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TITLE: Androgen Deprivation and Localized Radiotherapy to Metastases In Patients with Oligometastatic Hormone – Sensitive Prostate Cancer.

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TYPE:

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Androgen Deprivation and Localized Radiotherapy to Metastases In Patients with Oligometastatic Hormone - Sensitive Prostate Cancer.

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A. Common Terminology Criteria for Adverse Events, v3 (CTCAE Publish date 12/12/03)

SCHEMA

Start
36 (±2 weeks) weeks
Androgen Deprivation Treatment
(may start treatment before consenting to study)
(may join study at any point of 36 weeks of treatment or at the end of treatment if PSA has normalized)

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PSA Normalizes
Start Radiation to all known sites of disease
(if joining study after start of Androgen Deprivation Treatment, may start Radiation at the same time, if PSA normalized)
(may join study after completion of 36 weeks of treatment and receive Radiation if Serum Testosterone remains at castrated levels)

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End Androgen Deprivation Treatment when a total of 36 weeks of Treatment has been received

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Follow until PSA Relapse
Off Study
Restart Androgen Deprivation Treatment
Long term followup of patients: PSA, Local Control of stage IV disease, PFS, OS, site and number of new metastases, systemic treatments, long term toxicity.

1.0 OBJECTIVES

1) To evaluate time to PSA relapse in patients with oligometastatic (≤ 5 lesions) hormone – sensitive prostate cancer treated with 36 weeks of androgen deprivation and localized radiotherapy to all known tumor sites.
2) To assess the Prostate-Specific Antigen (PSA) and objective response rate to treatment with 36 weeks of androgen deprivation and localized radiotherapy in patients with oligometastatic hormone-sensitive prostate cancer.
3) To assess the toxicity of 36 weeks of androgen deprivation and localized radiotherapy to oligometastases in patients with oligometastatic hormone-sensitive prostate cancer.
4) In appropriate situations evaluate the feasibility and toxicities of using helical tomotherapy image-guided IMRT to treat oligometastatic sites.
5) Long term follow-up of patients: PSA, Local Control of stage IV disease, PFS, OS, site and number of new metastases, systemic treatments, long term toxicity.

2.0 BACKGROUND AND HYPOTHESIS

2.1 Metastatic prostate cancer and cancer metastases:

Carcinoma of the prostate remains a significant health problem in the United States, with 230,000 new cases and 30,000 deaths estimated in 2004 (1). Despite progress in early detection thanks to the widespread use of serum Prostate Specific Antigen (PSA) about 15% of patients present with metastatic disease at diagnosis and 30% of patients suffer relapse to regional lymph nodes or distant organs despite local therapy.

Historically several hypotheses based on clinical evidence attempted to explain mechanisms of metastatic tumor cell spread. Halsted suggested that tumors spread in an orderly manner initially spreading to regional lymph nodes and then centrifugally to distant organs (2). In contrast the "systemic hypothesis" most clearly articulated by Fisher proposed two principal types of cancer: those that cannot metastasize and those that have metastasized widely before clinical detection (3). In an attempt to reconcile clinical and laboratory features in a unified hypothesis, the "spectrum" model has been proposed (4). This theory accepts that some tumors spread widely before clinical detectability while others never metastasize, but for the majority of cancers, metastatic capacity evolves during the clinical phase of tumor growth. During the evolutionary process there may be a stage, termed "oligometastases", when metastases are limited in number and location because metastatic capacity has not fully evolved (5).

With a few exceptions such as testis cancer and some hematologic malignancies, the treatment of metastatic cancer by hormonal or cytotoxic agents is rarely curative and in many instances ineffective. In this context an important question is whether in the natural history of metastatic spread there is a time when metastases are limited in number and/or in destination organs and therefore treatment with systemic agents augmented by regional treatments may be effective. Examples of this include resection of lung metastases from sarcoma, liver metastases from colorectal cancer and isolated resection of breast metastases (6,7,8). Despite their limitations hormone therapy and chemotherapy have been effective in eradicating subclinical deposits when used as an adjuvant to local therapy. But all too often

the tumor recurs in a few locations, the likely consequence of the large number of tumor cells at these sites or limited drug availability at the site. These remaining oligometastases then may serve as a nidus for further dissemination.

Since testosterone is the main growth and survival factor for prostate cancer most patients will respond initially to ablation of gonadal androgen production through surgical (bilateral orchiectomy) or medical (luteinizing hormone-releasing hormone [LHRH] agonist therapy) approaches (9). Combined androgen blockade is achieved by the addition of an androgen receptor blocker and confers small survival advantage over castration alone (10). Triple hormone therapy involves the use of LHRH agonist, antiandrogen agent and 5 alpha reductase inhibitor finasteride (Proscar®) that prevents conversion of testosterone to more potent dihydrotestosterone (DHT) (11). Unfortunately, eventually all patients will develop progressive disease despite continued androgen suppression, with a median time to progression of 14 to 30 months (12).

There are many mechanisms responsible for the development of resistance to androgen deprivation. They include amplification of androgen receptors, increased sensitivity of androgen receptors, mutations of androgen receptors that allow activation by non-androgenic ligands and activation of alternative survival pathways (13). There are several approaches that are proposed to circumvent or delay the development of androgen independence, but none of them have been proven clinically. Intermittent androgen deprivation has been shown to delay the development of hormone-refractory disease in preclinical models (14,15). Intermittent hormonal therapy usually consists of initial androgen deprivation for 6-12 months followed by an off - therapy interval until time of relapse (6-15 months). When PSA values meet threshold criteria (usually pre-treatment levels) treatment is re-started. Most of the initial responders (57-100 %) respond to re-treatment. This cyclic treatment continues until the development of hormone-refractory disease. While off-treatment, many patients experience improvement in their libidos, erections, hot flushes and energy (16). Unfortunately once resistance to hormone-refractory occurs, prognosis is dismal. This so-called “hormone- refractory prostate cancer” (HRPC) or “androgen - independent prostate cancer” is characterized by virulent biologic and clinical behavior with median survival of 18 months despite treatment with chemotherapy (17,18,19).

Metastatic prostate cancer is a heterogeneous disease and patients with ≤ than 5 lesions have better survival than patients with > 5 metastatic lesions (20). It is more likely that patients with limited number of metastases will benefit from local therapy and the patients with ≤ than 5 metastases will be the focus of this study.

We hypothesize that it is possible and safe to treat patients with prostate cancer oligometastases with androgen deprivation and localized radiotherapy and that aggressive treatment of oligometastases early in the course of disease when disease is still sensitive to hormone manipulation will improve treatment outcomes of patients with metastatic prostate cancer.

2.2 Helical tomotherapy

Rapid advances in computer and medical imaging technologies have resulted in the ability to deliver radiotherapy with greater precision and conformality. External beam radiotherapy

has traditionally relied on radiologic imaging to direct therapy to appropriate anatomic regions. The integration of CT imaging into radiation treatment planning, allows for a three dimensional view of each patient's tumor relative to dose-limiting adjacent normal organs, allowing for customized beam shaping, beam orientation and dose conformality. The use of 3D conformal radiotherapy allows for further escalation of dose, which has resulted in higher tumor control, while maintaining risks and side effects at acceptable levels.

Intensity modulated radiation therapy (IMRT) has opened a new era in radiation oncology. By delivering therapy from multiple directions using multiple segmented or modulated beamlets, one can now sculpt radiation doses to fit the unique shape of each patient's tumor, optimizing radiation delivery to complex volumes and regions of the body. Some compare IMRT to "painting" radiation with a finer brush, where more precise, conformal and sophisticated dose patterns are now possible. This has also resulted in a greater degree of conformal dose avoidance of adjacent normal organs. Dose escalation is now possible with IMRT, which was not possible with technology just a decade ago. For example, radiation doses for prostate cancer, which have been limited to approximately 7000 cGy with conventional technologies, are now >8000 cGy using IMRT. As a result, a significant improvement in tumor control and a reduction in bladder and rectal toxicities have been reported (21).

Helical tomotherapy (HT) represents the next major advance in external beam radiotherapy delivery systems. HT is an FDA approved radiation therapy delivery device, which is a marriage of spiral CT and IMRT technology. Specifically, a 6 MV linear accelerator is mounted on a CT ring gantry and rotates around the patient as the patient translates through the ring. The treatment fan beam is segmented using a 64-leaf collimator. Each leaf casts a 0.6 mm width shadow at 85 cm isocenter distance with the fan beam, which varies in width from 0.5 to 5 cm. The minimum voxel or beamlet size is therefore 5 x 6 mm. By rapid opening and closing of leaves as a function of gantry angle while the patient slides through the ring, helical tomotherapy provides unprecedented ability to sculpt radiation doses to complex shaped tumor regions while simultaneously avoiding dose to normal organs (22,23,24).

Evaluating HT treatment plans for prostate cancer demonstrated rapid drop-off of dose around the target (prostate gland) in all directions resulting in excellent sparing of rectum, bladder and femoral heads superior to prior IMRT techniques (25). It is predicted that for select patients with lung cancer, tumor doses as high as 16,000 cGy will be achievable while maintaining normal lung doses (and therefore risks) at comparable levels as with conventional delivery methods, which are limited to doses of 6,000 cGy to the tumor in most patients.

In addition, an array of detectors mounted on the same rotating gantry and positioned directly opposed to the beam source, gives the HT delivery system two unique capabilities not found on any other delivery systems. First, these detectors allow for the generation of megavoltage CT (MVCT) images using the 6 MV beam. Resolution and contrast of MVCT is more than adequate to easily distinguish tissue planes and organ boundaries. This allows the HT system to automatically align beam orientation to anatomic external landmarks and internal organs in 3 dimensions prior to each daily session, vastly improving the precision of

radiation delivery. Second, these same arrays can be used to monitor output of the beam as it exits through the patient, providing an additional level of dose verification. It is anticipated that future software and hardware modifications will allow for this type of "adaptive radiotherapy" to occur in real time, constantly modulating beam output to account for minute-by-minute variations in tumor and organ motion.

The advent of HT brings for the first time to the clinic the potential to deliver highly conforming dose distributions to large complex target shapes. For example, with HT shaping the dose to the entire pleural surface, while sparing lung parenchyma is now possible for patients with mesothelioma.

3.0 DRUG INFORMATION:

3.1 Zoladex® (Goserelin)

Description: Zoladex is an LHRH analog with substitutions for the L-amino acid Glycine in positions 6 and 10. These substitutions produce an analog with 50-100 times the potency and longer duration of action then naturally occurring peptide when assessed in acute animal tests.

Supply: Zoladex® is commercially available as either 3.6 mg (one month) or 10.8 mg (three month) pellet for subcutaneous injection.

Storage: The Zoladex® 3.6 mg depot is supplied with 16-gauge needle, and the Zoladex® 10.8 mg depot is supplied with a 14-gauge needle. The unit is sterile and comes in a sealed, light-and moisture-proof package. The pack should be stored at room temperature. Before being opened, each package must be inspected for damage in which case the syringe must not be used. Being sterile, the syringe should be removed from its package only by the physician/nurse immediately before use.

Administration: If requested by the patient, a local anesthetic, i.e., 0.2 to 0.5 ml of 1% lidocaine hydrochloride may be given intradermally. Zoladex® will be injected subcutaneously using an aseptic technique. Insert the needle to its full length, pull it back 1 cm, then inject. The manufacturer recommends inserting the needle into the subcutaneous fat then changing the direction of the needle so it parallels the abdominal wall before inserting the needle to its full length. This will create a little pocket for the Zoladex® plug so that it doses not extend when the needle is withdrawn. After checking to ensure that the depot has been discharged, the used syringe will be discarded in a safe manner. One can ensure that the depot has been discharged by ensuring that the tip of the plunger is visible within the tip of the needle. The tear off portion of the depot package label will be removed and affixed to the patient's permanent record.

Toxicity: During routine screening of Zoladex®, no significant pharmacological activity was apparent in the cardiovascular, respiratory, central nervous, renal, metabolic, coagulation or gastric systems. However, the following can occur: vasomotor, hot flashes, edema, gynecomastia, bone pain, thrombosis, decreased bone mineral density, lethargy,

dizziness, insomnia, anorexia, nausea, upper respiratory tract infection, rash, sweating, COPD, congestive heart failure, and GI disturbances. Please refer to the Package Insert for further information. Studies have shown that serum levels of testosterone can be reduced and maintained within the castrate range resulting in objective evidence of tumor regression. Other than the occasional transient worsening of cancer symptoms tumor flare due to an initial temporary rise in testosterone serum levels on initiating therapy, no significant toxicity apart from that attributed to castration has been reported. In general, allergic reactions have been extremely uncommon with Zoladex® therapy. There have been isolated reports of urethral obstruction, urticaria, or spinal cord compression.

3.2. Leupron® (leuprolide acetate implant)

Description: Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses greater potency than the natural hormone. Leuprolide acetate, an LH-RH agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. Animal and human studies indicate that following an initial stimulation, chronic administration of leuprolide acetate results in suppression of ovarian and testicular steroidogenesis. This effect is reversible upon discontinuation of drug therapy. Administration of leuprolide acetate has resulted in inhibition of the growth of certain hormone dependent tumors (prostatic tumors in Noble and Dunning male rats and DMBA-induced mammary tumors in female rats) as well as atrophy of the reproductive organs. In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females. However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to castrate levels. In premenopausal females, estrogens are reduced to postmenopausal levels. These decreases occur within two to four weeks after initiation of treatment, and castrate levels of testosterone in prostatic cancer patients have been demonstrated for more than five years.

Supply: Leuprolide is commercially available as either 7.5 mg (one month), 22.5 mg (three month), or 30 mg (four month) depots for intramuscular injection. Each kit contains a vial of sterile lyophilized microspheres, which is leuprolide incorporated in a biodegradable polymer of polylactic acid. Any formulation may be used.

Storage: The vial of leuprolide and the ampule of diluent may be stored at room temperature. Product does not contain preservative; discard if not used immediately.

Administration: As with other drugs administered by injection, the injection site should be varied periodically.

Toxicity: In the majority of patients, testosterone levels increased above baseline during the first week, declining thereafter to baseline levels or below by the end of the second week of treatment. The most common side effect of Leuprolide is hypertension, depression, insomnia, headache, dizziness, nervousness, impotence, decreased libido, anorexia, nausea and vomiting, myalgia, neuromuscular disorders, dyspnea, anemia, skin reactions, asthenia,

and injection site reactions. Please refer to the Package Insert for further information. Potential exacerbations of signs and symptoms during the first few weeks of treatment is a concern in patients with vertebral metastases and/or urinary obstruction or hematuria which, if aggravated, may lead to neurological problems such as temporary weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms.

3.3 Casodex® (bicalutamide)

Description: Casodex bicalutamide is a nonsteroidal antiandrogen, which has no androgenic or progestational properties. The chemical name is propanamide, N-[4-cyano-3(trifluoromethyl)phenyl]- 3- [(4fluorophenyl)sulphonyl]- 2- hydroxy- 2methyl, (+,-). Casodex is a racemic mixture with the antiandrogen activity residing exclusively in the (-) or (R) enantiomer. Casodex 50 mg has the status of an approved new drug. Casodex has a long half-life compatible with once-daily dosing. Casodex is well tolerated and has good response rates in phase 11 trials (Kennealey and Furr, 1991, Tyrrell 1994).

Supply: Casodex is commercially available as a 50 mg tablet.

Storage: Casodex should be stored in a dry place at room temperature between 69^{o}-77^{o}F.

Administration: Casodex is administered orally at a dose of one 50 mg tablet per day. Administration will be suspended only if there is an apparent or suspected reaction to the drug.

Toxicity: In animal experiments, birth defects (abnormal genitalia, hypospadias) were found in male offspring from female animals dosed with Casodex during pregnancy. Although offspring from male animals dosed with Casodex did not show any birth defects, patients enrolled in this trial are advised to neither cause pregnancy nor to donate sperm while receiving protocol therapy or during the first 3 months after cessation of therapy. The use of barrier contraceptives is advised.

The most frequent adverse events reported among subjects receiving bicalutamide therapy are breast tenderness, breast swelling, and hot flashes. Adverse events not directly related to the pharmacological properties of bicalutamide were infrequent. Nonpharmacological adverse events, reported in the trial using bicalutamide 50 mg as monotherapy include asthenia, pelvic pain, peripheral edema, pruritus, rash, constipation, impotence, dyspnea, nausea, hypertension, dizziness, paresthesia, insomnia, sweating, diarrhea, increased liver enzyme tests, nocturia, hematuria, UTI hyperglycemia, weight loss, anemia, and chest pain (Kaisary 1994). There has been no observed change in cardiac parameters during long-term administration of bicalutamide 50 mg daily.

When bicalutamide 50 mg was given in combination with an LHRH analogue, the LHRH analogue adverse event profile predominated with a high incidence of hot flashes (53%) and relatively low incidences of gynecomastia (4.7%) and breast pain (3.2%).

4.0 STAGING CRITERIA

STAGE	SUB-STAGE	DEFINITION
T1		Clinically unapparent tumor, not detected by DRE nor visible by imaging
	T1a	Incidental histologic finding; <5% of tissue resected during TURP
	T1b	Incidental histologic finding; >5% of tissue resected during TURP
	T1c	Tumor identified by needle biopsy due to elevated PSA
T2		Confined within the prostate (detectable by DRE)
	T2a	Tumor involves half of the lobe or less
	T2b	Tumor involves more than one half of one lobe but not both lobes
	T2c	Tumor involves both lobes
T3		Tumor extends through the prostate capsule but has not spread to other organs
	T3a	Extracapsular extension
	T3b	Tumor invades seminal vesicle(s)
T4		Tumor is fixed or invades adjacent structures other than seminal vesicles
	T4a	Tumor invades bladder neck and/or external sphincter and/or rectum
	T4b	Tumor invades levator muscles and/or is fixed to pelvic wall

STAGE	SUB-STAGE	DEFINITION
Node (N)		Regional lymph nodes
	N0	No lymph nodes metastasis
	N1	Metastasis in single lymph node <2 cm in greatest dimension
	N2	Metastasis in single lymph node >2cm but <5 cm in greatest dimension, or multiple lymph nodes, none >5 cm
	N3	Metastasis in lymph node >5 cm in greatest dimension

STAGE	SUB-STAGE	DEFINITION
Metastasis		Systemic spread
	M0	No distant metastasis
	M1a	Non-regional lymph node metastasis
	M1b	Bone metastasis 1) Axial skeleton only 2) Extending also to peripheral skeleton
	M1c	Metastasis at other sites

STAGE	SUB-STAGE	DEFINITION
Histopathologic		Differentiation
	GX	Grade cannot be assessed
	G1	Well differentiated (slight anaplasia)
	G2	Moderately differentiated (moderate anaplasia)
	G3	Poorly differentiated or undifferentiated (marked

STAGE GROUPING:

				Gleason
I	T1a	N0	M0	G1
II	T1a	N0	M0	G2, 3-4
	T1b	N0	M0	Any G
	T1c	N0	M0	Any G
	T1	N0	M0	Any G
	T2	N0	M0	Any G
III	T3	N0	M0	Any G
IV	T4	N0	M0	Any G
	Any T	N1or N2 or N3	M0	Any G
	Any T	Any N	M1a or M1b or M1c	Any G

5.0 ELIGIBILITY CRITERIA

5.1 Inclusion Criteria

5.1.1 Patients with histologically proven diagnosis of adenocarcinoma of the prostate stage N1, N2, N3, M1a, M1b, M1c with ≤ 5 metastatic lesions. If the diagnosis of metastasis in the lymph node is based solely on imaging CT scan or MRI, the longitudinal diameter of the lymph node has to be ≥ 2.0 cm. If the lymph node is positive on PET or Prostascint scan, the longitudinal diameter of the lymph node on CT scan or MRI has to be ≥ 1.5 cm.

5.1.2 Patients who have measurable disease must have had X-rays, scans or physical examination used for tumor measurement completed within 28 days prior to registration. Patients must have non-measurable disease assessed within 42 days prior to registration.

5.1.3 Patients must have had documented PSA level of > 2 prior to onset of androgen deprivation.

5.1.4 Patients might have received up to 36 weeks of adjuvant androgen deprivation therapy and up to 36 weeks of androgen deprivation therapy for metastatic disease prior to enrollment to this study. Patients may be on androgen deprivation for metastatic disease at the time of enrollment to the protocol. Adjuvant therapy must have been completed at least 2 years before

androgen deprivation for metastatic disease and patients must remain hormone sensitive.

5.1.5 Prior radiation therapy for metastatic disease is not allowed.

5.1.6 Prior chemotherapy for metastatic disease is not allowed. Prior neoadjuvant and adjuvant chemotherapy is allowed. Patients must have recovered from all acute side-effects related to previous systemic therapy.

5.1.7 Patients are allowed to receive one prior systemic non-chemotherapeutic treatment (i.e. immunotherapy, receptor tyrosine kinase inhibitor, antiangiogenic agent, differentiating agent) for recurrent or metastatic disease. Patients must have recovered from all acute side-effects related to previous systemic therapy.

5.1.8 Use of bisphosphonates is allowed at the discretion of treating physician

5.1.9 Patients must be at least 18 years of age.

5.1.10 Patient must be capable of understanding the nature of the trial and must give written informed consent.

5.1.11 Patients must have a WHO Performance status of 0, 1, or 2.

5.2 Exclusion Criteria

5.2.1 Patients with unstable or severe intercurrent medical conditions or active, uncontrolled infection.

5.2.2 Patients with history of orchiectomy.

5.2.3 Patients undergoing therapy with other investigational agents. Patients must have recovered from all acute effects of previously administered investigational agents and sufficient time must have elapsed since last administration to ensure the drug interactions not occur during this study.

5.2.4 Patients with a history of brain metastases or who currently have treated or untreated brain metastases.

5.2.5 Patients who have demonstrated refractoriness to hormone therapy with LHRH agonist. Refractoriness is defined as occurrence of one of the following while on therapy with LHRH agonist: Increase in PSA by 25% over baseline (to at least > 2 ng/ml) on two consecutive PSA measurements, 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, clear worsening of any non-measurable disease, reappearance of any lesion that had disappeared, appearance of any new lesion.

6.0 TREATMENT PLAN

Treatment will be given according to the Schema described in section 6.1.
A treatment may be stopped for up to 4 weeks to allow for recovery from toxicities. Patients unable to safely resume treatment at that point will be taken off study. 12 weeks constitutes one cycle of hormone therapy.

6.1 Treatment schedule:

6.1.1 Patients will begin radiation therapy only after they have demonstrated evidence of PSA normalization after initiation of androgen deprivation therapy (stable or declining PSA level of ≤ 4 (or stable or declining PSA ≤ pre-treatment level whichever is smaller) on two consecutive measurements. Patients who do not meet these criteria will be taken off protocol.

6.1.2 Patients will be divided into two strata:

Stratum 1:

a) Patients who are not on androgen deprivation therapy at the time of enrollment to the protocol will begin androgen deprivation and start radiation therapy after PSA normalization (see section 6.1.1)

b) Patients who are already treated with androgen deprivation therapy at the time of enrollment to the protocol (see 5.1.4) will continue androgen deprivation therapy and begin radiation after meeting criteria for PSA normalization (see section 6.1.1). Radiation therapy will be finished before 36 weeks (±2 weeks) of hormone therapy is completed.

Stratum 2:

Patients who are enrolled on the protocol towards the end (or after completion) of 36 weeks (±2 weeks) of androgen deprivation so radiation treatment cannot be finished before the completion of 36 weeks of androgen deprivation therapy can still initiate and/or complete radiation therapy as long as their serum testosterone level remains at the castrated levels (<50 ng/dL) and they meet the criteria for PSA normalization (section 6.1.1). Patients will not receive more than 36 weeks of androgen deprivation therapy.

Androgen deprivation therapy will include LHRH agonist (goserelin 3.6 mg subcutaneously q 4 weeks or goserelin 10.8 mg subcutaneously q 12 weeks, or leuprolide 7.5 mg intramuscularly q 4 weeks or leuprolide 22.5 mg intramuscularly q 12 weeks) and bicalutamide 50 mg po q day. Androgen deprivation therapy will last for a total of 36 weeks (±2 weeks) (i.e. patient who received 12 weeks of androgen deprivation therapy prior to enrollment to this protocol will receive additional 24 weeks of androgen deprivation treatment, patient who received 32 weeks of androgen deprivation therapy prior to enrollment to this protocol, will receive additional 4 weeks of androgen deprivation treatment etc.).

Radiation therapy will be delivered to all known metastatic sites. Most are anticipated to be bone metastases or lymph node metastases. No more than 5 metastatic sites and, if indicated, a primary site will be treated.

6.1.3. Duration of the protocol:

Following 36 weeks (±2 weeks) of androgen deprivation therapy patients will remain off treatment until PSA relapse (see 9.2.8) defined as increase in PSA level to the pre-androgen deprivation therapy level or > 10 (whichever is smaller). For example: patient with pre-treatment PSA level of 40 will resume

androgen deprivation therapy when PSA level increases to > 10, patient with pre-treatment PSA level of 3 will resume androgen deprivation therapy when PSA level is > 3. At the time when patients meet the criteria for re-treatment with androgen deprivation therapy they will be taken off the protocol. After patients are taken off protocol we will do a chart review for long term outcomes.

6.2 Radiation:

6.2.1 The gross tumor volume (GTV) will be defined as the radiological dimensions of the lesion as identified by CT and/or MRI. The planning tumor volume (PTV) is defined as the GTV plus 1 cm.

6.2.2 For lesions that move with respiration (Rib and lung parenchymal lesions for example) CT simulation will be performed at inspiration and expiration to define lesion position during the respiratory cycle. The GTV will be defined based on lesion position during the respiratory cycle.

6.2.3 All sites will be treated using one of the following fractionation schemes: 1) 300 cGy/day to 3000 cGy; 2) 250 cGy/day to 3750 cGy; 3) 200 cGy/day to 4000 cGy.

6.2.4 All patients will be planned using helical tomotherapy given its ability to treat multiple sites with conformal RT in a single treatment session. However, at the discretion of the treating radiation oncologist, other technology, beam arrangements, photon energies and treatment plan is allowed if felt to be more appropriate for treatment of the specific lesion.

6.2.5 If previously untreated, the primary tumor (GTV = prostate gland) and potential areas of regional spread (GTV = seminal vesicles and pelvic nodes) are to be treated the PTV is the GTV + 5 mm margin and tomotherapy with daily 3-D image-guidance must be utilized. The total dose to the PTV will be 4500 cGy to the nodes, 4500 to 5400 to the seminal vesicles, and 7500 to 7800 to the prostate at 180-200 cGy/day.

6 .3 Criteria for Removal From Treatment

6.3.1 Progression of disease at the time of androgen deprivation therapy (minimum of 12 weeks of treatment if progression is by PSA criteria only)
6.3.2 Patients do not meet the criteria for PSA normalization after 36 weeks of androgen deprivation (see section 6.1.1)
6.3.3 Unacceptable toxicity (as defined in section 7.0.)
6.3.4 Delay of treatment > 4 weeks from planned date of therapy due to toxicity.
6.3.5 Patient may always discontinue treatment whenever he wishes.
6.3.6 Patients will be taken off the protocol when they meet the criteria for PSA relapse following completion of 36 weeks of androgen deprivation therapy (see section 6.1.3)

7 TOXICITIES MONITORED, DOSAGE MODIFICATIONS

7.3 This study will use Common Terminology Criteria for Adverse Events v3, which can be found at the CTEP, website: http://ctep.cancer.gov/reporting/ctc.html

7.4 Management of Anticipated Toxicities: Missed days and doses will not be made up. Treatment should be stopped for any protocol treatment related Grade 3 toxicity or greater that cannot be controlled with good medical practice intervention. Treatment may be resumed upon resolution of that toxicity to Grade 2. A patient who experiences a Grade 3 or higher toxicity again will be removed from the study. There are no provisions for dose reductions of hormone therapy. The maximum delay in treatment will be 28 days.

8.0 STUDY PARAMETERS AND CALENDAR

Assessment	**Prior to Enrollment**	**Day 1 of each cycle***	**Every 4 weeks until PSA relapse**	**At the time of PSA relapse**
History and Physical Exam	X[1]	X[2]		
Weight and WHO PS	X[1]	X[2]		
Toxicity using CTC v3.0		X[2]		
CBC, Diff, Plts, Na, K, Cl, CO_2, Creatinine, BUN, glucose, Calcium, phosphorus, albumin, LDH, SGPT (ALT), SGOT (AST), Alkaline Phos, Total Bilirubin	X[1] X[1]	X[2]		
EKG	X[3]			
Chest X-Ray	X[3]			
PSA	X[3]		X[7]	
Serum testosterone	X[3]		X[8]	
Tumor Measurements (measurable disease)	X[4]	X[6]		X
Tumor Evaluation (evaluable disease)	X[5]	X[6]		X
Treatment: LHRH agonist (goserelin or leuprolide)		q 4 weeks x 9 doses or q 12 weeks x 3 doses (total duration of androgen deprivation- see section 6.1) [9]		
Treatment: bicalutamide		daily x 36 weeks (total duration of androgen deprivation- see section 6.1) [9]		

Assessment	Prior to Enrollment	Day 1 of each cycle*	Every 4 weeks until PSA relapse	At the time of PSA relapse
Treatment: Radiation		daily x 2-7 weeks during or after completion of androgen deprivation therapy (see section 6.1)		

*Each cycle = 12 weeks
[1]Within 7 days of d1 of cycle #1 (can be done on d#1 cycle #1)
[2]Except cycle 1 if done within 7 days of d1 of cycle #1
[3]Within 14 days of d1 of cycle #1
[4]Within 28 days of d1 of cycle #1
[5]Within 42 days of d1 of cycle #1
[6]At the time of completion of 36 weeks of androgen deprivation therapy or radiation therapy (whichever comes later)
[7] Can be done on the day of clinic visit or up to 14 days before or after.
7 PSA; every 4 weeks for 2 years, and every 3mos after year 2, every 6 mos. thereafter or until relapse which ever occurs first.
[8] Four weeks after the first LHRH injection, afterwards no repeat measurements will be done until the day of the last LHRH injection, and then monthly until the normalization of testosterone levels or resumption of androgen deprivation therapy (whichever comes first). Testosterone level will also be drawn to confirm castrated levels in patients who completed 36 weeks of androgen ablation and are considered for radiation therapy (see section 6.1.2.) To simplify schedule, testosterone level can be drawn on the same day that PSA test
[9] $\pm$ 2 weeks

9.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Patients who complete radiation therapy and 1 cycle (12 weeks) of androgen deprivation treatment on protocol will be included in analysis of tumor response and time to PSA relapse

9.1 Disease Status

9.1.1 Measurable disease: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain X-ray, CT, MRI, or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is only suitable for superficial disease (superficial palpable nodules, subcutaneous lesions, thyroid lesions). Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

9.1.2 Non-measurable disease: Lesions too small to be considered measurable, masses with margins not clearly defined, bone disease, pleural or pericardial disease, leptomeningeal disease, pneumonitis, lymphangitis.

9.2 Objective Status

(To be recorded at each evaluation.) All measurable lesions (patients eligible for this protocol will have no more than 5 metastases) should be identified at baseline. Measurements must be provided for all measurable lesions, while presence or absence must be noted for non-measurable disease. Unless progression is observed, objective status can only be determined when all measurable and non-measurable sites and lesions are assessed.

9.2.1 Partial response in non-measurable disease (PRNM). Decrease in PSA level of > 50% compared to baseline pre-treatment level. No progression of non-measurable disease. No new lesions.

9.2.2 Partial response (PR): Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline in the sum of longest diameters of all target measurable lesions. No progression of non-measurable disease. No new lesions. All measurable and non-measurable lesions and sites must be assessed using the same techniques as baseline.

9.2.3 Complete response (CR): Complete disappearance of all measurable and non-measurable disease. No new lesions. No disease-related symptoms. For patients status post previous prostatectomy - PSA level <0.2. For patients with remaining prostate declining or stable PSA level <1. All measurable, and non-measurable lesions and sites must be assessed using the same technique as baseline.

9.2.4 Stable/No response: Does not qualify for CR, PR, or progression. All measurable and non-measurable sites must be assessed using the same techniques as baseline.

9.2.5 Progression: One or more of the following must occur **at the time of androgen deprivation therapy:** Increase in PSA by 25% over baseline (to at least > 2 ng/ml), 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, clear worsening of any non-measurable disease, reappearance of any lesion that had disappeared, appearance of any new lesion/site, failure to return for evaluation due to death, deteriorating condition (unless clearly unrelated to this cancer).

9.2.6 a) Non-measurable disease does not affect objective status except in determination of CR (must be absent - a patient who otherwise has CR, but who has non-measurable disease present or not assessed, will be classified as having a PR), and in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

b) Appearance or worsening of pleural effusions do not constitute unequivocal progression unless cytologically proven of neoplastic origin.

c) For “scan-only” bone disease, increased uptake in previously seen lesions does not constitute clear worsening.

d) In cases for which initial tumor flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms must persist beyond 4 weeks or there must be additional evidence of progression.

e) Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

9.2.7 Unknown: Progression has not been documented and one or more measurable or non-measurable sites have not been assessed.

9.2.8 PSA relapse after completion of initial 36 weeks of androgen deprivation therapy is defined as an increase in PSA value to above pre-therapy level or > 10 (whichever is smaller). For example patient with pre-treatment PSA level of 40 will resume androgen deprivation therapy when PSA level is > 10, patient with pre-treatment PSA level of 3 will resume androgen deprivation therapy when PSA level is > 3.

9.3 Best Response: This is calculated from the sequence of objective statuses

a) CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression or symptomatic deterioration.

b) PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression or symptomatic deterioration, but not qualifying as CR.

c) Unconfirmed CR: One objective status of CR documented before progression or symptomatic deterioration but not qualifying as CR or PR.

d) Unconfirmed PR: One objective status of PR documented before progression or symptomatic deterioration but not qualifying as CR, PR or unconfirmed CR.

e) Stable/no response: At least one objective status of stable/no response documented at least six weeks after registration and before progression or symptomatic deterioration, but not qualifying as anything else above.

f) Increasing disease: Objective status of progression or symptomatic deterioration within twelve weeks of registration, not qualifying as anything else above.

g) Inadequate assessment, response unknown: Progression or symptomatic deterioration greater than twelve weeks after registration and no other response category applies.

9.4 Time-Related Endpoint Definitions

9.4.1 Survival: Defined as the time from registration to time of death due to any cause. If a patient is not known to have died, survival time is censored at the time of last follow-up.

9.4.2 Progression-free survival: Defined as the time from registration to the first observation of disease progression (as defined in 9.2.5) or death due to any cause. If a patient has not progressed or died, progression-free survival is censored at the time of last follow-up.

9.4.3 Time to treatment failure: Defined as the time from registration to the first observation of disease progression, death due to any cause, or early discontinuation of treatment. If failure has not occurred, failure time is censored at the time of last follow-up.

9.4.4 Time to PSA relapse: Time from the date of the last dose of bicalutamide or the last day of radiation therapy (whichever comes later) until the date the criteria are met for the PSA relapse (see 9.2.8)

10.0 **STATISTICAL CONSIDERATIONS**

This is a phase II study to evaluate the efficacy and safety of radiation to metastatic sites plus 36 weeks months of androgen deprivation in patients with hormone-sensitive prostate cancer. The primary endpoint in this trial will be time to PSA relapse as defined in 9.2.8 and 9.4.4. Secondary endpoints include PSA response to treatment, safety, feasibility and tolerability.

Based on the prior data, the median time to PSA relapse (PSAR) following 36 weeks of androgen deprivation therapy, is approximately 40 weeks. This study would then look to detect an improvement beyond 40 weeks. For a one-sample, one-sided, 0.05-level test using the large-sample normal approximation for the distribution of the logarithm of the maximum likelihood estimator of the exponential parameter, with 28 patients and assuming accrual of 24 months and follow-up of 12 months, there will be 83% power for the test of the null hypothesis that the median PSAR is 9 months vs. the alternative that the median PSAR is 16 months as measured from the end of the twelve months of androgen deprivation therapy. If the parametric estimate of median PSAR is 13 months, this would suggest activity for the addition of radiation therapy. The initial analysis will include all patients, although analysis by strata will also be conducted in an exploratory fashion as will the role of previous adjuvant hormone treatment.

In addition to obtaining an early estimate of the effect of this therapy based on survival, feasibility and toxicity will also be carefully monitored in this novel approach.

10.1 Interim analysis for toxicity

With 28 patients, we will be able to estimate the complication rate (any grade 3 or higher toxicity attributable to the radiation or combination of androgen deprivation/ radiation therapy) with a maximum standard error of 19%. If less than 2 cases have radiation induced complications, we can rule out a 17% complication rate or higher with 95% confidence. Since this therapy is not expected to cause severe toxicities, if at any time more than 25% of the patients experience a radiation induced complication, the study will be halted pending review.

The outcome status (in terms of toxicity, response, reason off study, progression, and survival) of all eligible patients who are registered will be reported. All patients who receive any treatment will be included in the summaries of toxicities. The CTCAE v. 3.0 toxicity criteria will be used. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Time to progression and overall survival will be estimated using the product-limit method of Kaplan and Meier.

The sample-size, as justified above, is 28 patients. With an expected accrual of 14 patients per year, it will take approximately two years to complete the accrual.

11.0 REGISTRATION GUIDELINES

11.1 Registration will be done at City of Hope.

11.2 Once all pretreatment evaluations have been performed, patients will be entered on study after review of patient eligibility by a member of the Department of Biostatistics. Patients may be screened for registration by calling the City of Hope Department of Biostatistics, ext. 62468.

12.0 RECORDS TO BE KEPT, DATA COLLECTION AND SUBMISSION SCHEDULE

12.1 Confidentiality of Records: The forms will be kept in secure cabinets in the Department of Biostatistics.

12.2 Patient Consent Form: At the time of registration, three signed and dated copies of the patient Informed Consent form with the Human Rights must be available (for patient, patient's medical chart and one for the Biostatistics Office.

12.3 Data collection forms and submission schedule: All data will be collected using COH Biostatistics Information Tracking System (BITS) data collection forms. Copies of the completed forms will be submitted to City of Hope Department of Biostatistics for entry and stored in a secure location. The original data collection forms will reside at the originating institution in secure location.

12.3.1 The data manager will complete the Eligibility Checklist Worksheet at the time of registration.

12.3.2 Within two weeks of registration, the data manager will complete the On-Study Form (Form OS).

12.3.3 Within four weeks of completion of each course of treatment, the data manager must complete the following:

12.3.3.1 Treatment and Adverse Event Form

12.3.3.2 Supplemental data form (if applicable)

12.3.3.3 Flow sheets (These are to be submitted along with each treatment form)

12.3.4 Each time a patient is evaluated for response and/or new follow-up information is obtained the data manager will complete the Response/Off-Study/Follow-Up Form.

12.4 Analysis will be carried out by Department of Biostatistics.

13.0 MINORITIES AND WOMEN STATEMENT

Prostate cancer is limited to men. Patients from all racial/ethnic groups are eligible for this study if they meet the eligibility criteria outlined in Section 5.0.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

All institutional, NCI, Federal, and State of California regulations will be fulfilled.

15.0 PATHOLOGY REVIEW

All patients will have malignancy confirmed by review of their biopsy specimens by the Division of Pathology of the City of Hope National Medical Center.

16.0 DATA AND SAFETY MONITORING

A) Definition of Risk Level

This is a Risk Level 3 study, as defined in the "Guidance, Policy and Procedures for Data and Safety Monitoring for In-House Trials at City of Hope", http://www.infosci.coh.org/gcrc/doc/dsmp.doc because it is a Phase II clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of knowledge that may result.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Data and safety will be reported to the COH DSMB. Reporting of data to DSMB will occur at intervals separated by no more than 12 months, 14 patients or a treatment related death. The PMT report will include a summary of accrual, adverse events and treatment related mortality.

C) Adverse Events

Reporting: Adverse events will be reported to the COH DSMB, and IRB according to definitions and guidelines at http://www.infosci.coh.org/gcrc/doc/dsmp.doc and http://resadmin.coh.org/doc/irb3810.doc, which are defined below. AEs will be monitored by the PMT. Less than serious adverse events will be reported only at the time of protocol continuation reports.

Adverse Event - An adverse event (AE) is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention. All AEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be recorded on the City of Hope National Medical Center Adverse Events (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) form**.**

Serious Adverse Event**- A serious adverse event (SAE) is defined as *any expected or unexpected adverse event* (AE, generally equivalent to CTCAE grades 3, 4 or 5) that is *related or unrelated* to the intervention that results in any of the following outcomes:**

- Death
- A life-threatening event
- In-patient hospitalization (not required as part of the treatment) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Causes cancer
- Is an overdose

Certain medical events that may not result in death, be life threatening, or require Hospitalization, may also be considered a serious adverse event when appropriate medical or surgical intervention is necessary to prevent one of the outcomes listed above.

Unexpected Adverse Event – Any event in which the severity or specificity is not consistent with the risk information described in the protocol, and the event is not anticipated from the subject's disease history or status.

Expected Adverse Event - Any event in which the severity or specificity is consistent with the risk information described in the protocol or is anticipated based on the subject's medical history.

Attribution - For reporting purposes, attribution is the assessment of the likelihood that an AE is caused by the research agent or protocol intervention. The attribution is assigned by the Principal Investigator after considering the clinical information, the medical history of the subject, and past experience with the research agent/intervention. This is recorded using the Adverse Event Report (COH AER) form (http://resadmin.coh.org/doc/irb3820.doc) in one of 5 categories scored as the following: 5=related, 4=probably related, 3=possibly related, 2=unlikely related and 1=unrelated. The attribution is subject to change as follow-up information becomes available, and it can be changed by the DSMB or by the IRB in the process of review.

REFERENCES:

1. Jehal A, Tivari R, Murray T: Cancer Statistics 2004. CA Cancer J. Clin 2004; 54:8-29.
2. Halsted W: The results of radical operations for the cure of cancer of the breast. Ann Surg 46; 1,1907.
3. Fisher B: Laboratory and clinical research in breast cancer- a personal adventure: the David A. Karnofsky memorial lecture. Cancer Res 40:3863-3874, 1980.
4. Hellman S: Karnofsky memorial lecture. Natural history of small breast cancers J. Clin Oncol 12:2229-2234, 1994.
5. Hellman S, Weeichselbaum RR: Oligometastases. J. Clin Oncol 13:8-10, 1995.
6. Hughes KS, Simon R, Songhorabodi, Adson MA, Ilstrup DM, Fortner JG, Maclean BJ, Foster JH, Daly JM, Fitzherbert D, et al. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. Surgery 100:278-284, 1986.
7. McDonald ML, Deschamps C, Ilstrup DM, Allen MS, Trastek VF, Pairolero PC: Pulmonary resection for metastatic breast cancer. Ann Thorac Surg 58:1599-1602, 1994.
8. Nordlinger B, Vaillant JC, Guiguet M, Balladur P, Paris F, Bachellier P and Jaeck D: Survival benefit of repeat liver resections for recurrent colorectal metastases: 143 cases. Association Francaise de Chirurgie. J. Clin Oncol 12:1491-1496, 1994.
9. Loblaw DA, Mendelson DS, Talcott JA, Virgo KS, Somerfield MR, Ben-Josef E, Middleton R, Porterfield H, Sharp SA, Smith TJ, Taplin ME, Vogelzang NJ, Wade, Jr. JL, Bennett CL, Scher HI: American Society of Clinical Oncology. Recommendations for the initial hormonal

management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. JCO Jul 15,2004: 2927-2941.
10. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomized trials. Lancet 2000; 355:1491-1498.
11. Leibowitz RL, Tucker SJ: Treatment of localized prostate cancer with intermittent triple androgen blockade. Preliminary result sin 110 consecutive patients. Oncologist 2001; 6:177-182.
12. Scher HI, Steineck G, Kelly WK: Hormone-refractory (D3) prostate cancer: refining the concept. Urology, 46:142-248.
13. Feldman B, Feldman D: The development of androgen-independent prostate cancer. Nature Reviews Cancer. October 2001, Vol 1:34-45.
14. Langeler EG, Connie JC, van Uffelen CJC, Blankenstein MA, can Steenbrugge GJ, Mulder E: Effect of culture conditions on androgen sensitivity of the human prostatic cancer cell line LNCaP. Prostate 1993; 23:213-223.
15. Akakura K, Bruchovsky n, Goldernberg SL, Rennie PS, Buckley AR, Sullivan LD: Effects of intermittent androgen suppression on androgen-dependent tumors. Apoptosis and serum prostate-specific antigen. Cancer 1993; 71:2782-2790. And large randomized study is underway to establish its role in treatment of patients with metastatic prostate cancer.
16. Hurtado-Coll A, Goldenberg SL, Gleave ME, Klotz L: Intermittent androgen suppression in prostate cancer. The Canadian experience. Urology 2002; 60 (Suppl 3A):52-56.
17. Harris KA, Reese DM: Treatment options in hormone-refractory prostate cancer: current and future approaches. Drugs, 61:2177-2192.
18. Eisenberger MA, De Wit R, Berry W, et al: A multicenter phase III comparison of Docetaxel (D) + prednisone (P) and mitoxantrone (MTZ) + P in patients with hormone-refractory prostate cancer (HRPC). Proceedings of ASCO 2004, Abstract #4.
19. Petrylak DP, Tangen C, Hussain M, et al: SWOG 99-16: Randomized phase III trial Docetaxel (D)/estramustine (E) versus mitoxantrone (M)/prednisone (p) in men with androgen-independent prostate cancer (AIPCA). Proceedings of ASCO 2004, Abstract 3.
20. Singh D, Yi WS, Brasachio RA, Muhs AG, Smudzin T, Williams JP, Messing E, Okunieff P. Is there a favorable subset of patients with prostate cancer who develop oligometastases? Int J Radiat Oncol Bio Phys. 2004 Jan 1;58(1):3-10.
21. Leibel, SA, Fuks Z, Zelefsky MJ, Hunt M, Burman CM, Mageras GS, Chui CS, Jackson A, Amols HI, and Ling CC: Technological advances in external-beam radiation therapy for the treatment of localized prostate cancer. Seminars in Oncology 30: 596-615, 2003.
22. Mackie TR, Kapatoes J, Ruchala K, Lu W, Wu C, Olivera G, Forrest L, Tome W, Welsh J, Jeraj R, Harari P, Reckwerdt P, Paliwal B, Ritter M, Keller H, Fowler J, and Mehta M: Image guidance for precise conformal radiotherapy. Int J Radiation Oncology Biol Phys 56: 89-105, 2003.
23. Balog J, Mackie TR, Pearson D, Hui S, Paliwal B, and Jeraj R: Benchmarking beam alignment for a clinical helical tomotherapy device. Med Phys 30: 1118-1127, 2003.
24. Grigorov, et al (Grigorov G, Kron T, Wong E, Chen J, Sollazzo J, and Rodriquez G: Optimization of helical tomotherapy treatment plans for prostate cancer. Phys Med Biol 48: 1933-1943, 2003.
25. Scrimger, et al (Scrimger RA, Tome WA, Olivera GH, Reckwerdt P, Mehta MP, and Fowler JF: Reduction in radiation dose to lung and other normal tissues using helical tomotherapy to treat lung cancer, in comparison to conventional field arrangements. Am J Clin Oncol 26: 70-8, 2003.

APPENDIX A

A Common Terminology Criteria for Adverse Events v3 (CTCAE Publish date 12/12/03)

Website: ctep.cancer.gov/reporting/ctc.html