Abbreviated Title: A Pilot Study of Brachytherapy
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Title: A Pilot Study High Dose Rate Brachytherapy in the Radiation Oncology Branch

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Radiation

PRECIS

BACKGROUND

- High dose rate brachytherapy (HDR) is a challenging technique utilized in many malignancies in order to deliver a high dose of radiation therapy to tumor in a conformal fashion with a rapid dose fall-off with the objective of sparing normal surrounding tissue
- HDR therapy has been targeted to particular subsites as an integral part of either definitive management of palliation for malignancy-related symptoms.

OBJECTIVES

- The primary objective is to determine the quality of high dose rate brachytherapy implants performed in the radiation oncology branch. An implant will be adequate if 90% of the GTV receives 90% of the dose prescribed and 80% of the CTV receives 85% of the prescribed dose. An implant will be inadequate if the above dose limitations are not met.
- To evaluate local control and late toxicity rates following brachytherapy at the NCI ROB
- To increase the flow of oncology participants requiring brachytherapy to the NCI ROB, as these participants lend themselves to special study and have unique educational value for the purpose of educating nurses, medical students, residents, physicists, clinical fellows, and physicians.

ELIGIBILITY

- Participants with cancer who could potentially benefit from the use of high dose rate brachytherapy as a component of their treatment.

DESIGN

- Participants will undergo appropriate work-up and clinical evaluation to determine if high-dose brachytherapy would be beneficial in either primary treatment or palliation of their disease. Participants will be treated with high-dose brachytherapy appropriately sequenced with other modalities in their treatment regimen. This treatment will be administered in accordance with standard radiation oncology practice and per the ABS (American Brachytherapy Society) guidelines.
- The participant's disease status and toxicity outcomes will be documented for a 12-month period at 3 months intervals.

TABLE OF CONTENTS

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary

The primary objective is to determine the quality of high dose rate brachytherapy implants performed in the radiation oncology branch. An implant will be adequate if 90% of the GTV receives 90% of the dose prescribed and 80% of the CTV receives 85% of the prescribed dose. An implant will be inadequate if the above dose limitations are not met.

1.1.2 Secondary

- To evaluate local control and late toxicity rates following brachytherapy at the NCI ROB
- To increase the flow of oncology participants requiring brachytherapy to the NCI ROB, as these participants lend themselves to special study and have unique educational value for the purpose of educating nurses, medical students, residents, physicists, clinical fellows, and physicians

1.2 BACKGROUND AND RATIONALE

1.2.1 High Dose Rate Brachytherapy (HDR)

This protocol is designed to treat participants with cancer who could potentially benefit from the use of high dose rate brachytherapy as a component of their treatment. Brachytherapy, the placement of a radioactive source close to a tumor, is a well-established part of the treatment of many malignancies, both for palliative and definitive applications. High dose brachytherapy is useful in many malignancies in order to deliver a high dose of radiation therapy to tumor in a conformal fashion with a rapid dose fall-off with the objective of sparing normal surrounding tissue. Typically, high dose rate is delivered after the applicators are properly secured, dose calculations are made and a remote afterloader is activated.

Here in the department of radiation oncology, our attending physicians have experience with a Nucletron afterloader in the treatment of cervical cancer, prostate cancer and cholangiocarcinoma and seek to train our residents in these procedures as well.

1.2.2 Selection of HDR Sites

HDR is a challenging technique that can be used alone or combined with external beam therapeutic irradiation in various settings. HDR can be utilized for both definitive cases as well palliative setting for relief of obstructive symptoms or bleeding. HDR can increase the quality of life or provide a potential avenue for re-treatment in those participants already treated with external beam regimens. In this regard, HDR brachytherapy can provide a unique opportunity to study and customize therapy to each individualized participant. Common sites of disease in which the role of brachytherapy has been well described include but are not limited to gynecological tract, (endometrial or cervical cancer), pulmonary, breast and prostate cancer. HDR can be potentially useful in any clinical situation in which a high-dose of radiation is needed for tumor control while potentially sparing sensitive-surrounding critical structures.

For example, gynecologic brachytherapy has proven to be an integral treatment in curing even locally advanced malignancies while allowing sparing of the normal surrounding tissues. Gynecologic brachytherapy has proven very effective in curing even locally advanced malignancies while allowing sparing of the normal surrounding tissues. For cervical cancer, external beam radiation therapy (EBRT) and/or brachytherapy is used in the definitive management of locally advanced malignancies. In large- scale randomized trials, brachytherapy has proven useful in decreasing the risk of local recurrence for certain high-risk endometrial cancers (1). In cases of inoperable endometrial cancer, some reports have shown that this subset of participants can be treated with radiation therapy alone. Additionally, participants with potentially curable recurrences at the vaginal cuff are also possible candidates who benefit from high dose rate brachytherapy. (12)

Lung brachytherapy can be particularly helpful and may provide relatively quick relief to those who are suffering from severe local symptoms (hemoptysis, obstruction as a result of their cancer) secondary to endobronchial component or those who have received the maximum safely tolerated lung dose as a result of previous treatment with external beam radiotherapy (8).

Breast HDR brachytherapy provides a potential benefit to woman who may suffer from diminished cosmesis as a results of their larger breast size or those who are unable to travel the long distances daily for a conventional 6-week course of external radiation therapy. (6)

Prostate HDR has a long history in the radiation oncology branch in which there was significant accrual to the previous "phase II study of MR-guided high dose rate brachytherapy boosts for prostate cancer". Guidelines from this study represent a natural extension of the protocol that we are completing here. In general, clinical evidence has shown that dose escalation in organ confined prostate cancer improves local disease control (13, 14). HDR brachytherapy represents an elegant method of accomplishing dose escalation in prostate cancer (15) but precise evidence guiding dose and fractionation is lacking (16). HDR brachytherapy has three potentially significant roles in the curative intent treatment of prostate cancer: 1) as a boost in conjunction with supplemental EBRT for intermediate and high risk prostate cancer and 2) as monotherapy in low and low intermediate risk prostate cancer and 3) as salvage for localized recurrence after prior external beam irradiation or radical prostatectomy. The use of HDR brachytherapy as a boost as per 1) has significant evidence for the ability to dose escalate by way of hypofractionation with excellent biochemical relapse-free survival rates with a low incidence of severe late genitourinary or gastrointestinal toxicities (16,17) and this has been formalized in the NCCN guidelines. The use of HDR brachytherapy as monotherapy is supported by data from several institutions (18,19) and a recent systematic review (20). Prostate-specific antigen progression-free survival using monotherapy ranged from 79% to 100% and local control from 97% to 100% with low toxicity rates. The use of HDR brachytherapy for localized recurrence while an exciting prospect remains investigational. As a whole, high dose rate brachytherapy is technically complicated but increasingly practiced in the United States with significant heterogeneity in terms of the doses and fractionations being employed. HDR for various body sites has so many advantages over low-dose rate or simple external radiation therapy which include but is not limited to: faster treatment times on an outparticipant basis resulting in less resources utilized on the participant and hospital's behalf, better optimization secondary to the ability to vary dwell time versus low-dose rate therapy and a sharp dose fall-off allowing for decreased dose to adjacent critical organs

We anticipate that the majority of participants treated will fall into one of these aforementioned subsites. However, almost all anatomic subsites have the ability to undergo HDR treatment with the objective of either primary cancer treatment or effective, expedited palliation of symptoms.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Pathologically confirmed malignancy for which high-dose rate brachytherapy is appropriate as a component of their therapeutic regimen.

2.1.1.2 Age ≥ 18 years of age.

2.1.1.3 ECOG performance status of 0, 1, or 2 (see **Appendix B**)

2.1.1.4 Participant must have a primary medical or surgical oncologist in the community or at NCI who is willing to collaborate with the ROB staff in the clinical management of the participant.

2.1.1.5 Participants of childbearing or child- fathering potential must be willing to use a medically acceptable form of birth control, which includes abstinence, while they are being treated on this study.

2.1.1.6 Site-specific inclusion criteria (any one or more of the following):

2.1.1.6.1 Gynecologic cancers

2.1.1.6.1.1 Endometrial cancer

- Participants at a higher risk of recurrence (because of either grade, myometrial invasion, lymphatic vascular space invasion, tumor size, lymph node status, tumor extension, presence or absence of surgical staging)
- Participants who have suffered a recurrence at the vaginal cuff
- Participants who are unable to undergo surgery and must have treatment for an inoperable primary endometrial cancer.

2.1.1.6.1.2 Cervical cancer

- Participants who are unable to undergo surgery and must have treatment for an inoperable primary cervical cancer.
- Participants with locally advanced cervical cancer in whom brachytherapy will be integrated as a boost to external beam radiation either a palliative or curative setting (definitive or post-operative setting).

2.1.1.6.2 Lung cancer

- Participants with a endobronchial component causing symptoms
- Participants who cannot undergo resection because of poor lung function or distant lung metastasis

2.1.1.6.3 Breast cancer

- Infiltrating ductal carcinoma or DCIS, stage T0, T1, and T2 ≤ 3.0 cm, N0 and M0,

- Participants benefiting from HDR as either as a boost or accelerated partial breast irradiation regimen.

2.1.1.6.4 Prostate Cancer

- Participants with localized prostate cancer (T1b-T3b) in whom brachytherapy will be integrated as a boost to external beam radiation or used as monotherapy for definitive management.

2.1.2 Exclusion Criteria

2.1.2.1 Cognitively impaired participants who cannot give informed consent.

2.1.2.2 Participants receiving concurrent investigational chemotherapeutic agents.

2.1.2.3 Participants receiving concomitant chemotherapy administration in the 5 days preceding brachytherapy (except for gynecological cancer participants who may have received concurrent chemotherapy as a component of their treatment regimen)

2.1.2.4 Pregnant or breast-feeding females are excluded because of the potential mutagenic effects on a developing fetus or newborn.

2.1.2.5 Clinically significant unrelated systemic illness (serious infections or significant cardiac, pulmonary, hepatic or other organ dysfunction), which in the judgment of the Principal or Associate Investigator would compromise the participant's ability to tolerate this therapy or are likely to interfere with the study procedures or results.

2.1.2.6 Participants who are in the estimation of the PI, deemed unable or unlikely to adhere to protocol treatment.

2.1.2.7 Abnormal bleeding times or active anti-coagulation therapy.

- platelets < 100,000 per mm^3
- PT/PTT>1.5 ULN

2.1.2.8 Any participant or tumor/anatomical factors that may prevent brachytherapy apparatus from being properly and safely inserted and positioned and from radiation therapy being administered per ABS guidelines (**Appendix A**) (5, 6, 8, 10, 11, 12)

2.1.2.9 Participants whose malignancy has one or more of the following site-specific criteria disqualifying them from the study:

2.1.2.9.1 Breast cancer:

- Participants inappropriate for standard breast conservation therapy (Multicentric disease, inability to achieve clear margins);
- male participants with breast cancer
- autoimmune disorders, including SLE, Scleroderma, etc.
- distant metastases;

2.1.2.9.2 Prostate cancer:

- distant metastases
- lymph node metastases

2.1.3 Recruitment Strategies

This protocol may be abstracted into a plain language announcement posted on NIH websites and on NIH social media platforms.

2.2 SCREENING EVALUATION

Note: Screening evaluation testing/procedures are conducted under the separate screening protocol, 01-C-0129 (Eligibility Screening and Tissue Procurement for the NIH Intramural Research Program Clinical Protocols). Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a participant has signed the consent.

2.2.1 Clinical Evaluation

- All participants will have a problem-based history and directed physical examination performed. This should include measurements of disease status, stage of disease, signs, and symptoms caused by the cancer, performance status, weight and concomitant medications.
- All pertinent medical records, pathology reports, and radiographic imaging studies will be reviewed.
- Vital signs, including ECOG
- Anesthesia consult if sedation will be required

2.2.2 Laboratory Evaluation

- Outside Pathology report confirming histological diagnosis of cancer.
- Pre- treatment blood tests should be performed within 72 hours prior to enrollment
  - Urine Pregnancy required for females of childbearing potential
  - CBC, platelet count, PT/PTT

2.2.3 Radiographic Evaluation

2.2.3.1 For disease sites that can be imaged, imaging of target(s) will occur within 4 weeks of enrollment.

- The appropriate imaging modality will be chosen based on the site(s) of target however if the lesion is visible on CT imaging, this will be the preferred modality for this protocol. The selected imaging modality will be used at each follow-up to determine local control.
- Additional radiographic studies will be obtained depending on the known sites of disease and as the clinical situation dictates (i.e. bone scan, plain films).
- When deemed necessary (i.e. outdated or inadequate prior studies) MRI, CT, PET scans, may be obtained to complete clinical and pathologic staging.

2.2.3.2 Evaluation of target lesions

- For disease sites that can be imaged, each lesion to be treated with HDR will be clearly identified in the medical record and will be measured at baseline.
- The lesion(s) will be measured with margins defined as the largest measurement on CT, MRI, or other appropriate site-specific imaging dependent on the site of metastasis.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Treatment Assignment Procedures

Cohorts

Number	Name	Description
1	Gynecologic	Participants who have been diagnosed with gynecologic cancer
2	Pulmonary	Participants who have been diagnosed with pulmonary cancer
3	Breast	Participants who have been diagnosed with breast cancer
4	Prostate	Participants who have been diagnosed with prostate cancer

Arms

Number	Name	Description
1	Radiation therapy	Radiation therapy given as HDR Brachytherapy.

Arm Assignment

Participants in cohorts 1-4 will be directly assigned to arm 1.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

In this study, participants will undergo appropriate work-up and clinical evaluation to determine if high-dose brachytherapy would be beneficial in either primary treatment or palliation of their disease. Participants will be treated with high-dose brachytherapy appropriately sequenced with other modalities in their treatment regimen. This treatment will be administered in accordance with standard radiation oncology practice and per the ABS (American Brachytherapy Society) guidelines. The participant's disease status and toxicity outcomes will be documented for a 12-month period at 3-month intervals.

3.2 PROTOCOL THERAPY ADMINISTRATION

3.2.1 Treatment Coordination

The participant will be evaluated by study investigators as to the appropriateness and feasibility of brachytherapy on an individual basis. This will necessitate close and continued collaboration with the participant's referring oncologist. Study investigators will coordinate the timing of brachytherapy session(s) with other modalities in the participant's treatment regimen.

3.2.2 High Dose Rate Brachytherapy (HDR)

3.2.2.1 Pre-plan

- In diseases where targets can be imaged, volumes will be outlined based on CT or ultrasound images, which include (but are not limited to) a Gross Tumor Volume (GTV), Clinical Tumor Volume (CTV), and normal structures. GTV will encompass the known tumor volume as seen clinically and on CT. CTV includes a margin for areas of suspected microscopic disease based on Clinical and imaging data. Treatment planning software will then be utilized to plan therapy in order to ensure maximum dose to the tumor while observing outlined dose constraints to the normal structures. For prostate brachytherapy, the pre-plan may be conducted prior to the brachytherapy procedure or integrated in the brachytherapy procedure as part of real-time planning.

3.2.2.2 Applicator/ Catheter Placement Procedure

- If the participant is to receive sedation, instruction will be given per the anesthesia department.
- The participant will arrive in the ROB clinic the morning of the procedure and be prepared for the HDR procedure by the ROB staff.
- In diseases where catheters have been previously placed at the time of surgery (i.e., breast cancer), the participant will arrive with catheters in place. Otherwise, the participant will be positioned, the area cleansed with an antimicrobial solution and draped according to standard sterile technique. Brachytherapy applicators or catheters are inserted in anatomical sites defined by the physician and secured by sutures or packing as needed.
- If the site can be imaged, ultrasound or CT images will again be obtained.
- The placement of the applicators may be adjusted as needed based on the images until the radiation oncologists are satisfied with applicator placements.

3.2.2.3 Implant Dosimetry and Treatment Planning

- In diseases where targets can be imaged, the final CT images are transferred to the treatment planning system, where optimization of dosimetry is performed. For prostate cancer, planning is accomplished based on ultrasound imaging to which other imaging modalities may be fused.

3.2.2.4 Radiation Delivery

- Participants will be transferred to the NRC approved brachytherapy treatment room in the ROB. A radiographic film may be obtained on the treatment table and applicators may require a final adjustment at that time.
- Once a treatment plan has been completed, verified and accepted, the brachytherapy will be administered with a remote afterloading system using a stepping ^{192}Ir source. (Nucletron Inc.)
- Radiation delivery will take approximately 10-30 minutes depending on the strength of the source and the dose to be delivered.
- Suggested guidelines for proposed radiation doses are included in the **Appendix A**.

3.2.2.5 Device Removal

- HDR applicator/ catheters will be removed by ROB investigators or the appropriate clinical staff.

3.3 TREATMENT MODIFICATIONS

Modifications to the radiation treatment plan will be made at the discretion of the radiation oncologist. Deviations from the planned treatment schedule may be required secondary to expected toxicity.

3.4 ON STUDY EVALUATION

3.4.1 Active Treatment Phase

- Pre-plan obtained (**3.2.2.1**)
- Applicator/ Catheter Placement Procedure (**3.2.2.2**)
- Implant Dosimetry and Treatment Planning (**3.2.2.3**)
- Radiation Delivery (**3.2.2.4**)
- Device removal (**3.2.2.5**)

3.4.2 Post-Active Treatment Phase

- Following completion of protocol therapy, participants will be seen in follow-up. Follow-up evaluations should occur at NIH at one month after the completion of radiation therapy, at three months after completion of radiation therapy, followed by every 3 month intervals up to 12 months
- Follow- up evaluations will include:
    - Clinical Evaluation- complete interval history and directed physical examination, notation of any ongoing or recently delivered systemic therapy
    - Any medical procedures/tests will be based on the participant's diagnosis, treatment, and supporting clinical information.
    - Assessment of acute and long-term effects of radiation therapy using the RTOG and CTC 4.0
    - In diseases where targets can be imaged, CT, MRI, or other appropriate imaging of the tumor site(s). In general, CT will be the preferred imaging modality unless the lesion is not visible on this modality. PSA will be adequate for follow up in prostate participants unless otherwise indicated.
    - Scoring of local control at each treated site will be based on RECIST criteria (limited to local disease status). Each site will be scored separately.

3.5 SURGICAL GUIDELINES

In some cases, participants may require placement of brachytherapy catheters at the time of surgical resection. This will be coordinated by the referring oncologist or surgeon. Surgical therapy is not included on this protocol

3.6 RADIATION THERAPY GUIDELINES

This protocol involves radiation therapy given as HDR brachytherapy. In some cases, participants may also need to receive external beam radiation therapy. Generally, participants are expected to receive their standard external beam radiation therapy care by their referring oncologist. Occasionally, however, participants may not have timely or appropriate access to care at home, and in these rare cases, the external beam component may be provided at the NCI ROB clinic.

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy.

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.8.1 Criteria for removal from protocol therapy

Prior to removal from study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

Protocol therapy is complete when the participant has completed the brachytherapy component of treatment. This will vary depending on the site of disease treated, see **Appendix A**.

3.8.2 Off Study Criteria

3.8.2.1 Administrative

Participants who are removed from the study for non-medical or administrative reasons prior to the completion of the active course of treatment may be replaced. A participant may be taken off study for the following non- medical or administrative reasons:

- Participant refusal of further treatments (reasons must be noted in the participant's records).
- We are no longer able to maintain contact with the participant and/ or their oncologist.
- It is deemed in the best interest of the participant by the PI.
- Serious protocol deviation as determined by the PI.
- Participant loses capacity to provide consent.

3.8.2.2 Toxicity

Any participant who develops a grade 4 toxicity considered primarily due to the study treatment. However, the toxicity will be followed to assess the duration and resolution.

3.8.2.3 Tumor Progression

Any participant with clinical or radiographic evidence of progressive disease during the active course of treatment will be removed from the study if it is deemed by the PI that additional therapy would not be in the best interest of the participant.

3.8.2.4 Concurrent Illness

The development of a concurrent serious medical condition that might preclude or contraindicate the further administration of radiation therapy.

3.8.2.5 Completion

- The completion of HDR and 12 months follow up
- The participant is unable to complete the radiation treatment process for any reason or is non-compliant with the treatment &/ or follow- up requirements
- Follow-up is no longer deemed necessary at ROB, and participant has other adequate medical care in the community.

3.8.2.6 Death

4 CONCOMITANT MEDICATIONS/MEASURES

4.1 SUPPORTIVE CARE

Most participants are expected to receive their standard supportive care by their referring oncologists. Occasionally, however, participants may not have timely or appropriate access to supportive care at home, and in these rare cases, supportive care will be provided at the NIH Clinical Center. Examples of such care include, but are not limited to, the management of acute radiation effects/complications, steroid medication, conscious sedation, analgesics, anti-emetics, and intravenous hydration.

4.2 CONCURRENT THERAPIES

No investigational drugs or therapies will be administered by NCI ROB personnel in this protocol. However, the participant may be receiving other appropriate cancer therapy based on standard practice. This will be coordinated by the referring oncologist.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

- Clinical data and acquired images will be recorded in a NCI CCR database (C3D)**.**
- Clinical data collection will include: demographic information, pathologic diagnosis, clinical stage, history including prior and concurrent therapies, location and measurement of lesions, CT reports, lab reports, vital signs, dose of radiation delivered, and toxicity assessment.
- The results of any procedures and/or tests will be included in the participants' hospital chart and/or research records as appropriate. Data from these records may be used in research and scientific publications.
- Data collected may be used anonymously, for publications not originally specified, concerning the disease processes and long term effects of treatment. The data may also be used as the basis for new protocols.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization. Document AEs from the first study intervention through 30 days after the intervention was last administered. Beyond the 30 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the participant's outcome.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule regulations as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **6.2.1**.

5.2 RESPONSE CRITERIA

Tumor Response for Solid Tumors: In diseases where targets can be imaged, response will be measured using the RECIST criteria only for local sites as this is not a trial of a systemic therapy. Response will be scored for each target lesion. Every effort should be made to objectively record changes in the participant's disease process after the HDR procedure. Measurable criteria should always take precedence over subjective criteria.

5.2.1 Evaluation of target lesions

In diseases where targets can be imaged, the target lesion is defined as the sites which are targeted with HDR as part of this protocol. The response will be measured with margins defined

as the longest diameter measurement on the appropriately specified radiographic imaging. The imaging modality will be that which provided the maximal measurement pretreatment. This imaging modality will be used at each follow-up to determine local control. If there is evidence of clinical progression, the imaging study will be repeated to assess for progression.

- Complete Response (CR): Complete disappearance of the target lesion.
- Partial Response (PR): at least a 30% decrease in the sum of the longest diameter (LD) of the target lesion taking into account the baseline sum LD
- Stable/No Response: Does not qualify for CR, PR, or progression.
- Progression: Interval increase in the maximal dimension of the target lesion.
- Local Control: will be defined as CR, PR, or stable disease of the treated site (s). Local progression on any imaging modality (bone scan, MRI, CT, or PET) obtained during the normal course of therapy and follow-up will be considered locally progressive disease.

5.3 TOXICITY CRITERIA

The study will use the RTOG/EORTC Radiation Morbidity Scoring Scheme to score late effects of radiation treatment. The RTOG scoring criteria can be obtained from the RTOG website:

- Acute: https://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx, and
- Late: https://www.rtog.org/ResearchAssociates/AdverseEventReporting/RTOGEORTCLateRadiationMorbidityScoringSchema.aspx

6 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

6.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

6.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

6.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

6.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

6.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

6.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

6.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis weekly, when participants are being actively treated on the trial to discuss each participant. Decisions about enrollment and dose escalation if applicable will be made based on the toxicity data from prior participants.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Events meeting requirements for expedited reporting as described in section **6.2.1** will be submitted within the appropriate timelines.

The principal investigator will review adverse event and response data on each participant to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7 STATISTICAL CONSIDERATIONS

The study is designed to determine, in a preliminary fashion, whether the quality of high dose rate brachytherapy implants performed in the radiation oncology branch reaches an acceptable level. The quality will be examined separately in four body sites. Specifically, we will stratify by gynecologic (endometrial and cervical), pulmonary, breast, and prostate cancer. In each strata, we will examine the quality of high dose rate brachytherapy with a two-stage optimal design (21). An implant will be considered acceptable if 90% of the GTV receives 90% of the dose prescribed and 80% of the CTV receives 85% of the prescribed dose. An implant will be unacceptable if the above dose limitations are not met.

The two-stage design is based on the following assumptions: (i) the procedure will be considered of poor overall quality (unacceptable) if less than 65% of participants have acceptable implants based on the above criteria (Po=0.65)., (ii) the procedure will be considered of good quality (acceptable) if over 90% of participants have acceptable implants based on the above criteria (P1=0.90), (iii) within each stratum, the probability of concluding that an unacceptable procedure is acceptable is less than 4 % (alpha=0.04), and (iv) within each stratum, the probability of concluding that an acceptable procedure is unacceptable is less than 10% (beta=0.10). Based on these operating characteristics, the following two-stage design is optimal. Separately for each of the four strata, the first stage will accrue 9 participants. If 7 or more of the 9 implants have an acceptable implant, then the study will accrue an additional 19 participants. In any stratum, accrual will stop in the first stage if 6 or fewer of 9 participants have an acceptable implant. Assuming that we accrue to the second stage, high dose brachytherapy for a particular tumor type (stratum) will be considered to be acceptably preformed at the clinical center if 23 or more of 28 participants have an acceptable implant.

The error rates stated above are for each of the four strata separately. We note that, with this design, there is less than an 12% chance that one or more strata will falsely conclude that the procedure is acceptable if the procedure is unacceptable in all 4 strata (Po=0.65).

Evaluating local control and late toxicity rates following brachytherapy are also objectives of this study. Other studies at NCI and at other institutions have found acceptable toxicity rates (16, 22, 23, 24). We will tabulate local control and late toxicity rates by stratum and combined over all four strata.

The maximum accrual will be 28 participants to each of the 4 strata (maximum accrual of 112 participants). We anticipate that accrual will be completed in 5 years.

8 HUMAN SUBJECTS PROTECTIONS

8.1 RATIONALE FOR SUBJECT SELECTION

Participants will be invited to enroll onto this trial if they are an adult and meet the eligibility criteria outlined in section **2.1**. No gender, racial or ethnic groups will be excluded from participation in this trial. Adults who are cognitively impaired prior to study entry will not be eligible for study entry because they cannot give informed consent.

8.2 PARTICIPATION OF CHILDREN

Children are not eligible for this protocol therapy due to the very different biology and clinical behavior of childhood malignancies. Normal tissue response and toxicity is significantly different as well given that many normal tissues are still growing and developing. In addition, the oncologic practice in childhood malignancies is to avoid high-dose brachytherapy procedures.

8.3 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

All procedures/tests in this protocol are used routinely in standard care settings with minimal associated risks and/or discomforts. Participants on this study will be receiving treatment for their malignancy per standard of care. There are no direct medical benefits expected from taking part in this study. We hope the information learned from this study will benefit participants in the future.

The risks and benefits of each procedure/test, as well as the implications of the procedure/test results will be discussed thoroughly with the participant prior to the intervention. Specific risks and potential complications of each procedure will be outlined in a consent form. When the procedure/test poses any risk to the participant, an additional consent will be obtained.

8.3.1 Radiation risk

Likely medical risks include fatigue, low blood counts and skin reactions at the radiation site. Rare medical risks associated with brachytherapy include infection, bleeding, and perforation of the treated organ or surrounding organs and development of new cancer.

Participants' tumors may be exposed to up to 15 Gy of radiation from High Dose Rate Brachytherapy. Participants will also receive a much smaller amount of radiation from scans used to plan treatment and measure progress. The total scans include up to 4 CT scans.

8.3.2 Imaging risk

Participants may feel discomfort from lying still during imaging. Some participants may also experience claustrophobia.

8.3.3 Contrast risk

Participants may experience an allergic reaction to contrast used during imaging. For participants that undergo an MRI with gadolinium, there is a risk for nephrogenic systemic

fibrosis for participants with kidney disease. Some participants may also have gadolinium retention. Participants with abnormal kidney function will not have an MRI with gadolinium.

8.3.4 Blood draw risk

Blood draws may cause pain, redness, bruising or infection at the site of the needle stick. Rarely some participants faint.

8.3.5 Anesthesia risk

8.3.6 The risks associated with anesthesia are nausea, vomiting, headache and back pain. Other less likely but serious risks include blood pressure problems, arrhythmias, respiration changes, allergic reactions, paralysis, heart attack, stroke, or death. High dose rate brachytherapy implants

Risks associated with implants are pain and discomfort.

8.4 INFORMED CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant. Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

8.5 PARTICIPANT ADVOCATE

The participant's rights representative is available to participants on this protocol at (301) 496-2626 in Building 10, Room 1C132, NIH. Participants may ask any questions about the study and may withdraw their consent at any time without compromising their medical care.

9 REGULATORY AND OPERATIONAL CONSIDERATIONS

9.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB.

9.2 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

9.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Cancer Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

9.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators and their staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence.

All research activities will be conducted in as private a setting as possible.

The study monitor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator,

including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the/each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB and Institutional policies.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the NCI CCR. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the clinical site(s) and by NCI CCR research staff will be secured and password protected. At the end of the study, all study databases will be archived at the NIH.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

10 COMMERCIAL DEVICE INFORMATION

10.1 RADIATION

There will be no IDE obtained for the use of any of the commercial agents used in this study.

This study meets the criteria under category #1 for exemption for an IDE as this investigation involves the use of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling.

10.2 SOURCE

The radiation device is a commercial device that will be located in the NIH Clinical Center.

10.3 TOXICITY

Refer to section **8.3**.

10.4 ADMINISTRATION PROCEDURES

Refer to section **3.2**.

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12 APPENDICES

12.1 APPENDIX A: SUGGESTED DOSES FOR BRACHYTHERAPY ADMINISTRATION PER ABS GUIDELINES

A. Cervical Cancer

1. Technique

Three to six HDR treatments will be delivered, based on host factors (inability to tolerate treatment, changes in physical findings, poor anatomy for implant) as well as the discretion of the treating radiation oncologists. Packing, followed by brachytherapy applicators, will then be removed, and the participants recovered in the PACU, where supportive care may include analgesia, antibiotics, and douches with hydrogen peroxide and water etc., may be delivered. HDR brachytherapy is an outpatient procedure, though very rarely, participants may be admitted overnight for observation.

Implants may be delivered either during or following the EBRT, with the goal of keeping the total duration of treatment to fewer than 8 weeks when possible because of the effect of prolonged treatment duration and decreased survival (4)

Per ABS guidelines, for early cervical cancer, the following guidelines will be adhered to:

EBRT (Gy) @ 1.8 Gy/fraction	No. of HDR fractions	HDR dose/fraction
20	6	7.5
20	7	6.5
20	8	6.0
45	5	6.0
45	6	5.3

Per ABS guidelines, for advanced cervical cancer, the following guidelines will be adhered to:

EBRT (Gy) @ 1.8 Gy/fraction	No. of HDR fractions	HDR dose/fraction
45	5	6.5
45	6	5.8
50.4	4	7.0
50.4	5	6.0
50.4	6	5.3

(5)

2. Implant Dosimetry And Treatment Planning And Dosage Recommendations

Optimization of dosimetry is performed that creates the optimal disease coverage. Packing can be used to stabilize the geometry. The target is to treat Point A to 80-85 Gy for early stage disease and 85-90 Gy for advanced disease. The dose constraints are to limit the bladder dose to the LDR equivalent of 80 Gy and the rectal dose below 75 Gy.

B. Endometrial Cancer

1. Technique

Participants eligible for the protocol shall have definitive adjuvant radiotherapy or be treated because they are deemed to have inoperable disease or are poor surgical candidates. In some cases this regimen may be changed to fit the individual needs and requirements of each participant and the number of external beam and brachytherapy treatments may be slightly different. These slight differences will be discussed with the participants prior to the beginning of therapy and if necessary during therapy as well. The radiation therapy for this study is considered the "standard of care" of the treatment of endometrial cancer.

Technical aspects that should be considered for endometrial participants in brachytherapy: a rectal tube should be placed, the largest vaginal cylinder possible should be used and 2/3 of the vaginal cuff should be targeted.

2.Implant Dosimetry And Treatment Planning And Dosage Recommendations

Suggested doses of HDR alone to be used for adjuvant treatment of postop are as follows:

No. of HDR fractions	HDR dose/fx	Dose-specific point	Equiv. dose for tumor effects	Equiv. dose (late effects with DRF)
3	7.0	0.5-cm depth	29.8	23.2
4	5.5	0.5-cm depth	28.4	21.1
5	4.7	0.5-cm depth	28.8	20.7
2*	16.2*	Vaginal surface	70.7	65.0
3	10.5	Vaginal surface	53.8	45.6
4	8.8	Vaginal surface	55.1	45.1
5	7.5	Vaginal surface	54.7	43.3

Suggested doses of EBRT and HDR to be used for adjuvant treatment of postop endometrial cancer are as follows:

EBRT (Gy) @ 1.8 Gy/fx	No. of HDR fractions	HDR dose/fx	Dose-specific point	Equiv. dose for tumor effects	Equiv. dose (late effects with DRF)
45	2	5.5	0.5-cm depth	58.5	53.7
45	3	4.0	0.5-cm depth	58.3	52.9
45	2	8.0	Vaginal surface	68.3	62.5
45	3	6.0	Vaginal surafce	68.3	61.3

The ABS recommends that the proximal 3–5 cm of the vagina be treated; however if a characteristic of the participant presentation dictates that more or less of the vagina should be treated, then this detail is left to the discretion of the investigator. For serous and clear cell histologies, treatment of the entire vaginal canal should be considered. The dose distribution should be optimized to deliver the prescribed dose either at the vaginal surface or at 0.5-cm depth. The physician should be mindful that when then vaginal recurrence is at the distal vaginal cuff, the entire vagina and the inguinal nodes should be considered for treatment.

In those cases in which HDR only for treatment of inoperable primary endometrial cancer

No. of HDR fractions	HDR dose/fx*	Equiv. dose for tumor effects	Equiv. dose (late effects with DRF)
4	8.5 Gy at 2 cm	52.4	42.6
5	7.3 Gy at 2 cm	52.6	41.4
6	6.4 Gy at 2 cm	52.5	40.3
7	5.7 Gy at 2 cm	52.2	39.0

In those participants cases in which external beam + HDR is needed for treatment of inoperable primary endometrial cancer, the following schedule should be adhered to:

EBRT (Gy) @ 1.8 Gy/fx	No. of HDR fractions	HDR dose/fx	Equiv. dose for tumor effects	Equiv. dose (late effects with DRF)
45	2	8.5 Gy at 2 cm	70.5	64.5
45	3	6.3 Gy at 2 cm	69.9	62.8
45	4	5.2 Gy at 2 cm	70.6	62.5

In participants with vaginal cuff recurrences, the following doses can be considered:

EBRT (Gy) @ 1.8 Gy/fx	No. of HDR fractions	HDR dose/fx	Dose-specification point	Equiv. dose for tumor effects	Equiv. dose (late effects with DR
45	3	7.0	0.5-cm depth	74.0	66.4
45	4	6.0	0.5-cm depth	76.3	67.4
45	5	6.0	Vaginal surface	84.3	73.4
45	4	7.0	Vaginal surface	83.9	74.2

ICRU reference points should be localized and calculated, respecting normal tissue tolerance as noted above.

The dose should be limited as follows: the upper vaginal mucosa should receive no more than 150 Gy, the lower vaginal mucosa should receive between 80-90 Gy and the rectal point dose should be less than 70 Gy, the bladder point should be less than 75 Gy. (12)

C. Lung Carcinoma

1. Technique

A flexible nylon catheter will be introduced through the bronchoscope into the lumen and is positioned at least 2 cm beyond the visible tumor. The prescription point should prescribe the radiation dose at 10mm from the center of the catheter. A margin of at least 1-2 cm beyond the disease is recommended.

2. Implant Dosimetry And Treatment Planning And Dosage Recommendations

The ABS recommends for those participants who are undergoing palliative brachytherapy only, 3 weekly fractions of 7.5 Gy each, 2 fractions of 10 Gy each or 4 fractions of 6 Gy each.

For participants with curative intent, the recommendations are as follows: as a boost to external beam radiation therapy, 3 fractions of 5 Gy each or 2 fractions of 7.5 Gy each. If it is used alone in participants who have not received radiotherapy, 5 fractions of 5 Gy each or 3 fractions of 7.5 Gy each prescribed to 1 cm can be considered.

The plan will be optimized and treatment delivered. (8)

D. Breast

1. Technique

Planning target volume is the lumpectomy site with 1-2 cm margin as clinically indicated. The CTV = PTV and the prescription dose must encompass the target volume and the dose will be prescribed to 1 cm from the applicator surface.

2. Implant Dosimetry And Treatment Planning And Dosage Recommendations

A minimum of 7mm between the skin and balloon should be maintained. During the planning process, normal tissue doses will be respected and a three-dimensional calculation with DVH-based analysis should be created. Breast dose parameters should include V100, V150, and V200. Skin dose parameters should include Dmax. (6)

- Target coverage: ≥ 90% of the dose delivered to ≥ 90% of the target volume
- V150: balloon catheter < 50 cm3
- V200: balloon catheter < 10 cm3
- DHI ≥ 0.75 where DHI = (1 – V150/V100)
- Maximum skin isodose: balloon catheter < 145%
- Primary treatment 34 Gy in 10 fractions over 5 treatment days

If treatment is being delivered as the primary treatment then it should be given as 34 Gy in 10 fractions over 5 days. Treatment should be administered either before or after chemotherapy (if persistent cavity or surgical clips placed). If chemotherapy will be administered, then the recommendation is to wait >2weeks after completion of APBI before initiating (6)

E. Prostate

1. Technique and dosage recommendations

Definitive boost therapy: For definitive boost therapy, a single HDR brachytherapy implant (1500 cGy/implant) will be delivered within 21 days of a course of external beam radiotherapy (4600 cGy, 2Gy/day or 4500 cGy, 1.8 Gy/day). Alternative fractionation schedules include 9.5 Gy- 11.5 Gy x 2 fractions, 5.5-7.5 Gy x 3, and 4.0-6.0 Gy x 4 fractions. These regimens are those described in the ABS and NCCN guidelines.

Definitive monotherapy: The regimen chosen will be based on participant and tumor factors. For definitive monotherapy, doses of 12-13.5 Gy x 2 fractions, 9.5 Gy x 4, 10.5 Gy x 3 are described by the NCCN and ABS as appropriate monotherapy doses and will be options for treatment on this protocol.

Salvage: For salvage, participants will receive 8 Gy x 4 fractions without external beam irradiation.

Simulation: Participants will undergo CT simulation for the external beam portion of treatment as per routine in the supine position. For EBRT the planning target volume (PTV) will be defined as the clinical target volume (CTV) plus a margin defined by the treating physician. The external beam component will be delivered in one phase. Treatment planning goals are to try to achieve an isodose distribution where the PTV is covered by at least the 90% isodose line, and the 100% isodose line encompasses the CTV. Doses will be prescribed to the 100% isodose line.

2. Implant Dosimetry And Treatment Planning

Clinical Target Volume*:* The clinical target volume will include at a minimum the prostate gland. The seminal vesicles or areas of extracapsular disease may be included at the discretion of the treating physician. For salvage, the volume will include suspected areas of recurrence. Real time planning and optimization based on ultrasound images obtained during the procedure will be performed.

The following volumes will be contoured: urethra, bladder, rectal wall, and PTV. The PTV will consist of the prostate gland + extraprostatic tumor +/- seminal vesicles. A separate expanded planning PTV will be used for optimization, but not for dose reporting. The dose goal for the PTV will include a V100 >95%, a V125 <55%, and a V150 <25%. The constraints will vary by the fractionation chosen. For example, for the 15 Gy boost, the goals will include urethra V118<10% and V125<1cc; Rectal V_{75} < 1cc, V_{80} < 0.5 cc.

Dose-volume histograms (DVHs) will be generated for the PTV, rectum, and urethra. The following isodose lines will be displayed on the treatment plan: 75% 100% 125%, 150%, and 200%. Additional isodose lines may be visualized if clinically necessary.

Dose prescription will be tailored according to the dosimetric parameters achieved in the optimized treatment plan (10, 11).

12.2 APPENDIX B: 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.