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NCI RADIATION RESEARCH PROGRAM MEETING REPORT

RESEARCH IN MEDICAL PHYSICS

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INTRODUCTION

A one and one-half day Medical Physics Workshop was convened at the request of the Radiation Research Program, Division of Cancer Treatment and Diagnosis, NCI, for the purpose of defining the current state of the science in medical physics as it may be applied to radiation oncology, and to discuss potential directions for future research.

The first morning was devoted to broad overview presentations of six research areas that were felt to be potential areas of new investigation: Opening Remarks (C. N. Coleman, R. Cumberlin); Presentations: Dose Calculation Algorithms and Treatment Plan Optimization (R. Mohan), Particle Beams (A. Smith), Electron Beams (K. Hogstrom), Delivery Devices (A. Boyer, L. Verhey), Imaging and Treatment Planning (G. Chen, C. Ling), Patient Immobilization, Set-up Errors and Organ Motion (R. Ten Haken). Appendix I includes the Workshop participants.

The participants separated into two breakout sessions in the afternoon. The following morning session included presentation and discussion each breakout session. These are presented below.

BREAKOUT GROUP A (CHAIR—ARTHUR L. BOYER, PH.D.)

This group identified eight discrete areas of research. These represent not only areas of immediate interest but also include areas that, while somewhat speculative at present, may quickly develop into important research topics as more is learned about the molecular effects of ionizing radiation on biologic systems.

Implementation of linac-based IMRT

Initial development of software and hardware for intensity-modulated radiotherapy (IMRT) has allowed a number of research centers to initiate pilot programs for investigating the efficacy of optimized computer-controlled radiotherapy using attachable or integrated multileaf collimators. The transition from research tool to routine clinical process requires further development.

DMLC Process optimization. The optimization IMRT delivery using dynamic multileaf collimators (DMLCs) requires integration of imaging, treatment planning, plan quality assurance, and treatment delivery into a single efficient system. The networking of computer workstations and servers is the key to achieving efficiency. The amount of information required for each patient can only be managed with large, effective servers and intelligently developed software. The use of multiple fields each modulated by a DMLC leaf sequence must be supported by effective and efficient quality-assurance processes. The quality assurance (QA) of the treatment dose as well as the patient positioning must be addressed. These requirements were foreshadowed by the development of stereotactic radiotherapy procedures. However, stereotactic radiotherapy requires about 0.3 FTE per patient per day and an hour or more of treatment machine time. However, the use of an hour or more of machine treatment time is not feasible for widespread application of IMRT. The development of an integrated, computer-based treatment process will make long treatment times unnecessary. Research into the use of imaging for the planning and delivery QA are important. The integration of amorphous silicon arrays is a ripe area of research. In particular, the use of these sensitive arrays to acquire data for cone-beam tomography for patient position verification is an important opportunity.

Tomotherapy. The helical tomotherapy treatment planning and delivery concept should be given an adequate investigation. The radical departure from conventional treatment planning and delivery processes may lead to new treatment results and may have applications that justify the considerable development costs needed to produce a sufficient number of adequately developed units. Commercial interests should be encouraged to undertake much of the risk, but federal support will also be important.

Robotic IMRT. The clinical implementation of a roboti-

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cally directed X-band 6-MV linear accelerator is being investigated using mostly private funding. The clinical potential of the real-time tumor targeting and highly noncoplanar opportunities of this treatment approach need to be thoroughly investigated. However, investigations using less-than-adequate treatment planning and delivery software and hardware would invalidate the results of conclusions based on their use in the studies.

Proton radiotherapy. The physical properties of proton beams offer significant improvements in dose localization over those achievable with X-rays. These advantages hold for conformal therapy techniques as well as intensity-modulated treatments. Improved dose distributions offer the potential for increased local control and disease-free survival and, especially for pediatric patients, reduction in treatment-related morbidity. There are significant opportunities for physics research in this field, particularly in the areas of scanned proton pencil beam delivery, Monte Carlo modeling and treatment planning, intensity modulation of proton beams, and rapid three-dimensional (3-D) dosimetry systems.

3D-CRT and IMRT in clinical trials. It is exceedingly difficult to design a generally acceptable clinical trial to investigate the relative effectiveness of three-dimensional conformal therapy (3D-CRT) or IMRT. Should historical controls or randomized controls be used? Is it ethical to treat some patients with conventional therapy at the same time one is using more advanced methods? What form of a rapidly evolving technology does one test? What endpoints are appropriate? Should chemotherapy or other gene therapies be included? These and many other decisions face the trial designer. However, the need for some documentation of the relative merits of 3D CRT and IMRT is becoming increasingly necessary.

Introduction of X-band technology

The next generation of high-energy linear accelerator will be based on X-band technology. The collateral technical opportunities for radiation oncology that will arise from Federal investments in this technology should not be missed. In principle, a new generation of linear accelerators should become available that are roughly one-third as large as current systems. The first implementation of this technology is a self-contained intraoperative linear accelerator. X-band technology will be integrated in the tomotherapy development as well. However, other configurations may well provide opportunities for research.

Introduction of gamma IMRT

A relatively low-cost, low maintenance IMRT delivery system based on ^{60}Co sources could well find an important place in the managed healthcare environment. The current extension of the applications possible with such units to sites below the floor of the cranium opens up new lines of investigation and research.

Monte Carlo calculations

The increasing power of computers and the introduction of clever computation tricks has brought this widely applicable technique into clinical applications. At present, there are several methods for calculating photon and electron transport using Monte Carlo computer code. There is no coordination and little communication among the groups working on this problem. It is clear that a considerable amount of research still needs to be carried out before Monte Carlo calculations replace conventional treatment-planning algorithms.

Radiation-activated gene therapy

The use of anatomic-specific delivery of radiation to genetically altered *in vivo* targets is a research agenda that begs for intense study. The simultaneous availability of IMRT and a variety of gene therapies provides a number of interesting combinations. Many antitumor processes are accompanied by effects harmful to normal tissue. If these effects can be localized to the tumor volume by IMRT, effective therapies may be investigated.

Chemo–IMRT

New chemotherapeutic agents could possibly be better introduced in combination with IMRT. Although drugs are usually not specific to localized organs, IMRT is. Evidence is gathering that the use of IMRT is effective at reducing side effects. The implementation of chemo–IMRT offers intriguing possibilities for further investigation.

Objective segmentation of normal and malignant structures

The intense use of imaging in radiotherapy treatment planning has been extraordinarily well received. However, the inefficiency by which normal structures are contoured places a significant burden on the treatment planning process, limiting the application of 3D-CRT. In addition, the ongoing collaborative effort between radiation oncology and diagnostic imaging to develop objective determinations of tumor volumes is a research area that must be continued. This interplay between the diagnostic imaging and radiation oncology community will become even more important when molecular imaging technology is developed to the point of widespread use. The development and promotion of standards between imaging sciences and radiotherapy would promote this area of research. It would be especially valuable to promote the rapid implementation of the DiCOM-RT data exchange standard, especially into large-scale database systems such as Oracle and Sybase.

Magnetic manipulation of electron beams

There are many problems associated with this concept. However, it is the sort of radical innovation that might possibly yield a large return if electron-beam accelerators and magnets can be coaxed to produce dose distributions similar to cyclotron-produced proton beams but at a much lesser cost.

BREAKOUT GROUP B (CHAIR—LYNN J. VERHEY, Ph.D.)

The group identified four specific areas of research. These represent not only areas of research interest, but they describe some of the most important problems that need to be solved to improve our capability to plan, deliver, and verify conformal dose distributions to patients.

Optimization for automated planning

The specific research objectives regarding automated treatment planning are (*1*) to define objective functions that reflect the physical and biologic dose constraints of the tissue volume to be irradiated, (*2*) to understand the impact of the optimization method on the resultant dose distribution, and (*3*) to accurately integrate dose response data into the objective function.

Currently, most automated treatment planning is done with commercial "inverse" treatment planning programs with objective functions and optimization schemes defined by the vendors. These programs obtain an optimized plan by minimizing the quadratic difference between current and desired dose in each region of the patient. The input to the program is typically a 3-point dose–volume histogram defining the minimum, goal and maximum doses desired for targets and for each defined normal tissue. Current experience with these programs shows that typically, small portions of the target receive doses much lower than the dose goal, that target dose heterogeneities of 15–20% are often observed when conformality of dose to target is a high priority and that unexplained rapid dose variations are observed in areas where none are expected. The ideal objective function that will result in dose distributions that more accurately reflect the desired dose remains to be discovered.

Dose optimization has traditionally been performed using iterative, trial and error methods, which have been described as "forward planning." The success of this method depends on the experience of the dosimetrist and the complexity of the problem. For the most complex problems, IMRT with photon beams has been demonstrated to yield superior dose distributions to conventional conformal 3D plans. Inverse planning has been proposed as the best method for determining the intensity profiles for a set of defined beam directions that can most closely approximate the desired dose distributions. Recent work has shown that there is also a role for simpler optimization schemes that are based on devising beam segments that are designed to cover the full target or spare certain structures that might overlay the projection of the target from certain directions. Simple optimization could be used simply to determine the optimal weighting of these beamlets to approximate the desired dose distribution.

Objective functions that are sensitive to the absolute difference of dose from desired values, rather than the square of the difference would, in principle, allow different penalties for overdose and underdose. It seems reasonable to propose that such objective functions might better reflect the desire to avoid cold spots in the target and hot spots in the normal tissues. Objective functions that accept dose–volume constraints with more than 3 points or other complex conditions, might prove useful. Traditionally, optimization programs vary the intensities of individual beamlets to minimize the objective function (or cost function) of a particular plan. Extensions of the optimization to include variation of beam energy and even particle modalities, would give more degrees of freedom and possibly, improved dose distributions. Research in this area could elucidate the connection between the objective function description and the resulting dose distribution.

Depending on the nature of the objective function and the complexity of the problem, the optimization algorithm might affect the results of an inverse planning exercise. For very complex problems and for certain types of objective functions, there may be multiple local minima in the cost function that would be clinically inferior to the global minimum. Using simulated annealing, the ability to tunnel out of a local minimum allows the possibility of finding a global minimum at the cost of more computer time. For simpler problems, such as simple beam weighting of defined beam segments, faster downhill gradient optimization algorithms should be adequate. Research into parameters that affect of the optimization scheme on the predicted dose distribution for a set of objective functions and clinical problems continues to be necessary.

The prediction of outcome is based on the dose distribution and clinical data. By evaluating dose–response data, it may be possible to define realistic objective functions that can optimize clinical results. In any event, the investigation of the clinical data and the parameterization of these data should improve the description of the objective function.

Treatment verification tools

Transit dosimetry is now possible because of the development of the amorphous silicon flat panel imager. These data can be used to compare the patient treatment with the treatment plan on a daily basis. If the dosimetric image is within accepted limits of the calculated transit dose, the treatment can be considered acceptable. In the event that it is not, it should be possible to back project the dosimetric information to the patient and then compare with the expected dose distribution and, if necessary, adaptively modify the subsequent treatments to adjust for the variation. It might even be possible to do this on a real time basis—that is, after delivery of only a few monitor units, calculate the variation of the dose from expected and, if too great, pause the treatment to adjust the patient position or the field shape as needed.

The position of the patient can also be verified using electronic portal images. Computer software that can detect contrast edges can be used to rapidly compare the patient's current treatment image with the reference treatment image and either pause or continue the treatment according to the results of this comparison. Although it is very difficult to do this in three dimensions, a pair of two-dimensional images can be used to improve the patient alignment significantly. In the event that the target organ is directly imageable or if radiographic markers are imbedded in the target organ, the target volume position can be directly determined on a daily basis.

The verification of 3D dose distributions is a difficult problem. Only a small number of dosimetric point measurements can be made in or on the patient. A good, though indirect, method of verifying the predicted dose distribution (particularly useful for IMRT) is to develop an instrumented phantom with an array of point detectors (e.g., diodes) in an anthropomorphic or geometric phantom, to measure the dose distribution. By using a phantom that has many dosimeters, it should be possible to verify the basic dose distribution and the MU calculation. In addition, if more precision is needed, there should be a possibility of inserting X-ray film into this phantom for high-resolution relative dose determinations. An important research effort would be to specify and construct a standard instrumented phantom that would be useful to many groups doing IMRT.

The dose-calculation algorithms used in treatment-planning programs might not be sophisticated enough to accurately predict dose in complex situations. In particular, leaf edge effects, transmission of dose between and through leaves, and the tongue and groove effect tend not be accounted for accurately in planning programs. It will be necessary for research into developing methods of easily measuring dose prior to a patient's first treatment.

Modeling treatment decisions

Many factors contribute to the final selection of a treatment plan by a physician for a patient in radiation therapy. The plan is selected on the basis of the physician's expectation of outcome based on clinical experience—presumably his own as well as that of others. This raises the possibility of using the perceived biologic response, correct or not, to predict outcomes, and then to combine the predicted outcome with medical, social, and personal criteria and patient preferences to select the treatment that optimizes the overall result of treatment in a consistent manner. Clinical application of this is somewhat academic at this time, but, with the advances made in computer science, artificial intelligence, and expert systems, this may become a useful aspect of the overall inverse-planning process, which would be able to present the physician with a choice of treatment plans for approval, optimized not only for physical parameters, but for medical and biologic ones as well. This area will require a great deal of research.

A related area of research in expert medical systems would be a quantitation of the subjective factors that the physician uses to make his decisions. Factors that are considered in the treatment decision include the tradeoff between recurrence and normal tissue injury, tradeoffs among the possible normal tissue injuries, the morbidities of the possible complications, the time to onset of the complications as compared to the patient's life expectancy, the patient's age, gender, lifestyle, comorbidities, etc.

Research into the design of evaluation tools that require physicians to rank plans according to their clinical judgement and experience (which may be considered a personalized expert system). By examining many radiation oncologists, it should be possible to determine consensus factors that could be included in objective functions. By examining physicians on a regular basis, the factors could be updated to include new clinical experience of each physician and experience of other clinicians reported in the literature. The consistency of individual physicians could also be evaluated by repeated examinations.

Tools for the use of multimodality treatment in radiation therapy

Although IMRT with photons has been shown to improve the conformality of dose distributions for many situations, the combination of IMRT photons with electrons, protons, and brachytherapy has not been adequately investigated. In particular, the combination of electrons and photon IMRT has the potential of further improving dose conformality. Because electrons and photons can be delivered with most modern linear accelerators, there is the potential for broad-based clinical application to result from investigating this particular combination of modalities.

Electron conformal therapy (ECT) has traditionally implied the use of a complex-shaped wax bolus that serves as a device that can eliminate sharp surfaces from the patient and modulate the energy distribution incident on the patient. It has been observed that the bolus increases dose inhomogeneity; however, it should be possible to restore dose homogeneity by modulating the incident fluence using a dynamic MLC or by controlling the beam scanning pattern for beams flattened using magnetic scanning. Another method of achieving ECT is treatment with multiple small beams whose energy and intensity are variable. The advantage of this approach is that bolus construction, a time-consuming procedure, is not required. One disadvantage of this technique, the coarse energy spacing on most commercial radiotherapy accelerator (2–3 MeV), could be solved by various methods that need investigating.

Technical areas in need of investigation for ECT include (*1*) methods of dose optimization, (*2*) methods of delivery, (*3*) time of treatment and resulting whole body dose, (*4*) quality assurance of delivery methods, and (*5*) sensitivity to patient positioning for each of the optimization techniques researched.

Electron–photon mixing may offer clinical advantages. For example, for superficial areas planned exclusively with photons, it may not be possible to achieve a sufficiently uniform dose, and an ECT boost may prove useful in achieving that. In contrast, areas planned exclusively with ECT may contain a high surface dose, which could benefit from photon irradiation to the same area. Additionally, photons may be useful for decreasing the beam penumbra in the vicinity of critical structures. In addition to the research and development of ECT described above, practical methods for optimization of combined IMRT and ECT need research and development prior to clinical use.

Both ECT and combined ECT/IMRT need to be studied for sites of potential clinical benefit, e.g., thoracic wall, head and neck, and extremity tumors. Research should demonstrate the potential improvement over conventional or IMRT techniques through offering more uniform doses to the target volume(s) and reduced dose to critical structures. The methods of delivering the electrons on top of a photon IMRT dose distribution needs to be explored. This might be done with conventional MLCs, with special MLCs or with simple shaped electron beams. Due to the scattering properties of electrons, helium bags could give better penumbra for the electron beams, if that is necessary. Scanned electron beams, available on some linear accelerators, would be particularly convenient.

The ability to calculate accurately the dose for combined electrons and photons is important. Independent of the delivery issues, combining brachytherapy and protons with IMRT photons should be investigated.

CONCLUSIONS FROM THE WORKSHOP

The development of IMRT is the most immediate challenge facing medical physics today. A great deal of work needs to be done. One area of great importance, because it affects present day clinical practice, is the issue of quality assurance, treatment verification, and phantom development. Another is the issue of inverse treatment planning. Much remains to be learned about the appropriate form of the optimization function and also the most suitable calculation algorithms.

The subject of interaction with diagnostic imaging is of great importance. Radiation oncology is more image based today than at any time in its history and will become moreso as functional imaging becomes more routine. The role of the medical physicist in this new environment must be defined.

The linear accelerator has been the mainstay of radiation therapy equipment for the last 20+ years. There are now new technologies being developed that have the potential to improve significantly on the standard hardware. The same may be said for the increasing interest in proton therapy. Much work needs to be done in integrating these disparate beams and configurations into a common framework so that optimal choices for patient treatment can be rationally made.

Of more longrange interest is the potential for medical physicists to develop expert systems to aid the radiation oncologist is evaluating what is rapidly going to become an unwieldy number of seemingly equivalent (but with clinically subtle but important differences) treatment plans that can be generated by modern inverse treatment-planning systems. There is also significant opportunity for medical physicists to work closely with physicians in planning radiation treatments not to treat a tumor but to locally activate a therapeutic gene vector.

Report submitted from the Workshop participants, and Drs. R. Cumberlin and C. N. Coleman.

ADDENDUM TO RESEARCH IN MEDICAL PHYSICS WORKSHOP REPORT (UPDATE: JUNE 20, 2000)

Since this meeting the Radiation Research Program (RRP) has taken the following preliminary steps toward implementing some of the recommendations. Updates will be made in the RRS and ASTRO newsletters and on the RRP website.

1. The RRP is currently searching for a medical physicist. Among the priorities will be increased interaction with the Biological Imaging Program and other programs within the National Cancer Institute. Dr. James Deye has joined the RRP as of January 2001.
2. A workshop dedicated to Monte Carlo techniques is under consideration.
3. The RRP will review the current quality-assurance programs for the cooperative groups to help assure appropriate uniformity of criteria and to facilitate the sharing of innovative approaches used by one group by the others, for example, the quality assurance for 3D conformal RT.
4. We encourage the Radiation Oncology Medical Physics community to help define the role and future contributions of medical physics to the emerging biological treatments. The concept that radiation is "focussed biology" has been proposed to stimulate interest in understanding the interaction of physical dose and biologic perturbations at the molecular level.

APPENDIX I. WORKSHOP PARTICIPANTS

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