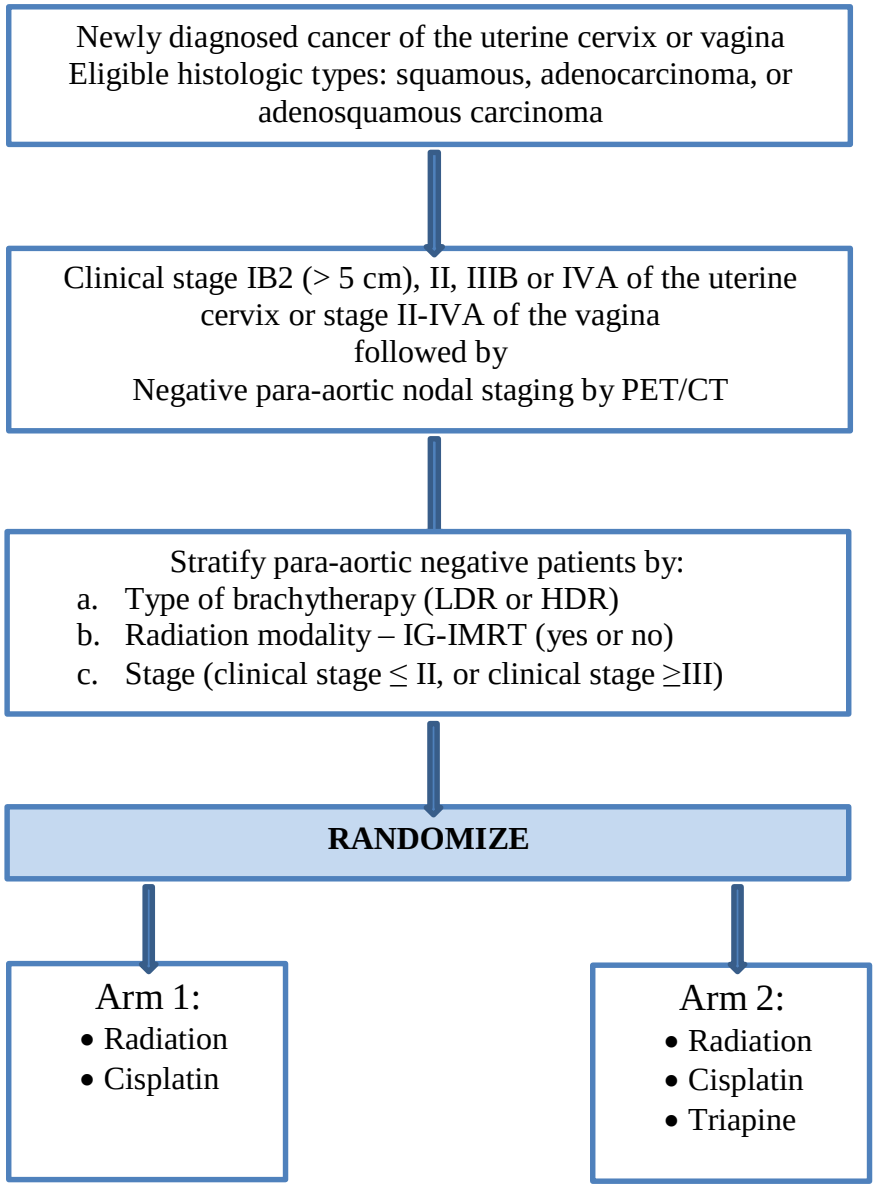
SCHEMA



Radiation: 45 Gy / 25 fractions of 1.8 Gy + 5.4 Gy / 3 fraction parametrium boost + 40 Gy LDR or 30 Gy HDR brachytherapy

Cisplatin: x1 weekly cisplatin 40 mg/m^2 (maximum 70 mg) days 2, 9, 16, 23, 30 of radiation (5 total infusions; a sixth administration on day 37 is permissible at the treating physician's discretion. Cisplatin may be given ± 1 day to accommodate scheduling issues for the control arm only.

Triapine: x3 weekly 3-aminopyridine-2-carboxaldehyde thiosemicarbazone (Triapine) 25 mg/m^2 (maximum 50 mg) days 1, 3, 5, 8, 10, 12, 15, 17, 19, 22, 24, 26, 29, 31, 33 of radiation (15 total infusions)

Statistics: This is an open label randomized (1:1) allocation ratio single stage phase II clinical trial.

3.0 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and to exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistical and Data Management Center-Pittsburgh Office (via the contact list, NRG web site).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Patient has a new, untreated histologic diagnosis of stage IB2 (> 5 cm), II, IIIB or IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix or stage II-IVA squamous, adenocarcinoma, or adenosquamous carcinoma of the vagina not amenable to curative surgical resection alone. The presence or absence of para-aortic lymph node metastasis will be based on pre-therapy 18F-FDG PET/CT. If the baseline 18F-FDG PET/CT identifies hypermetabolic para-aortic disease, such patients will NOT be eligible. The patient must be able to tolerate imaging requirements of an 18F-FDG PET/CT scan.

3.1.2 Patient must provide study specif informed consent prior to study entry.

3.1.3 Patient must have a GOG performance status of 0, 1, or 2 or equivalent (Appendix A).

3.1.4 Patient must have adequate organ and marrow function as defined below:

absolute neutrophil count	> 1,500/µL
platelets	> 100,000/µL
hemoglobin	> 10 g/dL
total bilirubin	< 2.0 mg/dL
AST(SGOT)/ALT(SGPT)	< 2.5 X institutional upper limit of normal
PT/aPTT	< 1.5 X institutional upper limit of normal
Creatinine	≤ 1.5 mg/dL to receive weekly cisplatin*

*Patients whose serum creatinine is between 1.5 and 1.9 mg/dL are eligible for cisplatin if there is no hydronephrosis and the estimated creatinine clearance (CCr) is ≥ 30 ml/min. For the purpose of estimating the CCr, the formula of Cockcroft and Gault for females should be used:

$$CCr = 0.85 \times (140\text{-age}) \times IBW / (Scr \times 72)$$

where age is the patient's age in years (from 20 to 80 years), Scr is the serum creatinine in mg/dL, and IBW is the ideal body weight in kg (according to the calculation IBW = 45.5 kg + 2.3 kg for each inch over 5 feet).

3.1.5 Patient does not have uncontrolled diabetes mellitus (i.e., fasting blood glucose >200 mg/dL).

3.1.6 Patient has a life expectancy of greater than 20 weeks.

3.1.7 Age is ≥ 18 years.

3.1.8 Patient does not have known brain metastases (testing *optional*).

3.1.9 Patient does not have known human immunodeficiency virus syndrome

(HIV, testing *optional*). Known HIV-positive patients receiving combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with triapine.

3.1.10 Patient does not have a known allergy to compounds of similar or biologic composition as triapine.

3.1.11 Patient does not have known glucose-6-phosphate dehydrogenase (G6PD) deficiency as the condition interferes with triapine antidote metabolism (G6PD testing *optional*).

3.1.12 Patient is not *actively* breastfeeding (or has agreed to discontinue breastfeeding before the initiation of protocol therapy).

3.2 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Patient has another concurrent *active* invasive malignancy.

3.2.2 Patient has had a prior invasive malignancy diagnosed within the last three years (except [1] non-melanoma skin cancer or [2] prior *in situ* carcinoma of the cervix). Patients are excluded if they have received prior pelvic radiotherapy for any reason that would contribute radiation dose that would exceed tolerance of normal tissues at the discretion of the treating physician.

3.2.3 Patient has uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, myocardial infarction within six months of protocol initiation, cardiac arrhythmia within six months of protocol initiation; known inadequately controlled hypertension; clinically significant pulmonary disease including dyspnea at rest, or patients requiring supplemental oxygen, or poor pulmonary reserve; proteinuria or clinically

significant renal function impairment (baseline serum creatinine >2 mg/dL); or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.4 Patient is receiving another investigational agent for the treatment of cancer.

3.2.5 Patient is *currently* pregnant. Patient must agree to use two forms of birth control if they are of child-bearing potential.

3.2.6 Patients who have had a hysterectomy or are planning to have an adjuvant hysterectomy following radiation as part of their cervical cancer treatment are ineligible.

3.2.7 Patients scheduled to be treated with adjuvant consolidation chemotherapy at the conclusion of their standard chemoradiation.

3.2.8 Patients with self-reported or known diagnosis of G6PD deficiency.