RADIATION MEDICINE INNOVATIONS FOR THE NEW MILLENIUM

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Purpose of the Study: To review technological advances in the field of radiation oncology in the management of benign and malignant diseases.

Basic Procedures: We reviewed major advances in the field of radiation oncology in the past decade with special emphasis on reduction of treatment related toxicities, and technological improvements in planning and delivery of radiation. Modalities reviewed include computerized three-dimensional conformal treatment planning, stereotactic radiosurgery, intensity-modulated radiation therapy, ultrasound-guided transperineal permanent brachytherapy of the prostate, and high-dose rate brachytherapy.

Main Findings: There have been major technological advances as evidenced by a decrease in treatment-related toxicities and better target definition resulting in higher local control rates.

Principal Conclusions: Significant improvements in technique and equipment have firmly positioned radiotherapy as major artillery in the fight against both benign and malignant diseases. (*J Natl Med Assoc.* 2003; 95: 55-63)

Key words: innovation ♦ radiation therapy ♦ cancer ♦ technological advances

Recent technological advances are having a profound impact on radiation treatment of cancer. New equipment and enhanced computer technologies foster the radiation oncologist's ability to deliver radiation more precisely, increasing the dose to tumor targets and reducing the dose to normal tissues and critical structures. New treatment protocols have the potential to improve tumor control and cure rates with reduced complications. Some of the most significant technological developments of the past decade are highlighted in this article. It is the intent of the authors to elucidate some of these exciting areas of clinical radiotherapy such that practicing clinicians develop a greater comfort level when referring patients to a radiation oncologist.

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COMPUTERIZED THREE-DIMENSIONAL CONFORMAL TREATMENT PLANNING

The ability to define tumor volume accurately and to tailor radiation dose to this volume has been a constant challenge for the radiation oncologist.

The introduction of axial computerized tomography (CT) technology in treatment planning has allowed for increasingly more precise anatomic definition of tumor volumes and surrounding normal tissues. The CT data set provides the basis for a three-dimensional rendering of tumor volumes and more accurate radiation dose calculations. The individual CT slices that define targets and normal tissues can be stacked like dishes, and the reconstructed figures provide images that can be viewed from any angle. Although research in three-dimensional (3-D) dose calculations and display began as early as 1973,[1] it is only within the past four years that functional 3-D radiation treatment planning systems have become available to community cancer centers; the full potential of these systems in now being realized. The importance of three-dimensional CT-based treatment planning on tumor control and reduced treatment complications has been recognized.

In lung cancer, researchers at Memorial Sloan-Kettering Cancer Center compared conventional and 3-D treatment planning for predominately stage III, non-small cell lung cancer (NSCLC). They were able to deliver higher doses of radiation to the tumor volume with the 3-D technique, while treating less volume of normal lung, and postulated an improvement in the therapeutic ratio with the use of 3-D technology.[2] Colleagues at the University of Michigan at Ann Arbor demonstrated that doses in excess of 84 Gy to limited tumor volumes using 3-D planning are possible with acceptable toxicity.[3] Dose escalation is, therefore, thought to be an important factor in improving local control and is believed by some to be essential in improving long-term survival. In addition, quantitative ventilation/perfusion and single photon emission computed tomography (SPECT) imaging can also complement the information provided by the CT scan in order to design treatment ports that spare larger volumes of functional lung.[4]

For prostate cancer, 3-D treatment planning has allowed dose-escalation in excess of 90 Gy. It is unknown whether this will translate into greater long-term local control and survival. A recent article reported an actuarial survival and biochemical PSA (prostate-specific antigen) failure -free rate at eight years of 95% and 85%, respectively.[5] Toxicity appeared to be reduced. Of more than 700 patients treated, the actuarial risk of Radiation Therapy Oncology Group (RTOG) grade 3-4 rectal complications was 3% at five years.[6] In addition, up to two-thirds of patients maintained sexual potency following external beam radiation using this technology, contributing to a superior quality of life.[7] An ongoing phase I/II RTOG trial is underway and may clarify the potential benefits of 3-D treatment planning for localized prostate cancer.

In head and neck cancer, xerostomia (dry mouth) is often a long-term complication from treatment to the salivary glands. This can be minimized with 3-D treatment planning. Eisbruch et al. demonstrated that it is feasible to treat sites of disease and spare the contralateral parotid gland, without compromising local control.[8] Tumors in this region of the body are often located close or adjacent to critical structures such as the spinal cord and major salivary glands. The use of 3-D planning has proven helpful in minimizing toxicity and complications in these challenging patients.[9]

For hepato-biliary tract malignancies, 3-D treatment planning has been able to limit the amount of normal liver treated and minimize development of radiation-induced liver disease (RILD).[10] Doses in excess of 80 Gy have been safely delivered to localized hepatic tumors with only 5% (1 of 21 patients) developing RILD, an improvement over predicted normal tissue complication probability models.[11,12] Although this sophisticated computational technology is now readily available, the degree of accuracy in the planning and daily delivery of radiation treatment is extremely critical, and demands highly trained and meticulous personnel.

STEREOTACTIC RADIOSURGERY

Stereotactic radiosurgery (SRS) is a specialized application of 3-D conformal treatment planning for treatment of an assortment of brain tumors and arteriovenous malformations. The technique delivers a high dose with millimeter tolerances, with a

sharp dose gradient. Dr. Lars Leksell, from the Karolinska Institute in Stockholm, Sweden, first described SRS in 1949.[13,14] However, practice of the technique did not experience explosive growth until the 1980s. SRS can be accomplished using one of three radiation modalities—gamma knife, linear accelerator (LINAC), or heavy particles such as protons.

With the advent of IMRT-based treatment planning, intensity modulated radiosurgery (IMRS) has yielded conformal plans that are easily reproducible.[15] The gamma knife is a large device that uses a fixed hemispherical assembly of 201 cobalt-60 sources focused at a defined point. Plugging the apertures of selected cobalt sources results in the shaping of the desired radiation field.

The linear accelerator generates megavoltage x-rays and electrons that are used to provide routine external beam radiotherapy. An SRS treatment may typically involve rotating the radiation beam in arcs around the patient. Since linear accelerators are readily available in radiation oncology centers, LINAC-based radiosurgery is most commonly used.

The use of heavy particles or protons is sometimes referred to as Bragg-peak therapy. This requires bulky and expensive particle generators called cyclotrons or synchrotrons. Their singular advantage is a rapid decrease in radiation dose beyond the focus (Bragg peak) depth. Currently, there are a limited number of such facilities in the United States capable of treating patients.

Because of small target volumes, SRS demands high precision in all aspects of treatment planning and delivery. A special headframe (often screwed into the patient's cranium) is used in conjunction with CT and MRI imaging to provide precise localization information, and is utilized to position the patient during treatment. Modern planning systems allow for fusion of an MRI image with the corresponding CT slice in order to maximize the strengths of each imaging modality.

Most published reports of SRS have focused on its use to treat primary malignant brain tumors, metastases from other solid tumor sites, schwannomas, and arteriovenous malformations.

For glioblastoma multiforme (GBM), SRS has been utilized as a form of boost therapy and has yielded two-year survivals approaching 30%, without significant acute toxicity.[16,17] However, more than 10% of patients may develop clinically detectable radionecrosis. Compared to historical controls, the use of SRS as a boost to external beam radiotherapy is superior to external beam radiotherapy alone.[18,19] Patients with lower pathologic grade, younger age, better performance status, smaller tumor volume, and unifocal disease benefit most from SRS.[20,21] This subgroup is being further investigated in the RTOG 9305 trial.

In the treatment of brain metastases, most studies have suggested patients with controlled extracranial disease, higher performance status, greater disease-free interval, and age <70 are more likely to benefit from SRS. Median survivals of 7 to 18 months are reported.[22,23] Emerging data also suggest that SRS is more cost-effective than surgical resection for isolated brain metastases.[24-27] The RTOG 9508 trial may help clarify if SRS is beneficial following whole brain radiation.

Vestibular schwannomas (or acoustic neuromas) are controlled locally (95%) following SRS, although most lesions may take up to two years to show an objective response. The most serious toxicity is trigeminal neuralgia, which can occur in up to one-half of patients.[28,29]

Arteriovenous malformations have also been managed effectively with SRS. A complete radiographic response may take several years, but most patients experience symptomatic relief much sooner.[30-34]

Movement disorders and trigeminal neuralgia have been treated successfully in patients who have failed more conventional medical and surgical approaches. In most cases, resolution of tremor or neuropathic pain has been seen within one to two months of treatment.[35-37] This remains a fertile area of ongoing research and efforts are being made to evaluate this approach in the first-line setting.

INTENSITY-MODULATED RADIATION THERAPY

Intensity-modulated radiation therapy (IMRT) is a revolutionary new technology in the planning and delivery of external radiation. This methodology varies the intensity of the radiation beam across the treatment field, enabling the radiation oncologist to deliver high doses of radiation to volumes that tightly conform to irregular tumor geometries. Nearby, normal structures benefit from less exposure, therefore, resulting in less toxicity.

IMRT also is ideal for treating regions of the body that have uneven surfaces (e.g. head and neck sites) by homogenizing the dose that reaches the tumor. This minimizes the "hot" and "cold" areas in the tumor volume and potentially improves local control. A common technology to modulate the radiation beam utilizes multi-leaf collimators. The multi-leaf collimator consists of small, independently moveable, high-density rods that can be programmed to sequentially block the radiation field over short time intervals. In this manner, the radiation intensity of the volume under the rod can be differentially modified or "modulated." High-speed computers enable optimization of the rod positions with time and produce the radiation distributions prescribed by the radiation oncologist.

IMRT has been used to treat head and neck cancer successfully for more than five years; clinical experience has been positive.[38-40] The primary reason for using IMRT in these cases is to spare critical structures, such as the normal parotid gland and spinal cord. Without this technique, it is sometimes difficult to limit the dose to these structures. If the entire parotid receives greater than 30 Gy, the risk of xerostomia is dramatically increased. In these patients, dental caries, difficulty with eating, and phonation[41] pose major challenges to the treating physician. Various drugs have been used to reduce xerostomia, with only moderate efficacy.

IMRT can produce the desired radiation coverage of the primary tumor target and nodal volume while simultaneously avoiding overexposure to the spinal cord and other adjacent normal tissues. The potential for treatment set-up errors is reduced if complex treatment field arrangements are not utilized.

For prostate cancer, the critical structures at risk are the bladder, rectum, and small bowel. The utilization of IMRT in this disease is an attempt to decrease gastrointestinal and genitourinary morbidity. Work done by Shu et al. compared toxicity profiles in patients treated with 3-D conformal therapy vs. IMRT in patients that received $\geq$82 Gy. At Memorial-Sloan Kettering Cancer Center, Zelefsky and colleagues have been instrumental in dose escalation studies where radiation doses up to 90 Gy were delivered to the prostate. Without the use of IMRT, radiation dose to the prostate would have been significantly limited to 70-72 Gy secondary to unacceptably high bowel and bladder toxicity.[42] Data appear to suggest an improvement in the therapeutic ratio, which allows dose escalation and a decrease in late RTOG grade 2 or higher rectal toxicity.[43-48]

For pancreatic cancer, Emory University School of Medicine has led the effort in radiotherapeutic management using IMRT. IMRT allows the dose to the pancreas to be increased to 61.2 Gy, while maintaining acceptable dose and toxicity levels in the small bowel, kidneys, and spinal cord.[49,50] Some reports suggest a dose-response relationship, and in a disease where outcomes can be as dismal as those for pancreatic cancer, higher doses may improve the chance of disease-free survival.[51] This regimen, along with the concurrent administration of gemcitabine, is usually tolerated without many treatment breaks. Using conventional or 3-D conformal therapy for pancreatic cancer, patients often require treatment breaks secondary to small bowel toxicity, even at much lower doses of radiation than those used for IMRT.[49]

Clinically, preoperative irradiation for rectal cancer is considered when tumors are bulky, and/or locally advanced, in an attempt to make them resectable. Landry and colleagues have generated protocols in which preoperative radiation doses have been increased to 60 Gy in 1.5-Gy fractions (twice daily) with 5FU-based chemotherapy.[52] Investigations continue regarding

escalation of radiation dose to 70.5 Gy, in hopes of eliminating the need for surgery. This aggressive approach still respects the 45-Gy tolerance of the small bowel, while decreasing the high dose volume.

ULTRASOUND-GUIDED TRANSPERINEAL PERMANENT BRACHYTHERAPY OF THE PROSTATE (PROSTATE SEED IMPLANTS)

The optimal management of clinically localized prostate cancer remains controversial. The technique of ultrasound-guided transperineal radioactive seed implants has rapidly gained popularity in the treatment of early-stage prostate cancer with a five-year disease-specific survival of 90%.[53-55] This methodology has several potential advantages to external beam radiotherapy or other implantation techniques, such as (1) pre-treatment planning; (2) precision of seed placement; (3) higher total dose to the prostate; (4) the ability to place seeds in the periprostatic region; (5) outpatient treatment; (6) low morbidity; and (7) preliminary PSA progression-free survival rates equal or superior to external beam irradiation and radical prostatectomy.[56-58] It remains to be seen whether the long-term (15-year) results are as encouraging. RTOG 9805 is a multi-institutional phase II trial that will help clarify the indications and role of this popular treatment option. There has been such an increase in the utilization of these procedures that by the year 2005, it is expected that one-third of all prostate cancer patients with organ confined disease will be treated by brachytherapy only (2000-2001 ACR Standards for Radiation Oncology).

HIGH-DOSE RATE BRACHYTHERAPY

High-dose rate (HDR) brachytherapy has become a popular treatment modality for cervical cancer, endobronchial lung and esophageal lesions, and for prostate cancer. It also has been used as an adjunct after resection of soft tissue sarcomas, or recurrent rectal carcinoma. More recently, it has been utilized for coronary stenosis. The advantages of this technique include the ability to deliver treatment on an out-patient basis, with its associated potential for reduced cost, while eliminating radiation exposure to medical personnel. In the case of cervical cancer, one also avoids the inpatient risk of bed-rest induced venostasis and the associated risk of pulmonary embolus, which has been reported with Cesium-137 low-dose rate (LDR) brachytherapy.[59-61] The history of HDR in the treatment of cervical cancer is well documented.[59,60,62] The role of HDR in palliative treatment of bronchial obstruction has been established.[63]

Unlike recurrences from colon cancer, patients with an isolated local recurrence from rectal cancer should be given the opportunity for aggressive surgical treatment, since approximately 50% of patients with locally recurrent disease have isolated lesions that are amenable to surgical resection.[64]

At the time of surgery, HDR catheters can be positioned, externalized, and secured to the skin with silk ties. Similar doses of radiation as with intra-operative radiotherapy (IORT) can be achieved, because the treatment plan can be fractionated. Since the catheters are remotely afterloaded, treatment of patients in postoperative care units can be delayed until patients are stable. Approximately one-quarter of patients survive more than two years, as compared to six months for those treated with supportive care or chemotherapy only.[65]

Researchers at the University of Southern California examined the combination of external beam irradiation, protracted infusion (PI) chemotherapy plus intraluminal brachytherapy boost in the treatment of esophageal carcinoma. The goal was to assess the effect of this combined modality treatment on improving local and regional control as well as on overall survival. The combined modalities of external beam radiation, continuous infusion chemotherapy, and intraluminal brachytherapy boost appears to have led to prolongation of survival in patients with esophageal carcinoma.[66] However, the toxicity of pain and stricture were significant.

The role of preoperative neoadjuvant chemoradiation and adjuvant high-dose rate brachytherapy in the management of unfavorable soft tissue sarcomas of the extremities was examined at the University of Southern California. The effect of high-dose rate interstitial brachytherapy

(HDR-IBT) on reducing the risk of local recurrence following limb-sparing resection was evaluated with a secondary goal of shortening the overall treatment time. Following an en bloc resection, HDR-IBT was administered after catheters (4.7 Fr. Teflon) were secured in the tumor bed and the distal end was externalized. Radiation doses ranged from 13 to 30 Gy given in twice-daily fractions prescribed to a distance of 5mm to 7.5mm from the center of the radioactive source. HDR-IBT reduced local recurrence of high-risk soft tissue sarcomas of the extremity following en bloc resection.

Adjuvant chemotherapy may play a role in local control, as well as in overall and disease-free survival.[67] This modality is a viable alternative since preoperative radiation therapy only increases wound complications, and in many tumors with negative margins, postoperative high-dose rate brachytherapy will suffice, with catheters placed at the time of surgical resection.

High-dose rate brachytherapy is being investigated in the treatment of prostate cancer as an adjunct to definitive external beam radiation therapy, with excellent results,[68] or as monotherapy,[69] always as a temporary interstitial implant. There appear to be some inherent biological advantages of high-dose rate radiation over low-dose rate irradiation in terms of improved tissue tolerance,[70] but this has yet to be confirmed in prospective randomized trials.

Considerable attention has been given over the last five years, to interstitial brachytherapy as an adjuvant to lumpectomy in breast-conserving therapy. The technique was developed more than 40 years ago by Ulrich Henschke, as boost therapy after external beam radiation using low-dose rate Ir-192 wires. This preceded and was later replaced by the availability of linear accelerators with electron capability that became the standard way to deliver the radiation boost in breast cancer. Renewed interest in breast brachytherapy has led to its increasing use as the only treatment after lumpectomy using an Ir-192 HDR source. It was first employed by Robert Kuske et al. at the Oschner Clinic in New Orleans[71] and led to the Radiation Therapy Oncology Group (RTOG) Clinical Trial[95-17] for early stage breast cancer, along with a separate experience at William Beaumont Hospital (near Detroit, MI) of 50 patients.[72,73] The RTOG trial closed March 1, 2001, and analysis has not been completed. Kuske et al. had a mean follow-up of 46 months, whereas Vicini et al. had a median follow-up of 36 months. In the Oschner and William Beaumont groups, there have been no recurrences in the target volume. Both clinicians and patients have expressed great interest in this technique, as it may dramatically reduce the treatment time of six to seven weeks, to approximately one week.

Vascular restenosis remains a vexing problem for patients with coronary and other arterial diseases. Percutaneous transluminal coronary angioplasty (PTCA), with or without stent placement, has dramatically improved the outcome in patients with coronary artery disease.[74-78] Nevertheless, the majority of patients suffer restenosis within six months, and this remains the "Achilles' heel" of PTCA. Nearly 75% of the 700,000 cases of PTCA require a repeat procedure due to re-occlusion. Anatomic and radiographic studies have suggested that the greatest incidence of neointimal proliferation predisposing to vascular restenosis occurs within the first seven days after angioplasty.[79]

Coronary intravascular brachytherapy, when delivered soon after PTCA, can markedly reduce the incidence of restenosis. Condado et al. reported the first clinical experience in human subjects in a non-randomized trial from Venezuela using an Ir-192 source inserted on a monorail catheter.[80] The procedure was well tolerated, without adverse treatment-related effects, and with significant rate of vascular patency. Subsequently, several trials, including two lead articles in the *New England Journal of Medicine*, have demonstrated the efficacy of this technique.[81-83] Reasonable expectations for improved patency of the coronary vessel, reduction in the need for repeat PTCA, and a reduction in cardiac events have been reported. Further

refinement of this technique is ongoing and relates to the timing of radiation and mechanism of radiation delivery, radiation source (i.e. alpha or beta particle emitters), as well as criteria for patient selection.

CONCLUSION

Radiation oncology has experienced major technological advances during the past decade. Complications and side effects, recognized and reported by early pioneers in this field, are now significantly reduced. Recent advances have followed a well-established concept that deliverable radiation dose is inversely proportional to the volume treated. As the target (i.e. tumor) definition improves, dose to normal surrounding and critical structures can be markedly reduced, thus improving the therapeutic ratio. This reduction in toxicity may also permit dose escalation with the potential improvement in local control and survival. Technological advances in equipment and techniques have positioned radiation therapy as a major modality in the multidisciplinary management of benign and malignant disease.

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