Randomized Trial for Treatment of Localized Cancer of the Prostate: Radiotherapy versus Radical Prostatectomy

Michelle Svatos
Jeannie Song

Statistics 542
Clinical Trial Protocol
April 21, 1994

Abstract

This paper specifies a first draft for a full scale, phase III, multi-center randomized clinical trial protocol. The trial proposes to test two widely used treatments for Stage A1 and B localized cancer of the prostate, radical prostatectomy and radiotherapy. The primary outcome variable is overall survival at 5, 10 and 15 years. Secondary outcome variables are disease-specific survival after 5, 10 and 15 years, time to local failure, and quality of life.

Although the subject and his primary physician will know which treatment the subject has received for obvious reasons, the protocol incorporates use of several independent committees to ensure that as many aspects of the trial as possible are blinded. Independent committees will be set up for analysis of all laboratory tests, analysis of cause of death, statistical analysis of data, and data monitoring. The trial is scheduled to last 17 years and involve approximately 550 subjects.
## Contents

1 Introduction  
   1.1 Background and Overview  
   1.2 Motivation for this Study  

2 Objectives  
   2.1 Primary Question and Response Variables  
   2.2 Secondary Questions  
   2.3 Subgroups  

3 Sample Size Estimation  

4 Selection Criteria  
   4.1 Treatment Center Inclusion  
   4.2 Patient Inclusion and Exclusion  
      4.2.1 Staging  

5 Pre-Randomization Evaluation  

6 Randomization  

7 Intervention Strategy  
   7.1 Surgery Group  
   7.2 Radiotherapy Group  

8 Follow Up  
   8.1 Schedule  
   8.2 Quality of Life Rating  
   8.3 Subject Withdrawal Policy  

9 Data Monitoring  
   9.1 Schedule and Duties  
   9.2 Criteria for Early Termination  
   9.3 Criteria for Trial Extension  

10 Non-Compliance Policies  
   10.1 Crossovers  
   10.2 Dropouts  

11 Statistical Analysis  
   11.1 Estimation of Survival Curves  
   11.2 Comparison of Survival Curves  

12 Conclusions  

1
1 Introduction

1.1 Background and Overview

Prostate cancer is the most common tumor diagnosed in men in the United States and accounts for 20% of all newly diagnosed cancers. It is also the second most common cause of male cancer deaths in the United States, accounting for approximately 11% of them. Although it is rarely found in men younger than 40 years old, its incidence and prevalence increase steadily with increasing age. It is the only cancer that exists with no peak age of occurrence. Because of this, as the life expectancy for men increases, so does their chance of developing prostate cancer. Clearly the problem will only continue to gain importance in the future.

Autopsy studies have previously demonstrated 30% incidence of occult disease in men by age 50 and up to 70% of men 80 years of age or older. Race also appears to play a role, with black males in this country having a slightly higher rate of development of prostate cancer (9.4% versus 8.7% for whites) and a higher mortality rate than whites. The western lifestyle and diet have also been implicated on the basis of population comparisons and hormonal changes with dietary manipulation.

Despite its high incidence, the epidemiology of prostate cancer is still poorly understood. This stems in part from the fact that little is known about the specific causes of the disease. In addition, the natural history of prostate cancer is extremely variable and has not been well studied.

The disease itself is extremely complex and much more needs to be learned about it. Because most patients with this cancer have a nonclinical form of the disease, there is a dilemma concerning the best diagnostic and treatment approach. Although there are various techniques such as digital rectal examination, PSA (prostate specific antigen), prostate ultrasonography, and needle biopsy available today to detect this type of cancer, new and more improved methods are still being researched.

Prostate cancer is usually discovered by rectal examination performed during a physical examination or detected incidentally in the histologic material obtained from a transurethral prostatectomy being performed for enlargement of the prostate. Patients with localized disease may be asymptomatic at the time of the diagnosis or may have symptoms of urinary retention.

The extent of tumor involvement (stage) is described by a classification system that has gone through many modifications over the years. Clinical staging refers to the extent of the disease as determined by means of laboratory tests, including biopsy and physical examination of the patient. Pathologic staging is done by microscopic assessment of the surgically removed tissue and organs and often exceeds the clinical estimation of the extent of the disease.

Difficulties in describing the disease extent have arisen from the use of different staging systems. At least two accepted clinical staging systems are in use
in the U.S. The American Urologic System consists of A, B, C and D stages, and the American Joint Committee uses a T, N, and M system. The major problem with both systems is the failure to offer accurate prognosis for the patient with an intermediate-grade tumor. In a given prostate cancer, many variations in the genetic make-up and morphology exist, which make it difficult to assess prognosis based on grade alone. However, it is important from the standpoint of prognosis and application of appropriate treatment to at least ascertain whether localized or metastatic disease is present before the intervention commences.

Therapeutic intervention is offered with the objective of achieving cure, local disease control, lessened metastasis, and increased duration of survival and quality of life. The best method of achieving any or all of these ends is still highly surrounded in controversy. One possible treatment, as alluded to above, is the surgical procedure of radical prostatectomy. In this procedure, the prostate gland, the seminal vesicles, and ampulla of the vasa deferentia are totally removed.

Another possible treatment is that of radiotherapy of the prostate. This can either be accomplished by external photon-beam radiation of very high energy, or by radioactive seeds (brachytherapy) implanted in the pelvis. Presently, the best results are still obtained with external beam irradiation, and therefore a standard course of external beam prostate radiation will be used in the second arm of this study. However, it will be highly interesting to note the progress and growing availability of brachytherapy, since it may be advantageous in the future to evaluate the combined effects of brachytherapy and external beam therapy.

1.2 Motivation for this Study

At the present time, it is not clear which treatment modality is most effective for intermediate-grade prostate tumors. In particular, one can find many articles that claim with equal vigor that either radical prostatectomy or radiotherapy of the prostate is the "gold standard" for treatment. There has been one other randomized trial between surgical and radiotherapeutic treatment for localized prostate cancer[2], but it has been highly criticized for involving a number of biases in several aspects of the trial[5]. In addition, that study was conducted fourteen years ago; there has been considerable progress in the radiotherapy equipment and techniques since then, as well as some modest refinements in surgical practice.

2 Objectives

The primary objective for this trial is to evaluate the effectiveness of surgery and radiotherapy for treatment of localized prostate cancer for men in the U.S. In the future, it is hoped that the results of this trial will serve as a starting point
for recommending a particular treatment for U.S. men with newly diagnosed prostate cancer.

2.1 Primary Question and Response Variables

The primary objective of this trial is to determine whether radical prostatectomy or radiotherapy of the pelvis is significantly more effective in improving the overall survival at 5, 10, and 15 years post-treatment. The cause of death for each subject will be determined by an independent death review committee.

2.2 Secondary Questions

Because there is such a dearth of information about prostate cancer, a study of this magnitude should attempt to shed some light on other aspects of the disease, in order that new studies may eventually be designed with a quantitative basis. Therefore, in addition to overall survival, we are interested in three secondary outcome variables.

**Time to Local Failure** At each follow-up examination, a local biopsy of the diseased area will be taken and sent to the an independent laboratory team. It is not clear at this point whether or not a positive biopsy of the prostate is linked to decreased survival, as there have been numerous opposing views on this technique[4]. It is hoped that the results of this trial will provide a clearer picture of the value of biopsies.

**Time to Metastatic Disease** Every six months subjects will be re-examined for evidence of metastatic disease. This will be done in three ways: radioisotopic bone scan, prostate-specific antigen test(PSA), and prostatic acid phosphatase test (PAP). If no metastases were found at the last examination before death, but autopsy results reveal metastases at the time of death, then the time to metastatic disease will be considered the time from treatment until death.

**Quality of Life** Any study intervention may induce changes in a subject's quality of life. In this case, one treatment arm is receiving a very invasive, but rather short-lived intervention (surgery), while the other treatment arm is receiving a less invasive but more drawn-out intervention, radiotherapy. Because of the different way each treatment impacts the patient's life, the treatment that extends life the most may not necessarily be the best treatment to recommend for each patient. In particular, some men with prostate cancer may have little life expectancy left, and might therefore prefer a treatment associated with higher quality of life. Each subject will evaluate his own quality of life by using a simple questionnaire filled out on a regular basis. See the discussions under Section 8.2 for more information.
2.3 Subgroups

As in most multicenter trials, the data will be stratified by treatment center. This will be helpful in ascertaining whether or not the results may be generalized to all appropriate treatment centers. It also important to identify whether there is a problem or other effect unique to a particular treatment center.

Subjects will also be stratified by age at the time of enrollment in the study. Age has been arbitrarily broken into 3 groups: under 60, 60-70, and over 70 years of age.

The data will also be stratified according to tumor stage, as this variable has been found to play a very significant role in other studies [4]. The stages included upon entry into this study will be A2, A3, B1, and B2.

3 Sample Size Estimation

The sample size for the survival analysis may be estimated by a procedure described by Demets et al [3]. The null hypothesis for this situation is that the force of mortality in the surgery group, \( \lambda_S \), is the same as that in the radiotherapy group, \( \lambda_{RT} \)

\[ H_0 : \lambda_S = \lambda_{RT} \]  

If \( H_0 \) is not true, then there must be a difference between the forces of mortality, and hence between the radiotherapy and surgery survival curves.

The next step in estimating the sample size is to choose a "significance level", \( \alpha \), and a "power", \( 1 - \beta \). The significance level is simply the probability of observing a falsely positive result. In this trial, a false positive would occur if a difference in the survival curves for the surgery and radiotherapy groups was by chance found to be significantly large, even though in reality the difference was not significant. The selection of \( \alpha \) is arbitrary, but it is conventionally accepted to choose values of 0.01 or 0.05 in most clinical studies. The value chosen here is 0.05.

The parameter \( \beta \) is the probability of accepting a falsely negative result. A false negative here means that the difference between the surgery and radiotherapy survival curves groups was by chance found to be insignificantly small, even though in reality the difference was significant. The probability of not rejecting a significant result is given by \( 1 - \beta \), which is termed the power of the study as mentioned above. For this estimate, a power of 95% has been selected.

Once the significance level and the power of the study have been chosen, the number of subjects needed for each group may be estimated by

\[ 2N = 2(Z_\alpha + Z_\beta)^2 \left[ \phi(\lambda_S) + \phi(\lambda_{RT}) \right] \left( \lambda_S - \lambda_{RT} \right)^2 \]  

where \( Z_\alpha \) (for a two-sided test) and \( Z_\beta \) can be found from Tables 7-1 and 7-2 in DeMets et al for the stated values of \( \alpha \) and \( \beta \). The functions \( \phi(\lambda) \) depend...
on the overall length of the trial, \( T \), the length of the recruitment period, \( T_0 \), and the forces of mortality themselves. Then can each be found respectively from

\[
\phi(\lambda) = \frac{\lambda^2}{1 - e^{-\lambda(T-T_0)} - e^{-\lambda T}}
\]

(3)

The recruitment period has been set to two years and the overall length of the trial is to be 15 years. The only remaining difficulty comes from estimating values for the forces of mortality, which are the inverse of the mean survival times in each group. Using data from the previous studies, [8, 2] these values can be roughly estimated as \( \lambda_s = \frac{1}{6\text{years}} \), and \( \lambda_{RT} = \frac{1}{4\text{years}} \), based on overall survival. This then implies values of \( 3.077 \times 10^{-2} \) per year and \( 6.441 \times 10^{-2} \) per year for \( \lambda_s \) and \( \lambda_{RT} \) respectively.

Putting these values into equation (3) above, one obtains a required sample size of

\[
2N \approx 350.
\]

(4)

It is anticipated that the actual number of participants required will be higher than this due to noncompliance. The previous randomized study by the Uro-Oncology group had a 15% crossover rate and approximately a 10% dropout rate. This trial is expected to have slightly fewer crossovers because of a better screening and a shorter delay between randomization and treatment [see section 6], but more dropouts because of the longer duration. Therefore overall non-compliance will be estimated at 25%, which brings the total sample size to approximately

\[
2N \approx 440.
\]

(5)

It should be emphasized that this is only a rough estimate, since there are several assumptions involved in the derivation that are questionable. First, we have assumed a constant force of mortality throughout the trial for each group. This is erroneous, because relatively many patients are expected to die during the first year after treatment due to complications of the intervention, before the rate levels off slightly. Towards the end of the trial the mortality rate will again be expected to increase, because by that point other age-related causes will affect the overall survival significantly. To keep this problem in perspective, disease-specific mortality has been named as a secondary variable.

Another assumption in the sample size estimate is that the patients are enrolled at a constant rate throughout the two year recruitment period. This is not generally true; however, since \( T_0 \) is relatively small compared to \( T \), this is probably not an overwhelming effect.

Perhaps the most significant problem with this sample size estimate is the values for the forces of mortality. The data that led to the estimated values is at least fourteen years old, and radiotherapy techniques have improved significantly enough since then to close the gap between the mortality rates in the two groups. It is difficult to quantify the extent of this effect, but a conservative approach
would be to increase the sample size by another 25%, which gives a final estimate of

\[ 2N \approx 550. \]  

(6)

4 Selection Criteria

4.1 Treatment Center Inclusion

Only U.S. treatment centers with adequate radiation and surgical resources will be invited to participate in this trial.

Adequate radiotherapy resources include megavoltage machines having photon energies of at least 24 MV, bellyboards for patient positioning and immobilization, and a three-dimensional CT-based planning system.

Adequate surgical resources include surgeons who are certified by the American Medical Association to perform radical prostatectomy.

Participating physicians must agree that they are in a state of equipoise with respect to the preferential treatment and to adhere to the protocol to the best of their ability.

4.2 Patient Inclusion and Exclusion

Patients presenting with newly diagnosed, previously untreated, biopsy-proven, prostatic adenocarcinoma are candidates for this study. Patients must be able to attend to one of the approved centers (above) regularly for therapeutic intervention and follow-up.

4.2.1 Staging

It is extremely important the stage of each candidate’s disease is carefully evaluated before he is admitted for randomization. Only subjects with tumor of stages A2 or B will be included in this study. This enables us to exclude from treatment those patients who are destined to do well without treatment (stage A1) and, similarly, to exclude those patients who already have metastatic disease and are therefore bound to die relatively soon regardless of intervention.[5]

The staging system that will be used is the Whitmore-Jewett system, which is the most commonly used system in the U.S. today. It is summerized in Table 1 below. The previous randomized trial by the Uro-Oncology group defined patients with localized prostatic cancer as:

1. Digital rectal examination demonstrating freedom from capsular penetration or seminal vesicle examination.

2. Normal serum prostatic acid phosphatase (PAP) determination.
3. Normal radioisotopic bone scan and radiologic bone survey.

In this study, these three criteria as well as a normal serum prostate specific antigen (PSA) level will be used to define a localized cancer.

The preliminary step in the clinical staging of the tumor is the digital rectal examination. This commonly occurs during a routine physical examination, and, if suspicious, is repeated by a uro-oncologist, who may refer the patient to further testing. For the purposes of this trial the absence of metastatic disease will be determined in three ways after the digital rectal examination:

1. Bone Scan- This provides the most sensitive means available of detecting skeletal metastases. Approximately 10-50% of patients with metastatic prostate cancer have positive bone scans despite normal bone radiographs. [1]

2. Prostate Specific Antigen Test (PSA)- PSA originates in the acinar and ductal cells of the prostate and is not found in other body tissues in the absence of metastatic prostate cancer. Numerous studies have confirmed that serum PSA levels rise with increasing stage of disease. A PSA level less than 10ng/ml is often found in organ-confined cancer and is rarely seen in metastatic disease; a level greater than 50ng/ml is rarely seen in organ-confined cancer and usually indicates local or distant metastasis.[7]

3. Prostatic Acid Phosphalase Test (PAP)- The acid phosphatases are a group of enzymes that hydrolyse phosphate esters at an acidic pH, yielding inorganic phosphate. The enzymes occur normally in many body tissues, and the isoenzymes known as prostatic acid phosphatase (PAP) are produced in the glandular epithelium of the prostate. Elevated PAP reflects clinically apparent metastatic disease and is associated with extraprostatic or metastatic disease. [6]

The results of the bone scan, the PAP and the PSA will be determined by a single independent laboratory which will know the patients only by an identification number. Their results will be sent to the statistical analysis committee, who will decide whether or not the patient has met the eligibility criteria. If so, he will be given a consent form. When this is returned he will receive a pre-randomization examination and be randomized to an intervention group immediately thereafter.
Definition of Clinical Stage by the Whitmore-Jewett System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Nonpalpable, with $\leq 5%$ of resected tissue with cancer</td>
</tr>
<tr>
<td>A2</td>
<td>Nonpalpable, with $&gt; 5%$ of resected tissue with cancer</td>
</tr>
<tr>
<td>B1N</td>
<td>Palpable, $&lt; \text{ one lobe surrounded by normal tissue}$</td>
</tr>
<tr>
<td>B1</td>
<td>Palpable, $&lt; \text{ one lobe}$</td>
</tr>
<tr>
<td>B2</td>
<td>Palpable, one entire lobe or more</td>
</tr>
</tbody>
</table>

Table 1 - Adapted from W.F. Whitmore, "Hormone Therapy in Prostate Cancer", Amer J Med 1956; 21:697.

5 Pre-Randomization Evaluation

Before the subject is randomized to an intervention, it is important to obtain baseline information concerning the patient's general health and well-being. The data will then be pooled with the rest of the data from each group after randomization, and the groups will be compared for equivalency. The baseline data will include things such as age, race, and socio-economic status in addition to the results of a general physical examination (weight, blood-pressure, etc.). The subject will also have to contribute information regarding his previous medical history. In particular, high risk factors such as a history of heart disease, diabetes, heavy smoking, or regular use of prescription medications may cause a difference in the expected survival for a particular patient. It is important to know whether or not these differences are equally distributed between the two intervention arms.

6 Randomization

After the admission into the trial and a baseline examination, subjects will be randomized to either surgery or radiotherapy groups. Approximately equal numbers will be assigned to each group at each participating center. This will be achieved through use of a computer program which will generate random assignment numbers between zero and (not including) one. The program will operate on a permuted block design with $n=8$, such that after every eighth assignment the numbers in the two groups will be equal. This is necessary to prevent long runs of random numbers allowing one group to grow larger than the other.

The participating center will receive a letter instructing them to schedule the patient for the treatment to which he has been randomized. The patients will be notified of their therapy three days before the first radiotherapy treatment.
or surgery in order to comply with any special preparation instructions and to make arrangements for appropriate transportation, etc. It is hoped that by reducing the amount of time the subjects have to contemplate their assigned therapy, the number of crossovers will stay relatively low.

7 Intervention Strategy

7.1 Surgery Group

To cure carcinoma of the prostate with surgery, all tumor must be excised. Men with tumors confined to the prostate are ideal candidates for cure by surgery intervention, and this protocol has accomodated this by ruling patients with metastasis ineligible. There are two approaches to radical prostatectomy, retropubic and perineal. In this study, we will use the retropubic approach due to its several distinct advantages for the patient, namely it provides the opportunity to perform a simultaneous staging pelvic lymphadenectomy, and has the ability to preserve potency. Furthermore, it has the theoretical advantage of improved urinary continence, because the pelvic floor is not violated.[8]

In order to ensure some degree of uniformity across surgeons participating in this trial, the following issues must be addressed as can be found in Cancer of the Prostate, “Radical Retropubic Prostatectomy”[7]

1. Positioning of the Patient

2. Incision and Exposure

3. Extent of Pubic Lymphadenectomy

4. Incision of Endopelvic Fascia and Division of Puboprostatic Ligaments

5. Nerve Sparing

6. Control of the Dorsal Uein complex and Transection of the Urethra

7. Control of the Superior Vascular Pedicles

8. Division of the Bladder Neck
9. Excision of the Seminal Vesicles

10. Closure of the Bladder Neck and Completion of the Urethrovesical Anastomosis

7.2 Radiotherapy Group

To provide some uniformity and assurance of consistent quality of radiotherapy treatment planning, all patient plans must be submitted to the University of Wisconsin Radiotherapy Department for approval. The following criteria will be used in granting approval:

1. Treatment plans must be generated from a three-dimensional treatment planning software package, based on a CT scan of the subject's anatomy.

2. The minimum source to skin surface distance (SSD) permitted is 80 cm.

3. The minimum photon energy allowed is 24 MV.

4. The treatment set up must use 4 fields (anterior-posterior and posterior-anterior), aimed directly at the prostate. Conformal blocks may be used where appropriate.

5. The plan should use the smallest field size to include prostate gland, periprostatic region, and pelvic lymph nodes, as determined by CT (Computed Tomography) scan of the pelvic volume.

6. The upper margin of field is to be at the iliac crest, the lateral margin at least 1 cm beyond the external iliac nodes and the lower margin at least 1 cm below the inferior extent of the prostate.

7. All fields will be treated daily, 5 fractions per week, delivering a total dose of 70 Gray to the 80% isodose line.

8. Total treatment time must not exceed a span of 54 days.

9. Use of a bellyboard to allow the small gut to distend out of the irradiation field is recommended to minimize symptoms of diarrhea.
8 Follow Up

8.1 Schedule

Patients will be followed at 2-month intervals for the first year and at 3-month intervals thereafter, up to 5 years post-treatment. After 5 years, follow-up will be at 6 month intervals. Complete serum biochemical profiles with acid phosphatase determinations, quality-of-life rating and physical examination including rectal palpation and biopsy of tumor region will be included in each follow-up visit. Tumors should be reclassified as appropriate. Chest x-rays and isotopic bone scans shall be conducted at 6 month intervals to be evaluated for evidence of metastatic disease. These evaluations will be conducted by a team of researchers the University of Wisconsin Oncology Department, who will be blind to the identity and treatment center of the the patient. Their findings will be faxed to an independent, blinded statistical analysis team.

8.2 Quality of Life Rating

This trial will use the definition of quality of life proposed by Levine and Croog, as modified by Demets et al[3]. In addition, a category will be added under the “Functioning” dimension to reflect the subject’s satisfaction with his sexual functioning. Both surgery and, to a lesser extent, radiotherapy, have been shown to cause impotency or other sexual disfunctions in some patients. This can be an important factor for some men who are choosing between available prostate cancer treatments.

Patients will receive a questionnaire at the initial consultation and at each follow-up visit, which they are to take home, complete, and mail directly to the statistical analysis committee. A sample form is shown in Table 2 below.

<table>
<thead>
<tr>
<th>Quality of Life Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please rate each applicable line below with a number from 1 (extremely poor) to 10 (extremely good).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I. Functioning</th>
<th>II. Perceptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Social</td>
<td>1. Life satisfaction</td>
</tr>
<tr>
<td>ability to work and interact with family, friends and community</td>
<td>well-being</td>
</tr>
<tr>
<td>2. Physical</td>
<td>2. Health status</td>
</tr>
<tr>
<td>mobility, energy, independence, freedom from symptoms</td>
<td>compared to others of own age</td>
</tr>
<tr>
<td>3. Emotional</td>
<td></td>
</tr>
<tr>
<td>stability, self-control, freedom from impairments</td>
<td></td>
</tr>
<tr>
<td>4. Sexual</td>
<td></td>
</tr>
<tr>
<td>ability to have satisfactory sexual interaction</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - A sample form for evaluating quality of life.
8.3 Subject Withdrawal Policy

Withdrawals are subjects that have been enrolled in the study but are deliberately taken out of the analysis. In this study, enrollment will not be made until all diagnostic tests have been confirmed and the patient has agreed to comply with the therapy schedule to the best of his ability. For this reason, no withdrawals due to retrospective ineligibility or noncompliance will be allowed. Furthermore, since the primary outcome variable is survival, and since survival information should be available even for patients who do not attend their follow-up visits, no subjects will be censored due to missing data. Every effort will be made to obtain the date and cause of death for all subjects. For subjects who decide to drop out of the study, see Section 10.2.

9 Data Monitoring

An independent data monitoring committee of statisticians will be overseeing this trial.

9.1 Schedule and Duties

The committee will meet on an annual basis, beginning after the second year of the start of the trial. This coincides with the scheduled end of the recruitment period. The committee will evaluate any data that has already been received from the patients who have been in the study for up to a year, and determine whether or not it is necessary to extend the recruitment period, or if the assumptions made in the sample size estimation were appropriate.

After the first meeting, the committee will meet again at approximately yearly intervals for the duration of the trial and monitor the available data. This will involve 14 "looks" or analyses of the results. In each case, the committee will decide if it is ethically and scientifically necessary to terminate the trial early, to extend the trial, or to continue as scheduled.

9.2 Criteria for Early Termination

The data will be evaluated according to the O'Brien-Flemming group sequential procedure.[3] If the test statistic $Z_{i}$ is outside of the limits dictated by this procedure, the committee has an adequate reason for choosing to terminate the study. However, in addition to this statistical outcome, other the following other factors should also be weighed:

1. The impact of missing data should be evaluated. Due to the size and length of this trial, there will undoubtedly be missing data. It should not be assumed that this data is missing at random. The committee should estimate the range of possible statistics based on extreme but reasonable
values for the missing data.

2. Possible differences in baseline factors between the two groups should be examined. In particular, since overall survival is the primary outcome variable, it is important to establish whether or not the two groups were of approximately equal health at the beginning of the trial. If the group who received the superior therapy was healthier to begin with, it may be controversial to end the trial early.

3. The presence of bias in the trial at any stage should be looked at carefully. Since this is not a double-blind trial, there are many potential avenues for personal beliefs to interfere with treatment. These should be carefully weighed and taken into account.

4. The committee should check for internal consistency across subgroups. If the result is the same for all stages of tumor and all ages of subjects, for example, the results may be considered more compelling.

5. Finally, it should be remembered that it is extremely important that the results of this trial are credible. The attitude of the committee should be to prioritize credible results over early termination, in the absence of any undue adverse effects of either intervention.

9.3 Criteria for Trial Extension

It is possible that the committee may find that the assumptions used in the design of this study were for some reason inadequate, and therefore may feel a need to extend the follow-up period, the recruitment period, or the sample size to enhance the results of the study. In particular, it is possible that the overall mortality rates will be lower than estimated in the sample size calculation. A preliminary estimate should be made after the scheduled end of the two-year recruitment period. If the assumed values were too low, the sample size should be increased by extending the recruitment period as necessary. Because seventeen years is already a long trial, extending the follow-up period is probably not desirable.
10 Non-Compliance Policies

10.1 Crossovers

A "crossover" patient is a subject who either (1) is assigned to the radiotherapy group but instead opts to have surgery, or (2) is assigned to the surgery group but instead opts to have radiotherapy. This study assumes a crossover rate of approximately 10%, which is slightly better than that achieved by the Uro-Oncology group[2]. It should be emphasized that crossover patients do not occur randomly across the subject group, and therefore they must be included in the analysis, not censored. Possible reasons for crossover include a change in the clinical assessment of disease or reconsideration due to a second external opinion. There is also the possibility that some patients may be deemed to require both surgical and radiotherapy treatments by a physician not associated with the study. Appropriate statistics will be kept on all such subjects, and reported separately, however they will also still be included with the analysis of the group to which they were originally randomized.

10.2 Dropouts

Because of the unusually long follow-up times associated with this study, it is especially important specify the policy governing dropouts. A dropout is a subject who terminates his participation in the study by either not completing his therapy or not attending subsequent follow-up visits. We assume a 15% dropout rate in this study. They will not be censored from the primary outcome, because it should be possible to obtain a date and cause of death for all patients, regardless of whether they attended follow-up visits.

For the secondary outcome variables, their numbers will be reported alongside the data from compliant subjects. Since it is assumed the dropouts will not be a random event, it is extremely difficult to know what type of data is missing from the secondary variables. For this reason, every effort will be made to get the noncompliant subject to complete a withdrawal form. The form will ask the subject to rank a number of reasons for dropping out of the study, as well as filling in his own. It will include a section for reporting adverse effects of the therapy, which will ask for information concerning the type, frequency and duration of the adverse effect. It will also attempt to determine whether or not the condition was pre-existing in the subject.

11 Statistical Analysis

11.1 Estimation of Survival Curves

The survival curves will be estimated through use of the Kaplan-Meier method [3]. This method uses the product of conditional probabilities after each event
to determine the overall probability of surviving to a given time. It assumes that
a death and a loss of follow-up do not occur at the same time; but if they do, it
will be assumed that the death occurred slightly before the loss of follow-up.

Each event (either a death or a loss of follow-up) may be represented by the
length of time after the start of treatment. To construct the estimation of the
true survival curve, these data are ordered chronologically according to "trial-
time". Temporal intervals are defined between two consecutive times of death,
and for each interval, the conditional probability of surviving is computed as

$$P_j = \frac{n_j - \delta_j}{n_j},$$  \hfill (7)

where \(n_j\) is the number of follow-up subjects alive at the beginning of the \(j^{th}\)
interval, and \(\delta_j\) is the number of subjects who died during the \(j^{th}\) interval.
Thus the cumulative probability of surviving to a time \(T\) after the intervention
is the product of the corresponding \(P_j\)'s, which gives \(P(t)\). The survival curve
is obtained by plotting \(P(t)\) versus \(t\). The variance at each interval is given by

$$v[P_j] = P^2(t)\sum_{j=1}^{K} \frac{\delta_j}{n_j(n_j - 1)},$$  \hfill (8)

where \(K\) is the total number of intervals.

11.2 Comparison of Survival Curves

The two survival curves will be compared in an overall sense, to determine
whether one curve is consistently higher than another. This will be accomplished
through the use of the Mantel-Haenszel procedure of 2x2 tables. Note that if
the curves cross, these results must be interpreted with caution.

Application of this method is described by Demets et al[3] in Chapter 14.
First, the times of deaths and losses in both groups are ranked in ascending
order. At the time of each death, the total number of subjects in each group
who were at risk just prior to the death, as well as the number of deaths in each
group must be determined. This information is used to fill in the appropriate
2x2 tables. The Mantel-Haenszel test statistic can be computed directly from
these tables; it is given by

$$MH = \frac{[\sum_{j=1}^{K} a_j - E(a_j)]^2}{\sum_{j=1}^{K} V(a_j)}$$  \hfill (9)

where \(K\) is the number of distinct event times, \(a_j\) is the observed number of
deaths in the \(j^{th}\) interval, \(E(a)\) is the expected number of deaths in the surgery
group, and \(V(a)\) is the variance in the expected number of deaths.
12 Conclusions

A full scale, phase III, multi-center randomized clinical trial protocol has been proposed to test the relative effects of radical prostatectomy and radiotherapy on the overall survival in men with localized prostate cancer. The primary outcome variable is overall survival at 5, 10 and 15 years. Secondary outcome variables are disease-specific survival after 5, 10, and 15 years, time to local failure, and quality of life.

Clinical staging will be evaluated according to the outcome of four different tests, and only those patients with stages A2 or B will be considered eligible for this trial. Although the subject and his primary physician will know which treatment the subject has received for obvious reasons, the protocol incorporates use of several independent committees to ensure that as many aspects of the trial as possible are blinded. Independent committees will be set up for analysis of all laboratory tests, analysis of cause of death, statistical analysis of data, and data monitoring.

The trial is scheduled to last 17 years and involve approximately 550 subjects. Survival curves will be constructed using the Kaplan-Mier method, and compared by using Mantel-Haenszel procedure of 2x2 tables. The data monitoring committee will meet annually to decide whether to terminate the trial early, extend the trial, or to continue as planned. Criteria for making these decision is outlined in the protocol.

References


Appendix 1

Informed Consent Form
University of Wisconsin-Madison
Department of Human Oncology
Madison, Wisconsin 53792

Title: Randomized Trial for Treatment of Localized Cancer of the Prostate: Radiotherapy vs. Radical Prostatectomy.

Institution: University of Wisconsin-Madison
Principal Investigator: Michelle Svatos & Jeannie Song

Name ___________________________ History #____________________

PURPOSE:
You are invited to participate in a research study of treatment of localized cancer of the prostate using radiotherapy versus radical prostatectomy. Due to many controversies on the efficacy of various treatments for this disease, this study will help in assessing the optimal therapeutic strategies to more effectively fight this disease. During the study we will regularly check for the safety of the techniques, biologic effects and side effects of these treatments.

WHY HAVE YOU BEEN SELECTED?
You are being asked to participate because you have been diagnosed with previously untreated, biopsy-proven, prostatic adenocarcinoma and you are without evidence of metastatic disease at present.

WHAT DOES PARTICIPATION INVOLVE?
This study is a followup time of 15 year period. You will be among group of people who will be randomly assigned to two different method of treatment, radiotherapy or radical prostatectomy. Patient will be checked at 2 month intervals for the first year and at 3 month intervals thereafter, up to 5 years post-treatment. After 5 years, followup will be at 6 month intervals. At each visit, you will have a brief physical exam including digital rectal examination(DRE), prostatic acid phosphatase (PAP) test, complete serum biochemical profiles, Karnofsky's performance rating done at each followup visit.

ARE THERE ANY BENEFITS TO ME?
If the treatment is effective, you may experience some relief of your symptoms of this disease. However, it is possible that no health benefit may result from your participation.
WHAT IS THE IMPACT OF TREATMENT?

Due to the nature of these treatments, sexual performance may be affected by both surgical procedure and radiation therapy. Radical prostatectomy and radiation therapy for the treatment of localized prostate cancer may result in impotence. Changes in your sexual performance may also lead to stress incontinence, anxiety, depression, and mood alterations. In addition, radiotherapy treatment may result in temporary discoloration and burning of skin. Upon release from the hospital after the surgery, you will be given a discharge information instructions similar to appendix 2.(6)

WILL COMPENSATION BE AVAILABLE FOR INJURY RESULTING FROM THE STUDY?

If injury occurs as a result of this research, (name of sponsor) does not automatically provide reimbursement for medical care or offer other compensation. In the unlikely event of such injury or for more information, please call the investigators in charge, Michelle Svatos or Jeannie Song at (608) 555-5555. For info on study subject rights you may contact the patient representative at (608) 263-0000.

WHEN AND WHERE WILL THE TREATMENT AND EXAMINATION BE DONE?

All treatments, examinations and tests will take place at the initial treatment center. After the initial treatment, appointments will be set up at 2 month interval for the first year, 3 month interval thereafter, up to 5 years post-treatment. After 5 years, appointments will be set up at 6 months interval until the end of the study.

ARE THERE COSTS INVOLVED?

After the initial treatment, all follow-up tests and examinations required as part of this study will be our responsibility. These numerous visits may result in additional miscellaneous expenses to you, such as transportation, gas, meals etc. these routine costs will be provided through our research funds.

WHO WILL HAVE ACCESS TO YOUR MEDICAL RECORDS?

Any information collected in this study will be kept in strictest confidence. No mention of your name or any other identifying information will be published. However the National Cancer Institute or associated drug companies may review your records at any time. A record of your status and progress will be sent to the statistical headquarters of University of Wisconsin-Madison Oncology Department. This group may also review your records. The results of these studies may also be used for medical and scientific publications, but you will not be identified personally.

IF YOU CHANGE YOUR MIND ABOUT PARTICIPATION:

Should you decide not to participate in this study, there are other treatments available such as hormonal therapy, chemotherapy, and Laparoscopic Pelvic Lymphadenectomy...
Appendix 2

Radical Retropubic Prostatectomy Discharge Information Instructions:

You have undergone a major urological procedure (RRP) and now comes the time for your discharge from the hospital. You will find here lots of useful information to help you know what you should or should not be doing when you are at home.

Activity
From the next 6 weeks try to walk up to one mile day. Avoid running, fast walking, walking on inclines and declines, heavy lifting (over 10 pounds), or any heavy exercise. Climb stairs slowly and carefully. A good rule of thumb is that if anything unduly hurts your incision, then avoid it. Do not ride long distances in cars. If this is necessary, take breaks every 1-2 hrs. Do not cross your legs. All these precautions will promote the venous circulation in your legs and prevent you from developing a clot.

Driving
You should not drive a care until after your catheter comes out approximately 2 weeks after your operation. The discomfort from the catheter will make your reactions using the foot pedal suboptimal in case of emergency breaking, even though you may feel you can drive. You may resume driving after 2 weeks but limit this to short distances only for a further 2 weeks before you resume normal driving.

Bathing and Showers
After the skin staples have been removed and adhesive tapes applied to the skin, you may shower at home and wash your incision with soap and water. Avoid scrubbing the incision. Avoid baths. After showering, dry the incision and the adhesive tapes by dabbing with a dry towel.

Diet
There is no restrictions to your diet. Please note that constipation may result from taking pain medication (Vicodin) and iron tablets. By eating a balanced diet with high fiber, such as fresh fruits, vegetables, whole grain, and bran, you can help avoid constipation. Keep well hydrated by drinking 6-8 glasses of fluid each day. You may drink alcohol in moderation (1-2 drinks per day).

Foley Catheter
You have a catheter inside your bladder to drain the urine. This catheter will stay in for 2 weeks from the day of surgery. Make sure that the catheter is well secured to the thigh by tape and avoid traction and tension on it. The urine may become intermittently blood-stained due to walking or having a bowel movement. This is not unusual, and as long as the catheter is draining well and there are no blood clots, it is of no consequence. Occasionally, the catheter may become blocked and stop draining due to a small blood clot. Within a few hours, you will start to get the feeling of your bladder distending. Call us if this occurs and we will instruct you on what to do next.
You may take as much time as you wish to think this over. Before you sign this form, ask any questions on any aspects of the study that are unclear to you. We will attempt to fully answer any questions you may have prior to, during, or following this study.

AUTHORIZATION

I have read all the information, and give my consent to participate in the research described above. My signature indicates that I have received a signed copy of the consent form.

__________________________  __________________________
Patient Signature            Date

__________________________  __________________________
Physician Signature         Date