Advances in Radiation Therapy: Conventional to 3D, to IMRT, to 4D, and Beyond

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ABSTRACT Modern advances in computers have fueled parallel advances in imaging technologies. The improvements in imaging have in turn allowed a higher level of complexity to be incorporated into radiotherapy treatment planning systems. As a result of these changes, the delivery of radiotherapy evolved from therapy designed based primarily on plain (two dimensional) x-ray images and hand calculations to three-dimensional x-ray based images incorporating increasingly complex computer algorithms. More recently, biologic variables based on differences between tumor metabolism, tumor antigens, and normal tissues have been incorporated into the treatment process. In addition, greater awareness of the challenges to the accuracy of the treatment planning process, such as problems with set-error and organ movement, have begun to be systematically addressed, ushering in an era of so-called Four-Dimensional Radiotherapy. This review article discusses how these advances have changed the way the most common neoplasms are treated now and will be treated in the near future. (*CA Cancer J Clin 2005;55:117–134.*) © American Cancer Society, Inc., 2005.

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INTRODUCTION

The greatest challenge for radiation therapy or any cancer therapy is to attain the highest probability of cure with the least morbidity. The simplest way in theory to increase this therapeutic ratio with radiation is to encompass all cancer cells with sufficient doses of radiation during each fraction, while simultaneously sparing surrounding normal tissues. In practice, however, we have been hampered by our abilities to both identify the cancer cells and target them with radiation. Over the past decade, enormous progress has been made on both fronts. Technical improvements in the application of x-rays, computed tomography scans, magnetic resonance imaging with and without spectroscopy, ultrasound, positron emission tomography scans, and electronic portal imaging—and our understanding of their limitations—have greatly improved our ability to identify tumors. Although, 15 years ago, we became aware that the position of target volumes (such as lung nodules and prostates) can be mobile and highly variable, we were poorly equipped to compensate for this motion. Similarly, when treating patients with cancers of the head and neck, we knew that high doses to the salivary glands caused dry mouth, a reduction in taste, and poor dental health, but we were unable to reduce these side effects without risking a compromise in cure.

Modern radiotherapy has evolved from non-site-specific techniques using bony anatomy and hand-drawn blocking toward specialized planning incorporating three-dimensional reconstructions of images and computer optimization algorithms. Corresponding to these changes, there has been specialization in the types of technology used for different cancer sites. For example, the obvious advantages associated with sparing the salivary glands have pushed intensity modulated radiotherapy (IMRT) in the standard treatment of head and neck cancer faster than other cancer sites. A different set of strategies was required to address organ movement and set-up error problems associated with the treatment of prostate cancer. Respiratory movements associated with lung cancer and the opportunity to reduce treatment times for adjuvant breast irradiation also resulted in the development of unique site-specific

solutions. In this review, we highlight the unique features of some of the common sites and how new technologies are being used now and are likely to be used in the near future.

IMRT: A MORE SOPHISTICATED FORM OF THREE-DIMENSIONAL CONVENTIONAL RADIOTHERAPY

Two-dimensional (2D) radiotherapy consisted of a single beam from one to four directions. Beam setups were usually quite simple; plans frequently consisted of opposed lateral fields or four-field "boxes" (Figure 1). Three-dimensional (3D), or CT-based, planning was a major advance because it took into account axial anatomy and complex tissue contours such as the hourglass shape of the neck and shoulders. While 3D planning allowed for accurate dose calculations to such irregular shapes, we were still limited in the corrections we could make. As its name implies, intensity-modulated radiation allows us to modulate the intensity of each radiation beam, so each field may have one or many areas of high intensity radiation and any number of lower intensity areas within the same field, thus allowing for greater control of the dose distribution with the target. By modulating both the number of fields and the intensity of radiation within each field, we have limitless possibilities to sculpt radiation dose (see Figure 2). Advanced treatment planning software has furthered our ability to modulate radiation dose. Instead of the clinician choosing every beam angle and weighting, computer optimization techniques can now help determine the distribution of beam intensities across a treatment volume, which often include a nonintuitive distribution of "beamlets," or 1-cm^2 areas of isointensity. For a more in-depth review of IMRT, the reader is referred to the IMRT Collaborative Working Group paper.[1]

Despite the capability of planning and calculating doses accurately to within millimeters, we are limited by our inability to identify microscopic disease with such accuracy. We are also limited by the logistic difficulties of immobilizing a patient for the duration of an IMRT treatment (typically 15–30 minutes). Patients and tumors move both as a result of voluntary movement and visceral motion such as respiration and digestion. Additionally, when we're successful, tumors shrink with treatment. Patients may lose weight over the course of the treatment, which will further alter their geometry and therefore dosimetry.[2,3] The next direction in radiation oncology is to account for this movement and is being called four-dimensional (4D) conformal radiotherapy (CRT), a logical progression from 3D CRT.

Researchers have recently developed megavoltage cone-beam CT (MVCT) for clinical use.[4] MVCT will allow the reconstruction of the actual daily-delivered dose based on the patient's anatomy in real time.[5] This will lead to "adaptive radiotherapy," the modulation of prescription and delivery based on the actual daily delivered dose, as opposed to planned dose.[6]

ADVANCES IN RADIOTHERAPY FOR PROSTATE CANCER

An increasing number of men choose radiotherapy for the treatment of localized prostate cancer because of the perception that there is a lower risk of impotence and incontinence[7] Radiotherapy also avoids the need to take as much time off from work and is thus is less disruptive in terms of daily living. The downside of radiotherapy is a higher risk of rectal complications.[8,9] Some men also are fearful that the results of radiotherapy may not be as good as radical prostatectomy. Recent data based on a large number of patients suggest that with higher doses of external beam radiation (>72Gy) or brachytherapy, the likelihood of remaining disease-free at five years is comparable with radical prostatectomy.[10] Although these data are from nonrandomized studies, they suggest that there are not likely to be large differences in the cancer control rates in the first five years after treatment. Furthermore, there is no good evidence that there are more late failures after either form of radiotherapy than after prostatectomy.[11–15]

3D CRT first became available in the mid 1980s, and by the early 1990s reports from several institutions supported the notion that compared with conventional therapy, rectal toxicity was lower than expected despite higher doses. In a multicenter Phase I-II study, investigators from the Radiation Therapy Oncology

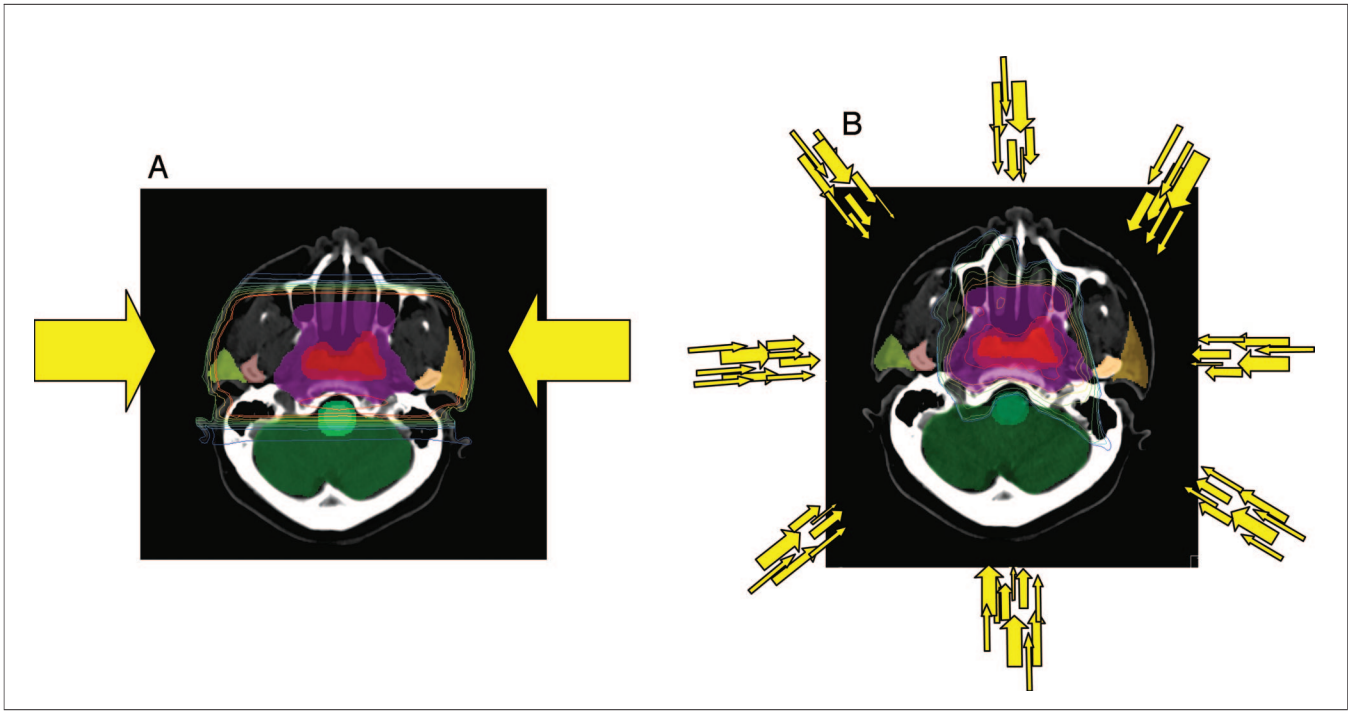


FIGURE **1** **A**, Two opposing beams of single intensities, represented by the yellow arrows, create a single-dose distribution through a nasopharynx tumor (GTV in red, CTV in purple) and normal tissue alike. **B**, Simplified schematic of intensity modulated radiotherapy allows multiple beams of different intensities from any number of angles about the patient (in this case, eight angles) to create a highly sculpted dose distribution with relative sparing of the brain, brainstem, and parotid glands. Isodose lines from actual patient.

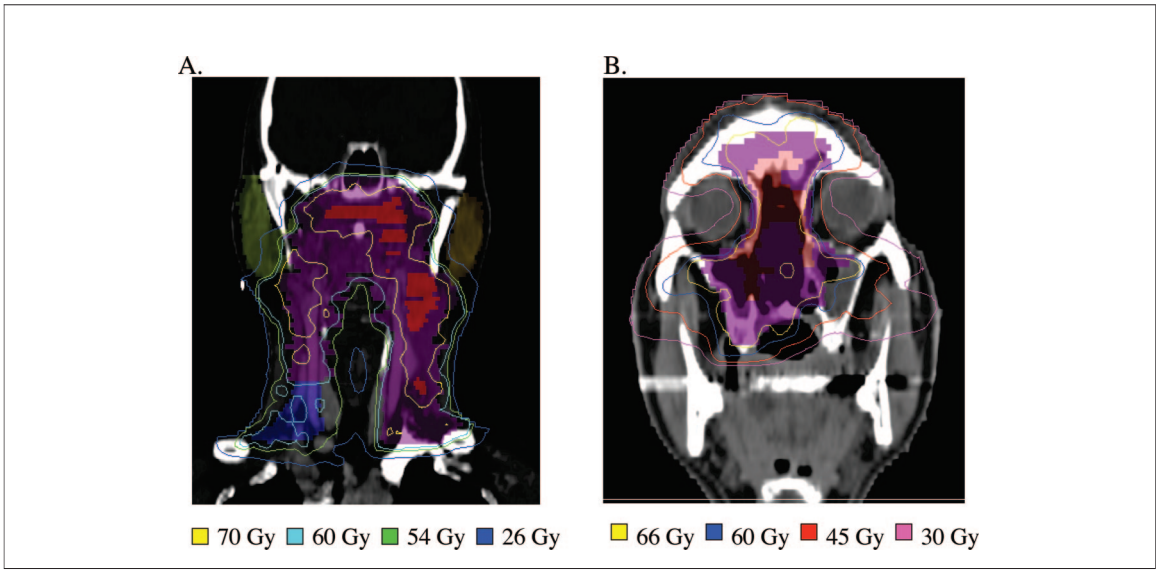


FIGURE **2** Highly Conformal Intensity Modulated Radiotherapy Head and Neck Plans.
A, Parotid sparing in a patient with nasopharynx cancer. **B**, Sparing of optic structures in a patient with sinonasal cancer.

Group (RTOG) demonstrated that radiation-induced gastrointestinal complications appeared to be substantially lower than expected at various dose levels.[16–18] Similar preliminary results were reported from two small Phase III studies using cruder techniques.[19–21] How-

ever, the side effects reported in both of these trials appeared to be somewhat higher than in the larger multicenter RTOG trial. Furthermore, with longer follow-up, the incidence of late rectal bleeding was higher on the high dose arm in one of these studies, despite the use of 3D technology for the last part of treatment (or the "boost" dose).[21] Other studies that have used 3D planning for the entire course of treatment, rather than just the last part of the treatment, had a lower incidence of gastrointestinal complications.[16,22] The major lesson learned is that the risk of late complications may be increased if the 3D radiotherapy technique does not compensate for the additional dose. External beam radiation doses in excess of 70 Gy are required to yield the best results,[10,21,23,24] but the optimal dose remains to be determined.

Although there are no prospective randomized clinical studies proving that IMRT reduces complications compared with 3D CRT, improvements in the radiation dose distribution with IMRT are easily shown.[25–29] Sequential dose escalation studies conducted at Memorial Sloan Kettering Cancer Center support the notion that the use of IMRT can reduce morbidity compared with 3D CRT.[30] In their analysis of over 772 patients who received doses in excess of 81 Gy (roughly 20% higher doses conventionally used in the past), with a median follow-up of 24 months, only 4.5% developed acute Grade 2 rectal toxicity, and none experienced acute Grade 3 or greater toxicity. Based in part on such favorable reports and with widespread availability, IMRT has become the standard therapy at many academic and private institutions. Despite the improved dose distribution associated with IMRT, the application of this technology to routine practice is limited by the increased potential for treatment errors that can result from organ movement and or daily errors in patient positioning.[31] The challenge of ever more accurately delivering radiotherapy precipitated the need for improved image-guided strategies spawning the concepts of image guided radiotherapy (IGRT) and 4D CRT. The fourth dimension in this setting refers to the impact of time on the position and/or shape of the target volume.

Moving Towards Image-Guided Four-Dimensional Radiotherapy

Recent advances in the accurate delivery of radiotherapy for prostate cancer have involved three critical steps. The first step involves selecting the proper target (eg, prostate only versus prostate and pelvic lymph nodes). Next, the target must be accurately defined using an imaging modality (usually CT) such that the appropriate fields and beam weights can be determined manually or with computerized assistance (inverse planning). Finally, a vigorous quality assurance program that allows corrections for day-to-day setup variations and target motion is crucial.

Determining and Defining the Appropriate Target Volume to Irradiate

The recent findings of a large Phase III trial conducted by the RTOG (9,413) have now made it clear that patients with intermediate to high-risk disease (defined as patients with a risk of lymph node involvement of $> 15\%$) benefit from prophylactic pelvic nodal radiotherapy administered with neoadjuvant hormonal therapy. The risk of lymph node involvement expressed as a percentage ($LN+$) in this study was estimated by the equation $(LN+) = (2/3)$ prostate specific antigen $+ [(\text{Gleason Score} - 6) \times 10]$.[32] A recently completed subset analysis also suggests that the use of a so-called mini-pelvic (MP) radiotherapy (a field usually designed such that the top of the field is at the bottom of the sacral iliac joints and typically measures approximately 10 to 11×11 cm) is not an adequate replacement for whole pelvic (WP) radiotherapy.[33] The risk of disease progression associated with MP radiotherapy was greater than with WP and not statistically different from prostate only radiotherapy. MP radiotherapy was also associated with a higher risk of gastrointestinal complications than prostate only radiotherapy and not statistically different from WP radiotherapy.

After determining that the pelvic lymph nodes require treatment, the next major question is where are they actually located in an individual patient? The standard approach has been to sim-

ply use bony landmarks and plain pelvic x-rays or CT scans to design the treatment fields that cover drainage patterns of the associated vascular structures. Unfortunately, there is a higher incidence of gastrointestinal and urinary morbidity associated with the use of a large field compared with treatment limited to the prostate. Radiotherapy that spares greater portions of the bowel and bladder and delivers the highest doses selectively to nodal areas at greatest risk should theoretically provide a therapeutic advantage. A number of imaging modalities have been incorporated into defining the nodal target volumes, including Indium-111 labeled prostate specific membrane antigen antibody (Capromab Pendetide)-based imaging and high-resolution MRI after intravenous administration of lymphotropic superparamagnetic ferrous-oxide nanoparticles.[34–36] Fusion of multiple imaging modalities such as Indium-111 Capromab Pendetide volume data sets withMRI and CT appears to improve the accuracy in assessing potential sites for salvage radiotherapy in patients with progression after radical prostatectomy (Table 1).[35] Future studies should help determine whether incorporating these or other imaging modalities will improve our ability to cure prostate cancer and/or reduce the morbidity of our treatment.

Accurately Defining the Prostate and Intraprostatic Disease

Despite the fact the CT scans are the standard imaging modality for defining the prostate for external beam radiotherapy, a number of studies have demonstrated that there is significant interobserver variation with CT, and that MRI is more precise in defining the prostate anatomy.[37–39] Clearly more work is needed in this area, with real potential to reduce morbidity by minimizing the doses of radiation delivered not only to the rectum, bladder, and penis (see discussion below) but also muscles that may control sphincter function. Accurately defining subregions within the prostate that contain the largest concentration of tumor could in theory help guide therapy because these are the regions most likely to be sites of recurrences after radiotherapy.

TABLE **1** Comparison of Positive Indium-111 Capromab Pendetide SPECT Findings Before and After Image Fusion with Magnetic Resonance Imaging or Computer Tomography

Uptake	Positive Before and After	Positive Before, Negative After	Negative Before, Positive After
Prostate bed	55	9	0
Lymph nodes	32	61	10
Seminal vesicles	0	4	3
Total	87	74	13

Modified from Schettino J, Kramer EL, Noz ME, et al.[35]

Recent studies have shown that it is feasible to selectively target areas of higher tumor burden within the prostate, known as dominant intraprostatic lesions (DIL) by applying information provided by multiple biopsies and endorectal MRI with spectroscopy.[26] An example is shown in Figure 3. In this example, these investigators demonstrated that it was technically possible to deliver 9,000 cGy to two different areas of the prostate while not exceeding the tolerance of surrounding normal tissues and hence, at least in theory, not increasing the risk of side effects.[28] Preliminary data suggest that MRI with spectroscopy may also play a role in following responses to radiotherapy and could provide an early surrogate endpoint for clinical trials comparing external beam radiotherapy with brachytherapy.[40]

After defining the prostate as precisely as possible, an even greater challenge arises from the realization that setup error and organ movement limit our ability to deliver definitive radiotherapy with the desired precision. The standard of practice for monitoring daily setup involves the use of weekly port films.[41] This in essence assumes that a 20% sampling (ie, on one of five days) of setup provides an accurate reflection of what is happening the other 80% of the time. Unfortunately, on more than one occasion patients have asked me, "why is it that on the days port films are taken, some therapists spend more time setting me up for treatment than on the other days?" This suggests that the weekly port film may be a biased sample that poorly represents the accuracy of the average setup. In addition, pretreatment port films do not allow corrections to be made to account for organ movement.

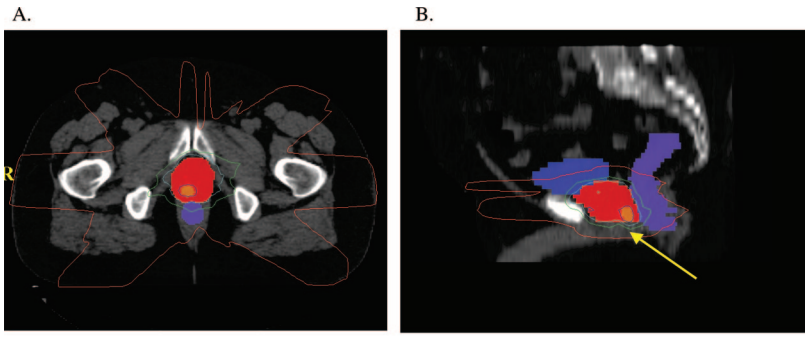


FIGURE **3** IMRT Prostate Plan.
A, Sagittal and **B**, axial treatment planning computed tomography slices of an intensity modulated radiotherapy plan of a dominant intraprostatic lesion. 7 field IMRT plan allows dose escalation of 90 Gy to small volume of tumor within the prostate (orange volume) and highly conformal dose of 76 to the prostate (red volume). Yellow arrow highlights the sharp dose gradient by the bulb of the penis. The 90-Gy isodose line covers the dominant intraprostatic lesion (shown in orange) and the 75.6-Gy line covers the prostate (shown in red). The bladder (shown in blue) and the rectum (shown in purple) are spared.

4D IGRT to Reduce Toxicity

A number of recent studies have demonstrated that the accuracy of delivering treatment for localized prostate cancer can be improved with the use of online imaging.[42–45] Investigators at the University of California San Francisco (UCSF) have shown that the gold marker seeds can be placed into the prostate for routine daily monitoring using an electronic portal imaging device (EPID) and can provide an accurate guide such that treatments can be delivered within ~2 mm. Implanted seeds don't migrate significantly if properly placed.[42] EPID-based online imaging is probably somewhat more accurate than first generation ultrasound-based systems because of less interobserver variability. Intraprostate markers appear to be particularly critical to the accurate treatment of obese patients who are at a very high risk for setup errors because of inconsistencies associated with using skin marks in these patients.[45] An example of how gold marker seeds can be used to accurately target small volume is shown in Figure 4A-D. This patient had a biopsy-proven recurrence after radical prostatectomy, and his tumor was marked with two gold seeds as shown in the AP and lateral port films (Figure 4A,B). Figure 4C is a digitally reconstructed radiograph, and Figure 4D demonstrates that the location of the tumor can be easily seen on this later EPID-based image while the patient is lying on the table immediately before each treatment. This allows a very small margin to be used so that the dose of radiation incidentally received by the rectum is minimized.

Promise of Potency Sparing Radiotherapy?

The preponderance of the peer reviewed published literature suggest that sexual function tends to be slightly better following treatment with radiotherapy compared with radical prostatectomy.[7] Of note, these findings are based on data published before the recent body of evidence that suggests radiation-induced impotence is related to the dose of radiation received by the proximal portion of the penis (bulb).[46–49] Data based on animal studies, as well as retrospective and limited prospective data from patients treated with 3D CRT and brachytherapy, suggest that the risk of impotence can be substantially reduced if the bulb (most proximal portion) of the penis is spared during radiotherapy.[46,47,49,50] The potential for radiotherapy to be the preferred approach for potency preservation is strengthened further by the relatively high response rate to sildenafil (up to 75% or more).[51,52] IMRT can be used to

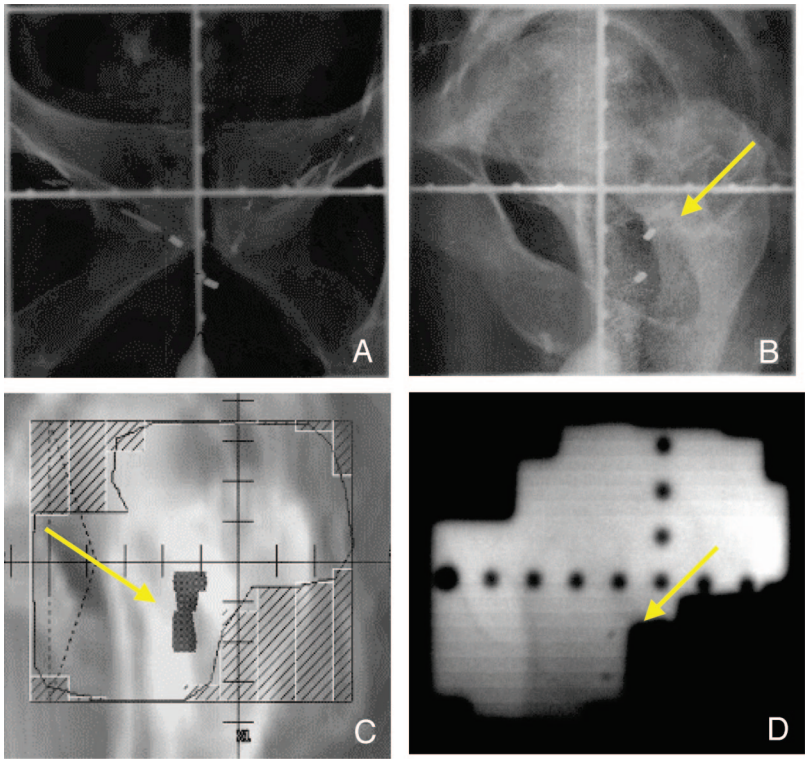


FIGURE **4** Gold Marker Seeds Can Be Used to Accurately Target the Prostate.
This patient had a biopsy proven recurrence after radical prostatectomy. His tumor was marked with three gold seeds as shown in the **A**, AP and **B**, lateral simulation films. Digitally reconstructed radiograph **C** demonstrates that the location of the tumor can be easily seen in **D**, an electronic portal imaging device based image, taken while the patient is lying on the table immediately before treatment.

substantially reduce the dose of radiation delivered to the bulb of the penis.[53,54] Figure 3A (see black arrow) demonstrates how a very sharp dose gradient can be generated between the prostate and the bulb of the penis using IMRT to potentially reduce the risk of impotence.

Conclusions About Advances in Radiotherapy for Prostate Cancer

The improvements in accurately defining the prostate and regions of dominant intraprostatic disease as well as an increased awareness about when treatment of regional disease is appropriate have ushered in a new era in understanding how to define our target volumes in men with clinically localized disease. These developments occurred concurrently with enhancements in our ability to apply radiotherapy incorporating computer optimization and online monitoring to allow corrective actions to be taken for day-to-day setup error and organ movement. In the years to follow, altered fractionation schemes and the addition of cytotoxic and biologic agents are likely to result in further improvements in our radiotherapy-based options and outcomes.

ADVANCES IN RADIATION THERAPY FOR HEAD AND NECK CANCERS

Head and neck, while an uncommon tumor site, is an important site in radiotherapy for several reasons. First, as IMRT has become widely used in the head and neck to decrease the substantial radiation-related toxicities, preliminary clinical outcome data are emerging from this area. Second, the recent publication of multiple major, practice-changing randomized trials in this area[55–58] highlight the clinical

relevance of biologic principles such as altered fractionation, chemosensitization, and molecular targeting.

Technologic Advances

Any technologic improvements must be backed by clinical data showing an actual benefit to patients. The expected benefit from advanced treatment planning such as 3D CRT and IMRT and improved patient localization methods introduced in tandem with these techniques is two-fold: (1) improvement in tumor control and (2) decrease in side effects and toxicities. The potential for an improvement in tumor control lies within the ability to increase the tumor dose, either by more accurately delivering 100% of the prescription dose to the tumor or through dose-escalation (ie, prescribing doses higher than those that have been traditionally used). Decrease in toxicity should naturally follow from a decrease in dose to normal tissue; however, this must be supported by clinical data. IMRT has been used in the head and neck region at several academic institutions, including ours, since 1995, such that we now have clinical results on a patient cohort extending back nearly 10 years.[59]

Rationale for IMRT in Head and Neck

The head and neck is an ideal site for IMRT due to the complex geometry of this area and the severity of radiation-associated toxicity. Frequently, the distance between either gross tumor (gross tumor volume) or areas at high risk for microscopic disease (clinical target volume) and critical structures such as optic apparatus, inner ear, or salivary gland is no more than a few millimeters. Traditionally it has been extremely difficult or impossible to deliver a tumoricidal dose of radiation to the target volume while limiting the dose just a few millimeters away. Furthermore, the geometric relationships are complex. Targets are not centered in a 2D plane between critical structures; rather they are eccentric in a 3D volume, such as the ethmoid sinuses in relation to both optic nerves, retinas, optic chiasm, and brain.

The toxicity from head and neck radiotherapy is among the worst seen in the field. Radiation toxicities are defined as acute or late; acute toxicities are those seen during treatment and are usually self-limited, and late toxicities are those seen months to years after treatment and can be permanent. Acute toxicities related to radiation of the head and neck region include mucositis and its accompanying dysphagia and odynophagia, salivary changes including increased salivary viscosity, and dermatitis as severe as confluent moist desquamation. Late toxicities include xerostomia, sensorineural hearing loss, and the potentially catastrophic complication of vision loss. Loss of salivary function is by far the most common of these. Xerostomia negatively impacts quality of life, interfering with speech and swallowing and can contribute to the widely feared complication of mandibular osteoradionecrosis. Because of its potential to decrease dose to normal tissue and therefore spare toxicity, IMRT has been utilized in this area since its inception, and we now have up to seven-year follow-up on patients treated with this technique.

Clinical Results

The initial UCSF experience with IMRT in nasopharynx cancer was published in 2002.[60] With a median follow-up of 31 months for 67 patients, the 4-year estimates of local progression-free survival, distant-metastasis-free survival, and overall survival were 97%, 66%, and 88%, respectively. These results compare favorably with historical controls[61] and have held up with longer follow-up.[59] Grade 2 ("moderate") xerostomia decreased from a 64% incidence at 3 months to 2.4% at 24 months, while Grade 0 ("no xerostomia") increased from 8% to 66%.

Other investigators using IMRT for head and neck cancers have also reported a low incidence of xerostomia.[62] Importantly, the reduction in xerostomia has been shown to correspond with an improvement in quality of life.[63]

Claus et al. reported on 47 patients treated with IMRT for sinonasal cancers; early toxicity data are available on 32 patients.[64,65] While long-term toxicity endpoints such as optic nerve and retinal toxicities are not available,

there was no evidence of a common acute side effect—dry eye.

While technologic advances are exciting and enticing to the practitioner, the major improvement in cancer outcomes over the last decade have been gained through exploiting the known biologic behavior of cancer. The difference in damage caused by therapeutic agents to cancer cells versus healthy cells is known as the therapeutic ratio. The greater number of cancer cells killed with the fewest number of healthy cells damaged provides a higher therapeutic ratio. Maximizing this ratio is the goal of oncology. This ratio can be modulated through several ways. The classic biologic explanation for any therapeutic ratio advantage from radiotherapy is the "4 Rs": (DNA) repair, redistribution (throughout the cell cycle), repopulation (or the rate at which cells divide), and reoxygenation (the diffusion of oxygen into a tumor as it shrinks in size). All four of these Rs have different mechanisms and happen at different rates in normal cells versus cancer cells. Fractionated radiation, or a limited dose each day over a four to seven week course rather than a large amount of radiation at once, capitalizes on all four Rs.

Hyperfractionation

Standard radiation fractionation is a course of 1.8 to 2.0 Gy/day in single daily doses. Accelerated fractionation refers to delivering the same total dose over a shortened treatment time, most often through the use of twice or thrice daily fractions. Hyperfractionation refers to the same total delivered dose over the same treatment time but in an increased number of fractions; smaller fractions are delivered more frequently than once daily. Multiple different schemes have been used in the head and neck area, most notably 1.1 to 1.2 Gy twice daily, 1.6 Gy twice daily with a planned 2 week break, and accelerated fractionation with concomitant boost, which delivers 1.8 Gy daily, 5 days a week to a large field, with a 1.5 Gy "boost" field as a second daily dose during the last 12 days.

Early in vitro work showed the potential to expand the therapeutic ratio by altering radiation fractionation,[66,67] and early trials confirmed the clinical benefit of altered fractionation in head and neck cancer[68] and other sites, most notably lung.[69] The landmark trial confirming the benefit of altered fractionation in head and neck cancer is RTOG 90–03.[55] This 4-arm, 1,073 person trial compared once-daily radiation (70 Gy in 35 fractions over 7 weeks) with 3 different altered fractionation schemes: 1.2 Gy twice daily to 81.6 Gy (68 fractions over 7 weeks), 1.6 Gy twice daily with a planned 2 week break to 67.2 Gy (42 fractions over 6 weeks), and the concomitant boost regimen of 1.8 Gy/fraction/day, 5 days/week and 1.5 Gy/fraction/day to a boost field as a second daily treatment for the last 12 treatment days (72 Gy/42 fractions/6 weeks).

Both the purely hyperfractionated regimen (1.2 Gy twice daily to 81.6 Gy) concomitant boost showed a significant improvement in local control over the control arm with no increase in long term toxicities despite an increase in acute toxicities. Since the publication of this trial in 2000, twice-daily radiation for all or part of the treatment course is considered standard when treating moderately advanced squamous cell head and neck cancers with radiation alone. More advanced cancers should be treated with a combination of chemotherapy and radiotherapy.

Concurrent Chemotherapy and Radiation

Organ-preservation therapy became a standard treatment option for laryngeal cancer after the publication of the VA Larynx Trial in 1991.[70] This landmark trial randomized patients to definitive surgery (with postoperative radiation as needed) versus two cycles of cisplatin and 5-fluorouracil followed by an assessment for response, with a third cycle of chemotherapy and radiation therapy for responders or salvage surgery for nonresponders. This regimen became the standard organ-preservation regimen until it was directly compared with concurrent chemoradiotherapy in RTOG 91–11. This three-arm trial randomized 547 patients to 1) induction cisplatin plus fluorouracil followed by radiotherapy, 2) radiotherapy with concurrent administration of cisplatin, or 3) radiotherapy alone. The rates of laryngeal preservation, the primary endpoint,

were 75%, 88%, and 70%, respectively. Local control was also significantly improved in the concurrent arm, with local control rates of 61%, 78%, and 56%, respectively. For patients similar to those included in the study (ie, those with Stage III of IV tumors without significant invasion of the base of tongue or gross destruction of thyroid or cricoid cartilage), concurrent chemoradiotherapy with cisplatin is now the standard of care. Organ preservation has become more common in other subsites within the head and neck as well, including the hypopharynx[71] and oropharynx,[72] after randomized trials have shown no increased benefit from primary surgery.

Oropharyngeal cancer has notably become less of a surgical disease over the last five years, as cure rates with organ preservation therapy are widely recognized to equal those achieved with surgery followed by postoperative radiation therapy.[72,73] Preliminary, single-institution results of IMRT in the treatment of oropharynx cancer have recently been published, both for radiation alone in early-stage cancer[74] and chemoradiation in locoregionally advanced oropharyngeal cancer.[75] Results in this site, as in the nasopharynx, have been quite encouraging, with two-year locoregional control rates of 91% for early-stage disease and 89% for advanced stage in these small series of selected patients. To further investigate IMRT in the treatment of both oropharyngeal and nasopharyngeal cancer, the RTOG is currently conducting two single-arm, Phase II trials testing the feasibility of IMRT delivery in multi-institutional settings. Xerostomia will be prospectively evaluated in both trials.

While neoadjuvant chemotherapy followed by radiation alone is no longer a standard treatment option for head and neck cancer, neoadjuvant chemotherapy followed by concurrent chemoradiotherapy has not been directly compared with concurrent chemoradiotherapy in a multicenter randomized trial. A valid concern is the inevitable delay in treatment that occurs during the approximately two weeks necessary for radiation planning. A single cycle of chemotherapy may be given in this interval and will usually result in both debulking of the tumor and a decrease in the patient's ability to tolerate a full course of chemoradiation; patients who have received a cycle of chemotherapy before starting radiation are more likely to experience radiation-related toxicities earlier and are more likely to require treatment breaks. It is not known if any advantage to giving an early cycle of chemotherapy can offset the known disadvantages of treatment breaks and delays[76,77]and the hazards of accelerated repopulation.[78,79]

Concurrent Chemoradiotherapy in the Postoperative Setting

While it logically follows that if concurrent chemotherapy confers a benefit to radiation in the definitive setting, it would add a similar benefit in the postoperative setting; this had not been shown until the publication of two landmark trials earlier this year.[57,58] Two similar trials, one in the United States and one in Europe, randomized high-risk, postoperative patients with head and neck cancers to radiation alone versus concurrent chemoradiation with cisplatin, 100 mg/m2 every 3 weeks. In both studies, the chemoradiation arm demonstrated a local control benefit, and in the European trial, the chemoradiation arm showed an overall survival advantage as well.

Biologic Targeted Therapy

The epidermal growth factor receptor (EGFR) has been an attractive target for therapy because of its upregulation in nearly two-thirds of solid tumors and its association with malignant phenotypes. Preclinical models demonstrated enhancement of radiation sensitivity with blockade of the EGFR, and it was hypothesized that a combination of anti-EGFR therapy with radiation would lead to improved outcome in epithelial cancers such as those of the head and neck. A recent randomized trail of 424 patients affirmed this hypothesis. Patients with advanced head and neck cancer were randomized to received radiation alone or with cetuximab (also know as C225, or Erbitux), a monoclonal, chimeric murine-human antibody. The addition of cetuximab increased two-year survival from 55% to 62%, with a near doubling in median

survival from 28 to 54 months. Skin toxicity was increased, however, with Grade 3 to 4 skin reactions in 34% of patients on the cetuximab arm versus 18% on the radiation alone arm.[76,80] While these results need to be confirmed by further studies, cetuximab is now a reasonable option for radiation patients with advanced cancer who are unsuitable for or unable to receive chemotherapy.

The combined role of chemotherapy and hyperfractionation is unknown. This question is being addressed by the ongoing RTOG study 01–29, which randomizes patients to concurrent cisplatin with standard fractionation radiation or concurrent cisplatin with the concomitant boost regimen or accelerated fractionation. A question for future trials is the role of cetuximab with concurrent chemoradiation.

ADVANCES IN RADIOTHERAPY FOR BREAST CANCER

Breast cancer is the most common form of nondermatologic cancer in women.[81,82] As more women choose breast conservation therapy (BCT), breast radiation therapy is a large component of a radiation oncology practice. The advances in radiation technology have made standard radiotherapy much more precise and discriminating.

Until recently, the total time and dose of standard radiation had not significantly changed in over 20 years with the exception of a possible 10 to 16 Gy electron boost to the surgical cavity.[83,84] Nagging questions persisted, driving current clinical research into a new era, particularly for women with early-stage breast cancer who are candidates for BCT. The key questions are: can we shorten the duration of standard breast irradiation, can we treat a portion of the breast instead of the whole, and can we select women who can avoid radiotherapy altogether?

The issue of avoiding radiotherapy in BCT has been explored in the past and recently revisited in two current articles published in the *New England Journal of Medicine*.[85,86] Before these articles, the National Surgical Adjuvant Breast and Bowel Project-21 trial randomized approximately 1,000 women of all ages with invasive tumors less or equal to 1 cm treated with lumpectomy and axillary node dissection to radiotherapy and tamoxifen, radiotherapy and placebo, or tamoxifen alone. The cumulative incidence of ipsilateral breast tumor recurrence was 2.8%, 9.3%, and 16.5%,[87] respectively. Distant metastases and overall survival were the same for all groups. This study did not select patients based on age, estrogen receptor status, or grade. The first of the two *New England Journal* articles, from the Princess Margaret Hospital, randomized 769 women aged 50 years or older with node negative invasive breast cancer 5 cm or less to breast irradiation and tamoxifen versus tamoxifen alone. Again, there was no difference in the rates of relapse or overall survival; however, local recurrence in the breast and axilla were significantly reduced in the radiotherapy arm including a subgroup analysis of those with tumors less than 2 cm.[86] The only study where the authors concluded that it may be reasonable to omit breast irradiation and treat with tamoxifen alone randomized 636 women who were 70 years or older with estrogen receptor-positive, early-stage breast cancer (node negative and $\leq$2 cm) to breast irradiation plus tamoxifen or tamoxifen alone and at five years median follow-up showed a rate of local or regional recurrence rate of 1% and 4%, respectively, with no significant difference in the rates of mastectomy, distant metastases, and overall survival.[85] The main criticism of the study is that longer follow-up is needed.

The eligibility for BCT is assessed by clinical examination, imaging studies, pathology, individual preference, and expected cosmetic outcome (best with small tumor to large breast size). Still today, women who qualify for breast preservation may opt for a mastectomy to avoid the 5 to 6.5 weeks of Monday through Friday radiotherapy. Radiotherapy is often at the tail end of surgery and months of chemotherapy, presenting a final test of endurance and a new source of anxiety. Distance from the radiation facility plays a factor in the decision making process, as the inconvenience of daily transportation and the time commitment must be integrated into an already busy schedule.[88]

Two current aspects of breast irradiation are hot topics and have provided the momentum for ongoing and future investigations. The first of these is the role of advanced treatment techniques in producing conformal homogeneous dose throughout the breast while attempting to protect the critical structures such as the ribs, lung, and heart. The second is the provocative topic of shortening the course of radiotherapy. The current climate for addressing accelerated treatment is often mixed with the concept of only treating a portion of the breast, or partial breast irradiation, instead of the whole breast. In part, this is because the design of the popular devices used to deliver the radiation can only treat the part of the breast at highest risk of recurrence—the surgical cavity and the adjacent tissue. Candidates for accelerated irradiation are low-risk, early-stage patients for which a variety of definitions apply.

3D CRT and IMRT

As mentioned in previous sections, CT-based treatment planning in conjunction with new capabilities of the linear accelerator has revolutionized radiotherapy for breast cancer. Targets and avoidance structures can be easily defined on axial imaging. The goal of treatment planning software algorithms is to produce discriminating radiation fields that conform to the breast, chest wall, and/or regional nodes to achieve a homogenous dose to the breast and decrease or avoid dose to the ribs, lung, and most importantly the heart. This technology allows us to adapt the treatment to fit the variety of breast and chest wall shapes.

More frequently, radiation oncologists are using IMRT to treat the breast or chest wall because of the possible decreased dose delivered to the heart and lung.[89–91] Long-term follow-up studies are needed to confirm the clinical benefit of these improvements in dose delivery. Previously, breast irradiation consisted of two fields, one on each side of the breast, generated from 2D planning techniques. With IMRT, we typically use six to eight fields or more (Figure 5). At UCSF, we utilize a type of IMRT called segmental multileaf collimator IMRT (SLMC-IMRT), in which each field consists of a series of multileaf collimator shapes delivered from the same angle. The multiple segmental fields at select orientations are under computer control, and the radiation is only turned on when the multileaf collimator leaves are fixed in place. In general, several plans are generated for each patient. More fields are not necessarily better using SLMC-IMRT for breast and chest wall irradiation and require longer treatment times and possibly more scatter radiation.

Accelerated Breast Irradiation

The Canadians have pioneered hypofractionated radiotherapy in early-stage breast cancer patients. This technique, used to treat the whole breast, delivers a slightly higher single daily dose (>2.0 Gy) of radiation but decreases the total number of treatments to 16 over 3 weeks rather than 25 to 28 over 5 to 6 weeks. A large randomized trial compared standard daily doses of whole breast radiation (2 Gy $\times$ 25 fractions) with a hypofractionated course of radiation (2.66 Gy $\times$ 16 fractions). With a median follow-up of 6 years, the local failure rate was 3% in both arms with no difference in cosmesis or toxicity.[92] While hypofractionation is not as popular as standard whole breast irradiation for young patients in the United States due to the lack of long-term toxicity data, select institutions including ours have begun to offer it in select cases. In our experience, patients tolerate hypofractionation well, in fact, maybe even better than standard fractionation.

There are several methods for delivering accelerated partial breast irradiation (APBI), including intracavitary and interstitial brachytherapy and 3D conformal external beam and intraoperative radiation. All of these techniques are investigational and are being tested on prospective, multi-institutional randomized trials. Interstitial brachytherapy involves implanting multiple catheters into the high-risk portion of the breast in the operating room and postoperatively loading these catheters with high dose rate radiation sources to a dose of 34 Gy in 10 twice-daily fractions with high dose iridim-192 over 5 days. Up to five-year follow-up data suggest that this technique is comparable with whole breast irradiation in terms of safety and

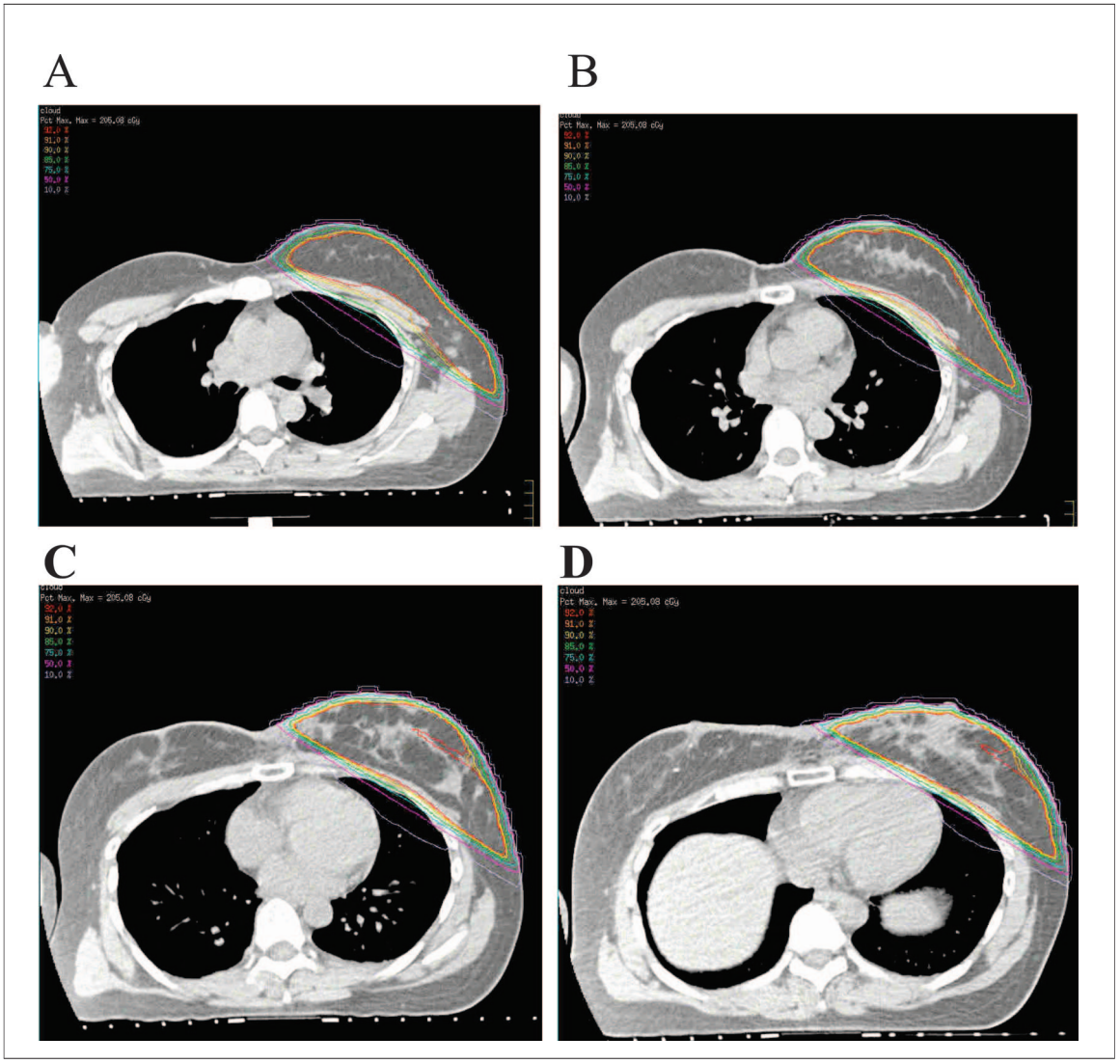


FIGURE **5** Six- to Eight-field Intensity Modulated Radiotherapy–Segmental Multileaf Collimator Technique Leads to Homogenous Dose Distributions Throughout the Breast.
A to **D**, Axial slices from superior to inferior.

efficacy.[93,94] Intracavitary brachytherapy uses the new balloon-based catheter device, Mammosite (Proxima Therapeutics, Alpharetta, GA), which is Food and Drug Administration approved for safety and performance based on a Phase I/II eight center study with 43 patients.[94,95] The balloon is inserted into the lumpectomy site at the time of surgery in the operating room and inflated with saline to conform to the topography of the cavity (Figure 6). Outside of the operating room, the balloon is loaded with a single radioactive point source to a dose of 34 Gy in 10 twice-daily fractions over 5 days with iridium-192. The balloon is then deflated and removed. Mammosite is much simpler to use, and many radiation facilities have started using Mammosite routinely in their practice, despite the small number of patients in the Phase II trial.

The other two types of APBI use external beam radiotherapy. Intraoperative radiotherapy delivers low energy electrons or 50 kV photons to the surgical cavity with a single dose of radiation in the operating room.[96–98] The fourth method uses a conventional external beam source and 3D-conformal or IMRT planning software to

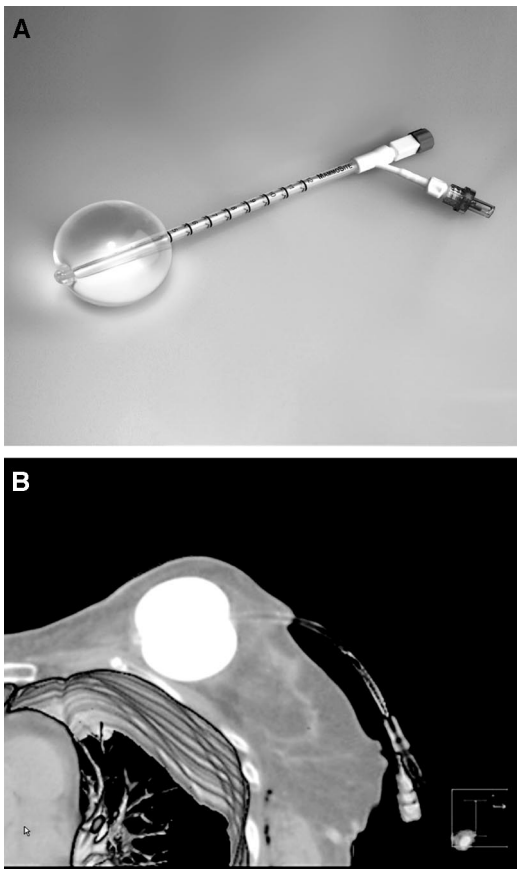


FIGURE 6 **A**, The Mammosite balloon-based catheter device. **B**, A computed tomography scan of the balloon inflated with sterile saline. Photos courtesy of Mammosite.

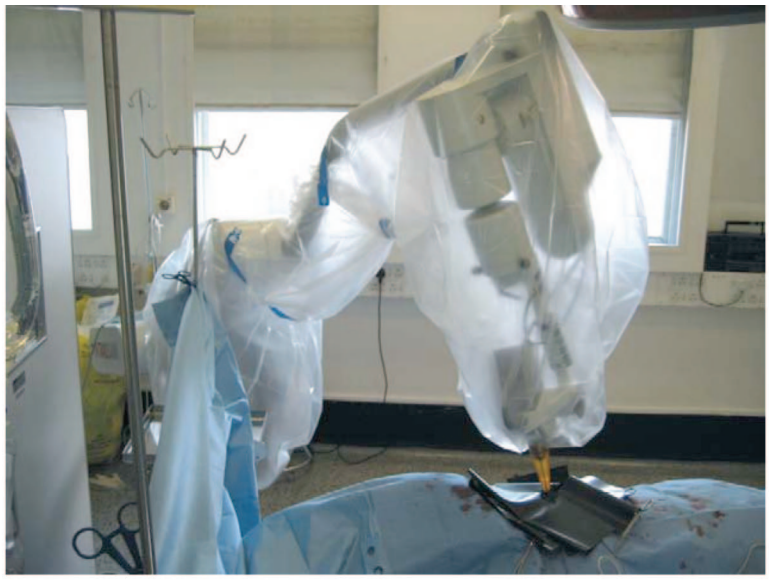
deliver 3.8 Gy per fraction for 10 twice-daily fractions over 5 days after the patient has healed from surgery.[99]

Given the intense interest in these techniques, the National Surgical Adjuvant Breast and Bowel Project and RTOG are opening a trial that randomizes patients with early-stage breast cancer to standard whole breast radiotherapy or APBI. If randomized to APBI, one is further randomized to either (1) interstitial implants, 2) Mammosite, or (3) 3D-conformal radiotherapy.[100] The trial has been approved by the National Cancer Institute and should begin accruing later this year.

The Targeted Intraoperative Radiotherapy Trial is a Phase III international randomized, controlled, multicenter trial investigating superficial, intracavitary radiation with a new device called Intrabeam (Zeiss Surgical, Oberkochen, Germany).[101] Intrabeam delivers low energy x-rays (50 kV) using a choice of spherical applicators that conform to the surgical cavity and treat to a depth of 1 cm, after which the dose falls off steeply. Once the device is inserted and the edges of the cavity are pulled around the applicator to be in contact with the surface, the time of treatment varies from 20 to 40 minutes depending on the size of the applicator (Figure 7). The dose falls from 20 Gy at 0.2 cm to 5 Gy at 1 cm, which translates to a treated area of tissue in a 1-cm circumferential rim around the resection rite. Patients must be carefully selected for tumors that are likely to have only this limited area at risk if the overlying skin is within this 1-cm perimeter, serious skin injury may occur. Alternatively, an irregular cavity or hematoma/seroma may place the target tissue too far from high-dose area, potentially increasing the risk of disease relapse.

The Targeted Intraoperative Radiotherapy Trial randomizes patients to standard whole-beam radiotherapy (5 to 6.6 weeks) versus a single dose of radiation with this investigational device. Sentinel lymph node biopsy is performed at the time of the excision. Patients may require further surgery, chemotherapy, and/or standard whole breast irradiation if the pathology reveals high-risk features such as an extensive intraductal component, positive lymph nodes, positive surgical margins, or high histological grade. The primary endpoint of the study is local control. Secondary endpoints are site of relapse, relapse-free and overall survival, and late toxicity.

There is intense pressure to bring a new era of breast irradiation into fruition from patients, physicians, and manufacturers of new devices. It is important that we moderate our enthusiasm. Lack of long-term data from large-scale, multi-institutional, randomized trials, limited efficacy data, and lack of establishment of equivalency of APBI and whole breast irradiation create uncertainties in the expected results.[100] The foremost concern is progression-free outcome and secondarily, long-term cosmesis of the breast. Breast cancer can remain dormant for years before becoming clinically apparent, so long-term follow-up is mandatory. Because late effects such



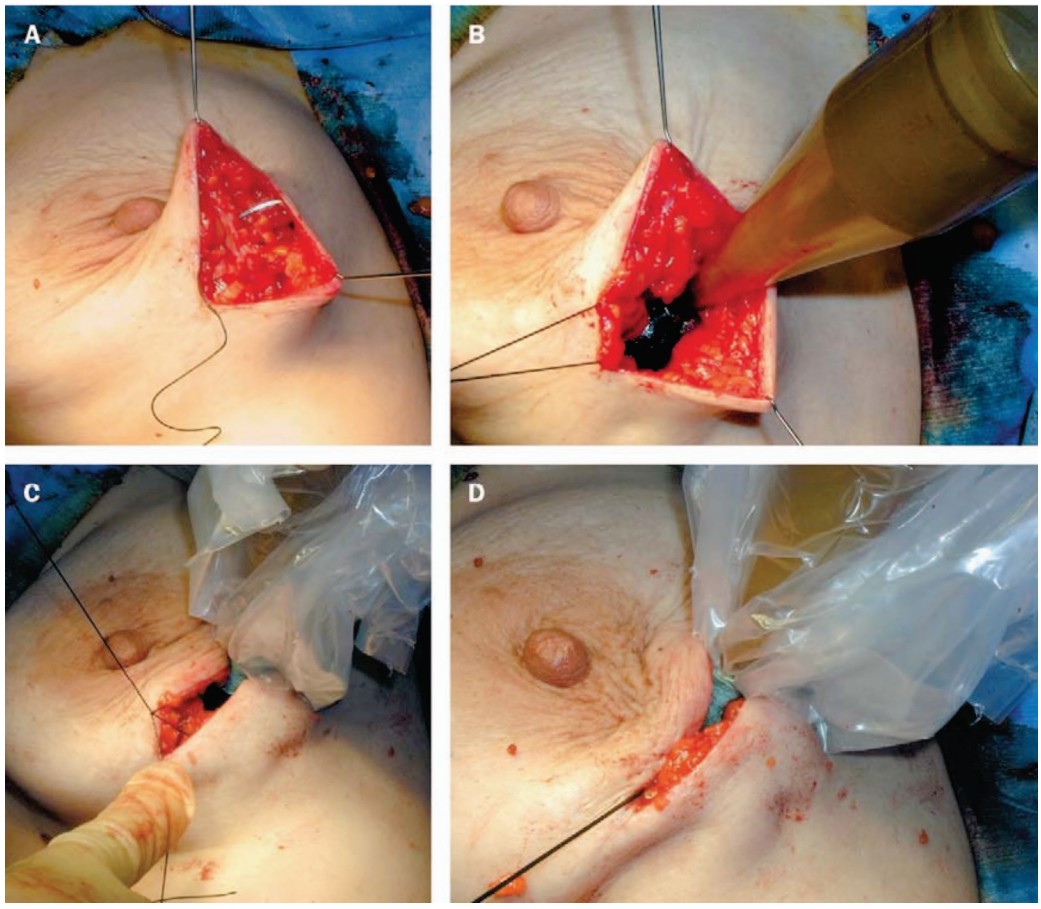


FIGURE 7 **Top**, Intrabeam device delivering radiation therapy in the operating room. **A-D**, Intrabeam inserted into the surgical cavity. Reprinted with permission from Vaidya et al.[101]

as fibrosis, telangiectasias, retraction, and fat necrosis often become clinically apparent as late as 10 years after treatment, follow-up of at least 10 years is mandatory to fully asses the long-term side effects of treatment. In locations where conventional fractionated breast radiation therapy is readily available and accessible, APBI will not be recommended by most practitioners outside of the setting of clinical trials until long-term safety and efficacy data are available. The RTOG has recently opened a Phase I/II trial to evaluate 3D CRT confined to the lumpectomy cavity (for more information, visit www.rtog.org).

Other uncertainties of APBI are the optimal dose and fractionation schemes, the basic principles of radiobiology. The various techniques differ in volume of breast tissue irradiated, and it is crucial the exact site of relapse is documented. There are quality assurance considerations such as individual practitioner's techniques, consistency of treatment planning, and dose homogeneity. Again, patient selection has a tremendous impact on the interpretation of trial results. As of now, we do not know who can avoid radiotherapy altogether. Advances in molecular profiling and new imaging techniques may eventually help us select those fortunate patients in the future.

SUMMARY

In summary, there have been several exciting technical advances in radiation therapy, including IMRT, IGRT, and 4D RT, and several investigational new devices in the treatment of breast cancer. These modalities are more commonly finding their way into clinical practice, and early data are emerging on their effectiveness. Data have recently become available confirming the advantages to concurrent chemotherapy and targeted therapies such as cetuximab with concurrent radiation in the head and neck, adding to data about the role of combined modality therapy in other sites, such as lung and colorectal cancers, gained over the last decade. We are optimistic that the next decade is likely to yield more advances regarding the role of radiotherapy in an increasingly multidisciplinary oncology environment.

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