# Prospective randomized phase III trial comparing postsurgical radiotherapy alone versus adjuvant radiotherapy plus hyperthermia in patients with localized prostate cancer.

**A MULTI-INSTITUTIONAL PHASE III RANDOMIZED STUDY**
**Atzelsberg Circle**

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| Synopsis | |
|---|---|
| Title | **Prospective randomized phase III trial comparing postsurgical radiotherapy alone versus adjuvant radiotherapy plus hyperthermia in patients with localized prostate cancer.** |
| Investigators / study location | The Atzelsberg Circle Study |
| Clinical phase | Phase III |
| Study objectives | **Primary Objectives**<br>To assess whether the addition of hyperthermia to adjuvant radiation therapy improves freedom from progression (FFP) as defined as PSA < 0.2 ng/ml, and no clinical failure (local-regional, or distant failure) at 5 years<br><br>**Secondary Objectives**<br>To assess freedom from local-regional progression, distant metastases, disease-free survival, prostate cancer specific survival, non-prostate cancer specific survival, overall survival, and time to biochemical (PSA) failure<br>To evaluate treatment-related “acute” and “late” toxicity |
| Study design | Multi- institutional randomized phase III study in patients with R1 localized prostate cancer.<br><br>Patients will be randomized to received conventional adjuvant radiotherapy with and without hyperthermia<br><br>Arm 1(control cohort): radiotherapy (standard treatment)<br><br>Arm 2 (experimental cohort): radiotherapy plus hyperthermia<br><br>Irradiation modality: adjuvant 3D-conformal radiotherapy (IMRT optional):<br><br>Target volume: prostate tumor bed and vesicle area<br>Dose: 64 Gy (2 Gy x 32 fractions) to the seminal vesicle area and prostate tumor bed (ICRU-report 50).<br><br>Local hyperthermia (LHT): |

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| | Hyperthermia session will be scheduled twice weekly during the time of external irradiation. It should start within one hour before or preferably after irradiation to at least a total of 10 sessions. The interval between two HT sessions has to be a minimum of 72 hours.<br>Thermometry probes have to be positioned in the rectum, and in the bladder for continuous thermometry and thermal mapping of tumor-related temperatures.<br>Therapeutic time starts when the tumor-related temperature in the rectum reaches a minimum of 41.5°C or 30 min after enabling power. Therapeutic time is scheduled to be 60 min, the maximum total duration should not exceed 90 min.<br>Hyperthermia will be delivered in accordance with ESHO quality guidelines for regional hyperthermia |

| Study population | |
|---|---|
| Inclusion criteria | • Age ≥ 18 years < 80 years<br>• ECOG performance status 0-3<br>• pT2, pT3a/b, GS 5-10, with surgical specimen proven with positive margins (R1) after surgery.<br>• pT3b, with surgical specimen proven with negative margins (R0)<br>• PSA ≤ 0.2 ng/ml<br>• No lymph node or distant metastases (pN0, M0), based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration with no evidence of osseous metastases and no pelvic lymph nodes > 1.5 cm in the greatest dimension unless the biopsy of the enlarged lymph node is negative.<br>• Patients under treatment for concurrent disease will be eligible if the concurrent medical treatment not add risks or complications.<br>• No prior pelvic irradiation or orchiectomy<br>• No previous chemotherapy for malignancy.<br>• No previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers<br>• Life expectancy of at least 24 months<br>• All patients must have signed an informed consent form prior to registration on study |
| Exclusion criteria | • Patient R0 without high-risk prostate cancer as defined above<br>• Patients with positive nodes or with distant metastasis based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration<br>•<br>• Patients with unstable cardiac status (angina pectoris, documented cardiac infarction or heart failure requiring medication)<br>• Patients with cardiac arrhythmia and severe hypertension<br>• Patients with chronic renal failure<br>• Patients with severe vascular disease<br>• patients with FEV <50% of expected<br>• Very obese patients<br>• Patients with large incorporated metallic implants such as: Pacemakers; Orthopedic rods and plates of dimensions > 1000/frequency (MHz) [e.g., > 10 cm at 100 MHz] |
| Number of patients | • The sample size for the study is estimated to be 268 (+ 10%) patients for arm |

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| Study will be stopped | • The study will be stopped if any Grade 5 toxicity is observed. The study will be stopped if there is evidence that Grade 3 and Grade 4 toxicity combined exceed 20%. |

# Short protocol

## Study design

Randomized phase III study

## Rationale

Patients with high risk pathologic features such as a positive margin or vesicle involvement have a 40 to 50% risk of developing biochemical failure. Radiotherapy in the prostate bed has been used as adjuvant treatment and at least 3 randomized trials show a consistent improvement in biochemical failure rate when radiotherapy is delivered as compared with radical prostatectomy (RP) alone.
Adjuvant Radiotherapy (ART) after RP in these phase III studies achieved a better biochemical control of about 18-20%. ART increased b-NED survival at 5 years to 72% compared with 54% of wait and see policy [1]. By adding postoperative irradiation to radical prostatectomy the 5-year biochemical control rate was 52% versus 30% ($p<0.01$) in patients with extra-capsular extension, 60% versus 18% ($p< 0.01$) in case of vesicle invasion and 64% versus 27% ($p<0.01$) in patients with positive margins [2]. In the ARO study, only a subgroup of R1-patients with preoperative PSA level > 10 ng/ml, a Gleason score of 8 and with invasion of seminal vesicle (pT3b) achieved a statistically significant benefit. It is noted that in the SWOG and EORTC trials patients with positive lymph nodes were excluded.
Randomized clinical trials demonstrated the efficacy of RT and local hyperthermia (LHT) in many tumors [3],[4],[5].

The Stanford University reported four locally recurrent prostate cancers initially treated with Iridium 192 brachytherapy, successively retreated with LHT and re-irradiation to a dose of 60 Gy, in two 30 Gy split course treatments. Three of 4 patients achieved complete clinical response at 7-24 months following treatment. The authors concluded that this therapy had the potential to control local disease with minimal complications [6]. Kalapurakal reported seven pre-irradiated patients treated by using RT and LHT. All patients responded well to re-treatment achieving complete tumor response by 2-6 months after re-treatment [7].

The aim of this study is to evaluate the feasibility and efficacy of LHT combined with irradiation in patients treated with radical prostatectomy affected by prostate cancer with high-risk of recurrence (R1, vesicle involvement, and /or extracapsular extension).

## Objectives

## Primary Objectives

To assess whether the addition of hyperthermia to adjuvant radiation therapy (ART) improves freedom from progression (FFP) as defined as PSA < 0.4 ng/ml, and no clinical failure (local-regional, or distant failure) at 5 years

## Secondary Objectives

To assess freedom from local-regional progression, distant metastases, disease-free survival, prostate cancer specific survival, non-prostate cancer specific survival, overall survival, and time to biochemical (PSA) failure.

To evaluate treatment-related “acute” and “late” toxicity.

## Inclusion criteria

- Age ≥ 18 years < 80 years
- ECOG performance status 0-3
- pT2, pT3a/b, GS 5-10, with surgical specimen proven with positive margins (R1) after surgery
- pT3b, with surgical specimen proven with negative margins (R0)
- PSA < 0.2 ng/ml
- No lymph node or distant metastases (pN0, M0), based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration with no evidence of osseous metastases and no pelvic lymph nodes > 1.5 cm in the greatest dimension unless the biopsy of the enlarged lymph node is negative.
- Patients under treatment for concurrent disease will be eligible if the concurrent medical treatment not add risks or complications
- No prior pelvic irradiation or orchiectomy
- No previous chemotherapy for malignancy
- No previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers
- Life expectancy of at least 24 months
- All patients must have signed an informed consent form prior to registration on study

## Exclusion criteria

- Patient R0 without high-risk prostate cancer as defined above
- Patients with positive nodes or with distant metastasis based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration
- Patients with unstable cardiac status (angina pectoris, documented cardiac infarction or heart failure requiring medication)
- Patients with cardiac arrhythmia and severe hypertension

- Patients with chronic renal failure
- Patients with severe vascular disease
- patients with FEV <50% of expected
- Very obese patients
- Patients with large incorporated metallic implants such as: Pacemakers; Orthopedic rods and plates of dimensions > 1000/frequency (MHz) [e.g., > 10 cm at 100 MHz].

**Treatment protocol**

Arm 1 (control cohort) : adjuvant radiotherapy (standard)
Arm 2 (experimental cohort): adjuvant radiotherapy plus hyperthermia

**Treatment**

Irradiation modality: adjuvant 3D-conformal radiotherapy (IMRT optional):
Target volume: prostate tumor bed and vesicle area.
Dose: 64 Gy (2 Gy x 32 fractions) to the seminal vesicle area and prostate bed tumor (ICRU-report 50).

**Local hyperthermia (LHT)**

Hyperthermia session will be scheduled twice weekly during the time of external irradiation. It should start within one hour before or preferably after irradiation to at least a total of 10 sessions. The interval between two LHT sessions has to be a minimum of 72 hours. Thermometry probes have to be positioned in the rectum, and in the bladder for continuous thermometry and thermal mapping of tumor-related temperatures.

Therapeutic time starts when the tumor-related temperature in the rectum reaches a minimum of 41.5°C or 30 min after enabling power. Therapeutic time is scheduled to be 60 min, the maximum total duration should not exceed 90 min.
Hyperthermia will be delivered in accordance with ESHO quality guidelines for regional hyperthermia

**Statistics**

- In order to achieve a gain of 15% in terms of FFP the sample size for the study is estimated to be 268 (+ 10%) patients for single arm.
- The study will be stopped if any Grade 5 toxicity is observed. The study will be stopped if there is evidence that Grade 3 and Grade 4 toxicity combined exceed 20%.

**Special Considerations***:*

For questionnaires or quality of life assessment tools:

Study questionnaires should be provided with the protocol and mentioned in the model consent.

# Full protocol

## INDEX

## 1.0 Introduction

Prostate cancer (CaP) is the third leading cause of cancer death [8] and the first tumor as incidence among men (WHO data). After primary treatment with surgery or radiation therapy alone the overall incidence of biochemical progression ranges from 15 to 40% [9,10,11]. Radiotherapy (RT) plus androgen suppression therapy (AST) reduces the incidence of biochemical progression of 15-20% at 5 yrs. In patients with T3 and T4 tumors and with high-grade disease, a statistically significant benefit in cause specific and overall survival was seen when treated by using RT and AST for at least three years[12]. In the RTOG study 85-31, a similar statistically significant benefit for cause specific and overall survival was observed in patients with T3 and T4 disease and Gleason score of 8-10 [13]. In a subset analysis of patients with Gleason score of 8-10, there was a significant improvement in absolute and cause specific survival [14]. In patients treated with RT and long-term hormone therapy the 8 yr local failure rate, distant metastases rate and overall survival were 30%, 52% and 51% respectively. A subset analysis of RTOG 85-31 and 86-10 indicates an advantage for long-term versus short-term adjuvant hormones for patients with locally advanced non-metastatic CaP treated with RT [15]. These promising results suggested the use of ionizing radiations as adjuvant treatment after radical prostatectomy (RP) in patients with high risk of local recurrence.

### 1.1 Adjuvant radiotherapy

Adjuvant radiotherapy (ART) in patients affected by CaP after RP remains controversial. In spite of the widespread use of ART in high risk patients affected by others cancers, ART has not been routinely used after RP. Probably the reasons could be the following: 1) some tumors fail not only locally but systemically; 2) the PSA level evaluation allows an easy follow up and predict recurrence before it clinically appears; 3) even if ART may prevent local disease, distant metastases are not cured; 4) potential toxicity of ART may contrast with benefit.

Analysis of results of large clinical studies indicated that the positive rate of surgical margin after radical prostatectomy is 20-40% and suggested that the presence of positive margins will have an impact on the patient's prognosis.

The predictive risk factors of positive surgical margin and pelvic lymph node involvement include an elevated preoperative PSA and a high Gleason score. Patients with high risk pathologic features such as positive surgical margins or seminal vesicle involvement have a 40 to 50% risk of developing biochemical failure (BF). RT on the prostate cancer bed has been used as adjuvant treatment and at least 3 randomized trials show a consistent improvement in biochemical failure rate when RT is delivered as compared with RP alone. Consequently, when pathologic high risk factors are present, ART should be considered. ART after RP in these phase III studies achieved a better biochemical control of about 18-20%. In particular, ART increased b-NED survival at 5 years to 72% compared with 54% of wait and see policy [1]. Whole pelvic irradiation (WPRT) with concurrent AST in patients at high risk of occult nodal metastases improved biochemical relapse-free survival compared with prostate bed irradiation (PBRT) alone. The advantage of

WPRT was limited to high-risk patients, with a 5-year b-RFS rate of 47% after WPRT vs 21% after PBRT as reported in RTOG 94-13 study [16]. In patients with poor pathologic features such as extracapsular extension, seminal vesicle invasion, positive margins, postoperative PSA level, ART improved the biochemical outcome independent on other prognostic factors. By adding postoperative irradiation to RP, the 5-year biochemical control rate was 52% versus 30% ($p<0.01$) in patients with extra-capsular extension, 60% versus 18% ($p< 0.01$) in case of vesicle invasion and 64% versus 27% ($p<0.01$) in patients with positive margins [2]. In particular, in the ARO study, only a subgroup of R1-patients with preoperative PSA level > 10 ng/ml, a Gleason score (GS) of 8 and with invasion of seminal vesicle (pT3b) achieved in a preliminary analysis a statistically significant benefit. In conclusion, adjuvant RT in patients with pathological risk factors (stage pT3a or b and/or positive surgical margins ) after RP adds a beneficial outcome. But it is noted that in the SWOG and EORTC trials patients with positive lymph nodes were excluded and in the EORTC study only surgical margin status was significantly predictive for the magnitude of the benefit, whereas in the SWOG study only results by combined data and no by margin status alone are reported. Furthermore, in a separate report of EORTC study it was shown that the margin status reviewed by a central pathology was a stronger predictor than the margin status determined by local pathology alone.

### 1.2 Local hyperthermia plus RT

Randomized clinical trials demonstrated the efficacy of RT plus local hyperthermia (LHT) in many tumors [3,4,5].

No randomized studies are investigating until now the use of LHT in CaP in the adjuvant setting and only phase II trials reported results in terms of feasibility and toxicity profile in the no resectable locally advanced CaP or in the salvage setting (see table 1) [17, 18, 19, 20, 21, 22, 23, 24, 25, 26].

In the Duke University experience, 18 patients with stage T3 or T4 prostate cancer, GS of 7-9 and mean serum PSA of 69 ng/ml had definitive RT (65-70 Gy) and LHT. The 3-year disease free survival was 25%. The 3 yr. local control and distant failure free survival was 93% and 68%, respectively [9].

The Stanford University reported four locally recurrent prostate cancer initially treated with Iridium 192 brachytherapy, successively retreated with LHT and re-irradiation to a dose of 60 Gy, in two 30 Gy split course treatments. None of the patients experienced severe rectal or bladder reactions. Three of 4 patients achieved complete clinical response at 7-24 months following treatment. The authors concluded that this therapy had the potential to control local disease with minimal complications [6]. Kalapurakal reported seven pre-irradiated patients treated by using RT and LHT. All patients responded well to re-treatment achieving complete tumor response by 2-6 months after re-treatment. Two patients developed urethral stricture [7].

The aim of this study is to evaluate the feasibility and efficacy of LHT combined with irradiation in patients treated with RP affected by CaP with high-risk of recurrence (R1, vesicle involvement, extracapsular extension).

### 1.3 Design of the study

The trial has to be considered as a multicentric randomized phase III study. Patients with R1 resection and high risk factors after RP and without distant metastases will randomly enroll in one of the two arms:

Arm 1(control cohort): adjuvant radiation therapy

Arm 2 (experimental cohort): adjuvant radiation therapy + local hyperthermia twice a week

## 2.0 Primary and secondary endpoints

### 2.1 Primary endpoints

To assess whether the addition of local hyperthermia (LHT) to adjuvant radiation therapy (ART) improves freedom from progression (FFP) as defined as PSA < 0.4 ng/ml, and no clinical failure (local-regional, or distant failure) at 5 years.

### 2.2 Secondary Endpoints

To assess freedom from local-regional progression, distant metastases, disease-free survival, prostate cancer specific survival, non-prostate cancer specific survival, overall survival, and time to biochemical (PSA) failure
To evaluate treatment-related “acute” and “late” toxicity

## 3.0 Patient selection

### 3.1 Eligibility Criteria

- Age ≥ 18 years < 80 years
- ECOG performance status 0-3
- pT2, pT3a/b, GS 5-10, with surgical specimen proven with positive margins (R1) after surgery
- pT3b, with surgical specimen proven with negative margins (R0)
- PSA ≤ 0.2 ng/ml
- No lymph node or distant metastases (pN0, M0), based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration with no evidence of osseous metastases and no pelvic lymph nodes > 1.5 cm in the greatest dimension unless the biopsy of the enlarged lymph node is negative.
- Patients under treatment for concurrent disease will be eligible if the concurrent medical treatment not add risks or complications.
- No prior pelvic irradiation or orchiectomy
- No previous chemotherapy for malignancy.
- No previous or concurrent invasive cancers other than superficial non-melanomatous skin cancers
- Life expectancy of at least 24 months

- All patients must have signed an informed consent form prior to registration on study.

### 3.2. Ineligibility Criteria

- Patient R0 without high-risk prostate cancer as defined above
- Patients with positive nodes or with distant metastasis based upon the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: bone scan and CT or MRI of the pelvis within 16 weeks prior to registration
- Patients with unstable cardiac status (angina pectoris, documented cardiac infarction or heart failure requiring medication)
- Patients with cardiac arrhythmia and severe hypertension
- Patients with chronic renal failure
- Patients with severe vascular disease
- patients with FEV <50% of expected
- Very obese patients
- Patients with large incorporated metallic implants such as: Pacemakers; Orthopedic rods and plates of dimensions > 1000/frequency (MHz) [e.g., > 10 cm at 100 MHz].

## 4.0 Patient Registration

4.1 Obtain the patient's informed consent and complete the Patient Registration Form.

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| Call the Clinical Research Office of Radiotherapy of Akademisches Lehrkrankenhaus Radiologie- Zentrum of Fulda- 36013 Fulda ( Germany)<br>Phone: 0661 846340<br>Fax: 0661 846342 |

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4.2 When eligibility is confirmed, the patient will be entered and a study I.D. number will be faxed or given to the investigator over the phone/fax or by e-mail to principal investigators.

4.3 A patient must not start the treatment prior to the registration.

## 5.0 Adjuvant radiotherapy

Megavoltage equipment is required with photon energies of $\geq$ 6 MV. Typical field arrangements will be 4 field or 6 field technique for the prostate bed boost area. The use of patient immobilization, Computerized Tomography (CT) simulation and three-dimensional conformal radiation therapy (3D CRT) is mandatory for all patients. Patients receive 64 Gy (2 Gy x 32 fractions) to the seminal vesicle area and CaP bed (ICRU-report 50). A Colin PET and fusion imaging could be used when available. CT treatment planning and conformal techniques are

recommended.

A bladder filling protocol should be utilized to ensure that the bladder is comfortable full at the time of planning and during treatment.

Patients should evacuate their bowels prior to planning and treatment.

## 5.1 CTV boundaries

Central to the CTV delineation is an accurate identification of the vesicourethral anastomosis, a site of considerable risk of recurrence. The anastomosis is often difficult to identify on conventional CT images and may be better visualised following intravenous contrast with delayed scanning to allow contrast accumulation in the bladder, or with MRI fusion.

The inferior border of the CTV will be 5-6 mm below the vesicourethral anastomosis depending on CT slice thickness but should extended lower to include all surgical clips inferiorly. The anastomosis can be identified on axial, coronal and sagittal reconstruction as the first slice below where urine is last visible. When the anastomosis is not clearly defined the inferior border will the slice above the penis bulb.

Anterior border: From the lower border of the CTV to 3 cm superior, the anterior border of the CTV is the posterior aspect of the symphysis pubis. More superiorly the anterior border of the CTV encompasses the posterior 1.5 cm of the bladder.

Posterior border: The space delineated by the elevator and rectal wall is at risk for recurrence and should be encompassed in the CTV if the rectal dose constraints allow. Ensure a minimum 2 cm margin from the posterior extent of the CTV to the posterior rectal wall to prevent the entire circumference of rectum receiving the full radiation dose.

Lateral border: The medial border of the elevator ani muscle or obturator internal muscle.

Superior border: The superior border should encompass all of the seminal vesicle bed as defined by non-vascular clips and should include the distal portion of the deferens.

If the seminal vesicles are pathologically involved by tumor, ensure any residual vesicles are also included in CTV ( paragraph 5.1).

Rectal, bladder and femoral neck dose constraints should be in accordance with those applied for definitive prostate radiotherapy.

Critical structure delineation and planning target volume delineation should be described in detail (paragraph 5.3).

## 5.2. Seminal vesicle

The seminal vesicles or remnants, if identified on CT or MRI as being present, should be included in the CTV in their entirety and may be treated to full dose at the discretion of the treating physician. The immediate peri-prostatic bed clips, if present, should receive the full dose.

The prostate tumor bed should be designed according to the previous prostate volume, as determined by the preoperative CT, with a 1.0 cm margin around the prostate gland area. The total irradiation dose should be of 64 Gy.

Radiation will begin at least 6 weeks following prostatectomy and lymphadenectomy.

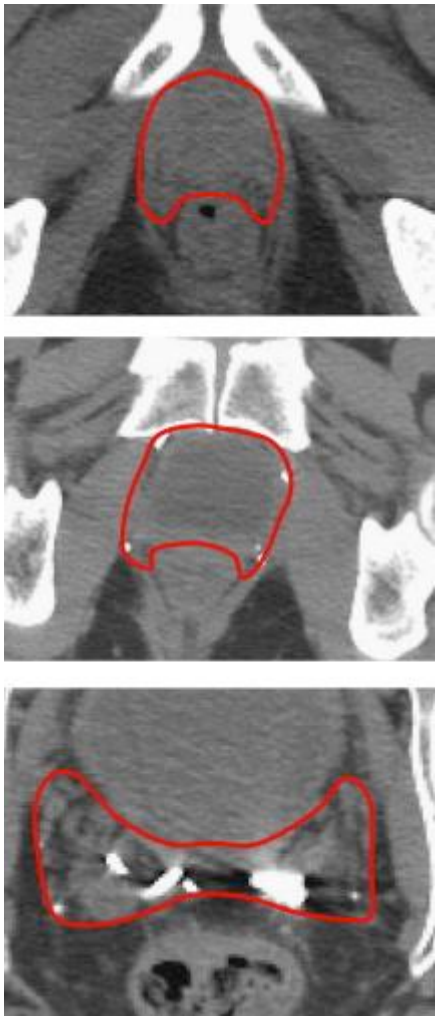
### 5.3. Intensity Modulated Radiation Therapy (IMRT)

The Intensity Modulated Radiation Therapy ( IMRT) is strongly recommended, for centers where this technique is available. The PTV will be the same as for 3DCRT; there is no need to add additional margin for penumbra. A series of dose-volume histograms ( DVHs ) will be generated and analyzed to determine the adequacy of the plan. At least 95% of the PTV should receive the prescribed dose; a variation will be noted if <95% to 90% of the PTV receives the prescribed dose, and a protocol violation will be noted if <90% of the PTV receives the prescribed dose. The dose marker levels for bladder and rectum have been modelled after prior studies in men treated definitively with IMRT for prostate cancer. The plan will be deemed acceptable under the following conditions:the maximum dose heterogeneity allowable in the PTV will be 15%; a variation will be >15% and a violation >25%. Since the dose is prescribed to the minimum isodose line of the PTV, the dose variability is seen in portions of the target volume receiving higher than the specified dose.

### 5.4. Constraints and protocol violation

Less than or equal to 25% and 50% of the rectum should receive ≥64 Gy and ≥50 Gy, respectively. Less than or equal to 40% and 60% of the bladder should receive ≥64 Gy and ≥50 Gy, respectively. A variation will be noted if up to an additional 7.5% of the rectal and bladder volumes receive above the target doses specified. The inclusion of rectal volumes beyond these constraints will be considered a protocol violation. The inclusion of bladder volumes beyond these constraints will be considered a secondary protocol variation; it will not be considered a protocol violation. For IMRT, no specific field arrangement is required.

**Figure 1. Example of CT simulation in a patient submitted to radical prostatectomy. The CTV to receive 64 Gy is delineated including tumor bed and seminal vesicle area.**



## 5.5. **Critical Normal Structures**

The normal structures to be contoured will include bladder, rectum, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. Contours of normal structures should be present on all CT slices on which they appear. Software with an interpolation function may be used with the accuracy of interpolations confirmed by the treating radiation oncologist .The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosities) for a length of 15 cm or to the rectosigmoid flexure. This generally is below the bottom of the sacroiliac joints. The large and small bowels in the pelvis below the L4-5 interspace need to be contoured in the event that IMRT is used. The bladder should be kept distended during treatment.

Doses to the entire rectum shall not exceed 55 Gy. Doses to the small bowel

shall not exceed 50 Gy. Portions of the anterior rectal wall will receive the same dose as prostate tumor bed. In case of IMRT technique the doses delivered to organs at risk should be reported.

### 5.6. Radiation Toxicity

In the EORTC 22911 trial, the cumulative incidence of grade 3 toxicity at 5 years was 4.2% in the adjuvant radiotherapy arm and 2.6% in the control arm (P=0.073). The ARO 96-02 study reported in the adjuvant radiotherapy arm an acute grade 3 bladder and grade 2 rectal toxicity of 3% and 12% , respectively. No acute grade 3 toxicity was found. The rate of late grade 2 and 3 bladder toxicity was 16% and 2%, respectively, whereas the rate of late grade 2 rectal toxicity was 10%. It has to consider that these studies started in the late 1980s and radiation therapy was delivered by using old techniques. Today, new devices allow a better patient positioning control and a more defined target, with a dose reduction of organ at risk surrounding the volume to be irradiated. Consequently, acute and late effects are expected to be inferior to rate previously reported. However, an accurate symptoms monitoring is necessary in order to evaluate possible complications and to reduce acute and late toxicity.

For this reason all patients will be seen by the Radiation Oncologist during radiation therapy and patient weight, blood counts and tolerance of treatment should be accurately documented.

The following side effects may occur:

-Skin reactions

-Small bowel or rectal irritation as abdominal cramping, diarrhea, rectal urgency.

-Bladder complications including urinary frequency, dysuria, hematuria, urinary tract infections and incontinence.

Acute morbidity will be scored using the revised NCI Common Toxicity Criteria version (Appendix 2).

### 5.7. Treatment Interruptions

If a grade 3 hematologic toxicity develops (ANC < 1000/mm3 or Platelet count < 50,000 cells/mm3), radiotherapy and hyperthermia will be discontinued until the counts rise above these levels. In the presence of toxicities related to radiation therapy such as urinary frequency, dysuria, or diarrhea that does not respond to appropriate medications, a treatment interruption of one or more weeks may be necessary until the patient recovers.

## 6.0. Androgen Suppression Therapy (AST)

AST has traditionally been used for the management of metastatic prostate cancer; however, following the publication of several trials in early 2000 examining the use of AST in combination with RT for patients with high-risk or locally advanced prostate cancer, the administration of AST with RT has become the standard of care for these patients. There has also been a trend for increasing use of AST in non-metastatic patients with rising prostate-specific antigen levels. In particular,

intermediate and high-risk patients treated with RT plus AST had significantly better outcomes than those treated with RT alone. Especially, data suggest a significant benefit in 5-year PSA outcomes for men with clinically localized prostate cancer in intermediate- and high-risk groups treated with RT plus AST versus those treated with RT alone.

## 6.1. Adjuvant Androgen Suppression Therapy

Randomized controlled phase III clinical trials have examined the efficacy of AST as adjunctive therapy to prostatectomy and radiation therapy. Whereas neoadjuvant AST before radical prostatectomy did not improve overall survival, only a small randomized trial demonstrated the benefit in terms of overall survival (OS) of adjuvant AST in patients with nodal metastases who underwent prostatectomy and lymphadenectomy.

In the Bicalutamide Early Prostate Cancer program in patients without nodal metastases treated by RP the adjuvant AST didn't improve OS and only a delay in progression was reported.

Only in the RT group there was an advantage in OS, whereas in patients with localized disease, initially underwent watchful waiting, there was a trend (not statistically significant) to decreased survival [27].

In the present study, patients with nodal metastases are excluded, consequently no benefit in OS is expected by adding AST . As yet, no large randomized study has addressed the benefits of adjuvant AST after radical prostatectomy and use of such treatment in not recommended outside of the context of a clinical trial [28]. Furthermore, the evidence indicates that AST might be associated with an increased risk of non-cancer-related mortality. A randomized clinical trial of expectant management compared with expectant management plus AST showed increased cardiac mortality in men who received AST. Additionally, AST has been shown to be associated with an increased risk of cardiac-related events in claims-based analyses of large cohorts. In particular, AST combined with radiotherapy was associated with fatal myocardial infarction in men of age $\geq$ 65 years who were treated for only 6 months as compared with men who were nor treated with AST [29].

It has to be noted that patients with unstable cardiac status (angina pectoris, documented cardiac infarction or heart failure requiring medication) or with cardiac arrhythmia and severe hypertension should be excluded from this study even if at high risk of distant recurrence (paragraph 3.2).

## 7.0 Hyperthermia

Local hyperthermia (LHT) is scheduled twice weekly during the time of external irradiation and it should start within one hour before or preferably after irradiation to at least a total of 10 sessions. The interval between two LHT sessions has to be a minimum of 72 hours. Thermometry probes have to be positioned in the rectum, and in the bladder for continuous thermometry and thermal mapping of tumor-related temperatures.

Therapeutic time starts when the tumor-related temperature in the rectum

reaches a minimum of 41.5°C or 30 min after enabling power. Therapeutic time is scheduled to be 60 min, the maximum total duration should not exceed 90 min.
The positioning of Sigma 60 or Sigma Eye array should be clearly indicated by using anatomical reference points. All participant centers must use the same reference points (to be defined).

## 7.1 Thermometry and E – Field Measurements

Catheter location: closed ended catheters (Somatex ® catheters are recommended) could be placed in the bladder and in the rectum. Catheter location and spatial designation of catheter sites in tumor or normal tissue must be documented on at least one occasion by CT or radiotherapy simulation.

E-Fields: a minimum of 4 averaging multiple dipole E-field sensors must be placed on the patient's surface in longitudinal direction such that the sensor is longitudinally centered within the device. In addition, "scanning" of a single E-field sensor will be performed within one or more of the thermometry catheters. Phase and amplitude steering will be tested at low levels of forward power (<250 W) to attempt to maximize the ratio of E-field strengths detected in the tumor to normal tissue.

## 7.2 Temperature Measurements

All temperatures will be measured by sensors calibrated with an NBS traceable standard. High resistant lead or fiber-optic type sensors are permissible if calibration determines their inaccuracy to be < 0.2°C. Single sensors will be "mapped" manually or automatically within the entire thermometry catheter length in tissue on a minimum of 2 occasions (once near the beginning and once near the end of treatment) during each hyperthermia session if technically feasible. As an alternative, multisensor thermometry may be used in a stationary or mapped mode. Systemic temperatures must be determined by intermittent (at least every 10 minutes) oral or rectal measurement, depending on the treatment site, (rectal temperature is not representative of systemic temperature during pelvic treatments) or by continuous measurement per N.G. tube. The temperature of the circulating coupling medium should also be recorded.

<u>Hyperplan System</u>

The use of Hyperplan System, when available, is strongly recommended. All centers using this system should came to an agreement in order to follow the same rules in recording thermal parameters. All participant centers should indicate a physicist responsible of temperature measurements.

## 7.3 Additional Monitoring

Some parameters have to be monitored during hyperthermia and some rules to be observed (paragraph 7.7):
-Heart rate at least continuously

-Blood pressure continuously
-Observe patient status every 5 minutes
-Document areas of discomfort

The use of analgesia will be at the discretion of the investigator, but drug and dose must be documented in the treatment record. Patients will not be sedated to a level where responsiveness to stimuli is suspect, especially during LHT session, to obtain an efficient patient's collaboration. This is a requisite for modifying treatment parameter in order to avoid "hot spot" and related complications.
A physician from the Department of Radiation Oncology will be in attendance during all the hyperthermia treatments.

## 7.4 Concomitant Medications

All concomitantly administered medications and therapy which, by virtue of direct pharmacologic action or possible heat interaction, could influence the intended effects of the study therapy or mask its side effects must be documented on case report forms. A concerted effort should be made to control the dosage of concomitant medications.

## 7.5 Treatment Parameters

The objective of treatment is achievement of a minimum tumor temperature of 41.5°C. If this is achieved, power will be regulated to maintain temperature for 30 to a maximum of 60 minutes. If this is not achieved, power will be increased to maximum tolerated levels or until reasonable normal tissue temperatures are exceeded. (Maximum intra-tumoral temperature should not exceed 50°). A maximum duration of 100 minutes of applied power will be permitted. Failure to achieve 41.5°C in at least one intra-tumoral location for 20 minutes in at least two sessions will make the case not evaluable for response and toxicity.

## 7.6. Conditions dictating a reduction of applied power and/or cessation of hyperthermic treatment.

The following conditions may reduce applied power or interrupt the treatment:
-Patient request
-Intractable pain
-Nausea/Vomiting
-Monitored Normal Tissue Temperature (MNTT) > 44°C
-Pulse > 160
-Blood Pressure : systolic > 180 or < 90 mmHg, diastolic > 100 or < 50 mmHg
-Altered Mental Status
-Systemic Temperature (ST) > 40°C.

## 7.7. Rules to be observed during the treatment

The following treatment and patient parameters must be observed during the treatment:

a) Clinical observation of patient on a regular basis, including response to stimuli.

b) Core temperature must not at any time rise above 40°C maximum. Since thermal run-on can cause systemic temperature to exceed the limit specified, the clinician should establish a maximum allowable core temperature at a level somewhat below 40°C to provide a margin of safety.

c) Emergency cardiopulmonary resuscitation and hypothermia inducing equipment must be on regular standby availability

d) Patient must be observed post treatment until core temperature, hemodynamic parameters and mental status have normalized (at least 30 min of observation is required).

### 7.8. Non – Ionizing Radiation Protection and Monitoring

Although protection will be the responsibility of each individual department, it is in the interest of all participants that safety rules be adopted for protection of patients, medical and technical staff (see Section 5-1 of the BSD-2000 manual). For the high power and the non-I.S.M. (Industrial, Scientific, Medical) frequencies required for deep regional heating with electromagnetic radiation, an adequately shielded enclosure around patient and applicator is required. All patients will therefore be treated within a Faraday cage type enclosure through which visual contact between the patient and the responsible investigation can be maintained throughout the treatment. Faraday cage characteristics and type, specifying the visual contact, should be reported.
Stray field measurements at 1 meter from the patient's feet and head and on a perpendicular 1 meter from the center of the applicator will be determined during at least one session during the course of treatment.

### 7.9. Sequencing

Hyperthermia treatment will start following the delivery of 1 test-session before the irradiation course (this test has to be considered mandatory ) to evaluate the feasibility and the compliance of patient and it will be delivered once weekly thereafter, within 60 minutes of an individual radiation fraction and should be recorded and continued until completion of radiation. If the feasibility of heating or compliance of patient will appear negative (negative test), patient will be excluded from the study. In case of good compliance (positive test) hyperthermia will be delivered throughout the entire course of radiation therapy if the patient’s tolerance permits but should not exceed two treatments per week. Hyperthermia will be delivered two / weekly for five-six weeks, for a minimum of ten treatments. If a hyperthermic session weekly scheduled is not delivered, it couldn’t be replaced the next week by adding a third session. Only a maximum of two sessions per week should be scheduled.

### 7.10. Toxicity

Toxicity will be assessed using the formulation reported by the NCI Hyperthermia equipment evaluation contractors group, including:
- Acute toxicity defined as occurring during the session and dependent on application of power.
- Subacute toxicity defined as occurring within 24h of a session and persisting for >24h thereafter.
- Complications defined as adverse reactions which require cessation of treatment, and/or medical or surgical intervention.

Subacute pain should be evaluated with serum creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and alkaline phosphatase determinations at 24 and 48 hours post treatment. Elevated levels should be followed until they return to normal. Large CPK elevation should also be evaluated by limited CT of the painful site. Subsequent hyperthermia sessions should be deferred until the subacute pain has resolved and serum chemistries have normalized.

## 8.0 Surgery

Radical prostatectomy is widely used today in men in whom it is felt that the malignancy is completely removable by surgery. This, in general, applies to those men with a stage T1 or T2 disease with low-to-moderate grade pathology and a life expectancy of more than 10 years. Cure may be achieved in some patients with minimal T3 disease, and perhaps a very few with minimal lymph node metastases.
The goal of radical prostatectomy, whether by the retropubic or perineal or laparoscopic approach, is to achieve complete excision of the prostate, seminal vesicles and adjacent tissue.

Significant advances in surgical technique have made the operation considerably safer, with reduction of blood loss and decrease in significant urinary incontinence [30,31]. Moreover, when a nerve-sparing approach is elected, preservation of potency in at least a proportion of younger men may be achieved [32,33]. The urologist would report the nerve sparing technique if it was used. Radical perineal prostatectomy (RPP) is considered the original prostate cancer operation. Radical retropubic prostatectomy (RRP) is an alternative to RPP for patients having pelvic lymph node metastasis at diagnosis. After that, the importance of pelvic lymph node dissection (PLND) for staging became evident. Over time, RRP became the most common method of radical prostatectomy. Surgeons who performed radical perineal prostatectomy had been performing open PLNDs first. If the PLND findings were negative, they would then proceed with the radical perineal prostatectomy. More recently, many surgeons have performed laparoscopic PLNDs or minilap PLNDs. If the findings from frozen section pathologic analysis are negative for lymph node metastasis, they perform the radical perineal prostatectomy at the same setting.

The type of radical prostatectomy and PLND performed should be accurately described by the surgeon to correctly plan the adjuvant treatment. A radical prostatectomy (RPP or RRP) should be performed 4-5 weeks before the starting of adjuvant radiotherapy. The summary of operation describing the suspect of any tumoral residual should be reported by the urologist in the patient's sheet. Every

surgical complication has to be described in order to avoid further side effects by adding ART and HT.

In order to select patients to include in this study, PLND is strongly recommended if pelvic lymph nodes are > 1.5 cm in greatest dimension.

## 9.0 Biochemical failure

A PSA failure is defined as a consistent and significant rise in the PSA. A number of different proposals have been made for a definition of biochemical failure following radiation therapy; these definitions depended on the post-treatment PSA nadir, the number of consecutive rises, and the magnitude of the increase.

The estimates of biochemical failure rate will vary considerably depending on which definition of biochemical failure is used. In recognition of this controversy, the American Society for Therapeutic Radiology and Oncology (ASTRO) convened a panel of experts in 1996 to establish a common definition of biochemical failure after radiation. The ASTRO definition of rising PSA will be used. Thus, when the PSA rises on three consecutive occasions, biochemical failure has occurred and the date of failure is midway between the last non-rising PSA and the first rise in PSA [34,35]. Biopsies are strongly recommended for patients with evidence of distant failure to assist in accurately determining the local control rate. In the absence of a biopsy, such patients will be considered local failures if their exam is abnormal. A second Consensus Conference was sponsored by ASTRO and RTOG in 2005 to revise the ASTRO definition [36]. The panel recommended: 1) a rise by 2 ng/ml or more above the nadir PSA be considered the standard definition for biochemical failure after RT; 2) the date of failure be determined at call not back dated; 3) the ASTRO definition be allowed to use after RT alone (no hormonal therapy).

## 10.0 Quality of life analysis

Quality of life analysis has to be performed by serial measurements using four validated questionnaires. They usually include FACT-P questionnaire [Functional Assessment of Cancer Therapy-Prostate], International index of erectile function questionnaire, I-PSS questionnaire [International Prostate Symptom Score] and the RTOG [Radiation Therapy Oncology Group] FACE [Functional Alterations due to Changes in Elimination] questionnaire [37,38]. In this study Quality of life will be measured using the UCLA Prostate Cancer Index (UCLA PCI) and Medical Outcome Study 36-item SF (SF 36) questionnaires.

## 11.0 Response Assessment

For the purposes of this study, patients should be reevaluated for response at 3 months and then every six months post therapy.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee [*JNCI* 92(3):205-216, 2000]. Changes in only the largest

diameter (uni – dimensional measurement) of the tumor lesions are used in the RECIST criteria.

### 11.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with conventional techniques (PET, CT, MRI, x-ray) or as ≥10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

### 11.2 Measurement of Effect

All PSA levels done during a follow-up interval will be recorded on the data forms. After study entry, disease activity evaluations will be made and recorded using the following criteria:

### 11.3 Response Criteria and evaluation of target lesions

a) Complete Response (CR): Disappearance of all target lesions

b) Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

c) Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

d) Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

## 12.0 Other Response Parameters

### 12.1 Freedom from biochemical (PSA) failure

For this study the ‘PSA nadir’ will be defined as the lowest PSA value reached immediately preceding a ‘PSA failure’. A biopsy will be performed for all patients with evidence of biochemical failure or growth of a palpable abnormality. A PSA failure is defined as a consistent and significant rise in the PSA. The ASTRO consensus definition of rising PSA will be used according to the second ASTRO-RTOG Consensus Conference recommendations (2005).

### 12.2 Time to Local Progression

The time to progression will be measured from the date of study entry to the date of documented local progression. Patients who have a normal exam and no evidence of having a PSA failure will be considered controlled locally. Patients with a residual abnormality or a PSA failure shall undergo biopsy to distinguish between local and distant failures.

### 12.3 Time to Distant Failure

The time to distant failure will be measured from the date of randomization to the date of documented metastatic disease. Patients with evidence of PSA failure but a negative biopsy will be considered to have experienced only a distant failure.

### 12.4 Disease-Free Survival

The progression-free survival will be measured from the date of inclusion in the study to the date of documentation of progression or until the date of death. This endpoint includes all measures of disease including physical exam, PSA, bone scans and biopsies.

### 12.5 Survival

The survival time will be measured from the date of study entry to the date of death. All patients will be followed for survival. Every effort should be made to document the cause of death.

### 12.6 Duration of overall response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

### 12.7 Duration of stable disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

## 13.0 Follow up

Follow up should be performed every 3 months (PSA controlling) for 2 years and every 6 months for additional 3 years. Before starting the treatment, Colin CT-PET is strongly recommended.

Performance status, PSA, should be obtained at the end of RT (4 months) and then every 3 months (until the end of year 3).
A PSA should be obtained after year 2, every 6 months for 3 more years, then at least annually for the remainder of the patient's life. If a PSA of > 0.4 ng/ml is recorded, a repeat PSA should be obtained to verify progression.

A bone scan will be performed on any patient with complaints of bone pain that cannot be attributed to any intercurrent disease. Discretionary plain films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.

Bone scans and a pelvic CT or MRI are recommended at least yearly, or more often if clinically indicated, after PSA progression to determine rates of metastatic progression. All PSA levels done during a follow-up interval will be recorded on the data sheet.

### 13.1. Protocol treatment interruption

Protocol treatment may be discontinued for any of the following reasons:
• Progression of disease;
• Unacceptable toxicity at the discretion of the treating physician (the reasons for removal must be clearly documented on the appropriate case report form);
• Toxicities that do not resolve within 15 days;
• A delay in protocol treatment ≥ 8 weeks.
If protocol treatment is discontinued, follow up and data collection will continue as specified in the protocol.

Parameters evaluation planning

| Parameters | Pre-treatment | Weekly during RT | Post RT |
|---|---|---|---|
| Weight, Performance Status | X | | X |
| CBC, Platelets | X | X | X |
| Chemistry | X | | X |
| PSA | X | | X |
| Bone Scan | X | | |
| Pelvic CT / Endoscopy | X | | X |
| Toxicity Assessment | | X | X |
| QoL Questionnaire | X | | X |
| Colin TC-PET | X | | X |

a. PSA: Every 3 months for 1 year, every 6 months for 3 years, then annually.

b. Chemistry: Serum ALT, Alkaline phosphatase, Bilirubin, BUN, Creatinine, every month.
c. Bone scan: At baseline and every 8-12 months X 3 , then as clinically indicated. A bone scan will be performed on any patient with complaints of bone pain that cannot be attributed to any intercurrent disease. X-films may be needed to evaluate lesions seen on bone scan to confirm the diagnosis of metastatic disease.
d. Pelvic CT / endoscopy: To be performed annually X 4 and later if clinically indicated.
e. QoL: UCLA PCI and SF 36 questionnaires before and after RT
f. Colin PET: before RT and 1 year after

## 14.0 Statistical considerations (modified after Atzelsberg meeting 8.04.2011)

The primary endpoint freedom for progression (FFP) rate by 5 years is defined as the proportion of patients with a FFP failure by 5 years from the registration among all eligible patients at baseline.

### 14.1. Sample Size

The primary goal of this study is to estimate the rate of freedom from progression (FFP) by 5 years of the addition of Hyperthermia (HT) to adjuvant radiation therapy (ART) in men receiving post-prostatectomy therapy. We expect that ≥ 50% of patients will experience a FFP failure event without treatment post-prostatectomy, which is a projected rate by a recent update of SWOG 8794 [39].

Based on previously reported data in paragraph 1.1 ( EORTC 22911 and ARO 96-02/ AUO AP 09/95 trials), radical prostatectomy + ART, in patients R1 or pT3N0M0 achieved a therapeutic gain in terms of 5-yr biochemical relapse-free survival ranging from 18 to 22% (74% vs 52% and 72% vs 54% in the EORTC and ARO trial, respectively).

Hyperthermia + ART will be considered to have superior therapeutic efficacy vs. ART alone if the FFP is ≥ 15% at 5 years. The null hypothesis (Ho) is that HT + ART after prostatectomy will yield a FFP rate at 5 years ≤ 70% versus the alternative hypothesis (Ha) that HT + ART after prostatectomy will improve the FFP rate at 5 years to 80.5%.

To demonstrate a difference in FFP at 5 years of 10.5 (gain of 15% by adding LHT) the number of patients to be enrolled is 268. Adjusting the number of cases by 10% ( for ineligible or un-analyzable cases) the minimum number per arm is 294.8 [40,41].

### 14.2. Toxicity

The study will be stopped if any Grade 5 toxicity is observed. The study will be stopped if there is evidence that Grade 3 and Grade 4 toxicity combined exceed 20%.

### 14.3. Efficacy (to be discussed)

We hypothesize that the addition of hyperthermia (HT) to adjuvant radiation therapy (ART) will improve freedom from progression (FFP) at 5 years by 15% in men at high risk of failure post-prostatectomy despite use of ART. A failure event for FFP is defined as biochemical (PSA) failure (a PSA ≥ 0.40 ng/ml confirmed by a second PSA higher than the first by any amount, or initiation of hormone therapy), clinical failure (local regional or distant failure), or death from any cause by 5 years from registration. The FFP rate, is defined as the proportion of patients without a failure event for FFP by 5 years from the registration among all eligible patients at baseline. We will report the conclusion of the primary endpoint when all patients have at least 3 years of follow-up from the registration unless we stop at any interim stage. The FFP rate by 5 years will be calculated as the number of patients who do not have FFP failure events by 5 years divided by the total number of analyzable patients at the evaluation time point. Analyzable patients are defined as eligible patients who received any protocol treatment with at least 5 years follow-up from registration.
If a Grade 5 adverse event definitely, probably, or possibly related to treatment is reported within 2 years from the registration, it will be reviewed by the study chairs, the study statistician, source documentation, and a statistical report summarizing the study data will be reviewed as soon as possible. During this review, accrual will be suspended. Following this review, the study chairs, the study statistician, and the ESHO Committee will discuss the findings and make a decision about amending and/or continuing the study.

**15.0. Data analysis**. Data will be analyzed with the help of the qualified Biostatistics staff .

a) Rates, ratios and confidence intervals will be provided to estimate toxicity and success of the treatment combination.

b) QoL will be analyzed using standard methods UCLA PCI and SF 36 questionnaires.

## 16.0 Adverse Event Reporting

- The following guidelines for reporting adverse drug reactions (ADRs) apply to any research protocol that uses anticancer agents. The following ADR's experienced by patients should be reported to the dedicated Hospital committee within 10 working days and to the BSD Medical Corporation Clinical Study Monitor by telephone within 24 hours and confirmed in writing within five working days

- Any ADR which is life threatening (grade 4) or fatal (grade 5) and unknown. Any occurrence of secondary AML (Acute myelogenous leukemia) or MDS (Myelodysplastic syndrome) must also be reported.

## 16.1. Serious Adverse Event (SAE)

**Definition of a SAE:** Any adverse experience occurring during any part of protocol treatment and 30 days after that results in any of the following outcomes:
• Death;
• A life-threatening adverse drug experience;
• Inpatient hospitalization or prolongation of existing hospitalization;
• A persistent or significant disability/incapacity;
• A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

## 17.0 Records to be Kept

In addition to the regular hospital chart, a separate patient folder will be kept which includes:

- The patient's signed, dated and witnessed consent.
- The completed Patient Registration Form and all other study forms.
- Flow Sheet reflecting pretreatment test results and the first therapy.
- Measurement Form showing baseline measurement (measurable disease).
- Pathology Report (pathologic confirmation of disease).
- Follow-up forms : at each follow- up every 3 months for two year, every 6 months for three years and then annually. Also at progression/ relapse and at death. A Follow-Up Form is submitted at the time the patient goes off study and every 6 months thereafter until death.
- A final Treatment Summary Form and a Toxicity Summary Form are to be submitted when the patient progresses, dies, or goes off study for any other reason. Death must be reported, using the Follow-Up Form.

## 18.0 Pathology Requirements

Pathological confirmation of adenocarcinoma with the Gleason score of the

tumor is required prior to treatment by specimen examination.

Special Considerations*:*

For special laboratory/pathology samples:

Identify personnel who will process the samples:

Give specific instructions for preparation and shipment (types of tubes, spun, frozen, on wet/dry ice or at room temperature, sent by overnight mail or batched, etc.)

Give name and address of person to whom samples are to be sent and name of phone number of contact person to consult prior to shipping.

For questionnaires or quality of life assessment tools:

Study questionnaires should be provided with the protocol and mentioned in the model consent.

**Table 1. results of HT added to RT in locally advanced prostate cancer-phase II studies**

| Reference | N° pts | Therapy | Results | Toxicity |
|---|---|---|---|---|
| Anscher 1997 | 21 | 65-70 Gy + RHT | Feasible | No grade III |
| Deger 2002 | 59 | 68.4 Gy + IHT | Feasible | Well tolerated |
| Kalapurakal 2003 | 13 | 39.6-66.6 Gy + RHT | Feasible | - |
| Van Vulpen 2002 | 12 | 70 gy + IHT | Feasible | - |
| Algan 2000 | 26 | 68 Gy + UHT | Feasible | Well tolerated |
| Hurwitz 2002 | 30 | 68 + UHT | - | Rectal toxicity |
| Hurwitz 2005 | 37 | RT+ UHT | | No grade III |
| Van Vulpen 2004 | 26 | 70 Gy + IHT | Feasible | Well tolerated |
| Tilly 2005 | 22 | 68.4 Gy + RHT | Correlation with thermal dose | - |
| Maluta 2007 | 144 | 74 Gy + RHT | Feasible | No grade III |



1.

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**Appendix 1** :

**FACT-P, Quality of Life Form**

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

| | **PHYSICAL WELL-BEING** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy……. | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea…… | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family……. | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain…… | 0 | 1 | 2 | 3 | 4 |
| GP4 | I am bothered by side effects of treatment……. | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill……. | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed……. | 0 | 1 | 2 | 3 | 4 |
| | **SOCIAL/FAMILY WELL-BEING** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
| GS1 | I feel close to my friends..……... | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family…...…… | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends…...……..……. | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness……..…… | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness……..…….. | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support)…...……. | 0 | 1 | 2 | 3 | 4 |

Q1 *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box* ☐ *and go to the next section.*

| | | | | | | |
|---|---|---|---|---|---|---|
| GS7 | I am satisfied with my sex life……. | 0 | 1 | 2 | 3 | 4 |

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

| | **EMOTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GE1 | I feel sad…….. | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness..... | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness..... | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous…… | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying……. | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse……. | 0 | 1 | 2 | 3 | 4 |

| | **FUNCTIONAL WELL-BEING** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home)……..... | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling…...… | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life…… | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness……..… | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well……...….. | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun…… | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now... | 0 | 1 | 2 | 3 | 4 |

By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

| | **ADDITIONAL CONCERNS** | **Not at all** | **A little bit** | **Somewhat** | **Quite a bit** | **Very much** |
|---|---|---|---|---|---|---|
| C2 | I am losing weight……. | 0 | 1 | 2 | 3 | 4 |
| C6 | I have a good appetite…….. | 0 | 1 | 2 | 3 | 4 |
| P1 | I have aches and pains that bother me…… | 0 | 1 | 2 | 3 | 4 |
| P2 | I have certain areas of my body where I experience significant pain…….. | 0 | 1 | 2 | 3 | 4 |
| P3 | My pain keeps me from doing things I want to do... | 0 | 1 | 2 | 3 | 4 |
| P4 | I am satisfied with my present comfort level…….... | 0 | 1 | 2 | 3 | 4 |
| P5 | I am able to feel like a man……..… | 0 | 1 | 2 | 3 | 4 |
| P6 | I have trouble moving my bowels……..….. | 0 | 1 | 2 | 3 | 4 |
| P7 | I have difficulty urinating…… | 0 | 1 | 2 | 3 | 4 |
| Bl2 | I urinate more frequently than usual…… | 0 | 1 | 2 | 3 | 4 |
| P8 | My problems with urinating limit my activities….. | 0 | 1 | 2 | 3 | 4 |
| BL5 | I am able to have and maintain an erection……. | 0 | 1 | 2 | 3 | 4 |

# Appendix 2:

## NCI COMMON TOXICITY CRITERIA (Version 2.0)

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| **ALLERGY/IMMUNOLOGY** | | | | | |
| Allergic reaction/ hypersensitivity (including drug fever) | none | transient rash, drug fever <38°C (<100.4°F) | urticaria, drug fever ≥38°C (≥100.4°F), and/or asymptomatic bronchospasm | symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema | anaphylaxis |
| Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category. | | | | | |
| Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) | none | mild, not requiring treatment | moderate, requiring treatment | - | - |
| Autoimmune reaction | none | serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required | evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs | reversible autoimmune reaction involving function of a major organ or other toxicity (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment | autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required |
| Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis. | | | | | |
| Serum sickness | none | - | - | present | - |
| Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above. | | | | | |
| Vasculitis | none | mild, not requiring treatment | symptomatic, requiring medication | requiring steroids | ischemic changes or requiring amputation |
| Allergy/Immunology-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **AUDITORY/HEARING** | | | | | |
| Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category. | | | | | |
| Earache is graded in the PAIN category. | | | | | |
| External auditory canal | normal | external otitis with erythema or dry desquamation | external otitis with moist desquamation | external otitis with discharge, mastoiditis | necrosis of the canal soft tissue or bone |
| Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category. | | | | | |
| Inner ear/hearing | normal | hearing loss on audiometry only | tinnitus or hearing loss, not requiring hearing aid or treatment | tinnitus or hearing loss, correctable with hearing aid or treatment | severe unilateral or bilateral hearing loss (deafness), not correctable |
| Middle ear/hearing | normal | serous otitis without subjective decrease in hearing | serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge | otitis with discharge, mastoiditis or conductive hearing loss | necrosis of the canal soft tissue or bone |
| Auditory/Hearing-Other (Specify, _____) | normal | mild | moderate | severe | life-threatening or disabling |

| **Grade** | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| **BLOOD/BONE MARROW** | | | | | |
| Bone marrow cellularity<br><br>Normal ranges:<br>children (≤18 years)<br>younger adults (19-59)<br>older adults (≥60 years)<br>Note: Grade Bone marrow cellularity only for changes related to treatment not disease. | normal for age<br><br>90% cellularity average<br>60-70% cellularity average<br>50% cellularity average | mildly hypocellular or 25% reduction from normal cellularity for age | moderately hypocellular or >25 - ≤50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity | severely hypocellular or >50 - ≤75% reduction in cellularity for age or 4-6 weeks to recovery of normal bone marrow cellularity | aplasia or >6 weeks to recovery of normal bone marrow cellularity |
| CD4 count | WNL | <LLN - 500/$mm^3$ | 200 - <500/$mm^3$ | 50 - <200/$mm^3$ | <50/$mm^3$ |
| Haptoglobin | normal | decreased | - | absent | - |
| Hemoglobin (Hgb) | WNL | <LLN - 10.0 g/dl<br><LLN - 100 g/L<br><LLN - 6.2 mmol/L | 8.0 - <10.0 g/dl<br>80 - <100 g/L<br>4.9 - <6.2 mmol/L | 6.5 - <8.0 g/dl<br>65 - 80 g/L<br>4.0 - <4.9 mmol/L | <6.5 g/dl<br><65 g/L<br><4.0 mmol/L |
| Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies. | | | | | |
| For leukemia studies or bone marrow infiltrative/ myelophthisic processes | WNL | 10 - <25% decrease from pretreatment | 25 - <50% decrease from pretreatment | 50 - <75% decrease from pretreatment | ≥75% decrease from pretreatment |
| Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)<br><br>Also consider Haptoglobin, Hgb. | none | only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes] | evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion | requiring transfusion and/or medical intervention (e.g., steroids) | catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy) |
| Leukocytes (total WBC) | WNL | <LLN - 3.0 x $10^9$ /L<br><LLN - 3000/$mm^3$ | ≥2.0 - <3.0 x $10^9$ /L<br>≥2000 - <3000/$mm^3$ | ≥1.0 - <2.0 x $10^9$ /L<br>≥1000 - <2000/$mm^3$ | <1.0 x $10^9$ /L<br><1000/$mm^3$ |
| *Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.* | | *≥75 - <100% LLN* | *≥50 - <75% LLN* | *≥25 - 50% LLN* | *<25% LLN* |
| Lymphopenia | WNL | <LLN - 1.0 x $10^9$ /L<br><LLN - 1000/$mm^3$ | ≥0.5 - <1.0 x $10^9$ /L<br>≥500 - <1000/$mm^3$ | <0.5 x $10^9$ /L<br><500/$mm^3$ | - |
| *Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.* | | *≥75-<100%LLN* | *≥50-<75%LLN* | *≥25-<50%LLN* | *<25%LLN* |
| Neutrophils/granulocytes (ANC/AGC) | WNL | ≥1.5 - <2.0 x $10^9$ /L<br>≥1500 - <2000/$mm^3$ | ≥1.0 - <1.5 x $10^9$ /L<br>≥1000 - <1500/$mm^3$ | ≥0.5 - <1.0 x $10^9$ /L<br>≥500 - <1000/$mm^3$ | <0.5 x $10^9$ /L<br><500/$mm^3$ |
| Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies. | | | | | |
| For leukemia studies or bone marrow infiltrative/ myelophthisic process | WNL | 10 - <25% decrease from baseline | 25 - <50% decrease from baseline | 50 - <75% decrease from baseline | ≥75% decrease from baseline |
| Platelets | WNL | <LLN - <75.0 x $10^9$ /L<br><LLN - 75000/$mm^3$ | ≥50.0 - <75.0 x $10^9$ /L<br>≥50000 - <75000/$mm^3$ | ≥10.0 - <50.0 x $10^9$ /L<br>≥10000 - <50000/$mm^3$ | <10.0 x $10^9$ /L<br><10000/$mm^3$ |
| Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies. | | | | | |
| For leukemia studies or bone marrow infiltrative/ myelophthisic process | WNL | 10 - <25% decrease from baseline | 25 - <50% decrease from baseline | 50 - <75% decrease from baseline | ≥75% decrease from baseline |
| Transfusion: Platelets<br><br>Also consider Platelets. | none | - | - | yes | platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions) |
| Transfusion: pRBCs<br>Also consider Hemoglobin. | none | - | - | Yes | - |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Blood/Bone Marrow-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **CARDIOVASCULAR (ARRHYTHMIA)** | | | | | |
| Conduction abnormality/ Atrioventricular heart block | none | asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach) | symptomatic, but not requiring treatment | symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block) | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Nodal/junctional arrhythmia/dysrhythmia | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Palpitations | none | present | - | - | - |
| Note: Grade palpitations only in the absence of a documented arrhythmia. | | | | | |
| Prolonged QTc interval (QTc >0.48 seconds) | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Sinus bradycardia | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Sinus tachycardia | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment of underlying cause | - |
| Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter) | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Syncope (fainting) is graded in the NEUROLOGY category. | | | | | |
| Vasovagal episode | none | - | present without loss of consciousness | present with loss of consciousness | - |
| Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia) | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic and requiring treatment | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| Cardiovascular/ Arrhythmia-Other (Specify, _____) | none | asymptomatic, not requiring treatment | symptomatic, but not requiring treatment | symptomatic, and requiring treatment of underlying cause | life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock) |
| **CARDIOVASCULAR (GENERAL)** | | | | | |
| Acute vascular leak syndrome | absent | - | symptomatic, but not requiring fluid support | respiratory compromise or requiring fluids | life-threatening; requiring pressor support and/or ventilatory support |
| Cardiac- ischemia/infarction | none | non-specific T-wave flattening or changes | asymptomatic, ST- and T- wave changes suggesting ischemia | angina without evidence of infarction | acute myocardial infarction |
| Cardiac left ventricular function | normal | asymptomatic decline of resting ejection fraction of ≥10% but <20% of baseline value; shortening fraction ≥24% but <30% | asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥20% of baseline value; <24% shortening fraction | CHF responsive to treatment | severe or refractory CHF or requiring intubation |
| CNS cerebrovascular ischemia is graded in the NEUROLOGY category. | | | | | |
| Cardiac troponin I (cTnI) | normal | - | - | levels consistent with unstable angina as defined by the manufacturer | levels consistent with myocardial infarction as defined by the manufacturer |
| Cardiac troponin T (cTnT) | normal | ≥0.03 - <0.05 ng/ml | ≥0.05 - <0.1 ng/ml | ≥0.1 - <0.2 ng/ml | ≥0.2 ng/ml |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Edema | none | asymptomatic, not requiring therapy | symptomatic, requiring therapy | symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation | anasarca (severe generalized edema) |
| Hypertension | none | asymptomatic, transient increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment | recurrent or persistent or symptomatic increase by >20 mmHg (diastolic) or to >150/100* if previously WNL; not requiring treatment | requiring therapy or more intensive therapy than previously | hypertensive crisis |
| **Note: For pediatric patients, use age and sex appropriate normal values >95th percentile ULN.* | | | | | |
| Hypotension | none | changes, but not requiring therapy (including transient orthostatic hypotension) | requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences | requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences | shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion) |
| Also consider Syncope (fainting).<br>Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.<br>*For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.* | | | | | |
| Myocarditis | none | - | - | CHF responsive to treatment | severe or refractory CHF |
| Operative injury of vein/artery | none | primary suture repair for injury, but not requiring transfusion | primary suture repair for injury, requiring transfusion | vascular occlusion requiring surgery or bypass for injury | myocardial infarction; resection of organ (e.g., bowel, limb) |
| Pericardial effusion/ pericarditis | none | asymptomatic effusion, not requiring treatment | pericarditis (rub, ECG changes, and/or chest pain) | physiologic consequences resulting from symptoms | tamponade (drainage or pericardial window required) |
| Peripheral arterial ischemia | none | - | brief episode of ischemia managed non-surgically and without permanent deficit | requiring surgical intervention | life-threatening or with permanent functional deficit (e.g., amputation) |
| Phlebitis (superficial) | none | - | present | - | - |
| Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category.<br>Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category. | | | | | |
| Syncope (fainting) is graded in the NEUROLOGY category. | | | | | |
| Thrombosis/embolism | none | - | deep vein thrombosis, not requiring anticoagulant | deep vein thrombosis, requiring anticoagulant therapy | embolic event including pulmonary embolism |
| Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category. | | | | | |
| Visceral arterial ischemia (non-myocardial) | none | - | brief episode of ischemia managed non-surgically and without permanent deficit | requiring surgical intervention | life-threatening or with permanent functional deficit (e.g., resection of ileum) |
| Cardiovascular/ General-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **COAGULATION** | | | | | |
| Note: See the HEMORRHAGE category for grading the severity of bleeding events. | | | | | |
| DIC (disseminated intravascular coagulation)<br>Also grade Platelets.<br>Note: Must have increased fibrin split products or D-dimer in order to grade as DIC. | absent | - | - | laboratory findings present with no bleeding | laboratory findings and bleeding |
| Fibrinogen | WNL | ≥0.75 - <1.0 x LLN | ≥0.5 - <0.75 x LLN | ≥0.25 - <0.5 x LLN | <0.25 x LLN |
| Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies. | | | | | |
| For leukemia studies: | WNL | <20% decrease from pretreatment value or LLN | ≥20 - <40% decrease from pretreatment value or LLN | ≥40 - <70% decrease from pretreatment value or LLN | <50 mg% |
| Partial thromboplastin time (PTT) | WNL | >ULN - ≤1.5 x ULN | > 1.5 - ≤2 x ULN | >2 x ULN | - |
| Phlebitis is graded in the CARDIOVASCULAR (GENERAL) category. | | | | | |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Prothrombin time (PT) | WNL | >ULN - ≤1.5 x ULN | > 1.5 - ≤2 x ULN | >2 x ULN | - |
| Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category. | | | | | |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)<br><br>Also consider Hemoglobin (Hgb), Platelets, Creatinine.<br>Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments). | absent | - | - | laboratory findings present without clinical consequences | laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention |
| Coagulation-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **CONSTITUTIONAL SYMPTOMS** | | | | | |
| Fatigue (lethargy, malaise, asthenia) | none | increased fatigue over baseline, but not altering normal activities | moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities | severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities | bedridden or disabling |
| Fever (in the absence of neutropenia, where neutropenia is defined as AGC <1.0 x $10^9$/L)<br>Also consider Allergic reaction/hypersensitivity.<br>Note: The temperature measurements listed above are oral or tympanic. | none | 38.0 - 39.0°C (100.4 - 102.2°F) | 39.1 - 40.0°C (102.3 - 104.0°F ) | >40.0°C (>104.0°F ) for <24 hrs | >40.0°C (>104.0°F ) for >24 hrs |
| Hot flashes/flushes are graded in the ENDOCRINE category. | | | | | |
| Rigors, chills | none | mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication | severe and/or prolonged, requiring narcotic medication | not responsive to narcotic medication | - |
| Sweating (diaphoresis) | normal | mild and occasional | frequent or drenching | - | - |
| Weight gain<br>Also consider Ascites, Edema, Pleural effusion. | <5% | 5 - <10% | 10 - <20% | ≥20% | - |
| Weight loss<br>Also consider Vomiting, Dehydration, Diarrhea. | <5% | 5 - <10% | 10 - <20% | ≥20% | - |
| Constitutional Symptoms-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **DERMATOLOGY/SKIN** | | | | | |
| Alopecia | normal | mild hair loss | pronounced hair loss | - | - |
| Bruising (in absence of grade 3 or 4 thrombocytopenia)<br>Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category. | none | localized or in dependent area | generalized | - | - |
| Dry skin | normal | controlled with emollients | not controlled with emollients | - | - |
| Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis) | absent | - | scattered, but not generalized eruption | severe or requiring IV fluids (e.g., generalized rash or painful stomatitis) | life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support) |
| Flushing | absent | present | - | - | - |
| Hand-foot skin reaction | none | skin changes or dermatitis without pain (e.g., erythema, peeling) | skin changes with pain, not interfering with function | skin changes with pain, interfering with function | - |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Injection site reaction | none | pain or itching or erythema | pain or swelling, with inflammation or phlebitis | ulceration or necrosis that is severe or prolonged, or requiring surgery | - |
| Nail changes | normal | discoloration or ridging (koilonychia) or pitting | partial or complete loss of nail(s) or pain in nailbeds | - | - |
| Petechiae is graded in the HEMORRHAGE category. | | | | | |
| Photosensitivity | none | painless erythema | painful erythema | erythema with desquamation | - |
| Pigmentation changes (e.g., vitiligo) | none | localized pigmentation changes | generalized pigmentation changes | - | - |
| Pruritus | none | mild or localized, relieved spontaneously or by local measures | intense or widespread, relieved spontaneously or by systemic measures | intense or widespread and poorly controlled despite treatment | - |
| Purpura is graded in the HEMORRHAGE category. | | | | | |
| Rash/desquamation<br><br>Also consider Allergic reaction/hypersensitivity.<br>Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme. | none | macular or papular eruption or erythema without associated symptoms | macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area | symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area | generalized exfoliative dermatitis or ulcerative dermatitis |
| Urticaria<br>(hives, welts, wheals) | none | requiring no medication | requiring PO or topical treatment or IV medication or steroids for <24 hours | requiring IV medication or steroids for ≥24 hours | - |
| Wound- infectious | none | cellulitis | superficial infection | infection requiring IV antibiotics | necrotizing fascitis |
| Wound- non-infectious | none | incisional separation | incisional hernia | fascial disruption without evisceration | fascial disruption with evisceration |
| Dermatology/Skin-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **ENDOCRINE** | | | | | |
| Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae)<br>Also consider Hyperglycemia, Hypokalemia. | absent | - | present | - | - |
| Feminization of male | absent | - | - | present | - |
| Gynecomastia | none | mild | pronounced or painful | pronounced or painful and requiring surgery | - |
| Hot flashes/flushes | none | mild or no more than 1 per day | moderate and greater than 1 per day | - | - |
| Hypothyroidism | absent | asymptomatic, TSH elevated, no therapy given | symptomatic or thyroid replacement treatment given | patient hospitalized for manifestations of hypothyroidism | myxedema coma |
| Masculinization of female | absent | - | - | present | - |
| SIADH (syndrome of inappropriate antidiuretic hormone) | absent | - | - | present | - |
| Endocrine-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **GASTROINTESTINAL** | | | | | |
| Amylase is graded in the METABOLIC/LABORATORY category. | | | | | |
| Anorexia | none | loss of appetite | oral intake significantly decreased | requiring IV fluids | requiring feeding tube or parenteral nutrition |

| **Grade** | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Ascites (non-malignant) | none | asymptomatic | symptomatic, requiring diuretics | symptomatic, requiring therapeutic paracentesis | life-threatening physiologic consequences |
| Colitis | none | - | abdominal pain with mucus and/or blood in stool | abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation | perforation or requiring surgery or toxic megacolon |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension. | | | | | |
| Constipation | none | requiring stool softener or dietary modification | requiring laxatives | obstipation requiring manual evacuation or enema | obstruction or toxic megacolon |
| Dehydration | none | dry mucous membranes and/or diminished skin turgor | requiring IV fluid replacement (brief) | requiring IV fluid replacement (sustained) | physiologic consequences requiring intensive care; hemodynamic collapse |
| Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis). | | | | | |
| Diarrhea<br>Patients without colostomy: | none | increase of < 4 stools/day over pre-treatment | increase of 4-6 stools/day, or nocturnal stools | increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration | physiologic consequences requiring intensive care; or hemodynamic collapse |
| Patients with a colostomy: | none | mild increase in loose, watery colostomy output compared with pretreatment | moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity | severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity | physiologic consequences, requiring intensive care; or hemodynamic collapse |
| Duodenal ulcer (requires radiographic or endoscopic documentation) | none | - | requiring medical management or non-surgical treatment | uncontrolled by outpatient medical management; requiring hospitalization | perforation or bleeding, requiring emergency surgery |
| Dyspepsia/heartburn | none | mild | moderate | severe | - |
| Dysphagia, esophagitis, odynophagia (painful swallowing) | none | mild dysphagia, but can eat regular diet | dysphagia, requiring predominantly pureed, soft, or liquid diet | dysphagia, requiring IV hydration | complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation |
| Fistula- esophageal | none | - | - | present | requiring surgery |
| Fistula- intestinal | none | - | - | present | requiring surgery |
| Fistula- pharyngeal | none | - | - | present | requiring surgery |
| Fistula- rectal/anal | none | - | - | present | requiring surgery |
| Flatulence | none | mild | moderate | - | - |
| Gastric ulcer (requires radiographic or endoscopic documentation) | none | - | requiring medical management or non-surgical treatment | bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery | perforation or bleeding, requiring emergency surgery |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia. | | | | | |
| Gastritis | none | - | requiring medical management or non-surgical treatment | uncontrolled by out-patient medical management; requiring hospitalization or surgery | life-threatening bleeding, requiring emergency surgery |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia. | | | | | |
| Hematemesis is graded in the HEMORRHAGE category. | | | | | |
| Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia. | | | | | |
| Ileus (or neuroconstipation) | none | - | intermittent, not requiring intervention | requiring non-surgical intervention | requiring surgery |
| Mouth dryness | normal | mild | moderate | - | - |
| Mucositis<br>Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginitis. | | | | | |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Nausea | none | able to eat | oral intake significantly decreased | no significant intake, requiring IV fluids | - |
| Pancreatitis | none | - | - | abdominal pain with pancreatic enzyme elevation | complicated by shock (acute circulatory failure) |
| Also consider Hypotension.<br>Note: Asymptomatic amylase and Amylase are graded in the METABOLIC/LABORATORY category. | | | | | |
| Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis). | | | | | |
| Proctitis | none | increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication | increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure | increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads | perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy) |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation.<br>Note: Fistula is graded separately as Fistula- rectal/anal. | | | | | |
| Salivary gland changes | none | slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required | thick, ropy, sticky saliva; markedly altered taste; alteration in diet required | - | acute salivary gland necrosis |
| Sense of smell | normal | slightly altered | markedly altered | - | - |
| Stomatitis/pharyngitis (oral/pharyngeal mucositis) | none | painless ulcers, erythema, or mild soreness in the absence of lesions | painful erythema, edema, or ulcers, but can eat or swallow | painful erythema, edema, or ulcers requiring IV hydration | severe ulceration or requires parenteral or enteral nutritional support or prophylactic intubation |
| Taste disturbance (dysgeusia) | normal | slightly altered | markedly altered | - | - |
| Typhlitis (inflammation of the cecum) | none | - | - | abdominal pain, diarrhea, fever, or radiographic documentation | perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy) |
| Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia. | | | | | |
| Vomiting | none | 1 episode in 24 hours over pretreatment | 2-5 episodes in 24 hours over pretreatment | ≥6 episodes in 24 hours over pretreatment; or need for IV fluids | Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse |
| Also consider Dehydration. | | | | | |
| Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category. | | | | | |
| Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category. | | | | | |
| Gastrointestinal-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **HEMORRHAGE** | | | | | |
| Note: Transfusion in this section refers to pRBC infusion.<br>For any bleeding with grade 3 or 4 platelets (<50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion- pRBCS, and transfusion-platelets in addition to the grade that incorporates the site or type of bleeding.<br>If the site or type of hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding.<br>If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is not listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category. | | | | | |
| Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia | none | mild without transfusion | | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs.<br>Note: This toxicity must be graded for any bleeding with grade 3 or 4 thrombocytopenia. Also grade the site or type of hemorrhage/bleeding. If the site is not listed, grade as Other in the HEMORRHAGE category. | | | | | |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia | none | mild without transfusion | | requiring transfusion | catastrophic bleeding requiring major non-elective intervention |
| Also consider Platelets, Hemoglobin, Transfusion-platelet, Transfusion-pRBCs.<br>Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category. | | | | | |
| CNS hemorrhage/bleeding | none | - | - | bleeding noted on CT or other scan with no clinical consequences | hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms |
| Epistaxis | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Hematemesis | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Hematuria (in the absence of vaginal bleeding) | none | microscopic only | intermittent gross bleeding, no clots | persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion | open surgery or necrosis or deep bladder ulceration |
| Hemoptysis | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Hemorrhage/bleeding associated with surgery<br>Note: Expected blood loss at the time of surgery is not graded as a toxicity. | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Melena/GI bleeding | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Petechiae/purpura (hemorrhage/bleeding into skin or mucosa) | none | rare petechiae of skin | petechiae or purpura in dependent areas of skin | generalized petechiae or purpura of skin or petechiae of any mucosal site | - |
| Rectal bleeding/ hematochezia | none | mild without transfusion or medication | persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Vaginal bleeding | none | spotting, requiring <2 pads per day | requiring ≥2 pads per day, but not requiring transfusion | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| Hemorrhage-Other (Specify site, _____) | none | mild without transfusion | - | requiring transfusion | catastrophic bleeding, requiring major non-elective intervention |
| **HEPATIC** | | | | | |
| Alkaline phosphatase | WNL | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Bilirubin | WNL | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 10.0 x ULN | >10.0 x ULN |
| GGT (γ - Glutamyl transpeptidase) | WNL | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Hepatic enlargement<br>Note: Grade Hepatic enlargement only for changes related to VOD or other treatment related toxicity. | absent | - | - | present | - |
| Hypoalbuminemia | WNL | <LLN - 3 g/dl | ≥2 - <3 g/dl | <2 g/dl | - |
| Liver dysfunction/failure (clinical)<br>Note: Documented viral hepatitis is graded in the INFECTION category. | normal | - | - | asterixis | encephalopathy or coma |
| Portal vein flow | normal | - | decreased portal vein flow | reversal/retrograde portal vein flow | - |
| SGOT (AST) (serum glutamic oxaloacetic transaminase) | WNL | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| SGPT (ALT) (serum glutamic pyruvic transaminase) | WNL | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN |
| Hepatic-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **INFECTION/FEBRILE NEUTROPENIA** | | | | | |
| Catheter-related infection | none | mild, no active treatment | moderate, localized infection, requiring local or oral treatment | severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization | life-threatening sepsis (e.g., septic shock) |
| Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) (ANC <1.0 x $10^9$/L, fever ≥38.5°C) | none | - | - | Present | Life-threatening sepsis (e.g., septic shock) |
| Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. | | | | | |
| Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia (ANC <1.0 x $10^9$/L) | none | - | - | present | life-threatening sepsis (e.g., septic shock) |
| Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia, grade as Febrile neutropenia. | | | | | |
| Infection with unknown ANC | none | - | - | present | life-threatening sepsis (e.g., septic shock) |
| Note: This toxicity criterion is used in the rare case when ANC is unknown. | | | | | |
| Infection without neutropenia | none | mild, no active treatment | moderate, localized infection, requiring local or oral treatment | severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization | life-threatening sepsis (e.g., septic shock) |
| Infection/Febrile Neutropenia-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| Wound-infectious is graded in the DERMATOLOGY/SKIN category. | | | | | |
| **LYMPHATICS** | | | | | |
| Lymphatics | normal | mild lymphedema | moderate lymphedema requiring compression; lymphocyst | severe lymphedema limiting function; lymphocyst requiring surgery | severe lymphedema limiting function with ulceration |
| Lymphatics-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **METABOLIC/LABORATORY** | | | | | |
| Acidosis (metabolic or respiratory) | normal | pH < normal, but ≥7.3 | - | pH <7.3 | pH <7.3 with life-threatening physiologic consequences |
| Alkalosis (metabolic or respiratory) | normal | pH > normal, but ≤7.5 | - | pH >7.5 | pH >7.5 with life-threatening physiologic consequences |
| Amylase | WNL | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 - 5.0 x ULN | >5.0 x ULN |
| Bicarbonate | WNL | <LLN - 16 mEq/dl | 11 - 15 mEq/dl | 8 - 10 mEq/dl | <8 mEq/dl |
| CPK (creatine phosphokinase) | WNL | >ULN - 2.5 x ULN | >2.5 - 5 x ULN | >5 - 10 x ULN | >10 x ULN |
| Hypercalcemia | WNL | >ULN - 11.5 mg/dl<br>>ULN - 2.9 mmol/L | >11.5 - 12.5 mg/dl<br>>2.9 - 3.1 mmol/L | >12.5 - 13.5 mg/dl<br>>3.1 - 3.4 mmol/L | >13.5 mg/dl<br>>3.4 mmol/L |
| Hypercholesterolemia | WNL | >ULN - 300 mg/dl<br>>ULN - 7.75 mmol/L | >300 - 400 mg/dl<br>>7.75 - 10.34 mmol/L | >400 - 500 mg/dl<br>>10.34 - 12.92 mmol/L | > 500 mg/dl<br>> 12.92 mmol/L |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Hyperglycemia | WNL | >ULN - 160 mg/dl<br>>ULN - 8.9 mmol/L | >160 - 250 mg/dl<br>>8.9 - 13.9 mmol/L | >250 - 500 mg/dl<br>>13.9 - 27.8 mmol/L | >500 mg/dl<br>>27.8 mmol/L or ketoacidosis |
| Hyperkalemia | WNL | >ULN - 5.5 mmol/L | >5.5 - 6.0 mmol/L | >6.0 - 7.0 mmol/L | >7.0 mmol/L |
| Hypermagnesemia | WNL | >ULN - 3.0 mg/dl<br>>ULN - 1.23 mmol/L | - | >3.0 - 8.0 mg/dl<br>>1.23 - 3.30 mmol/L | >8.0 mg/dl<br>>3.30 mmol/L |
| Hypernatremia | WNL | >ULN - 150 mmol/L | >150 - 155 mmol/L | >155 - 160 mmol/L | >160 mmol/L |
| Hypertriglyceridemia | WNL | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 10 x ULN | >10 x ULN |
| Hyperuricemia<br>Also consider Tumor lysis syndrome, Renal failure, Creatinine, Potassium. | WNL | >ULN - ≤10 mg/dl<br>≤0.59 mmol/L without physiologic consequences | - | >ULN - ≤10 mg/dl<br>≤0.59 mmol/L with physiologic consequences | >10 mg/dl<br>>0.59 mmol/L |
| Hypocalcemia | WNL | <LLN - 8.0 mg/dl<br><LLN - 2.0 mmol/L | 7.0 - <8.0 mg/dl<br>1.75 - <2.0 mmol/L | 6.0 - <7.0 mg/dl<br>1.5 - <1.75 mmol/L | <6.0 mg/dl<br><1.5 mmol/L |
| Hypoglycemia | WNL | <LLN - 55 mg/dl<br><LLN - 3.0 mmol/L | 40 - <55 mg/dl<br>2.2 - <3.0 mmol/L | 30 - < 40 mg/dl<br>1.7 - <2.2 mmol/L | <30 mg/dl<br><1.7 mmol/L |
| Hypokalemia | WNL | <LLN - 3.0 mmol/L | - | 2.5 - <3.0 mmol/L | <2.5 mmol/L |
| Hypomagnesemia | WNL | <LLN - 1.2 mg/dl<br><LLN - 0.5 mmol/L | 0.9 - <1.2 mg/dl<br>0.4 - <0.5 mmol/L | 0.7 - <0.9 mg/dl<br>0.3 - <0.4 mmol/L | <0.7 mg/dl<br><0.3 mmol/L |
| Hyponatremia | WNL | <LLN - 130 mmol/L | - | 120 - <130 mmol/L | <120 mmol/L |
| Hypophosphatemia | WNL | <LLN -2.5 mg/dl<br><LLN - 0.8 mmol/L | ≥2.0 - <2.5 mg/dl<br>≥0.6 - <0.8 mmol/L | ≥1.0 - <2.0 mg/dl<br>≥0.3 - <0.6 mmol/L | <1.0 mg/dl<br><0.3 mmol/L |
| Hypothyroidism is graded in the ENDOCRINE category. | | | | | |
| Lipase | WNL | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 - 5.0 x ULN | >5.0 x ULN |
| Metabolic/Laboratory-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **MUSCULOSKELETAL** | | | | | |
| Arthralgia is graded in the PAIN category. | | | | | |
| Arthritis | none | mild pain with inflammation, erythema or joint swelling but not interfering with function | moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living | severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living | disabling |
| Muscle weakness (not due to neuropathy) | normal | asymptomatic with weakness on physical exam | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | bedridden or disabling |
| Myalgia is graded in the PAIN category. | | | | | |
| Myositis (inflammation/damage of muscle)<br>Also consider CPK.<br>Note: Myositis implies muscle damage (i.e., elevated CPK). | none | mild pain, not interfering with function | pain interfering with function, but not interfering with activities of daily living | pain interfering with function and interfering with activities of daily living | bedridden or disabling |
| Osteonecrosis (avascular necrosis) | none | asymptomatic and detected by imaging only | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | symptomatic; or disabling |
| Musculoskeletal-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **NEUROLOGY** | | | | | |
| Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category. | | | | | |
| Arachnoiditis/meningismus/ radiculitis<br>Also consider Headache, Vomiting, Fever. | absent | mild pain not interfering with function | moderate pain interfering with function, but not interfering with activities of daily living | severe pain interfering with activities of daily living | unable to function or perform activities of daily living; bedridden; paraplegia |

| **Grade** | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Ataxia (incoordination) | normal | asymptomatic but abnormal on physical exam, and not interfering with function | mild symptoms interfering with function, but not interfering with activities of daily living | moderate symptoms interfering with activities of daily living | bedridden or disabling |
| CNS cerebrovascular ischemia | none | - | - | transient ischemic event or attack (TIA) | permanent event (e.g., cerebral vascular accident) |
| CNS hemorrhage/bleeding is graded in the HEMORRHAGE category. | | | | | |
| Confusion | normal | confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae | confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living | confusion or delirium interfering with activities of daily living | harmful to others or self; requiring hospitalization |
| Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial. | | | | | |
| Delusions | normal | - | - | present | toxic psychosis |
| Depressed level of consciousness<br>Note: Syncope (fainting) is graded in the NEUROLOGY category. | normal | somnolence or sedation not interfering with function | somnolence or sedation interfering with function, but not interfering with activities of daily living | obtundation or stupor; difficult to arouse; interfering with activities of daily living | coma |
| Dizziness/lightheadedness | none | not interfering with function | interfering with function, but not interfering with activities of daily living | interfering with activities of daily living | bedridden or disabling |
| Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category. | | | | | |
| Extrapyramidal/ involuntary movement/ restlessness | none | mild involuntary movements not interfering with function | moderate involuntary movements interfering with function, but not interfering with activities of daily living | severe involuntary movements or torticollis interfering with activities of daily living | bedridden or disabling |
| Hallucinations | normal | - | - | present | toxic psychosis |
| Headache is graded in the PAIN category. | | | | | |
| Insomnia<br>Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia. | normal | occasional difficulty sleeping not interfering with function | difficulty sleeping interfering with function, but not interfering with activities of daily living | frequent difficulty sleeping, interfering with activities of daily living | - |
| Memory loss | normal | memory loss not interfering with function | memory loss interfering with function, but not interfering with activities of daily living | memory loss interfering with activities of daily living | amnesia |
| Mood alteration- anxiety agitation | normal | mild mood alteration not interfering with function | moderate mood alteration interfering with function, but not interfering with activities of daily living | severe mood alteration interfering with activities of daily living | suicidal ideation or danger to self |
| Mood alteration- depression | normal | mild mood alteration not interfering with function | moderate mood alteration interfering with function, but not interfering with activities of daily living | severe mood alteration interfering with activities of daily living | suicidal ideation or danger to self |
| Mood alteration- euphoria | normal | mild mood alteration not interfering with function | moderate mood alteration interfering with function, but not interfering with activities of daily living | severe mood alteration interfering with activities of daily living | danger to self |
| Neuropathic pain is graded in the PAIN category. | | | | | |
| Neuropathy- cranial | absent | - | present, not interfering with activities of daily living | present, interfering with activities of daily living | life-threatening, disabling |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Neuropathy- motor | normal | subjective weakness but no objective findings | mild objective weakness interfering with function, but not interfering with activities of daily living | objective weakness interfering with activities of daily living | paralysis |
| Neuropathy-sensory | normal | loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function | objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living | sensory loss or paresthesia interfering with activities of daily living | permanent sensory loss that interferes with function |
| Nystagmus<br>Also consider Vision-double vision. | absent | present | - | - | - |
| Personality/behavioral | normal | change, but not disruptive to patient or family | disruptive to patient or family | disruptive to patient and family; requiring mental health intervention | harmful to others or self; requiring hospitalization |
| Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination) | normal | asymptomatic with abnormality on physical examination | symptomatic or interfering with function but not interfering with activities of daily living | interfering with activities of daily living | bedridden or disabling; paralysis |
| Seizure(s) | none | - | seizure(s) self-limited and consciousness is preserved | seizure(s) in which consciousness is altered | seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy) |
| Speech impairment (e.g., dysphasia or aphasia) | normal | - | awareness of receptive or expressive dysphasia, not impairing ability to communicate | receptive or expressive dysphasia, impairing ability to communicate | inability to communicate |
| Syncope (fainting)<br>Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia. | absent | - | - | present | - |
| Tremor | none | mild and brief or intermittent but not interfering with function | moderate tremor interfering with function, but not interfering with activities of daily living | severe tremor interfering with activities of daily living | - |
| Vertigo | none | not interfering with function | interfering with function, but not interfering with activities of daily living | interfering with activities of daily living | bedridden or disabling |
| Neurology-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **OCULAR/VISUAL** | | | | | |
| Cataract | none | asymptomatic | symptomatic, partial visual loss | symptomatic, visual loss requiring treatment or interfering with function | - |
| Conjunctivitis | none | abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation) | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Dry eye | normal | mild, not requiring treatment | moderate or requiring artificial tears | - | - |
| Glaucoma | none | increase in intraocular pressure but no visual loss | increase in intraocular pressure with retinal changes | visual impairment | unilateral or bilateral loss of vision (blindness) |

| **Grade** | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Keratitis (corneal inflammation/ corneal ulceration) | none | abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation) | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | unilateral or bilateral loss of vision (blindness) |
| Tearing (watery eyes) | none | mild: not interfering with function | moderate: interfering with function, but not interfering with activities of daily living | interfering with activities of daily living | - |
| Vision- blurred vision | normal | - | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Vision- double vision (diplopia) | normal | - | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Vision- flashing lights/floaters | normal | mild, not interfering with function | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Vision- night blindness (nyctalopia) | normal | abnormal electro-retinography but asymptomatic | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Vision- photophobia | normal | - | symptomatic and interfering with function, but not interfering with activities of daily living | symptomatic and interfering with activities of daily living | - |
| Ocular/Visual-Other (Specify, _____) | normal | mild | moderate | severe | unilateral or bilateral loss of vision (blindness) |
| **PAIN** | | | | | |
| Abdominal pain or cramping | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Arthralgia (joint pain) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category. | | | | | |
| Bone pain | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Chest pain (non-cardiac and non-pleuritic) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Dysmenorrhea | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Dyspareunia | none | mild pain not interfering with function | moderate pain interfering with sexual activity | severe pain preventing sexual activity | - |
| Dysuria is graded in the RENAL/GENITOURINARY category. | | | | | |
| Earache (otalgia) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Headache | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Hepatic pain | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Myalgia (muscle pain) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Pelvic pain | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Pleuritic pain | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Rectal or perirectal pain (proctalgia) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Tumor pain (onset or exacerbation of tumor pain due to treatment) | none | mild pain not interfering with function | moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain: pain or analgesics severely interfering with activities of daily living | disabling |
| Tumor flair is graded in the SYNDROME category. | | | | | |
| Pain-Other (Specify, _____) | none | mild | moderate | severe | disabling |
| **PULMONARY** | | | | | |
| Adult Respiratory Distress Syndrome (ARDS) | absent | - | - | - | present |
| Apnea | none | - | - | present | requiring intubation |
| Carbon monoxide diffusion capacity ($DL_{CO}$) | ≥90% of pretreatment or normal value | ≥75 - <90% of pretreatment or normal value | ≥50 - <75% of pretreatment or normal value | ≥25 - <50% of pretreatment or normal value | <25% of pretreatment or normal value |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Cough | absent | mild, relieved by non-prescription medication | requiring narcotic antitussive | severe cough or coughing spasms, poorly controlled or unresponsive to treatment | - |
| Dyspnea (shortness of breath) | normal | - | dyspnea on exertion | dyspnea at normal level of activity | dyspnea at rest or requiring ventilator support |
| $FEV_1$ | ≥90% of pretreatment or normal value | ≥75 - <90% of pretreatment or normal value | ≥50 - <75% of pretreatment or normal value | ≥25 - <50% of pretreatment or normal value | <25% of pretreatment or normal value |
| Hiccoughs (hiccups, singultus) | none | mild, not requiring treatment | moderate, requiring treatment | severe, prolonged, and refractory to treatment | - |
| Hypoxia | normal | - | decreased $O_2$ saturation with exercise | decreased $O_2$ saturation at rest, requiring supplemental oxygen | decreased $O_2$ saturation, requiring pressure support (CPAP) or assisted ventilation |
| Pleural effusion (non-malignant) | none | asymptomatic and not requiring treatment | symptomatic, requiring diuretics | symptomatic, requiring $O_2$ or therapeutic thoracentesis | life-threatening (e.g., requiring intubation) |
| Pleuritic pain is graded in the PAIN category. | | | | | |
| Pneumonitis/pulmonary infiltrates | none | radiographic changes but asymptomatic or symptoms not requiring steroids | radiographic changes and requiring steroids or diuretics | radiographic changes and requiring oxygen | radiographic changes and requiring assisted ventilation |
| Pneumothorax | none | no intervention required | chest tube required | sclerosis or surgery required | life-threatening |
| Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category. | | | | | |
| Pulmonary fibrosis | none | radiographic changes, but asymptomatic or symptoms not requiring steroids | requiring steroids or diuretics | requiring oxygen | requiring assisted ventilation |
| Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV) | | | | | |
| Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis) | normal | mild or intermittent hoarseness | persistent hoarseness, but able to vocalize; may have mild to moderate edema | whispered speech, not able to vocalize; may have marked edema | marked dyspnea/stridor requiring tracheostomy or intubation |
| Note: Cough from radiation is graded as cough in the PULMONARY category. Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category. | | | | | |
| Pulmonary-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **RENAL/GENITOURINARY** | | | | | |
| Bladder spasms | absent | mild symptoms, not requiring intervention | symptoms requiring antispasmotic | severe symptoms requiring narcotic | - |
| Creatinine | WNL | >ULN - 1.5 x ULN | >1.5 - 3.0 x ULN | >3.0 - 6.0 x ULN | >6.0 x ULN |
| *Note: Adjust to age-appropriate levels for pediatric patients.* | | | | | |
| Dysuria (painful urination) | none | mild symptoms requiring no intervention | symptoms relieved with therapy | symptoms not relieved despite therapy | - |
| Fistula or GU fistula (e.g., vaginal, vesicovaginal) | none | - | - | requiring intervention | requiring surgery |
| Hemoglobinuria | - | present | - | - | - |
| Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category. | | | | | |
| Incontinence | none | with coughing, sneezing, etc. | spontaneous, some control | no control (in the absence of fistula) | - |
| Operative injury to bladder and/or ureter | none | - | injury of bladder with primary repair | sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation | septic obstruction of both kidneys or vesicovaginal fistula requiring diversion |
| Proteinuria | normal or <0.15 g/24 hours | 1+ or 0.15 - 1.0 g/24 hours | 2+ to 3+ or 1.0 - 3.5 g/24 hours | 4+ or >3.5 g/24 hours | nephrotic syndrome |
| Note: If there is an inconsistency between absolute value and Uristix reading, use the absolute value for grading. | | | | | |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| Renal failure | none | - | - | requiring dialysis, but reversible | requiring dialysis and irreversible |
| Ureteral obstruction | none | unilateral, not requiring surgery | - | bilateral, not requiring surgery | stent, nephrostomy tube, or surgery |
| Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia. | none | asymptomatic, not requiring treatment | mild, reversible and manageable with oral replacement | reversible but requiring IV replacement | irreversible, requiring continued replacement |
| Urinary frequency/urgency | normal | increase in frequency or nocturia up to 2 x normal | increase >2 x normal but < hourly | hourly or more with urgency, or requiring catheter | - |
| Urinary retention | normal | hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period | hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks | requiring frequent in/out catheterization (≥4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy) | bladder rupture |
| Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria) | normal | asymptomatic, change in urine color | - | - | - |
| Vaginal bleeding is graded in the HEMORRHAGE category. | | | | | |
| Vaginitis (not due to infection) | none | mild, not requiring treatment | moderate, relieved with treatment | severe, not relieved with treatment, or ulceration not requiring surgery | ulceration requiring surgery |
| Renal/Genitourinary-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |
| **SECONDARY MALIGNANCY** | | | | | |
| Secondary Malignancy-Other (Specify type, _____) excludes metastatic tumors | none | - | - | - | present |
| **SEXUAL/REPRODUCTIVE FUNCTION** | | | | | |
| Dyspareunia is graded in the PAIN category. | | | | | |
| Dysmenorrhea is graded in the PAIN category. | | | | | |
| Erectile impotence | normal | mild (erections impaired but satisfactory) | moderate (erections impaired, unsatisfactory for intercourse) | no erections | - |
| Female sterility | normal | - | - | sterile | - |
| Femininization of male is graded in the ENDOCRINE category. | | | | | |
| Irregular menses (change from baseline) | normal | occasionally irregular or lengthened interval, but continuing menstrual cycles | very irregular, but continuing menstrual cycles | persistent amenorrhea | - |
| Libido | normal | decrease in interest | severe loss of interest | - | - |
| Male infertility | - | - | Oligospermia (low sperm count) | Azoospermia (no sperm) | - |
| Masculinization of female is graded in the ENDOCRINE category. | | | | | |
| Vaginal dryness | normal | mild | requiring treatment and/or interfering with sexual function, dyspareunia | - | - |
| Sexual/Reproductive Function-Other (Specify, _____) | none | mild | moderate | severe | disabling |

| Grade | | | | | |
|---|---|---|---|---|---|
| **Toxicity** | **0** | **1** | **2** | **3** | **4** |
| **SYNDROMES (not included in previous categories)** | | | | | |
| Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category. | | | | | |
| ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category. | | | | | |
| Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category. | | | | | |
| DIC (disseminated intravascular coagulation) is graded in the COAGULATION category. | | | | | |
| Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category. | | | | | |
| Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category. | | | | | |
| Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category. | | | | | |
| SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category. | | | | | |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS) is graded in the COAGULATION category. | | | | | |
| Tumor flare<br>Also consider Hypercalcemia.<br>Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances. | none | mild pain not interfering with function | moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living | severe pain; pain or analgesics interfering with function and interfering with activities of daily living | Disabling |
| Tumor lysis syndrome<br>Also consider Hyperkalemia, Creatinine. | absent | - | - | present | - |
| Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded under the RENAL/GENITOURINARY category. | | | | | |
| Syndromes-Other (Specify, _____) | none | mild | moderate | severe | life-threatening or disabling |

## Informed Consent Form

### Adjuvant 3DCRT/IMRT in Combination with Androgen Suppression +/- Hyperthermia for High Risk Prostate Cancer Patients Post-Prostatectomy: A Phase III Trial

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation. You are being asked to take part in this study because you have prostate cancer that has been treated surgically and it has been determined that you have a 50% or greater risk of recurrence of your prostate cancer within 3 years following surgery.

**Why is this study being done?**
The purpose of this study is to find out what effects a combination of local (radiation therapy) and systemic (hormonal therapy) treatments +/- hyperthermia has on the risk of recurrence of your prostate cancer.

**How many people will take part in the study?**
About 400 people will take part in this study.

**What will happen if I take part in this research study?**

You will need to have exams, tests, or procedures to find out if you can be in the study. These exams, tests, or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.
If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care. They are being done more often because you are in this study.
• Routine blood studies (for blood count, liver function, and to measure testosterone and PSA) to be obtained by vein (IV).
There are two parts to the hormone therapy. You will take injections (LHRH agonists: leuprolide or goserelin) either under the skin or in the muscle, and you will take a pill, either flutamide (Eulexin) three times per day or bicalutamide (Casodex) once per day. These medicines block the production and effectiveness of the male hormone testosterone.
If you are given flutamide, you will take six (6) capsules by mouth every day for 2 months. If you are given bicalutamide, you will take one (1) tablet by mouth every day for 2 months. It is important that you take bicalutamide at the same time each day. After the 2 months are up,you will have radiation to your pelvis and prostate once a day, 5 days a week, for almost 8 weeks. The hormones and flutamide or bicalutamide will be given on the same schedule during radiation as before radiation began. Once radiation is completed, you will stop taking the flutamide or bicalutamide. Hormone treatment with the LHRH agonist and flutamide or bicalutamide will be continued for about 2 more months for a total of 6 months.

**When you are finished receiving treatment.**
When you are finished with treatment including hormonal therapy, radiation therapy +/- hyperthermia you will have follow-up visits with your doctor every 3 months for 2 years, then every 6 months for years 2 through 5 after finishing treatment, then yearly after 5 years. At each visit a prostate specific antigen (PSA) will be drawn by vein (about 2 teaspoons of blood). The schedule of follow-up visits and the PSA blood test are part of routine follow-up care. In addition, your testosterone level will be checked by drawing blood

at the same time as the PSA is done every 6 months for 3 years following completion of the treatment.

**How long will I be in the study?**
Once enrolled on the study you will be given hormonal therapy medicines that block the production and effectiveness of the male hormone testosterone. You will be asked to take a hormonal therapy pill (flutamide or bicalutamide) by mouth every day for a total of 6 months. In addition to taking flutamide or bicalutamide, you will receive a second hormonal therapy drug (leuprolide or goserelin) which is given as a shot once every month or every 3 months for a total of 6 months. Approximately 6- 8 weeks after your first hormonal therapy shot you will begin your radiation treatment. Radiation treatment will be given 5 days a week for almost 8 weeks.

**Can I stop being in the study?**
Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.
It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of radiation, hormone therapy, or hyperthermia can be evaluated by him/her.

**What side effects or risks can I expect from being in the study?**
You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, researchers don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop radiation or hyperthermia. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.
You should talk to your study doctor about any side effects that you have while taking part in the study.

**HORMONE THERAPY**
**A. Risks and side effects related to LHRH agonists (leuprolide and goserelin) include those that are:**
**Likely**
• Hot flashes or sweating episodes
• Impotence and loss of libido (sex drive), which can be permanent
• Weight gain

**Less Likely**
• Dizziness
• Breast swelling or tenderness
• Diarrhea
• Unusual taste in the mouth
• Skin redness or hives
• Increased thirst and urination
• Anemia
• Loss of bone density
• Loss of muscle strength
• Loss of the amount of muscle you have (muscle mass)
• Loss of penis length
• Decrease in the size of your testicles
• Increased cholesterol
• High blood pressure

• Worsening or onset of diabetes (high blood sugar)
• Nausea
• Vomiting
• Changes in the texture of your hair
• Feelings of depression or other emotional changes
• Increased percentage of body fat

**Rare but serious**
• Allergic generalized rash and difficulty breathing
• Increased risk of heart attacks and/or heart rhythm problems

**B. Risks and side effects related to flutamide (Eulexin) and bicalutamide (Casodex) include those that are:**
**Likely**
• Impotence
• Loss of libido (sex drive)
• Hot flashes
• Fatigue
• Diarrhea (for flutamide)

**Less Likely**
• Anemia
• Breast swelling and tenderness
• Diarrhea (for bicalutamide)
• Photosensitivity (sensitivity of the skin to light)

**Rare but serious**
• Liver function changes

**RADIATION THERAPY**
**Risks and side effects related to radiation therapy include those that are:**
**Likely**
• Hair loss in the treatment area
• Temporary tiredness
• Diarrhea
• Abdominal cramps and rectal urgency
• Bladder irritation
• Infertility

**Less Likely**
• Reddening or tanning of the skin
• Permanent impotence
• Occasional rectal bleeding

**Rare but serious**
• Bladder injury with bleeding
• Urethral scar tissue
• Severe rectal bleeding
• Urinary or bowel incontinence
• Injuries to the rectum, bowel, or urinary system that could result in colostomy (surgical creation of an artificial opening in the colon) or other major surgical procedures

**Reproductive risks:** If semen cannot be released from the penis during an orgasm following surgery to remove the prostate, there are no reproductive risks. If semen can be released during an orgasm, the patient needs to use birth control while on this study because the drugs and radiation in this study can affect an unborn baby.
For more information about risks and side effects, ask your study doctor.

**Are there benefits to taking part in the study?**
Taking part in this study may or may not make your health better. While researchers hope hyperthermia in addition to radiation therapy and hormone therapy will be more useful against prostate cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help researchers learn more about hyperthermia in addition to radiation therapy and hormone therapy as a treatment for cancer. This information could help future cancer patients.

**What other choices do I have if I do not take part in this study?**
Your other choices may include:
• Getting treatment or care for your cancer without being in a study including the possibility of receiving radiation and/or hormonal therapy without hyperthermia
• Taking part in another study
• Getting no treatment
Talk to your study doctor about your choices before you decide if you will take part in this study.

**Will my medical information be kept private?**
If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

**What are my rights if I take part in this study?**
Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.
We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

**You will get a copy of this form. If you want more information about this study, ask your study doctor.**
**Signature**
**I have been given a copy of all _____** *[insert total of number of pages]* **pages of this form. I**
**have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

**Participant _____**

**Date _____**

**AJCC STAGING SYSTEM**
**PROSTATE, 6th Edition**
**DEFINITION OF TNM**
**Primary Tumor, Clinical (T)**

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically inapparent tumor neither palpable or visible by imaging
T1a Tumor incidental histologic finding in 5% or less of tissue resected
T1b Tumor incidental histologic finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined with prostate*
T2a Tumor involves one-half of one lobe or less
T2b Tumor involves more than one-half of one lobe but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through prostate capsule**
T3a Extracapsular extension (unilateral or bilateral)
T3b Tumor involves the seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external
sphincter, rectum, levator muscles and/or pelvic wall

*Note: Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified as T1c
**Note: Invasion into the prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3, but as T2.

**Regional Lymph Nodes (N)**

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in regional lymph node(s)

**Primary Tumor, Pathologic (pT)**

pT2* Organ confined
pT2a Unilateral, involving one-half of one lobe or less
pT2b Unilateral, involving more than one-half of one lobe but not both lobes
pT2c Bilateral disease
pT3 Extraprostatic extension
pT3a Extraprostatic extension**
pT3b Seminal vesicle invasion
pT4 Invasion of bladder, rectum
*Note: There is no pathologic T1 classification
**Note: Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).

**Distant Metastasis (M)***

MX Presence of distant metastasis cannot be assessed (not evaluated by any modality)
M0 No distant metastasis
M1 Distant metastasis

M1a Nonregional lymph node(s)
M1b Bone(s)
M1c Other site(s) with or without bone disease

*Note: When more than one site of metastasis is present, the most advanced category is used;
pM1c is most advanced.

**Histopathologic Grade (G)**

**GX:** Grade cannot be assessed
**G1:** Well-differentiated (slight anaplasia [Gleason 2-4])
**G2**: Moderately differentiated (moderate anaplasia [Gleason 5-6])
**G3-4:** Poorly undifferentiated or undifferentiated (marked anaplasia [Gleason 7-10])

***Stage Grouping***

**Stage I:** T1a N0 M0 G1

**Stage II:** T1a N0 M0 G2, G3-4
T1b N0 M0 Any G
T1c N0 M0 Any G
T1 N0 N0 Any G
T2 N0 M0 Any G
**Stage III:** T3 N0 M0 Any G

**Stage IV:** T4 N0 M0 Any G
Any T N1 M0 Any G
Any T Any N M1 Any G

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