Intraoperative Radiotherapy for Breast Cancer: Its Perceived Simplicity

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With many centers seeking to adopt IORT, there are licensing, proctoring, staffing, technical support, and reimbursement issues that need to be considered. We have reviewed the current international experience and describe one community cancer center’s experience with initiating an IORT breast cancer program.

Over 226,000 cases of breast cancer are diagnosed annually in the United States.[1] Local therapeutic strategies for early breast cancer have changed greatly over the past 3 decades. After multiple prospective randomized clinical trials demonstrated equivalent survival, the standard-of-care options have transitioned from radical surgery only (ie, total mastectomy) to a bimodality treatment consisting of breast-conserving surgery (BCS; partial mastectomy, segmentectomy, lumpectomy) followed by whole-breast irradiation (WBI).[2,3] Subsequently, a number of clinical trials evaluated the required role of radiotherapy in breast conservation. Survival was not compromised in the cohorts of patients in whom radiotherapy was omitted, but the local recurrence rates were found to be unacceptably high, thus securing the importance of radiation as a component of treatment.[4-7]

While WBI significantly reduces the risk of local recurrence, it is associated with significant costs. Conventional WBI ranges from 5 to 7 weeks of daily treatments, with the associated inconvenience and financial burden. Distance to a radiation center, the need to find transportation for the daily treatments, physical limitations, and/or lack of family support prevent many patients from selecting breast-conserving therapy. In addition, WBI is associated with potential acute and chronic toxicities to the surrounding normal tissue, such as dermatitis, soft-tissue fibrosis, rib fractures, hyperpigmentation, volume loss in the treated breast, and increased risk of cardiac disease in patients with left-sided breast cancer.[8]

An attractive therapeutic alternative to WBI would be a treatment that has at least equivalent efficacy while reducing overall toxicity and treatment duration. The concept of partial or accelerated partial-breast irradiation (APBI) was introduced to address several of the drawbacks of WBI. Intraoperative radiotherapy (IORT) is a form of partial-breast radiotherapy that delivers radiation to the tumor bed. This treatment can reduce or even eliminate the need for WBI. Such a treatment strategy has the potential to significantly reduce normal tissue toxicity. IORT avoids radiation to the skin and limits radiation to the surrounding normal breast tissue since it is a form of partial-breast irradiation. Radiation dose to the deeper structures, such as the heart, lung, and ribs, is greatly reduced, since IORT utilizes an electron or low-energy x-ray. In addition, a shielding device is often employed over the chest wall to further reduce the radiation dose to the deeper, normal tissues. Direct visualization of the target volume at the time of treatment also ensures appropriate coverage of the breast tissue at risk.

| TABLE 1 | Single-Fraction and Boost IORT Studies for Breast Cancer |

Over the past decade, the use of IORT in breast cancer has steadily increased. It is increasingly being used as a replacement for the electron boost portion of breast radiation, or in appropriately
selected patients as the replacement for the entire course of WBI. The first clinical data on IORT boost were reported by Lemanski et al.[9] The 50 early-stage breast cancer patients in their initial series were treated with 10 Gy IORT followed by 50 Gy WBI (Table 1). These patients had excellent cosmesis and a low toxicity profile; two patients had a local recurrence. Soon after, a group from Salzburg[10] reported their results in 378 stage I and II breast cancer patients who received BCS and postoperative radiation therapy (50–54 Gy), but different boost strategies. A total of 188 were treated with standard electron boost (12 Gy), and the other 190 patients were treated with IORT boost radiation (9 Gy). Their data showed 5-year actuarial rates of ipsilateral breast tumor recurrence (IBTR) of 4.3% and 0.0% in the standard electron boost and IORT boost groups, respectively. They concluded that IORT boost yielded a statistically significant decrease in the rate of IBTR compared with a similar cohort treated with standard electron boost. A pooled European analysis of 1,110 patients treated with IORT boost also reported encouraging results regarding this treatment strategy. With a median follow-up of over 73 months, the analysis identified only 16 patients with IBTR, yielding a 99.2% local control rate. At 7 years, 88% disease-free survival, 93% disease-specific survival, and 90% overall survival were reported.[11] Our results at St. Joseph Hospital (Orange, Calif) have confirmed excellent tolerance of IORT boost accompanying WBI. None of the 50 patients treated at our center experienced grade 3 or greater toxicity. Two patients had delayed wound healing, but there were no wound infections.[12] Longer follow-up will be needed before we can confirm tumor control rates.

The role of IORT boost has also been explored in combination with hypofractionated WBI. A series from Milan was published that reviewed 211 women with a diagnosis of early-stage breast cancer treated with BCS. These patients were treated with a 12-Gy IORT boost followed by 37.05 Gy WBI in 13 daily fractions of 2.85 Gy. Of the 108 patients who were evaluated for late toxicity, one patient had grade 3 and one had grade 4 skin toxicity. The remaining 106 patients had grade 2 or lower skin toxicity. Given that the median follow-up in this series was 9 months, longer follow-up is required to determine treatment efficacy.[13] In our own institutional study, we have seen similar excellent tolerance of IORT boost with hypofractionated WBI. Data regarding tolerance and efficacy will continue to emerge as other studies continue to enroll patients for evaluation of this treatment combination.

More recently, there has been great interest in using IORT to replace the entire course of WBI. The approach of employing IORT as a “single-fraction” treatment was first used at the European Institute of Oncology (EIO) in Milan, Italy, in 1999. The EIO eventually progressed to a phase III study, which started in 2002 and finished accruing patients in 2009. Results from this trial are currently pending. However, the EIO researchers have published results on 1,822 patients who were treated “off protocol” with IORT.[14] These patients were treated with a single 21-Gy fraction between 2000 and 2008, with a median follow-up of 36 months. A 2.3% local recurrence rate was reported, with 5-year and 10-year survivals of 97% and 90%, respectively. Local side effects were primarily fat necrosis (4.2%) and fibrosis (1.8%). A smaller phase II French trial reported on 94 patients also treated with a single 21-Gy fraction.[15] The median follow-up in this trial was 30 months, and the median age was 72 years. No acute grade 3 toxicity was observed. Only two patients experienced recurrence, and cosmesis was reported to be good to excellent. While results of the EIO randomized trial are pending, single-institution and early-phase studies have indicated that single-fraction IORT is safe and effective in appropriately selected patients. The results of these studies are summarized in Table 1.

Starting an IORT Program: Logistical Challenges

TABLE 2

Intraoperative Radiation Devices

A variety of photon and electron beam IORT delivery systems are currently available (Table 2). The choice of an IORT device may be driven by several factors, including intended clinical application, physical parameters of the machine and associated radiation safety issues, and the cost of accessories and maintenance. Treatment of breast cancer has emerged as the most common...
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application of IORT, but the utility of this modality was first established in the treatment of abdominal, pelvic, and thoracic tumors. IORT programs that have a practice limited to breast cancer may find that the capabilities of kilovoltage x-ray units are adequate. The range of treatment depths and larger field sizes available with an electron beam device may be more suitable for hospital-based programs where IORT would also be utilized in the treatment of visceral sites, such as sarcomas, or rectal, head and neck, pancreatic, or pediatric cancers. Although dedicated IORT units are designed to be portable and self-shielded, differences in storage, portability, and shielding requirements should be evaluated. IORT is delivered using applicators that are reusable for some devices, and single-use for other devices; therefore, an analysis of the upfront and per patient costs of a machine and accessories is essential to determine the economic viability of a new IORT program. Finally, the costs and manpower required for maintenance of an IORT delivery system, as well as the technical support offered by a manufacturer, can vary considerably and should be researched before making a purchase.

When establishing a new IORT program, the proctoring process begins with a site visit by the entire team to an IORT center of excellence. The visiting team members should include surgeons, radiation oncologists, physicists, dosimetrists, operating room nurses, and nurse navigators who will be involved in the program. Ideally, a minimum of three cases should be observed. When the IORT device has been installed and commissioned, temporary hospital privileges at the new IORT center should be requested for an outside expert to proctor the first two cases. The IORT expert then submits a letter of competency to Medical Staff. Depending on the availability of cases, the process to obtain privileges to perform IORT may take weeks to months to complete. Physics and therapy personnel from the radiation oncology department are essential participants in the planning and commissioning process for an IORT program. Training and proctoring support for the physicists should be arranged with the device manufacturer. Visits to other sites with active IORT programs, as well as dry runs with a proctor, should include physics staff. Upon delivery of the IORT system, machine calibration measurements must be taken by a physicist to establish specific dosimetric properties of the device in preparation for treatment planning. The physicist will need to submit documentation to the state regulatory agency for approval prior to commencing treatments for patients with a new radiation device. Depending on the state agency involved, it may take several weeks for this approval to be obtained. The physics department is responsible for developing policies and procedures for machine warm-up and treatment quality assurance. Initially, a longer period of time may need to be blocked in the IORT suite for the radiation therapist to perform machine warm-up procedures and troubleshooting before the surgical case begins. Physicians are also responsible for scheduling periodic maintenance inspections, and they should be involved in negotiating a service contract with the manufacturer if needed.

New operating room policies and procedures may need to be developed and approved prior to treating the first IORT patient. The hospital radiation safety officer should be involved in educating operating room staff on radiation precautions specific to the IORT system that will be used. Radiation devices that are not typically sterilized in a conventional radiation therapy setting may need to be sterilized for use in IORT cases. These can include in vivo dosimetry tools, such as diodes and nanodots, or dose-shaping tools, such as boluses and shields. If manufacturer guidelines are not available for sterilizing these materials, they may not be approved for use by hospital operating room management, and alternatives will have to be researched, purchased, or developed locally. The delineation of privileges and proctoring requirements for the radiation oncologists performing IORT are specific for each institution, and individual Medical Staff regulations may need to be satisfied. IORT is usually a special privilege similar to other advanced radiation skills, such as APBI and yttrium bead delivery. Competency for this privilege could be met by completing training in residency or a fellowship with a recommendation by a program director, or by a certificate of training from a hands-on post-residency course approved by the department of radiation oncology. A new physician without specific IORT training who requests privileges could be proctored (for a minimum of two cases) by a Medical Staff member with IORT privileges or an industry expert. Medical Staff is then supplied with a letter of certification from the proctor regarding competency. At our institution, a decision was made to implement the IORT breast program in three phases. Phase one consisted of postoperative adjuvant whole-breast standard fractionated radiation in conjunction with an IORT boost. Phase two consisted of whole-breast hypofractionated radiation in conjunction with an IORT boost. Phase three consisted of single-fraction IORT using dosing and eligibility criteria similar to that of the Milan protocol without WBI. Phases two and three of our breast IORT program are being carried out using in-house protocols that were approved by our institutional review board. These eligibility criteria are outlined in Table 3. The primary endpoints of these...
protocols are feasibility and acute toxicity. 

TABLE 3

Eligibility Criteria for Breast IORT

Starting an IORT Program: Financial Considerations

Reimbursement: technical charges

Although clinical advances in the radiotherapeutic management of early-stage breast cancer have been rapid, advances in remuneration for IORT are evolving at a slower pace. Certainly, there are remuneration implications for treating with a single fraction. The reimbursement for standard external beam radiation is divided into professional physician fees, including consultation, treatment planning, and weekly radiation treatment management, as well as technical fees, including CT simulation, dosimetry, and treatment delivery. Both components are impacted by single-fraction delivery. 

TABLE 4

Comparison of Technical Charges for Whole-Breast RT vs Single-Fraction IORT

The current Medicare fees for technical reimbursement for a course of standard fractionated WBI, including treatment planning and delivery, amount to $10,275: $8,381 for the whole-breast external beam component plus $1,894 for the electron boost component (Table 4). The current technical reimbursement for a 3-week hypofractionated course of WBI is $6,032 (plus/minus the electron boost component).[16,17] Other radiation modalities offering patients the partial-breast radiation option (implanted devices and external beam) shorten treatment times and reimburse more. The Medicare technical reimbursement for APBI (brachytherapy) is $11,793.[16,17] In comparison, the current technical reimbursement for a single IORT breast treatment is less than one-fifth that of standard fractionated WBI: the Medicare reimbursement is currently $1,322. This is less than the current reimbursement for the electron component when delivered as a boost with standard traditional and hypofractionated external beam radiation therapy.
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Professional charges

In addition to technical reimbursement adjustments, the use of IORT also has a significant impact on the radiation oncologists’ professional reimbursement. The current Medicare professional reimbursement, including global charges, for a standard 6½-week course of WBI (including electron boost) ranges from approximately $5,200 to $5,500, depending upon whether a two- or three-field plan is utilized. Similarly, professional charges for a 3- to 4-week course of hypofractionated WBI is just over $4,000. In comparison, the professional fees for single-fraction IORT are approximately $696. This reflects the loss of reimbursement for simulation, treatment device, immobilization, port film verification, and daily treatment delivery.

The professional IORT codes continue to evolve, however. At present, the Current Procedural Terminology (CPT) codes for single intraoperative delivery (electrons or x-ray), 77424/25, are not separately reimbursed according to the 2012 Medicare fee schedule. The charge is bundled into other ambulatory payment classifications (ie, surgical). For 2013, the Centers for Medicare and Medicaid Services (CMS) has assigned a national average payment of $483 for these codes. With regard to treatment management codes, the IORT management code, 77469, is similar to other radiation treatment management codes, such as 77427. Currently, the IORT management code is assigned 8.74 Relative Value Units (RVUs), is reimbursed $279, and is a one-time billable code. (CMS is proposing to increase the RVUs to 9.11 in 2013). In contrast, the weekly management code for standard WBI is assigned an RVU of 3.37 by CMS and pays $170 to $190. This amounts to a total management reimbursement of $1,190 to $1,330 over a 6½-week course of standard WBI, compared with $279 for a single fraction for IORT. In 2012, CPT 77470 is considered part of the treatment management code and should not be billed separately.[18]

Whether at a free-standing facility or a hospital-based facility, the loss of reimbursement from both technical and professional fees is an important consideration, and one must realize that overall, reimbursement can drop to as low as 10% of that from standard fractionated WBI. Although it is possible that an intraoperative radiation breast program could increase patient volume, in reality the increase may not be sufficient to offset the severe reimbursement losses.

Conclusion

The establishment of a breast IORT program provides an attractive alternative for the radiotherapeutic management of select patients with early-stage breast cancer. The IORT program, however, creates logistical challenges, requires new treatment paradigms, and has a potential financial impact on the radiation oncologist and institution. The scheduling of cases requires coordination of surgeons, radiation oncologists, and OR resources, as well as demanding additional manpower from medical physicists and radiation therapists. Decisions regarding the subsequent management of patients who have been irradiated but who have positive margins, as well as regarding the sequencing of systemic therapy in patients requiring WBI, need to be agreed upon prior to starting the program. Radiation oncology departments must consider the reimbursement impact and additional manpower resources that are required to establish an IORT program. It is imperative that all members of the multidisciplinary team be involved from the inception.

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