

## 3D-CRT ONCOLOGY GROUP

3D/OG 94-06

### A PHASE I/II DOSE ESCALATION STUDY USING THREE DIMENSIONAL CONFORMAL RADIATION THERAPY FOR ADENOCARCINOMA OF THE PROSTATE

Operations Center  
*ACR, Philadelphia*

James D. Cox, M.D.  
(713) 792-3411  
FAX # (713) 792-3660  
*Jcox@notes.mdacc.tmc.edu*

Quality Assurance Center  
*Washington University*

James Purdy, Ph.D.  
(314) 362-2631  
FAX # (314) 362-2682  
*Purdy@radonc.wustl.edu*

Jeff Michalski, M.D.  
(314) 362-8566  
FAX # (314) 362-8521  
*michalski@radonc.wustl.edu*

William Harms, B.S.  
(314) 362-2648  
FAX # (314) 362-2682  
*Harms@castor.wustl.edu*

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## INDEX

Schema

Eligibility Check

- 1.0 Introduction
- 2.0 Objectives
- 3.0 Patient Selection
- 4.0 Pretreatment Evaluations
- 5.0 Registration Procedures
- 6.0 Radiation Therapy
- 7.0 Drug Therapy
- 8.0 Surgery
- 9.0 Other Therapy
- 10.0 Pathology
- 11.0 Patient Assessments
- 12.0 Data Collection
- 13.0 Statistical Considerations

References

- Appendix I - Sample Consent Form
- Appendix II - Karnofsky Performance Status
- Appendix III - Staging System
- Appendix IV - Toxicity Criteria
- Appendix V - Adverse Reaction Reporting Guidelines
- Appendix VI - 3D - CRT Guidelines
- Appendix VII - Grouping Table
- Appendix VIII - Facility Questionnaire
- Appendix IX - Participants' List

# 3D-CRT ONCOLOGY GROUP

## 3D/OG 94-06

### A Phase I/II Dose Escalation Study Using Three Dimensional Conformal Radiation Therapy for Adenocarcinoma of the Prostate

#### SCHEMA

S		R	
	<b><u>Group 1*</u></b>		<b>Minimum Dose to PTV or PTV2 (<i>Group 2</i>)<sup>a</sup></b>
T		E	Level I     68.4 Gy <sup>b</sup> (closed)
	<b><u>Group 2*</u></b>		Level II     73.8 Gy <sup>b</sup> (closed)
R		G	Level III    79.2 Gy <sup>b</sup> (closed)
A	<b><u>Group 3 (closed)</u></b>	I	Level IV    74.0 Gy <sup>c</sup> (closed)
T		S	Level V     78.0 Gy <sup>d</sup> (opened 2/14/00)
I		T	a. Group 2 patients will have a field reduction ( <i>off seminal vesicles</i> ) after 55.8 Gy
F		E	b. one fraction of <u>1.8 Gy</u> ( <i>minimum</i> ) per day 5 x per week
Y		R	c. one fraction of <u>2.0 Gy</u> ( <i>minimum</i> ) per day 5 x per week
	* See Appendix VII		d. 2 Gy per fraction

**Group 1:** Clinical stages T1b-c or T2a-b with PSA + ( $[Gleason -6] \times 10$ ) is  $\leq 15$ .

**Group 2:** Clinical stages T1b-c or T2a-b with PSA + ( $[Gleason -6] \times 10$ )  $> 15$ . Any clinical T2c with PSA  $< 70$ . Must be lymph node negative.

**Group 3:** Clinical stage T3 with PSA  $< 70$ . Must be lymph node negative.

**Eligibility** (See Section 3.0 for details)

- All stages, previously untreated, adenocarcinoma of the prostate (M0) except T1a, or T1b-c and T2a-b with Gleason score  $\leq 5$  and PSA  $\leq 4$ , or clinical stage T4
- KPS  $\geq 80$
- Hgb  $\geq 11$  gm %, WBC  $\geq 4000$ /ml, platelets  $\geq 100,000$
- PSA  $< 70$
- No positive nodes by imaging or surgical sampling. Patients at high risk for lymph node metastases (*Groups 2 and 3*) should be considered for staging lymphadenectomy
- No distant metastases or other synchronous primary
- If clinically indicated, prior neoadjuvant androgen suppression (*nonsurgical*) is allowed if initiated 2-6 months prior to registration to this study
- No prior pelvic irradiation
- Study-specific informed consent

**Required Sample Size: Dose tolerance dependent**  
5/12/95, 6/16/95, 10/5/98, 2/14/00

Institution # \_\_\_\_\_  
3D/OG 94-06 \_\_\_\_\_  
Case # \_\_\_\_\_

**ELIGIBILITY CHECK** (2/14/2000)  
(page 1 of 2)

- \_\_\_\_\_ (Y) 1. Is there histologically confirmed adenocarcinoma of the prostate?
- \_\_\_\_\_ (T1b-T3) 2. What is the T Stage?
- \_\_\_\_\_ (N) 3. Is the Gleason  $\leq 5$  and the PSA  $\leq 4$ ?
- \_\_\_\_\_ ( $\leq 10$ ) 4. What is the Gleason score?
- \_\_\_\_\_ ( $< 70$ ) 5. What is the pre-treatment PSA (*Hybritech or equivalent*)? The PSA should be prior to all therapy including induction hormones.
- \_\_\_\_\_ (Y) 6. Was the PSA done within 3 months prior to registration?
- \_\_\_\_\_ (1-2) 7. What is the patient's stratification group? (*If Group 1, skip to Q10. If on hormones, stratify per "pre-hormone" information*)
- \_\_\_\_\_ 8. What is the status of the regional lymph nodes radiographically?  
(1. not done, 2. positive [ineligible], 3. negative)
- \_\_\_\_\_ 9. What is the status of the regional lymph nodes pathologically?  
(1. not done, 2. positive [ineligible], 3. negative)
- \_\_\_\_\_ ( $\geq 80$ ) 10. What is the KPS?
- \_\_\_\_\_ ( $\geq 11$ ) 11. What is the hemoglobin (*gm %*)?
- \_\_\_\_\_ ( $\geq 4$ ) 12. What are the results of the WBC (*x 1000*)?
- \_\_\_\_\_ ( $\geq 100$ ) 13. What is the platelet count (*x 1000*)?
- \_\_\_\_\_ (N) 14. Is there evidence of distant mets?
- \_\_\_\_\_ (N/Y) 15. Does the patient have a concurrent or prior malignancy? (*excluding basal cell or non-invasive squamous cell carcinoma of the skin which is eligible*)  
\_\_\_\_\_ (Y) If yes, has the patient been disease-free for  $\geq 5$  years?
- \_\_\_\_\_ (N) 16. Has the patient had prior pelvic irradiation?
- \_\_\_\_\_ (Y/N) 17. Has the patient had previous hormonal therapy?  
\_\_\_\_\_ (Y) If yes, was it initiated 2-6 months ago?
- \_\_\_\_\_ (N) 18. Has the patient had previous or concurrent cytotoxic chemotherapy?

Institution # \_\_\_\_\_  
 3D/OG 94-06 \_\_\_\_\_  
 Case # \_\_\_\_\_

**ELIGIBILITY CHECK** (2/14/00)  
 (page 2 of 2)

\_\_\_\_\_(N) 19. Are there any major medical or psychiatric illnesses which would prevent completion of treatment and interfere with follow-up?

**The following questions will be asked at Study Registration:**

- \_\_\_\_\_ 1. Name of institutional person registering this case?
- \_\_\_\_\_(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- \_\_\_\_\_(Y) 3. Is the patient eligible for this study?
- \_\_\_\_\_ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- \_\_\_\_\_ 5. Patient's Name
- \_\_\_\_\_ 6. Verifying Physician
- \_\_\_\_\_ 7. Patient's ID Number
- \_\_\_\_\_ 8. Date of Birth
- \_\_\_\_\_ 9. Race
- \_\_\_\_\_ 10. Social Security Number
- \_\_\_\_\_ 11. Gender
- \_\_\_\_\_ 12. Patient's Country of Residence
- \_\_\_\_\_ 13. Zip Code
- \_\_\_\_\_ 14. Patient's Insurance Status
- \_\_\_\_\_ 15. Will any component of the patient's care be given at a military or VA facility?
- \_\_\_\_\_ 16. Treatment Start Date
- \_\_\_\_\_ 17. T Stage/Pathologic
- \_\_\_\_\_ 18. Combined Gleason
- \_\_\_\_\_ 19. PSA Value
- \_\_\_\_\_ 20. Stratification Group (*Group 1 or Group 2*)
- \_\_\_\_\_ 21. Treatment Assignment

Completed by \_\_\_\_\_

Date \_\_\_\_\_

## **1.0 INTRODUCTION**

### **1.1 Background**

Radiotherapy represents one of two primary treatment modalities for patients with carcinoma of the prostate.<sup>35</sup> With radiotherapy, local control is directly related to dose,<sup>18,40</sup> as well as the technical accuracy with which the dose is delivered to the target volume. The proximity of critical normal structures (*i.e. the bladder and the rectum*) to the primary tumor sets a limit on the prescription dose to between 65 and 70 Gy. In an effort to reduce the dose to the normal structures, a variety of "boost" techniques have evolved including the use of three or four static fields<sup>67</sup> and rotational arc techniques<sup>2</sup> as well as brachytherapy<sup>12,16,63</sup> and high LET particle beams.<sup>22,62</sup>

The specific goal of three dimensional conformal radiation therapy (*3D-CRT*) is to provide a mechanism for increasing the tumor dose as a means of enhancing local tumor control.<sup>11</sup> Laboratory and clinical reports indicate that there is a direct correlation between radiation dose and the probability of achieving local control in a variety of tumors.<sup>9,29,33,34,46,74</sup> The maximum dose that can be delivered to the tumor is restricted by the tolerance of normal tissues within the high-dose volume. The radiation dose-response relationships for tumor control and normal tissue injury are site-specific and are influenced by a number of factors. The more important technical factors include the precision of target volume definition and of dose delivery, the dose given to this volume, and the degree to which uninvolved normal tissues are excluded from the treatment volume.<sup>7,56</sup> With 3D-CRT therapy it is possible to design the spatial dose distribution to conform to the target volume and reduce the dose to normal tissues. This approach, therefore, has the potential to decrease the probability of normal tissue toxicity and permit dose escalation to the tumor to produce higher rates of local control.<sup>11,13,14,28,31</sup>

In 1993, the American Cancer Society has estimated approximately 165,000 new cases of prostate cancer and anticipated 35,000 deaths. The incidence rate is 40% higher for black men than that for white men.<sup>66</sup> Patients with stages A2 and early B disease and negative lymph node biopsies are successfully treated using radiation therapy with local control rates equal to that reported for radical surgery.<sup>17</sup> For these patients (*treated with either surgery or radiation*) the 15-year survival rate is similar to that expected in an age-matched normal population.<sup>2</sup> However, at least 40-50% of patients initially present with locally advanced disease (*stages B2 and C*).<sup>4,38</sup> For these patients, external beam radiation therapy is the most commonly used treatment modality. The long term therapeutic results in this patient population appear to vary with the size of the primary tumor. For patients with stage C tumors, the 5- and 10-year survivals range from 58-65% and 35-38%, respectively, while for stage B tumors the 5- and 10- year survival rates are 75% and 48-56%, respectively.<sup>2,17,43,64</sup> Although excellent local control rates have been demonstrated for small lesions, local failure rates for patients with bulky stage B-2 and C disease range from 10-38%.<sup>18,64</sup> Shipley et al.<sup>65</sup> reported that the actuarial rate of local tumor re-growth for patients with T3 and T4 tumors was 35% at 8 years, compared to 8% for T2 lesions. Even at 8 years the local relapse curve for T3 and T4 tumors appeared to be rising, without any suggestion of a plateau. Investigators at the Mayo Clinic recently reported the results of definitive external irradiation for prostatic carcinoma over a 15 year period. The local failure rates for patients with Stage B and C tumors were 30% and 62%, respectively.<sup>72</sup> Local failure has also been shown to correlate with tumor size at the time of clinical presentation. Pilepich et al.<sup>48</sup> have reported a greater than 50% local failure rate by the sixth year after definitive external irradiation when the product of the dimensions in cm of the palpable tumor exceeded 25, compared to 25% or less for smaller lesions. Most local recurrences reported in these series are limited to clinically detectable (*by digital rectal examination*) and symptomatic recurrences. These rates of recurrence, therefore, may underestimate the true incidence of persistent asymptomatic local disease.<sup>18</sup> Few studies have used biopsies to address the issue of local relapse. Freiha and Bagshaw<sup>10</sup> reported that among 53 patients with bulky B2 and Stage C tumors who underwent biopsies 18 months after completion of therapy, 36 (68%) were found to have persistent or recurrent disease, compared to 3 of 11 (27%) patients with earlier stage disease ( $p = 0.03$ ). In view of the high rate of local residual tumor present after conventional radiotherapy, the question may be asked if conventional methods of external beam radiotherapy are sufficiently accurate to encompass the prostatic target volume. It was indeed shown that when traditional treatment planning techniques were reexamined by 3D methods, 20 - 35% of the target volume was found to be missed.<sup>73</sup> These data provide additional support for the use of 3D treatment planning in the radiotherapeutic management of prostatic carcinoma

### **1.2 Dose-Response Relationships in Carcinoma of the Prostate**

The probability of achieving local control in a tumor for a given dose is dependent on the number of surviving clonogens in the stem cell population.<sup>33,55,77</sup> The dependence is best described by the Poisson

distribution<sup>20,34</sup> which graphically leads into a sigmoid shaped curve.<sup>51</sup> Accordingly, at low radiation doses tumor control probabilities are small followed by a steep rise in tumor control with dose until a plateau is reached. A similar dose response pattern has been observed for radiation induced damage in normal tissues. Dose response studies in humans have been infrequently reported, but available clinical data have confirmed the sigmoidal nature of dose-response for tumor control.<sup>3,9,19,29,46,74,78,79</sup> The steepness of published dose-response curves vary significantly between reports suggesting significant variations in the sensitivity of clonogenic cell populations within human tumors and differences in the accuracy of radiation treatment.<sup>11</sup>

There have been several retrospective studies in the literature indicating that dose has a significant impact on local control in prostatic cancer.<sup>36</sup> Perez et al.<sup>40</sup> found improved local control rates for higher doses in a range of 60 to greater than 70 Gy. For stage C patients, 5/18 (38%) developed local recurrence when tumor dose was less than 60 Gy, compared to 10/51 (20%) for 60-70 Gy and 9/75 (12%) for doses of greater than 70 Gy. Hanks et al.<sup>18</sup> observed a significant dependence of local control on tumor dose in for 1,348 stage B and C cancer patients in the Patterns of Care Outcome Survey. The actuarial 5-year local recurrence rate was 37% for Stage C patients treated to doses of less than 60 Gy, 36% for 60-64.9 Gy, 28% for 65-69.9 Gy and 19% for those who received 70 Gy or more. By 7 years, 32% of patients receiving 65-69 Gy and 24% receiving higher doses recurred locally. The authors suggest that with the use of digital examination to assess local failure, these local recurrence rates are underestimated by at least 20%. Based on these data as well as the observations of Shipley et al.<sup>65</sup> and post treatment biopsy data<sup>10,59</sup> a dose escalation study using sophisticated 3D conformal treatment planning and dose delivery techniques appears to be justified.

### **1.3 Influence of Local Control on Metastatic Dissemination**

Several laboratory studies have demonstrated that failure to control the primary tumor leads to increased rates of metastatic dissemination.<sup>45,52,61,75</sup> The data support the hypothesis that the development of metastatic disease in many instances secondary to the re-growth of the primary tumor after failure to control it with surgery or radiotherapy. Until recently, there have been few clinical reports which have specifically focused on this issue. However, retrospective analyses of patterns of failure in patients undergoing curative local-regional therapy indicate that many human tumors conform in general with the patterns of relapse observed in animal models and exhibit an increase in metastatic dissemination after failure to control the primary tumor.<sup>1,5,12,23,25,26,39, 41,42,44,56, 60,69,70,71, 76</sup>

This issue has been addressed specifically by Fuks et al.<sup>12</sup> who reviewed the outcome of 679 surgically staged patients with carcinoma of the prostate treated with retropubic permanent implantations of encapsulated 125I sources at the Memorial Sloan-Kettering Cancer Center (MSKCC). A Cox proportional regression analysis demonstrated that local control was the most significant factor affecting the metastatic outcome in patients with disease confined to the prostate and without evidence of spread to pelvic lymph nodes (*Stage B-CNO*). The relative risk of distant metastases subsequent to local relapse was 4 times greater than the risk without evidence of local failure. The actuarial 15-year distant metastasis-free survival in 351 locally controlled patients was 77%, compared to 24% in 328 patients who relapsed locally ( $p < 0.00001$ ). The impact of the local outcome on the development of distant metastatic disease was observed regardless of stage, grade, or implant dose and was present even in the favorable stage B1NO-Grade I disease ( $p < 0.00001$ ). Distant metastases in patients with local control, apparently arising from micrometastases already present before treatment, were detected earlier (*median 37 months*) than in patients with local relapse (*median 54 months*) ( $p = 0.009$ ), supporting the hypothesis that in patients with local residual tumors metastases are formed and disseminated secondary to re-growth of the occult local residuum.

Similar results were previously observed by Kuban et al.<sup>23</sup> in patients treated with either implantation or external beam irradiation. Of those patients who developed local recurrence after definitive treatment, 68% ultimately developed distant metastases, compared with 37% of patients without evidence of local recurrence ( $p = 0.0025$ ). In this study the follow up was shorter than that of Fuks et al, and the patients were not staged by pelvic lymphadenectomy. The 5-year actuarial survival of patients with locally controlled tumors was 86% compared with 56% for those with locally recurrent disease ( $p < 0.05$ ). In a series of patients who underwent biopsies after external beam radiotherapy, Freiha and Bagshaw<sup>10</sup> reported that 28 of 39 patients (72%) with positive biopsies subsequently developed metastases compared with 6 of 25 patients (24%) with negative biopsies. The data in the literature thus support the suggestion that improved local control may decrease the rate of subsequent metastatic disease, but this hypothesis needs to be tested in prospective studies once methods for enhanced local control are established.

### **1.4 Dose Escalation**

Attempts to deliver higher doses of radiation with traditional techniques are limited by the risk of severe radiation injury to the bladder anteriorly and the rectum posteriorly. Although increasing the prescribed dose to greater than 70 Gy using traditional radiation therapy techniques may theoretically sterilize a greater percentage of prostate tumors, a concomitant increase in unacceptable treatment related complications may prevent such doses from being delivered. While it is expected that the risk of late complications should decrease by reducing the volume of the bladder and rectum irradiated using 3D techniques, there is very limited data on the tolerance of the rectum and bladder to external irradiation as a function of volume irradiated.<sup>8</sup> An analysis of the Radiation Therapy Oncology Group (RTOG) randomized prostate study 77-06 has documented the late complications to be expected with conventional radiation therapy techniques.<sup>49</sup> In that study the incidence of proctitis was 10%, of rectal/anal stricture, 5%, and of rectal ulceration 2%. Doses to the prostate (*with or without pelvic irradiation*) in excess of 70 Gy resulted in a significant increase in the incidence of rectal bleeding (20% compared to 12% or less) while there was no correlation between dose and the other rectal complications noted above. There was no correlation between dose (62.5 to 70+ Gy) and GU morbidity including cystitis (11%), hematuria (8%), or urethral stricture (7%). There was in addition no significant increase in morbidity with volume irradiated (*pelvis plus prostate or prostate alone*). However, the actual volume of bladder and rectum receiving high dose irradiation was not described. Smit et al.<sup>67</sup> retrospectively analyzed the incidence of radiation proctitis among 154 patients treated with external radiation utilizing CT treatment planning. The 2-year actuarial incidence of moderate or severe proctitis was 22% for anterior rectal doses of less than 70 Gy and increased to 60% when the dose exceeded 75 Gy. These patients were treated utilizing AP/PA portals for the initial 40 Gy with a 24 MV photon beam. An additional 30 Gy or higher was given utilizing a three-field plan where the dose was prescribed to the 90-95% isodose line. The treatment technique employed (*including the use of AP/PA portals in the initial phase of treatment*) may have contributed to the increased complication rate observed.<sup>17</sup> Furthermore, it is not possible to estimate the volume of rectal wall encompassed in the treatment fields or the volume treated to high dose levels. Thus, it cannot be determined if these complication rates would be as high with carefully designed 3D conformal techniques.

Data from the Patterns of Care Study,<sup>17</sup> confirmed by analyses of two large prospective trials of the RTOG (Lawton et al.) showed that standard fractionation with total doses up to 70 Gy resulted in serious late sequelae in less than 3% of patients. Statistically significant increases in morbidity in the order of 7% were associated with total doses above 70 Gy. The use of AP-PA technique only produced a doubling effect on the rate of complication.

Ten Haken et al.<sup>73</sup> have compared the dose distributions of traditional unblocked 4-field box, bilateral arc, and a 6-field 3D conformational technique to treat the prostate. The former two techniques were found to cover five times as much normal tissue in the high dose region compared to the latter technique. Dose-volume histograms clearly demonstrated that when using the 3-D treatment plan, at least 50% less normal bladder and rectal tissue was treated. Thus with appropriate 3D conformal plans, dose escalation to 80 Gy or more appears to be feasible, but the true tolerance and effectiveness of these dose levels must be addressed in clinical trials.

These investigators reported a prospective dose-escalation study<sup>58</sup> using a CT-based, 3D treatment planning system and a six field conformal boost technique. Doses of 44 Gy to 50.4 Gy were administered to a field which encompassed the regional lymph nodes, followed by the boost field which received from 24 Gy to 32 Gy yielding total doses of 74 Gy to 80.4 Gy (*dose specified at isocenter, AS Lichter, personal communication*). Three rectal complications (*intermittant bleeding*) were observed resulting in an estimated two year rate of 22%. No relationship between total dose and risk of complications were observed.

At MSKCC, 43 patients with stages A2-C carcinoma of the prostate have been treated using a 3D conformal approach (Leibel et al., unpublished data, 1991). Patients were planned with three different conformal plans (4-, 6-, and 8-field configurations using BEV derived tumor conforming blocks) and with the standard 2D bilateral 120 degree arc technique. Thirteen patients were treated using a 4-field conformal plan, 28 were treated using a 6-field technique and 2 were treated with an 8-field plan to doses of 64.8-70.2 Gy. Except for one patient with intermittent hematochezia (*not requiring transfusions*) and three patients who developed acute bladder outlet obstruction early in the course of their treatment, no patient has experienced greater than grade 2 acute GI or GU symptoms (RTOG Acute Toxicity Scale). There have been no late complications observed to date although the median follow up is only 8 months and 14 patients have been followed for longer than 1 year.



While the target coverage for each conformal plan was excellent, the advantages for each plan varied for different normal organs. For the rectum, in terms of the percent of the volume receiving at least 30 Gy, there was no significant difference between the plans. There was a difference, however, when the rectal wall volume receiving at least 50 Gy was considered. In this case the bilateral arc technique was clearly inferior to the other plans. However, there was essentially no difference between the conformal plans which involved blocking of the rectum in some or all of the fields. The percent of bladder volume receiving at least 35 Gy was similar with all techniques. However, when doses above 35 Gy are considered, the bilateral arc technique irradiated the largest volume. Among the remaining 3 types of plans there was a very slight reduction in the volume of rectal wall treated with the 4-field plan. However, this was probably not clinically significant. With regards to the femur dose, the 4-field plan was clearly the worst choice. The dose to the femurs was significantly reduced with either the 6- or 8-field plan, although the rectal dose was higher. While none of the conformal plans exhibited a significant advantage over other plans at a prescription dose of 64.8 Gy, when the tumor prescription dose was escalated, significant differences began to emerge. Based on tolerance data from the literature and the assumption of strong volume effects for normal pelvic organs, it was estimated that at 80 Gy the arc technique could no longer be considered as appropriate because the associated toxicities to normal organs exceeded acceptable levels. Whereas the 4-field plan appeared to be superior to the 6- and 8-field plan in terms of rectal dose, the femoral head dose would be prohibitive at this dose level compared to the 6- and 8-field plans. However, with the latter two techniques, the expected increase in rectal dose is confined to approximately 20% of the rectal volume, with the remainder of the volume receiving between 30 and 50 Gy. This indicates that dose escalation for prostatic tumors is highly feasible using these techniques.

- 1.5** The most appropriate exploration of the potential of 3D-CRT is in patients who are at moderate to high risk for local recurrence with standard radiation therapy initiated to total doses of 65 Gy to 70 Gy. At the same time, the patients must not have a high risk of regional lymph node metastases that would necessitate large tumor volumes.

Patients with clinical stage T1a-c and T2a with Gleason scores  $\leq 5$  and PSA  $\leq 4.0$  ngm (*Hybritech*) are at such low risk for failure<sup>21,57,80</sup> with standard radiation therapy that dose escalation seems unwarranted. Patients with clinical stages T1b-c and T2a-b with Gleason scores  $\leq 6$  and PSA  $< 15$  have a moderate risk ( $\geq 20\%$ ) of local recurrence, but a low risk of lymph node metastasis; they are suitable for dose escalation studies without lymph node sampling, with the smallest tolerated volumes.<sup>21,37,53,54,57,80</sup> Patient with more advanced clinical stages, higher Gleason scores and higher PSA levels have a much greater risk of local failure ( $> 50\%$ ), but also a high risk of pelvic lymph node metastasis; these patients are suitable<sup>21,37,57,80</sup> for dose escalation trials with larger target volumes (*including seminal vesicles*) only if they have no evidence of lymph node metastasis after surgical nodal sampling.

## **2.0 OBJECTIVES**

- 2.1** To establish the maximum tolerated dose (*MTD*) of radiation that can be delivered to the prostate gland and immediate surrounding tissues in patients with carcinoma of the prostate using three dimensional conformal radiation therapy (*3D-CRT*).
- 2.2** To quantify the normal tissue toxicity rate (*normal tissue complication probability [NTCP]*) for rectum and bladder using 3D-CRT.
- 2.3** To evaluate local control by clinical, pathologic, and PSA (*stable in normal range*) determinations.
- 2.4** Distant metastasis and survival will be assessed but they are not primary endpoints for this study.

## **3.0 CRITERIA FOR PATIENT ELIGIBILITY (5/12/95, 1/22/96)**

### **3.1 Eligibility Criteria**

- 3.1.1** Patients with previously untreated adenocarcinoma of the prostate. All clinical stages (*Appendix III*) will be eligible except T1b-c and T2a-b who have Gleason score  $\leq 5$  and PSA  $\leq 4$ , or clinical stage T4.
- 3.1.2** Karnofsky performance status  $\geq 80$ .
- 3.1.3** No evidence of distant metastasis or other synchronous primary. Prior malignancy does not exclude the patient if disease-free  $\geq 5$  years. Prior or concurrent basal cell or non-invasive squamous cell cancer of the skin is eligible.
- 3.1.4** Hgb  $\geq 11$  gm%, WBC  $\geq 4000/\mu\text{l}$ , platelet count  $\geq 100,000/\mu\text{l}$ .
- 3.1.5** Patients must give study-specific informed consent before being placed on study.
- 3.1.6** PSA values  $< 70$  (*Hybritech equivalent*). Must be done within 3 months prior to study entry and  $\geq 10$  days after prostate biopsy.

3.1.7 Induction hormone therapy beginning 2-6 months prior to registration is acceptable. Prehormone PSA must be available.

**3.2 Ineligibility Criteria (5/12/95)**

- 3.2.1 Clinical stages T1b-c and T2a with Gleason score  $\leq 5$  and PSA  $\leq 4$ , or clinical stage T4. T1a is excluded regardless of Gleason and PSA.
- 3.2.2 Evidence of distant metastases.
- 3.2.3 Regional lymph node involvement.
- 3.2.4 Previous radical surgery (*prostatectomy*) or cryosurgery for prostate cancer.
- 3.2.5 Previous pelvic irradiation.
- 3.2.6 Previous hormonal therapy including agents such as finasteride(*Proscar*) beginning  $< 2$  months or  $> 6$  months prior to registration.
- 3.2.7 Previous or concurrent cytotoxic chemotherapy.
- 3.2.8 Major medical or psychiatric illness which in the investigator's opinion would prevent completion of treatment and interfere with follow-up.
- 3.2.9 Karnofsky performance status  $< 80$ .
- 3.2.10 PSA values  $\geq 70$ .

**4.0 PRETREATMENT EVALUATIONS (5/12/95, 1/22/96, 11/17/97)**

- 4.1 Complete history, physical examination, and evaluation of Karnofsky Performance Status required.
- 4.2 Histological evaluation of prostate biopsy with assignment of a Gleason grade to the biopsy material. Gleason pattern scores will be divided into 2-4 (*well differentiated*), 5-7 (*moderately differentiated*), and 8-10 (*poorly differentiated*).
- 4.3 Laboratory evaluations to include CBC, biochemistry survey including BUN, creatinine, alkaline phosphatase, testosterone, and prostatic specific antigen (*PSA*). PSA must be done within 3 months prior to registration and no less than 10 days after biopsy.
- 4.4 PA and lateral chest X-ray (*optional*).
- 4.5 Radionuclide bone scan must be done if patient is in Group 2 with PSA  $> 15$  or in Group 3.
- 4.5.1 No bone scan is required for Group 1.
- 4.5.2 Bone scan is optional for Group 2 if PSA is  $\leq 15$ .
- 4.6 Diagram of findings by digital examination of prostate.
- 4.7 Urethrogram to be done at the time of simulation or CT scan for treatment planning. See Section 6.3.2.
- 4.8 Nodal assessments as follows:
  - 4.8.1 Group 1 patients by definition have a low risk of pelvic lymph node metastases and therefore pelvic CT (*MRI*) and/or pelvic lymphadenectomy are optional.
  - 4.8.2 For Groups 2 and 3 patients, lymph node assessment is recommended by pre-registration diagnostic pelvic CT scan (*or MRI*) and/or pelvic lymphadenectomy.

**5.0 REGISTRATION PROCEDURES (1/24/97, 4/1/97, 3/10/98)**

- 5.1 Only institutions that have met the technology requirements and that have provided the baseline physics information that are described in Appendix VI (3D Conformal Radiation Therapy Prostate Group Quality Assurance Guidelines) may enter patients to this study. The 3D questionnaire (one per institution, Appendix VIII) is to be sent to the Washington University (*WU*) 3D Quality Assurance (*QA*) Center for review prior to entering any cases. Upon review and successful completion of "Dry-Run" QA test (*See page 32, 7a*), the WU 3D QA Center will notify both the registering institution and RTOG Headquarters that the institution is eligible to enter patients onto this study.
- 5.2 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
  - Institution Name & Number
  - Patient's Name & ID Number
  - Verifying Physician's Name
  - Eligibility Criteria Information
  - Demographic Data
  - Treatment Start Date

- Stratification Group
- 5.3 After the patient is registered to a treatment arm, RTOG will notify the WU 3D QA Center (by FAX) providing the following information:
  - Case Number
  - Institution Name
  - Institution Number
  - Date of Registration
  - Treatment Option
  - Stratification Group
- 5.4 After the patient is registered to a treatment arm, the institution will submit the required data (both hardcopy and digital) to the WU 3D QA Center (See Section 12.2) and to the RTOG (See Section 12.1).

## 6.0 RADIATION THERAPY

### 6.1 Dose Specification (5/12/95, 6/16/95, 1/24/97, 4/1/97, 10/5/98)

#### • DOSE LEVELS I AND II

6.1.1 The prescription dose is the minimum dose to the planning target volume(s) (Section 6.4) . The maximum dose should not exceed the prescription dose by more than 7% (inhomogeneity  $\leq 7\%$ ) and will be scored as: no variation,  $\leq 7\%$ ; minor variation,  $> 7$  to  $\leq 10\%$ ; major variation  $> 10\%$ .

6.1.2 Prescription dose to the PTVs shall be according to the following dose escalation schema delivered in 1.8 Gy minimum dose fractions. All fields treated once daily, 5 fractions per week.

<i>PTV</i>	
<u>Groups 1 and 3</u>	<u>Minimum Dose</u>
	68.4 Gy
	73.8 Gy
	79.2 Gy
<u>Group 2</u>	<u>Minimum Dose</u>
	55.8 Gy + 12.6 Gy = 68.4 Gy
	55.8 Gy + 18.0 Gy = 73.8 Gy
	55.8 Gy + 23.4 Gy = 79.2 Gy

Patients in Group 2 will undergo a field reduction that excludes the seminal vesicles after 55.8 Gy.

#### Treatment Group

##### Group 1

GTV=Prostate CTV = prostate (no margin)  
PTV = CTV + 0.5-1.0 cm

##### Group 2

GTV=Prostate CTV<sub>1</sub> = Prostate + BSV<sup>a</sup> CTV<sub>2</sub> = Prostate  
PTV<sub>1</sub> = CTV + 0.5-1.0 cm PTV<sub>2</sub> = CTV<sub>2</sub> + 0.5-1.0 cm

##### Group 3

GTV=Prostate+BSV<sup>a</sup> CTV = Prostate + BSV (no margin)  
PTV = CTV + 0.5-1.0 cm

Group 1: Clinical Stages T1 b-c or T2 a-b with PSA + ([Gleason -6]x10) is  $\leq 15$ .

Group 2<sup>b</sup>: Clinical Stages T1 b-c or T2 a-b, with PSA + ([Gleason -6] x 10)  $> 15$ .  
Any clinical T2c with PSA  $< 70$ .

Group 3<sup>b</sup>: Clinical Stage T3 with PSA  $< 70$ .

a. BSV = Bilateral seminal vesicles.

b. Groups 2 and 3 represent high-risk patients. The Group 3 patients will have seminal vesicles treated to full escalated dose. **Patients in Groups 2 and 3 must be clinically lymph node negative.**

• **DOSE LEVEL III**

**6.1.3** Prescription dose for dose level 3 to be delivered in 1.8 Gy fractions, all fields treated once daily, 5 fractions per week.

	<i>PTV</i>	<i>CTV/GTV</i>	
<u>Group 1</u>	<u>Minimum Dose</u> 73.8 Gy	<u>Minimum Dose</u> 79.2 Gy (1.8 Gy/fx)	
	<i>Total PTV1</i>	<i>Total CTV2</i>	<i>Total PTV2</i>
<u>Group 2</u>	<u>Minimum Dose</u> 55.8 Gy (1.8 Gy/fx)	<u>Minimum Dose</u> 79.2 Gy (1.8 Gy/fx)	<u>Minimum Dose</u> 73.8 Gy

Treatment Group

Group 1

GTV = Prostate                      CTV = prostate (no margin)  
PTV = CTV1 +0.5 to 1.0 cm

Group 2

GTV = Prostate                      CTV1 = prostate + BSV<sub>a</sub>                      CTV2 = prostate  
PTV1 = CTV1 + 0.5 to 1.0 cm                      PTV2 = CTV2 + 0.5 to 1.0 cm

Group 1:                      Clinical Stages T1 b-c, T2 a-b, with PSA + ([Gleason -6] x 10) is ≤ 15.

Group 2<sub>b</sub>:                      Clinical Stages T1 b-c, T2 a-b, with PSA + ([Gleason -6] x 10) > 15  
Any T2c with PSA < 70

a. BSV = Bilateral seminal vesicles.

b. Group 2 represents high-risk patients. **Patients in Group 2 must be clinically lymph node negative.**

• **DOSE LEVEL IV**

**6.1.4** Prescription dose for Dose Level IV is to be delivered in 2.0 Gy minimum dose fractions, all fields treated once daily, 5 fractions per week.

	<b>PTV</b>	
<u>Group 1</u>	<u>Minimum Dose</u> 74.0 Gy	
	<b>PTV1</b>	<b>PTV2 (Boost)</b>
<u>Group 2</u>	<u>Minimum Dose</u> 54.0 Gy	<u>Minimum Dose</u> 20.0 Gy
	+	=
		<b>Total PTV2</b>
		<u>Minimum Dose</u> 74.0 Gy

• **DOSE LEVEL V (2/14/00)**

**6.1.5** This dose escalation study was originally designed with three total dose levels; Level I 68.4 Gy, Level II 73.8 Gy and Level III 79.2 Gy; all given at 1.8 Gy per day. After dose level II (disease groups 1 and 2) was shown to be safe<sup>81</sup> and the patient accrual to dose level III (79.2 Gy) had been completed a fourth dose level was added. It was the consensus of the participating investigators to increase the daily fraction size from 1.8 Gy to 2.0 Gy for dose level IV and any additional dose levels in order to keep the total treatment time at a reasonable level for the patient. Therefore the minimum PTV dose for dose level IV was 74.0 Gy given at 2.0 Gy per day. The preliminary analysis of dose level III shows it to be safe. Dose level IV (for disease groups 1 and 2) has finished accruing and the participating investigators have decided to escalate to one final dose. The minimum PTV dose for dose level V will be 78.0 Gy given at 2.0 Gy per day.

**6.1.6** The three disease groups defined by disease extent will be receiving the following dose levels:

Disease Group 1                      Dose Level V: 78.0 Gy/ 2.0 Gy per fraction

Disease Group 2  
Disease Group 3

Dose Level V: 78.0 Gy/ 2.0 Gy per fraction  
Closed to accrual.

6.1.7 Disease group 3 has recently reached its accrual for dose level II and will not be escalated due to slow accrual.

6.1.8 The reported doses shall include the dose to the ICRU Reference Point (*Section 6.4.4*) as well as the maximum point dose, minimum (*prescription*) point dose, and mean dose to PTV.

6.1.9 The dose prescription is to be based on a dose distribution uncorrected for heterogeneities.

## 6.2 External Beam Equipment

6.2.1 Megavoltage equipment is required with effective photon energies  $\geq 10$  MV.

6.2.2 3D conformal radiotherapy capabilities as defined and confirmed by the QA Center. See Appendix VI for 3D Guidelines.

## 6.3 Treatment Planning Imaging and Localization Requirements (5/12/95)

6.3.1 A urethrogram will be required to establish the most inferior portion of the prostate. Seeds within the prostate are optional for defining the apex. If the urethrogram is not done with the planning CT scan, then an AP simulation radiograph with urethrogram will be submitted with the planning CT.

6.3.2 A treatment planning CT scan will be required to define tumor, clinical, and planning target volumes. **If the patient began hormones prior to registration (*Section 3.1.7*), the target volume will be based on the prostate and seminal vesicle volume at registration.** The treatment planning CT should be acquired with the patient in the same position, immobilization device, and conditions, as he will be for treatment. That is, if treatment is planned with a full bladder, the simulation CT should be performed with a full bladder. The rectum should be empty (*except for contrast material for its visualization*). Each patient will be positioned in the supine position in an individualized thermoplastic immobilization cast or molded foam cradle in the treatment position on a flat tabletop in the cast. The CT scan of the pelvis should start at or above the iliac crest down to the perineum. All tissues to be irradiated must be included in CT scan. CT scan thickness should be  $\leq 0.5$  cm through the region that contains the target volumes (*i.e., from the bottom of the sacroiliac joints down to the penile urethra*). The regions above and below the target volume region may be scanned with slice thickness  $\leq 1.0$  cm.

The GTV, CTV and PTV (*see Section 6.4*), and normal tissues must be outlined on all CT slices in which the structures exist. Beam's eye view display must be used to design beam aperture.

## 6.4 Volume and ICRU Reference Point Definitions (5/12/95)

The definition of volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy.

6.4.1 The Gross Tumor Volume (GTV) is defined by the physician as all known disease as defined by the planning CT, urethrogram, and clinical information. At the minimum, the GTV will encompass a volume inferiorly 5mm superior to the tip of the dye column as seen on urethrogram and no less than the entire prostate. Prostate dimensions should be defined as visualized on CT scan.

Group 1: GTV = Prostate

Group 2: GTV = Prostate

Group 3: GTV = Prostate and bilateral seminal vesicles

6.4.2 The Clinical Target Volumes (CTV) are the GTV plus areas considered to contain microscopic disease, delineated by the treating physician, and is defined by group as follows:

Group 1: CTV is the GTV (*prostate*) with no margin.

Group 2: CTV<sub>1</sub> is the GTV (*prostate*) plus the bilateral seminal vesicles.

CTV<sub>2</sub> is the GTV (*prostate*) with no margin.

Group 3: CTV is the GTV (*prostate and bilateral seminal vesicles*) with no margin.

6.4.3 The Planning Target Volume (PTV) will provide a margin around the CTV to compensate for the variabilities of treatment set up and internal organ motion. Currently a study is ongoing to define the magnitude of the uncertainty components of the PTV. Until the results of that study are available, a minimum of 5-10 mm around the CTV is required to define each respective PTV. Superior and inferior margins (*capping*) should be 5-10 mm depending on the thickness and spacing of the planning CT scan. Careful consideration should be made when defining the 5-10 mm margin in three dimensions.

6.4.4 The ICRU Reference Points are to be located in the central part of the PTV and, secondly, on or near the central axis of the beams. Typically these points should be located on the beam axes or at the intersection of the beam axes.

6.4.5 Critical Normal Structures

The normal tissue volume to be contoured will include bladder, rectum, bilateral femora (*to the level of ischial tuberosity*), and skin. The normal tissues will be contoured and considered as solid organs. The bladder should be contoured from its apex to the dome, and the rectum from the anus (*at the level of the ischial tuberosities*) for a length of 15 cm or when the rectosigmoid flexure is identified. The tissue within the skin and outside all other critical normal structures and PTV's is designated as unspecified tissue.

## **6.5 3D Planning**

### **6.5.1 PTV**

Treatment will be given only to the PTV using three dimensional conformal fields shaped to exclude as much of the bladder and rectum as possible. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical normal structures.

### **6.5.2 Critical Normal Structures**

Custom shielding shall be used in conjunction with conformal planning to restrict the dose to the normal structures. DVH's must be generated for all critical normal structures and the unspecified tissues (*see Section 6.4.5*). Portions of the bladder and rectum will, by necessity receive the full dose to the PTV; however, careful 3D planning must be performed to ensure that the volume of the bladder and rectum receiving the full dose is kept to a minimum.

## **6.6 Treatment Verification (1/22/96)**

First day port films or portal images of each field must be obtained. Twice weekly (*at least 48 hours apart*) verification films or images of orthogonal views (*anterior to posterior and lateral projection*) are required during the first two weeks of RT and will be reviewed by the treating physician. Subsequent port films will be done weekly. The required accuracy of patient positioning and the use of multi-leaf collimator apertures suggests the daily use of on-line imaging.

## **6.7 Quality Assurance of Target Volumes and Critical Structure Volumes**

The 3D QA Center will review PTV, CTV, GTV and designated critical structures on, as a minimum, the first five cases submitted by each institution. After an institution has demonstrated compliance with protocol, future cases will be spot checked only.

## **6.8 Quality Assurance of Field Placement (5/12/95)**

The 3D QA Center will review a set of orthogonal set-up films and the first day placement film of each field by comparing with the submitted digital reconstructed radiographs (*DRRs*) or alternatively, submitted simulation verification radiographs.

## **6.9 Quality Assurance of Dose Distribution (5/12/95)**

**6.9.1** The 3D QA Center will display, and compare with hard copies, isodose distributions for the axial, and coronal planes (*or multiple axial planes as outlined in Appendix VI, QA Guidelines*) through the planning target volume to verify correct digital submission and conversion.

**6.9.2** The 3D QA center will compare the submitted digital dose-volume histograms (*DVHs*) for the PTV, designated critical structures, and unspecified tissues with DVHs calculated by the 3D QA Center.

**6.9.3** *Each treatment shall be judged as:*

- 1) No variation (*total coverage*); each prescription isodose surface covers 100% of the appropriate PTV.
- 2) Minor variation (*marginal coverage*); each prescription isodose surface coverage between  $\geq 95\%$  to  $< 100\%$  of the appropriate PTV.
- 3) Major variation (*miss*); each prescription isodose surface coverage  $< 95\%$  of the appropriate PTV.

### **6.9.4 Dose Heterogeneity**

Maximum dose to PTV should not exceed the prescription dose by  $> 7\%$  (*no variation,  $\leq 7\%$ ; minor variation,  $> 7$  to  $\leq 10\%$ ; major variation,  $> 10\%$* ). The maximum point dose to critical normal structures outside the PTV including the unspecified tissue should not exceed the prescription dose. The treating physician must carefully consider the tolerance dose/volume to each critical normal structure and unspecified tissue.

## **6.10 RTOG 3D-CRT Summary of 1993 ICRU Report 50 on Recommendations for Prescribing, Recording, and Reporting External Beam Radiation Therapy**

**6.10.1** Complete descriptions of volumes to be treated have been included in the 3D-CRT protocols in order to minimize the institutional variation of tumor and target volume delineation for protocol cases. Please consult the ICRU 1993 document for complete descriptions of the various target volumes defined. The next paragraphs summarize the ICRU definitions which are relevant for this protocol.

- 6.10.2** The gross tumor volume (*GTV*) includes the known disease as determined by physical examination, imaging studies and other diagnostic information. More than one *GTV* can be defined.
- 6.10.3** The clinical target volume (*CTV*) includes the area of subclinical involvement around the *GTV*. The *CTV* is the *GTV* plus the margin for micro extensions of the tumor. More than one *CTV* can be defined.
- 6.10.4** The planning target volume (*PTV*) is the *CTV* plus a margin to ensure that the prescribed dose is actually delivered to the *CTV*. This margin accounts for variations in treatment delivery, including variations in set-up between treatments, patient motion during treatment, movement of the tissues which contain the *CTV* (e.g. *respiration*), and size variations in the tissue containing the *CTV*. The *PTV* is a geometric concept. More than one *PTV* can be defined.

**6.11 Toxicity Reporting Guidelines**

- 6.11.1** All fatal toxicities (*grade 5*) resulting from protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management and to the Study Chairman within 24 hours of discovery.
- 6.11.2** All life-threatening (*grade 4*) toxicities from protocol treatment must be reported by telephone to the Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.
- 6.11.3** Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report (*FAX # 215/928-0153*).

**7.0 DRUG THERAPY**

Does not apply to this study.

**8.0 SURGERY**

Does not apply to this study.

**9.0 OTHER THERAPY (5/12/95, 1/22/96)**

Neoadjuvant androgen suppression (*nonsurgical*) is permitted for protocol patients if clinically indicated. The following conditions apply:

- Must begin 2-6 months prior to registration to this study
- Pre hormone bone scan and PSA must be available
- CT scan may be repeated just prior to RT
- Treatment volume will be based on prostate and seminal vesicle volume at registration

**10.0 PATHOLOGY**

Does not apply to this study.

**11.0 PATIENT ASSESSMENTS**

**11.1 Study Parameters (5/12/95, 1/22/96, 11/17/97)**

<b>Parameter</b>	<b>Pre RT</b>	<b>Weekly on RT</b>	<b>Follow-up</b>
History & Physical	X	X	X
Karnofsky ( <i>KPS</i> )	X	X	X
CBC, platelets	X	X <sup>a</sup>	X <sup>a</sup>
Alkaline phosphatase	X <sup>a</sup>		
PSA ( <i>≤ 3 months</i> )	X <sup>e</sup>		X
Acid phosphatase	X <sup>a</sup>		
BUN, Creatinine, testos.	X		
Urethrogram	X		X <sup>g</sup>
Bone scan <sup>f</sup>	X		X <sup>b</sup>
Pelvic CT	X <sup>d</sup>		
Toxicity Evaluation		X	X

Tumor Biopsy	X		X <sup>c</sup>
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- a. Optional
- b. If acid phos, alk phos, or PSA is elevated or patient symptomatic.
- c. As indicated, for rising PSA or clinical failure.
- d. Optional for Group 1. If the patient receives hormones, the CT scan may be repeated prior to the start of RT.
- e. If the patient is on hormones, prehormone PSA must be available.
- f. Group 1, not required; Group 2 with PSA ≤ 15, optional; Group 2 with PSA > 15 or Group 3, required.
- g. Testosterone will be repeated at first followup.

### **11.2 Evaluation During Treatment (5/12/95)**

**11.2.1** Patients will be seen and evaluated at least weekly during radiation therapy with documentation of tolerance, including acute reactions and weight.

### **11.3 Evaluation Following Treatment (5/12/95, 2/9/96)**

**11.3.1** At each visit (*See Section 12.1*) the patient will have an interval history, complete physical examination (*including digital rectal examination with diagram of findings*) and assessment of specific GU and GI morbidity.

**11.3.2** PSA will be drawn at each follow-up visit (*prior to the rectal exam*).

**11.3.3** A bone scan will be performed if the PSA, acid phosphatase or alkaline phosphatase become elevated, or when the patient develops symptoms suggesting the presence of metastatic disease.

**11.3.4** A needle biopsy will be obtained from the site of original tumor within the prostate and/or other site of original tumor identified by the transrectal ultrasound, as indicated for rising PSA or clinical failure.

### **11.4 Criteria for Toxicity**

**11.4.1** *Acute and late toxicity* related to radiation therapy may include fatigue, myelosuppression, skin erythema, subcutaneous fibrosis, genital and/or leg edema, diarrhea, small bowel obstruction, proctitis, rectal bleeding, rectal ulceration, rectal-anal stricture, rectal necrosis, cystitis, hematuria, bladder ulceration, urethral stricture, vesicle neck contracture, and impotency.

**11.4.2** *Acute toxicity monitoring*: Acute side effects (*≤ 90 days of treatment start*) will be documented using the RTOG Acute Radiation Morbidity Scoring Criteria (*Appendix IV*).

**11.4.3** *Late toxicity monitoring*: Late post treatment (*appearing or persisting 90 days after treatment start*) gastrointestinal, rectal, and genitourinary complications will be evaluated and graded according to the RTOG Late Radiation Morbidity Scoring Scale (*Appendix IV*). The incidence of late complications have been established in RTOG prostate cancer protocols 75-06 and 77-06.<sup>49,50</sup> Of 526 patients entered into these trials, 20% suffered grade 2 toxicity (*symptoms responding to outpatient management, KPS not affected*), 9% developed grade 3 toxicity (*alters KPS, may require hospitalization or minor surgical intervention*), 0.7% developed grade 4 toxicity (*major surgical intervention or prolonged hospitalization required*) and only 1 patient experienced grade 5 toxicity (*fatal complications*). The incidence of bladder complications by grade was 6% grade 2, 6% grade 3, and 0.2% grade 4. The incidence of bowel complications was 11% grade 2, 2% grade 3, 0.6% grade 4, and 0.2% grade 5.<sup>47</sup> In RTOG 77-06 the addition of pelvic irradiation did not significantly increase the incidence of treatment related morbidity compared to prostate irradiation only.<sup>49</sup>

### **11.5 Criteria for Local Control**

**11.5.1** *Clinical criteria* for local failure are progression (*increase in palpable abnormality*) at any time, failure of regression of the palpable tumor by two years, and redevelopment of a palpable abnormality after complete disappearance of previous abnormalities. Needle biopsy is recommended.

**11.5.2** *Histologic criteria* for local failure are presence of prostatic carcinoma upon biopsy resulting from any of the clinical criteria in Section 11.5.1, and positive biopsy of the palpably normal prostate more than two years after the start of treatment.

**11.5.3** *PSA criteria* for local failure are failure of PSA to fall below 4 ngm 12 months after the start of radiation therapy or 2 consecutive increases, (*at least 1 month apart*) in PSA during first 12 months after start of treatment, (*or start of hormone therapy after one increased value*). For PSA < 4, a rising PSA to double nadir value or a rise of 1 ngm in the absence of clinical or bone scan evidence of distant metastasis will be suggestion of local failure. Ultrasound-directed needle biopsy is required; if positive, local failure is confirmed.

### **11.6 Criteria for Nonlocal Failure**

Local control is the primary endpoint of the efficacy part of this study. Other types of failure will be documented as follows:

**11.6.1** Distant metastasis will be documented if clinical or bone scan evidence is demonstrated. Ultrasound evaluation of the prostate with needle biopsy as indicated by the findings is recommended at the time distant metastasis is reported.



- 11.6.2** PSA failure will be documented separately if there is no clinical, ultrasound, or biopsy evidence of local failure, and the PSA is > 4 ngm 12 months or more after the start of radiation therapy or if there is a rising PSA to double nadir value or 1 ngm for PSA ≤ 4 ngm, and there is no clinical or bone scan evidence of distant metastasis.

**12.0 DATA COLLECTION**

**12.1 Summary of Data Submission/ACR** (1101 Market Street, Philadelphia, PA 19107, Fax # 215/928-0153)

<u>Item</u>	<u>Due</u>
Demographic Form (A5)	Within 1 week of study entry
Initial Evaluation Form (I1) Diagnostic Pathology Report (P1)	Within 2 weeks of study entry
Radiotherapy Form (T1) (copy, original to WU per Section 12.2)	Within 1 week of RT end
Follow-up Form (F1) year; q 4 months x 1 year, q 6 months x 3 progression/	Every 3 months from treatment start for 1 years, then annually. Also at relapse and at death
Autopsy Report (D3)	As applicable

**12.2 Summary of RT QA Requirements** (Washington University) (5/12/95)

<b><u>Preliminary Dosimetry Information:</u></b> Digital Patient Submission Information Form (T2) CT data, critical normal structures, all GTV, CTV and PTV contours Films and/or digital film images for simulation, first day portals, and one orthogonal set-up pair Digital beam geometry for first set of beams (required) and for all additional beams (optional) Doses for first (or all) sets of concurrently treated beams are optional.	Within 1 week of start of RT
<b><u>Final Dosimetry Information:</u></b> Radiotherapy Form (T1) Digital Patient Submission Information Form (T2) Daily Treatment Record Digital dose data and beam geometry data for all beam sets is required First day boost and orthogonal setup films and/or digital data (simulation and portal, if any) Hard copy isodose distributions as defined in Section 6.9 Digital DVH data	Within 1 week of RT end

**12.2.1** For Mail or Federal Express:

James A. Purdy, Ph.D.  
RTOG 3D QA Center  
Washington University School of Medicine

510 S. Kingshighway  
St. Louis, MO 63110  
tel. 314/362-2631 Fax# 314/362-2682

- 12.2.2.** *To send over Internet or using magnetic tape:*  
Digital data submission may be accomplished using magnetic tape or the Internet. For network submission, the *ftp* account assigned to the submitting institution shall be used and *e-mail* identifying the data set(s) being submitted shall be sent to:

**rtog3dqa@castor.wustl.edu**

For tape submission, please contact the 3D QA Center about acceptable tape types and formats.

**12.3 Timely Data Submission for Toxicity Evaluation**

Timely data submission is critical in order to meet the study's objectives for toxicity evaluation and to safety assign treatment levels.

**13.0 STATISTICAL CONSIDERATIONS (5/12/95, 6/16/95, 2/14/00)**

**13.1 Sample Size**

**13.1.1 Evaluation of acute and late toxicity**

The phase I portion of this study is to identify acute and late GU and GI toxicities associated with three-dimensional conformal radiation therapy (*3D CRT*). The goal is to establish the maximum tolerated dose (*MTD*) with less than a 20% chance of a patient developing a severe (*Grade 3 or Grade 4*) GU or GI toxicity or no Grade 5 toxicities by 3D CRT. Acute toxicity is defined to be toxicities occurring within 90 days from the start of radiotherapy treatment and a late toxicity is after 90 days.

**13.1.2 Dose Escalation (1/21/96)**

There are three separate and independent groups (*Group 1, Group 2, and Group 3*) as defined by the different disease extent that are being analyzed for this phase I/II study. For each of the groups in this study, there are three proposed dose levels:

<u>Total Dose</u>	
Level I	68.4 Gy
Level II	73.8 Gy
Level III	79.2 Gy

Level I is considered a previously established safe dose and will be used to evaluate the methods of recording patient information outlined within this protocol and will also be used to determine when an institution is able to escalate to the highest available dose level.

The QA Center will monitor the data submission of at least two patients to Level I and will judge when an institution is able to escalate to the highest available dose level. When the QA Center deems the quality of the treatment plan and format of data submission is adequate, the Center will inform the study statistician, both in writing and by phone. When an institution is approved, that institution will be able to begin accruing to the highest available dose level.

The highest available dose level may be Level I, II or III, depending on the status of the trial as described below.

At Level II, using the methods of cumulative incidence, we can reject  $H_0$  : 20% toxicity at a given dose for  $H_1$  : 5% toxicity for a given dose level with 95% confidence ( $\alpha = 0.05$ , *one-sided test*;  $\beta = 0.20$ ) by following 75 eligible patients (*accrued during one year,  $\cong 7$  patients/month*) for one year of follow-up. An interim analysis will be done at 18 months after the level opened to determine if the dose is acceptable at that time. Exact criteria for acceptance or rejection of a dose depend upon the accrual and follow-up patterns. Following the assumptions used above in the estimation of the sample size, if no toxicities are observed at 18 months, then the dose will be deemed acceptable and accrual for Level III will begin. If necessary, at 24 months an additional analysis will be done. Assuming the same patterns as mentioned above, if two or less Grade 3 or 4 toxicities are observed, then the dose will be deemed acceptable and accrual for Level III will begin. If at any time more than two Grade 3 or 4 toxicities or

any Grade 5 toxicity is observed and confirmed by the study chair and Executive Committee, the dose will be deemed too toxic, accrual will stop, and Level I will be considered the MTD. An alpha-value of 0.01 will be used for the interim analysis and an alpha-value of 0.040 will be used in the analysis at 24 months to ensure an overall alpha = 0.05.

After the required accrual to Level II is completed, additional patients may be accrued to Level I until a decision about dose-escalation is made.

If Level II is deemed acceptable, then patients will be accrued to Level III. Using the methods as above, we can reject  $H_0$  : 20% toxicity at a given dose for  $H_1$  : 5% toxicity for a given dose level with 95% confidence ( $\alpha = 0.05$ , one-sided test;  $\beta = 0.19$ ) by following 60 eligible patients (*accrued during nine months, 7 patients/month*) for two years of follow-up. At the end of the accrual and follow-up (*33 months*), an analysis will be done. Assuming the same accrual and follow-up patterns as indicated above, if two or less Grade 3 or 4 are observed, then the dose will be deemed acceptable. If at any time more than two Grade 3 or 4 or any Grade 5 toxicity is observed and confirmed by the study chair and Executive Committee, the dose will be deemed too toxic, accrual will stop, and Level II will be deemed the MTD.

After the required accrual to Level III is completed, additional patients may be accrued to Level II. This will allow those patients who intended to receive Level III but did not register until initial hormonal therapy was completed.

**13.1.3** Dose Escalation Amendment (10/5/98)

This dose escalation study was designed with three total dose levels; Level I 68.4 Gy, Level II 73.8 Gy and Level III 79.2 Gy. For disease groups 1 and 2, dose level II was shown to be safe 81 and the patient accrual to dose level III (*79.2 Gy*) has been completed. If dose level III (*79.2 Gy*) proves to be acceptable, should a new dose level of 84.6 Gy be evaluated? It is the consensus of the principle investigators from the participating institutions that the treatment time for such a total dose would be too long for the patients. For this reason, it has been decided to increase the daily fraction from 1.8 Gy to 2.0 Gy. Because the daily fraction is higher and the acceptability of dose level III has not yet been determined, the total dose for this new fraction size will be set just above the current dose level II (*73.8 Gy*). The minimum PTV dose for this new fraction size will be 74.0 Gy.

The three disease groups defined by disease extent will be receiving the following dose levels:

Disease Group 1	Dose Level IV: 74.0 Gy/2.0 Gy per fraction
Disease Group 2	Dose Level IV: 74.0 Gy/2.0 Gy per fraction
Disease Group 3	Dose Level II: 73.8 Gy/1.8 Gy per fraction

Disease group 3, which has accrued much more slowly than the other groups, will continue to accrue at dose level II until it reaches the required 79 patients. After enough follow-up information had been obtained, a decision will be made as to whether or not to escalate disease group 3 to dose level III as outlined in Section 13.1.2.

Using historical data from RTOG studies 75-06 and 77-06, the probabilities of a patient experiencing a late grade 3+ toxicity are 0.0403, 0.0533, 0.0480 and 0.0256 for 0-6, 6-12, 12-18 and 18-24 months of late follow-up respectively. For each of the disease groups 1 and 2, 88 eligible patients (*accrued during one year, ~ 8 patients/month*) will be followed until there is enough late follow-up information to observe 5.5 expected late toxicities based on RTOG historical data.<sup>82</sup> This will require approximately 18 months of late follow-up. If there are no grade 3 or 4 late toxicities at that time, the daily fraction of 2.0 Gy to a total of 74.0 Gy will be deemed to be acceptable with a significance level of 0.01. If one or two grade 3 or 4 late toxicities occur, then a decision will not be made until the patients have been followed long enough to observe 6.5 expected late toxicities or approximately another 6 months of late follow-up. At that point another analysis will be done. If a total of two or fewer grade 3 or 4 late toxicities have occurred, then the treatment will be deemed to be acceptable at a significance level of 0.04. Using these two different statistical levels, an overall significance level of 0.05 is preserved for each disease group. If at any point in time more than two grade 3 or 4 or any grade 5 toxicities are observed and confirmed by the study chair, then the accrual will be stopped. This will be followed by a discussion involving the study chair and representatives from the 3D CRT and the GU committees to make a final determination whether this new level should be deemed to be unacceptable.

A 5 % adjustment for ineligible patients will be made for each of the two disease groups (*1 and 2*) that will be accruing to this new treatment plan. Therefore  $88/.95 = 93$  patients for each of disease groups 1 and 2 and thus **a total of 186 patients will be required.**

#### 13.1.4 Dose Escalation Amendment (2/14/2000)

This dose escalation study was originally designed with three total dose levels; Level I 68.4 Gy, Level II 73.8 Gy and Level III 79.2 Gy; all given at 1.8 Gy per day. After dose level II (*disease groups 1 and 2*) was shown to be safe<sup>81</sup> and the patient accrual to dose level III (79.2 Gy) had been completed a fourth dose level was added. It was the consensus of the participating investigators to increase the daily fraction size from 1.8 Gy to 2.0 Gy for dose level IV and any additional dose levels in order to keep the total treatment time at a reasonable level for the patient. Therefore the minimum PTV dose for dose level IV was 74.0 Gy given at 2.0 Gy per day. The preliminary analysis of dose level III shows it to be safe. Dose level IV (*for disease groups 1 and 2*) has finished accruing and the participating investigators have decided to escalate to one final dose. The minimum PTV dose for dose level V will be 78.0 Gy given at 2.0 Gy per day.

The three disease groups defined by disease extent will be receiving the following dose levels:

Disease Group 1	Dose Level V: 78.0 Gy/ 2.0 Gy per fraction
Disease Group 2	Dose Level V: 78.0 Gy/ 2.0 Gy per fraction
Disease Group 3	Closed to accrual.

Disease group 3 has recently reached its accrual for dose level II and will not be escalated due to slow accrual.

Using historical data from RTOG studies 7506 and 7706, the probabilities of a patient experiencing a late grade 3+ toxicity are 0.0403, 0.0533, 0.0480 and 0.0256 for 0-6, 6-12, 12-18 and 18-24 months of late follow-up respectively. For each of the disease groups 1 and 2, 88 eligible patients (*accrued during one year, ~ 8 patients/month*) will be followed until there is enough late follow-up information to observe 5.5 expected late toxicities based on RTOG historical data.<sup>82</sup> This will require approximately 18 months of late follow-up. If there are no grade 3 or 4 late toxicities at that time, the daily fraction of 2.0 Gy to a total of 74.0 Gy will be deemed to be acceptable with a significance level of 0.01. If one or two grade 3 or 4 late toxicities occur then a decision will not be made until the patients have been followed long enough to observe 6.5 expected late toxicities or approximately another 6 months of late follow-up. At that point another analysis will be done. If a total of two or fewer grade 3 or 4 late toxicities have occurred, then the treatment will be deemed to be acceptable at a significance level of 0.04. Using these two different statistical levels, an overall significance level of 0.05 is preserved for each disease group. If at any point in time more than two grade 3 or 4 or any grade 5 toxicities are observed and confirmed by the study chair, then the accrual will be stopped. This will be followed by a discussion involving the study chair and representatives from the 3D CRT and the GU committees to make a final determination whether this new level should be deemed to be unacceptable.

A 5 % adjustment for ineligible patients will be made for each of the two disease groups (*1 and 2*) that will be accruing to this new treatment plan. Therefore  $88/.95 = 93$  patients for each of disease groups 1 and 2 and thus **a total of 186 patients will be required for Dose Level V.**

#### 13.2 Expected Accrual

There are three separate dose escalation levels for this study with three groups within each level. There will be at approximately 40 patients accrued to Level I, all three groups combined. No adjustment will be made for ineligible patients for Level I. An adjustment for a 5% ineligibility rate will be made for Levels II and III. Level II will require  $75/.95 = 79$  patients in each arm. Level III will require  $60/.95 = 64$  patients in each arm. The total number of patients needed for this study to analyze all three dose levels with all three groups is 469 patients.

Due to the importance of the aforementioned accrual patterns for the proper statistical considerations, the accrual patterns of each group within each level will be monitored. If the accrual pattern observed deviates more than 20% from the expected pattern after six months of the level/group opening, then that level/group combination will be analyzed for feasibility if accrual rate is under what is expected, or considered fulfilled if accrual rate is greater than expected.

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- \* **added 10/5/98**

## APPENDIX I

### **3D-CRT ONCOLOGY GROUP**

#### **3D/OG 94-06**

### **A Phase I/II Dose Escalation Study Using Three Dimensional Conformal Radiation Therapy for Adenocarcinoma of the Prostate**

#### **Sample Patient Consent Form**

#### **RESEARCH STUDY**

I have the right to know about the procedures that are used in my participation in clinical research so as to afford me an opportunity to make the decision whether or not to undergo the procedure after knowing the risks and hazards involved. This disclosure is not meant to frighten or alarm me; it is simply an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

#### **PURPOSE OF THE STUDY**

It has been explained to me that I have prostate cancer. The standard treatment for this disease is surgery or radiation therapy with or without hormone therapy. The Department of Radiation Oncology is involved in a study which will use a treatment planning technique called 3-dimensional conformal radiation therapy. This technique allows the radiation beam to treat an area shaped like my tumor and also as deeply as my tumor is located. By treating this way the dose of radiation to the healthy areas near my tumor are minimized and the dose to my tumor is maximized. This study will try to increase the amount of radiation to the tumor above what has been achievable using standard treatment planning techniques. I have been asked to participate in this study.

#### **DESCRIPTION OF PROCEDURES (5/9/96)**

If I agree to participate in the study, I will be placed in the position in which I will be treated and will have treatment planning x-rays taken. I will be positioned in a special device while I am lying in the treatment position on a flat table. This ensures that I am treated in the exact same position every day that I have my radiation treatments. Either that same day or shortly thereafter, I will have a computed tomography (CT) scan for the three dimensional treatment planning. I may also have an MRI scan for tumor localization as well.

I will receive my radiation treatments every day, Monday through Friday for six to eight weeks. The dose of radiation I receive will depend on the size of my tumor and how many patients have entered the study before me. The first few patients entered on the study will receive a dose of radiation that previous research suggest will be safe. If they have no serious problems, the next patients will receive a higher dose. My doctor can tell me what dose I will receive before I make a decision about participating in the study.

I will have follow-up examinations in the Department of Radiation Oncology after finishing treatment. Follow-up examination will include periodic laboratory tests, x-rays, and scans. This schedule is similar to that of patients not participating in a research study, except that additional scans may be required.

#### **RISKS AND DISCOMFORTS**

Cancer treatments often have side effects. The treatment used in this program may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Risks:

**Radiotherapy** may cause reddening or tanning of the skin, rash, itching or peeling, hair loss in the treatment area, temporary fatigue, nausea, diarrhea, abdominal cramps, or bladder irritation. There is also a possibility of injury to the bladder, urethra, bowel and other tissues in the pelvis or abdomen. Side effects usually disappear after the treatment is stopped. Late developing (*long-term*) effects may include the possibility of developing rectal bleeding, intestinal or urinary obstruction, and impotence. If they occur, these late effects sometimes may require medical or surgical treatment.

My physician will be checking me closely to see if any of these side effects are occurring. Routine blood and urine tests will be done to monitor the effects of treatment. In the meantime, my doctor may prescribe medication to keep these side effects under control. I understand that the use of medication to help control side effects could result in added costs. This institution is not financially responsible for treatments of side effects caused by the study treatment.

### **CONTACT PERSONS**

In the event that injury occurs as a result of this research, treatment will be available. I understand, however, I will not be provided with reimbursement for medical care other than what my insurance carrier may provide nor will I receive other compensation. For more information concerning the research and research-related risks or injuries, I can notify Dr. \_\_\_\_\_ the investigator in charge at \_\_\_\_\_. In addition, I may contact \_\_\_\_\_ at \_\_\_\_\_ for information regarding patients' rights in research studies.

### **BENEFITS**

It is not possible to predict whether or not any personal benefit will result from the use of the treatment program. I understand that the information which is obtained from this study may be used scientifically and possibly be helpful to others. The possible benefits of this treatment program are greater shrinkage and control of my tumor and prolongation of my life but I understand this is not guaranteed.

I have been told that should my disease become worse, should side effects become very severe, should new scientific developments occur that indicate the treatment is not in my best interest, or should my physician feel that this treatment is no longer in my best interest, the treatment would be stopped. Further treatment would be discussed.

### **ALTERNATIVES**

Alternatives which could be considered in my case include radiation therapy without 3D planning, surgery, chemotherapy or treatments to make me feel better, but not necessarily cure me or make my disease less. An additional alternative is no further therapy, which would probably result in continued growth of my tumor. I understand that my doctor can provide detailed information about my disease and the benefits of the various treatments available. I have been told that I should feel free to discuss my disease and my prognosis with the doctor. The physician involved in my care will be available to answer any questions I have concerning this program. In addition, I understand that I am free to ask my physician any questions concerning this program that I wish in the future.

My physician will explain any procedures related solely to research which would not otherwise be necessary. Some of these procedures may result in added costs but may be covered by insurance.

### **VOLUNTARY PARTICIPATION**

Participation in this study is voluntary. No compensation for participation will be given. I understand that I am free to withdraw my consent to participate in this treatment program at any time without prejudice to my subsequent care. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care. In the event of a research-related injury, I understand my participation has been voluntary.

### **CONFIDENTIALITY**

I understand that records of my progress while on the study will be kept in a confidential form at this institution and also in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or

organizations that have a role in the conduct of this study may have access to medical records which contain my identity. However, no information by which I can be identified will be released or published. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

**I have read all of the above, asked questions, received answers concerning areas I did not understand, and willingly give my consent to participate in this program. Upon signing this form I will receive a copy.**

\_\_\_\_\_  
Patient Signature *(or Legal Representative)*

\_\_\_\_\_  
Date

## APPENDIX II

### **KARNOFSKY PERFORMANCE SCALE**

100	Normal; no complaints; no evidence of disease
90	Able to carry on normal activity; minor signs or symptoms of disease
80	Normal activity with effort; some sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

**APPENDIX III**  
**Prostate, AJCC 4th Edition, 1992**

**DEFINITION OF TNM**

**Primary Tumor (T)**

- TX** Primary tumor cannot be assessed  
**T0** No evidence of primary tumor  
**T1** Clinically inapparent tumor not palpable or visible by imaging.  
    **T1a** Tumor incidental histologic finding in 5% or less of tissue resected  
    **T1b** Tumor incidental histologic finding in more than 5% of tissue resected  
    **T1c** Tumor identified by needle biopsy (e.g., because of elevated PSA)  
  
**T2** Tumor confined within prostate\*  
    **T2a** Tumor involves half of a lobe or less  
    **T2b** Tumor involves more than half of a lobe but not both lobes.  
    **T2c** Tumor involves both lobes.  
  
**T3** Tumor extends through prostatic capsule\*\*  
    **T3a** Unilateral extracapsular extension  
    **T3b** Bilateral extracapsular extension  
    **T3c** Tumor involves the seminal vesicle(s).  
  
**T4** Tumor is fixed or invades adjacent structures other than the seminal vesicles.  
    **T4a** Tumor involves any of: bladder neck, external sphincter, or rectum  
    **T4b** Tumor involves levator muscles and/or is fixed to the pelvic wall

\*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c

\*\*Note: Invasion into the prostatic apex into (but not beyond) the prostatic capsule is not classified as T3, but as T2.

**Regional Lymph Nodes (N)**

- NX** Regional lymph nodes cannot be assessed  
**N0** No regional lymph node metastasis  
**N1** Metastasis in a single lymph node, 2 cm or less in greatest dimension  
**N2** Metastasis in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, metastases, none more than 5 cm in greatest dimension  
**N3** Metastasis in a lymph node more than 5 cm in greatest dimension

**Distant Metastasis\* (M)**

- MX** Presence of distant metastasis cannot be assessed  
**M0** No distant metastasis  
**M1** Distant metastasis  
    **M1a** Non regional lymph node(s)  
    **M1b** Bone(s)  
    **M1c** Other site(s)

\*Note: When more than one site of metastasis is present, the most advanced category is used.

**APPENDIX III (cont'd)**

**Histopathologic Grade (G)**

- GX** Grade cannot be assessed
- G1** Well differentiated, slight anaplasia
- G2** Moderately differentiated, moderate anaplasia
- G3-4** Poorly undifferentiated or undifferentiated, marked anaplasia

**STAGE GROUPING**

<b>Stage 0</b>	T1a	N0	M0	G1	
<b>Stage I</b>	T1a	N0 T1b, T1c, T1	M0 N0	G2, G3-4 M0	Any G
<b>Stage II</b>	T2	N0	M0	Any G	
<b>Stage III</b>		T3	N0	M0	Any G
<b>Stage IV</b>		T4 Any T Any T	N0 N1, N2, N3 Any N	M0 M0 M1	Any G Any G Any G

## APPENDIX V

### ADVERSE REACTION REPORTING GUIDELINES

#### A. General Guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all ACR studies and Intergroup Studies in which ACR participates. **When a protocol toxicity requires special handling, study specific reporting procedures supercede the general guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the ACR Group Chairman. In the absence of the Group Chairman, the report should be made to the Headquarters Data Management Staff (215/574-3214). When telephone reporting is required, the Principal Investigator should have all relevant material available. See the specific protocol for criteria to grade the severity of the reaction.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report containing all relevant clinical information concerning the reported event will be sent by the Principal Investigator to ACR Headquarters. This must be mailed within 10 working days of the discovery of the toxicity unless specified sooner by the protocol. (FAX #215/928-0153)
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call ACR (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of ACR-coordinated Intergroup studies) must also be submitted to ACR Headquarters when applicable.

6. The Principal Investigator, when participating in ACR coordinated Intergroup studies is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

#### B. Radiation Toxicity Guidelines

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to ACR Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities from protocol therapy must be reported by telephone to the Group Chairman, ACR Headquarters Data Management Staff and to the Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.



## APPENDIX VI (5/12/95)

### **3-D Conformal Radiation Therapy Prostate Group Quality Assurance Guidelines**

#### **I. Purpose**

To establish QA guidelines for the radiation oncologist, physicist, dosimetrist, technologist, and data manager pertaining to 3-D conformal radiation therapy (3-D CRT) Prostate Phase I, II and III studies.

#### **II. Background**

The report of the Collaborative Working Group on the Evaluation of Treatment Planning for External Photon Beam Radiotherapy published in the May 15, 1991 issue of the International Journal of Radiation Oncology, Biology, Physics (Vol 21, No 1) should be referred to for background information regarding 3-D treatment planning.

#### **III. Technology Requirements and Baseline Physics Information**

A. The following information must be submitted by each institution prior to enrolling patients in the protocols.

1. Treatment equipment: Documentation of linac model, energies to be used, and description of collimation to be used to define conformal fields, e.g. multileaf, cerrobend. Documentation of isocenter accuracy for gantry, collimator, and couch rotations.
2. Immobilization/repositioning system: Documentation of immobilization and repositioning system to be used. Submit copy of patient motion study (*set-up uncertainty, organ movement*).
3. Treatment verification system: Documentation of verification imaging system to be used, e.g., film, on-line imager.
4. Computer planning system: Documentation of 3-D RTP system to be used. To participate in Prostate 3-D CRT studies, the institution's 3-D RTP system must have the following capabilities:
  - a. CT data - system must be able to handle at least 40 axial CT slices.
  - b. Beam's-eye-view (*BEV*) display showing tumor and target volumes, critical structures, and beam aperture.
  - c. Calculate volumetric 3-D dose matrix for photon and electron beams. The minimum dose matrix size shall have a maximum dose point spacing of 3 mm or 10,000 points in axial planes (*whichever has least number of dose points*). The spacing between axial planes must be such that, at the minimum, a transverse distribution is computed for each axial slice.
  - d. Display and hardcopy of superimposed isodose distributions on axial CT images (*sagittal and coronal planes, while desirable, are optional*).
  - e. Calculate dose-volume histograms (*DVH*) using dose-volume element sampling at least as fine as the dose calculation grid in axial planes and shall, at the minimum, use spacing in the orthogonal direction identical to the CT slice spacing. These DVHs must identify both absolute volume and absolute dose for the entire structure (*irradiated, or not*).
  - \*f. Non-coplanar beams - system must provide capability of simulating each of the treatment machine motion functions including collimator length, width and angle, gantry angle, couch angle, and couch lateral, longitudinal and vertical position for both beam geometry definition and dose computation.
  - \*g. Calculate and display digital reconstructed radiographs (*DRRs*) with superimposed target volume, critical structure contours and treatment aperture.

\*recommended not required

5. Basic beam data: submit central axis dose ratios and dose profiles for 3 field sizes (*small, medium and large*), and corresponding isodose curves generated by 3-D RTP system for each beam modality and energy to be used. Submit three dose distributions (*via tape exchange format*) for a water phantom for a small, medium and large fields, for each beam modality and energy to be used.
6. Data transfer: Demonstrate capability of digital data exchange with the 3-D CRT QA Center for the data listed below. File formats will conform to the latest version of "*Specifications for Tape/Network Format for Exchange of Treatment Planning Information*" based on AAPM Report 10. All data will conform to treatment protocol requirements and these Quality Assurance Guidelines.
  - Patient CT data
  - Contours - gross tumor volume (*GTV*), clinical target volumes (*CTV*), planning target volumes (*PTV*) and critical normal tissues.
  - 3-D dose distribution data (*in absolute dose*) accounting for fractionation
  - Beam modality/geometry and reference point dose specification
  - Dose-volume histograms
  - Digital sim/portal images (*optional*)
7. Physics QA:
  - a. Dry Run Test: A patient's complete data set as specified by the treatment protocol is to be submitted to the 3-D QA Center to demonstrate compliance with 3-D technical requirements.
  - b. Phantom Dosimetry Test: A TLD dosimetry - treatment plan verification phantom will be sent to each institution. The phantom is to be scanned and the dose calculated per a defined dosimetry protocol. The TLD dosimeters are then to be placed in the phantom and the phantom treated according to protocol. The treatment planning digital data (*CT scans, contours, DVHs, beam geometries and calculated dose distribution*) are to be submitted to the 3-D QA Center for validation. The TLD's are to be submitted to the Radiological Physics Center in Houston, Texas for evaluation.

#### IV. Protocol Data and Quality Assessment Parameters

- A. The following information, in addition to forms T1 and T2, is to be submitted for each protocol patient at times specified in Section 12.2 of protocol 3D/OG 94-06:
  1. Hardcopy isodose distribution for the axial and coronal planes through the planning target volume for the total dose plan must be submitted. If coronal hard copy is a problem, five axial distributions may be substituted for them (*two cuts which are 2 slices superior and inferior of the superior and inferior slices containing the boost PTV, the superior and inferior cuts containing the boost PTV, and one through the center of the boost PTV*). These dose distributions must include
    - a. A reasonable number of isodose lines should be shown which can be used to determine that the digital dose and anatomy data are properly aligned relative to each other. The prescription dose for the boost PTV should be displayed. Additionally the maximum point dose for the distribution should be documented. If the hard copy isodose lines are in percentage, the conversion factor to convert them to absolute dose (*Gy or cGy*) must be indicated.
    - b. The above isodoses should be superimposed over the treatment planning CT images. However, if such hard copy presents difficulties, similar plots without the gray scale image are acceptable if enough critical structure contours are identifiable on the hard copies to verify correct isodose curve positions relative to the digital data submitted.
  2. First day portal films (*images*) for each portal and one set of orthogonal (*anterior-posterior and lateral*) films (*images*) for isocenter localization for each group of concurrently treated beams. If possible, these should be submitted in digital form as described below.
  3. Dosimetry and imaging digital data. (*to be submitted via the Specifications for Tape/Network Format for Exchange of Treatment Planning Information where possible*):
    - a. Volumetric CT data for all cuts required by the protocol (*required for the initial submission*).

- b. GTV, CTV, PTV and critical structure contours. They must be contoured on all slices in which each structure exists including skin on ALL CT cuts (*required for the initial submission*).
- c. Beam geometry specifications including ICRU 50 reference point doses (*for the purposes of this protocol, the isocenter dose should suffice*) in absolute dose units (*initial submission requires first set of beams with remaining beams optional, final submission requires all beams*).
- d. Volumetric 3-D dose distribution data in absolute dose for each set of concurrently treated beams computed without heterogeneity corrections (*optional for initial submission, required for final*). Corrected doses for the same sets of concurrently treated beams are optional.
- e. Dose-volume histogram's for all PTV and critical normal structures (*including Unspecified Tissue - tissue contained within the skin, but which is not otherwise identified by containment within any other structure*) computed without heterogeneity corrections (*optional for initial submission, required for final submission*).
- f. DRR or simulation verification radiograph (*initial submission only requires images for first set of beams, final requires remaining unsubmitted images*).
- g. Portal radiograph or on-line image (*initial submission only requires images for first set of beams, final requires remaining unsubmitted images*).
- h. Any corrections to previously submitted digital data should be discussed with the RTOG 3D QA Center prior to such submission.

## V. QA Review

### A. Quality Assurance of Target Volumes and Critical Structure Volumes

The 3-D QA Center will review PTV, CTV, GTV and designated critical structures on, at a minimum, the first 5 cases submitted by each institution. After institution has demonstrated compliance with protocol, future cases will be spot checked only.

### B. Quality Assurance of Field Placement

The 3-D QA Center will review initial placement films on, as a minimum, the first 5 cases submitted by each institution. At least one port film or pretreatment alignment film per field along with the digitally reconstructed radiograph from the treatment planning program or, alternatively, a simulation verification radiograph shall be submitted for evaluation. After institution has demonstrated compliance with protocol, future cases will be spot checked only.

### C. Quality Assurance of Dose Distribution

1. The 3-D QA Center will display, and compare with hardcopies, isodose distributions for the planes submitted to verify correct interpretation and conversion of the digital patient and dose data.
2. The 3-D QA Center will calculate DVH's for the sum of all dose distributions submitted (*each submitted distribution is for one set of concurrently treated beams*) and compare them with the digitally submitted dose-volume histograms for the PTV, designated critical structures, and unspecified tissue.

### D. The following QA score will be assigned to each case:

1. No variation (*total coverage*); each prescription isodose surface covers 100% of the appropriate PTV.
2. Minor variation (*marginal coverage*); each prescription isodose surface coverage between  $\geq 95\%$  to  $< 100\%$  of the appropriate PTV.
3. Major variation (*miss*); each prescription isodose surface coverage  $< 95\%$  of the appropriate PTV.

### E. Dose heterogeneity

1. The maximum dose within the boost PTV should not exceed the total prescription dose by greater than 7% (*no variation,  $\leq 7\%$ ; minor variation  $> 7$  to  $\leq 10\%$ ; major variation  $> 10\%$ ).*

**APPENDIX VII**

**GROUPING TABLE**

<i>Stages</i> <i>T1 b-c</i> <i>T2 a-b</i>	<i>PSA</i> <i>Value</i> <i>Range</i>	
<b>Gleason</b> <b>Score</b>	<b>Group 1</b>	<b>Group 2</b>
2	4.1 - 55.0	55.1 - 69.9
3	4.1 - 45.0	45.1 - 69.9
4	4.1 - 35.0	35.1 - 69.9
5	4.1 - 25.0	25.1 - 69.9
6	0.0 - 15.0	15.1 - 69.9
7	0.0 - 5.0	5.1 - 69.9
8	-	0 - 69.9
9	-	0 - 69.9
10	-	0 - 69.9

**APPENDIX IX** (2/14/2000)

**3D/OG Participants** (1/24/97, 6/9/97, 6/17/98)

Fox Chase (*G. Hanks, M.D., 9850*) (2212)  
Univ. of CA-SF (*M. Roach, M.D., 9851*) (2401)  
Univ. of Chicago (*S. Vijayakumar, M.D., 9852*) (7723)  
Univ. of Miami (*A. Markoe, M.D., 9853*) (2001)  
Univ. of Michigan (*H. Sandler, M.D., 9854*) (2235)  
Univ. of North Carolina (*S. Sailer, M.D., 9855*) (6501)  
Univ. of Washington (*K. Russell, M.D.*) (9856)  
Univ. of Wisconsin (*M. Ritter, M.D., 9857*) (801)  
Washington University (*C. Perez, M.D., 9858*) (2101)

**RTOG Participants** (1/22/96, 2/9/96, 5/9/96, 8/5/96, 4/1/97, 5/12/97, 11/17/97, 2/2/98, 3/10/98, 6/17/98)

University of CA-Davis (*J. Ryu, M.D.*) (2423)  
Emory University (*J. Landry, M.D.*) (1523)  
M.D. Anderson Hospital (*A. Pollack, M.D.*) (5901)  
University of Alberta (*M. Parliament, M.D.*) (7501)  
Thomas Jefferson Univ. Hospital (*R. Valicenti, M.D.*) (601)  
Mayo Clinic (*T. Pisansky, M.D.*) (184)  
Hahnemann University (*B. Micaily, M.D.*) (1301)  
Medical College of VA (*R. Schmidt-Ullrich, M.D.*) (1701)  
Albert Einstein Medical Center (*S. Asbell, M.D.*) (5101)  
Montefiore Medical Center (*B. Vikram, M.D.*) (1514)  
Western PA Hospital (*J. Figura, M.D.*) (7008)  
Ann Arbor Regional CCOP (*M. Pilepich, M.D.*) (7717)  
Medical College of WI (*R. Byhardt, M.D.*) (7001)  
Upstate Carolina CCOP (*J. Bearden, M.D.*) (2132)  
Toledo CCOP (*P. Schaefer, M.D.*) (8803)  
Ohio State University (*R. Gahbauer, M.D.*) (4101)  
Foudation for Cancer Research (*D. Brachman, M.D.*) (2503)  
Loyola University (*E. Melian, M.D.*) (3001)  
South WI Radiotherapy Center (*P. Littman, M.D.*) (7006)  
St. Joseph Cancer Center (*G. Wong, M.D.*) (503)  
Lutheran General Hospital (*W. Hartsell, M.D.*) (722)  
Northwest Community (*A. Herskovic, M.D.*) (7705)  
Massachussets General Hospital (*C. Willett, M.D.*) (5801)  
University of MD (*N. Suntharalingam, M.D.*) (5702)