CHAPTER

17 Intraoperative Irradiation

Brian G. Czito, Felipe A. Calvo, Michael G. Haddock, Manisha Palta, and Christopher G. Willett

Intraoperative radiation therapy (IORT) is the delivery of radiation at the time of surgery. The rationale is straightforward: increasing doses of radiation therapy enhance local tumor control. In many clinical situations, the dose delivered by external-beam radiation techniques is limited by tolerance of surrounding normal tissues. To overcome this, intraoperative irradiation has been employed as a technique facilitating tumor dose escalation. Recent Phase III trials have explored IORT, testing noninferiority or equivalence in patients with early breast cancer.[1,2]

This chapter reviews the rationale and treatment strategies of intraoperative electron irradiation (IOERT), intraoperative high-dose-rate brachytherapy (HDR-IORT), as well as orthovoltage techniques with surgery. These strategies frequently integrate external beam irradiation (EBRT) and chemotherapy.

HISTORY

The use of IORT was first employed almost 100 years ago.[3] The contemporary approach to IORT was initiated in the 1960s by Abe et al in Japan. These investigators advocated resection (where possible) with large, single dose radiation therapy (25 to 40 Gy using Cobalt-60).[4] In the mid- to late 1970s, many institutions in the United States had adopted IORT as a treatment approach, primarily as a radiation boost component, using linear accelerator-based electron treatment in the operating room, including Howard University, Massachusetts General Hospital (MGH), Mayo Clinic, and the National Cancer Institute (NCI). Presently, there are about 90 centers in at least 16 countries worldwide with active IORT programs.[5]

RATIONALE

IORT has the potential to improve local control and the therapeutic ratio in many tumor sites by reducing the volume of the irradiation "boost" field by direct tumor/tumor bed visualization and conformal treatment, exclusion of part or all of dose-limiting normal structures by operative mobilization, direct shielding, or varying electron beam energy, and allowing the delivery of high dose irradiation by the preceding methods.

Although early investigators studied this modality separately in the treatment of resected and unresectable malignancies, current approaches frequently employ this technique in combination with fractionated EBRT (with or without concomitant chemotherapy) and resection. The rationale is that EBRT fields encompass the primary tumor and surrounding tissues harboring potential microscopic disease. In contrast to a large single fraction of irradiation, fractionated radiation (EBRT) is radiobiologically advantageous in promoting tumor control while minimizing late normal tissue injury.

Shrinking field techniques permit dose escalation. This approach is used in many malignancies, including head and neck cancers, breast cancer, and cervical cancer with excellent local control and acceptable morbidity to dose limiting normal tissues. These "boost" fields can be delivered in a multitude of ways, including interstitial and intracavitary techniques as well as superficial electrons. For selected intraabdominal, pelvic, thoracic, and other malignancies, IORT is a technique for localized dose escalation while optimizing normal tissue protection.

BIOLOGY OF IORT

When EBRT is fractionated there is a preferential therapeutic advantage for normal tissues relative to tumor as defined by the 4R's of classical radiobiology (normal tissue repair, tumor reoxygenation, cell-cycle redistribution, and normal tissue repopulation). With a single large fraction of radiation therapy, these advantages are lost. In addition, large doses per fraction may result in increased risk of late effects. There is evidence that small vessel injury caused by large doses per fraction may contribute to late effects, and ischemic complications are dose dependent.[6] Furthermore, tumor response to single and fractionated radiation therapy depends on the percentage of hypoxic cells within a tumor. This differential sensitivity between hypoxic and well-oxygenated cells increases with increasing dose.

Using alpha/beta calculations (α/β), biologically equivalent doses to a fractionated EBRT course using 2 Gy per fraction for varying IORT doses have been estimated (Table 17-1). As shown, there are disadvantages from a late effects standpoint with IORT; however, many of these disadvantages are mitigated by exclusion of nontarget tissues from the radiation field by direct inspection, mobilization, and shielding.[7] When combined with EBRT and resection, IORT doses of 10 to 20 Gy provide local control for most solid tumors, especially in the setting of microscopic residual disease. When combined with EBRT and surgery, there is little reason to exceed IORT doses of 10 to 20 Gy. Late normal tissue complications are often the limiting sequelae of IORT administration, and careful planning and administration with techniques designed to reduce dose to nontarget tissues is of paramount importance. Experimental animal data and clinical studies have documented the tolerance of normal tissues to IOERT, EBRT, or both modalities combined, with detailed description of incidence and characteristics of reported observations and toxic events expected in the clinical practice scenario.[8]

LOCAL CONTROL: AN IMPORTANT ENDPOINT

For any treatment, a patient is incurable if local control of the tumor is not achieved. If conventional treatment methods of EBRT, chemotherapy, and surgery provided high local control rates, IORT as a component of treatment would be unnecessary. Single-dose irradiation with precise radiotherapy techniques has also emerged as a valid alternative in patients with metastatic disease[9] or as a potentially cost-effective technique for patients with tumors in early stages and with a favorable prognosis[10] tumors. Although local control rates are satisfactory in many tumor sites using conventional techniques, local failure is problematic in other sites, including abdominal and

TABLE 17-1 Estimated Biologically Equivalent EBRT Doses (2 Gy per Day) of Varying IORT Doses

IORT Dose	10 Gy	15 Gy	20 Gy
Normal tissue (acute) ($\alpha/\beta = 7$)	20 Gy	37 Gy	60 Gy
Tumor ($\alpha/\beta = 10$)	17 Gy	31 Gy	50 Gy
Normal tissue (late) ($\alpha/\beta = 2$)	30 Gy	65 Gy	120 Gy

pelvic malignancies. Treatment of these areas employing standard EBRT techniques is limited by normal tissue tolerance. Examples of such sites are discussed herein.

Pancreatic Cancer

EBRT with 5-fluorouracil (5-FU) based chemotherapy employed in the treatment of unresectable pancreatic cancer results in a doubling of median survival compared to surgical bypass/stenting alone (3 to 6 months versus 9 to 13 months) and an increase in 2-year survival from between 0% to 5% and 10% to 20%.[11] Unfortunately, these techniques result in poor local control rates (20% to 30%). The use of IORT has been evaluated in patients with both resectable and unresectable pancreatic cancer patients.

Retroperitoneal Sarcoma

When surgery is used as the primary treatment modality for retroperitoneal sarcomas, local failure has been reported to range from 40% to 90%. Despite the addition of EBRT to surgery, local failure rates are 40% to 80%. This is in contrast to extremity sarcomas where local control rates approach 90%. Because of the limited tolerance of surrounding normal tissue (small intestine, stomach, liver, kidney, spinal cord), EBRT doses are limited. A randomized NCI trial evaluating IORT in retroperitoneal sarcomas demonstrated that patients receiving IORT with EBRT experienced significantly improved local control and less small bowel toxicity versus patients treated with EBRT alone (80% in-field relapse; discussed later).[12]

Colon and Rectal Cancer

In patients with locally advanced (T4) or locally recurrent colon and rectal cancers, local control is difficult to achieve, despite multimodality therapy. Studies from Princess Margaret Hospital and Mayo Clinic report local failure rates of 90% or greater in evaluable patients treated with EBRT with or without systemic therapy.[13,14] In patients who are radiation naive, the optimal approach in locally advanced patients is preoperative EBRT combined with 5-FU-based chemotherapy followed by resection. Despite this, local recurrence occurs in 30% to 70% of patients.[15]

Cervical Cancer

For patients with cervical cancer, paraaortic nodal metastases are common. Despite the presence of these "distant" metastases, approximately 15% to 20% of patients are cured by radical radiotherapy techniques employing EBRT doses of 55 to 60 Gy. However, high complication rates have been reported with these doses and techniques.[16,17] As in rectal cancer, patients with recurrent cervical cancer in the pelvis or paraaortic region have a poor long-term prognosis with five-year overall survival (OS) rates ranging from 5% to 30%. These patients have often been previously irradiated and retreatment with meaningful doses of EBRT is usually not feasible given normal tissue tolerance. When patients have paraaortic or locally recurrent disease, administration of IORT is a feasible method to escalate dose and enhance local control.

Oligorecurrences: Miscellaneous Intraabdominal Sites

Active follow-up of patients with cancer initially treated for cure has identified new entities including oligometastatic or oligorecurrent disease still amenable to salvage treatment by combining surgical and radiotherapy components. Recent analyses of patient cohorts including varying cancer primaries and histological subtypes have reported local control rates of greater than 80% and 5-year survivals of 35% in patients with extrapelvic, oligotopic disease.[18] In the case of intrapelvic gynecological oligorecurrences, salvage therapy with extended surgery and IOERT has demonstrated a 10-year locoregional control of 58%, with improved results if EBRT treatment was integrated into this approach.[19]

LOCAL CONTROL: RADIATION DOSE, COMPLICATIONS, SHRINKING FIELD TECHNIQUES, AND DISTANT METASTASES

Influence of Dose

In both animal and human models, the probability of local control of a tumor by radiation is generally proportional to the total dose administered. The dose of radiation to control a tumor locally depends on several factors, including tumor type, clonogen number, and tumor microenvironment. Thus, a given radiation dose may be able to control a small tumor with high probability and acceptable morbidity; however, that same dose may be insufficient against disease of larger volume. Clinical experience has generated a body of data correlating local control by tumor type and radiation dose. Figure 17-1 summarizes in vivo data for a variety of irradiated human tumors of varying sizes and types.[20]

The studies of Fletcher examined local control probability as a function of radiation dose for patients undergoing treatment for breast carcinoma and squamous cell carcinoma of the upper aerodigestive tract (eTable 17-1). For patients with breast cancer, control of subclinical disease was approximately 60% to 70% with 30 to 35 Gy, 85% with 40 Gy, and 95% with 45 to 50 Gy. For larger/palpable tumors, EBRT doses of 46 Gy, 59 Gy, and 76 to 90 Gy result in a local control probability of 20%, 35% to 50%, and 70% to 80%, respectively.[21-24] Dose response data is summarized for patients with squamous cell carcinomas of the upper aerodigestive tract in eTable 17-2. These data suggest that marked improvements in local control can be achieved by escalating radiation doses.

Dose versus Complications

The chief limitation of EBRT to control macroscopic disease in the abdomen and pelvis is normal tissue tolerance. Normal organs such as stomach, small bowel, and kidney have tolerance levels well below the radiation doses required to eradicate most abdominal and pelvic malignancies. Exceeding these, EBRT doses results in prohibitive risk of late normal tissue damage (see eTable 17-2). Because of this, "conventional" tolerable doses of EBRT from 45 to 55 Gy using 1.8 to 2 Gy per fraction are not curative in most abdominal and pelvic malignancies, with resultant local persistence/local recurrence of disease common in patients treated with

eTABLE 17-1 Tumor Control Probability Correlated with Irradiation Dose and Volume of Cancer

Dose (Gy)	Tumor Control Probability
SQUAMOUS CELL CARCINOMA: UPPER AERODIGESTIVE TRACT	
50*	>90% subclinical ~60% T1 lesions of nasopharynx ~50% 1-cm to 3-cm neck nodes
60*	~90% T1 lesions of pharynx and larynx ~50% T3 and T4 lesions of tonsillar fossa ~90% 1-cm to 3-cm neck nodes ~70% 3-cm to 5-cm neck nodes
70*	~90% T2 lesions of tonsillar fossa and supraglottic larynx ~80% T3 and T4 lesions of tonsillar fossa
ADENOCARCINOMA OF THE BREAST	
50*	>90% subclinical
60*	90% clinically positive axillary nodes, 2.5-3 cm
70*	65% 2-3 cm primary
70-80 (8-9 wk)	30% >5 cm primary
80-90 (8-10 wk)	56% >5 cm primary
80-100 (10-12 wk)	75% 5-15 cm primary

Modified from Fletcher GH, Shukovsky LJ: The interplay of radiocurability and tolerance in the irradiation of human cancers. J Radiol Electrol 56:383–400, 1975.
**10 Gy in five fractions each week.*

eTABLE 17-2 Gastrointestinal Radiation Tolerance

		Doses (in Gy)*		
Organ	**Injury at 5 Yr**	**$TD_{5/5}$**	**$TD_{50/5}$**	**Volume or Length**
Esophagus	Ulcer, stricture	60-65	75	75 cm^3
Stomach	Ulcer, perforation	45-50	55	100 cm^3
Intestine (small)	Ulcer, stricture	45-50	55	100 cm^3
Colon	Ulcer, stricture	55-60	75	100 cm^3
Rectum	Ulcer, stricture	55-60	75	100 cm^3
Anus	Ulcer, stricture	60-65	≥75	—
Pancreas	Secretory functions	—	—	—
Liver	Liver failure, ascites	35	45	Whole
Biliary ducts	Stricture, obstruction	50	70†	—

Modified from Gunderson LL, Martenson JA: Gastrointestinal tract radiation tolerance. Front Radiat Ther Oncol 23:277–298, 1989.
$TD_{5/5}$, *5% chance of severe intolerance within 5 years;* $TD_{50/5}$, *50% chance of severe intolerance within 5 years.*
**Data based on supervoltage (6/18 MV), 9 Gy/wk (5 × 1.8).*
†External beam radiation to 50.4 Gy (28 × 1.8/5½ weeks) plus 20 Gy at 1-cm radius with iridium 192.

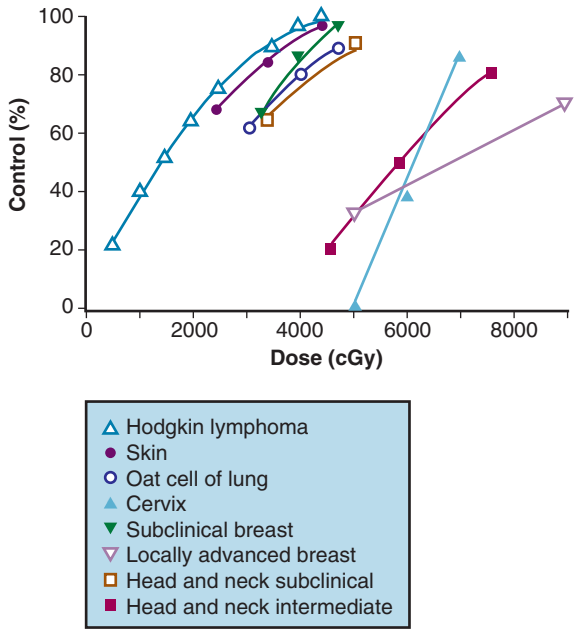


Figure 17-1 Local control versus dose of irradiation.
Modified from Gunderson LL, Tepper JE, Biggs PJ, et al: Intraoperative ± external beam irradiation. Curr Probl Cancer 7(11):1–69, 1983.

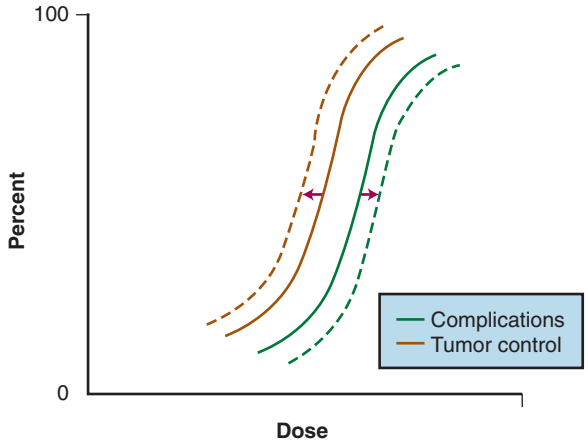


Figure 17-2 Radiation dose versus incidence of tumor control or complications.
Modified from Gunderson LL, Tepper JE, Biggs PJ, et al: Intraoperative ± external beam irradiation. Curr Probl Cancer 7(11):1–69, 1983.

radiation therapy alone. This often results in tumor-related morbidity and mortality such as bowel obstruction and perforation, ureteral obstruction, and neuropathy.

Although local control is enhanced with increasing doses of radiation, tumor dose response curves with EBRT closely resemble normal tissue complication curves. Therefore, efforts to improve local control through escalating EBRT doses may also result in treatment-related complications (Figure 17-2). In an R1 (microscopic residual) resection, EBRT doses of 60 Gy or higher using conventional fractionation schemes are necessary to achieve a high probability of local control. In an R2 (gross residual) resection, even higher doses are usually required. Such doses exceed normal tissue tolerance (see eTable 17-2).

Because of the risks associated with dose escalation beyond normal tissue tolerance, an attractive alternative in patients with locally advanced malignancies is to deliver moderate doses of EBRT (i.e., at or below accepted tolerance of surrounding normal tissue). A typical course would range from 45 to 50 Gy at 1.8 to 2 Gy per fraction, followed by surgical exploration. After resection, IORT would be performed, avoiding or minimizing irradiation of surrounding organs by shielding or mobilization. With this approach, an increase in local control with decreased risk of normal tissue complications (relative to an EBRT-only approach) can be achieved (see Figure 17-2—local control curve shifts to left with IORT; complication curve shifts to right with increasing EBRT doses).

Shrinking-Field (Boost) Techniques

The concept of shrinking-field irradiation, otherwise known as administering "boost" treatments, has been used for decades by radiation oncologists. This strategy entails treating larger fields encompassing the primary/recurrent tumor along with local-regional lymph node basins and other tissues at risk for subclinical disease. These larger fields receive a dose sufficient to control microscopic disease yet respect normal organ tolerance (often 45 to 50 Gy using 1.8 to 2 Gy per fraction). Fields are then reduced to encompass gross disease with smaller margins, excluding dose-limiting normal tissues. An additional 20 to 35 Gy may then be administered to these fields using either EBRT or brachytherapy techniques, bringing the cumulative dose to 65 to 80 Gy. These approaches are employed in many tumor sites including gynecologic and head and neck cancers with excellent long-term outcomes and local control with relatively low and acceptable morbidity levels. The concept of administering IORT in conjunction with EBRT is a logical application of this approach.

Local Control and Development of Distant Metastases

Preclinical data suggests that the incidence of distant metastases is related to both tumor size as well as the development of locally recurrent disease in multiple spontaneous tumor systems.[25-27] In fibrosarcoma and squamous cell carcinoma cell lines in rodent models, Ramsay et al reported increased rates of distant metastases in tumors measuring 6 mm versus 12 mm in size, as well as primary versus recurrent tumors.[25] Additionally, Suit et al showed that in mouse mammary tumors treated with single-dose irradiation, increasing rates of local failure were associated with increasing rates of distant metastases.[27] Specifically, the incidence of metastatic disease was 31% (16 of 52) of mice with local control, 50% (9 of 18) in those with local relapse salvaged by resection, and 80% (12 of 15) in mice with local relapse in whom salvage was not attempted. Similar high rates of metastases associated with local failure have been observed in human malignancies including cervix,[28] prostate,[29] head and neck,[30] and breast[31] cancers. These and other data suggest that metastases may arise from locally recurrent disease.

PATIENT SELECTION AND EVALUATION

Patient Selection Criteria

Candidates for IORT should be evaluated by the treating surgeon and radiation oncologist in the multidisciplinary setting. This allows for joint decisions regarding the appropriateness of IORT and whether further studies that may influence IORT and EBRT planning are appropriate. Additionally, joint decisions can be made defining the optimal sequencing

of surgery/IORT and EBRT. Informed consent should be obtained from both specialties, specifically with regard to potential risks, benefits, and side effects of proposed treatments. Criteria for the appropriate selection of patients for IORT generally include:

1. Surgery alone will result in a high probability of incomplete resection (microscopic or gross residual disease) and resultant high probability of failure within the tumor bed. Potential candidates must be appropriate for surgical attempts at gross total resection. IORT administration should be performed at the time of a planned operation.
2. There is no evidence of distant metastases. Rare exceptions include resectable single-organ metastasis, slow progression of systemic disease, excellent chemotherapy options, and patients with oligometastatic disease with slow systemic progression and high probability of symptomatic local failure.
3. EBRT doses required for high probability of local control following subtotal or no resection exceed normal tissue tolerance (Total doses required for eradication in this setting: 60 to 70 Gy for microscopic disease and 70 to 90 Gy for gross disease at 1.8 to 2 Gy per fraction)
4. Surgical displacement or shielding of dose-limiting structures or organs can be accomplished during IORT administration, allowing for acceptable risks of immediate and late effects. Theoretically, EBRT in conjunction with IORT should result in an improved therapeutic ratio between disease eradication and normal tissue complications.

Patient Evaluation

Pretreatment patient evaluation in patients eligible for IORT should include a thorough history and physical examination, with attention to palpable disease and its relationship to anatomically immobile normal structures. Examples include pelvic disease and its relationship to the pelvic sidewall, presacral space, prostate, or vagina. Computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound may aid in identifying adherence to structures (e.g., bony pelvis, large vessels) that may be surgically unresectable for cure. Examination under anesthesia may be helpful in some situations including locally advanced gynecologic and rectal cancers. Routine blood counts including complete blood count (CBC), liver function tests, renal function tests, and tumor-specific serum test (e.g., carcinoembryonic antigen, CA19-9) should be obtained where appropriate. Patients should be evaluated clinically and radiographically for evidence of distant spread. Positron emission tomography (PET), preferably in conjunction with CT, may facilitate defining local disease extent as well as unsuspected distant metastases. Evaluation of distant metastases is particularly important in the recurrent setting where concurrent distant failure is common. Biopsy confirmation of disease should usually be obtained before proceeding with resection.

SEQUENCING AND DOSE OF EBRT AND IORT

Sequencing of EBRT, IORT, and Surgery

For patients with localized malignancy, the goal of curative oncologic surgery is an R0 (margin-negative) resection. Because of the locally advanced and infiltrative nature of many primary tumors (including colorectal, gynecologic, and upper gastrointestinal [GI] malignancies, sarcomas, etc.) and locally recurrent malignancies, surgery may be compromised with close margins or microscopic/gross residual. For patients with locally advanced tumors, preoperative EBRT to doses of 45 to 50 Gy using 1.8 to 2 Gy fractions (with or without chemotherapy) followed by laparotomy, resection, and IORT offers theoretical and clinical advantages over resection and IORT followed by EBRT. These are listed as follows:

1. By postponing surgical resection until after preoperative therapy is completed, patients with disease that is rapidly progressive may avoid an unnecessary surgical procedure with associated morbidity.
2. Preoperative therapy may allow for tumor downstaging and facilitate resection with curative intent.
3. Preoperative therapy may reduce the risk of tumor seeding/dissemination at resection.
4. Preoperative therapy allows delivery of treatment to disease with an intact vasculature, potentially improving the delivery of chemotherapy and improving oxygen delivery for EBRT.
5. The morbidity and delayed recovery time associated with extensive surgical procedures may prevent the timely delivery of postoperative therapy in a high percentage of patients.[32,33]

The role of preoperative versus postoperative therapy has been evaluated in rectal cancer. A large German randomized trial demonstrated that patients undergoing neoadjuvant irradiation and chemotherapy experienced significantly improved local control and less toxicity than patients receiving postoperative irradiation and chemotherapy.[34]

Radiation Dose and Technique

Techniques combining EBRT and IORT have been fairly uniform in the United States and Europe. In previously untreated patients, EBRT doses of 45 to 54 Gy have been employed delivering 1.8 to 2 Gy per fraction, 5 days per week, over a period of 5 to 6 weeks. Because of the anatomical location of pelvic and abdominal malignancies, high-energy (>10 MV) photons delivered via linear accelerators using multifield, shaped techniques are required. CT-, PET-, or MRI-based treatment planning permit accurate definition of the target volume. For extrapelvic, unresected or residual disease following resection, radiation doses of 40 to 45 Gy delivered at 1.8 to 2 Gy per fraction with a 3- to 5-cm margin accounting for microscopic extension and target mobility are sometimes used. Treatments are generally delivered through multifield techniques aided by three-dimensional (3D) or IMRT-based treatment planning. Reduced-field or "boost" techniques are often used to bring the total dose to 45 to 54 Gy as dictated by tolerance of surrounding normal tissue (see previous discussion). Concurrent chemotherapy administration during EBRT varies by tumor site; for patients with gastrointestinal malignancies, concurrent 5-FU–based regimens (plus cisplatin or mitomycin C) are frequently implemented, and for patients with gynecologic cancers, concurrent cisplatin is frequently given. In carefully selected patients who have received prior irradiation, low-dose preoperative EBRT doses of 20 to 30 Gy at 1.5 to 1.8 Gy per fraction (often with concurrent chemotherapy) may be employed.

Dose of IORT

IORT dose should be based on extent of residual disease at resection, the amount of EBRT delivered previously, and the type and volume of normal tissue irradiated. For patients who have received preoperative doses of 45 to 54 Gy (1.8 to 2 Gy per fraction, 5 days per week), IORT doses usually range from 10 to 20 Gy. For patients with microscopic residual or close margins, doses of 10 to 12.5 Gy are often administered. Patients with gross residual disease require higher doses and 15 to 20 Gy is usually administered. In previously irradiated

patients, in whom additional EBRT is feasible (20 to 30 Gy), the dose of IORT generally ranges between 15 Gy and 20 Gy. In patients in whom no or very limited EBRT is planned, IORT doses from 25 to 30 Gy have been administered; however, doses in this range should be judiciously employed given the risk of normal tissue damage, specifically peripheral nerve injury.

The biological effectiveness of single-dose IORT in early responding tissues (tumor) relative to an equivalent total dose of fractionated EBRT has been estimated to be 1.5 to 2.5 times the IORT dose delivered (Table 17-1).[7,35,36] Therefore, the effective tumor dose (when "normalized" to fractionated EBRT doses) of IORT treatment added to 45 to 50 Gy given by EBRT are as follows: 10 Gy IORT dose, 60 to 80 Gy; 15 Gy IORT dose, 75 to 87.5 Gy; 20 Gy IORT dose, 85 to 100 Gy. These figures are not intended to be exact but represent educated estimates.

Technical Aspects

The technical aspects of IORT administration are beyond the scope of this chapter and have been discussed in other publications (see reference list). In brief, the implementation of IORT-based treatment is a multidisciplinary effort including one or multiple surgeons, radiation oncologist, anesthesiologist, operating room nurse, radiation physicist/dosimetrist, and therapist. In its broadest sense, IORT may be administered with either electrons (IOERT) or HDR photon afterloading techniques (HDR-IORT). Each method has potential advantages and disadvantages, which are summarized later.

IORT DOSE-LIMITING STRUCTURES AND TOLERANCE

The development of normal tissue late effects increases with increasing radiation dose as well as dose delivered per fraction. Therefore, the incidence of late normal tissue effects in patients receiving IORT plus EBRT would be higher than those receiving EBRT alone.[37] However, in this context the severe morbidity and mortality associated with locally recurrent tumor is often overlooked. As an example, when EBRT alone is used as the primary treatment modality for locally advanced rectal cancer, more than 90% of patients experience local persistence or local recurrence of disease with associated symptomatology. These symptoms include severe pelvic pain and neuropathy, which are difficult to manage clinically and the vast majority of patients experience disease-related death within two to three years. An argument can be made that the tumor-related morbidity/mortality approaches 100% in these patients.[38]

IORT tolerance for intact or surgically manipulated organs or structures in animals (primarily canines) is seen in Table 17-2. Much of this information has been derived from studies from the NCI[39-44] and Colorado State University (CSU).[45-47]

Several dose-sensitive structures have been studied in humans receiving IORT, including the ureter and peripheral nerve. These are discussed next.

Ureter

Clinical studies of the effect of IOERT on the ureters of patients with cancer have been undertaken at the Mayo Clinic. Doses

TABLE 17-2 Normal Tissue Tolerance to Intraoperative Electron Irradiation in Animals (Usually Dogs)

Tissue	Maximum Tolerated Dose (Gy)	Tissue Effect	Dose (Gy)
INTACT STRUCTURE			
Aorta, vena cava	50	Fibrosis of wall (patency up to 50 Gy)	≥30
Peripheral nerve	15	Neuropathy, sensory-motor	≥20
Bladder	30	Contraction and ureterovesical narrowing	≥25
Ureter	30	Fibrosis and stenosis	≥30
Kidney	<15	Atrophy and fibrosis	≥20
Bile duct	20	Fibrosis and stenosis	≥30
Small intestine	<20	Ulceration, fibrosis, stenosis	≥20
Large bowel	15	Ulceration, fibrosis, stenosis Perforation	≥17.5 50
Esophagus Full thickness Partial thickness	 ≤20 40	 Ulceration, stricture No sequelae at this dose	 ≥30 ≥40
Muscle (psoas)	23	50% decrement muscle fibers	38
Heart (right atrium)	20	Fibrosis	≥30
Lung	20	Fibrosis	≥20
Trachea	30	Submucosal fibrosis	≥30
SURGICALLY MANIPULATED			
Aorta anastomosis (end to end)	20	Fibrosis and stenosis No anastomosis disruption	≥20 ≤45
Aortic prosthetic graft	25	Graft occlusion	25
Portal vein anastomosis	40	Stenosis	>40
Biliary-enteric anastomosis	<20	Anastomotic breakdown	≥20
Small intestine (defunctionalized)	45	Fibrosis and stenosis No suture line breakdown	≤20 ≤45
Bladder	30	Healing but contraction	≥30
Bronchial stump	>40	Absence of air leak	>40

of 10 Gy administered intraoperatively resulted in a 50% incidence of ureteral obstruction, increasing to 70% with doses from 15 to 25 Gy. This high complication rate relative to canine models may be as a result of age-related factors, surgical manipulation, EBRT, or tumor bed effects.[48]

In an update of this experience, investigators from the Mayo Clinic reported on 146 patients with locally advanced malignancies receiving IORT to one or both ureters of doses between 7.5 Gy and 30 Gy. They reported the risk of obstruction following IOERT is significant and increases with time and IORT dose. The rates of clinically apparent type 1 obstruction (obstruction from any cause) after IOERT at 2, 5, and 10 years were 47%, 63%, and 79%, respectively. The rates of clinically apparent type 2 obstruction (obstruction occurring at least 1 month after IOERT, excluding obstruction caused by tumor or abscess and patients with stents) at 2, 5, and 10 years were 27%, 47%, and 70%, respectively. Multivariate analysis revealed that the presence of obstruction before IOERT was associated with an increased risk of clinically apparent type 1 obstruction ($p < 0.001$). Increasing IOERT dose was associated with an increased risk of clinically apparent type 2 obstruction ($p < 0.04$). Obstruction rates in ureters not receiving IOERT at 2, 5, and 10 years were 19%, 19%, and 51%, respectively, suggesting an underlying risk. However, obstruction risk for ureters not receiving IOERT was also high, which suggests an underlying risk of ureteral injury from other causes (EBRT, surgical manipulation of ureters).[49]

Peripheral Nerve

Peripheral nerve is the principal dose-limiting normal tissue for IORT in the pelvis and retroperitoneum. Data regarding peripheral nerve tolerance and neuropathy comes from canine models as well as clinical analyses from patients treated intraoperatively.[40,43,45,48,50-60] Peripheral nerve is often situated adjacent to or directly involved by tumor in the abdomen and pelvis. Because of this, the relative surgical "immobility" of peripheral nerves and inability to shield the nerve from the IORT field, nerve tissue will often receive full dose EBRT and IORT.

The mechanism of neuropathy following IORT is poorly understood. Peripheral nerve tolerance depends on the volume of nerve irradiated and total dose delivered. In animal models, histomorphologic findings following IORT have demonstrated decreased central nerve fiber density, particularly in large nerve fibers receiving >20 Gy. Electron microscopy analysis has demonstrated increased microtubule density and neurofilament accumulation within axons without associated myelin changes, suggesting possible hypoxic injury related to vascular changes.[60]

A Spanish study evaluated 45 patients with primary or locally recurrent extremity soft-tissue sarcoma undergoing resection with IOERT (10 to 20 Gy). Nine patients received IOERT alone secondary to prior EBRT or patient refusal. Five patients developed neurotoxicity at a median of 13 months; 4 of 5 showed objective weakness or sensory loss. Most patients developing neuropathy received IOERT doses greater than 15 Gy.[61]

An analysis from the Mayo Clinic evaluated peripheral nerve tolerance in 51 patients undergoing IOERT for primary or recurrent pelvic malignancies. Patients received EBRT (median dose 50.4 Gy), maximal resection where possible, and IOERT boost from 10 to 25 Gy using 9 MeV to 18 MeV electrons. Sixteen patients (32%) experienced grades 1 to 3 peripheral neuropathy as manifested by pelvic/extremity pain, leg weakness, numbness, or tingling. Pain was severe (grade 3) in 3/51 patients (6%)[48] (eTable 17-3).

A follow-up study from the Mayo Clinic evaluated 178 patients with locally advanced colorectal cancer receiving IOERT. This study suggested a relationship between increasing doses of IOERT and the incidence of clinically significant neuropathy (Table 17-3). In patients with primary and locally recurrent colorectal cancer, the incidence of severe (grade 3) neuropathy was approximately 5%, and the incidence of any neuropathy was approximately one third. This is consistent with canine studies suggesting increasing IOERT doses are related to the incidence of clinical and electrophysiologic neuropathy.[51,52]

TABLE 17-3 Colorectal IOERT, Mayo Clinic IOERT Dose versus Neuropathy

Disease Presentation	IOERT Dose versus Grade 2 or 3 Neuropathy ≤12.5 Gy	≥15 Gy	*p*
Primary[52*]	1/29 (3%)	6/28 (21%)	0.03
Recurrent, no prior EBRT[51†]	2/29 (7%)	19/101 (19%)	0.12
Primary + recurrent	3/58 (5%)	25/129 (19%)	0.01

EBRT, *External beam irradiation;* IOERT, *intraoperative electron irradiation.*
**57 IOERT fields in 55 evaluable patients. Incidence of grade 3 neuropathy by dose: ≤12.5 Gy, 0 of 9; 15 Gy or 17.5 Gy, 1 of 19, or 5%; ≥20 Gy, 2 of 9, or 22%.*
†130 IOERT fields in 123 patients.

A more recent Mayo Clinic analysis of 607 patients with locally recurrent colorectal cancer receiving IORT reported an incidence of grades 1 to 3 neuropathy of 15% (grade 1, 5%; grade 2, 7%; grade 3, 3%). A dose-related increase in grades 2 and 3 neuropathy was seen in patients receiving ≥15 Gy compared to ≤12.5 Gy.[53]

Conclusions

All patients considered for IORT should undergo thorough pretreatment informed consent, including a discussion regarding neuropathy-related side effects. It should also be remembered that uncontrolled tumor frequently causes symptoms related to neural impingement, and in fact many potential IORT candidates present with neuropathic symptoms related caused by primary or recurrent disease. Based on human and animal data evaluating IORT induced neuropathy, IORT doses are generally limited to 10 to 20 Gy when a full course of EBRT is administered (45 to 54 Gy using 1.8 to 2 Gy per fraction). Doses exceeding 20 Gy in the intraoperative setting should be used with caution, and our general policy regarding such is to administer higher doses only in the setting of limited EBRT options (i.e., prior EBRT treatment).

IORT RESULTS FOR SELECTED DISEASE SITES

A summary of IORT results and future possibilities in selected disease site (pancreas, breast, colorectal, gynecologic cancers, and retroperitoneal/pelvic sarcomas) are now presented. For a more detailed discussion, the reader is referred to dedicated chapters on each site in an IORT text.[64]

Pancreas Cancer: EBRT and IORT

Given local failure rates of 50% to 80%, the use of IORT in the setting of pancreatic cancer is rational. Available data in patients receiving IORT after pancreaticoduodenectomy

eTABLE 17-3 Clinical Peripheral Neuropathy Characteristics with Pelvic IOERT, Mayo Clinic

Characteristic	Incidence*	Severity		Time Course (mo from IORT)	
		Mild/Moderate	Severe	Onsets†	Resolution, Range
Pain	16/50 (32%)	13 (26%)	3 (6%)	1/2-18 (15)	6/14 (42%),‡ 5-32§
Motor	8/50 (16%)	6 (12%)	2 (4%)	3-22 (7)	1/8 (13%), 20
Sensory	11/50 (22%)	11 (22%)	0 (0%)	3-22 (7)	4/11 (36%), 1, 7, 19, 20

Modified from Shaw E, Gunderson IL, Martin JK, et al: Peripheral nerve and ureteral tolerance of intraoperative radiation therapy: Clinical and dose-response analysis. Radiother Oncol 18:247–255, 1990.

IOERT, *Intraoperative electron irradiation;* IORT, *intraoperative irradiation.*

**One patient excluded who died postoperatively.*

†Values in parentheses represent median.

‡Two patients excluded who were lost to follow-up.

§Median, 15 months.

demonstrates an improvement in local control; however, a clear survival benefit has not been demonstrated. Series of patients with locally advanced pancreatic cancer suggest local control and pain relief, with select studies demonstrating an OS benefit.

IORT in Resected Disease

In the United States, initial feasibility of IORT in conjunction with surgery was demonstrated at the NCI. Thereafter, the NCI reported a series evaluating 24 further patients randomized to receive IORT (20 Gy) versus EBRT. After excluding 7 perioperative deaths, an improvement in local control (67% versus 0%) and median survival (median OS 18 versus 12 months, $p = 0.01$) was seen in the patients who received IORT.[65]

Further data on IORT at the time of surgery are limited to single and multiinstitutional retrospective series (Table 17-4A). The largest of the single institution series evaluated 127 patients treated with surgery and IORT compared to a cohort of 26 patients who underwent surgery alone. No additional operative morbidity or mortality was seen with the addition of IORT; however, for patients with Stage I/II disease IORT resulted in lower rates of local failure and significantly longer time to local failure, time to failure, and OS compared to surgery alone. These data suggest possible local control benefit with the use of IORT after resection in select patients.[63]

These data are corroborated by two multiinstitutional series. A Japanese series evaluated 210 patients undergoing surgery and IORT with and without EBRT. Median IORT and EBRT doses were 25 Gy and 45 Gy, respectively. Seventy-one percent of patients experienced disease relapse with local failure occurring in 15% of patients. Median and 2-year OS were 19.1 months and 42%, respectively. The combination of IORT and chemotherapy resulted in improved survival compared to IORT alone. The authors concluded that IORT yields excellent local control rates for pancreatic cancer with a low incidence of toxicity, and IORT combined with chemotherapy confers a survival benefit compared to IORT alone.[62]

A European multiinstitutional series evaluated 270 patients treated at five institutions between 1985 and 2006.[69] Neoadjuvant EBRT or concurrent chemoradiation (CRT) was delivered in 24% of cases and median IORT dose was 15 Gy (range 7.5 to 25 Gy). Significantly better local control was seen in patients undergoing preoperative radiation therapy (RT) with a median time to local relapse not reached and median OS of 30 months compared to 22 months with postoperative EBRT or CRT and 13 months with IORT alone. The authors concluded preoperative EBRT increases the effect of IORT in terms of local control and survival, with favorable long-term local control rates.[69] Compared to historical controls, these low rates of local failure and reasonable median survival reflect the possible benefit of IORT in patients with resected pancreatic cancer.

IORT in Locally Unresectable Disease

The role of IORT has been more clearly defined in the treatment of patients with locally unresectable pancreatic cancer. Many studies have documented both safety and pain control with IORT, resulting in complete pain resolution in 75% to 90% of cases.[72] Table 17-4B shows outcomes of select series using IORT in locally unresectable pancreatic cancer patients.

A study from Mayo Clinic evaluated 159 patients with locally unresectable pancreatic cancer who underwent exploratory laparotomy; 122 had postoperative EBRT alone or plus concurrent 5-FU and 37 received an IOERT boost followed by EBRT alone or plus 5-FU. One-year local control (LC) with the combination of EBRT and IORT was 82% compared to 48% with EBRT alone (2-year LC was 66 versus 20%, $p = 0.0005$).

TABLE 17-4A Results of Selected Studies of IORT in Patients with Resected Pancreatic Cancer

Series/ Treatment	Year/ Pt No.	IORT Dose (Gy)	EBRT (%)	Operative Mortality	Postop Complication	Local Recurrence	Survival	
							Median	2-yr
Sindelar et al[62,135]	(1999)	—	100%	27%	71%	—	—	
Surgery/EBRT	12	—		Overall	Overall	100%	12 mo	
Surgery/IORT/EBRT	12	20 Gy				33%	18 mo (p = .01)	
Zerbi et al[136]	(1994)	—	36%	—	—	—	—	
Surgery alone	47	—	—	2.1%	23.4%	56.3%	12 mo	16%
Surgery & IORT	43	12.5-20	—	2.3%	23.2%	27%*	19 mo	24%
Alfieri et al[137]	(2001)	—	67%	—	—	(5 year)	—	
Surgery ± EBRT	20	—		8%	43%	71.2%	10.8 mo	
Surgery/IORT ± EBRT	26	10		9%	57%	41.6%	14.3 mo	
Reni et al[63]	(2001)	—	28%	—	—	(median to LR)	—	
Surgery ± EBRT	76	—		4%	45%	11 months	12 mo	
Surgery/IORT ± EBRT	127	10-25		3%	39%	14 months	15.5 mo	
Ogawa et al[64]	(2010)	—	—	—	—	—	—	
Surgery/IORT ± EBRT	210	20-30	30%	—	—	16.3%	19 mo	42%
Valentini et al[65]	(2009)	—	—	—	—	—	—	
Surgery/IORT ± EBRT	270	7.5-25	64%	2%	24%	(median to LR)	—	
Preop EBRT/CRT	63					Not reached	30 mo	
Postop EBRT/CRT	106					28 mo.	22 mo	
IORT/no EBRT	95					8 mo.	13 mo	
Bachireddy et al[138]	(2010)	(Ortho)	—	—	—	—	—	
Surgery/IORT ± EBRT	23	6-15	78%	—	6%	39%	—	27%
Calvo et al[139]	(2013)	—	100%	—	—	(5 year)	20% (5year)	
Surgery + EBRT/CRT	41	—		0%	39%	72%		
Surgery/IORT + EBRT	29	10-15		7%	48%	8%		

CRT, *Chemoradiation;* EBRT, *external beam irradiation;* IORT, *intraoperative irradiation;* LR, *local recurrence;* mo., *months;* Ortho, *orthovoltage;* Postop, *postoperative;* Preop, *preoperative;* Pt No., *patient numbers;* yr, *year.*

*$p < 0.01$.

TABLE 17-4B Results of Selected Studies of IORT in Patients with Locally Unresectable Pancreatic Cancer

Author/ Reference Institution or Group	Year	Pt. No./Type of Treatment	IORT Dose, Gy	Local Recurrence	Survival	
					Median	2-yr
Roldan et al[67]; Mayo Clinic	1988	159	—	(2-yr)	—	—
		122 EBRT ± 5FU	—	80%	12.6 mo	16.5%
		37 IORT/EBRT ± 5FU	20	34%	13.4 mo	12.0%
Shibamoto et al[68]	1996	115	30-33	—	No difference	
		44 EBRT, 16 IORT				
		55 EBRT & IORT				
Tepper et al[140]; RTOG	1991	51 analyzable	20	Not assessable	9 mo	—
		EBRT & IORT				
Willett et al[70,71]; MGH	2013	194	15-25	(2-yr)	12 mo	16%
		EBRT & IORT		59%		
Mohiuddin et al[72]; TJUH	1995	49	—	—	—	—
		EBRT & IORT	10-20	29%	16 mo	22%
Schuricht et al[73]; TJUH	1998	105	15-20	(2-yr)	—	—
		33 EBRT & IOERT		30%	18 mo	17%
		43 EBRT & ^{125}I			15 mo	19%
		29 EBRT alone			9 mo	NS

CRT, *Concurrent chemoradiation;* EBRT, *external beam irradiation;* IORT, *intraoperative irradiation;* MGH, *Massachusetts General Hospital;* mo., *months;* Pt. No., *patient numbers;* RTOG, *Radiation Therapy Oncology Group;* TJUH, *Thomas Jefferson University Hospital;* yr, *year.*

Despite a benefit in LC, there was no difference in median or long-term survival between the groups because of the high incidence of liver or peritoneal relapse in both groups (>50%).[73]

A Japanese study evaluated the use of IORT in the treatment of 115 patients with locally unresectable pancreatic cancer. Patients received either a combination of EBRT and IORT, EBRT alone, or IORT alone. In the subgroup of patients with a CA19-9 <1000, the combination of EBRT and IORT produced superior survival compared to EBRT alone.[74]

Investigators at MGH initially published early results of the use of IORT (15 to 20 Gy) in patients with locally unresectable pancreatic cancer.[80] Updated publication of 194 consecutive MGH patients with locally unresectable cancer demonstrated a median survival of 12 months and long-term survival in 6 patients. Patients treated with a smaller diameter applicator, a surrogate for smaller tumor size, had superior survival rates and the only long-term survivors were within the smaller applicator diameter cohort. On multivariate analysis small applicator size, low comorbidity index, and receipt of chemotherapy predicted improved OS.[76,77]

Two retrospective studies from the Thomas Jefferson University Hospital (TJUH) evaluated the use of IORT in patients with locally unresectable primary disease. In the initial TJUH series, 49 patients were treated with IORT and perioperative chemotherapy followed by concurrent CRT. Median survival was 16 months with a 4 year OS of 7%.[78] In a follow up series from TJUH, 105 patients received multimodality therapy including surgery, chemotherapy, and radiation therapy. Patients were subdivided into three groups: IORT via electrons (IOERT), IORT with Iodine 125 implant, and no IORT. Median OS in the group receiving IOERT was 18 months with 2-year LC of 70%.[79] The median and long-term survival results from these IORT series are significantly longer than outcomes seen in other studies evaluating patients with locally advanced pancreatic cancer treated with conventional combined modality approaches.

Future Possibilities

Although slight gains in survival may be achieved by improving LC in patients with pancreatic cancer, the high rate of distant metastases limits significant improvements in long-term survival by IORT approaches. Given the high incidence of failure in the peritoneal cavity and liver, pilot studies are evaluating novel combinations of systemic agents in the treatment of this disease, including "targeted" agents as well as novel combinations of more traditional chemotherapeutics.

Breast Cancer

IORT Alone

Randomized trials have demonstrated equivalent disease-free survival (DFS) and OS in selected patients with breast cancer undergoing either mastectomy or breast-conserving surgery followed by EBRT.[81] Local recurrences frequently occur at or adjacent to the original tumor bed following breast-conserving surgery. There is increasing interest in the use of IORT as a supplement to or alternative to EBRT in selected cases in both Europe and the United States.[82-92]

Phase III Trials

The Italian ELIOT trial of 1305 patients was a randomized Phase III trial comparing 21 Gy IOERT versus standard EBRT whole-breast/boost therapy.[83] IOERT was delivered with a mobile linear accelerator (the NOVAC 7) while shielding the thoracic wall with a lead plate. Women aged 48 to 75 years with early breast cancer, a maximum tumor diameter of up to 2.5 cm, and suitable for breast-conserving surgery were randomly assigned to the two treatment arms. This was an equivalence trial with a primary endpoint of ipsilateral breast tumor recurrence (IBTR). After a median follow-up of 5.8 years, 35 patients in the IOERT group and 4 patients in the EBRT group had experienced an IBTR ($p < 0.0001$). The 5-year outcomes for the IOERT compared to EBRT arms included an IBTR rate of 4.4% compared to 0.4% (hazard ratio 9·3 [95% confidence interval, 3.3 to 26.3]) and 5-year OS of 96.8% compared with 96.9%. Significantly fewer skin side effects occurred in women in the IOERT than in the EBRT arms ($p = 0.0002$). The authors concluded the rate of IBTR was significantly greater with IOERT than with EBRT, and OS did not differ between groups, while improved selection of patients could reduce the rate of IBTR with IOERT.[93]

An approach of targeted IORT using the INTRABEAM system (TARGIT) implements a 50 kV x-ray generator mounted on a flexible floor stand with a set of spherical applicators ranging from 1.5 cm to 5 cm in diameter (eFigure 17-1) Radiotherapy is delivered to the tumor bed by placing the applicator within the tumor cavity and conforming the adjacent breast tissues around the applicator before treatment. A potential disadvantage of this approach is that low-energy x-rays could potentially lead to underdosing of residual tumor cells removed from the tumor cavity.

In an international phase III TARGIT-A trial, patients were randomized to IORT alone (n = 1721) or a typical course of EBRT (n = 1730). If resected patients were at high risk of local recurrence in other quadrants (extensive intraductal component, extensive lymphovascular invasion, nodal metastases, etc.) then EBRT could be delivered postoperatively. Supplemental EBRT after TARGIT was necessary in 15.2% of patients who received TARGIT. Median follow-up for 3451 patients was nearly 2.5 years and 1222 had median follow-up of 5 years. The 5-year risk for local recurrence in the conserved breast was 3.3% for TARGIT versus 1.3% for EBRT (p = 0.042). Overall, breast cancer mortality was similar between groups (2.6% for TARGIT versus 1.9% for EBRT; p = 0.56), but there were significantly fewer deaths related to breast cancer with TARGIT (1.4% versus 3.5%; p = 0.0086), attributable to fewer deaths from cardiovascular causes and other cancers. Overall mortality was 3.9% for TARGIT versus 5.3% for EBRT (p = 0.099). Wound-related complications were similar but grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1720 versus 13 of 1731, p = 0.029). The authors concluded TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for carefully selected, eligible patients with breast cancer as an alternative to postoperative EBRT.[94] Late toxicity data was available in 305 patients with significantly fewer telangiectasias in the IORT arm.[95]

In summary, randomized trials to date show that IORT alone may result in slightly higher rates of ipsilateral breast cancer recurrence when compared to adjuvant EBRT techniques and that careful patient selection when using this approach is warranted.

Phase II Trials

Extensive Phase II data from single or multiinstitutional IORT alone series is also available. Series design and outcomes can be found on the Expert Consult website.[85,88,96,97]

IORT Plus EBRT

In the Medical College of Ohio and Centre Regional de Lutte Contre le Cancer (France) combined series, 72 patients with early stage breast cancer underwent lumpectomy with axillary lymph node dissection followed by 10 to 15 Gy IOERT using 6 MeV to 20 MeV electrons. Patients later received EBRT doses of 45 to 50 Gy at 1.8 to 2 Gy per fraction. No significant complications were observed and cosmetic results were described as excellent. Eight of 72 patients developed minor palpable fibrosis at the lumpectomy site. At a minimum two-year follow-up in all patients, no patients had experienced local relapse.[90]

The University of Salzburg investigators used IOERT combined with EBRT in 351 consecutive patients from October 1998 to April 2002 and reported their results in the initial 170 patients treated through December 2000.[91] LC results were compared to patients treated with EBRT alone. At the time of publication, 3-year LC with an IOERT compared to EBRT boost was 100% to ~97%.

The University of Heidelberg reported a preliminary experience in 155 patients with breast cancer using a 20 Gy orthovoltage IORT boost followed by EBRT in women with T1-T2 breast cancers. The 5-year local relapse-free survival was 98.5% at a median follow up of 34 months. Grade 3 fibrosis of the tumor bed was found in 5% of patients at 3 years.[92]

A European pooled analysis by Sedlmayer et al evaluated 1200 patients with limited breast cancer resection plus IOERT (median dose 9.7 Gy, range 5 to 17 Gy) followed by whole-breast EBRT using standard fractionation. Patients undergoing immediate secondary mastectomy as a result of extensive margin involvement were excluded. At median follow up of 59.6 months, local tumor control was 99.3%. The authors concluded IOERT boost during breast-conservation therapy results in optimal dose delivery and outstanding LC rates.[98,99] The most recent update of this experience with long-term follow-up (72.4 months median follow-up) reported a 99.2% local tumor control with an annual in-breast recurrence rate of 0.64%, 0.34%, 0.21%, and 0.16% in patients younger than 40 years, 40 to 49 years, 50 to 59 years, and older than 60 years, respectively.[100]

Early results of the TARGIT trial using IORT as boost therapy reported 183 patients treated with the INTRABEAM system of 5 Gy or 7.5 Gy followed by EBRT. At a median follow up of 16 months, actuarial 2-year LC was 99% with serious complications (including fistula, wound dehiscence, and ulceration) occurring in 11% of patients.[87] In summary, the available data suggest that IORT used as a boost technique with EBRT results in low rates of ipsilateral breast tumor recurrence.

Future Possibilities

Multiple Phase II or III trials evaluating adjuvant IORT continue to actively accrue patients in the United States, Europe, United Kingdom, and Australia. These trials use varying IORT techniques including 50 kV photons as well as low-energy electrons. Identification of patients appropriate for breast IORT remains an area of investigation. Long-term results from these and other trials will be necessary to demonstrate ultimate local recurrence, late effect, and survival data with these approaches.

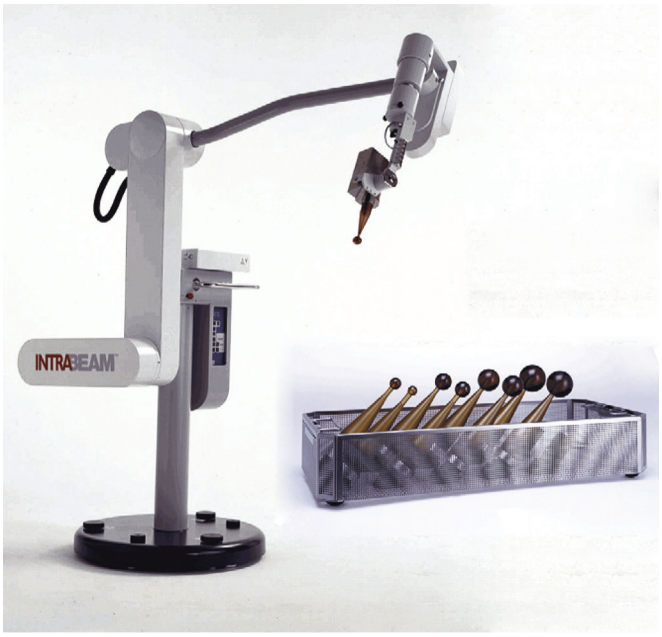
Retroperitoneal and Pelvic Soft-Tissue Sarcomas

NCI Randomized Phase III Trial

The NCI conducted a randomized Phase III trial in patients undergoing surgical resection of primary retroperitoneal sarcoma. All patients underwent gross total resection, although most had microscopically involved margins. Patients were randomized to receive 20 Gy IOERT followed by 35 to 40 Gy of EBRT postoperatively versus postoperative EBRT alone to a dose of 50 to 55 Gy. Patients receiving IOERT were treated with concurrent misonidazole given 15 to 30 minutes pretreatment. EBRT treatments were delivered over 4 to 5 weeks at 1.5 to 1.8 Gy per fraction in both arms; however, patients receiving EBRT only received an additional 15 Gy using similar fractionation by reduced fields. The incidence of in-field local-regional recurrence was significantly lower among patients receiving IOERT compared to patients receiving EBRT only (3/15 versus 16/20, $p < 0.001$). Patients receiving IOERT experienced fewer episodes of radiation enteritis than EBRT alone patients (2/15 versus 10/20, $p < 0.05$); however, radiation-related peripheral neuropathy was more frequent in patients receiving IOERT (9/15 versus 1/20, $p < 0.01$).[12]

Mayo Clinic Experience

Investigators at Mayo Clinic Rochester reported on 87 patients with primary or recurrent retroperitoneal or intrapelvic sarcomas receiving IOERT as a component of treatment.[101]



eFigure 17-1 The INTRABEAM system for IORT of breast cancer. This consists of a 50-kV x-ray generator mounted on a flexible floor stand and a set of applicators ranging from 1.5 to 5 cm in diameter.
Figure used with permission-PENDING.

A preliminary report from the Italian Collaborative Breast IOERT Group described a multicenter trial comparing IOERT alone following lumpectomy to conventional fraction EBRT in tumors less than 3 cm with negative margins. IORT patients received a single 21-Gy fraction using 6 MeV to 9 MeV electrons. Of 314 evaluable patients, no local recurrence was detected in either treatment group at a median follow-up of 31 months, although a significant difference in the incidence of grades 1 to 2 late toxicity was seen in favor of the IORT group (3% versus 63%).[84]

A systematic review of seven published IORT alone series in early breast cancer suggested that short-term LC, DFS, and OS were similar to reported EBRT series. Local recurrence rates ranged from 0% to 29% with IORT. However, many of these small, single institution studies had short follow-up (median, 2 years).[85]

Veronesi et al reported on 237 patients with primary tumors ≤2 cm undergoing wide excision with either sentinel lymph node biopsy or axillary lymph node dissection. Patients received IOERT using 3 MeV to 9 MeV electrons with doses of 17 to 21 Gy (>90% received 21 Gy as the prescribed dose). At a median follow-up of 19 months, the rate of posttreatment complications was low, with 1.7% developing breast fibrosis. A follow-up report from this group of 574 patients revealed 3 patients with local recurrence and 3 additional patients with ipsilateral recurrence in other quadrants at median follow-up of 20 months.[88] A similar report by Veronesi et al of 1822 patients treated with the ELIOT strategy, but outside of a randomized trial, showed that after a mean follow-up of 36 months, the incidence of local recurrence was 2.3% and new primary ipsilateral carcinomas was 1.3%.[96]

Another report of long-term side effects and cosmetic results has been analyzed in 119 patients selected randomly selected from 1200 cases. After a median follow-up of 71 months, grade 2 fibrosis was observed in 31.9% of patients and grade 3 in 5.9% of patients. Physicians and patients scored cosmesis as excellent or good in 84% and 77% of cases, respectively.[97]

The addition of boost treatment following lumpectomy and conventional EBRT has been shown to reduce local recurrence rates by 50% in all age groups versus EBRT alone.[89] Potential advantages of an IORT boost compared to EBRT boost are as follows: more precise delivery of irradiation to the tumor bed, skin sparing with avoidance of associated late cosmetic sequelae, and a smaller boost area with a more homogeneous dose distribution.

TABLE 17-5 Mayo Clinic IOERT Analysis: Factors Influencing 5-Year Local Control and Survival in Resected Primary Retroperitoneal Sarcomas

	n	OS (%)	*p*	LC (%)	*p*
RESIDUAL AT IOERT					
None	11	62		100	
Microscopic	25	54		92	
Gross	7	29	0.15	60	<0.01
BRODERS GRADE					
1-2	9	42		100	
3-4	34	54	0.70	84	0.32
TUMOR SIZE* **(cm)**					
≤10	23	66		83	
>10	19	33	0.15	92	0.80

LC, *Local control;* IOERT, *intraoperative electron irradiation;* OS, *overall survival.*
**From references 101-108.*

Seventy-seven patients received EBRT (53 preoperatively, 12 postoperatively, and 12 both) to a median dose of 48 Gy, usually through a shrinking field technique. Fifteen patients (17%) had gross residual disease following resection, 56 (64%) microscopic residual, and 16 (18%) either negative margins or no residual disease. Median IOERT dose was 15 Gy (range 9 to 30 Gy). Five-year OS was 47%. Patients with tumors >10 cm experienced a significantly worse survival compared to smaller lesions (5-year OS 28% versus 60%, $p = 0.01$) and patients with gross residual disease following resection experienced worse 5-year survival versus gross totally resected patients (37 versus 52%, $p = 0.08$). Five-year LC rates in patients with gross, microscopic and no residual tumor were 37%, 57%, and 100%, respectively. Factors influencing 5-year LC and survival for patients with primary disease are shown in Table 17-5 and eTable 17-4. Patients with R0 or R1 resection experienced significantly improved LC and those with tumors greater than 10 cm were less likely to be long-term survivors.[101]

A further update of the Mayo Clinic reported on 226 IORT patients (52% primary) treated from 1981 to 2008.[102] Most (63%) had high-grade tumors and 36 (16%) had received prior EBRT. In previously unirradiated patients, EBRT was delivered preoperatively in 70% of patients, postoperatively in 10%, and both in 10%. R0 and R1 resection was achieved in 39% and 50% of patients, respectively. Median IORT dose was 12.5 Gy. Five-year OS was 50% (R0 resection, 52%; R1, 55%; R2, 28%). For the entire population, 5-year local failure was 29% (R0, 18%; R1, 31%; R2, 61%), with distant metastases developing in 42% of patients. Central failure in the IORT field occurred in only 10% of patients. The authors concluded that: (1) patients with retroperitoneal sarcoma undergoing gross total resection experience improved LC relative to subtotal resection when treated with combined modality treatment including IORT; (2) improved outcomes were seen in patients with primary versus recurrent disease; and (3) the high rates of distant relapse suggest more effective systemic therapy is needed for patients with high-grade disease.

Massachusetts General Hospital Experience

Investigators from MGH described 37 patients with primary or recurrent retroperitoneal sarcoma who underwent EBRT (median dose, 45 Gy) and resection. Twenty patients received IOERT (10 to 20 Gy). In twenty-nine (78%) patients receiving gross total resection and IOERT, 5-year survival and LC rates were 74% and 83%, respectively. In comparison, 13 patients undergoing gross total resection without IOERT had 5-year survival and LC rates of 30% and 61%, respectively. Four patients receiving IOERT experienced significant complications including neuropathy, hydronephrosis, and fistula formation.[103]

A subsequent report from MGH described 103 patients with primary retroperitoneal sarcoma, 62 of who underwent gross total resection. In this group, patients with high-grade disease or involved margins received EBRT with or without IOERT, particularly when a localized area of close margin of residual tumor was identified. This study again demonstrated a trend for IORT to further improve survival versus EBRT alone with significant increased time to both local and distant relapse. In patients who were completely resected, a trend toward improved survival with IOERT was seen compared to EBRT alone (5-year OS of 77% versus 45%, $p = 0.13$).[104]

Pooled European Analysis

A pooled European analysis described 122 curatively approached patients (81 recurrent) with retroperitoneal sarcoma undergoing maximum resection plus IOERT (median dose 15 Gy). Most received adjuvant EBRT. Five-year OS, DFS, LC, and freedom from metastatic disease rates were 64%, 28%, 40%, and 50%, respectively. Five-year LC within the IOERT field was 72%. In patients receiving IOERT, EBRT, and R0 resection, 5- and 10-year OS were 80% and 5- and 10-year LC were 100%. Only 5% of patients experienced an in IOERT-field relapse after R0 resection, 23% after R1 resection, and 75% after R2 resection. Late complications ≥grade 2 were seen in 21% of patients. The authors concluded that in selected patients, IOERT resulted in excellent LC and survival with accepted morbidity.[105]

Conclusions and Future Possibilities

IORT combined with EBRT and resection offers an effective means of improving LC in patients with primary and recurrent retroperitoneal sarcomas, as demonstrated in a randomized trial from the NCI as well as multiple U.S. and European single-institution studies.[101-108] A randomized NCI trial showed an 80% tumor bed relapse rate with adjuvant EBRT alone, likely as a result of an inability to deliver effective EBRT doses given normal tissue constraints. Because these results are similar to reports of resection alone, the use of adjuvant EBRT without IORT following marginal resection could be questioned. A more practical approach would be to administer preoperative EBRT following confirmation of diagnosis by thin-needle biopsy. This would be followed by resection at an institution with IORT capabilities.

Even with improved LC rates, locoregional and distant failure remains common modes of failure, emphasizing the need for improved therapies. Pilot studies are evaluating dose escalated EBRT using IMRT techniques in combination with IORT, as well as the role of concomitant radiochemotherapy with preoperative EBRT, IORT, and maintenance chemotherapy for resectable moderate- and high-grade retroperitoneal and pelvic sarcomas.[109] An Italian Sarcoma Group Phase II study is evaluating preoperative EBRT with high-dose continuous infusion ifosfamide, using IOERT or postoperative EBRT for radiation dose escalation following maximal resection.

Gynecologic Cancers

Patients with locally advanced or locally recurrent gynecologic cancers often have involvement of the pelvic sidewall, pelvic lymph nodes, or paraaortic nodes. The use of radical resection and IORT with or without EBRT or chemotherapy may benefit patients when compared with EBRT alone.

A Mayo Clinic analysis described 148 patients with primary (23 patients) or recurrent (125 patients) gynecologic

eTABLE 17-4A Mayo Clinic IOERT Analysis: Factors Influencing 5-Year Local Control in Resected Retroperitoneal Sarcomas

	Primary Tumors			Recurrent Tumors			All		
Factor	***n***	**LC (%)**	***p***	***n***	**LC (%)**	***p***	***n***	**LC (%)**	***p***
RESIDUAL AT IOERT									
None	11	100		5	100		16	100	
Microscopic	25	92		31	36		56	57	
Gross	7	60	<0.01	8	67	0.12	15	37	0.04
BRODERS GRADE									
1-2	9	100		24	28		33	47	
3-4	34	84	0.32	20	58	0.52	54	75	0.16
TUMOR SIZE (cm)									
≤10	23	83		30	50		17	64	
>10	19	92	0.80	14	34	0.69	69	62	0.96

IOERT, *Intraoperative electron beam radiotherapy;* LC, *local control.*

eTABLE 17-4B Mayo Clinic Analysis: Factors Influencing Survival in Resected Retroperitoneal Sarcomas with IOERT

	Factors Influencing Overall Survival at 5 Years								
	Primary Tumors			Recurrent Tumors			All		
	I	**OS (%)**	***p***	***n***	**OS (%)**	***p***	***n***	**OS (%)**	***p***
RESIDUAL AT IOERT									
None	11	62		5	80		16	68	
Microscopic	25	54		31	44		56	48	
Gross	7	29	0.15	8	45	0.60	15	37	0.12
BRODERS GRADE									
1-2	9	42		24	53		33	50	
3-4	34	54	0.70	20	35	0.36	54	48	0.32
TUMOR SIZE* (cm)									
≤10	23	66		30	54		53	60	
>10	19	33	0.15	14	19	0.04	33	28	0.01

IOERT, *Intraoperative electron beam radiotherapy;* OS, *overall survival.*
**One value missing.*

TABLE 17-6 Mayo Clinic Analysis: Factors Influencing Local Control and Survival in Resected Gynecologic Malignancies with IOERT

		Survival %			Relapse: 5 year		
Treatment Group	**#Pts**	**Med (mo.)**	**2 yr**	**5 yr**	**Local**	**Distant**	**Central**
All patients	148	19	41	27	40	51	28
Amount residual							
≤Microscopic	115	21	44	31*	42	49*	29
Gross	33	15	31	13	26	58	19
Site of primary							
uterine, ovary	58	30	53	41†	30	na	17‡
cervix, vagina	86	17	34	18	47	na	34
Prior EBRT							
None	63	22	47	35*	37	46	26
Yes	85	15	33	15	45	58	32

EBRT, *External beam irradiation;* Med, *median;* mo., *months;* Pts, *patients;* na, *not available;* yr, *year.*
*$p = 0.01$.
†$p = 0.002$.
‡$p = 0.007$.

malignancies treated with IOERT-containing regimens.[110-112] Preoperative or postoperative EBRT was delivered in 113 patients; 85 (57%) had received prior EBRT. The 5-year OS for all patients was 27%, and the 5-year local failure rate was 40% (Table 17-6).[111,112] On subset analysis, patients with R0 or R1 resection ($N = 115$) had improved 5-year OS compared to patients with R2 resection (31% versus 13%, $p = 0.01$); patients with uterine or ovarian primary origin had better survival than those with cervical or vaginal primaries (5-year OS 41% versus 18%, $p = 0.002$); patients with no prior EBRT had better 5-year OS than those with prior EBRT (35 versus 15%, $p = 0.01$). The rate of distant metastases at 5 years was 49% (R0 resection, 63%; R1/R2, 41%; $p = 0.04$). Fewer metastases were seen in patients treated with MVAC (methotrexate, vinblastine, doxorubicin, cisplatin) chemotherapy in a prior analysis.[110]

Cervical Cancer: Primary Locally Advanced Disease

IOERT containing regimens for locally advanced primary cervical cancers have been reported by several investigators. A Mayo Clinic analysis[113] of 13 patients with locally advanced cervical cancer treated with preoperative EBRT followed by resection and IOERT (median 12.5 Gy) and adjuvant chemotherapy in 77% reported a 29% 3-year survival and pelvic control in 69%. Spanish investigators treated 31 patients with primary locally advanced cervical cancer with 45 Gy EBRT in 1.8 Gy fractions followed by resection and 12 Gy IOERT. Survival at 10 years was 58% and LC was observed in 93%.[114]

A study from Xian Jiaotong University in China reported on 78 patients with stage IIb squamous cell carcinoma of the cervix who received IOERT during hysterectomy and selected lymphadenectomy. A comparison group of 89 patients was treated contemporaneously with standard therapy without surgery. IOERT-treated patients received 20 Gy EBRT at 2 Gy per fraction followed by 1 to 2 intracavitary brachytherapy HDR treatments with Ir-192, receiving 7 Gy per fraction to point A, followed by surgery and IOERT using 12 MeV electrons with doses of 18 to 20 Gy. Patients treated with standard therapy received 30 Gy EBRT whole pelvis and 20 Gy split pelvis, all in 2 Gy fractions, followed by 5 to 6 HDR insertions with Ir-192 delivering a dose of 35 to 40 Gy to point A. The 5-year OS, DFS, and LC in the IOERT patients were 89%, 87%, and 96%, respectively, versus 73%, 67%, and 73% in the standard therapy group ($p < 0.05$). Ten-year OS and LC were 85% and 94%, respectively, in the patients who underwent IOERT compared to 55% and 65%, respectively, in patients who underwent standard therapy. The patients who underwent IOERT had fewer rectal and bladder complications.[115]

Italian investigators reported the results of a Phase II trial containing IOERT as part of the multimodality regimen in patients with stage IIA bulky-IVA cervical cancer.[116] Forty-two patients were treated with 50.4 Gy EBRT in 1.8 Gy fractions with concomitant cisplatin and 5-FU followed by radical hysterectomy and IOERT (11 Gy median; range, 10 to 15 Gy). Seven patients were not resected because of refusal (1), progression (3), unresectability (2), and hemorrhage (1). For the 35 patients with radical hysterectomy and IOERT, the 5-year OS and DFS were 49% and 46%, respectively. Crude pelvic control was observed in 63% and control within the IOERT fields was 89%.[116]

Cervical Cancer: Recurrent Disease

Treatment of patients with recurrent cervical cancer is challenging, especially in those treated with high-dose radiotherapy for primary disease. There are several reports in the literature of curative attempt regimens including surgery and IOERT with or without EBRT. Stanford investigators evaluated 17 patients with recurrent cervical cancer treated with orthovoltage IORT (median 11.5 Gy). LC, distant metastasis-free survival, and disease-specific survival (DSS) rates at 5 years were 45%, 60%, and 46%, respectively.[117] A University of Washington series included 22 patients with recurrent cervical cancer. IOERT doses ranged from 14 to 27.8 Gy and 12 patients had R2 resections, with R1 or close R0 in 10 patients. LC at 5 years was 48% and DSS was 48%. Peripheral neuropathy was observed in 32%.[118]

Spanish investigators reported on 36 patients with recurrent cervical cancer treated with IOERT (median, 15 Gy).[114] Previously unirradiated patients were generally treated with preoperative EBRT to 45 Gy at 1.8 Gy per fraction with concurrent cisplatin and 5-FU. Previously irradiated patients underwent immediate resection or neoadjuvant chemotherapy if unresectable. Ten-year LC rate (within the IOERT field) was 47%, control in pelvic and paraaortic region was 42%, and 10-year survival was observed in 14%. Factors adversely influencing LC included involved parametrial margins, gross residual disease, and pelvic lymph node involvement. Patients with two or more risk factors had a 10-year LC rate of 0%, and there were no 10-year survivors with R2 resection. Six of 36 (17%) patients experienced nerve pain that resolved after a few months. All failures within the IOERT field occurred concomitant with relapse in the pelvis or distant metastases.[114]

Contrary to the relatively favorable results reported in most series, a French multiinstitutional analysis found relatively poor survival and LC with IORT. Seventy patients were treated in seven institutions with IORT alone (40 patients) or IORT with EBRT (30 patients) in addition to surgery. The pelvic sidewall was involved in 80% of cases and resection was macroscopically complete in only 47% of patients. IORT doses ranged from 10 to 30 Gy with a median of 18 Gy in patients with R0-R1 resections and 19 Gy in patients with R2 resections. LC was observed in only 21% and 5-year survival was 8%.[119]

A Mayo Clinic series included 73 patients with recurrent cervical cancer treated with IOERT to a median dose of 17.5 Gy. EBRT (median, 45 Gy) was included as part of the treatment in 66% of patients and 48% received perioperative chemotherapy. The median OS was 17 months with 25% survival observed at 3 years. The 3-year cumulative incidences of central relapse, locoregional relapse, and distant relapse were 23%, 39%, and 44%, respectively. On multivariate analysis, central control and locoregional control were associated with pelvic exenteration and use of EBRT. R2 resection was associated with a higher risk of distant metastases and poorer cause-specific survival (CSS). High-tumor grade and relapse within 6 months of primary diagnosis were associated with poor cause-specific survival and no patients treated within 6 months of primary diagnosis survived 3 years. Some degree of peripheral neuropathy was observed in 19% of patients.[113]

Endometrial Cancer: Recurrent Disease

Mayo Clinic investigators reported on 25 patients treated with IOERT for recurrence of endometrioid endometrial cancer.[120] Most patients (21/25, 84%) had involvement of the pelvic sidewall and the remaining 4 patients had paraaortic with and without upper abdominal involvement. EBRT was delivered to 21 patients (84%) to a median dose of 45 Gy (range, 9 to 50.7 Gy). EBRT was given preoperatively in 81% of cases. The median IOERT dose was 15 Gy (range, 10 to 25 Gy). The surgical resection was R0 with close margins in 7 (28%) patients, R1 in 11 (44%) patients, and R2 in 7 (28%) patients. The 5-year OS was 47% and median survival was 57 months. Survival was associated with resection margins with 5-year OS of 71%, 40%, and 0% in R0, R1, and R2 patients, respectively. Central relapse within the IOERT field was observed in 4 patients (16%), local relapse with control in IOERT field in 2 patients (8%), and distant relapse in 6 patients (24%). Peripheral neuropathy was observed in 8 patients (32%).[120]

Uterine Sarcoma

Mayo Clinic investigators reported on the use of IOERT as component of therapy in 16 patients with primary (3) or recurrent uterine sarcoma, including 9 patients with leiomyosarcoma, 4 with stromal sarcoma, and 3 with carcinosarcoma. All were treated with perioperative EBRT (median, 50.4 Gy; range, 20 to 62.5 Gy) and 6 (38%) received perioperative chemotherapy. Surgical resection was classified as R0 in 8 (50%) patients, R1 in 2 (12.5%) patients, and R2 in 6 (37.5%) patients. The median IOERT dose was 12.5 Gy with a range of 10 to 20 Gy. The 5-year OS was 43% and CSS was 47%. There were no central relapses within the IOERT field and only 1 local relapse (6%). Nine patients (56%) relapsed in distant sites. Peripheral neuropathy was observed in 3 patients (19%).[121]

Ovarian Cancer

Although the primary pattern of relapse of ovarian cancer is peritoneal, a subset of ovarian cancer patients experience isolated locoregional relapse. There are several reports on the use of IOERT in selected patients with ovarian cancer. A Chinese series included 25 patients with primary ovarian cancer and 20 with isolated local relapse. Intraperitoneal chemotherapy was delivered to 33 patients (73%) and intravenous chemotherapy to 7 (16%) patients. No EBRT was used. The IOERT dose was 18 to 20 Gy in 43 patients and 10 Gy in the remaining 2 patients. Five-year survival was observed in 64% in the primary group and 60% in the recurrent group. In the primary group 8 patients (32%) relapsed locally and 3 (12%) distantly. In the recurrent group there were 6 local relapses (30%) and 2 distant relapses (10%). The rate of central relapse within the IOERT field was 9% for the entire group. Five patients (11%) experienced peripheral neuropathy.[122]

Stanford investigators reported on 22 patients with recurrent ovarian cancer who received orthovoltage IORT as a component therapy.[123] The median IORT dose was 12 Gy (range, 9 to 14 Gy) and treated sites included pelvis, paraaortic nodes, inguinal nodes, and the porta hepatis. Nine patients received whole abdominal EBRT, 5 locoregional EBRT, and 6 chemotherapy. The median survival was 26 months, 5-year OS was 22%, and DFS 18%. Locoregional control was 68% at 22 months and 55% of patients experienced distant relapse. There were no long-term peripheral neuropathies.[123]

A Mayo Clinic analysis described 20 patients with recurrent ovarian cancer treated with IOERT as a component of therapy.[124] Thirteen patients (70%) had epithelial ovarian carcinomas and the remaining histologies were granulosa cell tumor, malignant teratoma, adenosarcoma, stromal tumor, and squamous cell carcinoma. The site of recurrence was pelvis in 14 patients, paraaortic nodes in 6, and inguinal nodes in 1. Sixteen patients received a median EBRT dose of 50 Gy (range, 20 to 54.3 Gy). Surgical resection was classified as R0 in 9 patients, R1 in 11, and R2 in 1. The median IOERT dose was 12.5 Gy (range, 10 to 22.5 Gy). Median survival was 30 months with 49% 5-year OS. Central control within the IOERT field was observed in 76% with all central relapses occurring in patients with R1 resections. Distant relapse was observed in 9 patients (45%). Three patients experience grades 1 to 2 peripheral neuropathy.[124]

Future Possibilities

Because of the high incidence of distant metastases observed in patients with gynecologic cancer with microscopic and gross residual disease following resection, evaluation of newer systemic and maintenance regimens is indicated. Investigation of newer chemotherapeutic and targeted biologic agents may hold promise in improving distant metastases rates and ultimate survival in these malignancies.

Colorectal Cancer: Primary and Recurrent Disease

Primary Locally Advanced Cancers

Locally advanced colorectal cancers are tumors that cannot be resected without microscopic or gross residual secondary to tumor adherence to adjacent structures. In selected patients, the optimal approach is to administer preoperative chemoradiation in efforts to "downstage" disease and facilitate surgical resection. At the time of resection, if clinical suspicion for involved margins is high, the use of IORT may be appropriate.

In an MGH series, 64 patients with locally advanced primary rectal cancer underwent preoperative irradiation (with or without 5-FU) followed by resection and IOERT. Patients undergoing R0 resection had a 5-year LC and DSS of 91% and 63%, respectively. Patients with R1 resection experienced 5-year LC and DSS of 65% and 47%, respectively, and patients with R2 resection, 57% and 14%, respectively (Table 17-7).[125]

A Mayo Clinic Rochester report described 56 patients with primary locally advanced colorectal cancer undergoing EBRT

TABLE 17-7 Primary Rectal (MGH) or Colorectal (Mayo Clinic) IOERT Series: Disease Control and Survival by Degree of Resection and Amount of Residual Disease

	MGH Results 5-Yr Act (%)*†			Mayo Clinic Results 5-Yr Act (%)			
Degree of Resection	***N***	***LF***	***DSS***	***N***	***LF***	***DF***	**OS**
No tumor	—	—	—	2	0	0	100
Complete resection	40	9	63	18	7	54†	69
Partial (subtotal) resection	24	37	35	—	—	—	—
Microscopic residual	17	35	47	19	14	50†	55
Gross residual	7	43	14	16	27	83†	21
No resection	—	—	—	—	—	—	0
Total series	64			56	16	59	46

Act, *Actuarial;* DF, *distant failure;* DSS, *disease-specific survival;* LF, *local failure;* MGH, *Massachusetts General Hospital;* OS, *overall survival.*

**Data from Gunderson LL, Nelson H, Martenson JA, et al: Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation ± 5-FU. Int J Radiat Oncol Biol Phys 37(3):601–614, 1997 and Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 9(5):843–849, 1991.*

†Three-year actuarial DF of 43%, 38%, and 66%, respectively, for complete resection, microresidual, and gross residual.

(45 to 55 Gy, usually with concurrent 5-FU administration) followed by resection and IOERT (10 to 20 Gy). Five-year OS for all patients was 46%. Patients with R0 or R1 resection had an improved OS relative to patients with R2 resection (5-year OS of 59% versus 21%, $p = 0.0005$). Failure within the IOERT field occurred in 4 of 16 patients (25%) with R2 resection versus 2 of 39 (5%) with R0 or R1 resection ($p = 0.01$)[52] (see Table 17-7).

An update from Mayo Clinic Rochester analyzed 146 patients with locally unresectable primary colorectal cancers who received IOERT in addition to preoperative or postoperative combined modality therapy. Median survival was 44 months with 5-year OS of 52%. Three-year local and distant relapse rates were 10% and 43%, respectively. Patients receiving preoperative combined modality therapy appeared to have a survival advantage versus those receiving postoperative therapy (median survival 76 months versus 26 months, 5-year OS of 55% versus 38%, $p = 0.02$).[53]

Madrid investigators from the General University Hospital Gregorio Marañon described 558 patients with T3-T4 rectal cancer, 281 of which received preoperative combined modality therapy plus IOERT and 277 who received postoperative chemoradiotherapy without IOERT. Patients receiving preoperative therapy plus IOERT (despite higher stage disease at presentation) had a significant improvement in pelvic control (92% versus 84%, $p = 0.03$), DFS (65% versus 56%, $p = 0.05$), and OS (68% versus 58%, $p = 0.016$).[55] In a recent and selected update of the postchemoradiation plus IORT presacral boost experience, 335 patients treated from 1995 to 2011 (median follow-up 52.2 months) showed 5-year LC, in-field and out-field control rates of 94.4%, 97.0%, and 93.4%, respectively. In multivariate analysis, nonsphincter-preserving surgery and grade 3 histology were associated with increased risk of presacral relapse.[56]

A pooled European analysis of 651 patients treated with IOERT from four major centers showed that 5-year OS was 67% with 5-year LC of 88% in patients with locally advanced rectal cancer.[57] Positive circumferential margins were a strong predictor for both OS and local relapse, and the addition of preoperative CRT appeared to improve 5-year OS (70% versus 64%, $p < 0.05$). An update of the pooled European analysis in 605 patients demonstrated that chemoradiotherapy led to more downstaging and complete remissions compared to radiotherapy alone.[58] Local recurrence, distant metastasis, and OS rates were 12%, 29%, and 67%, respectively. Risk factors for local recurrence included lack of downstaging with preoperative therapy, lymph node involvement, margin involvement, and lack of postoperative chemotherapy. The authors concluded that oncological results following multimodality therapy including IORT showed promising outcomes and the addition of adjuvant chemotherapy could potentially improve local recurrence rates.

The feasibility of IOERT at the time of laparoscopic resection of locally advanced rectal cancer, after preoperative chemoradiation, has been reported by the Gregorio Marañon Hospital team. In a group of 125 patients, laparoscopic resection plus IOERT had significantly less blood loss and shorter hospital stay. Oncological and toxicity results were similar.[59]

Locally Recurrent Colorectal Cancer

Patients developing local recurrence following curative resection of primary colon or rectal cancer are treated with palliative intent at most institutions. Local recurrence from rectosigmoid cancer often causes pelvic pain due to nerve involvement in the presacral space or pelvic sidewall. The likelihood of margin negative resection is low. Patients undergoing surgery alone for pelvic recurrence from rectal cancer have reported 5-year survival rates of 0%.[126]

When IOERT is combined with EBRT with or without chemotherapy and surgical salvage, 5-year OS in the range of 20% to 30% has been achieved.[51,126-130] In an MGH analysis of 41 patients with locally recurrent rectosigmoid cancer undergoing IOERT, patients with gross residual disease experienced 5-year LC and DFS of 21% and 7%, respectively, versus 47% and 21% with clear or microscopically positive margins.[127] Eindhoven investigators described a series of 147 patients with locally recurrent colorectal cancer receiving IOERT. Median OS was 28 months with 5-year OS, DFS, metastases-free survival, and LC rates of 32%, 34%, 50%, and 54%, respectively. R0 resection was associated with improved disease outcomes. Patients treated with IOERT alone had worse outcomes vs those who were reirradiated or treated with full dose preoperative EBRT.[128]

The potential of extended resection in combination with IOERT and EBRT has been analyzed at the University Hospital Gregorio Marañon. In a 16-year experience an adaptive surgical approach based on extent of recurrence extension was systematically combined with IOERT: 60 patients underwent extended surgery (43% multiorgan, 28% bone, 38% soft-tissue resection) and 22 had nonextended resection. With a median follow-up time of 36 months, locoregional control was 44% at 5-years and OS was 43%. On multivariate analysis, positive margins, EBRT at the time of rescue, lack of tumor fragmentation, and lack of lymph node metastasis were significant factors associated with locoregional relapse.[131]

A Mayo Clinic Rochester report described the outcome of 106 patients undergoing palliative resection of locally recurrent, nonmetastatic rectal cancer. Forty-two patients received IOERT as a component of treatment (most 15 to 20 Gy) and 41 EBRT (most ≥45 Gy). Patients with R2 resection had a significantly worse outcome versus R1 resection (5-year OS of 9% versus 33%, $p = 0.03$). Patients who underwent IOERT compared to those that did not had 5-year OS of 19% versus 7% ($p = 0.0006$).[126]

An updated Mayo Clinic analysis described 175 patients with locally recurrent colorectal cancer (123 no prior EBRT, 52 prior EBRT) undergoing IOERT. Five-year OS in previously unirradiated patients was 20% versus 12% in previously irradiated patients. Three-year LC rate in previously unirradiated patients was 75% versus 51% in those previously irradiated. Three-year distant metastases rates were 64% and 71%, respectively.[132]

An even more recent Mayo Clinic analysis described 607 patients with recurrent colorectal cancer who received IOERT as a component of treatment. Five-year OS was 30%. In patients undergoing R0 resection, 5-year OS was 46%. Prior in-field radiation was associated with an increased risk of local relapse (3-year local relapse of 39% versus 20%, $p < 0.0001$) but not with survival. On multivariate analysis, complete resection, no prior chemotherapy, and treatment after 1996 were associated with improved survival. Three-year local and distant relapse rates were 27% and 55%, respectively.[54]

Systematic reviews and meta-analysis are available to evaluate results of IORT in colorectal cancer. From 1965 to 2011, 14 prospective and 15 retrospective studies were identified meeting methodological quality and design (3003 patients involved: 1792 primary locally advanced category). When comparative studies were evaluated, a significant effect favoring improved LC ($p = 0.003$), DFS ($p = 0.009$), and OS ($p = 0.001$) was noted with no increase in total urologic or anastomotic complications, although increased wound complications were observed after IORT ($p = 0.049$). Heterogeneity in methodology and reporting practice warrant caution in the interpretation of these results.[133]

Future Possibilities

Based on the preceding and other data, it appears improved LC and survival may be achieved when IORT is combined with preoperative chemoradiation for locally advanced or locally recurrent colorectal cancer. Many patients will develop distant metastases; relapse within the IORT and EBRT fields is common if gross total resection is not obtained. Based on the proven survival benefit of concurrent 5-FU–based regimens with EBRT in colorectal and other gastrointestinal malignancies, 5-FU–based chemotherapy should be administered concurrent with EBRT. Although adjuvant 5-FU with leucovorin has previously been shown to improve survival in patients with advanced stage colorectal cancer, the addition of newer therapies (oxaliplatin, capecitabine, irinotecan, bevacizumab, cetuximab, panitumumab) has demonstrated further survival benefit in patients with stage IV cancer. These agents have been evaluated as adjuvant therapy in patients with stages II and III cancer (see Colon and Rectal Cancer, Chapters 50 and 51). Given the high rate of subsequent distant metastases in patients with locally advanced and recurrent colorectal cancer, significant improvement in long-term survival will likely be achieved through further improvements in systemic agents.

CONCLUSIONS AND FUTURE POSSIBILITIES

Conclusions

IORT is the delivery of radiation at the time of operation. This can be accomplished using different techniques including IOERT, HDR-IORT, and orthovoltage. IORT is usually given in combination with EBRT with or without chemotherapy and surgical resection. IORT allows exclusion of part or all dose-limiting sensitive structures, thereby increasing the effective dose to the tumor bed (and therefore LC) without significantly increasing normal tissue morbidity.

Despite optimal therapy with non-IORT approaches, high rates of local relapse occur in patients with retroperitoneal sarcoma, pancreatic cancer, colorectal cancer, gynecologic cancer, and other malignancies. The addition of IORT to conventional treatment methods has improved LC as well as survival in many disease sites in both the primary and recurrent disease settings. In view of newer, lower cost treatment devices, the use of IORT in clinical practice will likely continue to grow, with increasing integration into the treatment of "nonconventional" malignancies. Cancer sites in which IORT has been explored and found to be feasible include renal cancer,[134] prostate cancer,[135] extremity sarcomas,[136] and pediatric cancers.[137]

IORT: Technical Considerations

Many limitations and perceived drawbacks of IORT in past decades were the result of inefficiencies associated with nondedicated facilities. Patients were often transported from the operating suite to the radiation oncology department where they were treated with nondedicated linear accelerators. These inconveniences have been overcome with dedicated IOERT, HDR-IORT, or orthovoltage facilities. Presently, dedicated IORT suites within or adjacent to the operating room exist at many institutions in the United States, Europe, and Far East. These facilities simplify treatment by avoiding transportation and sterility problems. A major limiting factor is the expense associated with outfitting a dedicated room (e.g., retrofitting an operating room with proper shielding, purchase of a linear accelerator dedicated for use in the operating room, construction of a separate IORT suite adjacent to the operating room, etc.). However, newer technologies have lowered these costs. Contemporary options include mobile IOERT units (Mobetron, Liac) as well as mobile HDR-IORT.[138] The Mobetron is a mobile, self-shielded compact linear accelerator with C-arm design that generates electron energies of 4 MeV to 12 MeV (Intraop Medical, Inc., Santa Clara, CA, Figure 17-3). This can be transported in and out of the operating theater. HDR-IORT units are remote afterloading devices that use an Ir-192 source (Figures 17-4, 17-5). In contrast to the Mobetron, HDR-IORT requires room shielding, which may be achieved by retrofitting an existing room or construction of a smaller shielded room adjacent to the operating suite. In either situation, patients are monitored by camera during radiation administration. After completion, the HDR-IORT unit can be transported to the radiation oncology department for outpatient HDR appropriate malignancies, including gynecologic and prostate malignancies. Mobile IOERT devices used in Europe include the Liac machine. The INTRABEAM system for breast cancer IORT consists of a 50-kV x-ray generator mounted on a flexible floor stand and a set of spherical applicators ranging from 1.5 cm to 5 cm in diameter (see eFigure 17-1).

Treatment planning systems specifically designed for IOERT are now commercially available (Radiance). Initial clinical testing demonstrated feasibility and multispecialist agreement for simulation of different cancer sites and anatomic locations, including breast cancer, locally advanced rectal cancer, retroperitoneal sarcoma, and isolated recurrence of rectal and ovarian cancer.[139] Research opportunities in IORT are a multidisciplinary endeaver that spans knowledge ranging from radiation beam adaptive development to advanced molecular biology for biopredictability of outcomes. Technical innovation requires further improvements in quality assurance and

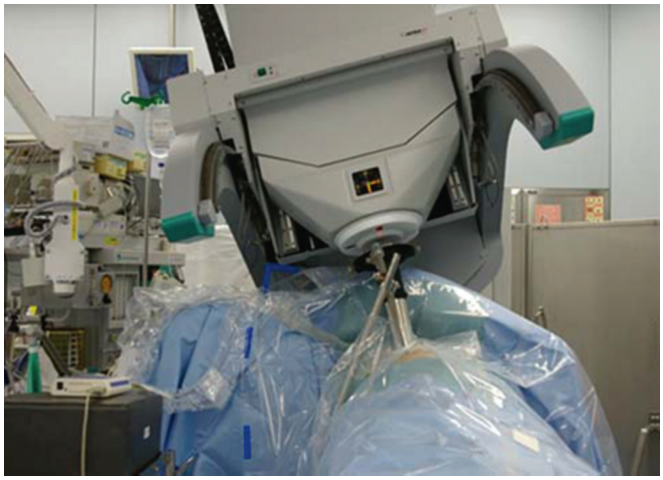


Figure 17-3 The mobile electron-beam radiation device (MOBETRON) (seen here in the operating room) allows use in an existing operating room with little or no additional shielding required.
Courtesy IntraOp Medical, Inc., Sunnyvale, California.

Figure 17-4 Source housing for Ir-192 source. This device allows computer-assisted treatment delivery during IORT.
Courtesy Varian Medical Systems.

clinical practice. The incorporation of treatment planning systems for IORT use will help decision-making processes and its registration will facilitate normalization of medical and surgical practice in IORT programs. Opportunities in radiation beam modulation, delivery, dosimetry and planning, infrastructure, and treatment factors are recognized and expected to be developed over the next decade.[140]

A detailed description of the relative advantages and disadvantages of IOERT and HDR-IORT has been discussed elsewhere and is beyond the scope of this chapter[36] (eTables 17-5 and 17-6). In summary, treatment or procedure times

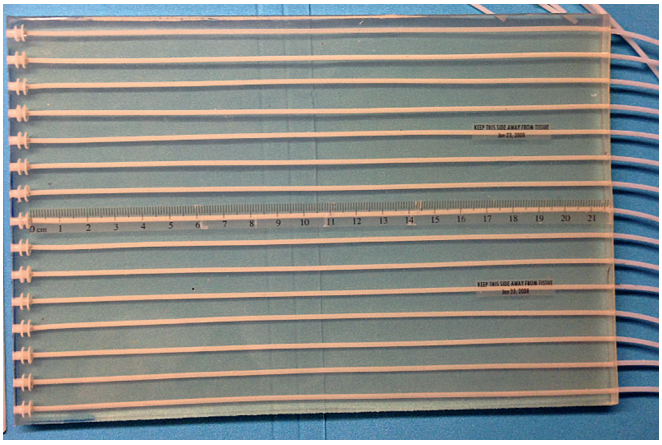


Figure 17-5 Harrison-Anderson-Mick (HAM) applicator used to guide Ir-192 source during HDR-IORT.

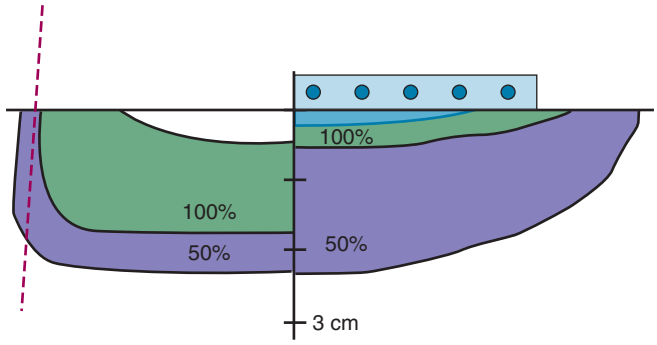


Figure 17-6 Dose distribution characteristics of IOERT *(left)* and in HDR-IORT *(right).* Note IOERT is utilizing 6 MeV electrons; HDR-IORT is utilizing 1 cm surface applicator with dose prescribed to 0.5-cm depth.

are generally shorter with IOERT compared to HDR-IORT. Additionally, IOERT allows variation of electron energies and therefore treatment of both superficial and deeper-seated targets, whereas HDR-IORT is appropriate only for targets ≤0.5 cm in thickness (Figure 17-6). The flexible Harrison-Anderson-Mick (HAM) applicator used in HDR-IORT may allow more conformal treatment along curved body surfaces (e.g., large pelvic sidewall fields, lateral abdominal wall, and thoracic cage) that may prove difficult with rigid IOERT applicators (Figure 17-5). Separate, matching fields may be required to treat larger target areas with IOERT-based applicators. A comprehensive IORT program would ideally have IOERT, HDR-IORT, as well as perioperative brachytherapy available to treat all disease sites and situations. These modalities should be viewed as complementary and not competitive.

Future Possibilities

Although there is a large body of data supporting the use of IORT in various malignancies, there is a relative paucity of Phase III randomized trials. This is at least in part because of the limited number of IORT facilities in any given country as well as relative rarity of diseases commonly treated with IORT. Completion of Phase II/III trials will likely require cooperation among multiple institutions and countries. Future treatment approaches should include "standard" courses of EBRT with or without concurrent chemotherapy and surgical resection with the integration of novel radiation sensitizers, protectors, and targeted biologic agents with IORT.[141]

eTABLE 17-5 Relative Advantages and Disadvantages of IOERT versus HDR-IORT Brachytherapy after Gross Total or Near-Total Resection (Maximum Tumor Thickness ≤0.5 cm)

IOERT Potential Advantage If Technically Feasible	Potential Disadvantages of IOERT	Potential Solution to Disadvantage
Better dose homogeneity	Surface dose <90% with 6 ± 9 MeV	Add bolus over tumor bed to improve surface dose; use HDR-IORT
Faster treatment time		
Less shielding required in OR	Unable to include area at risk in single field within either abdomen or pelvis	Use abutting IOERT fields (difficult in pelvis): use HDR-IORT
Can treat full thickness of organ or structure at risk with relative homogeneity (e.g., aorta or vena cava, bladder sidewall)	Area at risk is technically inaccessible because of location	Use HDR-IORT; surgically displace small bowel or stomach with vascularized flap (omentum, muscle) and give postoperative EBRT boost or perioperative brachytherapy

eTABLE 17-6 Potential Differences between IOERT and HDR-IORT

	IOERT	HDR-IORT
Actual treatment time	2-4 min	5-30 min
Total procedure lime	30-45 min	45-120 min
Treatment sites	Accessible locations	All areas where depth at risk is ≤5 cm from surface of applicator
Surface dose	Lower (75%-93%)	Higher (150%-200%)
Dose at depth (2 cm)	Higher (70%-100%)	Lower (30%)
Dosimetric homogeneity (surface to depth)	<10% variation	>100% variation

From Nag S et al: Intraoperative irradiation with electron-beam or high-dose-rate brachytherapy. Ch 7 in intraoperative irradiation. In Gunderson L, Willett C, Harrison L, Calvo F, editors: Humana Press, Inc., 1999, Totowa, NJ, pp 111–130.

ACKNOWLEDGMENTS

The chapter authors would like to thank Wanda Gentry for her assistance in the preparation of this work.

CRITICAL REFERENCES

A full list of cited references is published online at www.expertconsult.com.

1. Vaidya JS, Joseph DJ, Tobias JS, et al: Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. Lancet 376(9735):91–102, 2010.
11. Gunderson LL, Nagorney DM, Martenson JA, et al: External beam plus intraoperative irradiation for gastrointestinal cancers. World J Surg 19(2): 191–197, 1995.
12. Sindelar WF, Kinsella TJ, Ch P: Intraoperative radiotherapy and retroperitoneal sarcomas final results of a prospective, randomized, clinical trial. Arch Surg 128:402–410, 1993.
18. Calvo FA, Gonzalez ME, Gonzalez-San Segundo C, et al: Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome. Eur J Surg Oncol 38(10):955–961, 2012.
19. Calvo FA, Sole CV, Lozano MA, et al: Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: Long-term outcomes. Gynecol Oncol 130(3):537–544, 2013.
30. Leibel SA, Scott CB, Mohiuddin M, et al: The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: Results of an analysis from the RTOG head and neck database. Int J Radiat Oncol Biol Phys 21(3):549–556, 1991.
31. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337(14):949–955, 1997.
34. Sauer R, Heinz B, Werner H, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351(17):1731–1740, 2004.
44. Sindelar WF, Johnstone PA, Hoekstra H, et al: Normal tissue tolerance to IORT. The NCI experimental studies. In Gunderson LL, Willett CG, Harrison LB, et al, editors: Intraoperative irradiation—techniques and results, Totowa, NJ, 1999, Humana Press, pp 131–146.
51. Gunderson LL, Nelson H, Martenson JA, et al: Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Dis Colon Rectum 39(12):1379–1395, 1996.
52. Gunderson LL, Nelson H, Martenson JA, et al: Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation ± 5-FU. Int J Radiat Oncol Biol Phys 37(3):601–614, 1997.
54. Haddock MG, Miller RC, Nelson H, et al: Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 79(1):143–150, 2011.
58. Kusters M, Valentini V, Calvo FA, et al: Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: Adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol 21(6):1279–1284, 2010.
69. Valentini V, Calvo F, Reni M, et al: Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIORT-Europe experience. Radiother Oncol 91(1):54–59, 2009.
73. Roldan GE, Gunderson LL, Nagorney DM, et al: External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. Cancer 61(6):1110–1116, 1988.
75. Tepper JE, Noyes D, Krall JM, et al: Intraoperative radiation therapy of pancreatic carcinoma: A report of RTOG-8505. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 21(5):1145–1149, 1991.
76. Willett CG, Del Castillo CF, Shih HA, et al: Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. Ann Surg 241(2):295–299, 2005. PMCID: 1356915.
77. Cai S, Hong TS, Goldberg SI, et al: Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer 119(23):4196–4204, 2013.
81. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 355(9217):1757–1770, 2000.
88. Veronesi U, Orecchia R, Luini A, et al: Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery: Experience with 590 cases. Ann Surg 242(1):101–106, 2005. PMCID: 1357710.
89. Bartelink H, Horiot JC, Poortmans PM, et al: Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 25(22):3259–3265, 2007.
92. Wenz F, Welzel G, Blank E, et al: Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: The first 5 years of experience with a novel approach. Int J Radiat Oncol Biol Phys 77(5):1309–1314, 2010.
93. Veronesi U, Orecchia R, Maisonneuve P, et al: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 14(13):1269–1277, 2013.
95. Sperk E, Welzel G, Keller A, et al: Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: Results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat 135(1):253–260, 2012.
96. Veronesi U, Orecchia R, Luini A, et al: Intraoperative radiotherapy during breast conserving surgery: A study on 1,822 cases treated with electrons. Breast Cancer Res Treat 124(1):141–151, 2010.
102. Petersen IA, Haddock M, Stafford S, et al: Use of intraoperative radiation therapy for retroperioneal sarcomas: Update of the Mayo Clinic Rochester Experience. Rev Cancer 22, 2008.
103. Gieschen HL, Spiro IJ, Suit HD, et al: Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys 50(1):127–131, 2001.
114. Martinez-Monge R, Jurado M, Aristu JJ, et al: Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol 82(3):538–543, 2001.
116. Giorda G, Boz G, Gadducci A, et al: Multimodality approach in extra cervical locally advanced cervical cancer: Chemoradiation, surgery and intraoperative radiation therapy. A phase II trial. Eur J Surg Oncol 37(5):442–447, 2011.
125. Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 9(5):843–849, 1991.
131. Calvo FA, Sole CV, Alvarez de Sierra P, et al: Prognostic impact of external beam radiation therapy in patients treated with and without extended surgery and intraoperative electrons for locally recurrent rectal cancer: 16-year experience in a single institution. Int J Radiat Oncol Biol Phys 86(5):892–900, 2013.
132. Haddock MG, Gunderson LL, Nelson H, et al: Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. Int J Radiat Oncol Biol Phys 49(5):1267–1274, 2001.
140. Calvo FA, Sole CV, Gonzalez ME, et al: Research opportunities in intraoperative radiation therapy: The next decade 2013-2023. Clin Transl Oncol 15(9):683–690, 2013.

REFERENCES

1. Vaidya JS, Joseph DJ, Tobias JS, et al: Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): An international, prospective, randomised, non-inferiority phase 3 trial. Lancet 376(9735):91–102, 2010.
2. Orecchia R, Leonardo MC: Intraoperative radiation therapy: Is it a standard now? Breast 20(Suppl 3):S111–S115, 2011.
3. Medina R, Casas F, Calvo FA: Radiation oncology in Spain: Historical notes for the radiology centennial. Int J Radiat Oncol Biol Phys 35(5):1075–1097, 1996.
4. Abe M, Fukuda M, Yamano K, et al: Intra-operative irradiation in abdominal and cerebral tumours. Acta Radiol Ther Phys Biol 10(4):408–416, 1971.
5. Krengli M, Calvo FA, Sedlmayer F, et al: Clinical and technical characteristics of intraoperative radiotherapy. Analysis of the ISIORT-Europe database. Strahlenther Onkol 189(9):729–737, 2013.
6. Rubin P, Cassarett G: Clinical radiation and pathology, Philadelphia, 1968, Saunders.
7. Okunieff P, Sundararaman S, Chen Y: Biology of large dose per fraction radiation therapy. In: Gunderson L, Willett C, Harrison L, et al, editors: Biology of large dose per fraction radiation therapy, Totowa, NJ, 1999, Human Press.
8. Vujaskovic Z, Willett C, Tepper J, et al. In: Gunderson L, Willett C, Calvo FA, et al, editors: Normal tissue tolerance to IOERT, EBRT, or both animal and clinical studies, 2nd ed, New York, 2011, Humana Press.
9. Greco C, Zelefsky MJ, Lovelock M, et al: Predictors of local control after single-dose stereotactic image-guided intensity-modulated radiotherapy for extracranial metastases. Int J Radiat Oncol Biol Phys 79(4):1151–1157, 2011.
10. Schmidt C: Early breast cancer: Single dose of radiation during surgery gains support. J Natl Cancer Inst 102(17):1304–1309, 2010.
11. Gunderson LL, Nagorney DM, Martenson JA, et al: External beam plus intraoperative irradiation for gastrointestinal cancers. World J Surg 19(2):191–197, 1995.
12. Sindelar WF, Kinsella TJ, Ch P: Intraoperative radiotherapy and retroperitoneal sarcomas final results of a prospective, randomized, clinical trial. Arch Surg 128:402–410, 1993.
13. Brierly J, Cummings B, Wong C: Adenocarcinoma of the rectum treated by radical external radiation therapy. Int J Radiat Oncol Biol Phys 31:255–259, 1995.
14. O'Connell MJ, Childs DS, Moertel CG, et al: A prospective controlled evaluation of combined pelvic radiotherapy and methanol extraction residue of BCG (MER) for locally unresectable or recurrent rectal carcinoma. Int J Radiat Oncol Biol Phys 8(7):1115–1119, 1982.
15. Gunderson LL, Cohen AC, Dosoretz DD, et al: Residual, unresectable, or recurrent colorectal cancer: External beam irradiation and intraoperative electron beam boost ± resection. Int J Radiat Oncol Biol Phys 9(11):1597–1606, 1983.
16. Tewfik HH, Buchsbaum HJ, Latourette HB, et al: Para-aortic lymph node irradiation in carcinoma of the cervix after exploratory laparotomy and biopsy-proven positive aortic nodes. Int J Radiat Oncol Biol Phys 8(1):13–18, 1982.
17. Piver MS, Barlow JJ: High dose irradiation to biopsy confirmed aortic node metastases from carcinoma of the uterine cervix. Cancer 39(3):1243–1246, 1977.
18. Calvo FA, Gonzalez ME, Gonzalez-San Segundo C, et al: Surgery and intraoperative electron radiotherapy in recurrent or metastatic oligotopic extrapelvic cancer: Long-term outcome. Eur J Surg Oncol 38(10):955–961, 2012.
19. Calvo FA, Sole CV, Lozano MA, et al: Intraoperative electron beam radiotherapy and extended surgical resection for gynecological pelvic recurrent malignancies with and without external beam radiation therapy: Long-term outcomes. Gynecol Oncol 130(3):537–544, 2013.
20. Gunderson LL, Tepper JE, Biggs PJ, et al: Intraoperative ± external beam irradiation. Curr Probl Cancer 7(11):1–69, 1983.
21. Fletcher GH: Clinical dose-response curves of human malignant epithelial tumours. Br J Radiol 46(541):1–12, 1973.
22. Fletcher GH, Shukovsky LJ: The interplay of radiocurability and tolerance in the irradiation of human cancers. J Radiol Electrol Med Nucl 56(5):383–400, 1975.
23. Griscom NT, Wang CC: Radiation therapy of inoperable breast carcinoma. Radiology 79:18–23, 1962.
24. Tepper J: Clonogenic potential of human tumors. A hypothesis. Acta Radiol Oncol 20(4):283–288, 1981.
25. Ramsay J, Suit HD, Sedlacek R: Experimental studies on the incidence of metastases after failure of radiation treatment and the effect of salvage surgery. Int J Radiat Oncol Biol Phys 14(6):1165–1168, 1988.
26. Suit HD: Local control and patient survival. Int J Radiat Oncol Biol Phys 23(3):653–660, 1992.
27. Suit HD, Sedlacek RS, Gillette EL: Examination for a correlation between probabilities of development of distant metastasis and of local recurrence. Radiology 95(1):189–194, 1970.
28. Suit HD: The American Society of Therapeutic Radiologists Presidential Address: October 1981. Potential for improving survival rates for the cancer patient by increasing the efficacy of treatment of the primary lesion. Cancer 50(7):1227–1234, 1982.
29. Fuks Z, Leibel SA, Wallner KE, et al: The effect of local control on metastatic dissemination in carcinoma of the prostate: Long-term results in patients treated with 125I implantation. Int J Radiat Oncol Biol Phys 21(3):537–547, 1991.
30. Leibel SA, Scott CB, Mohiuddin M, et al: The effect of local-regional control on distant metastatic dissemination in carcinoma of the head and neck: Results of an analysis from the RTOG head and neck database. Int J Radiat Oncol Biol Phys 21(3):549–556, 1991.
31. Overgaard M, Hansen PS, Overgaard J, et al: Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 337(14):949–955, 1997.
32. Sohn T, Yeo C, Cameron J, et al: Resected adenocarcinoma of the pancreas—616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 4:567–579, 2000.
33. Spitz F, Abbruzzese J, Lee J, et al: Preoperative and postoperative chemoradiation strategies in patients treated with pancreaticoduodectomy for adenocarcinoma of the pancreas. J Clin Oncol 15:928–937, 1997.
34. Sauer R, Heinz B, Werner H, et al: Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351(17):1731–1740, 2004.
35. Gunderson LL, Shipley WU, Suit HD, et al: Intraoperative irradiation: A pilot study combining external beam photons with "boost" dose intraoperative electrons. Cancer 49(11):2259–2266, 1982.
36. Nag S, Gunderson LL, Willett CG, et al: Intraoperative irradiation with electron beam or high dose rate brachytherapy. Methodological comparisons. In Gunderson LL, Willett CG, Harrison LB, et al, editors: Intraoperative irradiation—techniques and results, Totowa, NJ, 1999, Humana Press, pp 111–130.
37. Azinovic I, Calvo FA, Puebla F, et al: Long-term normal tissue effects of intraoperative electron radiation therapy (IOERT): Late sequelae, tumor recurrence, and second malignancies. Int J Radiat Oncol Biol Phys 49(2):597–604, 2001.
38. Tepper JE, Gunderson LL, Orlow E, et al: Complications of intraoperative radiation therapy. Int J Radiat Oncol Biol Phys 10(10):1831–1839, 1984.
39. Johnstone P, Sindelar WF, Kinsella TJ: Experimental and clinical studies of intraoperative radiation. Int J Radiat Oncol Biol Phys 12:1687–1695, 1986.
40. Kinsella TJ, DeLuca AM, Barnes M, et al: Threshold dose for peripheral neuropathy following intraoperative radiotherapy (IORT) in a large animal model. Int J Radiat Oncol Biol Phys 20(4):697–701, 1991.
41. Kinsella TJ, Sindelar WF, DeLuca AM, et al: Tolerance of the canine bladder to intraoperative radiation therapy: An experimental study. Int J Radiat Oncol Biol Phys 14(5):939–946, 1988.
42. Sindelar WF, Tepper J, Travis EL: Tolerance of bile duct to intraoperative irradiation. Surgery 92(3):533–540, 1982.
43. Sindelar WF, Tepper JE, Kinsella TJ, et al: Late effects of intraoperative radiation therapy on retroperitoneal tissues, intestine, and bile duct in a large animal model. Int J Radiat Oncol Biol Phys 29(4):781–788, 1994.
44. Sindelar WF, Johnstone PA, Hoekstra H, et al: Normal tissue tolerance to IORT. The NCI experimental studies. In Gunderson LL, Willett CG, Harrison LB, et al, editors: Intraoperative irradiation—techniques and results, Totowa, NJ, 1999, Humana Press, pp 131–146.
45. LeCouteur RA, Gillette EL, Powers BE, et al: Peripheral neuropathies following experimental intraoperative radiation therapy (IORT). Int J Radiat Oncol Biol Phys 17(3):583–590, 1989.
46. Gillette EL, Gillette SM, Vujaskovic Z, et al: Influence of volume on canine ureters and peripheral nerves irradiated intraoperatively. In Schildberg FW, Willich N, Krämling H, editors: Intraoperative radiation therapy—proceedings of the 4th international IORT symposium, Munich, 1992, Essen, Germany, 1993, Verlag Die Blaue Eule, pp 61–63.
47. Gillette EL, Gillette S, Powers BE, et al, editors: Studies at Colorado State University of normal tissue tolerance of beagles to IOERT, EBRT or a combination, Totowa, NJ, 1999, Humana Press.
48. Shaw EG, Gunderson LL, Martin JK, et al: Peripheral nerve and ureteral tolerance to intraoperative radiation therapy: Clinical and dose-response analysis. Radiother Oncol 18(3):247–255, 1990.
49. Miller RC, Haddock MG, Petersen IA, et al: Intraoperative electron-beam radiotherapy and ureteral obstruction. Int J Radiat Oncol Biol Phys 64(3):792–798, 2006.
50. Johnstone PA, Sindelar WF, Kinsella TJ: Experimental and clinical studies of intraoperative radiation therapy. Curr Probl Cancer 18(5):249–290, 1994.
51. Gunderson LL, Nelson H, Martenson JA, et al: Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Dis Colon Rectum 39(12):1379–1395, 1996.
52. Gunderson LL, Nelson H, Martenson JA, et al: Locally advanced primary colorectal cancer: Intraoperative electron and external beam irradiation ± 5-FU. Int J Radiat Oncol Biol Phys 37(3):601–614, 1997.
53. Mathis KL, Miller R, Nelson H, et al: Unresectable colorectal cancer can be cured with multimodality therapy. Ann Surg 248:592–598, 2008.
54. Haddock MG, Miller RC, Nelson H, et al: Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 79(1):143–150, 2011.

55. Gomez M, Calvo F, Gonzalez C, et al, editors: Timing and intensity of neoadjuvant treatment in rectal cancer: results of pre (+IOERT) versus post (no IOERT) chemoradiation Rev Cancer ISIORT 2008, Madrid, 2008, Aran. 2008 June 10-13.
56. Calvo F, Sole CV, Gomez-Espi M, et al, editors. Post-Neoadjuvant intraoperative electron boost compensates adverse prognostic factors for pelvic recurrence in locally advanced rectal cancer: long-term results. 2013, ISIORT Europe.
57. Rutten H, Valentini V, Krempien R, et al, editors: Treatment of locally advanced rectal cancer by intraoperative electrobeam radiotherapy containing multimodality treatment, results of a European pooled analysis. Rev Cancer ISIORT 2008, Madrid, 2008, Aran. 2008 June 10-13.
58. Kusters M, Valentini V, Calvo FA, et al: Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: Adjuvant chemotherapy prevents local recurrence rather than distant metastases. Ann Oncol 21(6):1279–1284, 2010.
59. Calvo FA, Sole CV, Serrano J, et al: Postchemoradiation laparoscopic resection and intraoperative electron-beam radiation boost in locally advanced rectal cancer: Long-term outcomes. J Cancer Res Clin Oncol 139(11):1825–1833, 2013.
60. Vujaskovic Z: Structural and physiological properties of peripheral nerves after intraoperative irradiation. J Peripher Nerv Syst 2(4):343–349, 1997.
61. Azinovic I, Martinez Monge R, Javier Aristu J, et al: Intraoperative radiotherapy electron boost followed by moderate doses of external beam radiotherapy in resected soft-tissue sarcoma of the extremities. Radiother Oncol 67(3):331–337, 2003.
62. Ogawa K, Karasawa K, Ito Y, et al: Intraoperative radiotherapy for resected pancreatic cancer: A multi-institutional retrospective analysis of 210 patients. Int J Radiat Oncol Biol Phys 77(3):734–742, 2010.
63. Reni M, Panucci MG, Ferreri AJ, et al: Effect on local control and survival of electron beam intraoperative irradiation for resectable pancreatic adenocarcinoma. Int J Radiat Oncol Biol Phys 50(3):651–658, 2001.
64. Gunderson L, Willett C, Harrison L, et al: Intraoperative irradiation—techniques and results, 2nd ed, New York, 2011, Humana Press/Springer.
65. Sindelar WF, Kinsella TJ: Studies of intraoperative radiotherapy in carcinoma of the pancreas. Ann Oncol 10(Suppl 4):226, 1999.
66. Sindelar WF, Hoekstra H, Restrepo C, et al: Pathological tissue changes following intraoperative radiotherapy. Am J Clin Oncol 9(6):504–509, 1986.
67. Zerbi A, Fossati V, Parolini D, et al: Intraoperative radiation therapy adjuvant to resection in the treatment of pancreatic cancer. Cancer 73(12):2930–2935, 1994.
68. Alfieri S, Morganti AG, Di Giorgio A, et al: Improved survival and local control after intraoperative radiation therapy and postoperative radiotherapy: A multivariate analysis of 46 patients undergoing surgery for pancreatic head cancer. Arch Surg 136(3):343–347, 2001.
69. Valentini V, Calvo F, Reni M, et al: Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIORT-Europe experience. Radiother Oncol 91(1):54–59, 2009.
70. Bachireddy P, Tseng D, Horoschak M, et al: Orthovoltage intraoperative radiation therapy for pancreatic adenocarcinoma. Radiat Oncol 5:105, 2010. PMCID: 2987939.
71. Calvo FA, Sole CV, Atahualpa F, et al: Chemoradiation for resected pancreatic adenocarcinoma with or without intraoperative radiation therapy boost: Long-term outcomes. Pancreatology 13(6):576–582, 2013.
72. Valentini V, Balducci M, Tortoreto F, et al: Intraoperative radiotherapy: Current thinking. Eur J Surg Oncol 28(2):180–185, 2002.
73. Roldan GE, Gunderson LL, Nagorney DM, et al: External beam versus intraoperative and external beam irradiation for locally advanced pancreatic cancer. Cancer 61(6):1110–1116, 1988.
74. Shibamoto Y, Manabe T, Ohshio G, et al: High-dose intraoperative radiotherapy for unresectable pancreatic cancer. Int J Radiat Oncol Biol Phys 34(1):57–63, 1996.
75. Tepper JE, Noyes D, Krall JM, et al: Intraoperative radiation therapy of pancreatic carcinoma: A report of RTOG-8505. Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 21(5):1145–1149, 1991.
76. Willett CG, Del Castillo CF, Shih HA, et al: Long-term results of intraoperative electron beam irradiation (IOERT) for patients with unresectable pancreatic cancer. Ann Surg 241(2):295–299, 2005. PMCID: 1356915.
77. Cai S, Hong TS, Goldberg SI, et al: Updated long-term outcomes and prognostic factors for patients with unresectable locally advanced pancreatic cancer treated with intraoperative radiotherapy at the Massachusetts General Hospital, 1978 to 2010. Cancer 119(23):4196–4204, 2013.
78. Mohiuddin M, Regine WF, Stevens J, et al: Combined intraoperative radiation and perioperative chemotherapy for unresectable cancers of the pancreas. J Clin Oncol 13(11):2764–2768, 1995.
79. Schuricht AL, Spitz F, Barbot D, et al: Intraoperative radiotherapy in the combined-modality management of pancreatic cancer. Am Surg 64(11):1043–1049, 1998.
80. Shipley WU, Wood WC, Tepper JE, et al: Intraoperative electron beam irradiation for patients with unresectable pancreatic carcinoma. Ann Surg 200(3):289–296, 1984. PMCID: 1250473.
81. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet 355(9217):1757–1770, 2000.
82. Lemanski C, Azria D, Gourgon-Bourgade S, et al: Intraoperative radiotherapy in early-stage breast cancer: Results of the Montpellier phase II trial. Int J Radiat Oncol Biol Phys 76(3):698–703, 2010.
83. Veronesi U, Gatti G, Luini A, et al: Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery. Arch Surg 138(11):1253–1256, 2003.
84. Arcangeli G, Arcangeli S, Giordano C, et al: Intraoperative (IORT) versus standard radiotherapy (EBRT) in breast cancer, an update of an ongoing Italian multicenter, randomized study. ISIORT Rev Cancer 22:13, 2008.
85. Cuncins-Hearn A, Saunders C, Walsh D, et al: A systematic review of intraoperative radiotherapy in early breast cancer. Breast Cancer Res Treat 85(3):271–280, 2004.
86. Vaidya JS, Baum M, Tobias JS, et al: Targeted intraoperative radiotherapy (TARGIT) yields very low recurrence rates when given as a boost. Int J Radiat Oncol Biol Phys 66(5):1335–1338, 2006.
87. Majewski W, Wydmanski J, Kanieska-Dorsz Z, et al: Early results of a targeted intra-operative radiation therapy (TARGIT) as a boost in breast conserving treatment. ISIORT Rev Cancer 22:17, 2008.
88. Veronesi U, Orecchia R, Luini A, et al: Full-dose intraoperative radiotherapy with electrons during breast-conserving surgery: Experience with 590 cases. Ann Surg 242(1):101–106, 2005. PMCID: 1357710.
89. Bartelink H, Horiot JC, Poortmans PM, et al: Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol 25(22):3259–3265, 2007.
90. Battle JA, DuBois JB, Merrick HW, et al: IORT for breast cancer. In Gunderson LL, Willett CG, Harrison LB, et al, editors: Intraoperative irradiation—techniques and results, Totowa, NJ, 1999, Humana Press, pp 521–526.
91. Reitsamer R, Peintinger F, Kopp M, et al: Local recurrence rates in breast cancer patients treated with intraoperative electron-boost radiotherapy versus postoperative external-beam electron-boost irradiation. A sequential intervention study. Strahlenther Onko 180(1):38–44, 2004.
92. Wenz F, Welzel G, Blank E, et al: Intraoperative radiotherapy as a boost during breast-conserving surgery using low-kilovoltage X-rays: The first 5 years of experience with a novel approach. Int J Radiat Oncol Biol Phys 77(5):1309–1314, 2010.
93. Veronesi U, Orecchia R, Maisonneuve P, et al: Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): A randomised controlled equivalence trial. Lancet Oncol 14(13):1269–1277, 2013.
94. Vaidya JS, Wenz F, Bulsara M, et al: Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 383(9917):603–613, 2014.
95. Sperk E, Welzel G, Keller A, et al: Late radiation toxicity after intraoperative radiotherapy (IORT) for breast cancer: Results from the randomized phase III trial TARGIT A. Breast Cancer Res Treat 135(1):253–260, 2012.
96. Veronesi U, Orecchia R, Luini A, et al: Intraoperative radiotherapy during breast conserving surgery: A study on 1,822 cases treated with electrons. Breast Cancer Res Treat 124(1):141–151, 2010.
97. Leonardi MC, Ivaldi GB, Santoro L, et al: Long-term side effects and cosmetic outcome in a pool of breast cancer patients treated with intraoperative radiotherapy with electrons as sole treatment. Tumori 98(3):324–330, 2012.
98. Sedlmayer F, Fastner G, Merz F, et al: IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Results of an ISIORT pooled analysis. Strahlenther Onkol 183(2):32–34, 2007.
99. Sedlmayer F, Fastner G, Merz F, et al: ISIORT pooled analysis on linac-based IORT as boost strategy during breast conserving therapy. Rev Cancer 22:21–22, 2008.
100. Fastner G, Sedlmayer F, Merz F, et al: IORT with electrons as boost strategy during breast conserving therapy in limited stage breast cancer: Long term results of an ISIORT pooled analysis. Radiother Oncol 108(2):279–286, 2013.
101. Petersen IA, Haddock MG, Donohue JH, et al: Use of intraoperative electron beam radiotherapy in the management of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 52(2):469–475, 2002.
102. Petersen I, Haddock M, Stafford S, et al: Use of intraoperative radiation therapy for retroperitoneal sarcomas. Update of the Mayo Clinic Rochester Experience. ISIORT 2008 Proceedings. Cancer 22:57, 2008.
103. Gieschen HL, Spiro IJ, Suit HD, et al: Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys 50(1):127–131, 2001.
104. Pierie JP, Betensky RA, Choudry U, et al: Outcomes in a series of 103 retroperitoneal sarcomas. Eur J Surg Oncol 32(10):1235–1241, 2006.
105. Krempien R, Roeder F, Buchler MW, et al, editors: Intraoperative radiation therapy (IORT) for primary and recurrent retroperitoneal soft tissue sarcoma. First results of a pooled analysis, Madrid, 2008. Cancer ISIORT 2008.
106. Gunderson LL, Nagorney DM, McIlrath DC, et al: External beam and intraoperative electron irradiation for locally advanced soft tissue sarcomas. Int J Radiat Oncol Biol Phys 25(4):647–656, 1993.
107. Calvo FA, Azinovic I, Martinez R, et al: Intraoperative radiotherapy for the treatment of soft tissue sarcomas of central anatomic sites. IORT 94-5th International Symposium Abstracts. Hepatogastroenterology 41:4, 1994.

108. Dubois JB, Hay MH, Gely S, et al: Intraoperative radiation therapy (IORT) in soft tissue sarcomas. IORT 94-5th International Symposium Abstracts. Hepatogastroenterology 41:3, 1994.
109. Pisters PW, Ballo MT, Fenstermacher MJ, et al: Phase I trial of preoperative concurrent doxorubicin and radiation therapy, surgical resection, and intraoperative electron-beam radiation therapy for patients with localized retroperitoneal sarcoma. J Clin Oncol 21(16):3092–3097, 2003.
110. Haddock MG, Petersen IA, Webb MJ, et al: IORT for locally advanced gynecological malignancies. Front Radiat Ther Oncol 31:256–259, 1997.
111. Haddock MG, Petersen IA, Webb MJ, et al: Intraoperative radiation therapy for locally advanced gynecological (GYN) malignancies. Presented before the 3rd International ISIORT Meeting, Aachen, Germany. ISIORT Abstract 5.555, 2002.
112. Haddock MG: Intraoperative radiation therapy for locally advanced gynecologic malignancies. ISIORT 2005 Proceedings; personal communication.
113. Barney BM, Petersen IA, Dowdy SC, et al: Intraoperative electron beam radiotherapy (IOERT) in the management of locally advanced or recurrent cervical cancer. Radiat Oncol 8(1):80, 2013. PMCID: 3641982.
114. Martinez-Monge R, Jurado M, Aristu JJ, et al: Intraoperative electron beam radiotherapy during radical surgery for locally advanced and recurrent cervical cancer. Gynecol Oncol 82(3):538–543, 2001.
115. Liu Z, Gao Y, Soong YL, et al: Intraoperative electron beam radiotherapy for primary treatment of stage IIB cervical cancer: A retrospective study. J Int Med Res 40(6):2346–2354, 2012.
116. Giorda G, Boz G, Gadducci A, et al: Multimodality approach in extra cervical locally advanced cervical cancer: Chemoradiation, surgery and intraoperative radiation therapy. A phase II trial. Eur J Surg Oncol 37(5):442–447, 2011.
117. Tran PT, Su Z, Hara W, et al: Long-term survivors using intraoperative radiotherapy for recurrent gynecologic malignancies. Int J Radiat Oncol Biol Phys 69(2):504–511, 2007.
118. Stelzer KJ, Koh WJ, Greer BE, et al: The use of intraoperative radiation therapy in radical salvage for recurrent cervical cancer: Outcome and toxicity. Am J Obstet Gynecol 172(6):1881–1886, 1995.
119. Mahe MA, Gerard JP, Dubois JB, et al: Intraoperative radiation therapy in recurrent carcinoma of the uterine cervix: Report of the French intraoperative group on 70 patients. Int J Radiat Oncol Biol Phys 34(1):21–26, 1996.
120. Dowdy SC, Mariani A, Cliby WA, et al: Radical pelvic resection and intraoperative radiation therapy for recurrent endometrial cancer: Technique and analysis of outcomes. Gynecol Oncol 101(2):280–286, 2006.
121. Barney BM, Petersen IA, Dowdy SC, et al: Long-term outcomes with intraoperative radiotherapy as a component of treatment for locally advanced or recurrent uterine sarcoma. Int J Radiat Oncol Biol Phys 83(1):191–197, 2012.
122. Gao Y, Liu Z, Chen X, et al: Intraoperative radiotherapy electron boost in advanced and recurrent epithelial ovarian carcinoma: A retrospective study. BMC Cancer 11:439, 2011. PMCID: 3198723.
123. Yap OW, Kapp DS, Teng NN, et al: Intraoperative radiation therapy in recurrent ovarian cancer. Int J Radiat Oncol Biol Phys 63(4):1114–1121, 2005.
124. Barney BM, Petersen IA, Dowdy SC, et al: Intraoperative electron beam radiotherapy (IOERT) in the management of recurrent ovarian malignancies. Int J Gynecol Cancer 21(7):1225–1231, 2011.
125. Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for primary locally advanced rectal and rectosigmoid carcinoma. J Clin Oncol 9(5):843–849, 1991.
126. Suzuki K, Gunderson LL, Devine RM, et al: Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer 75(4):939–952, 1995.
127. Willett CG, Shellito PC, Tepper JE, et al: Intraoperative electron beam radiation therapy for recurrent locally advanced rectal or rectosigmoid carcinoma. Cancer 67(6):1504–1508, 1991.
128. Dresen R, Goesns M, Martijm H, et al: Radical resection after IOERT containing multimodality treatment is an important determinant for outcomes in patients treated for locally recurrent rectal cancer. ISIORT Rev Cancer 22:45–46, 2008.
129. Wallace HJ, 3rd, Willett CG, Shellito PC, et al: Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. J Surg Oncol 60(2):122–127, 1995.
130. Abuchaibe O, Calvo FA, Azinovic I, et al: Intraoperative radiotherapy in locally advanced recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 26(5):859–867, 1993.
131. Calvo FA, Sole CV, Alvarez de Sierra P, et al: Prognostic impact of external beam radiation therapy in patients treated with and without extended surgery and intraoperative electrons for locally recurrent rectal cancer: 16-year experience in a single institution. Int J Radiat Oncol Biol Phys 86(5):892–900, 2013.
132. Haddock MG, Gunderson LL, Nelson H, et al: Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. Int J Radiat Oncol Biol Phys 49(5):1267–1274, 2001.
133. Mirnezami R, Chang GJ, Das P, et al: Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surg Oncol 22(1):22–35, 2013.
134. Calvo FA, Sole CV, Martinez-Monge R, et al: Intraoperative EBRT and resection for renal cell carcinoma: Twenty-year outcomes. Strahlenther Onkol 189(2):129–136, 2013.
135. Krengli M, Terrone C, Jereczek-Fossa BA, et al: May intra-operative radiotherapy have a role in the treatment of prostate cancer? Crit Rev Oncol Hematol 83(1):123–129, 2012.
136. Call J, Stafford S, Petersen IA, et al: Use of intraoperative radiotherapy for upper-extremity soft-tissue sarcomas: Analysis of disease outcomes and toxicity. Am J Clin Oncol 37(1):81–85, 2014.
137. Rich BS, McEvoy MP, LaQuaglia MP, et al: Local control, survival, and operative morbidity and mortality after re-resection, and intraoperative radiation therapy for recurrent or persistent primary high-risk neuroblastoma. J Pediatr Surg 46(1):97–102, 2011.
138. Meurk ML, Goer DA, Spalek G, et al: The Mobetron: A new concept for IORT. Front Radiat Ther Oncol 31:65–70, 1997.
139. Pascau J, Santos Miranda JA, Calvo FA, et al: An innovative tool for intraoperative electron beam radiotherapy simulation and planning: Description and initial evaluation by radiation oncologists. Int J Radiat Oncol Biol Phys 83(2):e287–e295, 2012.
140. Calvo FA, Sole CV, Gonzalez ME, et al: Research opportunities in intraoperative radiation therapy: The next decade 2013-2023. Clin Transl Oncol 15(9):683–690, 2013.
141. Merrick HW 3rd, Gunderson LL, Calvo FA: Future directions in intraoperative radiation therapy. Surg Oncol Clin N Am 12(4):1099–1105, 2003.