Int. J. Radiation Oncology Biol. Phys., Vol. 43, No. 3, pp. 697–700, 1999

0360-3016/99/$–see front matter

LETTERS TO THE EDITOR

A MORE ROBUST BIOLOGICALLY BASED RANKING CRITERION FOR TREATMENT PLANS

To the Editor: In discussing the ranking of treatment plans based on estimated tumor control probabilities (*TCP*) and normal tissue complication probabilities (*NTCP*), Langer *et al.* (1) correctly point out that the figure-of-merit score

$$S = TCP\ (1 - NTCP), \tag{1}$$

which has been adopted by several authors (2–4), has some undesirable properties. For example, changing the absolute value of the *NTCP* in two competing treatments plans by the same proportion can sometimes change the relative ranking of the plans. Langer *et al.* (1) point out that this is because, if Eq. 1 is used as the score for ranking plans, for a given value of *TCP*, a small fractional change in *NTCP* (i.e., *dNTCP/NTCP*) is reflected in the fractional change in the score as

$$\frac{dS}{S} = -\frac{dNTCP}{NTCP}\left(\frac{NTCP}{1-NTCP}\right). \tag{2}$$

The problem here is that the term in brackets in Eq. 2 implies that, when the absolute value of *NTCP* is large, the score will be very sensitive to changes in *NTCP*, but when the absolute value of *NTCP* is small, the score will be relatively insensitive to changes in *NTCP*. Other suggested figures of merit, such as a ratio of biologically effective doses (e.g., $BED_{tumor}/BED_{late\text{-}responding\ tissue}$), suggested by Ling and Chui (5), or more complex function of these BEDs as suggested by Dale and Sinclair (6), are also prone to such problems.

This situation can easily be remedied by using, for example, a figure-of-merit score

$$R = TCP/NTCP. \tag{3}$$

In this case, a fractional change in the figure-of-merit score used for ranking treatment plans depends only on fractional changes in *TCP* and/or *NTCP*, as

$$\frac{dR}{R} = \frac{dTCP}{TCP} - \frac{dNTCP}{NTCP}, \tag{4}$$

i.e., independent of the absolute values of *TCP* and *NTCP*, as one would wish.

An extension of Eq. 3, which would allow for different relative weightings of *TCP* and *NTCP* would be

$$R' = TCP/NTCP^q, \tag{5}$$

where use of the weighting factor q (> 0) allows the physician's perspective on the relative importance of *NTCP* and *TCP* to be quantified (4). As in Eq. 4, fractional changes in R' depend only on fractional changes in *TCP* and *NTCP*.

(In fact, use of a reciprocal ranking score, $1/R$ or $1/R'$—which would, of course, be minimized rather than maximized—would have the same advantages in terms of ranking as R or R', but might be more stable. This is because *NTCP* is generally small, and small fluctuations in *NTCP* when it is in the denominator might cause unreasonably large fluctuations in the ranking score itself).

In conclusion, a treatment-plan ranking score defined using Eq. 3 or Eq. 5 (or their reciprocals) does not have the undesirable ranking properties, described by Langer *et al.* (1), which sometimes appear when using the standard ranking score defined in Eq. 1. Thus R from Eq. 3, or the more general R' from Eq. 5, or their reciprocals, are likely to represent more robust ranking criteria than S from Eq. 1.

D. J. BRENNER, D.SC.
Center for Radiological Research
Department of Radiation Oncology
Columbia University, New York, NY

R. K. SACHS, PH.D.
Departments of Mathematics and Physics
University of California, Berkeley
Berkeley, CA

PII S0360-3016(98)00436-2

1. Langer M, Morrill SS, Lane R. A test of the claim that plan rankings are determined by relative complication and tumor-control probabilities. *Int J Radiat Oncol Biol Phys* 1998;41:451–457.
2. Leibel SA, Kutcher GJ, Harrison LB, *et al.* Improved dose distributions for 3D conformal boost treatments in carcinoma of the nasopharynx. *Int J Radiat Oncol Biol Phys* 1991;20:823–833.
3. Jain NL, Kahn MG, Drzymala RE, *et al.* Objective evaluation of 3-D radiation treatment plans: A decision-analytic tool incorporating treatment preferences of radiation oncologists. *Int J Radiat Oncol Biol Phys* 1993;26:321–333.
4. Amols HI, Zaider M, Hayes MK, *et al.* Physician/patient-driven risk assignment in radiation oncology: Reality or fancy? *Int J Radiat Oncol Biol Phys* 1997;38:455–461.
5. Ling CC, Chui CS. Stereotactic treatment of brain tumors with radioactive implants or external photon beams: Radiobiophysical aspects. *Radiother Oncol* 1993;26:11–18.
6. Dale RG, Sinclair JA. A proposed figure of merit for the assessment of unscheduled treatment interruptions. *Br J Radiol* 1994;67:1001–1007.
permits.

IN RESPONSE TO DRS. BRENNER AND SACHS

To the Editor: We thank Drs. Brenner and Sachs for their interest in our paper and welcome their novel contribution (1). Two problems with a function used to score plans according to their probabilities of tumor control and normal tissue complications in different structures have been identified (2). One is that contrary to what has been claimed for them, the score ranking depends not merely on the relative probabilities for adverse events, but on their absolute levels. The probability of uncomplicated tumor control and the probability of producing none of several complications are examples of such score functions. Ordering plans by TCP and NTCP for individual events cannot be used to compare plans. Even when the risks of adverse events in different structures are correctly ordered for different plans, the overall plan ranking according to a score that is a function of several of these events may still be wrong. A second problem with score functions that have been used to rank plans based on the probability of uncomplicated tumor control is that the fractional error in the overall complication probability is not constant, but rather varies with the NTCP level.

The formula for scoring plans by the ratio of TCP to NTCP suggested by Drs. Brenner and Sachs in their letter remedies the second of these problems but not the first (1). It is an improvement upon the older score functions, but its ranking is still subject to error. The proposed ratio does not allow plans to be ranked only from knowledge of the ordering of individual tumor control and normal tissue complication probabilities. The ordering of plans according to the NTCP factor, or overall probability of complications, is subject to change, even when the ordering of the individual tissue complication probabilities is fixed. An example of this was

shown in our paper, where the NTCP for avoiding complications in any of two tissues are compared between two plans (2). Table 1 of that paper shows that the ranking of two plans according to the probability of being free from complications can change simply by multiplying the individual complication probability estimates by a constant correction factor. If so, the ranking of the two plans according to the TCP/NTCP ratio will be reversed, too, by a proportional change to the complication probability estimates of the individual tissues.

Of course, there is no guarantee that the ordering across plans of the TCP or NTCP for any one tissue is correct. Claims for improved dose distributions using some of the newer technologies are often based on scores formed from these probability estimates without benefit of any error display. Demonstration of improvement according to the historic rules for prescribing plans such as minimum tumor dose or dose–volume limits on normal tissues may be lacking. If novel technologies, often costly and with uncertain risk, are to substitute for standard treatments, it will be important to show that estimated gains in the risk of complication or recurrence meet standard tests of statistical significance. These tests have proved to be reliable guides to changes in medical practice over a wide range of situations. If complication or tumor control probabilities are to be used to support the introduction of new technologies, then the errors in these estimates will need to be forthcoming.

MARK LANGER, M.D.
Department of Radiation Oncology
Indiana University
Indianapolis, IN 46202-5289

S. MORRILL, PH.D.
R. LANE, PH.D.
Department of Radiation Oncology
University of Texas Medical Branch
Galveston, TX 77555-0484

PII S0360-3016(98)00437-4

1. Brenner DJ, Sachs RK. A more robust biologically based ranking criterion for treatment plans (letter). *Int J Radiat Oncol Biol Phys* 1998;43:697.
2. Langer M, Morrill S, Lane R. A test of the claim that plan rankings are determined by relative complication and tumor-control probabilities. *Int J Radiat Oncol Biol Phys* 1998;41:451–457.

IS IT POSSIBLE TO OPTIMIZE A RADIOTHERAPY TREATMENT PLAN?

To the Editor: There are many examples in the medical physics literature of computer optimizations. In the case of radiotherapy, authors claim to optimize beam-orientations, beam-weights and, in the case of intensity-modulated radiotherapy, fluence profiles. However, is the optimization of a treatment plan a realistic aim for such techniques and is the goal of optimization as clear as it could be? In all areas of research, the term optimization implies the best possible solution has been achieved subject to specified physical constraints. In radiotherapy, however, the ultimate aim of any computer optimization algorithm is not to find the optimum of some given objective cost function but the best radiotherapy treatment plan for each patient.

There would appear to be two areas of ambiguity regarding the idea of optimization in radiotherapy. The first area is that optimization in radiotherapy treatment planning is a multi-parameter problem. To find the best possible treatment plan for a patient, parameters such as the treatment modality, energy, number and orientation of the treatment fields and beam-weights, or fluence profiles in the case of intensity-modulated radiotherapy, would all require optimization. The parameters mentioned above do not independently determine the resulting plan and so all would need to be optimized simultaneously. The computer optimization of all the treatment parameters requires too much computer time and would be impractical on a routine basis. For this reason, most optimization algorithms optimize a limited number of treatment-planning parameters. The optimization algorithms attempt to find the best compromise between planning target volume (PTV) and organ-at-risk (OAR) doses but are only able to find the optimum of the limited parameters within a multi-parameter space. There is no reason to expect that the multi-parameter optimum and the limited-parameter optimum coincide. It is more likely that a change in any one of the other fixed parameters would result in a different limited parameter optimum to be found. The "optimum" found is therefore biased by the treatment parameter chosen for optimization.

The second area of ambiguity involves the fact that in radiotherapy a compromise is always sought between increasing the homogeneity and magnitude of the dose in the PTV and, simultaneously, reducing the dose to the OAR. Let us consider the fundamental concepts of tumor control probability (TCP) and normal tissue control probability (NTCP) and disregard the imperfections in the various models employed in the calculation of specific values. The goal of radiotherapy treatment planning can then be stated as the establishment of the plan that maximizes the tumor control probability (TCP) for fixed, low, normal tissue complication probability (NTCP). In most optimization algorithms the trade-off between the TCP and NTCP is achieved via the use of importance factors. In view of the uncertainty of converting dose into biological predictions, dose objectives usually substitute for these. For each patient the human planner then makes an informed judgement as to what PTV homogeneity and OAR dose is acceptable and sets the importance factors accordingly. The optimization algorithm then finds the best solution for the compromise introduced by the planner. Authors, including ourselves, refer to such a plan as the optimum, whereas it is manifestly not the optimum treatment plan for the patient. It is the best outcome for the user-defined, nonphysical constraints applied. If a different trade-off were chosen, different treatment parameters would be obtained from the algorithm. The importance factors are integral to many optimization techniques and greatly increase the flexibility of the computer optimization algorithms and allow the desired dose compromise to be customized for each individual patient. It is clear that many "optimization algorithms" therefore produce the best treatment parameters for the customized dose trade-off introduced by the planner and subject to human bias.

The optimization algorithms currently under development are invaluable in the continued improvement of radiotherapy treatment plans and hopefully treatment outcome. The importance of such algorithms is likely to increase with the future increase in computer speed. It has been regularly demonstrated that the optimization techniques improve radiotherapy treatment plans when compared to standard (nonoptimized) plans. "Improved" treatment plans are not necessarily optimum plans. The techniques can be seen to be finding the most feasible solutions given certain physical and parametric constraints. The question to be asked is whether this process leads to the best possible treatment plan for the patient.

These issues are more than mere semantic arguments. This philosophical discussion arose from increasing frustration with our own inability to rationalize how ongoing research in "optimization" (including our own) is consistent with the existence of papers (including our own) which already purport to present optimum solutions. We even found ourselves writing, in draft, phrases such as "more optimum" and "just short of optimum" whereas *optimum* clearly cannot take adjectives of the superlative degree. We needed to explain that our results depended not only on the skill to design algorithms but also on their constraints and tuning. We therefore recommend that:

- The phrase "optimum plan" should strictly be reserved for best plan achievable for the patient. Current optimization techniques do not find the best possible treatment plan, but the best solution within a predetermined subset of the possible treatment parameters and user-defined dose trade-off;
- The goal of treatment planning should be regarded as achieving the maximally improved plan due to customizing parameters within a subset of the full set of parameters open to change. This should take account of the physical constraints, the constraints of computer time, and subject to constraining choices of parameters (such as importance factors) which influence the outcome, made by the planner implementing the technique. Given the need for some kind of single word or phrase to mean all this, we suggest the term "constrained customization" for the technique and "constraint-customized plan" for the resulting plan. We feel that these terms adequately describe the situation in that the user can customize the acceptable dose trade-off via the importance factors and the customization is subject to physical and parametric constraints;
- Papers reporting techniques with this goal should always state clearly the limited search space of parameters (e.g., beam modality, energy, number of beams, class of beams, orientation of beams), i.e., should state which of these parameters are regarded as unavailable for change and which are the converse. Those choices of factors that influence the implementation of the technique but that are *a priori* selected should also be stated.

We recognize that these observations are relatively obvious but have not been formally stated before. It is also something of a mind-shift to expect