DOSE SPECIFICATION AND QUALITY ASSURANCE OF RTOG PROTOCOL 95-17, A COOPERATIVE GROUP STUDY OF $^{192}$IR BREAST IMPLANTS AS SOLE THERAPY.

W.F. Hanson¹, B. Martin², R. Kuske³, D. Arthur⁴, R. Rabinovitch⁵, J. White⁶, R. Wilenzick³, I. Harris¹, R.C. Tailor¹, D.S. Davis¹,

¹UT M.D. Anderson Cancer Center, Houston, TX, ²RTOG Headquarters, R T Quality Assurance, Philadelphia, PA, ³Ochsner Cancer Institute, New Orleans, LA, ⁴Medical College of Virginia Hospitals / VCU Health Systems, Richmond, VA, ⁵University of Colorado Cancer Center, Denver, CO ⁶Medical College of Wisconsin, Milwaukee, WI.

ABSTRACT

RTOG protocol 95-17 was a phase I/II trial to evaluate brachytherapy as the sole method of radiation therapy for stage I/II breast carcinoma. Low or high dose rate sources were allowed. Dose prescription and treatment evaluation were based on recommendations in ICRU Report 58, including mean central dose (MCD), average peripheral dose, dose homogeneity index (DHI), cold, and hot spots. Three levels of quality assurance were implemented: (1) Pre-approval of institutions was required prior to entering patients onto the study. (2) The study chairman and medical physicist evaluated each treatment plan prior to treatment (rapid review). (3) Retrospective review of treatment was performed by the Radiological Physics Center in conjunction with the study chairman and RTOG dosimetry staff. Pre-approval focussed on accuracy of the dose algorithm and compliance with protocol guidelines. Rapid review was designed to identify and correct deviations from protocol. The retrospective review involved recalculation of dosimetry parameters and review of dose distributions to attain a clinical evaluation of the treatment. Specifying both central and peripheral doses resulted in uniform dose distributions, with a DHI (prescribed dose/MCD), of 0.83 ± 0.06. Vigorous quality assurance resulted in a quality study with few deviations, only 4 of 100 patients judged as minor variations from protocol and no patient judged a major deviation. This study should be a model for dose specification and quality assurance of future trials.

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SCHEMA

RADIATION THERAPY ONCOLOGY GROUP
RTOG 95-17

A PHASE I/II TRIAL TO EVALUATE BRACHYTHERAPY
AS THE SOLE METHOD OF RADIATION THERAPY
FOR STAGE I AND II BREAST CARCINOMA

SCHEMA

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LDR</td>
<td>Breast Brachytherapy</td>
</tr>
<tr>
<td>2. HDR</td>
<td>Arm 1: LDR 45 Gy / 3.5-6 days</td>
</tr>
<tr>
<td></td>
<td>Arm 2: HDR 34 Gy / 10 fractions / 5-7 days</td>
</tr>
<tr>
<td></td>
<td>(3.4 Gy b.i.d. separated by 6 hours)</td>
</tr>
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</table>

2 plane implants recommended

Dose Prescribed to the Clinical Target Volume (CTV)
Tylectomy cavity as outlined by clips,
plus margin of 2 cm peripherally and 1 cm superficial and deep
DOSE REPORTING AND QUALITY ASSURANCE

Dose specification and reporting for this protocol was adapted from the ICRU [Chassagne, D., Dutreix, A., Ash, D., Hanson, W.F., Visser, A.G., and Wilson, J.F.: Dose and Volume Specification for Reporting Interstitial Therapy. ICRU Report #58: 1997]

The doses to be reported are listed in the protocol:

**Prescribed Dose:** -- the dose the physician intends to give and enters into the patient’s treatment chart.

**Peripheral Dose (PD):** [Minimum Target Dose in ICRU #58] -- the minimum dose at the periphery of the CTV. Ideally, this is the same as the Prescribed Dose.

**Mean Central Dose (MCD)** – average of all local dose minima, the geometric center doses (GCD) of the triangles formed by adjacent seed trains, measured in the central plane. MCD = the arithmetic mean of all GCDs in the implant (Figure 1).

**High Dose Region:** -- the area encompassed by the isodose corresponding to 150% of the MCD, as measured in the central plane. The dimensions of such regions are to be reported on the RTOG treatment form.

**Low Dose Region:** -- region within the CTV encompassed by an isodose line corresponding to 90% of the prescribed dose. The maximum dimensions of any low dose regions are to be reported.

**Dose Homogeneity Index (DHI):** -- The ratio Prescribed Dose/ MCD

In order to quantify deviations from protocol prescription, several other dose parameters were defined for RTOG 95-17

**Average Peripheral Dose (APD):** -- the average of the four doses at the intersection of the coordinate axes with the sides of the target volume in a specific plane. (See the diagram in figure 2). If the peripheral dose at any of the points exceeded the prescribed dose, the prescribed dose was used in the sum. Therefore, only doses less than the prescribed dose impact this parameter.

**Percent Deviation (Dc, Ds, D⊥):** -- The difference between the APD and the Prescribed Dose, expressed as a percentage: D = 100(PD-APD)/PD. The percent deviation is calculated in the Central (Dc) and Sagittal (Ds) planes, and the two averaged to obtain Dav = (Dc + Ds)/2
Figure 1: Sketch of the concept of the Mean Central Dose as used in RTOG Protocol 95-17. The intersection of the perpendicular bisectors of the sides of the triangles formed by adjacent seed trains (catheters) are in a reasonably large region of low dose gradient in the area between the sources. The MCD is defined in the Central Plane of the implant.

Figure 2: Sketch of the definition of the Average Peripheral Dose (APD). The CTV is depicted as the ellipse and the axes are approximately centered on the CTV. The equation for the APD is included. The APD is calculated in the Central and Sagittal Planes.
QUALITY ASSURANCE PROGRAM

The Quality Assurance Program was a three pronged effort: 1) Pre-approval of the institution, 2) Rapid review of the implant (prior to insertion of sources) and 3) Retrospective review of the treatment.

Pre-Approval of the institution: Evaluation by the RPC
- Questionnaire:
  - Demographics: Institution Name, Radiation Oncologist and Physicist
  - Treatment Techniques (HDR, LDR, both), Source supplier and equipment
  - Quality Assurance Procedures: Verify source strength, source position, dosimetry procedures, redundant calculations.
- Benchmark Case: Idealized two plane implant: (See Figure 3)

Rapid Review: Evaluated by the PI (R Kuske) and his Physicist (R Wilenzick)
- Dose calculations and isodose curves submitted within 24 hours:
  - Draw in tylectomy cavity.
  - Surgical Clips and CTV clearly labeled (central, sagittal, and coronal planes)
  - Dose distributions include: prescribed dose, 90% of PD, MCD, and 150% of MCD
- Evaluation: PD, D_{av}, and DHI within criteria. Institution contacted to improve.

Retrospective Review: Performed by PI, RPC, and RTOG dosimetrist
- RPC Review:
  - Accepted dose distribution as submitted (no reconstruction of distribution)
  - Verified margins around tylectomy cavity
  - Recalculated MCD, APD, D_c, D_s, D_{av}, and DHI
  - Identified hot and cold spots
  - Assessed >1cm gap from source to skin
- Joint Review: PI, RPC, RTOG
  - Reviewed films:
    - Clips
    - Gap from source to skin
    - Coverage of target
  - Dose evaluation
    - Reviewed hot and cold spots
    - Reviewed PD, MCD, APD, D_{av} and DHI for compliance with protocol.
Figure 3. The idealized two-plane implant used as the benchmark case for RTOG Protocol 95-17. The tylectomy cavity is marked by clips and provisions for both HDR and LDR are included.
RESULTS

Pre-Approval: The benchmark case, an idealized two plane implant, was reviewed by the RPC to verify the institutions dose calculation algorithm and their ability to calculate the MCD and other dose parameters for this study. Thus it was not necessary to reconstruct the dose distributions for each protocol patient.

- Institutions were required to:
  - Have a source verification system directly traceable to NIST (usually through an ADCL)
  - Produce a dose distribution with Peripheral Dose and Mean Central Dose within ±15% of those calculated by the RPC.
  - Properly calculate DHI, Dc, Ds, and Dav.

- 27 Institutions requested pre-approval; for HDR, LDR, or both:
  - HDR
    - 18 were ultimately approved
    - 7 entered patients onto the study
  - LDR
    - 17 were ultimately approved
    - 6 entered patients onto the study

Selected results are presented in Table 1.

Demographics: Some demographics of the patients and their implants are included in Table 2.

Rapid Review: Treatment plans for all patients were submitted to the Principle Investigator of the protocol, prior to treatment. The dosimetry parameters were reviewed, and if they fell outside the protocol criteria, recommendations on how to improve the implant were give. Such recommendations were given for:

- 6 of the 68 HDR patients
- 2 of the 32 LDR patients

Final Review:
- The criteria for compliance with the protocol are presented in Table 3.
- The results of the final review are presented in Table 4.
- These results would be considered 'very good' for an external beam study, and even more so for a brachytherapy study.
RESULTS

Selected results of the agreement on dose specifications are listed in Table 5.

- In brachytherapy, with the inherent large dose gradients, we have been looking for a dose parameter that is more or less insensitive to the evaluator. The very close agreement between the RPC and Institutions on the calculation of the Mean Central Dose, MCD, suggests strongly that this may be such a dose parameter.

- The dose homogeneity index (DHI = PD/MCD) is intended to be a quantitative measure of the dose gradient across the tumor, avoiding the complications of the high dose gradients near the sources. In this protocol, the target value was DHI ≥ 0.85, and a value of ≥ 0.75 was considered acceptable (per protocol). We see that only one implant had a DHI < 0.75, and that the average values were, in fact, quite close to the target value. The difference between HDR and LDR is not significant. It would be interesting to see if optimizing somehow on DHI would improve the implants.

- This protocol based prescription on a nominal value specified by the Radiation Oncologist, rather than on the Peripheral Dose (Minimum Target Dose). The average deviation, D_{av}, was designed to quantify the difference between the Prescribed Dose and the Peripheral Dose. The results are again very tight with average deviations of less than 5% and only two implants with deviations greater that 10%. Again the differences between the HDR and LDR are not significant.

- The reasons for the assignment of 'minor deviation' are listed. The small DHI appears to have resulted when the tylectomy cavity collapsed so that the two planes have minimal separation.

Table 5: Agreement between the RPC and the institutions on various dose parameters.

<table>
<thead>
<tr>
<th></th>
<th>HDR</th>
<th>LDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RPC/Inst for MCD</td>
<td>0.992 ± 4%</td>
<td>0.995 ± 3%</td>
</tr>
<tr>
<td>DHI (PD/MCD)</td>
<td>0.84 ± 0.06</td>
<td>0.81 ± 0.06</td>
</tr>
<tr>
<td>D_{av}</td>
<td>4.6 % ± 3.9%</td>
<td>3.4 % ± 4.5%</td>
</tr>
<tr>
<td>Minor Variations</td>
<td>D_{av} = 16.4 %</td>
<td>DHI = 0.66</td>
</tr>
<tr>
<td></td>
<td>D_{av} = 15.3%</td>
<td>Cold spot, dead space</td>
</tr>
</tbody>
</table>
RESULTS

Table 1: Results of dose intercomparisons for the benchmark case, during pre-approval. The RPC dose is 2 to 3% higher on average, with standard deviations of 4 to 6%.

<table>
<thead>
<tr>
<th></th>
<th>MCD</th>
<th>APD&lt;sub&gt;C&lt;/sub&gt;</th>
<th>APD&lt;sub&gt;S&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDR</td>
<td>Average (RPC/Inst)</td>
<td>1.029</td>
<td>1.032</td>
</tr>
<tr>
<td></td>
<td>Std. Dev. (%)</td>
<td>4.0%</td>
<td>4.2%</td>
</tr>
<tr>
<td>LDR</td>
<td>Average (RPC/Inst)</td>
<td>1.020</td>
<td>1.022</td>
</tr>
<tr>
<td></td>
<td>Std. Dev. (%)</td>
<td>6.0%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

Table 2: Selected demographics of the patients and their implants.

<table>
<thead>
<tr>
<th></th>
<th>HDR</th>
<th>LDR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td># of Catheters</td>
<td>16.6 ± 3.3</td>
<td>17.0 ± 3.9</td>
</tr>
<tr>
<td>Optimized?</td>
<td>Yes</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>unclear</td>
<td>11</td>
</tr>
<tr>
<td># of Planes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>more</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3: Criteria for compliance with the protocol.

<table>
<thead>
<tr>
<th>Per Protocol</th>
<th>Prescribed dose</th>
<th>DHI</th>
<th>D&lt;sub&gt;av&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>± 5%</td>
<td>≥ 0.75</td>
<td>≤ 10%</td>
</tr>
<tr>
<td>Minor protocol variation</td>
<td>5% &lt; D &lt; 10%</td>
<td>0.65 &lt; DHI &lt; 0.75</td>
<td>10% &lt; D&lt;sub&gt;av&lt;/sub&gt; &lt; 20%</td>
</tr>
<tr>
<td>Major protocol deviation</td>
<td>D &gt; 10%</td>
<td>&lt; 0.65</td>
<td>&gt; 20%</td>
</tr>
</tbody>
</table>

Table 4: Results of the final review of patients entered onto RTOG Protocol 95-17.

<table>
<thead>
<tr>
<th></th>
<th>Per Protocol</th>
<th>Minor protocol variation</th>
<th>Major protocol deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
CONCLUSIONS

The medical endpoints of The RTOG Protocol 95-17 will be treated in another venue.

This protocol however had a number of other endpoints, which were covered in this presentation. The protocol has shown that:

- The compliance rate for treatments on this study was exceptionally high. There were only 4% minor variations from protocol, with no major deviations from protocol.
- Multiple institutions were able to consistently report doses in a format based on ICRU recommendations for interstitial brachytherapy.

These two conclusions lead to the most important conclusion, that:

- Breast Brachytherapy can be performed in a Cooperative Clinical Trial setting.

All of us involved in the quality assurance of this study feel strongly that:

- The high level of Quality Control employed in this study was a major contributor to the high level of quality of the treatment in the study.
- This study should be a model for dose specification and quality assurance for future planar implant protocols.
- We learned a number of lessons that should be incorporated into future protocols. These are listed below.

POINTS TO IMPROVE FOR FUTURE PROTOCOLS

- Have the institution mark the first and last dwell positions on the films.
- Reinforce the use of hemi-spherical buttons.
- Urge the use of opaque buttons to mark the skin at the entry and exit.
- Use large 1cm surgical clips to define the tylectomy cavity.
- Use contrast in the tylectomy cavity.
- Direct lateral films are not helpful. The use of variable angle films helps to separate sources.
- Require 0.5cm separation between dwell positions in HDR, not the current 1cm.
- Reinforce the requirement of a 1cm dead space between the first source and the skin surface.
- Mark the skin surface on the plan, especially if it is used as a boundary.
- If the plan was modified due to rapid turnaround review, resubmit the modified plan used for the actual treatment.
- Request a central plane isodose plan with enough isodose lines so the reviewer can recalculate the MCD (≈ 10% increments in the CTV)(currently only 4 isodose lines are requested).
- Redesign the pre approval benchmark case. The current case is too geometric to test subtleties of MCD.
- Allow volume implants.
- Recommend CT dosimetry.
- Reassess how to calculate the peripheral dose. Continue with calculation on the axes or require calculation at the lowest isodose line in the plane.
- Reassess whether a DHI of 0.75 is too low. Our data suggests that a DHI limit closer to 0.80 may be accomplished.
- Reassess the acceptable levels for $D_{av}$. $D_{av} \leq 5\%$ may be an achievable level. However, the modified calculation of Peripheral Dose, as suggested above, would have an impact on $D_{av}$ also.
ACKNOWLEDGEMENTS

The authors wish to acknowledge the participation, cooperation, and hard work of the Radiation Therapy Teams at the participating institutions. These include the: Radiation Oncologists, Physicists, Dosimetrists, Therapists, Data Managers, and others who contributed to the quality assurance of this protocol.

This poster paper can be viewed on our website, 
http://rpc.mdanderson.org, select ‘recent postings.’

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