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Special Article

Technical Structure of a Radiotherapy Protocol

LAWRENCE E. REINSTEIN,*‡ ARVIN S. GLICKSMAN*† and FRANCES LAURIE*

**Quality Assurance Review Center, Department of Radiation Medicine and Biology Research, Rhode Island Hospital, Rhode Island* 02908, *U.S.A. and †Division of Biology and Medicine, Department of Radiation Medicine, Brown University, Providence, Rhode Island* 02912, *U.S.A.*

Abstract—*Multi-institutional cooperative group trials require conformity to a uniform set of therapeutic guidelines so that all patients entered on the study are treated the same regardless of which participating center enters the case. This can come about only if an unambiguous, clearly defined treatment program is included in the protocol. Examples of confusing protocol guidelines from recent Group studies demonstrate how well-meaning participants can inadvertently deviate from study requirements. The Quality Assurance Review Center has developed an outline for the radiotherapy component of a study which has alleviated this problem considerably.*

INTRODUCTION

THE prerequisite for the success of a multi-institutional cooperative group study is that each participant must be fully cognizant of the treatment requirements for each patient entered onto the study. Without clearly defined guidelines, ambiguity can increase the likelihood of protocol noncompliance as a result of the misunderstanding of protocol requirements. Therefore, the research protocol must clearly define the objectives of the study, the population to be studied with clear eligibility and exclusion criteria, the clinical stages of disease allowed in the study, the exact types of pathology to be entered in the study and the criteria of response. The exact details of the therapeutic regimens to be followed must be explicitly stated.

Over the last 5 years, the Quality Assurance Review Center has worked with investigators to develop a specific set of guidelines for the radiotherapy section of group protocols. These guidelines have been adopted by several national and international clinical trials groups under the titles 'Anatomy of a Radiotherapy Protocol' and 'The Structure of a Radiotherapy Protocol'. This document offers a protocol structure which carefully spells out all of the radiotherapy requirements in sufficient detail and regular sequence so that there can be no misunderstanding of the intent and the exact requirements of the treatment program.

These guidelines have been adopted in the United States by most NCI-funded cooperative groups which perform clinical trials with radiotherapy. This includes those monitored by QARC as well as those that are not. They are presented here in the belief that their wider use can improve the implementation of quality control of multi-institutional clinical trials and may be of advantage to cancer center programs as well (Appendices I and II).

A large variation in the rate of protocol compliance has been observed and reported by QARC over the past nine years [1, 2]. Major deviation rates have averaged under 10% for some cooperative group protocols, while others have been in excess of 30%. Several factors contribute to this variation including differences in technical difficulty and overall treatment complexity which can lead to 'learning curves' with differing rates of increase. These effects have been demonstrated and discussed in detail in a previous paper [2].

Often, however, the problem lies with the description of the radiotherapy contained in the protocol, rather than the inherent treatment complexity or the performance ability of the participating radiotherapist.

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‡Present address: Department of Radiation Oncology, State University of New York at Stony Brook, Stony Brook, New York, 11794–7028, U.S.A., where all correspondence should be directed. (Tel: 516/444-2208).
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An increasingly important function at QARC has been the process of critiquing and revising the technical details of the radiotherapy sections of proposed studies for those cooperative groups which it serves. The need for tight guidelines is demonstrated by the following examples of radiotherapy instructions which are taken from protocols written prior to QARC involvement.

Example 1
'It is suggested that the entire cranial cavity be treated to a dose of 3000 rad in four weeks in continuity with the primary tumor, and that the portal of radiation therapy subtend the immediate cervical meninges to the level of the body of C2 . . . Care must be exercised to minimize the 'overlap' or 'underlap' between the portal, to encompass the entire cranial meninges and primary tumor and the smaller portal, for the reduced boost field . . . Consideration should be given to 'feathering the juncture point' between the large open portal and the smaller reduced portal, and also to 'calculating a gap on the skin' to attempt to reduce the problem of overlap and underlap at this juncture point.'

Comment. What is the 'overlap' or 'underlap' problem to which the author refers? Why does this section ask for 'feathering of the juncture point'? This is all rather confusing. Exactly how shall the 'feathering' be accomplished? What kind of 'gap on the skin' should be calculated? There is insufficient information to assure uniform treatment.

Example 2
'The total dose to the kidneys *should not exceed* 1750 rads in four weeks. The kidneys should be shielded with a posterior kidney shield to be introduced at 1500 rad in-plane dose.'

Comment. The total treatment dose specified in an earlier paragraph of this protocol is 2500 rad to mid-plane. Even if the shielding instructions described here were followed exactly, it would not be possible to keep the kidney dose to within the allowable maximum of 1750 rad. Direct radiation, transmission dose and scatter radiation will result in a dose to the kidney most likely in excess of 1900 rad. (Here is an example of a protocol which requires treatment which is not physically achievable.)

Example 3
'*Timing.* Patients who receive radiation will be treated following 1 cycle of induction chemotherapy (day 63—42 days of chemotherapy + approximately 2 weeks rest period . . .)'

Comment. According to these guidelines, patients receiving radiotherapy after 1 cycle of chemotherapy start on day 63. However, 42 days of chemotherapy plus a 2 week rest period would equal day 56.

Example 4
'*Spinal Fields.* The field shall extend from the lower margin of the cervical extension, the spinal field to include the entire thoracic, lumbar, sacral spine, and coccyx. The field width should cover the entire vetebral body in the cervical, thoraxic and lumbar area and should flair to cover the sacral illiac joints caudally (see Figure 11.3).'

Comment. When the reader turns to Figure 11.3, which is attached to the protocol as an Appendix, he finds a figure showing the spinal volume from the lower margin of the cervical spine to the SI jointith *no* flair.

In addition, we have found at QARC that the *Prescription Point* at which the dose should be calculated is often, at best, incomplete for the treatment techniques described elsewhere in the protocol. But many times it is left out, which leaves the opportunity for doses to be calculated for the entire patient population in a non-uniform manner. To address this, QARC has standardized the text for *Prescription Point* to cover treatment techniques of parallel-opposed equally weighted portals, parallel-opposed unequally weighted or single field unopposed beams, multiple convergent isocentric beams and electron beams. Examples are found in Appendix II.

DISCUSSION

It is difficult to quantify the improvement in protocol compliance which results from the current system of rigorous protocol revision. For most studies it is impossible to separate improvements in compliance which stem from effective protocol writing from those whose results can be attributed to the QARC review process (on-treatment review, post-treatment review letters, etc.).

The effect of the new guidelines on protocol compliance can in some measure be inferred by comparing the 2 recent protocols for Small Cell Carcinoma of the Lung. The original study description was unclear and did not explicitly state the minimum dose to be delivered to the mediastinum, while at the same time allowing the spinal cord dose to be limited through the use of a posterior cord block. This led to mediastinal dose variations of 3300–4500 cGy. Because of this experience the RT guidelines of the succeeding small cell study were revised by QARC to contain more precisely defined requirements. The link between protocol com-

pliance and the clarity of the protocol guidelines is demonstrated by comparing the major deviation rate of dose to the mediastinum in these 2 similar studies: 36% ($N = 260$) for the original study and only 16% ($N = 181$) for the subsequent study with the improved guidelines.

CONCLUSION

In order for multi-institutional clinical research to be effective, it is important for all participants to know exactly how to treat each patient entered on study. The 'Structure of a Radiotherapy Protocol: Technical Guidelines' were developed by QARC to clearly define the therapeutic regimen to be tested, and the criteria for quality assurance evaluation. The radiation quality, prescription dose, and dose homogeneity are all spelled out in detail so there can be no misunderstanding of the intent and requirements of the treatment arm. A great deal of attention must be given to the minute details of writing a protocol document; we believe it is well worth the effort in providing a sound basis of the ultimate analyses of the studies performed.

REFERENCES

1. Glicksman AS, Reinstein LE, Laurie F. Quality assurance of radiotherapy in clinical trials. *Cancer Treat Rep* 1985, **69**, 1199–1206.
2. Reinstein LE, Peachey S, Laurie F, Glicksman AS. Impact of a dosimetry review program on radiotherapy in group trials. *Int J Radiat Oncol Biol Phys* 1985, **11**, 1179–1184.

APPENDIX I

STRUCTURE OF A RADIOTHERAPY PROTOCOL: TECHNICAL GUIDELINES

1.0 *General Guidelines:*

The following information should be supplied in the Radiotherapy Section of the protocol. If the details differ for certain anatomical sites, the requirements for these sites should be indicated separately. If the radiotherapy requirements differ for different treatment arms, they should be listed in separate paragraphs.

1.01 *Eligibility:* A statement of which patients are eligible to receive radiotherapy on this protocol.

1.02 *Exceptions:* List exceptions to general requirements.

1.03 *Relation to Other Modalities:* State the timing of the radiation therapy with respect to the delivery of other treatment (i.e. chemotherapy or surgery).

1.1 *EQUIPMENT*

1.11 *Modality:* State whether photons, electrons, and/or implant may be used, and under what cicumstances.

1.12 *Energy:* A statement of minimum and maximum allowed energy based upon an assessment of the minimum depth 'at risk' and the treatment technique.

1.13 *Geometry:* A statement of minimum SAD. If isocentric apparatus is required, state explicitly whether 60 cm SAD Cobalt units with their large penumbras are acceptable.

1.14. *Dose Rate:* A statement of minimum (and maximum?) dose rate at a particular SSD and depth.

1.15 *Calibration and Beam Data Verification:* State requirements for beam verification by outside physics group.

1.2 *TREATMENT VOLUME*

Descriptions of the treatment volumes when multiple anatomical sites are involved shall be assigned to subparagraphs a, b, c, etc.

1.21 *Anatomical Description:* A detailed description of the volumes to be irradiated. A detailed description of the anatomical volume 'at risk' must be given. This should be done with anatomical reference points. *No* reference should be made to the field edges in this description.

1.22 *Physical Extent:* A description of the extent of the volume along each of the 3 patient dimensions, i.e. the right and left lateral, superior, inferior, anterior, and posterior extent. It is preferable if references are made only to anatomical structures and not to the field edges when describing treatment volume.

1.23 *Margins:* State the minimum field margins allowable.

1.24: *Diagnostic Determination:* On what diagnostic information should the treatment volume be based (e.g. AP X-rays, CAT scans, surgical reports, etc.)?

1.3 *TREATMENT DOSE*

1.31 *Prescription Point:* A statement of where the dose to each treatment volume is to be defined (e.g. mid-plane, isocenter, d_{max}, etc.).

1.32 *Dose Definition:*

1.321 Absorbed dose is described in rad (cGy) to muscle tissue. [1 rad = 1 centigray (cGy)].

1.322 *Tissue Inhomogeneity Considerations:* State whether inhomogeneity correction for bone and/or lung should be made.

1.33 *Total Treatment Dose:* State the required treatment dose for this volume. If multiple sites are treated, the descriptions of required dose for each site should be clearly labeled and assigned to subparagraphs a, b, c, etc.

1.34 *Dose Modification by Site:*
1.341 *Cone-downs or Boosts:* The required cone-down shall be stated clearly.

1.35 *Dose Modifications for Age, Field Size, etc.:* Any dose modifications to age or field size (e.g. abdominal bath, whole lung) shall be stated clearly and explicitly.

1.4 *TIME-DOSE CONSIDERATIONS*

1.41 *Daily Dose:*
1.411 Dose per fraction.
1.412 Number of fractions per day.
1.413 Number of treatment days per week.
1.414 Total treatment time.

1.42 *TDF Guidelines:* State required TDF, if appropriate.

1.43 *Planned Rests:* State treatment adjustments (if any) for 'unplanned rests'. State whether the total TDF should be maintained and, if so, whether daily dose, total dose, or number of fractions should be modified to keep the TDF constant.

1.44 *Sequential or Concurrent Sites:* State the time sequence for treatment of multiple sites.

1.5 *DOSE HOMOGENEITY AND OFF-AXIS REFERENCE POINTS*

1.51 *Uniformity Requirement (Central Plane):* Describe dose homogeneity required throughout central plane (usually ± 5% of treatment dose within tumor volumes).

1.52 *Uniformity Requirement (Sagittal Plane):* For long treatment volume, state maximum allowed dose variation along longitudinal axis.

1.53 *Dose Uniformity Reference Points:* Describe in detail the anatomical reference points (if applicable), at which dose must be calculated for assessment of dose uniformity. These reference point descriptions should be independent of the placement of field edge and refer to anatomical landmarks whenever possible. Include the 'skin dose' as a reference point whenever appropriate.

1.54 *Methods of Dose Compensation:* Describe allowed techniques (e.g. incremental blocking, tissue compensators, etc.).

1.55 *Critical Organ Dose Reference Points:* Describe anatomical sites at which dose should be calculated to assess critical organ dose.

1.6 *TREATMENT TECHNIQUE*

1.61 *Required (or Acceptable Treatment Techniques:* These techniques (e.g. AP/PA opposed laterals, rotations) should be described.

1.62 *Treatment SSD Limits:* Minimum treatment SSD allowed.

1.63 *Patient Treatment Position:* (e.g. supine, prone, head facing up, etc.)

1.64 *Field Shaping:* State whether 'divergent' (individually cut) blocks are required. State required minimum block thickness in terms of half value layer (HVL).

1.65 *Adjacent Fields Separation:* Describe method for 'skin gap' calculations when appropriate. State the aim of this method (i.e. to avoid overdose, to avoid field overlap, to avoid 'hot spots' or 'cool spots'?) State how these gap calculations should be documented.

1.66 *Superficial Tissue Boost Techniques:* State allowable techniques (e.g. electron beam, surface mold, etc.).

1.7 *NORMAL TISSUE SPARING*

1.71 *Critical Organ Dose:* State the maximum dose allowed for each relevant critical organ.
1.711 *Limits:* State the maximum dose allowed for each relevant critical organ.

1.712 *Methods of Determination:* State whether calculational or measurement methods are to be used. Describe these methods if necessary.

1.72 *Techniques to Limit Critical Organ Dose:* State techniques which can be used such as posterior kidney block, oblique beams, etc.

1.8 *CALCULATIONS AND TREATMENT PLANNING*

1.81 *Special Calculations or* In vivo *Measurements:* State these explicitly.

1.82 *Required Dose Calculations:* State explicitly what calculations are required (e.g. isodoses, off-axis points, etc.) If isodose maps are needed, is the central plane sufficient or should multi-plane calculations be performed? What anatomical information is needed to properly interpret these isodoses? If multiplaned, how should planes be spaced? What internal anatomy must be indicated on these isodose maps? How shall these isodose maps be normalized relative to the central plane

isocenter? How should isodose levels be labeled? Are isodose maps required for certain techniques while not required of other techniques used?

1.9 *QUALITY ASSURANCE DOCUMENTATION*

1.91 *Data Submission Times:* State when data should be submitted for on-treatment 'interventional' review as well as for post-treatment retrospective review.

1.92 *Radiotherapy Data Reporting Forms:* State which forms should be completed.

1.93 *Diagnositc and/or Clinical Data (if necessary):*

1.94 *Localization and Simulation:* State what kind of film copies are acceptable.

1.95 *Portal Films:* State which areas (probably all) require submission of portal films. (Should both opposed fields be portalled?) State how often portal films should be taken and submitted. State what copy methods are acceptable for submission. State whether 'double exposure' technique is required. State whether field modifications (boosts, cone-downs, etc.) require submission of portal films reflecting these changes.

1.96 Photograph of patient in treatment position.

1.97 Daily Treatment Chart.

1.98 Copies of Dose Calculations (Central Axis, Off-Axis, and Isodose). Dose calculations worksheets including all relevant beam parameters used for these calculations should be submitted.

1.99 Name and address of personnel to whom data should be sent. Telephone number of Radiotherapist, Physicist and Data Manager to whom questions can be directed.