bone metastases result from breast and prostate cancer.46,47 The diagnosis of this disease gives patients a median overall survival time of 7 to 9 months.47 When bone metastasis is discovered, it is found in the spinal column 50% of the time. Of spinal metastases, 60% to 80% are found in the thoracic spine, 15% to 30% in the lumbar spine, and less than 10% in the cervical spine.45

EBRT has been considered the standard treatment option and has been widely used to treat spinal metastases because it helps relieve patient pain and controls local tumors.47 Surgery is an alternative approach; however, when surgery alone is used no significant improvement in life expectancy is seen. Unlike EBRT, surgery can immediately stabilize the spine. The combination of surgery and IORT can provide immediate pain relief and excellent local tumor control.45,47
Kyphoplasty With IORT

To relieve pain symptoms, stabilize vertebrae, and sterilize disease, a German team introduced IORT during kyphoplasty (also called kypho-IORT). The combination treatment can deliver a high dose of radiation to the vertebral body intraoperatively during kyphoplasty. Kyphoplasty uses a cement substance to treat osteoporotic compression fractures by expanding the collapsed vertebra with the use of a small balloon at the tip of a catheter. Kyphoplasty attempts to directly reduce kyphosis, restore body height, and correct the deformity.

For IORT with kyphoplasty, the patient is placed under anesthesia. Using fluoroscopic guidance, a k-wire is inserted into the vertebra along with a cannula that contains 2 sleeves; 1 of the sleeves is metal and is positioned in the pedicle. A burr is used to make a hole in the vertebral body where the drift tube is placed over the metal sleeve. Electrons travel into the drift tube and strike a gold target at the end of the tube, producing the radiation energy necessary for treatment. A dose of 8 Gy per 5 mm to 13 mm distance is the typical prescribed dose for the IORT; delivery takes about 5 minutes.

Kyphoplasty then is performed with inflation of the balloon followed by the cement application. Figure 7 shows the kypho-IORT procedure. Kypho-IORT can be used only to treat metastases below the third thoracic vertebra because the procedure requires a transpedicular approach; above the T3 level, the vertebral arteries are too close and the cervical pedicles are too small. Overall, kyphoplasty with IORT is feasible and has been shown to relieve pain and improve quality of life in patients suffering from vertebral metastases. The technique also reduces the number of visits patients need for treatments.

Skin

Nonmelanoma skin cancer is the most common type of cancer in the United States, and the number of skin cancer procedures performed is increasing. Electronic brachytherapy is used for inpatient surgery, but also can be performed during outpatient procedures, such as those traditionally used to treat nonmelanoma skin cancer. Use of IORT is an alternative to Mohs surgery, surgical excision, curettage, or cryosurgery for treating nonmelanoma skin cancer. IORT has been reported to be nearly painless and is less invasive than surgical treatment.

Electronic brachytherapy is ideal for certain patients with lesions in sensitive or challenging locations such as the ear, nose, scalp, neck, eyelid, and lip. It also is ideal when surgery is contraindicated because the patient is on anticoagulant therapy or has comorbidities. Minimal shielding requirements and no need for procurement or transport of radioisotopes for implantation make IORT a clinical alternative.

A 5-year study by Bhatnagar and Loper included 200 patients with 297 nonmelanoma skin cancer diagnoses between 2009 and 2014. The patients were treated with high-dose-rate (HDR) electronic brachytherapy. The investigators used a 10-mm to 50-mm surface
applicator to deliver a dose of 40 Gy in 8 fractions twice weekly.\textsuperscript{55} This study concluded that electronic brachytherapy can provide a convenient nonsurgical option for patients diagnosed with nonmelanoma skin cancer.\textsuperscript{55}

The authors followed participants for a mean 16.5 months and recorded only 1 skin cancer recurrence. The most common acute side effects included dermatitis in 86% of lesions, pruritus in 27%, and hyperpigmentation in only 1%.\textsuperscript{55} Acute adverse effects were present in only 33% of lesions at 3 months and fewer than 1% of lesions at 1 year.\textsuperscript{55} The most common late adverse effects included hypopigmentation in 6% of lesions and alopecia in 1% of lesions.\textsuperscript{55} Cosmesis with electronic brachytherapy was either excellent or good at each annual follow-up for 5 years after treatment.\textsuperscript{55} The authors concluded that treatment of nonmelanoma skin cancer with HDR electronic brachytherapy resulted in local control with acceptable toxicities.\textsuperscript{55}

**Soft Tissue**

Sarcomas appear in the soft tissue or bone; gastrointestinal stromal tumor is the most common type and is more prevalent in adults. Still, most sarcomas are found in children (15% of all childhood cancers vs 1% of adult cancers).\textsuperscript{56} Reports show that incidence has risen for the past 35 years, and sarcoma is associated with a 65% survival rate at 5 years.\textsuperscript{57,58}

The first known treatment of sarcomas with IORT dates back to 1973.\textsuperscript{59} In more current studies and treatments, IOERT, HDR-IORT, or IORT along with surgery and EBRT have shown success, especially in local control and overall survival, as an approach to treatment of soft tissue sarcomas.\textsuperscript{58,59}

In general, EBRT improves local control in soft tissue sarcoma patients whether delivered preoperatively or postoperatively. Still, patients tend to have higher rates of local recurrence or distant metastases following treatment of high-grade and locally recurrent tumors, lesions at high risk for positive margins, and those next to unresectable critical structures.\textsuperscript{58}

Although research on IORT for soft tissue sarcoma is rare, a randomized trial from Sindelar et al reported on a combination of IORT and EBRT. The investigators reported a 60% local control rate with a dose of 20 Gy IORT and 34 Gy to 50 Gy EBRT. This compared with a 50 Gy to 55 Gy dose delivered by EBRT postoperatively, which showed only a 20% local control rate.\textsuperscript{58,59}

Further, comparing IORT in combination with EBRT vs EBRT alone, a higher number of local complications were found in patients having EBRT only.\textsuperscript{59} Studies of IOERT and HDR-IORT to treat retroperitoneal sarcomas reported good results when delivering a dose of 15 Gy as a boost to positive margins, avoiding joint spaces, and shared similar toxicity with EBRT treatment only.\textsuperscript{60}

For extremity soft tissue sarcomas, limb-sparing surgery and radiation therapy are the standard curative treatment (vs amputation), leaving these patients with an overall local failure rate of about 20%.\textsuperscript{61} A study conducted from May 2000 to July 2011 analyzed 26 patients who had limb-sparing surgery to determine disease control and survival. Of the 26 patients, 15 received EBRT before recurrence, and 11 received EBRT after IORT.\textsuperscript{61} At 5 years, local recurrence for those having limb-sparing surgery and IORT was 58%, and 81% needed no amputation. Toxicities were equal between all patients, which suggests that prior EBRT did not influence toxicity or disease control. Overall, the authors achieved high rates of local control when IORT was part of a multimodality approach in extremity soft tissue sarcomas.\textsuperscript{61}

Numerous additional studies have reported similar results: When IORT is combined with EBRT and radical surgery to treat soft tissue sarcomas, it provides high local control rates that range from 40% to 100% at 5 years. In these studies, IORT doses of approximately 7.5 Gy to 25 Gy were combined with 36 Gy to 60 Gy of EBRT. The combined treatment produced overall survival rates at 5 years of 45% to 84% with limited acute toxicities.\textsuperscript{56,59}

**Gastrointestinal Cancers**

Stomach (Gastric)

The feasibility and efficacy of IORT for gastric cancer care first was reported in the early 1980s by Abe.\textsuperscript{62} However, adding IORT to treatment of gastric cancer is only minimally effective at increasing survival rates.\textsuperscript{63} Intraoperative radiation therapy for gastric cancer also leads to a high rate of complications.\textsuperscript{64}

When used for local-regional control, IORT has shown 12% to 15% higher control than for local-regional cancers with no IORT treatment. Even with the improved
local-regional control, however, overall survival rates were not improved. The risk-to-benefit ratio must be considered before IORT is added to gastric cancer treatment.

Esophagus

Historically, few randomized trials have evaluated the benefits of IORT for treating esophageal cancer. Tumor infiltration of the trachea or main bronchi and potential radiation damage restrict use of IORT in the esophagus. More recent studies have been published that used IORT to treat the abdominal lymph node area; these studies concluded that survival rates were higher when patients were treated with IORT as part of a multidisciplinary approach. One study indicated that IORT can be a convenient option for patients requiring treatment of lymph node volumes; as many as 74% of patients undergoing esophagectomy have lymph node metastasis. When IORT is used as an electron boost following combination chemotherapy and radiation therapy for locally advanced esophageal and gastroesophageal junction cancer, studies show an improvement in local control but no benefit for overall survival.

Gallbladder

Very little information is available on the use of IORT for treatment of gallbladder carcinoma. One study suggests, however, that IORT could provide a benefit when used as a curative and palliative treatment for patients with gallbladder carcinoma. To date, IORT treatment should not be used as part of standard treatment of gallbladder carcinoma outside of clinical trials.

Pancreas

The use of IORT for pancreatic cancer seems to offer little to no benefit. Ruano-Ravina reviewed 14 studies conducted from 1990 to 2007 and the evidence from these studies indicated no benefit in adding IORT to pancreatic resection. The treatment of pancreatic cancer can be challenging; only about 1 in 5 patients have a confined tumor that is resectable. Studies conducted since 2008 have shown similar results of no improvement in overall survival or local control with IORT. However, a multicenter study has reported that some improvement in local control occurs following IORT with a dose range between 7.5 Gy and 25 Gy. Complications from IORT and surgical technique include pancreatic fistula, delayed gastric emptying, hemorrhage, and abdominal abscesses. It is not uncommon for patients to receive EBRT and chemotherapy following IORT and surgery to improve outcomes. The use of IORT for pancreatic cancer has yet to be widely adopted because of the lack of evidence regarding its clinical benefit. Individual judgment must be used when considering IORT for borderline resectable or unresectable pancreatic cancers. Further, patients having IORT also need to receive induction chemotherapy, consolidation chemoradiation, and surgical resection, and have biomarkers predictive of local dominant biology monitored prospectively for toxicity.

Rectum

Recurrent rectal cancer can leave patients with debilitating complications. The primary goal of IORT for rectal cancer is to destroy remaining microscopic tumor cells at the surgical site while minimizing dose to the surrounding structures, which include the small bowel, ureters, and bladder. When rectal cancer recurs locally, some of the morbidities can include pelvic pain, bleeding, bowel obstruction, and poor quality of life. Current treatment for locally advanced rectal cancer is associated with a 6% to 10% recurrence rate following therapy that includes surgery, radiation therapy, and chemotherapy. The addition of IORT to this multidisciplinary approach is an attempt to improve local control rates for patients with locally advanced disease and to decrease the morbidity associated with recurrence. A study involving 26 patients with locally advanced or recurrent rectal cancer and a median tumor size of 2.8 cm included IORT at 3 months following EBRT and surgery. The combined treatment resulted in a median survival time of 34 months and an overall survival rate of 3 years at 49%. This led to a single phase III randomized trial comparing preoperative radiation therapy followed by surgery to IORT alone in 142 cases of clinically staged T3, T4, or N+ and M0 rectal cancer. The trial results suggested there is no significant difference between the 2 treatment methods. Neuropathy was related to dose; doses higher than 12.5 Gy caused neuropathy in 31% of patients. Addition
of IORT resulted in improved 5-year local control, disease-free survival, and overall survival compared with preoperative radiation therapy and surgery, but IORT for primary treatment with locally advanced disease provided no additional benefits over surgery alone. IORT might continue to be an option for patients in whom there is limited opportunity to increase radiation dose or receive irradiation a second time.14

**Head and Neck**

Head and neck cancers, found primarily in men, account for 3% of all malignancies in the United States.70 Patients with locally advanced cancer generally receive surgery and adjuvant EBRT. This treatment approach has a 5-year disease-free rate of only 30% to 40%.71 EBRT offers the highest rate of cure when intensity-modulated radiation therapy (IMRT) is combined with image-guided radiation therapy (IGRT). This treatment method offers the greatest sparing of healthy tissue while delivering the highest dose of radiation to the target volume. Because of the success of IMRT/IGRT, IORT and brachytherapy seldom are used for head and neck cancer.72

The most effective and preferred treatment for local advanced head and neck tumors is chemotherapy and EBRT following surgery. Still, the chemotherapy/EBRT method causes increased toxicity in patients.71 For tumor recurrence, IORT and brachytherapy can serve as treatment or an early boost. Another use for IORT and brachytherapy is as the second course of radiation for advanced disease.72 Several studies have demonstrated a median survival rate of 6.8 months when using IORT for locally advanced and recurrent head and neck cancer.

Schleicher et al used an IORT dose of 20 Gy to treat 113 patients who had disease primarily in the oropharynx, hypopharynx, and larynx portions of the neck. Of the 113 patients, 84 had previous EBRT. The median survival rate was 6.8 months and 88% of these patients had palliative symptom relief.73

A total of 137 patients with head and neck cancer recurrence at the primary site of disease were studied at the University of California, San Francisco, from 1991 to 2004. The participants received an IORT dose of 15 Gy following tumor resection. Of the participants, 83% also received adjuvant EBRT. Median survival rate for patients with recurrent disease was 12 months vs 20 months for patients treated for the recurrence.72

Memorial Sloan Kettering Cancer Center also used a median IORT dose of 15 Gy in 34 patients with previous EBRT; the participants’ median survival was 24 months and they had minimal severe complications.72 Scala et al retrospectively reviewed use of HDR-IORT in 76 patients from 2001 to 2010. The treatment delivered 12 Gy to patients with negative head and neck cancer margins and 15 Gy to 17.5 Gy to patients with positive margins. The patients who received HDR-IORT had a 19-month median survival outcome.72

For head and neck treatment, HDR-IORT typically delivers a total dose of 7.5 Gy to 15 Gy using 192Ir. Radiation is delivered through beveled or flat applicators that range in size from 2.5 cm to 9.5 cm. The cranial nerves, mandible, and carotid artery are protected using 1-mm to 2-mm lead shields.73 HDR-IORT is a preferred technique for head and neck treatments because the applicator can reach narrow passageways in the neck and sinuses.73 IOERT is preferred for tumors that are not located in small areas and in which the therapy requires the flexibility of the HDR-IORT applicators to work with different treatment times.73 HDR-IORT takes 5 to 20 minutes to deliver treatment, whereas IOERT takes 2 to 3 minutes.73

Zeidan et al and Marucci et al conducted studies on locally advanced cancer in the head and neck treated with IOERT.74 Zeidan et al treated 231 patients with 15 Gy to 20 Gy using IOERT in locally advanced head and neck cancers with cervical node metastases.74 Of the 231 patients, 50 patients received 45 Gy in adjuvant postoperative EBRT.74 Radiation therapy was the primary treatment in 81.4% of the patients.74 Twenty-one of the patients had flap surgeries. The authors concluded that IORT was effective in controlling local disease without significant toxicity.74

Marucci et al treated 23 participants with locally advanced cancer in the head and neck with radical surgery and a 12 Gy boost of IOERT.75 Of the 23 patients, 17 received microvascular flap reconstruction and 10 received 50 Gy delivered by EBRT.71 The 2-year survival rate was 64.5% and the disease-free rate was 50.6%.76 These studies showed that IORT was a safe and feasible approach to treating head and neck cancer, even when used with flap reconstruction.71
Additional research has been conducted on use of IORT as an early boost for head and neck cancer treatment. Multiple studies have shown IORT is an effective treatment option for patients with head and neck cancer who have had EBRT as primary treatment and return with locally advanced or recurrent disease. Still, use of the technique is limited for head and neck cancer treatment until additional randomized trials provide evidence of IORT efficacy. Until that time, short-term use of IORT for palliation continues at doses of 20 Gy or less to minimize adverse effects.

**Pediatric Cancer**

Cancer is the No. 1 cause of childhood death by disease. Incidence has increased in the past few decades, and although more than 10 000 children were diagnosed with cancer in 2016, treatment advances have led to 80% of children with cancer surviving 5 years or more. Heart failure, infertility, or secondary malignancies can occur later in life in nearly 60% of childhood cancer survivors; of these late morbidities, 18% are secondary malignancies.

The use of IORT to treat pediatric cancer has shown acceptable morbidity and a decrease in damage to soft tissue and skeletal structures, which still are developing. In general, the skin and normal tissue tolerance is more critical in children than in adults; children’s developing bodies do not tolerate surgery or high doses of radiation as well as adults’ bodies. The relationship between growth compromise, radiation dose, and age in children first was evaluated by Neuhauser et al.

IORT currently is part of multimodality therapy approaches for treating central nervous system, brain, bone, and soft tissue sarcomas in children. Several IORT treatment delivery methods, including IORT, IOERT, and HDR-IORT are options in treating certain pediatric cancers. A benefit of HDR-IORT is its use in confined spaces and reliance on a flexible applicator, whereas the spherical applicators used in IORT and IOERT do not always fit in the relatively smaller spaces of children’s anatomy when a tumor is near critical structures and organs.

Limited research has been conducted on the use of IOERT in treating pediatric cancer. Studies by Haase, Schomberg et al, and Nag et al reported on the use of IORT to treat several types of pediatric cancers. The results showed overall local control and survival rates similar to or better than results from conventional treatment regimens.

Haase analyzed 11 patients at the Children’s Hospital of Denver who had benign disease and 48 who had malignant disease. The patients were treated with IOERT using energies of 5 MeV to 11 MeV for a total dose of 10 Gy to 17 Gy; not all of the children treated received EBRT. Local control was 91% for benign tumors, with a survival rate of 100%, and 75% local control and a survival of 63% for children with malignancy.

Schomberg et al evaluated 11 pediatric patients with malignancies who had EBRT at a median dose of 45 Gy. Of those, 6 children also received IOERT after EBRT and surgical resection; 4 patients received IOERT after surgical resection; and 1 patient had both EBRT and IOERT before and after the procedure. Local control was 91% and survival 73%. The IOERT dose ranged from 7.5 Gy to 20 Gy and was delivered with 6 MeV to 15 MeV. Nag et al at The Ohio State University reported on 11 pediatric patients, 8 of whom received IOERT alone and 5 of whom received IOERT with EBRT for a total dose ranging between 35.4 Gy and 45 Gy. Local control was achieved in 72% of those studied, but survival was 26%.

**Pediatric Brain Tumors**

A study by Kalapurakal et al was conducted using the Intrabeam system to treat brain tumors in 14 children. The authors reported safe use of IORT that improved survival and left patients asymptomatic following treatment to the most radiosensitive part of the brain tissue.

The phase I clinical trial involved delivering 10 Gy to a depth of 2 mm to 5 mm with the spherical applicator and concluded that 2 mm was the safest depth for minimizing toxicities and providing local control in 8 of the 14 children studied. Folkert et al studied use of HDR-IORT for pediatric sarcoma, delivering 192Ir through a curved applicator (Harrison-Anderson-Mick). The treatment provided overall local control in pediatric patients with a low enough radiation dose to add local EBRT if necessary and still result in a lower total dose than the use of EBRT alone. The Folkert study took place between May 1993
and November 2013 and involved 75 patients younger than 21 years. The authors concluded that HDR-IORT could be part of multimodality treatment for children with sarcomas, and that if total dose from the technique ranged from 8 Gy to 12 Gy in patients up to 6 years old, the treatment was tolerated well.61

Other Pediatric Cancers
A study of pediatric patients treated with conjunctive use of EBRT and IORT between 1995 and 2012 showed local control for a number of childhood cancers.66 In 33 children, 10 had neuroblastoma carcinoma, 7 had Ewing sarcoma, 10 had sarcoma, 3 had fibromatosis, 1 had a teratoma, 1 a nephroblastoma, and 1 child had a primitive neuroectodermal tumor.66 The outcome was positive for local control rates with a 5-year follow-up of 68% in patients with neuroblastosomas, 57% in Ewing sarcoma, and 60% in sarcomas.66 The disease-free survival rate at 60 months was 52% for all participants combined.66

Because experience and data on IORT for childhood cancer treatment are limited, IOERT and HDR-IORT have not replaced EBRT, but the techniques are used as adjuvant therapy with EBRT in some pediatric cancers. When IORT is used with debulking surgery in some types of recurrent or locally advanced pediatric cancers, it shows excellent local control.79 Pediatric oncologists might choose IORT to protect healthy structures and lower risk of injury to tissues that would otherwise be compromised from high doses of EBRT.79 More clinical trials should be conducted to continue to monitor late effects, toxicities, local control rates, and overall survival in pediatric malignancies.79

Conclusion
Intraoperative radiation therapy can be used as a single-dose boost treatment for cancer patients, with the highest success demonstrated in treating breast cancer and spinal metastases. Advances are being made in the treatment of cervical metastases, nonmelanoma skin cancer, and soft tissue sarcomas, but IORT has demonstrated little to no advantage in treating prostate, brain, gastric, esophageal, gallbladder, pancreatic, rectal, pediatric, and head and neck cancers. Worldwide, more than 95% of centers use megavoltage electron linear accelerators for IORT.1 The advantages of IORT include decreased risk of a geographical miss, improved sparing of surrounding healthy tissues, increased sterilization of stem cells, improved biological efficacy per dose, reduced EBRT dose, and overall treatment time reduction.

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References


Intraoperative Radiation Therapy


Read the preceding Directed Reading and choose the answer that is **most correct** based on the article.

1. Quality assurance on the Intrabeam system (Carl Zeiss Meditec AG) should be performed within ________ hours before a patient’s treatment.
   a. 2
   b. 12
   c. 24
   d. 36

2. Which of the following statements is **false** about targeted intraoperative radiation therapy (IORT) for breast cancer?
   a. Applicators range in size from 1.5 cm to 5 cm.
   b. The tip delivers high-energy radiation.
   c. The applicator tip should be placed 5 mm from the skin surface.
   d. The beam stays on for 20 to 45 minutes.

3. The TARGIT-A trial results showed:
   1. slightly higher local recurrence with IORT than with external-beam radiation therapy (EBRT).
   2. similar toxicity results for IORT and EBRT.
   3. lower overall mortality with IORT compared with EBRT.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

4. Patients with glioblastoma multiforme who could benefit **most** from IORT:
   a. are older than 70 years.
   b. have partially resectable tumors.
   c. have untreatable tumors.
   d. have contraindications for chemotherapy.
5. According to the article, ________ metastasis is one of the leading causes of reduced quality of life in patients with cancer.
   a. brain  
   b. vertebral  
   c. bone  
   d. lung  

6. Kyphoplasty with IORT is performed using ________ guidance.
   a. computed tomography (CT)  
   b. ultrasound  
   c. fluoroscopic  
   d. laparoscopic  

7. Electronic brachytherapy is ideal for patients who have skin cancer lesions in sensitive or challenging locations, including the:
   1. neck.
   2. eyelid.
   3. nose.
   a. 1 and 2  
   b. 1 and 3  
   c. 2 and 3  
   d. 1, 2, and 3  

8. Which of the following statements regarding use of IORT to treat gastric cancer is false?
   a. The feasibility of the technique first was reported in the 1980s.  
   b. Local control is up to 15% higher when IORT is added to therapy.  
   c. Survival rates are much higher when IORT is used for local control.  
   d. IORT is associated with a high rate of complications.  

9. IORT treatment should not be used as the standard treatment for gallbladder carcinoma outside of clinical trials.
   a. true  
   b. false  

10. In a study regarding the addition of IORT to treatment of rectal cancer, authors found:
    1. neuropathy in nearly one-third of patients who received doses higher than 12.5 Gy.  
    2. improved 5-year local control.  
    3. no additional benefits over surgery alone for treating locally advanced disease.
    a. 1 and 2  
    b. 1 and 3  
    c. 2 and 3  
    d. 1, 2, and 3  

11. Patients with head and neck cancer treated with high-dose-rate IORT typically receive a total dose of up to ________ Gy delivered using ________ applicators.
    a. 7.5; flat or beveled  
    b. 7.5; spherical and flexible  
    c. 15; flat or beveled  
    d. 15; spherical and flexible  

12. Which of the following statements is true regarding IORT in treating childhood cancers?
    a. The technique has shown acceptable morbidity and decreased damage to soft tissue and skeletal structures.  
    b. IORT is used only for treating soft tissue sarcomas in children.  
    c. Use of a spherical applicator helps reach smaller spaces in children.  
    d. Only IOERT is used in treating childhood cancers.