PROTOCOL TO STUDY

THE VALUE OF RADIATION THERAPY USING NEUTRONS ALONE

OR IN COMBINATION WITH PHOTONS IN

THE TREATMENT OF CLINICAL STAGE C ADENOCARCINOMA

OF THE PROSTATE

Frank R. Hendrickson and Lionel Cohen
May 29, 1985
SCHEMA

ADENOCARCINOMA OF THE PROSTATE, STAGE C

Histology
Well differentiated
Poorly differentiated

Pelvic irradiation
with photons*

Previous orchiectomy
Yes
No

Pelvic irradiation
with mixed beam*,**

Pelvic Nodal Status No, Nx, N+

Pelvic irradiation
with neutrons*

*Includes boost to the prostate.
**3 photon, 2 neutron fractions per week.

A facility may choose to randomize patients into two or three arms but all must select photons only.

<table>
<thead>
<tr>
<th>DOSES (Gy):</th>
<th>Pelvis</th>
<th>Prostate Boost</th>
<th>Total</th>
<th>Fractions</th>
<th>Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons</td>
<td>45</td>
<td>21.6</td>
<td>66.6</td>
<td>37</td>
<td>7.5</td>
</tr>
<tr>
<td>Mixed Photon</td>
<td>27</td>
<td>12.6</td>
<td>66.6*</td>
<td>37</td>
<td>7.5</td>
</tr>
<tr>
<td>Neutron</td>
<td>6(18*)</td>
<td>3(9*)</td>
<td>20</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

* RBE of 3
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1 INTRODUCTION

Carcinoma of the prostate has been treated with surgical resection, hormonal manipulation and radiation therapy. Unfortunately, by the time of diagnosis, very few patients with carcinoma of the prostate are candidates for curative surgical procedures (Flocks). Estrogen therapy is effective in the treatment of inoperable and metastatic carcinoma of the prostate (Nesbit et al.), although in high doses, it was found to increase the risk of cardiovascular disease (The Veterans Administration Cooperative Research Group). Radiation therapy has been shown to be effective, by itself, in the treatment of inoperable carcinoma of the prostate when confined to the pelvis (Bagshaw, del Regato, George, Rubin). It has also been shown that there is early spread of disease to the pelvic and para-aortic lymph nodes in all stages of carcinoma of the prostate. In surgically staged patients 289/646 stage C patients had positive nodes. In the past 25 years, advances in the field of radiotherapy have resulted in a substantial improvement in local control, while the incidence of normal tissue complications has declined. Nevertheless, a significant number of tumors continue to be locally incurable at doses within tissue tolerance, and improved control rates are achieved only at the cost of increased radiation sequelae. While distant failure may be occult at the time of treatment, it is also plausible that distant failure occurs later from residual local persistence. In the management of human cancer, both the duration and quality of survival are important. Fast neutrons have been proposed as a means of improving the control of bulky tumors while keeping radiation injury to a minimum.

The recent analysis of the results of RTOG 77-04 which compared standard photon treatment to a mixed neutron-photon treatment indicated a statistically significant improvement for patients receiving part of their treatment with neutrons.

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Loc. Reg. Failure</th>
<th>Dist. Mets.</th>
<th>Any Failure</th>
<th>Survival</th>
<th>Severe Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photons</td>
<td>6686+496</td>
<td>22%</td>
<td>44%</td>
<td>56%</td>
<td>61%</td>
<td>1/31</td>
</tr>
<tr>
<td>Mixed</td>
<td>6685+207</td>
<td>7%*</td>
<td>36%</td>
<td>38%</td>
<td>80%*</td>
<td>4/47</td>
</tr>
</tbody>
</table>

*P value <0.05

The patient status was similar in both groups and a Cox regression analysis for survival and for local regional control indicated the treatment assignment as the most important factor.
<table>
<thead>
<tr>
<th>Survival</th>
<th>Local Reg. Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Stage</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Acid phosphatase</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>Dose</td>
<td>NS</td>
</tr>
<tr>
<td>Grade</td>
<td>NS</td>
</tr>
<tr>
<td>Nodes</td>
<td>NS</td>
</tr>
<tr>
<td>TURP</td>
<td>NS</td>
</tr>
<tr>
<td>Seminal ves +</td>
<td>NS</td>
</tr>
<tr>
<td>BPH</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>NS</td>
</tr>
<tr>
<td>Other diseases</td>
<td>NS</td>
</tr>
</tbody>
</table>

These results in the photon arm are similar to the results of RTOG 75-06 which evaluated various photon treatment volumes for stage C patients or patients with positive nodes. In that study the local regional failure was 20%, the distant mets were 50% and survival was 65%.

The principal rationale for fast neutron radiotherapy is related to the hypoxic cell problem (OER*). Numerous radiobiological studies have shown that hypoxic cells are 2.5 to 3.0 times more resistant to the effects of conventional X and gamma irradiation than are well oxygenated cells. While the cells in most normal tissues are well oxygenated, most solid tumors have hypoxic regions which have outgrown their vascular supply. It has been postulated that these cells remain viable and provide a focus for local recurrence. With neutrons, radiosensitivity is less dependent upon oxygenation. Other potential advantages for neutrons include less cell cycle or cell age dependence and less recovery of sublethal and potentially lethal damage.

This study is proposed to re-evaluate the results of RTOG 77-04. If the mixed beam patients do better an hypothesis would be that neutrons are superior for control of prostate cancer and the improved local regional control transforms into improved overall survival by reducing late distant metastases from local persistence. If the 40% neutron dose is superior to photons alone a treatment program of 100% neutrons must be tested. That was one arm of the 77-04 study, but because of the poor quality of the neutron sources, the neutron-only arm did not accrue patients. The current results from 77-04 should facilitate referral of patients so accrual to a three-arm study should be adequate.

*Oxygen enhancement ratio (OER) refers to the ratio of the radiation dose required to produce a specified biologic effect under anoxic conditions to the dose required to produce the same effect under well oxygenated conditions.
A current RTOG protocol (76-06) is studying pelvic versus pelvic and paraaortic nodal irradiation versus hormonal therapy in the treatment of locally advanced (Stage C) prostate carcinoma. The current study will use an identical photon arm as RTOG 76-06 so that comparisons may be possible between the two studies.

2 OBJECTIVE OF THE STUDY

2.1 To determine whether fast neutron or mixed beam radiotherapy is superior to megavoltage photons in the treatment of Stage C carcinoma of the prostate as measured by relapse-free survival and total survival.

3 SELECTION OF PATIENTS

The basis of selection will be histologically-proven adenocarcinoma of the prostate.

3.1 Conditions for Eligibility

3.1.1 Any patient with Stage C adenocarcinoma of the prostate who has not had curative surgery or previous irradiation.

3.1.2 Patients with informed consent to participate in the study.

3.1.3 Adequate bone marrow (WBC >4,000/mm³, Hct >35 and platelets >100,000) and renal (BUN <30 mg%) functions.

3.2 Conditions for Ineligibility

3.2.1 Previous radiation therapy, except for skin cancer irradiated outside potential pelvic treatment fields.

3.2.2 Previous or concurrent cancers other than skin cancer.

3.2.3 Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of the protocol requirements.

3.2.4 Patients not available for regular follow-up.

3.2.5 Performance status below 40% on Karnofsky scale.

3.2.6 Over 80 years of age.
3.2.7 Previous curative prostatic surgery.
3.2.8 Bone scan positive for cancer.
3.2.9 Serum acid phosphatase may be elevated.

4 STAGING WORK-UP

4.1 Mandatory

4.1.1 History and physical examination.
4.1.2 Histologic proof of adenocarcinoma.
4.1.3 Serum acid phosphatase.
4.1.4 Chest x-ray: PA, lateral.
4.1.5 IVP and/or retrograde pyelogram.
4.1.6 Bone scan (positive areas should have further radiographic investigation).
4.1.7 CT scan of prostate.

5 STRATIFICATION AND RANDOMIZATION

5.1 Stratification will include:

5.1.1 Histology: well-differentiated versus poorly differentiated.

5.1.2 Patient age over 65 and under 65.
5.1.3 Acid phosphatase normal or elevated.

5.2 Randomization will be to one of the following options:

5.2.1 Neutron therapy to pelvis with boost to prostate.
5.2.2 Mixed beam therapy to pelvis with boost to prostate.
5.2.3 Conventional radiation therapy to pelvis with boost to prostate.
5.3 Randomization will be with the RTOG Operational Office (215-574-3191); Monday – Friday; 9:00 a.m. – 5:00 p.m. EST) once a patient has been found acceptable by all the investigations and the patient has consented to participate in the study. The following information must be given to the Operations Office: Protocol name, Institution, Physician, Patient Name, and Histology. The physician will receive a treatment assignment that will later be confirmed by mail.

6 RADIATION THERAPY PROGRAM

6.1 Doses

6.1.1 With photons the daily dose will be 1.8 Gy, 5 days a week, delivering 45 Gy (25 fractions) to the pelvic field. The boost volume receives a further 21.6 Gy (12 fractions). The total dose to the prostate is thus 66.6 Gy in 37 fractions over 7.5 weeks.

6.1.2 Mixed beam consists of 3 photon fractions (1.8 Gy) and 2 neutron fractions (0.6 Gy) per week, a weekly equivalent dose of 9 Gy. A total of 25 fractions (15 photon fractions or 27 Gy + 10 neutron fractions or 6 Gy) is given to the pelvis and a further 12 fractions (7 photon fractions or 12.6 Gy + 5 neutron fractions or 3.0 Gy) to the prostate boost volume. Total doses are 39.6 Gy photons + 9 Gy neutrons or a total equivalent dose of 66.6 Gy in 37 fractions over 7.5 weeks.

6.1.3 With neutrons alone, treatment will consist of 12 fractions (each 1.666 Gy) 3 times a week over 4 weeks. The wider (pelvic) field will receive 8 fractions totaling 13.33 Gy; the prostate boost receives 4 fractions (a further 6.67 Gy). Total doses are then 20 neutron Gy in 12 fractions over 4 weeks.

6.2 Radiation Portal

6.2.1 Pelvic Fields:

Inferior border - 2 cm below the inferior border of the prostate or the lower border of the ischial tuberosity, whichever is lower.

Lateral borders - At least 1 cm lateral to the medial rim of the ilium.

Superior border - The sacral prominatory.
Such shaping of the fields as necessary to protect bone marrow is encouraged.

**Anterior margin** - The anterior edge of the symphysis pubis.
**Posterior margin** - Mid-plane of rectum (at level of prostate).

### 6.2.2 Prostatic Boost Fields:

A field large enough to give an adequate margin around the prostate, usually 6x6 cm to 8x8 cm will be centered on the prostate.

Any field arrangement delivering the prescribed dose to the prostate within tolerance limits of critical structures (see 6.4) is acceptable. Alternative arrangements include 4 field box, cross-fire lateral arcs and oblique fields. In any case, all fields will be treated at each session.

### 6.3 Physical Parameters

#### 6.3.1 Localization films will be obtained for each treatment field and must be submitted for review.

#### 6.3.2 Isodose distributions for the pelvis, one for a transverse section through the center of the field, and one for a transverse section through the prostate will be obtained and submitted with the on-study form.

### 6.3.3 External Radiation Sources

#### 6.3.3.1 Photons: X-ray generators capable of producing photon beams with a peak photon energy of 4 MeV or greater or Cobalt 60 shall be required. The output of the unit must be adequate to permit the use of an SSD of 80 cm or greater.

#### 6.3.3.2 Neutrons: For neutron irradiation, accelerators achieving neutron beams of 40 MeV or greater proton energy, or 14 MeV D-T neutron generators shall be required. The minimum acceptable SSD is 125 cm.

### 6.4 Critical Structures and Tolerance

#### 6.4.1 Bladder: The dose to the entire bladder should not exceed 60 Gy or Gy-equivalent. The dose to the trigone and portions of the posterior wall should not exceed the dose to the prostate.
6.4.2 Rectum: The dose to the rectum in its entirety should not exceed 55 Gy or Gy-equivalent. Portions of the anterior wall of the rectum will receive the same dose as the prostate.

6.4.3 Small bowel: The dose to any segment of the small bowel should not exceed 55 Gy or Gy-equivalent. Efforts should be made to exclude the small bowel from the true pelvis by such maneuvers as treating the patient in a prone position. Evaluation of small bowel location in patients with previous small bowel disease or previous abdominal surgery should be made by barium studies.

6.4.4 Bone marrow: The bone marrow will be unavoidably irradiated in all field arrangements. The percentage of bone marrow radiated will be about 25% with pelvic irradiation. The dose to these bone marrow areas will produce decreased function for at least 1 to 2 years.

6.5 Additional Treatment

A TUR is to be avoided unless absolutely necessary, since previous experience suggests that post-TUR patients tolerate radiation therapy less than those managed with lesser procedures. Prior to a TUR, attempt one week of drainage via a silastic catheter while treating with antibiotics, and/or radiation; if upon removal of the catheter, after one week of drainage, there is still obstruction, then a TUR is permissible. After the TUR, start or resume therapy as soon as possible (1 week). Do not adjust the dose of radiation. Estrogen therapy does not exclude a patient but must be reported on the appropriate forms.

7 STUDY PARAMETERS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Prior</th>
<th>Monthly for 3 months (post-random-</th>
<th>At Follow-Up</th>
<th>At 1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rectal Examination</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SMA-12</td>
<td>X</td>
<td>X(b)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Serum Acid Phosphatase</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Chest x-ray PA &amp; Lateral</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>IVP</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Bone Scan</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Transrectal Biopsy</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CT scan of pelvis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
8 SPECIFIC END-POINTS TO BE MEASURED

8.1 Tumor response (as determined by palpation, CT scan and biopsy):

8.1.1 Primary tumor response will be measured by palpation and CT scans. Estimate length (apex to base) and width of each nodule or tumor mass by the examining finger and record on anatomic diagrams. The following definitions of response will be used:

(A) Complete regression of primary: complete disappearance of primary tumor and local non-nodular extentation.

(B) Partial regression of primary: at least a 50% decrease in the product of the length and width of the tumor mass or nodule (in the case of more than one nodular tumor mass, the sum of the products will be used).

(C) No change in primary: changes too small to qualify for partial regression or progression.

(D) Progression of primary: at least a 25% increase in the product of perpendicular diameters of measurable disease; (or the sum of the products if more than one nodule or mass is measurable).

Biopsy information, when available will be used to evaluate primary tumor response.

8.1.2 Lymph node response using lymphangiogram and CT scans. If sufficient dye remains to evaluate lymph nodes, or if patient has a repeat lymphogram, or if nodes can be identified on the CT scan, then status will be graded as:

(A) Abnormal

(B) Normal
8.2 Effectiveness of local control (primary + direct extension).

8.3 Time to first metastases, as detected by radiograph or bone scan; biopsy proof not needed.

8.4 Loss of potency.

8.5 Urinary complications.

8.6 Rectal complications.

9 FOLLOW-UP EXAMINATION

9.1 Once a month for the first 3 months following onset of treatment.

9.2 Every 3 months for the remainder of the first year, plus year two.

9.3 Every 6 months for the remainder of the patient's life.

9.4 Additional visits as necessary.

10 TREATMENT FAILURE With proven recurrence of disease or the development of distant metastases, the patient is eligible for any additional appropriate therapy or inclusion in other investigative protocols, but should still be followed in order to document survival and late effects of treatment.

11 CENTRAL PATHOLOGY REVIEW Central pathology is desirable but has not been formalized.

12 STATISTICAL CONSIDERATIONS It is assumed that the main comparisons will be between photon and mixed photon-neutron therapy, and between photon and neutron therapy. The major endpoint will be the frequency and duration of local disease control. Furthermore, it is assumed that patient survival will follow an exponential distribution.

The null hypothesis (of equal ability to control local disease) will be tested against the alternative that employing neutron therapy can increase the frequency and duration of control.

It is assumed that patient accrual will continue for 2-3 years and that a statistical analysis will be made after the last patient entered has been followed by 2-3 years.

Using an anticipated entry rate of approximately 50 patients per year, and using a one-sided test of significance (P=0.05), it should be possible to declare the following therapeutic improvements as being statistically significant:
PROBABILITY OF DETECTION

<table>
<thead>
<tr>
<th>Improvement</th>
<th>Probability of Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>An increase of 20% in the percentage of tumors that are controlled.</td>
<td>80%</td>
</tr>
<tr>
<td>An increase from 5 year survival of 40% to 5 year survival of 60%</td>
<td>75%</td>
</tr>
</tbody>
</table>

These estimates are subject to revision based on the actual accrual.

13 STATISTICAL FORMS

Data will be submitted to the operations office in the following manner:

Prostate On-study Form and treatment planning information | Within 1 week of randomization
Prostate Radiotherapy Form | At end of radiotherapy
Prostate Follow-up Form | At each stipulated follow-up
| At recurrence/relapse
Prostate Death Form | At death

14 PATIENT CONSENT FORM

All institutional, federal and state requirements concerning human investigation will be satisfied.
REFERENCES


