High-Dose-Rate Intraoperative Radiation Therapy For Colorectal Cancer

Review Article [1] | July 01, 1995
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Intraoperative radiation therapy (IORT) has the obvious advantage of maximally irradiating the tumor bed while eliminating surrounding normal organs from the field of radiation. This approach has been especially useful when the required radiation dose exceeds the tolerance dose of the surrounding normal tissues. However, the application of IORT has been significantly limited by cost, logistic issues, and technical problems related to delivering treatment to difficult anatomic areas. We have developed a new approach to IORT that obviates the need for patient transport: In a dedicated, shielded operating room, the surgery is performed and IORT is delivered via HDR remote afterloading. We have found this approach to be cost effective, logistically sound, and suitable for a wide range of anatomic sites. The technical aspects of the procedure, as well our preliminary results in colorectal cancer, will be presented. Lastly, the authors present the technical aspects of delivering HDR intraoperative brachytherapy, their dosimetry atlas, and their results using HDR-IORT in the treatment of patients with colorectal cancer[ONCOLOGY 9(7):679-683, 1995]

Introduction

The efforts of radiation oncologists have long been thwarted by the therapeutic ratio. This ratio, which is expressed as the required dose to eradicate tumor divided by the tolerance dose of the surrounding normal tissues, often dictates the potential for tumor control with radiation therapy. When the required radiation dose exceeds the tolerance dose of the surrounding normal tissues, it becomes either difficult or impossible to control the tumor using conventional radiation therapy techniques. Such cancers as advanced pelvic tumors, abdominal and retroperitoneal tumors, liver tumors, certain pediatric tumors, and selected thoracic tumors frequently pose this therapeutic dilemma.

Over the years, radiation oncologists have developed numerous novel strategies to overcome the constraints of the therapeutic ratio and to increase the biologic effectiveness of radiation. These include radiation sensitizers, radiation protectors, brachytherapy, intra-operative radiation therapy (IORT), three-dimensional conformal external-beam irradiation, heavy-charged-particle irradiation, and various combinations of these techniques.

At Memorial Sloan-Kettering Cancer Center, we have developed a new program for intraoperative radiation therapy: high-dose-rate intraoperative radiation therapy (HDR-IORT), that attempts to combine the technical and dosimetric advantages of brachytherapy with the conceptual and logistic advantages of intraoperative electron-beam irradiation. The entire procedure is performed in a specially designed operating room. Thus, no intraoperative patient transportation is required. For intraoperative radiation therapy delivery, we use an HDR remote afterloader, a device that advances a cable-mounted radioactive (iridium-192) source out of its shield into proximity with the tissue to be treated. The machine permits stopping the source for prescribed "dwell" times at regularly spaced positions in one or more catheters. This equipment is far less expensive than a linear accelerator, allowing the treatment to be given in a more cost-effective manner. Because the remote after-loader is portable, it can also be utilized for other procedures in the outpatient facility when it is not needed for intraoperative cases. This further enhances the cost effectiveness of the program.

Advantages and Limitations of Novel Strategies

Conventional Brachytherapy

Brachytherapy involves the placement of interstitial or intracavitary sources of radioactive material either into or against the desired target region. This permits high doses of radiation to be successfully and safely delivered to tumors, with acceptable toxicity to the surrounding normal
structures. For this reason, brachytherapy has become a standard part of the sophisticated management of a wide variety of tumors, such as cancers of the oral cavity, oropharynx, nasopharynx, rectum, cervix, vagina, endometrium, prostate, brain, and eye and soft-tissue sarcoma.

Conventional brachytherapy is not always feasible, however. Advanced tumors of the pelvis or retroperitoneum require a large surface area to be irradiated after appropriate tumor resection. Interstitial techniques are often suboptimal in these anatomic regions, as they fail to cover the complex surfaces adequately with permanent or temporary implants. Catheter movement, risk of infection related to indwelling catheters, risk that normal tissues, such as the large and small bowel, will fall in close proximity to the implanted isotopes (increasing complications), and suboptimal implant geometry are all potential obstacles to adequate conventional brachytherapy.

**Intraoperative External-Beam Radiation Therapy**

Intraoperative external-beam irradiation has been explored for most of this decade in an attempt to improve the therapeutic ratio [1-3]. The concept on which this technique is based is quite simple. During an operation, the normal organs are physically moved out of the pathway of the radiation beam. A large, single fraction of radiation is directed onto the target surface during the operative procedure, with the normal tissues physically distanced and protected from the beam.

Although conceptually attractive, intraoperative external-beam irradiation also has several limitations:

1) The most common technique for administering this treatment, a linear accelerator, is quite expensive to install in a dedicated operating room. This expense has seriously limited the number of medical centers in this country that use this form of therapy.

Electron-beam irradiation can also be administered intraoperatively by transporting the patient from the main operating room to the radiation therapy facility. Afterward, the patient is either closed in the radiation therapy facility or transported back to the main operating room. There are obvious safety and logistic concerns about subjecting anesthetized patients to this process. It is also quite disruptive to the outpatient radiation therapy schedule.

2) It can be difficult to target complex surfaces, particularly in the pelvis, retroperitoneum, or chest, with available electron cones. Although the use of beveled cones enhances the capability to treat most anatomic surfaces, in many cases effective intraoperative orientation can prove quite awkward with the available or appropriate electron cones.

3) Available electron cones have size limitations. When a large surface requires treatment, it becomes necessary to use abutting electron fields. This introduces the potential both for underdosage and for overdosage at the junction of these fields [4]. Because relatively large fractions are delivered (1,000 to 2,000 cGy), the dose in an overlapped region can be substantial, increasing the risk of toxicity.

4) The electron beam delivers a relatively homogeneous dosimetry. Although not inherently disadvantageous, homogeneous dosimetry does not allow for dose intensification within the treatment volume that can be accomplished with brachytherapy.

All these issues notwithstanding, selected institutions have had substantial success using the intraoperative electron beam [1-3].

**High-Dose-Rate Intraoperative Radiation**

At Memorial Sloan-Kettering Cancer Center, we have developed a new program for intraoperative radiation therapy, high-dose-rate intraoperative radiation therapy (HDR-IORT), that attempts to combine the technical and dosimetric advantages of brachytherapy with the conceptual and logistic advantages of intraoperative electron-beam irradiation. The entire procedure is performed in a specially designed OR. Thus, no intraoperative patient transportation is required. For radiation therapy delivery, we use an HDR remote afterloader. This equipment is far less expensive than a linear accelerator, allowing the treatment to be given in a more cost-effective manner. Because the remote afterloader is portable, it can also be utilized for other procedures in the outpatient facility when it is not needed for intraoperative cases. This further enhances the cost effectiveness of the program.

We have developed an applicator system that employs flexible, intraoperative applicators of various sizes designed to contour to any surface within the body (Figure 1). These applicators are connected to the HDR remote afterloader using customized source guide tubes. With this applicator system, a large, single fraction of radiation therapy can be delivered to any tumor bed during the surgical procedure.
Our new facility opened in November 1992. In the following sections, we will describe the treatment facility, surgical procedure, and HDR-IORT equipment and technique. We will also outline our preliminary results using HDR-IORT in patients with locally advanced or recurrent colorectal cancer—the predominant area of investigation to date. Results of treatment in other tumors under study, including retroperitoneal sarcoma, selected pediatric tumors, advanced or recurrent gynecologic malignancies, and malignant pleural mesothelioma, will not be discussed.

**Treatment Facility**

As mentioned above, all HDR-IORT procedures take place in an operating room located in the Brachytherapy Suite in the Department of Radiation Oncology. This facility was designed and constructed under the auspices of a multidisciplinary group of radiation oncologists, surgical oncologists, anesthesiologists, nurses, physicists, and hospital administration personnel. The operating room is a full-service facility, allowing for the performance of all major operative procedures, and has all of the necessary support services of the main operating room. It is fully shielded for the delivery of radiation therapy.

During the actual radiation therapy delivery, all personnel obviously must leave the room, and thus, the anesthetized patient remains alone in the operating room for an extended period. Our facility has a remote-control station with a duplicate set of monitors immediately outside of the operating room in an area where the radiation oncologist, surgeon, and operating nurse can remain gowned and gloved. This station allows for identical monitoring of the patient during the delivery of radiation therapy as is possible in the operating room.

Video cameras, installed in several strategic locations in the operating room, can be controlled by the anesthesiologist, who sits at the monitoring station just outside the operating room. They provide complete, consistent visual backup to the online monitoring of the patient's vital signs, ECG tracing, arterial or central line, endotracheal tube, and face. A remote, computer-controlled software system regulates the rate of infusion of two intravenous fluids, three syringes with drugs, and blood products.

Using a separate video system, the radiation oncologist and surgeon can remain scrubbed and view the operative field and brachytherapy application. Any malfunction of the remote afterloader, movement of the applicator or disruption of the source guide tubing, or obvious bleeding would be immediately observed on the color video monitor. For any reason, whether related to anesthesia, radiation, or surgery, the treatment can be instantaneously interrupted by the press of a button. When the button is pressed, the radioactive source is immediately retracted, the door to the room opens, and the patient's needs can be handled literally within seconds. Once these needs have been satisfied, radiation treatment can be resumed.

Patients who undergo major operations and intraoperative radiation procedures recover in the main recovery room. They are transported from the Brachytherapy Suite to the recovery room on a life-support gurney that allows for full monitoring and resuscitation of the patient. Total transport time is 5 to 8 minutes.

**Patient Selection**

As in most other cases involving intraoperative radiation therapy, patients are selected for HDR-IORT when the natural history suggests that cure is possible. Many of these patients have undergone prior multidisciplinary treatment in a highly specialized setting and, for these patients, resection combined with IORT represents an extraordinary effort to effect a cure. No matter how well-defined the disease, these patients constitute a heterogeneous group with highly varied presentations and highly varied treatments.

Locally advanced primary rectal cancer recurs in the pelvis in 25% to 30% of cases, despite perioperative multidisciplinary therapy [5]. In 90% of cases, pelvic recurrences of rectal cancer involve the pelvic side wall [6]. The majority of such recurrences are diffuse, presenting only limited potential for resection with negative margins. Optimally, cases of recurrent rectal cancer being considered for curative resection should include localized recurrences or centrally located recurrences, which have a greater potential for negative margins.

Pain is a common presenting symptom of recurrence. Internal pain alone is not a contraindication to HDR-IORT. However, sciatic pain is a sign of incurable disease, and as such, precludes this form of treatment. Invasion of adjacent organs, such as the uterus, vagina, and seminal vesicles, or attachment resulting from postsurgical healing is common. In cases of centrally located recurrence, the principles guiding adjacent organ resection involvement will frequently necessitate either posterior or complete pelvic exenteration.
Patients who have known metastatic disease—ie, to the liver, lung, bone, brain, or peritoneal cavity—are excluded from consideration for surgery and intraoperative radiation. Patients are also not considered as candidates for resection if their original presentation is likely to lead to metastasis or incurable recurrence, eg, those with perforation. The established signs that a pelvic cancer is unresectable include sciatic notch invasion (and sciatic pain), major vessel involvement (ie, the common iliac vessels or vena cava), and ureteral involvement at the pelvic inlet (ie, the bifurcation of the internal and external iliac vessels). Ureteral involvement at the pelvic inlet almost invariably encompasses major vessels and is categorically unresectable. On the other hand, distal ureteral involvement in the true pelvis, closer to the ureterovesical junction, is highly amenable to resection and should not be excluded from attempted resection and HDR-IORT. Patients who are considered "unresectable" but who have not had previous treatment may be reclassified as resectable if given preoperative radiation or chemoradiation [7].

Preoperative Evaluation

Preoperative evaluation for surgery and HDR-IORT should include a thorough history and physical examination; flexible and/or rigid endoscopy, when indicated; blood work (including complete blood count); liver function tests; and tumor markers (ie, carcinoembryonic antigen, when indicated). A CT scan of the abdomen and pelvis is mandatory, in order to document truly localized disease. The most important feature of the preoperative evaluation of patients being considered for HDR-IORT is the interactive review process between the surgeon and radiation oncologist. The complex, heterogeneous nature of this patient population requires close personal interaction between these clinicians.

Goals of Surgery

The goals of surgery include curative resection, creation of an environment for adjuvant vs definitive radiation, achievement of functional reconstruction whenever possible, and reduction of surgical and radiation-related comorbidity.

Curative Resection

In our experience, the most common disease for which intraoperative radiation has been applied is locally advanced or recurrent rectal cancer. Curative resection requires a knowledge of the planes available for the resection of recurrent disease. The four planes available for pelvic resection include the visceral plane of the pelvic fascia (surrounding the mesorectum and rectum), the parietal planes of the pelvic fascia (including the musculoskeletal boundaries of the pelvic side wall and pelvic autonomic nerves), the internal iliac vascular adventitia, and the extravascular spaces, ie, obturator. In each case, the surgeon must determine by office examination, examination under anesthesia, imaging studies, and intraoperative findings those planes that will prove most appropriate for resection. In the rare case of a mesenteric or visceral recurrence, the parietal planes of the pelvic fascia may be used for resection. When the parietal planes are involved, the vascular adventitia or the extrapelvic planes may circumvent all existing recurrent disease. Rarely, an extravascular dissection is required, sacrificing the internal iliac arterial and venous distribution en bloc with the recurrent tumor, in order to resect recurrent disease with negative margins. In these resections, the sciatic nerve will be bare and will serve as the "bed of the resection."

It is important to understand that adjacent organ involvement does not preclude resection. En bloc adjacent organ resection is a hallmark of cancer resection, and is well founded in the surgical literature for malignant disease. In an effort to reduce the morbidity of such resection, conservative approaches, ie, partial vs complete cystectomy or immediate vaginal reconstruction using labial or rectus myocutaneous flaps, are being used with increasing frequency.

Reduction of Comorbidity

Concerns Related to Pelvic Dissection--A significant body of surgery for recurrent cancer involves pelvic dissection. The major consideration in pelvic dissection is the avoidance of potential damage to adjacent structures when operating to achieve negative margins of resection. For example, injury to the major pelvic side wall vessels can result in significant hemorrhage. Sharp dissection along the vascular adventitia is advocated if planes of dissection surrounding the parietal fascia are needed. An awareness of the anatomy of the internal iliac artery and veins, including the takeoff of the superior gluteal artery, is helpful in establishing planes of dissection that are outside of the vascular structures. As noted, hemostatic resections with negative margins can be achieved by complete resection of the internal iliac artery and veins on one side of the pelvis. Sharp dissection is virtually always required in attempted reresections, as previously dissected...
planes, radiation therapy, and scarring from previous operations almost never yield to blunt dissection. Injuries of the major pelvic vessels resulting from sharp dissection may bleed initially but are usually reparable. Such controllable bleeding contrasts markedly with the global hemorrhage that occurs from surgical misadventure, eg, the destruction of venous lakes often seen when primary cancers are treated by blunt dissection.

**Autonomic Nerve Injury**—The role of the pelvic autonomic nerves in the preservation of sexual, urinary, and bowel function is discussed elsewhere [8]. Briefly stated, injury to the sympathetic nerves results in disturbances of emission, ejaculation, and bladder filling, which may result in urinary incontinence. Injuries to the sacral parasympathetic nerves lead to impotence or erectile dysfunction, loss of bulbocavernous spasm, and a neurogenic bladder. A knowledge of the autonomic nerve pathways is essential to the preservation of normal sexual and urinary function. While this awareness is exceedingly important in the conduct of operations for primary rectal cancer, the anatomy of the pelvic autonomic nerves may be less evident during dissections for recurrent disease. In such instances, recurrent cancer, previous operative scarring, and the effects of prior radiation may all obscure normal anatomy within the true pelvis. Nevertheless, the preservation of a single unilateral set of both sympathetic and parasympathetic nerves can result in the preservation of normal sexual and urinary function.

**Sphincter Preservation**—The pelvic autonomic nervous system to the rectum itself represents the visceral branches of both the sympathetic and parasympathetic components of the system. These nerves are generally sacrificed along with the rectum. Despite such damage, some degree of rectal function is preserved whenever sphincter preservation is accomplished. Normal dietary fiber, biofeedback, and time are largely responsible for long-term improvements in rectal function. Many pelvic recurrences do not actually involve the distal rectum. Some recurrences may involve the rectal wall at the level of the seminal vesicles or other structures, and after resection of such recurrences is completed, the distal rectum remains unharmed. In such cases, sphincter preservation is possible by the techniques of stapled colorectal anastomosis or coloanal anastomosis.

In an effort to promote healing and preserve function, double-thickness lead shields (3 to 5 mm) are positioned in circular or elliptical patterns in order to protect the distal rectum from radiation. These shields are utilized routinely when sphincter preservation is possible and when the field undergoing radiation therapy will not be compromised.

In our initial experience with recurrent colorectal cancer, approximately one-third of all patients have had sphincter preservation.

**Sciatic or Femoral Nerve Injury**—On rare occasions, pelvic side wall dissection is possible for recurrent disease that has deeply infiltrated into the parasacral notch. In such cases, the sciatic nerve is vulnerable, and care must be exercised to avoid damage at that site. The technique of extrapelvic dissection alluded to above, ie, division of the internal iliac artery and mobilization of the pelvic side wall vessels en bloc with the recurrent tumor, can result in curative dissection. Such dissections provide direct visualization of the sciatic nerves and protection of all branches to the lower extremities.

Recurrence within the false pelvis can involve any degree of the psoas muscle, extending to the iliacus muscle or the quadratus lumborum. The course of the femoral nerve and its anterior branch is frequently compromised by the location of the recurrence. Damage to the anterior femoral nerve will result in quadriceps weakness, with impairment of both knee extension and some degree of ankle dorsiflexion. Vascular injury along the pelvic brim will significantly worsen long-term morbidity. It is a challenging dilemma in such resections to strike the right balance between leaving tumor behind and sacrificing the femoral nerve. The femoral nerve may be partially compromised with some degree of weakness that is acceptable to the patient. Certainly, the patient must be made aware prior to operation that permanent, potentially disabling weakness may be incurred.

**Technical Aspects of Surgery**

**Retractor Systems**
A reliable, self-retaining retractor system is essential for surgery performed in conjunction with HDR-IORT. In addition to all of the standard operative reasons for using a self-retraining retractor, it is an important part of the system used in such surgery to potentiate the inverse square law. Whenever possible, ie, in patients with a posterior or posterolateral recurrence, self-retaining retraction of the bladder or vagina can produce several additional centimeters of distance in air from the treatment source, further reducing the potential for toxicity.
Several self-retaining retractor systems are currently on the market. The bar-oriented systems (ie, Thompson retractor system) are somewhat better suited to surgery with HDR-IORT. In this system, the retractor blades that are placed on viscera can be adjusted to a different tension than the blades attached to the abdominal wall, thereby avoiding undue pressure and injury. Also, orientation of the blades is practically infinite, being dependent upon a universal joint. In contrast, most ring-based retractor systems distribute tension uniformly over all retractor blades, and are somewhat limited in the orientation of visceral retractor blades.

We use the Thompson retractor system because of its flexibility. In addition, the retainer for the source guide tubes that lead to our applicator system may be incorporated into the bars of this retractor at any point, further facilitating tube alignment.

Surgical Reconstruction
Our team constantly reviews numerous issues related to surgical reconstruction in an effort to reduce morbidity. As mentioned, one-third of patients undergoing resections for locally advanced or recurrent rectal cancer have had sphincter-preserving operations. To date, in seven out of the eight cases in which an anastomosis was possible, a temporary colostomy was utilized. Many of these patients have low-lying anastomoses situated in a heavily radiated field.

Pelvic side wall involvement or recurrent disease is the norm. Distal ureteral involvement may be encountered. Ureteroneocystostomy offers simple urinary tract reconstruction. Under such circumstances, a ureteral stent may be used in the postoperative period.

Ureteral Catheters
We routinely place ureteral catheters in these patients. In the presence of prior pelvic surgery, radiation therapy, and recurrent disease, ureteral catheters facilitate dissection by simplifying the identification of the ureters at various stages of the dissection.

Reconstruction of the Pelvic Floor
There are various indications for pelvic floor reconstruction. Some patients have had no prior irradiation, and a full course of postoperative radiation will be offered, making small bowel exclusion desirable. In other cases, ie, posterior or total pelvic exenteration, pelvic floor closure may be facilitated by various flaps. The decision of whether to perform a pelvic floor reconstruction is made on a case-by-case basis.

The best methods to use for pelvic floor reconstruction are also determined on an individual basis. Options include the insertion of an absorbable polyglycolic acid mesh or use of an omental pedicle graft, a rectus muscle flap, a rectus myocutaneous flap, or even a highly mobile cecum. In all cases, reconstruction should be accomplished with well-vascularized tissues. Because of the length of these procedures, plastic or reconstructive surgery is rarely undertaken.

Indications for reconstructive surgery should be well-founded, with clear-cut goals. The methods selected should consider the time that these procedures will add to the overall length of the case.

Autonomic Nerve Preservation
As previously indicated, sexual and urinary function depend upon preservation of the pelvic autonomic nervous system. In reoperations, preservation of the pelvic autonomic nervous system may prove extremely difficult when resecting recurrent disease. In patients with unilateral recurrent disease, every effort should be made to identify and preserve the hypogastric and sacral parasympathetic nerves on the opposite side, if the extent of cancer is compatible with a "lateralized" dissection.

HAM Applicator System
As mentioned previously, the goal of the IORT procedure is to deliver a large, single fraction of radiotherapy to the target area, with minimal doses to the surrounding normal tissues. This procedure is accomplished using an applicator developed at the Memorial Sloan-Kettering Cancer Center, the Harrison-Anderson-Mick (HAM) applicator (Figure 1). This applicator consists of a flexible pad of material (commonly called "super flab") that is exactly 1 cm in thickness. An array of catheters traverse the mid-plane of this pad in such a way that they are situated 5 mm from either surface of the applicator. Applicators with a wide range of sizes can be manufactured, thereby giving the radiation oncologist maximum flexibility to use an applicator that is adequately proportioned to the surface area to be treated.

Because of its flexibility, super flab can conform to the shape of the surface to which it is applied. In
particular, it is ideal for curved or complex surfaces, such as the pelvic side wall, presacral area, pubic region, or other abdominal or thoracic surfaces. Super flab is also translucent, allowing the radiation oncologist to place the applicator onto the desired surface under direct visualization of the region to be treated.

After the resection is completed, the area to be treated with intraoperative brachytherapy is delineated jointly by the surgeon and radiation oncologist. Adequate margins are placed around the surface to allow for proper anatomic coverage. The HAM applicator is then put on the surface to be treated and is fixed in place with packing or sutures, depending upon the anatomic situation (Figure 2). Dummy sources are placed in the channels of the applicator, and intraoperative x-rays are taken to document the position of the applicator and sources.

The intraoperative setting does not allow the luxury of time to calculate the dosimetry for the brachytherapy application. For this reason, we have prospectively developed an atlas of dosimetry that is utilized for this purpose. (The rationale as well as the details of this atlas are described below.) With the aid of this atlas, a plan for the HDR treatment is rapidly determined, and the computer-operated afterloader can be programmed in approximately 10 minutes.

The HAM applicator is then connected to the HDR remote afterloader using dedicated source guide cables that have been manufactured for this project (Figure 3). The cables attach to the HAM applicator on one end and insert into the appropriate channel of the remote afterloader on the other. In order to stabilize the source guide tubes properly, a special securing bar (the "HAM sandwich") is attached to the operating table. Clamping the source guide tubes securely eliminates vibration and other unwanted motion of the cables. This enables the source to pass smoothly from the machine into the applicator.

**HDR-IORT Delivery**

After the appropriate connections have been made, and the dwell times of the source have been programmed, HDR-IORT can be delivered. During this portion of the procedure, all personnel must leave the room. To assure patient safety, the remote-control video system is activated. Depending on the total dose to be delivered and the activity of the source, treatment time will vary. (This will be described in more detail in the following sections.) Once treatment is completed, the guide tubes are disconnected from the remote afterloader, and the applicator itself is removed. At this point, the surgical team can complete the operative procedure and close the patient.

Specially prepared intraoperative lead disks can be placed adjacent to normal tissues to augment radiation protection. These disks have proven particularly useful in protecting the distal rectum in order to allow for a primary anastomosis. Among other uses, the disks are used to protect the ureter, as well as an extraneous loop of bowel that cannot be moved far enough away from the treatment field to afford protection.

### Dosimetry Atlas

The rationale for planning from a dosimetry atlas is threefold:

1. The surgical setting makes it highly desirable to minimize the time spent in treatment planning after the target dimensions and dose prescription have been determined.
2. Although documentation radiographs are routinely taken with the applicator in treatment position, many of the dummy seeds inserted (in ribbons) to mark dwell positions are invariably obscured by the stainless steel retractors that provide access to the surgical field. Without adequate localization of source positions, meaningful dose calculations are impossible.
3. The geometrical constraints on dwell position that are built into the applicator and the dose prescription at a uniform distance (0.5 cm) from the applicator surface combine to make real-time planning unnecessary.

Because the treatment plane (or surface) is 1 cm from the source plane, a distance of 1 cm is also elected for the spacing of source positions along each catheter. (No "fine-tuning" advantage accrues from closer spacing.) Catheters are embedded 1 cm apart in the central plane of the applicator; therefore, the array of dwell positions available for each treatment comprises a square-mesh rectangular array of dimensions one greater, in each direction, than the linear dimensions (in cm) of the target area.

Our current atlas of treatment plans comprises optimized dwell-time arrays for all possible position arrays ranging from 3 x 3 to 20 x 24 (corresponding to target dimensions from 2 x 2 cm to 19 x 23 cm). Our remote afterloader permits as many as 40 source positions in each of 24 channels. Least-squares optimization methods, much used in brachytherapy planning, [9] have been invoked in the preparation of the atlas for HAM applicator treatments. In this type of optimization, dwell times
are selected that (1) minimize the sum of squares of differences between the prescription dose and
the doses achieved at points representing the target surface and (2) achieve roughly the same
percent standard deviation among doses at points representing the applicator surface as that
achieved among target-surface points.
Target-surface points are specified at 0.5-cm intervals in a rectangular mesh that extends to each
target-plane boundary, and applicator-surface points are specified along perpendicular lines drawn
to the center of each square formed by neighboring source positions. Target points are weighted
equally in the calculation, and the surface-point sum of squares is given a weighting factor of 0.5
relative to the target point sum of squares.
The fact that dwell time may be considered a continuous variable makes possible an analytic rather
than an iterative solution to the least-squares problem, ie, yielding a "global" rather than a "local"
minimum in the sum of squares of differences. Comparisons of the two optimization approaches for
other brachytherapy modalities have shown the analytic approach to produce a standard deviation
lower, typically, by about 1% [10].

Generating a Treatment Plan
As the first step in the production of a given treatment plan for the atlas, a computer program is run
to generate, interactively, coordinates of source locations, target points and "surface-dose
uniformity" points. These data are then used as input to our in-house BRACHY program for the
calculation of a two-dimensional table of the dose at each point from unit dwell time of a
full-strength source at each source location. This "individual contributions" table constitutes the
input data for the least-squares optimization program. The latter program then finds the dwell-time
array that minimizes the total of the sum of squares of differences between target-point doses and
prescribed dose, on the one hand, and the weighted sum of squares of differences between
individual doses and average dose among applicator surface points, on the other.
The effect of applicator curvature on dose in the treatment "plane" has been investigated. As a
result, in addition to planar-surface plans, plans for source positions on convex cylindrical surfaces of
both moderate and severe curvatures, in both transverse and longitudinal directions, were
generated for all array sizes involving 12 or fewer catheters. When it was found that curvatures
encountered clinically were never severe over more than a small fraction of the applicator area,
additional plans to include sizes involving as many as 24 catheters were calculated only for
moderate curvature.
In practice, the plan selected for clinical use is either planar or moderate-curvature, based on which
is closest to the estimated actual curvature of the applicator, as placed. Variations in dose are
acceptably small for intermediate curvatures when dwell-time data optimized for the nearest
planned curvature are used, as illustrated for one array size in Table 1. Dose standard deviation for
optimized plans, always less than 3% for target points and less than 5% for applicator-surface points
in the case of planar geometry is only slightly worse in the case of curvilinear geometry (less than
4% for target points and less than 7% for applicator surface points). Average dose is within 1% of
prescription dose in all cases.
All the source configurations indicated have been separately optimized for doses of 10 and 15 Gy.
Dwell times for other dose prescriptions are multiplied by the appropriate scaling factor.
Because the dosimetry atlas contains such a large number (over 3,000) of treatment plans, no
attempt has been made to create a hard copy version. Instead, the atlas is stored on a computer
disk, together with several other brachytherapy planning atlases, and retrieval of a desired plan is
facilitated by a menu-driven search program. A file is created containing the plan, as specified by
array dimensions, curvature (planar or 10-cm radius), and dose, together with patient demographic
data. The file also contains the current value of the factor by which dwell times are automatically
multiplied in the remote afterloader to correct for source decay. A printout is generated that states
the total actual time of treatment, and presents plan data in the form of console screen simulations
to verify data transferred automatically from the atlas, or in some cases, to facilitate accurate
manual entry. Printer output during and after treatment permits verification that the plan was
implemented correctly.
Finally, the plan is used to generate an isodose plot, via the BRACHY program, that displays isodose
contours in the central transverse plane, including the contour for the prescribed dose (Figure 4).
Signature approval of the attending radiation oncologist is obtained on this graphic, for
documentation purposes.

Preliminary Results in Colorectal Cancer
Most of our initial experience with HDR-IORT has been in the management of locally advanced and/or locally recurrent colorectal adenocarcinoma. We will present our preliminary results in such patients from November 1992 through July 1994. During this period, a total of 43 patients with colorectal cancer underwent surgical exploration, and 30 were treated with IORT.

In order to be selected for this program, patients were evaluated prior to surgery by the surgeon and radiation oncologist. Patients with primary, unresectable disease underwent preoperative radiation/chemotherapy to a total dose of 4,500 to 5,040 cGy. Four to six weeks after completion of this therapy, they underwent surgery in the Brachytherapy Suite. If there was no evidence of metastatic disease, resection was carried out and was followed by IORT to a dose of 1,200 cGy delivered at a depth of 5 mm from the surface of the HAM applicator.

Patients with pelvic recurrence of a previously treated colorectal cancer received individualized management. For such patients who had undergone prior radiation therapy, surgery alone was performed. If disease was limited to the pelvis, resection was combined with intraoperative radiation (1,500 cGy delivered at a depth of 5 mm from the surface of the HAM applicator). Among patients who had had no prior radiation therapy, a total of 1,200 cGy was delivered intraoperatively, followed by postoperative radiation to the pelvis to a total dose of 4,500 cGy.

We have treated 10 patients with primary unresectable rectal cancer and 20 patients with locally recurrent rectal cancer. Of these, there were 17 males and 13 females, who ranged in age from 37 to 80 years (median, 64.5 years). Table 2 shows the actual operative procedures that were performed. The one patient who underwent a subtotal resection had a small sheet of residual tumor in the presacral hollow, which was well encompassed within the intraoperative radiation field.

**Feasibility and Safety**

Our initial experience has enabled us to document the feasibility and safety of these procedures. The median follow-up is 8 months, with a range of 1 to 20 months. The entire procedure (surgery plus IORT) has taken 285 to 785 minutes to perform (median, 473 minutes).

Duration of the entire IORT procedure time has ranged from 45 to 170 minutes, with a median of 77 minutes. The actual IORT treatment delivery time has ranged from 19 to 83 minutes, with a median of 36 minutes. The difference between the overall procedure and actual IORT times relates to the time it takes to properly set up the retraction system for the normal tissues, appropriately situate the applicator, pack or suture it in place, position lead shields to protect adjacent normal structures that cannot be moved, take intraoperative x-rays under fluoroscopic control to document the applicator position, coordinate attachment of the applicator to the afterloader, and, after IORT is completed, dismantle the entire setup.

Our monitoring system has worked very well. To date, no case has had to be interrupted for a surgical or an anesthesia-related problem. All patients have remained stable during treatment and remote monitoring. In several cases, minor disruptions of the procedure were required to reattach a source guide tube, adjust the applicator position, or perform some other minor task.

During one procedure, the applicator itself was found to be defective, and the whole applicator system had to be changed prior to the delivery of IORT. In this particular case, there were multiple interruptions in therapy before the defect in the applicator was noted and the situation was rectified. In this case, the procedure time was 170 minutes.

**Complication Rates**—All patients have come through the actual procedure without difficulty, despite some very lengthy periods of anesthesia. There has been no operative mortality. Complications have been graded by the Cancer and Leukemia Group B Expanded Common Toxicity Criteria. No grade 4 toxicity has been noted to date. The complication rate (grades 2 and 3) is 36.7% for all patients, 60% for those with primary cancer, and 38% for those with recurrent disease (Table 3).

As these are patients with complex disease who have received intensive multimodality therapy, it is truly impossible to differentiate surgical from radiation toxicities. Therefore, all complications have been considered multifactorial and are referred to as comorbidity. Considering the complexity of these cases and intensity of prior therapy, we feel that the complication rates are acceptable. It should be added that the blood loss during these procedures has ranged from 300 to 5,800 cc, with a median of 1,500 cc. This range is considered within typical limits for major reoperative pelvic procedures. The length of hospital stay ranged from 7 to 39 days; the median stay of 13 days averaged 1 to 2 days longer than that for patients who were having abdominoperineal resection alone.

A sphincter-sparing procedure was done in many patients despite the use of IORT. Lead IORT shields were used to protect the distal portion of the anastomosis, while physical displacement of the proximal limb brought this portion far from the radiation therapy. When utilized, all temporary
diverting colostomies have been closed. To date, although functional results vary, no severe late radiation effects have been noted, but follow-up is still too short to make any assessment of late effects.

**Preliminary Local Control and Survival Data**

Finally, follow-up is also too short to make any durable assessment of local control or survival, and can only be considered a very early indication of the feasibility and success of this approach. The actuarial local control rate at 1 year is 79% for all patients, 86% for those with primary cancer, and 75% for those with recurrent tumors. The crude rate of local control for all cases is 83%, and for primary and recurrent cases, respectively, is 90% and 80%. The disease-free survival rate for all patients is 62% (57% and 61% for primary and recurrent cases, respectively). Overall, 62% of patients are free of distant metastases (57% of those with primary cancer and 61% of those with recurrences).

**Conclusions**

High-dose-rate intraoperative radiation therapy is both safe and feasible. Our preliminary data are encouraging, but more follow-up is needed on larger cohorts of patients. We are impressed by the ability of this technique to treat all anatomic regions encountered to date. This approach may provide a more versatile, less expensive approach to IORT than other available techniques, although all approaches have their special merits.

**References:**


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