University of Pennsylvania

A Phase II Study of Adjuvant Proton Radiation Therapy for the Treatment of Stage I, IIA, and IIB Seminoma

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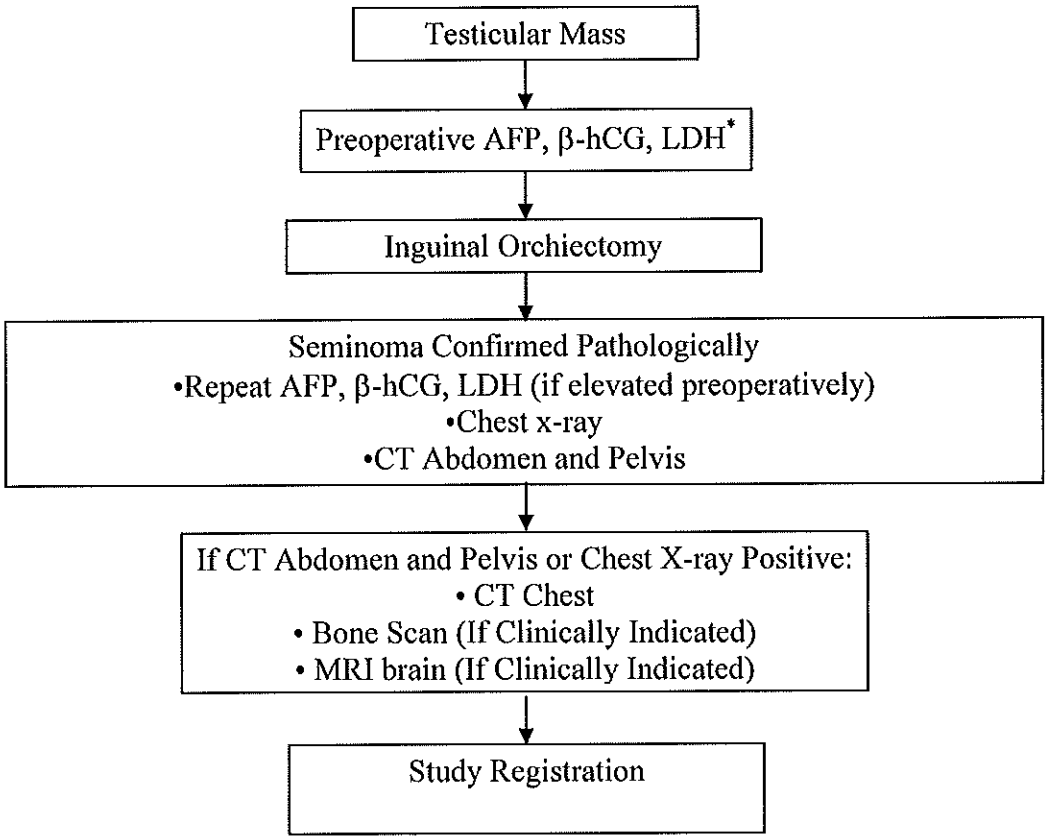
This will be a multi-institutional study. The Coordinating Center will be the University of Pennsylvania, Department of Radiation Oncology. Other participating Institutions include: Massachusetts General Hospital, additional sites to be later named.

Schema



*AFP=alpha-fetoprotein; β-hCG=human chorionic gonadotropic; LDH=lactate dehydrogenase

Required Sample Size: 56

For patients with Stage I Seminoma, treatment is prescribed to the clinical target volume (CTV) to be delivered to 20.0 Gy (RBE) to 30.0 Gy (RBE) in 150 cGy (RBE) to 200 cGy (RBE) fractions to $CTV_{para\text{-}aortic}$ for patients being treated to the para-aortic region alone or to $CTV_{para\text{-}aortic + pelvis}$ for patients being treated both to the para-aortic and pelvic regions. For patients with Stage IIA and IIB Seminoma, the CTV must include the both the para-aortic and pelvic regions and a boost volume comprised of the CTV_{nodal} (prescribed to an additional 9.0 Gy (RBE) to 10.0 Gy (RBE) in 180 cGy (RBE) to 200 cGy (RBE) fractions.

Patient Population: (See Sections 3.2 and 3.3 for Eligibility)

-Histologically proven diagnosis of testicular seminoma
-Stage I, IIA, and IIB seminoma according to AJCC, 7th Edition
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-No N1, N2 or M1 metastasis
-For stage I seminoma, definitive surgical intervention within ten weeks prior to registration

-For stage IIA and IIB seminoma, abdominal and pelvic computed tomography imaging demonstrating nodal disease.
-No prior radiotherapy to the region of study
-No prior chemotherapy or investigational drug administered or pelvic lymph node dissection performed for the diagnosis of seminoma.

Signature Page

The investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice; and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/independent Ethics Committee review and regulatory agency inspection of trial-related documents and procedures and provide for direct access to all study-related source data and documents.

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INVESTIGATOR SIGNATURE DATE

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Study Summary

Title	A Phase II Study of Adjuvant Proton Radiation Therapy for the Treatment of Stage I, IIA, and IIB Seminoma
Short Title	Proton Radiotherapy for Stage I, IIA, and IIB Seminoma
Protocol Number	*UPCC #17811*
Phase	*Phase II*
Methodology	*Open*
Study Duration	*72 months*
Study Center(s)	*University of Pennsylvania, Massachusetts General Hospital*
Number of Subjects	*56*
Diagnosis and Main Inclusion Criteria	*Testicular Seminoma Stage I, IIA, IIB*

1 Introduction

1.1 Background

Testicular cancers are the most common solid malignancies among men aged 20 to 35 years, with a projected 8,400 new cases of testicular malignancies in the Unites States annually (1). Approximately 60% of these malignancies represent pure seminomas, and 80% of patients diagnosed with seminoma have stage I disease (2-3). The standard initial treatment for stage I seminoma is radical inguinal orchiectomy. Photon external beam radiation therapy has been standard adjuvant treatment and can achieve cause-specific survival rates approaching 100% and long-term relapse-free survival rates in excess of 95%, with virtually no relapses within the radiation portal (4-8).

However, radiation-induced treatment morbidities for seminoma have been reported. Acute toxicities are generally mild and self-limiting and include fatigue and gastrointestinal symptoms. Patients, however, are at an increased risk of late gonadal toxicity (9-11) and cardiovascular disease (12-14). Cardiac risks are higher among patients treated with mediastinal radiotherapy when compared to those treated with infradiaphragmatic radiation alone (12), patients receiving chemotherapy in addition to radiation therapy, and smokers (13, 15).

Following adjuvant radiation therapy, patients with seminoma are also at increased risks of contralateral testicular germ cell tumors in the first decade following adjuvant radiation therapy (16-18) and non-germ cell solid malignancies (RR = 2.0, 95% CI = 1.9-2.2) 10 to 35 years following radiation therapy (12-13, 15, 18-24). The risk of solid malignancies is higher for patients diagnosed with testicular cancers at younger ages. Based on tumor registry data, a patient diagnosed with a seminoma at age 35 years has a 36% risk of developing a second solid cancer within 40 years of his diagnosis, compared with 23% for the general population. As seminoma largely affects younger patients, and the cure rates from standard therapy are excellent, second primary cancers have emerged as a leading cause of death among survivors of testicular malignancies (12-13, 24).

Attempting to decrease treatment morbidities and secondary malignancies, studies have investigated reducing the adjuvant radiation therapy dose and treatment volume. The United Kingdom Medical Research Council (MRC) randomized 625 patients with stage I seminoma to 20 Gy or 30 Gy in 200 cGy daily fractions following orchiectomy. Significantly fewer patients in the 20 Gy arm experiences moderate or severe lethargy (5% vs. 20%) or an inability to carry out normal work (28% vs. 46%) four weeks following therapy, with no difference in relapse-free survival or overall survival (4). As the incidence of pelvic recurrences is low in patients with stage I seminoma (26-27), and few pelvic failures have been reported in patients treated only to the para-aortic region (28-32), an MRC trial randomized 478 patients with stage I seminoma to receive adjuvant para-aortic and pelvic radiotherapy or para-aortic radiotherapy alone following orchiectomy. No significant differences in overall survival or relapse-free survival were demonstrated between the two arms (5). Although the pelvic relapse-free survival rate was higher (100% vs. 98.2%, p=0.04) for patients receiving radiation therapy to the pelvis, these patients experienced increased rates of hematologic toxicities and temporary azospermia. As a result of this trial, para-aortic field radiation therapy alone has generally been accepted as a standard radiation target volume for stage I patients with undisturbed lymphatic drainage. Patients treated in this manner, however, require more intensive follow-up with annual pelvic CT imaging for three years (8, 33-34).

Despite reductions in radiation doses and treatment fields, surveillance has emerged as an alternative and increasingly utilized adjuvant course. Approximately 15% to 20% of unselected patients with stage I seminoma who undergo surveillance following orchiectomy develop disease recurrence (35-43). As greater than 80% of these relapses occur in the para-aortic lymph nodes, deferring immediate adjuvant therapy and administering chemotherapy or radiation therapy upon relapse allows for successful salvage therapy in most patients, with equivalent overall survival rates as for patients receiving immediate adjuvant therapy (41-43). However, treatment of patients undergoing surveillance who relapse is usually more intensive and associated with increased morbidity (44-45). More recently, groups have advocated a risk-adapted management strategy to guide adjuvant therapy (46). As the risk of relapse is higher in patients with tumor sizes great than 4 cm, rete testis invasion, or pT3 or pT4 disease, in the absence of a contraindication to adjuvant therapy, only patients with pT1 or pT2 histologies and smaller tumors who are committed to long-term follow-up are ideal candidates for surveillance (8, 33, 43, 46).

Short-course adjuvant carboplatin for one or two cycles has emerged as an alternative to adjuvant radiation therapy or surveillance (8, 47-48). An MRC and European Organization for Research and Treatment of Cancer trial (MRC/EORTC ISRCTN27163214) randomized 1,447 patients with pT1 to pT3 stage I seminoma to one course of carboplatin or adjuvant radiotherapy to 20 Gy to 30 Gy in 200 cGy daily fractions primarily to the para-aortic region (16-17). At a median follow-up of 6.5 yrs, there was no difference in 5-year relapse-free survival rates between the carboplatin arm and the radiation therapy arm (94.7% vs. 95.5%, HR 1.25, 90% CI 0.83 to 1.89). Patients in the carboplatin arm had higher rates of Grade 1 or Grade 2 thrombocytopenia (12% vs. 2%, $p<0.0001$) and Grade 3 or Grade 4 thrombocytopenia (4% vs. 0%, $p<0.0001$), whereas patients in the radiation therapy arm had higher rates of dyspepsia (17% vs. 8%, $p<0.0001$) and a trend towards increased lethargy and time off of work in the acute setting. Additionally, fewer new contralateral testicular germ cell cancers were observed in the carboplatin arm (0.2% vs. 1.2%, HR 0.22, $p=0.03$).

Despite these promising early findings, carboplatin is associated with an uncertain frequency of late relapses and a need for more rigorous CT surveillance with abdominal and pelvic CT imaging at every visit for up to 10 years (8, 33-34, 49). The radiation exposure from this more frequent CT surveillance may result in an increase in secondary malignancies (50-52). Carboplatin also has potential risks of acute nephrotoxicity, ototoxicity, neurotoxicity, and gonadal damage, as well as long-term cardiac disease and secondary malignancies (15, 19). Population-based cancer registry studies of patients primarily treated with combination chemotherapy reveal an increased risk of secondary solid malignancies highest among patients receiving both chemotherapy and radiotherapy (RR=2.9, 95% CI=1.9-4.2), with similar risks for patients treated with adjuvant radiation therapy alone (RR=2.0, 95% CI = 1.9-2.2) or adjuvant chemotherapy alone (RR=1.8, 95% CI = 1.3-2.5) (19). Several studies have also reported increased risks of secondary leukemias and myelodysplastic syndrome following chemotherapy for testicular cancer (22, 53-60).

Proton beam radiation therapy is a way of delivering radiation that has the potential of minimizing both acute and late toxicities associated with standard photon radiation therapy. We propose to use beam proton radiation therapy to deliver 20.0 Gy (RBE) to 30.0 Gy (RBE) to the para-aortic lymph node region, with or without 20.0 Gy (RBE) to 30.0 Gy (RBE) to the ipsilateral pelvic nodal region, for the adjuvant treatment of patients with stage I testicular seminoma. Thus, we are examining in this study the ability of proton beam radiation therapy to reduce the risk of acute and late toxicities in this group of patients.

1.2 Rationale for Proton Therapy

The goal of radiation therapy is to deposit most of the radiation dose at the target, while minimizing the dose to the surrounding normal tissues. Conventional photon radiotherapy deposits dose along the entire beam path to the tumor or target volume and beyond the depth of the target. Unlike photons, proton radiotherapy deposits most of the energy at a specific depth known as the Bragg peak. The dose beyond the Bragg peak is essentially zero, which allows tissues on the distal side of the tumor or target to be spared. Proton therapy is an approved radiation therapy by the United States Food and Drug Administration.

Protons have a similar biological effect as photons against tumors. The biological effect of radiation is dependent on its linear energy transfer (LET), defined as the rate of energy transferred by ionizing radiation per unit path length. To compare different types of radiation, we use the relative biologic effectiveness (RBE), defined as the ratio of the dose of particle radiation to the dose of 60Co radiation producing the same biological endpoint. Standard photon radiation therapy has a RBE of 1.0. The RBE of protons is thought to be between 1.05 and 1.25 (61-63). A recent review of in vivo and in vitro experiments concluded that RBE varies with dose and dose per fraction, increases with an increasing depth in the spread out Bragg Peak (SOBP), and is greatest at the distal edge of the SOBP. Overall, an average RBE of approximately 1.1 in the entrance of the SOBP is considered standard among centers treating with proton radiation therapy (64). Therefore, the clinical advantage of proton radiation therapy over standard photon radiation therapy results from the more favorable dose distributions achievable with the particular physical properties of protons, as previously described (65-70).

Although no clinical trials or published data exist pertaining to the use of proton therapy for the treatment of patients with testicular malignancies, a comparative treatment planning analysis presented at the 48th Meeting of the Particle Therapy Co-Operative Group in 2009 and recently accepted for peer-reviewed publication demonstrated that proton radiation therapy may allow for similar high rates of relapse-free survival as with photon radiation therapy for patients with stage I seminoma, but with less acute and late toxicity (71). In that study, superior normal tissue sparing was observed with proton radiation therapy compared with photon radiation therapy. Lower doses to critical organs observed with protons may reduce acute toxicities previously reported with adjuvant photon radiation, including nausea, lethargy, and delay in return to work. Additionally, proton therapy was demonstrated to reduce the predicted secondary cancer risk compared with photon therapy, particularly for secondary gastric, large bowel, and bladder malignancies.

As the predominant pattern of relapse for adjuvant radiation therapy to the para-aortic region alone for patients with stage I seminoma occurs within the pelvis (5), the addition of an ipsilateral pelvic field to a para-aortic field with proton radiation therapy may reduce the risk of pelvic failures for these patients, while still allowing for fewer acute toxicities and secondary malignancies when compared with photon radiation therapy to the para-aortic region alone. In addition to potentially improving relapse-free survival rates, such treatment to the pelvis would allow for less rigorous surveillance without the need for annual pelvic CT imaging that is required for patients treated to the para-aortic region alone, potentially decreasing the risk of secondary malignancies associated with CT surveillance (8, 33-34, 50-52). This is of particular benefit for selected patients, including members of the United States Armed Forces, in which obtaining the necessary surveillance studies cannot be guaranteed to due frequent remote deployments and geographic relocations.

Stage II seminoma, either at presentation or at relapse following treatment for stage I disease, is a highly curable malignancy. Treatment for nonbulky (stage IIA/IIB) seminoma generally consists of RT, with chemotherapy

reserved for salvage of patients who subsequently relapse. Contemporary studies in patients with IIA and nonbulky IIB seminoma have yielded five-year disease-free survival rates of 90 percent or higher.

2 Study Objectives

This is a Phase II study of proton therapy for patients with stage I, IIA, and IIB testicular seminoma.

2.2 Phase II Study Primary Objective: *It is desirable for proton radiation to yield a reduced rate of lethargy, similar to single dose carboplatin.* ***Our hypothesis is that the 3 week lethargy rate is ≤35% with proton therapy.*** *Termination for acute toxicity will be considered as outlined in protocol section 7.2.3.*

2.3 Phase II Secondary Objectives

2.3.1 To evaluate the treatment efficacy of proton radiotherapy for all enrolled patients with seminoma as evidenced by time to local failure, time to distant failure, relapse-free survival, cause-specific survival, and overall survival, according to patient clinical stage and radiotherapy target volume treated.

2.3.2 To determine the incidence of additional acute toxicities of proton radiotherapy in patients with stage I, IIA, and IIB seminoma, including the incidence of hematologic toxicities, dyspepsia, and patients reporting being unable to perform normal work.

2.3.3 To assess late complications from irradiation to the para-aortic and pelvic regions using proton beam therapy, including late gonadal toxicity/spermatogenesis depression and the rates of contralateral testicular germ cell tumors, secondary solid cancers, and hematologic malignancies.

2.3.4 To compare the dose distribution to target volumes and surrounding normal structures using Dose Volume Histograms generated from proton plans used to treat study participants and photon plans that will be generated for comparison purposes.

2.3.5 To evaluate multiple domains of quality of life before, during, and after radiotherapy, including patient-reported assessments of lethargy, work or daily activity impairment, nausea/emesis, change in bowel habits, mobility, self-care, pain/discomfort, anxiety/depression, and sleep.

3 Subject Selection and Withdrawal

3.1 Accrual

This study plans to enroll 56 evaluable patients over 72 months. The University of Pennsylvania, Penn satellites, Walter Reed National Military Medical Center, other affiliated Department of Defense (DOD) hospitals, and Massachusetts General Hospital (MGH), see in excess of 20 patients with stage I, IIA, and IIB testicular seminoma per year. Of the patients with seminoma treated annually at these participating institutions, we would reasonably expect to accrue 8 to 10 patients on study annually. Only MGH and the University of Pennsylvania will be treating patients with protons. The Walter Reed National Military Medical Center/Department of Defense affiliates will be referring patients to the University of Pennsylvania

3.2 Inclusion Criteria

3.2.1 Histological diagnosis;

- Histologically proven diagnosis of testicular seminoma;
  - Histologically confirmed seminomatous germ cell tumor of the testis categorized as either "classical" or "anaplastic;"
- Stage I disease;
  - Any pT N0 M0 S0-3 (Appendix B) [AJCC, 7th Ed.] (72);
- Stage IIA or IIB disease;
  - Any pT N1 M0 S0-3 (Appendix B) [AJCC, 7th Ed.] (72);
  - Any pT N2 M0 S0-3 (Appendix B) [AJCC, 7th Ed.] (72);

(at the discretion of the principal investigators, bulky stage IIB may be excluded from the study, according to National Comprehensive Cancer Center Guidelines.

3.2.2 Laboratory evaluations;

- Semen analysis (patients will not be excluded if they do not wish to have an analysis or their insurance denies the claim) (prior to start of radiation)

- Follice-stimulating hormone (prior to start of radiation)
- Luteinizing Hormone (prior to start of radiation)
- Lactate Dehydrogenase (prior to start of radiation)
- Human Chorionic Gonadotropic (prior to start of radiation)
- Complete blood count (prior to start of radiation)
- Alpha FetaProtein (prior to start of radiation)
- Testosterone (prior to start of radiation)

3.2.3 Appropriate stage for protocol entry, as per protocol section 3.2.1, , based upon the following minimum diagnostic workup:

- History and physical examination, including a complete list of current medications;
- Chest x-ray (PA and lateral views) or CT chest (within 3 months of study registration);
- Abdominal/pelvic CT scan or Abd/Pelvic MRI (within 3 months of study registration);
- Brain MRI if clinically indicated;
- Bone scan if clinically indicated;
- For stage II disease recurrence, rebiopsy is not clinically indicated. Imaging may suffice for confirmation of recurrence.

3.2.4 For stage I seminoma patients only, definitive surgical intervention within ten weeks prior to registration;

- Patients undergoing scrotal violations (scrotal orchiectomy, transscrotal biopsy, testicular fine needle aspiration, scrotal exploration) will be eligible;

3.2.5 The patient is a candidate for definitive external beam radiotherapy;

- The patient has had no prior radiotherapy to the region of study;
- The patient has no inflammatory bowel disease, active collagen vascular or connective tissue disorders, and no other medical or social contraindications to radiotherapy, as determined by a participating radiation oncologist;

3.2.6 Patient age: ≥18 years;

3.2.7 Patient ECOG performance status: 0-1 (Appendix C);

3.3 Exclusion Criteria

3.3.1 Prior radiotherapy to the region of the study cancer;
- Prior radiation therapy for a different cancer or disease process is allowed, provided there will be no overlap of radiation therapy fields between the participant's prior and current course of radiation therapy, radiotherapy was completed more than four weeks from first fraction of proton therapy administered in this study, and the participant has recovered to Grade $\leq$1 toxicity related to prior radiotherapy;

3.3.2 Chemotherapy administered for the diagnosis of seminoma;
- Prior chemotherapy for a different cancer is allowed, provided therapy was completed more than twelve months from first fraction of proton therapy administered in this study and the participant has recovered to Grade $\leq$1 toxicity related to agents previously administered;

3.3.3 Incomplete definitive surgical orchiectomy, including diagnostic biopsy alone;

3.3.4 Pelvic lymph node dissection for the diagnosis of seminoma;

3.3.5 An investigational drug administered for the diagnosis of seminoma given concurrently or within four weeks of the first fraction of proton therapy administration.

3.3.6 Prior or concurrent second invasive malignancy other than non-melanoma skin cancer, unless disease free for a minimum of five years;

3.3.7 Known severe, active co-morbidity, defined as follows:
- Any clinically significant unrelated systemic illness, medical condition, or other factor, which at the discretion of the Principal Investigators, would interfere in the safe and timely completion of study procedures, compromise the patient's ability to tolerate the protocol therapy, or is likely to interfere with the study procedures or results;

3.3.8 Cognitively impaired patients who cannot provide informed consent.

3.4 Subject Recruitment and Screening

Subjects will be recruited from the oncology practices at Penn Medical Center, Department of Defense practices throughout the country, and Massachusetts General Hospital, which has already established the ability to deliver proton radiation therapy. Patients will be referred by their physician by calling the Clinical Research Coordinator (CRC) in the Department of Radiation Oncology at the University of Pennsylvania. After the subject signs the informed consent document and eligibility is established, a subject study number will be issued.

The University of Pennsylvania, Penn satellites, Walter Reed National Military Medical Center, other affiliated Department of Defense hospitals, and Massachusetts General Hospital, which has already established the ability to deliver proton radiation therapy, see approximately 20 patients with stage I testicular seminoma per year. Of the patients with seminoma treated annually at these participating institutions, we would reasonably expect to accrue 8 to 10 patients on study annually. Proton radiotherapy will be listed on Penn, the Department of Defense, and Massachusetts General Hospital websites as a formal protocol and information of its availability will be made known to treating professionals throughout Penn, its satellites and referring physicians, and the referral networks of the Department of Defense and Massachusetts General Hospital.

3.5 Evaluation of Prospective Patients at Each Trial Site:

All prospective patients will be evaluated by the attending radiation oncologist and other physicians as clinically indicated. In addition, at least one of the following eight physicians will review the patient's records to make recommendations regarding further work-up or appropriateness of the protocol therapies: Justin Bekelman, MD, Nathan Jones, MD, Neha Vapiwala, MD, Charles Simone, MD, John Christodouleas, MD, Curt Deville, MD, Jason Efstathiou, MD (MGH) Anthony Zietman, MD (MGH), Tim Mitin (MD), and David Miyamoto (MD). Physicians will not review records of their own patients. Should patients of any of these physicians be treated on study, the records of those patents will be reviewed by one of the other named physicians.

All patients participating in this study will be treated at the University of Pennsylvania or at Massachusetts General Hospital. Patients will have their medical records sent to the University of Pennsylvania research team to confirm eligibility.

3.6 Early Withdrawal of Subjects

3.6.1 Progressive Disease: Subjects who have clinical or radiologic evidence of progressive disease will undergo an evaluation to document the nature of the abnormality. If progressive cancer is diagnosed and further treatment planned, subjects will be considered off study and all efforts will be made to follow the patients for survival and toxicity data.

3.6.2 Principal Investigator Decision: Subjects may be withdrawn at any time during the study if the Principal Investigator believes it is in the subject's best interest to be withdrawn. In this event, the reasons for withdrawal will be documented.

3.6.3 Subject Participation: Refusal to continue treatment, follow-up, or comply with the protocol, or the withdrawal of consent. In this event, the reasons for withdrawal will be documented.

3.6.4 New information becomes available that warrants discontinuation of the protocol.

Once the subject is withdrawn from the study, the primary reason for withdrawing from the study must be clearly documented in the subject's records and on the CRF. The investigator will assess each subject for response at the time of withdrawal.

Every effort will be made to follow subjects off study for toxicity and survival. Survival will be followed for a minimum of five years by means of medical records and an annual phone call by a member of the research team to the subject if no medical records are available. Every effort will be made to follow patients for overall survival.

3.7 Subject Data Collection

All subject information obtained throughout this study will be entered directly into the Velos system at both the University of Pennsylvania and Massachusetts General Hospital using case report forms (CRFs). After the confirmation of eligibility the subject will be assigned a study specific number and be entered into the Velos system. Adverse Events (AEs) and Serious Adverse Events (SAEs) at each site will be entered into the Velos system within two weeks.

3.7.1 Vision Tree Assessments

Subjects will be completing Quality of Life forms using Vision Tree, Inc.. VisionTree Software, Inc, will enable patients to fill out their QOL forms from any location that has a computer with internet access. VisionTree has

developed a new tool, VisionTree Optimal Care (VTOC), a HIPAA-secure, user-friendly, web-based software system. The VTOC tool contains a Web-based system for global patient and trial administration access, which allows improved compliance and accuracy of data collection, validation, and reporting. It is compliant with the Title 21, *Code of Federal Regulations*, Part 11 statistical process control system, and provides a mobile solution for clinical trials. Outcomes data is collected with Microsoft Excel and PDF export of reports. VTOC also has mobile messaging and e-mail reminders. (See http://www.visiontree.com for details).
If patients decide to utilize VisionTree software in their participation in this study, they must have an e-mail address that they consent to use for this purpose. Patients' e-mail addresses are necessary for this study so that e-mail reminders may be sent to them to remind them to fill out QOL forms that are due. Patients who are interested in participating but do not yet have an e-mail address can obtain one for free from a number of sources (e.g., Yahoo!, Hotmail, or AOL) and thus, can still participate. The patient's e-mail address will be used for password-protected access to VTOC. Patients can complete the QOL forms anywhere with a secure login. Patients will receive a login card (either printed or sent via email) with which to log in using the secure, web-based VTOC portal. VTOC meets all HIPAA guidelines and is encrypted (via 128-bit SSL) for the security, privacy, and confidentiality of QOL information. It is similar to the secure login commonly used when performing on-line banking. The login card may be kept and maintained by the patient. Patients will be permitted to use paper versions of the forms if they experience difficulty using the Vision Tree website.

The patient's e-mail address will only be used for this study. Patients will only be sent e-mail reminders when QOL forms are due. A typical e-mail reminder would read: "Your Quality of Life forms for your study, "Proton Seminoma", are now due. Please go to http://www..... to use your secure login to log in to your portal and complete the on-line forms. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. If you have any questions, please e-mail or call your research coordinator at -UPenn coordinator's email or at MGH coordinator's email (for MGH patients). Thank you for participating in this study." The reminders will be created and placed into a study template that will be sent to patients at customized intervals The first reminder will be sent at the beginning of the "window" to complete a QOL form, with a second reminder halfway through the window period if the QOL forms are not yet completed at that time. A maximum of 3 reminders will be sent for each time point; after a patient has completed all forms in the portal, a dialogue box will appear that says "Thank you for completing your Quality of Life forms," and the patient will no longer receive any remaining notices for that time point. The site research associate or study administrator will be informed through the VTOC "At-A-Glance" form management system when QOL forms have been completed.

4 Radiation Therapy

4.1 Dose fractionation and specification

4.1.1 For patients with Stage I Seminoma, radiation fractions will be administered once daily, for five fractions per week from Mondays through Fridays, as well as weekends when deemed clinically appropriate, with the exclusion of Hospital Holidays, for a planned 10 to 25 fractions delivered over two to four weeks. For patients with Stage IIA and IIB Seminoma, an additional boost of 5 fractions will be delivered over 5 days. The number of fractions administered will be dependent of the clinical stage of each study subject.

4.1.2 For Stage I Seminoma, patients will be treated to a total dose of 20.0 Gy (RBE) to 30.0 Gy (RBE) in 150 cGy (RBE) to 200 cGy (RBE) fractions to $CTV_{para\text{-}aortic}$ for those being treated to

the para-aortic region alone or to $CTV_{para\text{-}aortic + pelvis}$ for those being treated both to the para-aortic and pelvic regions. For patients with Stage IIA and IIB Seminoma, the target volume must include the both the para-aortic and pelvic regions and a nodal volume encompassing nodal disease (prescribed to an additional 9.0 Gy (RBE) to 10.0 Gy (RBE) in 180 cGy (RBE) to 200 cGy (RBE) fractions. The treatment field and total radiation dose will be at the discretion of the treating radiation oncologist, and dependent on the clinical risk factors of each study subject. The maximum dose should not exceed the prescription dose by more than 7% (inhomogeneity less than or equal to 7% in a volume of 1 cc of the review structures).

4.1.3 Treatment breaks, if necessary, should not exceed two treatment days. Treatment breaks exceeding two days will be considered a major protocol violation. Treatment breaks should only be allowed as a means for study participants to recover from severe acute toxicity and/or for intercurrent illness, or due to treatment machine or cyclotron maintenance. To avoid treatment breaks, a photon-based backup treatment plan may be delivered. Any treatment break or delay for other social or logistical reasons will be considered a protocol deviation. Photon-based backup treatment should not exceed 2 days or 10% of the intended dose of radiation, whichever is less. All incidents of treatment breaks and the reasons for any such breaks must be clearly indicated in the treatment record.

4.2 Imaging and Localization Requirements

4.2.1 Patient immobilization will be performed under the supervision of the treating radiation oncologist to allow for a daily reproducible setup individualized for all study subjects.

4.2.2 Radiation therapy treatment planning CT scans will be required to define normal patient anatomy and target volumes. The treatment planning CT scan should be acquired with each subject in the same position and using the same immobilization device as will be used for treatment. The treatment planning CT scan, however, will be performed without the use of a scrotal shielding device in place so that the CT image quality is unaltered. Treatment planning will be done using a 3D-based CT treatment planning system. The treatment planning CT scan must provide images and encompass all tissues to be irradiated, with a slice thickness of ≤ 0.5 cm. Images will be acquired from the top of the T8 vertebral body cranially to the mid femurs caudally. Patients being treated to the pelvic region should undergo their treatment planning CT scans and daily treatments with a full bladder (optional). These patients may be instructed to drink 16-32 ounces of fluid 30-60 minutes prior to simulation and treatment.

4.2.3 All patients will receive radiation therapy to the para-aortic region to allow for coverage of radiation dose to the para-aortic lymph nodes, as this nodal region is the most likely site of microscopic disease and tumor recurrence among patients with early-stage seminoma. At the discretion of the treating radiation oncologist, patients may also be treated to the ipsilateral pelvic region to allow for coverage with radiation dose to the common iliac and internal iliac lymph nodes, as this nodal region is also a known site of disease recurrence in this patient population. For patients with Stage IIA and IIB disease, the target volume *must* include the para-aortic lymph nodes and the ipsilateral pelvic region.

4.2.4 Contrast: Intravenous contrast may be administered during simulation at the discretion of the treating radiation oncologist to better define patient vasculature and anatomy. If intravenous contrast is used, for treatment planning purposes, a non-contrast treatment planning CT scan prior to contrast administration should be obtained. Thereafter, contrast may be administered, and the subsequent CT simulation image set may be acquired.

4.3 Target Contouring and Planning

4.3.1 Gross Tumor Volume (GTV_{nodal}), defined as known measurable nodal disease, will only be employed in this study for patients with Stage IIA or IIB disease. For patients with Stage IIA or IIB seminoma, the GTV_{nodal} will encompass nodal disease as delineated on abdominal pelvic CT.

4.3.2 The Clinical Target Volume (CTV), defined as the region of potential microscopic disease, will include the lymph nodes that drain the involved site(s) of interest, the corresponding vessels, and adjacent perinodal soft tissue. $CTV_{para\text{-}aortic}$ and CTV_{pelvis} will be delineated by the treating radiation oncologist as follows:

- $CTV_{para\text{-}aortic}$
  - $CTV_{para\text{-}aortic}$ includes relevant lymph node groups (interaorto-caval, precaval, pre-aortic, paracaval, and para-aortic) that drain the involved site (estimated using vascular structures of the aorta and inferior vena cava) and adjacent perinodal soft tissue.
  - Cranial border: contouring of nodal and perinodal soft tissues should terminate caudally to the T10-T11 intervertebral space to allow for adequate coverage of the retrocrural lymph nodes.
  - Caudal border: contouring of nodal and perinodal soft tissues should terminate at the level of the bifurcation of the aorta into the right and left common iliac arteries. If this bifurcation occurs cranial to the L5-S1 intervertebral space, at the discretion of the treating physician, based on contouring of the right and left common iliac vessels, the $CTV_{para\text{-}aortic}$ caudal border can be extended caudally to the L5-S1 intervertebral space.
  - Left renal hilum: for patients with left-sided tumors, $CTV_{para\text{-}aortic}$ also should include the branch point from where the left renal vein originates from the inferior vena cava, with contouring extending distally from this branch point to a maximum of 8 cm along the course of the left renal vein, so that $CTV_{para\text{-}aortic}$ extends into the left renal hilum.
  - $CTV_{para\text{-}aortic}$ is defined as the defined vessels + 1.0-1.5 cm [posteriorly, laterally, superiorly, inferiorly] and 1.5-2.0 cm [anteriorly] (for a total depth of approximately 3.0-3.5 cm anterior to the vertebral bodies) to account for perinodal tissues.
- $CTV_{para\text{-}aortic + pelvis}$
  - CTV_{pelvis} includes relevant lymph node groups that drain the involved site (estimated using vascular structures of the internal iliacs, external iliacs, and common iliacs) and adjacent perinodal soft tissue. CTV_{pelvis} is defined as the defined vessels + 1.0 cm [anteriorly, posteriorly, laterally, superiorly, inferiorly] to account for perinodal tissues.
  - $CTV_{para\text{-}aortic + pelvis}$ also includes interaorto-caval, precaval, pre-aortic, paracaval, para-aortic, and right and left common iliac lymph node groups, such that $CTV_{para\text{-}aortic + pelvis}$ is one contiguous structure that encompasses $CTV_{para\text{-}aortic}$, so as to avoid treatment overlap of the two regions being targeted.
  - Cranial border: contouring of nodal tissues should terminate caudally to the T10-T11 intervertebral space, as per the cranial border of the $CTV_{para\text{-}aortic}$ field.
  - Caudal border: contouring of inguinal nodal tissues should terminate at the obturator foramen. At the discretion of the treating radiation oncologist, the caudal border may be raised more cranially, such that contouring of inguinal nodal tissue may be excluded and contouring of external iliac nodal tissues may terminate when the iliac vessels coarse over the pubic symphysis or at the top of the femoral heads (a boney landmark for the inguinal ligament).
- CTV_{nodal}

- The CTV_{nodal} volume is defined as GTV+ 0.2-0.5 cm [anteriorly, posteriorly, laterally, superiorly, inferiorly], with the variable margin added dependent on physician discretion.

- CTV Exclusions
  - Bone, intraperitoneal small bowel, large bowel, pancreas, and other normal adjacent structures outlined in protocol section 4.4 should be excluded from each CTV volume being targeted.
  - CTV_{pelvis} should not extend outside of the true pelvis.
- CTV_{nodal} should not extend outside the $CTV_{para\text{-}aortic}$ or the CTV_{pelvis}
- Planning Target Volume (PTV) Review
  - A review volume called an PTV will be created in order to facilitate the coverage evaluation process. PTV is defined as CTV + 0.3-1.0 cm [anteriorly, posteriorly, laterally, superiorly, inferiorly], with the variable margin added dependent on range uncertainties and setup error.

4.3.3. Treatment Planning: After delineating the CTV, margins are added to the CTV by means of enlarging the beam aperture both laterally and cephalo-caudally in the beam's eye view, and the distal and proximal margins are calculated and added. These margins cover the uncertainty due to range, set-up errors, and lateral fall off of the irradiation fields. A compensator is created to control the dose deposition distally. Smearing and border smoothing will be routinely calculated and applied. Compensator editing may be necessary to deliver the dose as prescribed by the physician. All the above parameters are calculated and recorded by the treatment planner under physicist supervision and are subject to discussion with the treating physician, as appropriate. All these parameters can be altered by the radiation oncology team, as appropriate, in order to deliver the prescribed dose and maintain paring of the organs at risk (OAR).

4.3.4 Conventional photon radiation therapy backup plans may be devised. The prescription for such plans is as specified above and administered using the same scheme. The planning target volume expansion margins will be defined on case-by-case basis from the CTV volumes. The lateral margins will be defined by the multileaf collimator and will also be defined on a case-by-case basis.

4.4 Normal Structures

4.4.1 Bilateral kidneys – will be outlined on every slice. The left renal hilum will be outlined at the discretion of the treating radiation oncologist for cases in which patients have left-sided primary tumors.

4.4.2 Bladder – will be outlined on every slice, including the portion inferior to the planning target volume.

4.4.3 Large Bowel – large bowel will be outlined on every slice as individual loops of bowel, including the portion inferior to the planning target volume.

4.4.4 Small Bowel – small bowel will be outlined on every slice as a compartment of potential space in which the small bowel may occupy, including the portion superior and inferior to the planning target volume.

4.4.5 Rectum – will be outlined on every slice, including the portion inferior to the planning target volume.

4.4.6 Stomach – will be outlined on every slice, including the portion superior to the planning target volume.

4.4.7 Pancreas – will be outlined on every slice, including the portion superior to the planning target volume.

4.4.8 Contralateral testicle – when possible, will be outlined on every slice, including the portion inferior to the planning target volume.

4.4.9 Normal Tissue Constraints

- The mean dose to the bilateral kidneys should be ≤ 18 Gy (RBE).
- The maximum dose to the spinal cord should be ≤ 36 Gy (RBE).
- The maximum dose to the small bowel should be ≤ 45 Gy (RBE).

4.4.10 As neutron contamination can result in the delivery of radiation dose to the contralateral uninvolved testicle, at the discretion of the treating radiation oncologist, study subjects may be offered the use of a scrotal shielding clamshell-type device for each treatment fraction to reduce the scatter dose of radiation to the contralateral uninvolved testicle.

4.5 Treatment Duration

Proton radiation therapy will be delivered over 10 to 20 treatment days and in most instances be completed within 2.0 to 4.0 weeks from the start of treatment. This may be extended if subjects require a break from treatment. Criteria for a treatment break would include any non-hematologic Grade ≥ 3 toxicity.

4.6 External Beam Equipment and Beam Delivery

Treatments will be administered at the University of Pennsylvania Roberts Proton Facility and The Francis H. Burr Proton Beam Therapy Center at Massachusetts General Hospital.

4.7 Quality Assurance

4.7.1. Daily portal films or daily online radiographic imaging will be performed during radiation therapy. The position of the bony landmarks will be compared with DRRs (digitally reconstructed radiographs). Weekly port films will be taken for all patients.

4.7.2. Coronal, transverse, and sagittal CT slices with overlaid dose representing the total dose to be delivered should be available.

4.7.3. Dose volume histograms (DVH) will be available.

4.7.4 A multilevel Physics Check will be performed based on departmental protocol from the time of the simulation to treatment and will include: imaging data integrity, dose calculation accuracy, compensator check, MU calculation, and electronic records accuracy.

4.8 Proton planning

4.8.1 For proton planning, either posterior (PA), posterior oblique, or anterior-posterior (AP-PA) field arrangements are acceptable. The minimum number of beams necessary to meet the required treatment parameters should be used.

4.8.2 Uniform dose distribution by means of passive double scattering, pencil beam, spot scanning, uniform scanning, intensity-modulated proton therapy, or other delivery methods are acceptable.

4.8.3 Aperture, distal, proximal margin, smearing and smoothing will be determined for each case and recorded under physicist supervision.

5 Chemotherapy

5.1 Chemotherapy as Primary Therapy

No chemotherapy is to be administered in the adjuvant setting during the primary protocol study treatment period.

5.2 Chemotherapy as Salvage Therapy

If a patient is found to have clinical or radiographic evidence of disease recurrence or a worrisome radiographic abnormality, pathological assessment is strongly encouraged, but not required, to confirm disease recurrence. The pathological confirmation of disease recurrence at any site or the initiation of salvage therapy will be considered a failure of protocol treatment, and such patients will be removed from study and followed for late effects and survival. Subsequent management and salvage therapy of patients who have failed protocol treatment will be left to the discretion of the treating oncologist, with the treatment modality and treatment regimen dictated by the location and extent of tumor recurrence at the time of evaluation.

6 Study Procedures

This study will be performed jointly at the University of Pennsylvania and Massachusetts General Hospital (MGH) The coordinating center will be the University of Pennsylvania. When a patient is being evaluated for this study, the study coordinator from Massachusetts General Hospital will contact the study coordinator at Penn to determine if an enrollment slot for this study is available. The study coordinator from the DOD will call the coordinating center to refer the patient and schedule an appointment with a physician. At the time of study enrollment and determination of eligibility, the study coordinator from MGH will contact the study coordinator at Penn to reaffirm that a slot is available. The study coordinators at Penn and MGH will have a formal teleconference monthly (or as needed) to discuss study progress and current toxicities. At any time a grade 3 toxicity has been observed, communication between the study clinicians will take place within 5 business days. A formal teleconference including the study coordinators and PIs at Penn and MGH will take place on a monthly basis (or as needed) to review study progress. The decision to proceed from one dose level to the next will be made at the time of a formal PI and study coordinator teleconference.

6.1 Study Parameters Table

	Eligibility/ Pre-Treatment	Weekly During Radiation Therapy	Weekly for 8 Weeks Following Radiation	90 Days From the Start of Treatme	Q6 Months for Year 2 Post Treatment	Q12 Months for Years 3-5 Post Treatment

		Treatment	Therapy Completion	nt and Then Q3 Months for Year 1 Post Treatme nt		(Approx.)
History and Physical Examination	X	X***		X	X	X
Performance Status Assessment	X	X		X	X	X
EORTC QLQ-C30*	X	X	X[1]	X[2]	X[3]	X[4]
Testicular Cancer Patient Diary Card*	X	X	X[1]			
EuroQol EQ5D*	X	X	X[1]	X[2]	X[3]	X[4]
Chest X-ray or CT Chest	X[6]			X	X	X
Abd/ Pelvic CT Scan or Abd/Pelvis MRI	X [6] (abdominal and pelvic CT scan)			X (once annually; not required for patients receiving pelvic radiation therapy)	X (once annually; not required for patients receiving pelvic radiation therapy)	X (once for year three; not required for patients receiving pelvic radiation therapy)
MRI Brain and/or Bone Scan	X (if clinically indicated)					
Toxicity Assessment	X	X		X	X	X

	Eligibility/ Pre-Treatment	Weekly During Radiation Therapy Treatment	Weekly for 8 Weeks Following Radiation Therapy Completion	90 Days From the Start of Treatment and Then Q3 Months for Year 1 Post	Q6 Months for Year 2 Post Treatment	Q12 Months for Years 3-5 Post Treatment

				Treatment		
Semen Analysis (recommended, but not required)	X[5]			X (at one year only)		
Complete Blood Count	X[5]	X[8]		X	X	X
Follicle-stimulating Hormone and Luteinizing Hormone	X[5]					
Lactate Dehydrogenase	X[5]			X	X	X
Human Chorionic Gonadotropic	X[5]			X	X	X
Alpha-fetoprotein	X[5]			X	X	X
testosterone	X[5]			X[7]	X[7]	X[7]

Follow up visits may be scheduled +/- 4 weeks
* All procedures **not** marked with "*" are standard of care procedures.
***During weekly treatment, a pertinent physical exam may be performed

[1] Forms may be obtained 1 day prior or 3 days post treatment
[2] Forms may be obtained +/- 1 week
[3] Forms may be obtained +/- 2 weeks
[4] Forms may be obtained +/- 1 month
[5] Must be obtained before radiation treatment begins. If these values are available pre-operatively, they will be recorded.
[6] Must be performed approximately within 6 weeks of study
[7] Testosterone assessment is required only at pre-treatment, 6 month, 2 year, and 5 year follow up visits.
[8] Complete Blood Count (CBC)- this lab will be optional, weekly during treatment.

6.2 Evaluation and Follow-up

6.2.1 Timing of Assessments: all subjects will be evaluated prior to initiation of treatment, weekly during the course of the primary protocol study treatment period and for eight weeks following the completion of proton beam radiation therapy, and 90 days following the start of radiation therapy by the treating radiation oncologist. Patients will be evaluated every three months during the first year following radiation therapy, approximately every six months during the second year following therapy, and annually for years three to five following therapy. Effort will be made to follow subjects beyond five years to assess for toxicity related to radiation treatment and survival, either by the treating radiation oncologist or a referring physician.

6.2.2 Pre-treatment: after determining eligibility, pre-treatment patient assessment will include history and physical examination, performance status assessment (Appendix C), toxicity assessment (as

per protocol section 6.2.5), and quality of life assessment with EORTC QLQ-C30 (Appendix D), Testicular Cancer Patient Diary Card (Appendix E), and EuroQol EQ-5D (Appendix F). Patients will also undergo pre-treatment laboratory evaluation to include complete blood count, semen analysis, follicle-stimulating hormone level, luteinizing hormone level, testosterone, and serum creatinine or creatinine clearance. **Patients who object to the semen anaylsis or are not covered by their insurance company to have the analysis will not be excluded from the study. If the semen analysis is performed, an optional DNA fragmentation will also be performed from the semen analysis if covered by the patients insurance. This portion of the analysis will only be performed at the Coordinating Center, University of Pennsylvania, and not at participating sites.**

6.2.3

6.2.4 During Radiation Therapy: each patient will be assessed at least weekly during radiation therapy treatment. Each assessment will include a pertinent physical examination, performance status assessment (Appendix C), toxicity assessment (as per protocol section 6.2.5), laboratory evaluation to include complete blood count (optional), and quality of life assessment with EORTC QLQ-C30 (Appendix D), Testicular Cancer Patient Diary Card (Appendix E), and EuroQol EQ-5D (Appendix F).

6.2.5 Immediately Following Radiation Therapy: each patient will be assessed weekly for the first eight weeks following the completion of radiation therapy. Each assessment will include quality of life assessment with EORTC QLQ-C30 (Appendix D), Testicular Cancer Patient Diary Card (Appendix E), and EuroQol EQ-5D (Appendix F). At the discretion of the treating radiation oncologist, these weekly assessments may be performed in the physician clinic, via Internet-based surveys, via questionnaires from the patient home, or over the phone.

6.2.6 Toxicity Assessment: Patients will be treated and followed for a minimum of 90 days after the start of radiation treatment to determine safety (acute toxicity). The Common Toxicity Criteria v4.0 (Appendix A) [73] will be used to report acute adverse events that occur within 90 days of treatment initiation and late adverse events that occur after 90 days of protocol therapy initiation for up to 5 years.

6.2.7 Years 1-5 Post Treatment: each patient will be assessed 90 days following the start of radiation therapy and then every three months for one year, every six months during the second year following therapy, and annual for years three to five or longer following therapy. Each follow-up assessment will include an interval history and physical examination, performance status assessment (Appendix C), toxicity assessment (as per protocol section 6.2.5), quality of life assessment with EORTC QLQ-C30 (Appendix D) and EuroQol EQ-5D (Appendix F), and laboratory evaluation with serum creatinine and/or creatinine clearance, complete blood count, testosterone (at specified timepoints), lactate dehydrogenase, human chorionic gonadotropic, and alpha-fetoprotein. Additionally, semen analysis will be obtained 12 months following the completion of therapy. A chest x-ray or CT Chest will be obtained at each patient follow-up visit during years one through five following the completion of therapy. In patients with continued follow-up beyond five years, chest x-rays or CT Chest thereafter will be performed at the discretion of the evaluating physician. For patients not receiving pelvic radiation therapy, follow-up assessments will include a CT abd/pelvis or MRI abd/pelvis scan annually for the first three years following the completion of therapy.

- Toxicity assessment from years five through 15 will include inquires of any renal disease, cardiac disease, and second malignancies that the study participants may have been diagnosed with since the completion of the primary protocol study treatment period. If a patient has been

diagnosed with a second malignancy, details of the disease primary location, histology, staging, treatment regimen received, and disease status should be obtained. Copies of pertinent pathology reports, imaging reports, and treatment details should also be obtained.

7 Statistical Plan

This is a study of proton therapy for patients with stage I, IIA, and IIB testicular seminoma. Feasibility (i.e., *logistics* of proton planning, dosimetry, scheduling and deliver) was established prior to this trial, based on 9 patients treated at PENN with proton therapy to the study region of interest for seminoma or other malignancies. All 9 patients met the feasibility criteria, as documented by the Director of Clinical Research, John Plastaras, MD, PhD. Thus, the feasibility endpoint has been sufficiently established and this trial will not include early termination for feasibility logistics of protons.

7.1 Phase II Study

7.1.1 Design and Objectives.

- In patients receiving adjuvant radiation therapy in MRC TE19, 30% reported moderate to severe lethargy at 3 weeks from starting treatment as compared to 8% in those treated with single-dose carboplatin. At 3 to 4 weeks (approximately day 25), 24% of radiation-treated and 7% of carboplatin-treated patients reported moderate to severe lethargy. We will monitor the rate of moderate to severe lethargy **at 3 weeks**, as reported on the patient symptom diary card.
- Because proton therapy is expected to spare normal tissues, the rate of moderate to severe lethargy should be less than experienced with photon therapy. It is desirable for proton radiation to yield a reduced rate of lethargy similar to single-dose carboplatin. Our hypothesis is that the 3-week lethargy rate will be less than <35%, which approximates the rate observed with photon therapy. This hypothesis holds for patients with Stage I, IIA, or IIB seminoma. The study is powered to detect a reduction in the lethargy rate to 20%. A single stage phase II design will be followed.

7.1.2 Endpoints

- Acute Toxicity is defined as any Grade 3 or higher non-hematologic toxicity that occurs within 90 days following the start of proton therapy. NCI Common toxicity criteria (CTC Version 4.0) grades will be employed (Appendix A).
- Late Toxicity is defined as any Grade 3 or higher non-hematologic toxicity that occurs beyond 90 days following the start of proton therapy. NCI Common toxicity criteria (CTC Version 4.0) grades will be employed (Appendix A).
- Clinical Efficacy: Time to local failure will be defined as the time from the start of radiation therapy to local failure. Time to distant failure will be defined as the time from the start of radiation therapy to distant failure. Relapse-free survival will be defined from the time from the start of radiation therapy to any failure or death. Cause-specific survival will be defined from the time from the start of radiation therapy to death due to seminoma. Overall survival will be

defined from the time from the start of radiation therapy to death due to any cause or last patient follow-up. These outcomes will be summarized at the end of the phase II study.

- Quality of Life Measures: EORTC QLQ-C30, Testicular Cancer Patient Diary Card, and EuroQol EQ-5D will be evaluated at multiple times during and post-radiation. We hypothesize that compared to baseline, quality of life measures will worsen during and immediately post-radiation and will then gradually improve after radiation. These deficits are expected to be less than those seen for photon treated patients and the time course to return to baseline should be shortened. These outcomes will be summarized at the end of the phase II study.
- Moderate to Severe Lethargy will be scored on the Testicular Cancer Patient Diary Card (Appendix E). The rate of moderate to severe lethargy at week 3 will be evaluated. This outcome will be summarized at the end of the phase II study.

7.1.3 Rules for Early Termination for Acute Toxicity.

- Bayesian probability calculations will be employed to define early termination rules for safety. The table below indicates termination rules after groups of patients have been treated, although the Bayesian probability of an event may be calculated at any time during the trial. Thousands of patients with certain types of cancer have undergone radiation therapy with protons. Thus, we will assume a modest amount of "prior" feasibility and safety data for protons delivered at the *standard radiation dose* for our Bayesian calculations. We will assume prior information equivalent to that of six treated patients, which is commonly required to establish safety in a standard 3+3 phase I trial design.
- Acute Toxicity. When examining the rate of acute toxicity from adjuvant radiation therapy in recent efficacy trials (4, 17), grade 3 acute toxicity differed between hematologic and non-hematologic (e.g. dyspepsia and nausea/vomiting) endpoints. In the MRC TE 18 trial, no patient experienced Grade 3 or higher thrombocytopenia, and Grade 3 dyspepsia was not reported. In the MRC TE 19 trial, <1% experienced Grade 3 or higher thrombocytopenia, and ~20% of patients experienced Grade 3 or higher Nausea/Vomiting. Because proton therapy is expected to spare normal tissues, an acute non-hematologic Grade 3 toxicity rate <20% is considered acceptable. We will assume a beta (1,5) prior, which is information equivalent to acute toxicity in one of six treated patients. If the number of patients with an acute toxicity is *greater than or equal to* the number in the table below, then termination will be considered, as it is likely that the toxicity rate is >20%, as noted by the Bayesian posterior probabilities.
  We will monitor the number of patients with acute toxicity several times during the accrual phase.

Bayesian Rule for Acute Toxicity									
Patients treated and followed 90 days	3	6	12	18	24	30	36	42	48
Patients who experience acute toxicity	2	2	4	6	7	9	10	12	14
Posterior Prob[acute toxicity rate >20%]	0.80	0.62	0.76	0.84	0.79	0.85	0.82	0.87	0.91

Action	Terminate enrollment

7.1.4 Statistical Analyses.

- Acute and Late Toxicity: All acute and late toxicities will be graded by CTC Version 4.0 and tabulated. Toxicity rates and 95% confidence intervals will be calculated.
- Analysis by Radiation Therapy Type: all subjects enrolled in this study will be followed and assessed for all endpoint analyses. However, a separate analysis may be performed for subjects who were treated with photon therapy as a portion of their planned course of radiation therapy.
- Moderate to Severe Lethargy: The 3-week rate and 95% CI will be computed. A one-sample one-sided chi-square test will be performed to test the null hypothesis that the lethargy rate is 35% (same as photon) versus the alternative hypothesis that the rate is reduced to 20%. Patients must have a minimum of 21 days of follow-up to be included. As a secondary analysis, the 3-week lethargy rate and 95% exact CI will be computed for each disease stage. A Fisher's exact test will be employed compare these rates, to determine whether lethargy rates significantly differ by disease stage.
- Clinical Efficacy: Time to local failure and time to distant failure will be estimated by the cumulative incidence method within a competing risks framework (competing risks are local failure, distant failure, death). Relapse-free survival, cause-specific survival, and overall survival will be estimated by the Kaplan-Meier method. Median values and 95% confidence intervals will be calculated.
- Quality of Life: Longitudinal quality of life measurements will be examined by plots of mean± SD over time. Repeated measures ANOVA or linear mixed effects models (to assess the impact of fixed effects covariates), will be used to analyze the repeated observations. Piecewise linear models may be required to fit non-linear trends, as expected for the initial decline and then gradual increase in quality of life measures.

7.2 Sample Size/Power and Trial Duration

A maximum of 59 patients may be enrolled, in order to accrue 56 evaluable patients, assuming that the attrition rate (i.e., missing patient symptom diary at 3 weeks) will be at most 5%. With 56 evaluable patients, there will be 80% power for a chi-square test at one-sided 5% type I error, to test the null hypothesis that the rate of moderate to severe lethargy at 3 weeks is $\geq$35% versus the alternative hypothesis that the rate is $\leq$20%. To complete accrual for the phase II portion of the trial, the entire trial should be active for six years.

8 Safety and Adverse Events

The investigator or research staff will be responsible for detecting, documenting and reporting all events that meet the definition of an adverse event (AE) or serious adverse event (SAE) as defined in this protocol.

8.1 Definitions

8.1.1 Adverse Event

- An **AE** is any unfavorable and unintended symptom, sign (including abnormal laboratory findings), illness/disease (new or exacerbated), or experience that develops or worsens in severity temporally associated with the use of the investigational agent/device/procedure.

Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal.
- Is associated with a SAE.
- Is associated with clinical signs or symptoms.
- Leads to additional treatment or to further diagnostic tests.
- Is considered by the investigator to be of clinical significance.

- AEs are not to include:
  - Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition leading to the procedure is an AE.
  - Situations where an untoward medical occurrence did not occur (elective and/or convenience admission to a hospital).
  - Anticipated day-to-day fluctuation of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen in grade or severity.
  - The disease/disorder that is being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

8.1.2 Serious Adverse Event

- Adverse events are classified as serious or non-serious. An **SAE** is any medical occurrence that at any dose and:
  - Is fatal.
  - Is life-threatening.
    - Note: the subject was at risk of death at the time of the event, not an event that hypothetically might have caused death if it were more severe.
  - Required hospitalization or prolongs hospital stay (hospitalization signifies, in general, that the subject has been detained [at least an overnight stay] at the hospital or emergency department for observation/treatment that would not have been appropriate in a physician's office or outpatient setting).
    - Note: hospitalization for elective treatment, diagnostic purposes or a pre-existing condition that did not worsen from baseline in not considered an AE or SAE. Hospitalization/prolong hospitalization to allow for study efficacy assessment is not an SAE.
  - Results in persistent or significant disability or incapacity.
    - Note: a substantial disruption of a person's ability to conduct normal life functions. This is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
  - Lead to a congenital anomaly or birth defect.
  - Result in an important medical event.

8.1.3 Clinical Laboratory and Other Safety Assessments

- Any abnormal laboratory test result (e.g. hematology, clinical chemistry, urinalysis) or other safety assessment (e.g. ECGs, radiological scans, vital signs), including those that worsen from baseline and are felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AE or SAEs if they meet the definition of an AE, as

defined above. However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be recorded as AEs or reported as SAEs.

8.2 Radiation Toxicities

8.2.1 Radiation therapy side effects are typically divided into acute, those that occur acutely (during radiation and up to three months after radiation), and late (greater than three months post-radiation) toxicities. Common acute radiation side effects include fatigue, skin irritation or erythema, nausea, emesis, acid-reflux symptoms, diarrhea, and hematologic depressions. Typically, these side effects are mild and can be controlled with medications. Late side-effects that are unlikely to occur may include permanent sterility or infertility, peptic ulcer disease, change in bowel patterns, small or large bowel obstruction, biliary stricture, liver damage, and decreased renal functioning. Another rare but serious late side effect is the development of secondary tumors. It is hoped that proton radiation therapy will substantially reduce both acute and late side effects by reducing the amount of normal tissue that is irradiated.

8.2.2 Acute and late radiation effects will be defined according to section according to section 7.1.2. Acute radiation toxicity will be scored up to 90 days from initiation of radiation therapy, for which CTCAE 4.0 (Appendix A) will be employed. Late radiation effects will be scored beyond 90 days from the start of radiation therapy at timepoints delineated according to the follow up schedule outlined in section 6.2.1 and will also be evaluated using CTCAE 4.0 (Appendix A).

8.3 Assessing and Recording Adverse Events

All Adverse Events and Serious Adverse Events will be assessed using NCI Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE 4.0) [Appendix A].

8.4 Reporting of Serious Adverse Events

Adverse Event Reporting Period: the study period during which Adverse Events must be collected and Serious Adverse Events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up (off study at progression). This protocol will begin assessment of AEs and SAEs following the first treatment fraction of radiation therapy. Therefore, only treatment emergent events will be evaluated.

8.5 Institutional Review Board (IRB) Notification by Investigator

All events meeting the Penn IRB Standard Operative Procedure for Unanticipated Events posing risks to subjects or others will be reported to the IRB as follows:

Unanticipated problems are:
(1) Unforeseen; and (2) indicate that participants are at increased risk of harm. The IRB requires investigators to submit reports of the following problems within 10 working days **with one exception**: an Adverse Event (regardless of whether the event is serious or non-serious, on-site or off-site) that occurs any time during or after

the research study, which in the opinion of the Principal Investigator is both unexpected and related to research procedures.

Note: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; an event is "related to the research procedures" if the event is deemed probably or definitely related.

The **one exception** for prompt reporting within 10 days applies to death of a research participant. If the adverse event involved death as unforeseen and indicates participants or others are at increased risk of harm, a submitted report will be required within three working days.

8.5.1 MGH/DOD Reporting

It is the responsibility of the participating investigator to notify the Principal Investigator and the local IRB of all SAEs. The participating investigator must report each SAE the Principal Investigator within 24 hours of learning of the occurrence. The participating center will report the event to the coordinating center at: Brittany Koons (215) 662-6418 or brittany.koons@uphs.upenn.edu. Within 24-28 hours, the participating investigator must provide follow-up information on the SAE which shall include if the issue has been resolved or is continuing, treatment that was given and whether the subject will continue with participation. MGH and DOD will submit all appropriate correspondence regarding SAEs to their respective IRBs.

All non-serious adverse events will be reported to the Principal Investigator via the toxicity care report forms. Further reporting details can be found in the accompanying manual of operating procedures.

8.6 Data and Safety Monitoring Committee (DSMC) Notification by Investigator

Any expected, unrelated event that is a Grade 3 or higher should be reported to the DSMC within 10 days. All unexpected deaths or deaths related to the study agent or device need to be reported to the DSMC within 24 hours. All other AEs should be reported within 30 days of knowledge.

Any SAEs, regardless of site, are to be reported to the Principal Investigator within 24 hours via telephone or email. For SAEs that occur at MGH and DOD, the site will submit documentation to their IRB according to their regulations in addition to submitting documentation to the Coordinating Center who will then submit to the IRB (as required) and to the DSMC in the manner specified above.

8.7 Safety Event Notification of Enrolling Sites

The lead institution will maintain documentation of all adverse event reporting and will be responsible for communicating all serious adverse events to all participating sites. The Principal Investigator is responsible for distributing all safety reports to all participating institutions for their review and subsequent submission to their IRB if required.

9 Medical Monitoring

9.1 Medical Monitor

9.1.1 It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see protocol section 12). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

9.1.2 The Medical Monitor (MM) will be Stephen Keefe, MD. Because of Stephen Keefe, MD's background and experience in the treatment of patients with seminoma, he is an appropriate MM for this study. In this role, he will be given a report to review that will include all AEs, including grading, toxicity assignments, dose modifications, appropriateness of dose escalation, and all other safety data and activity data observed in the ongoing clinical trial, along with discussing relevant animal and toxicology studies and similar investigational agents. The MM may recommend reporting of adverse events and relevant safety data not previously reported and may recommend suspension or termination of the trial. The Principal Investigator and the study coordinator will meet with the MM quarterly (or as needed) in person or via email. The MM will receive the report of the study's progress one week before the meeting. This report will include information from MGH, DOD and UPENN sites. Serious and unexpected issues will be handled on an ad hoc basis through calls or e-mail. Documentation of MM activity will be maintained in the study specific Regulatory Binder. Copies of an MM report requiring action on the part of the Principal Investigator to protect subject safety or study integrity must be submitted to the DSMC within 10 business days. Meetings that are held between the Medical Monitor and the PI will be recorded by the study coordinator.

9.2 Abramson Cancer Center's Internal Data and Safety Monitoring

9.2.1 Data and Safety Monitoring Committee

- The Abramson Cancer Center DSMC is charged with the responsibility of reviewing all SAEs, deviations, and Medical/Safety Monitoring reports for all cancer-based protocols conducted at the University of Pennsylvania. The DSMC reviews these document and data on a monthly basis and makes recommendation necessary to ensure subject safety and study integrity. The Department of Compliance and Monitoring (DOCM) will monitor and audit the progress and conduct of all cancer-based studies in accordance with their National Cancer Institute-approved Institutional Data and Safety Monitoring Plan.

9.2.2 Protocol Deviations/Exceptions

Occasionally, the investigator may need to deviate from the approved protocol. Deviations are categorized as reportable and non-reportable. Reportable deviations may be urgent or not. Urgent deviations may occur on the spot as necessary to protect the safety of a study subject and do not allow enough time for reporting in advance. However, they must be reported as soon as possible.

A one time, **intentional** action or process that departs from the IRB and CTSRMC approved study protocol, intended for **one** occurrence. If the action disrupts the study progress, such that

the study design or outcome (endpoints) may be compromised, or the action compromises the safety and welfare of study subjects, **advance** documented IRB and DSMC approval is required
A one time, **unintentional** action or process that departs from the IRB and DSMC approved study protocol, involving one incident and **identified retrospectively**, after the event occurred. If the impact on the protocol disrupts the study design, may affect the outcome (endpoints) or compromises the safety and welfare of the subjects, the deviation must be reported to the DSMC within 5 business days and the IRB within 10 business days.

- All deviations from the study protocol will be handled as follows:
  - **Eligibility** - Exceptions from established eligibility criteria will not be allowed. If the investigator believes that an ineligible subject would truly benefit from the protocol therapy and there are no other viable alternatives, then the protocol should be amended to reflect the change in restrictions. There may be situations where the exception from eligibility may not warrant a study amendment (e.g. a necessary test/procedure being a few days outside of the eligibility window, a subject taking a concomitant medication within a recent timeframe, etc.). These exceptions must still be reviewed and approved in advance of enrolling the subject. The IRB must be notified of the planned exception, and a copy of all applicable amended study documents must be sent to the IRB. The planned deviation must also be submitted to the DSMC for evaluation. **Other Reportable** - Deviations that affect the protocol treatment administration (i.e. dose administered, route/method of administration, etc.), dose adjustment schema, stopping rules, modification to follow-up, removal of safety assessments/follow-up visits, accrual goal, or any deviation that may affect the study outcome analysis or study integrity must be approved by the IRB and reviewed by the DSMC.
  - **Non-Reportable** - During the course of a study, there may be times when deviations are outside of the control of the investigator (i.e. a subject not showing up for a study visit, laboratory errors, subject confusion, etc.). These types of deviations are not reportable (unless they occur at a level that impacts any of the reportable categories), but they must be documented in a timely manner to show the impact of the deviation and corrective/follow-up actions that are being taken. Documentation can be in clinic/progress notes or in notes/memos to file. Notes/memos should be signed and dated.
  - **Reporting Deviations/Exceptions** - Reports to the IRB and DSMC will be done via the DSMC website at www.ctsrmc.org. Reportable deviations must also be sent to the study MM (if applicable). Please reference above section.

10 Data Handling and Record Keeping

10.1 Confidentiality

10.1.1 Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subject(s) in this study.
- Who will have access to that information and why.
- Who will use or disclose that information.

- The rights of a research subject to revoke their authorization for use of their PHI.

10.1.2 In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

10.2 Unintentional Disclosure:

Upon discovering that PHI may have been or has been disclosed to anyone not specified in the HIPAA disclosure consent, the investigator will report the disclosure to the Institutional Officer in the Office of Research Compliance and Integrity. The report should contain details about the type of data disclosed and the extent of the disclosure (number of subjects, who received it, etc.).

11 Study Monitoring, Auditing, and Inspecting

11.1 The study Principal Investigator is responsible for ensuring the ongoing quality and integrity of the research study. In addition, this study will be monitored or audited in accordance with Abramson Cancer Center's National Cancer Institute-approved Institutional Data and Safety Monitoring Plan.

11.2 Auditing and Inspecting: the Principal Investigator will permit study-related monitoring, audits, and inspections by the IRB, government regulatory bodies, and University compliance and quality assurance groups of all study-related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The Principal Investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

11.3 Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

12 Ethical Considerations

This study is to be conducted according to United States and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the Principal Investigator and a copy of this decision will be maintained in the study specific Regulatory Binder which contains "Essential Study Documents." In addition, the National Cancer Institute requires all cancer-based studies to have an independent scientific review. This protocol must be reviewed and fully approved by the Clinical Trials Scientific Review and Monitoring Committee (CTSRMC)

prior to enrolling any subjects. Documentation of CTSRMC approval must also be maintained in the study specific Regulatory Binder.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Appendix G for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB and CTSRMC for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject is submitted to any study procedure. This consent form must be signed and dated by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

13 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All University of Pennsylvania investigators will follow the University conflict of interest policy.

14 Publication Plan

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor and Principal Investigator. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

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17 Appendices

Appendix A: Common Terminology Criteria for Adverse Events, Version 4.0

Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0, DCTD, NCI, NIH, DHHS
May 28, 2009 (http://ctep.cancer.gov), Publish Date: June 14, 2010

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Individual Category content listings are available to investigators at http://ctep.cancer.gov, with attention to the following System Organ Classes and CTCAE Adverse Events:

- **General Disorders and Administration Site Conditions:** Karnofsky Performance Score (not CTC but we would like to include/track), Fatigue, Weight Loss, Treatment Related Secondary Malignancy
- **Blood and Lymphatic System Disorders:** Anemia, Blood and Lymphatic System Disorders - Other, Specify
- **Gastrointestinal Disorders:** Nausea, Vomiting, Constipation, Diarrhea, Dyspepsia, Gastric Ulcer, Gastritis, Small Intestinal Obstruction:
- **Renal and Urinary Disorders:** Acute Kidney Injury, Hematuria, Renal and Urinary Disorders - Other Specify (Nocturia: # / Night), Urinary Frequency, Urinary Urgency, Urinary Incontinence, Urinary Retention, Urinary Tract Pain
- **Reproductive System and Breast Disorders:** Azoospermia, Erectile Dysfunction, Ejaculation Disorder:
- **Skin:** Pain of Skin, Skin and Subcutaneous Tissue Disorders - Other, Specify:

Appendix B: American Joint Committee on Cancer Staging System

AJCC STAGING SYSTEM, 7th Edition: TESTIS

pT	**Primary Tumor (pathological staging after radical orchiectomy)**
pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor (e.g., histological scar in testis)
pTis	Intratubular germ cell neoplasia (carcinoma *in situ*)
pT1	Tumor limited to testis and epididymis without vascular/lymphatic invasion; tumor may invade into the tunica albuginea but not the tunica vaginalis
pT2	Tumor limited to testis and epididymis with vascular/lymphatic invasion, or tumor extending through the tunica albuginea with involvement of the tunica vaginalis
pT3	Tumor invades the spermatic cord with or without vascular/lymphatic invasion
pT4	Tumor invades the scrotum with or without vascular/lymphatic invasion
cN	**Regional Lymph Nodes (clinical staging)**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis with a lymph node mass 2 cm or less in greatest dimension; or multiple lymph nodes, none more than 2 cm in greatest dimension
N2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or multiple lymph nodes, any one mass greater than 2 cm but not more than 5 cm in greatest dimension
N3	Metastasis with a lymph node mass more than 5 cm in greatest dimension
pN	**Regional Lymph Nodes (pathological staging)**
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis with a lymph node mass 2 cm or less in greatest dimension and less than or equal to 5 nodes positive, none more than 2 cm in greatest dimension
pN2	Metastasis with a lymph node mass more than 2 cm but not more than 5 cm in greatest dimension; or more than 5 nodes positive, none more than 5 cm; or evidence or extranodal extension of tumor
pN3	Metastasis with a lymph node mass more than 5 cm in greatest dimension

M	Distant Metastasis
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional nodal or pulmonary metastasis
M1b	Distant metastasis other than to non-regional lymph nodes and lungs
S	**Serum Tumor Markers**
SX	Marker studies not available or not performed
S0	Marker study levels within normal limits
S1	LDH < 1.5 × N* (U/l) and hCG < 5,000 mIu/ml and AFP < 1,000 ng/ml
S2	LDH 1.5–10 × N* (U/l) or hCG 5,000–50,000 mIu/ml or AFP 1,000–10,000 ng/ml
S3	LDH > 10 × N* (U/l) or hCG > 50,000 mIu/ml or AFP > 10,000 ng/ml

N* indicates the upper limit of normal for the LDH assay.
AFP = α-fetoprotein; hCG = human gonadotropin; LDH = lactate dehydrogenase

Except for pTis and pT4, extent of the primary tumor is classified by radical orchiectomy. TX may be used for other categories in the absence of radical orchiectomy.

Stage I Testicular Cancer Stage Groupings

Substage	T Stage	N Stage	M Stage	Tumor Marker Stage
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-T4	N0	M0	S0
Stage IS	Any pT/TX	N0	M0	S1-S3 (post orchiectomy)

Stage IIA and IIB Testicular Cancer Stage Groupings

Substage	T Stage	N Stage	M Stage	Tumor Marker Stage
Stage IIA	Any pT/TX	N1	M0	S0-S1
Stage IIB	Any pT/TX	N1	M0	S0-S1

Appendix C: Performance Status Criteria

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

Appendix D: EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix E: Patient Diary Card*

Testicular Cancer Patient Diary Card

Please circle your most appropriate response to each question.
There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

1. Please rate the degree of lethargy or fatigue that you have experienced during the past week:

   None Mild Moderate Severe

2. Please rate the degree of impairment that you have experienced in completing work-related or other activities during the past week:

   None Mild Moderate Severe

3. Please rate the degree of nausea or vomiting that you have experienced during the past week:

   None Mild Moderate Severe

4. Please indicate the number of times that you have had episodes of vomiting during the past week:

   0 1-2 3-4 5+

5. Please rate the degree of diarrhea that you have experienced during the past week:

   None Mild Moderate Severe

6. Please indicate the number of times that you have had episodes of diarrhea during the past week:

   0 1-2 3-4 5+

7. Please indicate how frequently you have needed to take medications to manage your cancer-related symptoms or cancer treatment symptoms during the past week:

   No medication Rarely Often Very frequently

*Adapted from Jones WG, et al (4).

Appendix F: EuroQol EQ-5D

QF Radiation Therapy Oncology Group

EQ 5D

Date form completed ____-____-____

RTOG Study No. Case #

PLACE LABEL HERE

Institution Name Institution No.

Patient Initials RTOG Patient ID

Patient Instructions: Please answer one statement in each group below.

Mobility
Please circle one statement in each group below which best describes your health today.

1 I have no problems in walking about

2 I have some problems in walking about

3 I am confined to bed

Self-Care
Please circle one statement in each group below which best describes your health today.

1 I have no problems with self-care

2 I have some problems washing or dressing myself

3 I am unable to wash or dress myself

Usual Activities
Please circle one statement in each group below which best describes your health today.

1 I have no problems with performing my usual activities

2 I have some problems with performing my usual activities

3 I am unable to perform my usual activities

Pain/Discomfort
Please circle one statement in each group below which best describes your health today.

1 I have no pain or discomfort

2 I have moderate pain or discomfort

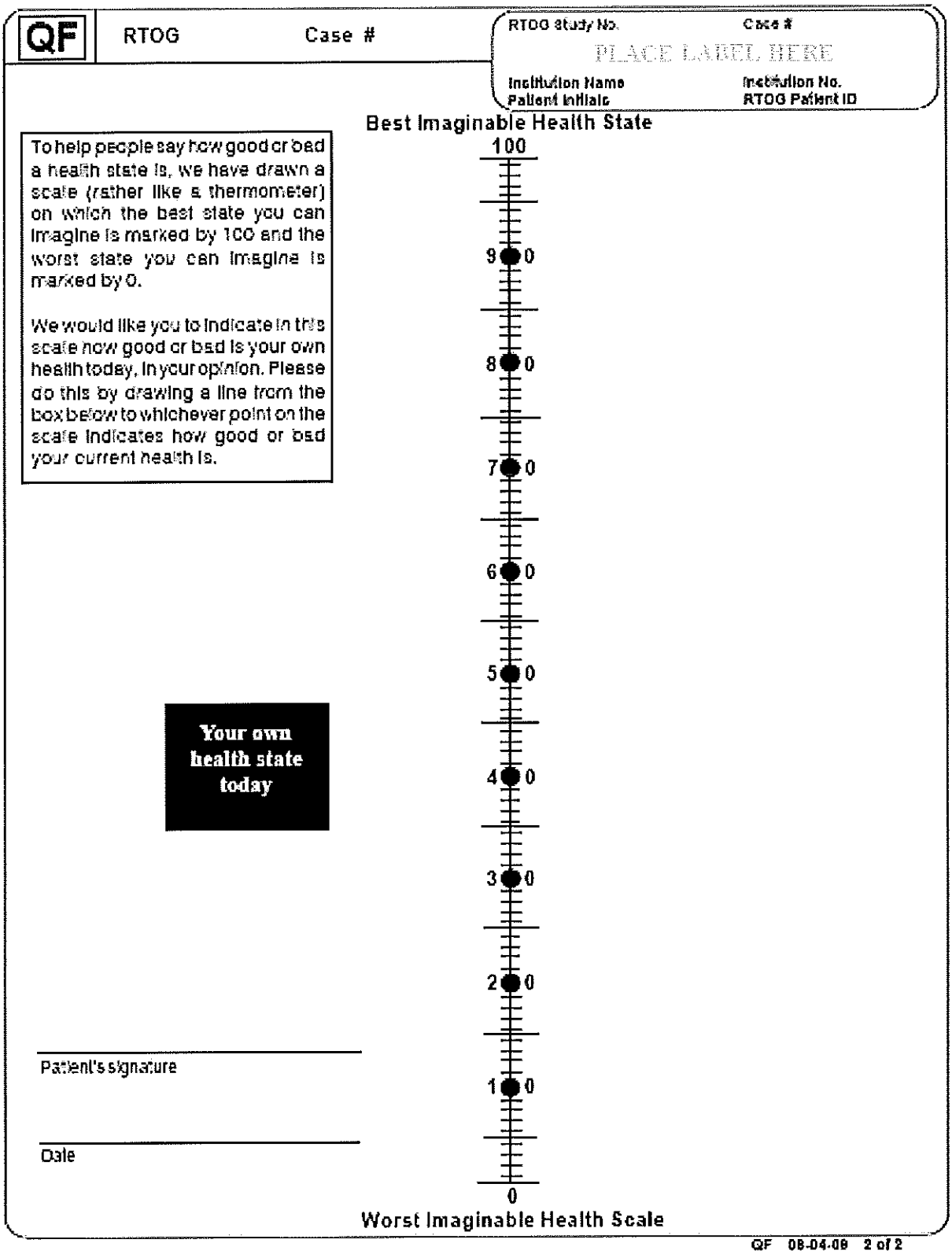
3 I have extreme pain or discomfort

Anxiety/Depression
Please circle one statement in each group below which best describes your health today.

1 I am not anxious or depressed

2 I am moderately anxious or depressed

3 I am extremely anxious or depressed


QF
RTOG
Case #
RTOG Study No.
Case #
PLACE LABEL HERE
Institution Name
Patient Initials
Institution No.
RTOG Patient ID
Best Imaginable Health State
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked by 100 and the worst state you can imagine is marked by 0.
We would like you to indicate on this scale how good or bad is your own health today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your current health is.
100
90
80
70
60
50
40
30
20
10
0
Your own health state today
Patient's signature
Date
Worst Imaginable Health Scale
QF 08-04-08 2 of 2

Appendix G: Subject Informed Consent Form