

**GYNECOLOGIC ONCOLOGY GROUP/
AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK**

GOG-0233/ACRIN 6671

**UTILITY OF PREOPERATIVE FDG-PET/CT AND FERUMOXTRAN-10 MRI SCANNING PRIOR TO
PRIMARY CHEMORADIATION THERAPY TO DETECT RETROPERITONEAL LYMPH NODE
METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED (IB2, IIA \geq 4 CM, IIB-IVA)
CARCINOMA OF THE CERVIX**

Agent Name: Ferumoxtran-10

Agent NSC Number: INTENTIONALLY LEFT BLANK

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Percapita Points: 15 Points

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***PARTIAL PROTOCOL—CONTACT ACRIN
PROTOCOL DEVELOPMENT AND
REGULATORY COMPLIANCE FOR A
COMPLETE PROTOCOL***

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STUDY PARTICIPANTS: ALL GYNECOLOGIC ONCOLOGY GROUP MEMBERS AND AFFILIATE GYNECOLOGIC SURGEONS WHO HAVE MET THE QUALIFICATION REQUIREMENTS FROM ACRIN. **(06/09/08)**

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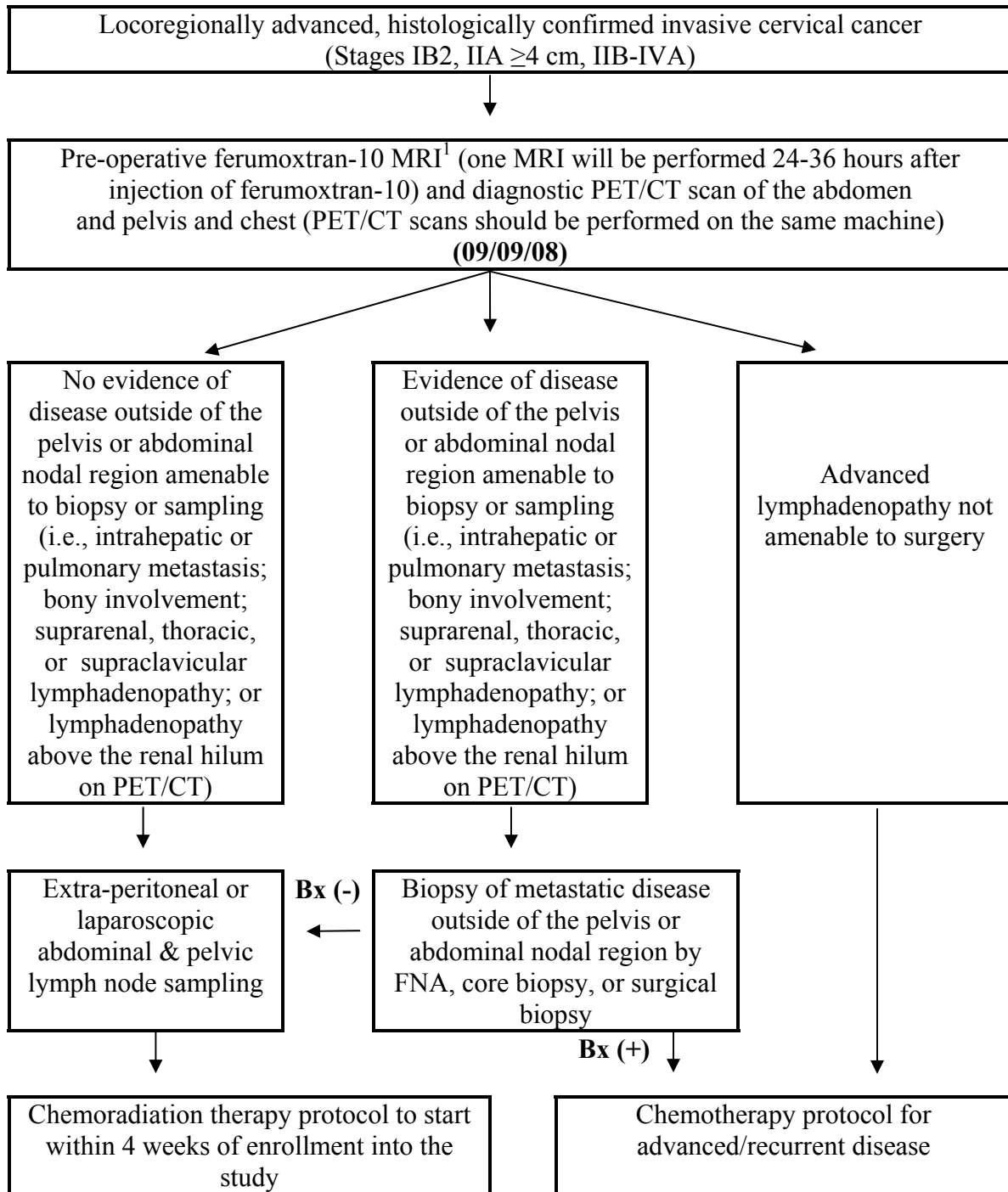
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ADVANCED (IB2, IIA \geq 4 CM, IIB-IVA) CARCINOMA OF THE CERVIX

SCHEMA (06/09/08)



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SPECIFIC AIMS/OBJECTIVES

The primary aim of this study is to define the utility of preoperative FDG-PET/CT and ferumoxtran-10 MRI scanning prior to primary chemoradiation therapy to detect retroperitoneal lymph node metastasis in patients with locoregionally advanced carcinoma of the cervix. The optional arm to the study will explore the use of a pre-ferumoxtran-10 MRI with parameters similar to post ferumoxtran-10 MRI to validate that Combidex does not change the size of lymph nodes on Combidex insensitive sequences.

METHODS/METHODOLOGY

In this study, 325 women will be enrolled. Enrollment will take place in at least 10 sites and is expected to be completed within 36 months from protocol activation. About 30-38 positive cases will have been enrolled by the end of the 20th month of the study. This will be the timing for the performance of the interim analysis. In the optional arm of the study, forty of the 325 patients who consent to undergo 2 MRI (one pre-ferumoxtran-10, and one post-ferumoxtran-10) will provide a cohort of MRI examinations in order to validate the similarity of nodal size in pre and post-ferumoxtran-10 MR images. The analysis for the optional arm is mainly exploratory.

ELIGIBILITY (*see Section 5.0 for details*)

1. Patients must have primary, previously untreated, histologically confirmed, locoregionally advanced invasive carcinoma of the cervix or be considered for chemoradiation therapy.
2. Patients that qualify with the above credentials must be able to undergo extra-peritoneal or laparoscopic lymph node sampling.
3. Normal organ function is required within specified parameters (see section 5.1.4 for details).
4. Patients of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT and ferumoxtran-10 MRI. In addition, they would undergo a urine pregnancy test on the day of PET/CT examination. Combidex is injected on the day of PET/CT examination. The urine pregnancy test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine pregnancy test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not to be of child-bearing potential.
5. Patients must sign an approved informed consent form that allows access to prior medical records.
6. Patients must be accrued at an ACRIN affiliated institution that is accredited by GOG.
7. Patients cannot have recurrent invasive carcinoma of the uterine cervix regardless of previous treatment.
8. There can be no known metastases to the lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis.
9. Patients cannot have had a pelvic or abdominal lymphadenectomy performed.
10. There can be no evidence of prior pelvic radiation therapy for any reason.
11. Any outside circumstances that interfere with the completion of the imaging studies or required follow-up are not permitted.

REQUIRED SAMPLE SIZE

A total of 325 participants will be enrolled into the study. For the optional arm of the study, 40 of these participants will be enrolled in the study.

1.0 ABSTRACT

This protocol for human research study is conducted according to US and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (Code of Federal Regulations), the American College of Radiology Imaging Network (ACRIN) and Gynecological Oncology Group (GOG) research policies and procedures. (09/09/08)

In the United States, cervix cancer is the third most common gynecologic malignancy, with approximately 15,000 new cases and 5,000 deaths annually. Primary radiotherapy (RT) fails to control locoregional disease in 20-85% of patients with locally advanced carcinoma. These estimates are based on stage, tumor bulk, and nodal status. When compared with surgical findings, clinical staging is accurate in only 60% of cases. In many instances, errors in staging are related to undiagnosed lymph node metastases.

More recently, FDG-PET imaging has demonstrated its utility in detecting nodal involvement in a few small series in cervical cancer. The sensitivity and specificity of MRI for detection of malignant lymphadenopathy has shown to improve by using superparamagnetic iron oxide nanoparticles. Ferumoxtran-10 (also known as Combidex®, Sinerem®, AMI_227), an ultra-small particle iron oxide (USPIO) agent, is the most widely investigated contrast medium in clinical trials. It has been used in a number of malignancies, including breast, lung, head, neck, abdominal, and pelvic malignancies. Results are favorable when compared to MRI without an iron oxide agent. However, there has been no published trial on the use of ferumoxtran-10 in cervical cancer. There have been no significant adverse reactions reported in the literature in a number of Phase II-III clinical trials on ferumoxtran-10 and other iron oxide agents, but some serious allergic events have been recorded and are shown in the drug brochure. The safety profile for ferumoxtran-10 is similar to iodine contrast agents.

The diagnostic sensitivity and specificity of the currently performed imaging modalities has been less than optimal in the evaluation of lymph node metastasis from cervical cancer. The preliminary results of FDG-PET and ferumoxtran-10 MRI for detection of lymph node metastasis in this cohort have been encouraging. The primary objective of this study is to evaluate the diagnostic sensitivity and specificity of FDG-PET/CT and ferumoxtran-10 (Combidex) MRI imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with cervical carcinoma who are to undergo chemoradiation therapy (stages IB2, IIA \geq 4 CM, IIB-IVA). Three-hundred twenty-five patients meeting the inclusion criteria will be enrolled in this multi-center study. The reference standard for confirmation or exclusion of lymph node metastasis will be pathological assessment of the lymph nodes removed by laparoscopic or retroperitoneal lymphadenectomy. The diagnostic sensitivity and specificity of these two modalities will be evaluated in a central reader study including seven (7) expert readers. Moreover, the inter-observer agreement between the readers will be assessed. Accrual for this protocol is expected to be reached within 36 months. The optional arm to this study will validate the similarity of nodal size in pre and post-ferumoxtran-10 MR images. A subset of patients will have the option of participating in this optional arm and will undergo a pre-ferumoxtran-10 MRI. For more information on this optional arm, please refer to section 2.3 of the protocol.

2.0 BACKGROUND AND SIGNIFICANCE

Cancer of the uterine cervix is the second most common cancer in females, representing 15% of all female cancers, 80% of which is diagnosed in underdeveloped countries (1). In the United States,

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cervical cancer is the third most common gynecologic malignancy, with approximately 11,000 new cases and 3,700 deaths annually (2). Though incidence and mortality in the United States dropped steadily from 1940 through 1990, there has recently been a plateau, arresting the decline (1, 3). The vast majority of cases are diagnosed with early-stage disease, but some with locally advanced disease require radiation therapy (60). Unfortunately, primary radiotherapy (RT) fails to control locoregional disease in 20-85% of patients with locally advanced carcinoma, depending on stage, tumor bulk, and nodal status (30, 39, 48, 59, 65).

One reason for the high failure rate may be that cervical cancer remains the only major gynecologic malignancy that is clinically staged (44). When compared with surgical findings, clinical staging is accurate in only 60% of cases (9, 10). A recent study by ACRIN/GOG cooperative group (31) shows improved clinical staging for local extent of disease which appears to be influenced by reduction in the use of projectional imaging and increasing use of cross sectional imaging such as CT and MRI (5, 31). In many instances, errors in staging are related to undiagnosed lymph node metastases (9, 10). It is commonly accepted that patients with lymph node metastases have lower overall survival, disease-free survival, and survival after recurrence (5, 31, 38). Although not permitted to alter FIGO staging (12), many modalities have been employed to determine the extent of disease prior to therapy. In a clinical-pathologic study performed by the GOG, sensitivity and specificity of CT was only 34% and 96%, respectively (14). However, a more recent meta-analysis, found the positive predictive value of CT to be 60% and the negative predictive value to be 91% for detection of retroperitoneal lymph node metastasis (55).

More recently, FDG-PET imaging has demonstrated its utility in detecting nodal involvement in a number of malignancies other than cervical cancer. In one study involving 48 patients with primary esophageal carcinoma, the patients were evaluated with PET, CT, and US prior to undergoing complete lymphadenectomy (15). PET demonstrated 57% sensitivity, 97% specificity, and 86% accuracy compared to CT, which was only 18% sensitive ($p < 0.0001$), 99% specific ($p = 0.03$), and 78% accurate ($p = 0.003$). Overall, for N staging, PET was correct in 83%, whereas CT and US were correct in 60% ($p = 0.006$) and 57% ($p = 0.003$), respectively. Similarly, in a study comparing PET with CT for diagnosing small (<1 cm), intermediate (1-3 cm), and large (>3 cm) mediastinal lymph node metastases from lung cancer, PET was equally reliable and accurate for detecting all sizes of lymph node lesions with better efficacy than CT (24). Overall sensitivity, specificity, and accuracy were 96%, 93%, and 94%, respectively, with a positive and negative predictive value of 86% and 98%. In summarizing the results from another study evaluating PET, CT, MRI, and US in the detection of lymph node metastases from head and neck cancer, the authors concluded that PET was the “procedure with the highest sensitivity and specificity” (4).

Several reports have also demonstrated the utility of FDG-PET imaging in the diagnosis of lymph node metastases from cervical carcinoma. Rose et al. (52) pre-operatively evaluated 32 patients with IIB–IVA cervical cancer with no evidence of extra-pelvic disease. Fluorodeoxyglucose was taken up by 91% of the cervical tumors and accurately diagnosed six of eight patients with positive para-aortic lymph node metastases. The sensitivity was 75%, the specificity 92%, the positive predictive value 75%, and negative predictive value 92%. Similarly, Sugawara et al. (62) correctly identified six of seven (86%) patients with known lymph node metastases using PET, compared to only four with CT. Reinhardt et al. (50) compared the diagnostic accuracy of MRI with that of PET in a group of 35 patients with stage IB and II cervical cancer. Eleven patients had surgically proven lymph node metastasis. FDG-PET had a sensitivity of 91%, a specificity of 100%, a negative predictive value of 96%, and an

accuracy of 97% for depicting lymph node metastases, while the respective values for MR imaging were 73%, 83%, 67%, 87%, and 80%. A recent analysis of 15 published PET studies in cervical cancer by Havrilesky et al. demonstrated that pooled sensitivity and specificity for detection of pelvic lymph node metastasis were 79% (95% CI 65%-90%) and 99% (96%-99%), respectively for FDG-PET; 72% (53%-87%) and 96% (92%-98%), respectively for MRI and 47% (21%-73%) for CT (the pooled specificity for CT not available) (28). In this review, the pooled sensitivity of FDG-PET for para-aortic lymph nodes are 84% (95% CI 68%-94%) and 95% (89%-98%), respectively (the pooled sensitivity and specificity for CT or MRI are not available).

There are limited data available on the utility of PET/CT on the evaluation of lymph node metastases in cervical cancer. Sironi et al. studied 47 patients with cervical cancer. Fifteen patients had metastatic lymph nodes at histopathologic examination, and 32 had no histopathologically confirmed nodal metastasis (58). Of the total 1081 pelvic lymph nodes histopathologically sampled, 18 were found to be positive for metastatic disease. The overall lymph node-based sensitivity, specificity, and accuracy of PET/CT were 72%, 99.7%, and 99.3%, respectively. The overall patient-based sensitivity, specificity, and accuracy of PET/CT were 73%, 97%, and 89% respectively. To date no PET/CT study is available in cervical cancer that compared PET with PET/CT. However, in various types of cancers, this comparison has been made and demonstrated improvement of PET performance when fused PET/CT images were used (68). For example in a study of 260 patients with various types of cancer, Antoch et al. reported that PET/CT is more accurate in lymph node staging than PET alone with sensitivities of 92% for PET/CT and 85% for PET and specificities of 93% and 88%, respectively (6). Thus, an improvement of approximately 10% in the performance of PET is expected when PET/CT is used. (11/25/08)

While to date, no study is available in cervical cancer that compared PET/CT with MRI in the detection of metastatic lymph nodes, limited comparison studies are available for these two modalities in other types of cancers. For example, in a study of 98 patients with various types of cancers, Antoch et al. compared whole-body PET/CT to whole-body MRI and demonstrated that for detection of lymph node metastasis, FDG-PET/CT had sensitivity and specificity of 95% and 92%, respectively and whole-body MRI had sensitivity and specificity of 79% and 78%, respectively (7). To date, there are no comparison studies for FDG-PET/CT and MRI using USPIO.

2.1 Ferumoxtran-10 MRI

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3.0 SPECIFIC AIMS/OBJECTIVES

3.1 Primary Objectives

- 3.1.1** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with locoregionally advanced cervical carcinoma.

- 3.1.2** To evaluate the diagnostic sensitivity and specificity of preoperative ferumoxtran-10 (Combidex) MRI scanning in identifying metastases to abdominal (common iliac, para-aortic, and para-caval) lymph nodes in patients with locoregionally advanced cervical carcinoma.

3.2 Secondary Objectives

- 3.2.1** To evaluate the diagnostic sensitivity and specificity of preoperative FDG-PET/CT imaging in identifying metastases to pelvic lymph nodes (obturator, external iliac) and pelvic and abdominal lymph nodes combined in patients with locoregionally advanced cervical carcinoma.

- 3.2.2** To compare the diagnostic sensitivity and specificity of preoperative ferumoxtran-10 MRI scanning in identifying metastases to pelvic lymph nodes (obturator, external iliac) and pelvic and abdominal lymph nodes combined in patients with locoregionally advanced cervical carcinoma.

- 3.2.3** To evaluate the additive diagnostic value of CT fusion (PET/CT) compared with PET scanning alone in the identification of metastases to pelvic (obturator, external iliac), abdominal (common iliac, para-aortic, and para-caval), and combined (all regions) lymph nodes in locoregionally advanced cervical carcinoma.

- 3.2.4** To compare the diagnostic sensitivity and specificity of PET/CT scanning to preoperative ferumoxtran-10 MRI scanning in the identification of metastases to pelvic (obturator, external iliac), abdominal (common iliac, para-aortic, and para-caval), and combined (all regions) lymph nodes in locoregionally advanced cervical carcinoma.

- 3.2.5** To compare the diagnostic sensitivity and specificity of Combidex MRI with MRI based on size criteria in the abdomen and pelvis.

- 3.2.6** To determine the percentage of patients with locoregionally advanced cervical cancer that have biopsy proven disease outside abdominal or pelvic lymph nodes detected by PET/CT.

- 3.2.7 To determine the complications associated with extra-peritoneal or laparoscopic abdominal and pelvic lymphadenectomy including delay in the initiation of radiation therapy or interruption in radiation therapy in patients with cervical carcinoma.
- 3.2.8 To collect data on the adverse effects of the ferumoxtran-10 agent.
- 3.2.9 Compare the size of lymph nodes on pre and post Combidex MRIs in a subset of 40 patients.

The primary metrics of diagnostic accuracy for all of the above will be sensitivity and specificity. The reference standard is the result of pathological evaluation of pelvic and abdominal lymph nodes. Objectives 3.1.1, 3.1.2, 3.2.1, 3.2.2, 3.2.3, and 3.2.4 will be evaluated primarily through central reader studies that also address inter-observer variability in diagnostic sensitivity and specificity. In addition, evaluations will be made of objectives 3.1.1, 3.1.2, 3.2.1, and 3.2.2 by blinded independent reading of PET/CT and ferumoxtran-10 MRI of patients accrued in each center by two different institutional PI radiologists at the same center.

4.0 STUDY OVERVIEW

A total of 325 women will be enrolled in this study from at least 10 sites. Eligible participants are women who have met the pre-entry requirements specified in the Eligibility Criteria section of the protocol. Participants must be accrued at GOG member institutions or affiliates who are also accredited by ACRIN. Enrollment is expected to be completed within 36 months from protocol activation. Forty of the 325 patients who consent to undergo 2 MRIs (one pre-ferumoxtran-10, and one post-ferumoxtran-10) will provide a cohort of MRI examinations in order to validate the similarity of nodal size in pre and post-ferumoxtran-10 MR images.

Assuming that approximately 20-25% of the enrolled women will actually have positive abdominal nodes, the expected number of women with positive nodes in the abdomen in the study sample is between 60 and 75. After a study initiation period of 6 months, a uniform rate of accrual over the duration of the study is expected, with steady rates of positive and negative cases. Thus, about 30-38 positive cases will have been enrolled by the end of the 20th month of the study. This will be the timing for the performance of the interim analysis.

5.0 PARTICIPANT SELECTION

5.1 Inclusion Criteria

- 5.1.1 Patients must have primary, previously untreated, histologically confirmed, locoregionally advanced (IB2, IIA \geq 4cm, IIB-IVA) invasive carcinoma of the cervix (any cell type) and be considered for chemoradiation therapy. **(06/09/08)**
- 5.1.2 Patients must be appropriate surgical candidates to undergo extra-peritoneal or laparoscopic lymph node sampling.
- 5.1.3 GOG performance status of 0, 1, or 2.

- 5.1.4** Patients must have normal organ and marrow function as defined below (06/09/08):
- Leukocytes $\geq 3,000/\mu\text{L}$
 - Absolute neutrophil count $\geq 1,500/\mu\text{L}$
 - Platelets $\geq 100,000/\mu\text{L}$
 - Total bilirubin ≤ 1.5 times the institutional upper limit of normal
 - Alkaline phosphatase ≤ 2.5 times the institutional upper limit of normal
 - Lactic dehydrogenase ≤ 2.5 times the institutional upper limit of normal
 - Prothrombin time within normal institutional limits
 - AST(SGOT)/ALT(SGPT) ≤ 2.5 times the institutional upper limit of normal
 - Creatinine within normal institutional limits OR, in participants with creatinine levels above institutional normal, creatinine clearance >60 mL/min/1.73 m²; there is no lower limit of normal for serum creatinine for this protocol (11/25/08)
- 5.1.5** Patients of child-bearing potential must have a negative urine or serum pregnancy test result within 7 days prior to undergoing PET/CT and ferumoxtran-10 MRI. In addition, they would undergo a urine test on the day of PET/CT examination. Combidex is injected on the day of PET/CT examination. The urine test at the institution should detect hCG at the sensitivity of 25 mIU/mL. If the urine test does not have the required sensitivity, a negative serum test is required. Postmenopausal women must have been amenorrheic for at least 12 consecutive months to be considered not to be of child-bearing potential.
- 5.1.6** Patients who have signed an approved informed consent and authorization permitting release of personal health information.

5.2 Exclusion Criteria

- 5.2.1** Patients with recurrent invasive carcinoma of the uterine cervix regardless of previous treatment.
- 5.2.2** Patients who have known metastases to lungs, scalene lymph nodes, or metastases to other organs outside of the pelvis or abdominal lymph nodes at the time of the original clinical diagnosis.
- 5.2.3** Patients with any stage of cervical cancer other than IB2, IIA $\geq 4\text{cm}$, and IIB-IVA.
- 5.2.4** Patients who had a prior pelvic or abdominal lymphadenectomy performed for any reason.
- 5.2.5** Patients who have received prior pelvic radiation therapy for any reason.
- 5.2.6** Patients with septicemia or severe infection.
- 5.2.7** Patients with circumstances that will not permit completion of the imaging studies or required follow-up.
- 5.2.8** Patients with renal abnormalities, such as a pelvic kidney, horseshoe kidney, or renal transplantation, which would require modification of the lymphadenectomy.
- 5.2.9** Patients with uncontrolled intercurrent illness, including but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina

pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

- 5.2.10 Patients with a history of anaphylactic or life-threatening allergic reactions to any contrast media.
- 5.2.11 Patients who are pregnant or lactating or who suspect they might be pregnant. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with ferumoxtran-10, breastfeeding should be discontinued if the mother receives ferumoxtran-10.
- 5.2.12 Patients with GOG Performance Grade of 3 or 4.
- 5.2.13 Patients with other invasive malignancies, with the exception of non-melanoma skin cancer, who had (or have) any evidence of the other cancer within the last 5 years or whose previous cancer treatment contraindicates this protocol therapy.
- 5.2.14 Any contraindication to the performance of MRI (i.e., severe claustrophobia, pacemaker, aneurysm clips, defibrillators, or other institutional contraindication to MRI).
- 5.2.15 Patients having a history of allergic reactions attributed to compounds of chemical or biologic composition similar to ferumoxtran-10 (i.e., iron preparations, parenteral iron, parenteral dextran, parenteral iron-dextran, or parenteral iron-polysaccharide preparations).
- 5.2.16 Patients with immunodeficiencies that predispose a participant to specific or non-specific mediator release.
- 5.2.17 Patients who have received ferumoxides within 2 weeks of enrollment.
- 5.2.18 Patients with pre-study ferritin levels greater than 600 ng/ml and percent saturation of transferrin level greater than 50%. However, patients with laboratory values above these limits may be included in the study if documented hematology consultation rules out iron overload. Patients with increased iron-levels in their blood are not included in the protocol. This is done to avoid adding to their iron overload.
- 5.2.19 Patients with a history of cirrhosis.
- 5.2.20 Patients receiving any other investigational agents within a 30-day period.
- 5.2.21 Patients with poorly controlled, insulin-dependent diabetes (fasting blood glucose level >200 mg/dL).
- 5.2.22 Patients weighing greater than 300 lbs, which is the limit for current PET/CT scanners. (09/09/08)

5.3 Recruitment and Screening

Potential study participants will be seen by a GOG investigator as part of their standard care for their cervical cancer. At the time of their visit, the standard of care treatment will be discussed along with possible participation in the GOG-0233/ACRIN 6671 trial. If the patient agrees to participate, they will be consented by the GOG investigator or investigator-designee. A subset of patients (40 total) can elect to participate in the optional arm of the protocol. Detailed information on this optional arm is found in section 2.3 of the protocol. More information about study participant enrollment is available on the GOG and ACRIN websites.

Investigators who wish to participate in the trial are required to complete an ACRIN Protocol Specific Application (PSA) found on the ACRIN web site (<http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ProtocolApplicationandSiteActivation>)

[/tabid/416/Default.aspx](#)). (06/09/08) The PSA requires the collaboration of the ACRIN and GOG researchers to complete the following information:

1. Documentation of the number of patients treated in the previous two years who would meet protocol eligibility;
2. Documentation of the site’s recruitment potential;
3. Detailed description of how the patients will be identified, informed about the study, and consented into the trial.

ACRIN will work with the protocol team and site investigators to determine materials that would be helpful for participant recruitment. Site investigators will be responsible for obtaining IRB approval recruitment materials provided by ACRIN.

5.4 Inclusion of Women and Minorities

The GOG/ACRIN participating institutions will not exclude potential participants from participating in this or any study solely based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire cervix cancer population treated by participating institutions.

Women of all ethnic groups are eligible for this trial. In conformance with the National Institutes of Health (NIH) Revitalization Act of 1993 with regard to inclusion of women and minority in clinical research the projected gender and minority accruals are shown below:

Gender and Minority Accrual Estimates

Ethnic Category	Sex			
	Females	Males	Unknown	Total
Hispanic or Latino	40	N/A	N/A	40
Not Hispanic or Latino	285	N/A	N/A	285
Ethnic Category: Total of all patients	325	N/A	N/A	325
Racial Category				
American Indian or Alaskan Native	3	N/A	N/A	3
Asian	15	N/A	N/A	15
Black or African American	90	N/A	N/A	89
Native Hawaiian or other Pacific Islander	0	N/A	N/A	0
White	217	N/A	N/A	215
Racial Category: Total of all patients	325	N/A	N/A	325

6.0 SITE SELECTION

6.1 Investigator & Institutional Requirements

GOG Requirements

Protocol requirements will be sent out to GOG sites. GOG investigators must be willing to perform pre-treatment surgical staging in cervical carcinoma and the other responsibilities outlined in the GOG investigator letter of participation that is sent as part of the GOG-0233/ACRIN 6671 PSA.

ACRIN Requirements

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. The gynecological surgeons at each participating site must sign a letter of agreement to facilitate recruitment of participants and to comply with the protocol. During the first year, accrual will be reviewed monthly with the intention of discovering and resolving any barriers. The trial PI will designate members for a “Patient Enrollment Support Committee.” Committee members will be responsible for monitoring the accrual rates for individual institutions and developing corrective action plans for institutions that fall below 75% of a site’s expected accrual after a six-month start up period from the time the site is open for participant enrollment.

6.2 IRB Approval and Informed Consent

All institutions must have study-specific Institutional Review Board (IRB) approval for the protocol and informed consent form. The informed consent form is included in this protocol as Appendix II. The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by the local IRB at the institution. A copy of the IRB approval letter and a copy of the IRB approved, institutional study-specific consent form must be on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: Protocol Development and Regulatory Compliance (PDRC) Department) prior to registering the first participant.

ACRIN PDRC will review the IRB documentation and grant sites approval after conducting the IRB review process. After the site is approved for participant enrollment, ACRIN PDRC will forward a copy of the institution’s IRB approval letter and IRB-approved informed consent form to the GOG Regulatory Office (ATTN: Shawn Griffin, email: sgriffin@gog.org; fax: 215-854-0716). GOG staff will enter the approval into the GOG regulatory database. The IRB approval information will appear in the web registration system, allowing the approved site to complete web registration.

7.0 ONLINE REGISTRATION SYSTEM

7.1 Using the Online Registration System

7.1.1 The institution must register the participant using the web-based registration application available at www.gog.org. Instructions for web-based registration can be found by going to the GOG Web Menu page, selecting “Start/finish a patient registration” and then selecting “Directions” found in the left side of the page. Call (800) 523-2917 for any questions regarding participant registration. **(06/09/08)**

7.1.2 The institution will enter the participant’s name, GOG number, and assigned regimen in the appropriate place in their Log Book to verify the participant’s

entry. Participant's will be registered at GOG only. ACRIN will be notified of each registration after GOG completes the registration process.

7.1.3 GOG will notify ACRIN and the primary investigators of enrollment/registration via Mercury.

7.1.4 If a data manager is unable to complete a Fast Fact Sheet (FFS) because the patient is ineligible the randomization is not to be completed.

8.0 SURGICAL TREATMENT & PET/CT SCAN EVALUATION

8.1 Pathologic Evaluation Prior to Pelvic and Abdominal Lymph Node Sampling

- Any evidence of disease outside of the pelvis or abdominal nodal region amenable to biopsy or sampling (i.e. intrahepatic or pulmonary metastasis; bony involvement; or suprarenal, thoracic or supraclavicular lymphadenopathy; or lymphadenopathy above the renal hilum) on PET/CT needs to be pathologically evaluated prior to performance of the pelvic and abdominal lymph node sampling. If surgical approach is required, this may be performed at the same surgery as the lymph node sampling as long as frozen section diagnosis is used in order to abort the lymph node sampling if the disease outside of the pelvis or abdominal nodal regions is found to be positive. Otherwise, percutaneous biopsy will be performed. **(06/09/08)**
- If metastatic disease is confirmed, the participant will not undergo lymph node dissection but rather will go on to palliative chemotherapy protocols at the investigator's discretion.
- All participants will remain in the study regardless of metastases, and all appropriate forms and follow-up information will need to be completed.
- Those unable to be confirmed (either biopsy not technically feasible or pathologically negative) may proceed with lymph node sampling at the investigator's discretion.

8.2 Pelvic and Abdominal Lymph Node Sampling

Lymph node dissection will be performed in accordance with strict anatomic boundaries.

NOTE: This differs from the standard GOG definitions. **(06/09/08)**

- External Iliac Lymph Nodes: From bifurcation of common iliac artery cranially to the point at which the deep circumflex iliac vein crosses over the external iliac artery caudally. Lateral boundary is the psoas muscle and genito-femoral nerve. Medial boundary is the ureter and superior vesical artery. Deep boundary is the inferior border of the external iliac vein.
- Obturator Lymph Nodes: Similar to the external iliac lymph node boundaries only extending between the inferior borders of the external iliac vein superiorly and the obturator nerve inferiorly.
- Common Iliac Lymph Nodes: from bifurcation of the common iliac artery caudally to the bifurcation of the aorta cranially. Lateral boundary is the psoas muscle and medial boundary the common iliac artery. At the surgeon's discretion, these may be arbitrarily divided in the middle into "high" and "low" common iliac lymph nodes and be sent as separate specimens.

- Left Para-aortic Lymph Nodes: The caudal boundary is the bifurcation of the aorta. Lateral boundary is the psoas muscle and medial boundary the aorta. The cranial boundary is the point at which the inferior mesenteric artery (IMA) exits the aorta. Positive lymph nodes above the IMA may be resected at the surgeon's discretion. Abdominal lymph nodes from above the IMA are to be sent as a separate specimen.
- Right Para-Caval Lymph Nodes: The caudal boundary is the bifurcation of the aorta. Lateral boundary is the psoas muscle and medial boundary the aorta. The deep boundary is the Vena Cava. The cranial boundary is the point at which the inferior mesenteric artery (IMA) exits the aorta. Positive lymph nodes above the IMA may be resected at the surgeon's discretion. Abdominal lymph nodes from above the IMA are to be sent as a separate specimen.
- Any lymph node sitting at the boundary between two regions will be considered to belong to the more cranial region by convention (i.e. a palpable lymph node at the bifurcation of the common iliac artery will be considered a common iliac lymph node and one at the bifurcation of the aorta will be considered para-aortic or para-caval). Lymph nodes overlying the aorta will be divided into left para-aortic and right para-caval based upon their relationship to the midline of the aorta.

8.3 Treatment Modifications (06/09/08)

8.3.1 Surgery will not be performed if there is advanced lymphadenopathy not amenable to surgery.

8.3.2 Lymph Node Sampling

- Surgery may be terminated if it is judged to be in the best interest of the participant. The reason for termination will be explained in the operative report.
- Successful completion of a lymph node sampling in all eight lymph node "regions" (left obturator, right obturator, left external iliac, right external iliac, left common iliac, right common iliac, right para-caval, and left para-aortic) is an endpoint of the study.
- If lymph nodes appear clinically negative in a particular region, then complete lymphadenectomy in that region is required.
- If lymph nodes appear overtly suspicious, the investigator may choose to perform anything from a complete lymphadenectomy to a biopsy.
- If anything less than a complete lymphadenectomy is performed, then frozen section confirmation of disease must be performed.
- If the frozen section is unable to confirm disease, then complete lymphadenectomy is required.
- Each lymph node "region" is to be considered independently of one another.
- Therefore, even if a biopsy is positive in one region, a complete lymph node dissection is required in all other regions not independently proven to be positive by intra-operative confirmation of metastatic disease.
- It is inappropriate to convert to a trans-peritoneal approach for the sake of removing lymph nodes.

8.3.3 Laparoscopic Lymphadenectomy

8.3.3.1 Technical Difficulty

- If the lymph node sampling is performed by a laparoscopic approach and cannot be completed successfully due to technical difficulties (i.e., inadequate exposure), an extra-peritoneal lymphadenectomy must be attempted.

8.3.3.2 Unresectable Lymph Nodes

- If the laparoscopic lymph node sampling was unsuccessful due to unresectable lymph nodes, extra-peritoneal lymphadenectomy is not required, but may be attempted at the surgeon's discretion. At the very least, intra-operative documentation of metastatic disease to the unresectable lymph node region must be documented.
- Finally, if an overtly suspect lymph node is encountered during a laparoscopic approach, conversion to an extra-peritoneal lymphadenectomy in order to completely remove the lymph node may be performed at the surgeon's discretion.

8.3.3.3 Retroperitoneal Fibrosis

- In the event of an inability to develop the retroperitoneal spaces (i.e., retroperitoneal fibrosis or adhesions), the procedure should be terminated.
- If, in the investigator's opinion, an extra-peritoneal lymph node dissection would be similarly unsuccessful, an extra-peritoneal attempt at lymph node sampling is not necessary.
- Every reasonable attempt should be made to perform a biopsy of any available lymph nodes. Trans-peritoneal lymph node sampling will not be performed.

8.3.4 Modified or Aborted Lymph Node Sampling

- In the event of a modified or aborted lymph node sampling (i.e., sampling from less than all eight regions), the surgeon must clearly document in the operative report precisely why the procedure could not be completed.
- Any operative procedure other than an eight-region staging as outlined above will be considered a "failed procedure," but not a protocol violation unless the operative note fails to provide sufficient detail explaining the deviation from the defined surgical objective.

NOTE: If the physical constraints of the participant prevent the lymphadenectomy from being performed per the protocol, the investigator will not be in violation of the protocol. However, if the procedure was not done or done incorrectly when it could have been done, it will be considered a protocol violation.

- This will also be documented on the Pelvic and Abdominal Lymphadenectomy form.
- Again, each lymph node region is to be evaluated independently of one another.
- Therefore, even if a biopsy is positive in one region, a complete lymph node dissection is required in all other regions not independently proven to be positive by intra-operative confirmation of metastatic disease.

8.4 PET/CT Identification of Advanced Disease

8.4.1 If the PET/CT identifies advanced disease outside of the pelvis or abdominal nodal region (i.e., intrahepatic, pulmonary, or thoracic or supraclavicular lymph nodes) that is amenable to biopsy, tissue confirmation (pathologically by tissue acquisition) must be obtained from the most technically accessible site.

8.4.1.1 Positive imaging findings unrelated to the cervical cancer (i.e. axillary lymph nodes) should not be considered as requiring biopsy as per the protocol. It is, however, a clinical decision as to whether these need to be biopsied. If they are, that data should be provided to the study.

8.4.2 Once metastatic disease is biopsy proven, the lymphadenectomy is to be abandoned and clearly documented on the Pelvic and Abdominal Lymphadenectomy form. **(06/09/08)**

8.4.3 In the case of a lesion seen on PET but not seen on dedicated diagnostic images (i.e. lung or liver metastasis), biopsy will not be required unless this involves the supraclavicular lymph nodes. In this case, supraclavicular lymph node dissection should be performed.

8.4.4 Participants with suspicious PET/CT findings unamenable to biopsy will undergo protocol specified lymphadenectomy followed by repeat imaging with conventional radiographs, CT, MRI, or bone scintigraphy at the time of the 6-month follow-up.

8.4.5 These lesions will be considered false-positive results if they remain unchanged over a follow-up interval of 6 months.

8.4.6 Otherwise, they will be considered true positive. If imaging reveals a lesion that is not amenable to biopsy (or if a biopsy is negative), these participants should go on to lymphadenectomy.

8.5 Evaluation Criteria

8.5.1 All procedures will be evaluated according to the schema for surgical evaluation and for pathologic evaluation.

8.5.2 All PET/CT and ferumoxtran-10 MRI scans will be required to undergo centralized/decentralized review to be organized by ACRIN (See Section 12.2.5 for instructions on submitting images to ACRIN). The central reading for PET/CT will be conducted at the ACRIN headquarters (Philadelphia, PA). The central reading for MRI will be conducted either at ACRIN or at the expert readers' institutions. There are a limited number of ferumoxtran-10 MRI readers and these readers are located mainly in Europe since the agent is not yet approved in North America. The central readers will be chosen from Europe or North America. The expert readers for ferumoxtran-10 MRI could be from the accruing institutions as long as they are not involved in the institutional reviews. All readers will be provided with the same interactive tool to review the cases.

8.5.2.1 Suspicious lymphadenopathy on PET/CT and ferumoxtran-10 MRI scanning will be defined as visible lymph nodes ≥ 10 mm in the short axis if the node is oval shaped and >8 mm in diameter if rounded. In addition, necrotic lymph nodes on contrast-enhanced CT will be considered abnormal. MRI review will start with evaluation of iron insensitive T1W sequences to determine normality/abnormality of LNs based on size criteria. After this information is entered in a locked box, iron sensitive sequences will be evaluated in conjunction with iron insensitive sequences. It has been shown in a phase II study that Combidex does not affect the signal intensity of LNs on T1W sequence but drops the signal on T2W and T2* sequences (31). The same study shows that the effect of iron on the size of LN on T2W and T2* is negligible. Overall, lymph node size changed only minimally (mean, ≤ 0.3 mm) from before the dose to after the dose (31). In the absence of signal intensity change in the LNs on T1W sequence, there is no reason for the size of LNs to be different on T1W sequence on the post Combidex MRI.

(06/09/08)

8.5.2.2 FDG-PET/CT images will be evaluated qualitatively for focal areas of abnormally increased FDG uptake. The likelihood of the spread of disease in pelvic lymph nodes, para-aortic lymph nodes and other sites is according to the following scale: definitely benign, most likely benign, probably benign, probably malignant, most likely malignant, definitely malignant. A positive finding is defined as the presence of abnormal FDG uptake (when accumulation of the tracer is moderately to markedly increased relative to the uptake in comparable normal structures or surrounding tissues, with the exclusion of physiologic bowel and urinary activity), even when the lymph node has normal size (see above section 8.5.2.1 for criteria used to characterized lymph node based on size). A negative finding is defined as no detectable FDG uptake, even when the lymph nodes are enlarged. Semiquantitative analysis of selected lesions (primary tumor and up to five additional lesions involving each lymph node group and/or distant organs) using the standardized uptake value

(SUV) method also will be performed. The SUV is the ratio of the decay-corrected concentration of FDG within the tumor ($\mu\text{Ci/g}$) to the average concentration of FDG in the body (i.e. the administered activity divided by the body weight). This will be performed by visually identifying the region or regions of the tumor on the PET images that qualitatively appear to have the most intense FDG uptake. A circular region of interest 1 cm in diameter centered on the maximum-value pixel will be drawn to calculate the mean SUV within the region. This value will be reported as peak SUV. Initially, attenuation-corrected and non-attenuation-corrected PET images will be evaluated for presence of primary cervical cancer, nodal and distant metastasis, and recorded on the data form. The SUV data obtained from this trial will be used to directly compare SUVs of the primary and nodal disease in comparison to biopsy proven metastatic deposits.

8.5.2.3 On MRI with ferumoxtran-10, lymph nodes are considered abnormal on T2*-weighted sequences if there are one or more discrete focal defects representing as foci of high signal intensity centrally or peripherally (excluding a fatty hilum), or if the node has diffuse high signal intensity. Lymph nodes are considered benign if their signal intensity relative to muscle low on T2*-weighted images and moderate or high on PD FSE images. Three-dimensional reconstructions of the relationship of the malignant or enlarged benign LNs to the adjacent vessels will be prepared to help surgical identification of the LNs. **(06/09/08)**

8.5.3 All participants are expected to initiate chemoradiation therapy within 4 weeks of their enrollment in the study as outlined in Section 9.5. Delays in initiation of radiation therapy as well as delays during treatment will be documented in order to assess the impact of the surgical procedure. Initiation date will be recorded on the Pelvic & Abdominal Lymphadenectomy Form. Any delay in initiation of therapy beyond 4 weeks must be clearly documented and an explanation provided. In addition, any subsequent delays in treatment must also be documented and an explanation provided. The date of completion of radiation therapy must also be documented.

8.5.4 The result of the ferumoxtran-10 MRI will not affect the treatment plan because all participants will undergo standard lymphadenectomy unless PET/CT shows disease outside lymph nodes.

9.0 STUDY PROCEDURES

9.1 Patient Entry & Registration Visit

- Obtain prior medical history, including allergy history;
- Perform a physical examination;
- Perform a urine or serum pregnancy test;
- Obtain labs;

- Perform a chest X-ray;
- Conduct an electrocardiogram (ECG);(11/25/08)
- Determine if patient meets all eligibility requirements according to section 5.0;
- Obtain signed consent on an IRB-approved informed consent form prior to performing any study related procedures including those not considered standard of care for the treatment/evaluation of cervical cancer such as MRI scans;
- Gather the Fast Fact Sheet (FFS);
- Register the participant using the web-based registration application or by phone (800-523-2917). Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page or in Section 7.0, Online Registration System.

9.2 Visit 1: PET/CT and Ferumoxtran-10 Administration¹-Within 7 days from Registration Visit

Visit 1 will occur within seven (7) days of the registration visit. Participants will undergo PET/CT scan as described in section 12.0.

- Conduct a urine or serum pregnancy test;(11/25/08)
- Perform the PET/CT with SUV calculation;
- Administer the ferumoxtran-10 after the completion of PET/CT, but only if the MRI can be scheduled on the next day.

NOTE: If not scheduled on two consecutive days, participants may undergo ferumoxtran-10 MRI scans within one week of their PET/CT scan. Participants will return to receive ferumoxtran-10 later within one week of PET/CT. Ferumoxtran-10 must be administered within 24-36 hours before the MRI. In extreme circumstances, the MRI may be performed up to approximately 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions **MUST** provide explanation on why MRI was performed after 36 hours or why MRI was performed in less than 24 hours. (06/09/08)

9.3 Visit 2: Ferumoxtran-10 MRI: 24-36 Hours after injection of Ferumoxtran-10

- Participants will return 24 – 36 hours after completion of receiving ferumoxtran-10 for an MRI examination as described in section 12.0.
- Glucagon should be injected prior to imaging (see Section 12.1 for details); (06/09/08)
- Perform an MRI scan;
- Assess for any study-related adverse event since Visit 1, especially in regards to ferumoxtran-10.

9.4 Visit 3: Within 2 Weeks after Visit 1

- All participants will subsequently undergo pelvic and abdominal lymph node sampling by either an extra-peritoneal or a laparoscopic approach (Section 8.0). This will occur no more than 2 weeks from the date of the PET/CT scan.

¹ On day 1, just prior to receiving ferumoxtran-10, subjects will have the option to undergo the same MR imaging as planned for all subjects in the post-ferumoxtran-10 protocol. Please refer to section 2.3 for more details.

- Assess for any study-related adverse event since Visit 2;
- Perform the lymph node sampling surgical procedure.

9.5 Visit 4: Within 4 Weeks from PET/CT Scan

- All participants are expected to initiate chemoradiation therapy within 4 weeks from PET/CT.
- Initiate the administration of the chemotherapy regimen.
- Assess for any study-related adverse events since Visit 3.

NOTE: Initiation date of chemoradiation therapy will be recorded on the Post-Surgery Follow-Up Form. Any delay in initiation of therapy beyond 4 weeks from PET/CT must be clearly documented and an explanation provided. In addition, any subsequent delays in treatment must also be documented and an explanation must be provided. The date of completion of chemoradiation therapy must be documented. Delays in initiation of therapy will not be counted as protocol violations.

9.6 Visit 5: Within 6 Weeks after Pelvic and Abdominal Lymph Node Sampling

- Perform a physical examination to monitor the effects of ferumoxtran-10 and all surgical procedures performed up to this time-point.
- Assess for any study-related adverse events since Visit 4.

9.7 Visit 6: 6 Months after PET/CT Scan

- Review the results of the physical examination;
- Perform a CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied.
- Assess for any study-related adverse events since Visit 5.

9.8 Visit 7 - 14: Every 3 Months for 2 Years after PET/CT Scan-Per Standard of Care

- Obtain routine blood tests at the discretion of the treating physician (no data collection is required);(11/12/08)
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator.
- Assess for any study related adverse events.

9.9 Visit 15 - 20: Every 6 Months for 3 Additional Years after Visit 14 – Per Standard of Care

- Obtain routine blood tests at the discretion of the treating physician (no data collection is required);(11/12/08)
- Perform physical examinations;
- Perform x-rays, per discretion of the investigator.
- Assess for any study related adverse events.

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NOTE: Participant will receive standard of care as recommended by the participant’s treating physician for 5 years following completion of their surgical evaluation. If enrolled on another GOG study, this can be done in conjunction. Follow-up information (Q-Forms) must be submitted per GOG requirements, if the participant is not enrolled in another GOG study.

9.10 Study Procedures Timetable (06/09/08)(11/25/08)

Procedures	Registration Visit	Visit 1: Day of PET/CT-7 Days from Registration ²	Visit 2: Day of MRI (Within 24-36 Hours after Ferumoxtran-10 administration ³)	Visit 3: Within 2 weeks after Visit 1	Visit 4: within 4 weeks from PET/CT Scan	Visit 5: Within 6 weeks Post-op	Visit 6: 6 months after PET/CT Scan	Visit 7-14: Every 3 months for 2 Years after PET/CT scan	Visit 15-20: Every 6 months for 3 additional years after visit 14
Informed Consent	X								
Eligibility/Registration	X								
Fast Fact Sheet	X								
Medical History (including allergy history)	X								
Physical Examination	X					X	X	X	X
Pregnancy Test (urine or serum): 7 days prior to PET/CT and ferumoxtran-10 MRI	X								
CBC/Diff/ platelets, Basic Metabolic Panel, Creatinine, Bilirubin, SGOT, SGPT, LDH, PT, PTT, Alk phos, Albumin, Calcium, Phosphorus, Serum Iron, Ferritin, % Saturation Transferrin, TIBC	X							X ⁴	X ⁴
Chest X-ray (per investigator’s discretion)	X							X	X
ECG	X								
PET/CT examination		X							
Ferumoxtran-10 injection (after PET/CT scan) ¹		X							
Ferumoxtran-10 MRI Scan			X						
Pelvic and Abdominal Lymph Node Sampling				X					
Chemoradiation Therapy					X				

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CT of the area with initial positive PET/CT outside abdomen and no biopsy proof of disease							X		
Adverse Event Assessment			X	X	X	X	X	X	X
Pregnancy Test - Urine hCG		X							

¹ If it is not possible to perform ferumoxtran-10 MRI scan the day after PET/CT, participants will return to receive ferumoxtran-10 later within one week after PET/CT. Ferumoxtran-10 must be administered within 24-36 hours before the MRI.

² On day 1, just prior to receiving ferumoxtran-10, the subjects will have the option to undergo the same MR imaging as planned for all subjects in the post-ferumoxtran-10 protocol. Please refer to section 2.3 for more details.

³ In extreme circumstances, the MRI may be performed up to 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions MUST provide explanation on why MRI was performed after 36 hours or why MRI was performed in less than 24 hours.

⁴ Blood testing is at the discretion of the treating physician; no data will be collected on these results.(11/25/08)

10.0 Data Collection and Management

10.1 General

10.1.1 The ACRIN web address is www.acrin.org.

10.1.2 Data collection and management will be performed jointly by the GOG Statistical and Data Center (SDC) and the Biostatistics and Data Management Center (BDMC) of ACRIN.

To minimize duplication of efforts and information, ACRIN BDMC will manage data elements related to imaging endpoints and the GOG SDC will manage data elements related to surgical endpoints and study monitoring.

To facilitate study obligations, there will be periodic transfers (between ACRIN BDMC and GOG SDC) of uniquely collected key data elements. Furthermore, the respective group will provide promptly elements deemed essential for interim and final analyses if these elements are not otherwise included in the periodic transfers. **(06/09/08)**

10.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the Data Management Center before attempting a re-registration.

10.2 Clinical Data Submission

10.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply to deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN website. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.

10.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as

open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.

10.2.3 To submit data via the ACRIN website, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for missing data, any out of range data, and data in the wrong format (e.g. character data in a field requiring numeric responses). Such errors will be detected as soon as the user attempts to submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the “Complete Form Submission” button is depressed.

10.2.4 Once data entry of a form is complete, and the summary form reviewed for completeness and accuracy, the investigator or the research staff presses the “Complete Form Submission” button on the form summary screen and the data are transferred into the clinical database. No further, direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data completed and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the Data Management Center for resolution of the submission.(11/25/08)

10.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

10.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

10.4 Electronic Data Management

10.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complimentary validation programs are initiated at the Brown Biostatistics Center and the Data Management Center. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC Research Associate (RA) for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DMC RA at the DMC needs to spend resolving problems. Additional data review will take place once the data are transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC RA for resolution. All BDMC communication with the participating sites is normally done through the Data Management Center. **(11/25/08)**

10.4.2 If checks at DMC or BC detect missing or problematic data, the DMC RA sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DMC RA updates the participant's data submission calendar with the due date for the site RA or investigator's response.

10.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or research associate may use the Forms Due and Future Due Reports as a case management tool.

10.6 Data Quality Assurance

10.6.1 The Biostatistical Center (BC) at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the Data Management Center (DMC). The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data

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verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

10.6.2 The goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the Biostatistical and Data Management Center (BDMC) will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance Department, until the problem has been resolved. If the BDMC, along with the Audit Group, cannot find a resolution to the problem, it will be brought to the Steering Committee for further discussion and resolution.

11.0 DATA COLLECTION FORMS (06/09/08)

The following forms must be completed for all participants and must be received in the GOG Statistical and Data Center in accordance with the schedule below. All forms except: F-form, Pathology report, and Operative report must be submitted via the SDC Electronic Data Entry System (SEDES), which is available through the GOG website (www.gogstats.org). Pathology material (F-form, pathology report and slides) should be submitted together via postal mail.

Form[±]	Due Within		Copies*	Comments
Form R (Registration Form)	2	Registration	1	Mandatory submission via SEDES
Form OSC (Primary Cervical Cancer - On Study Form)	2	Registration	1	Mandatory submission via SEDES
Form DR(Pre-treatment Summary Form)	4	Registration	1	Mandatory submission via SEDES
Form C (Surgical Reporting Form)	6	Surgery	2	Mandatory submission via SEDES
Operative report	6	Surgery	2	Mandatory submission via SEDES
Primary disease: Form F (Pathology Form)	6	Surgery	1	Submit together via postal mail to GOG SDC
Pathology Report	6	Surgery	2	
Slides	6	Surgery	**	
Form PAL (Pelvic and Abdominal Lymphadenectomy)	6	Surgery	2	Mandatory submission via SEDES
Form PRLN (Pathology Review of Lymph Nodes)	12	Surgery	1	Mandatory submission via SEDES
Form PSF (Post Surgery Follow-up)	4	6 week post operative follow-up visit	1	Mandatory submission via SEDES

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Form D2R (Cycle Dose Drug Form)	4	PET/CT	1	Mandatory submission via SEDES
Form T (Common Toxicity Reporting Form)	4	PET/CT	1	Mandatory submission via SEDES (see section 21.1.2)
Form T (Common Toxicity Reporting Form)	4	6 week post operative follow-up visit	1	Mandatory submission via SEDES (see section 21.1.2)
Form Q0 (Treatment Completion Form)	2	Completion of study Rx and change in Rx	1	Mandatory submission via SEDES
Form Q (Follow-Up Form)	2	Disease progression; death; normal follow-up	1	Mandatory submission via SEDES Quarterly for 2 years, semi-annually for 3 more years

- ± Use the SDC Electronic Data Entry System (SEDES), available on the GOG website, to view and print a copy of each form along with instructions, and to submit forms electronically. Check SEDES periodically as forms that are not currently available for electronic data entry will be made available for electronic data entry over time.
- * The number of required copies including the original form which must be sent to the Statistical and Data Center.
- ** At least one representative stained slide (or slides) documenting the primary.

12.0 IMAGE PROCEDURES

12.1 Combix MRI

12.1.1 MRI Technique

NOTE: Use of antiperistaltic medication is mandatory unless there is a contraindication to its use. (For the 40 participants not receiving Combix MRI, antiperistaltic medication is encouraged, but not mandated.) Glucagon (1 mg IM) should be injected prior to imaging, except in cases where it is contraindicated. Injection should be given with the patient on the table or immediately before she is put on the table. Glucagon gives 30 minutes of decreased bowel peristalsis, and thus decreases motion artifact and image blur. Contraindications include diabetes, pheochromocytoma, insulinoma, and known sensitivity. **(06/09/08)**

MRIs will be performed at 1.5 T with pelvic phased-array coils. Images of the pelvis and abdomen, extending from completion of the pubic symphysis to the level of the IMA will be obtained 24-36 hours after completion of the intravenous administration of ferumoxtran-10. In extreme circumstances, the MRI may be performed up to 48 hours after the completion of the intravenous administration of ferumoxtran-10. The institutions should provide explanation on why the MRI was performed after 36 hours or prior to 24 hours. Furthermore, a subset of patients will have the choice of participating in an optional arm to the protocol and will receive a pre-ferumoxtran-10 MRI. For more information on this optional arm, please refer to section **2.3** of the protocol.

The MR pulse sequences will consist of T1 GRE, FSE, and T2* GRE obtained in axial and obturator planes depending on the sequence. To better ensure image quality, the technical parameter charts will be distributed to the individual modalities to guarantee protocol compliance. The MRI scanning parameters can be found in Appendix XI.

12.1.2 Ferumoxtran-10 MRI Review at Imaging Institutions

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12.1.3 MRI Institutional Reviewers Training

Institutional reviewers will be trained at a central location at the outset of the study. The institutional MRI PIs will receive a tutorial lecture first followed by review of 10-15

proven known cases. At the end they will go through a quiz of 10-15 complete set of images of proven cases. All training cases will not be from this study.

12.2 PET/CT Imaging (06/09/08)(11/25/08)

Imaging examinations should be submitted to the ACRIN Imaging Core Laboratory after each time point/visit. A completed, signed Image Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN for each time point. For exams submitted via the Internet, complete the ITW and e-mail it to imagearchive@phila.acr.org or fax it to 215-923-1737. For exams submitted via media, complete the ITW and include it with the media shipment. Please affix a label to the jacket of the media that includes: study name, site name, case no., date of exam(s), time point, and type of imaging. **The ITW form MUST be completed in its entirety for the case to be credited.**

Participants must undergo whole-body PET and CT imaging with a PET/CT unit per institutional standard of care. ***Reminder for PET imaging: All PET exams should contain three trans-axial whole body series, attenuated and non-attenuated corrected PET scans, and the CT images.** The PET/CT unit should have a multi-slice CT (>1 slice) and BGO (Bismuth Germinate Oxide), LSO (Lutetium Oxyorthosilicate) or GSO only. Sodium Iodide (NaI) based scanners are not acceptable. The ability to calculate standardized uptake value (SUV) is also mandatory. The PET/CT scanner needs to be qualified by ACRIN before participating in this protocol.

Detailed information can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx> under ACRIN 6671/GOG 0233 Imaging Materials.

PET Technical Assessment Form will be used to ensure protocol compliance. The PET Technical Assessment Form can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

There is no set criteria that requires the original institution to repeat a PET/CT study. However, considering that PET/CT is standard of care for initial staging of cervical cancer, the study may be repeated if it is judged by the original institution that the study is suboptimal and does not provide clinical information to stage the patient prior to therapy. The most common reasons that result in a suboptimal study can be found in Form C1.

Participant/FDG Preparation: Please refer to Section 13.0 for detailed drug (FDG) information.

The order of FDG-PET/CT study will be as follows:(11/25/08)

1. Measure blood glucose level by glucometer. If it is below 150 mg/dL, continue. If blood glucose level is above 150 mg/dL, consult nuclear medicine physician.
2. If applicable, place Foley catheter.

3. Place an intravenous catheter. Give oral contrast to the participant.
4. Inject FDG, and flush catheter with 20-40 mL of normal saline solution. All participants will be well hydrated during the study (typically given an infusion of 500 mL 0.45% or 0.9% saline solution intravenously) or if intravenous hydration is not possible (e.g., if it is difficult to establish intravenous access), must drink a minimum of 4 cups of water.
5. See below (section 12.2.1) for detailed information about two options for CT acquisition. Approximately 60 minutes (+/- 10 minutes) after FDG injection, a diagnostic CT scan with contrast agents (oral and intravenous) or a low-dose CT (with oral contrast) will be performed. Patients must void prior to imaging. The diagnostic or low-dose CT of the chest, abdomen, and pelvis should be completed 60 minutes (+/- 10 minutes) after FDG injection, if it is performed before PET emission scan. The diagnostic or low-dose CT of the chest, abdomen, and pelvis should be initiated immediately after PET emission scan, if it is performed after PET emission scan. In either case, **the PET emission scan has to be performed approximately 60 minutes (+/- 10 minutes) after FDG injection.**
6. PET emission scan will be performed immediately after a low-dose CT or after the diagnostic CT depending on the CT option. At some sites, the diagnostic CT will be taken immediately after PET imaging without moving the patient (see options described in section 12.2.1 below).

Per one of the CT protocols described in section 12.2.1 below, some centers may perform a second CT scan only for attenuation correction of the PET images. Thus, a second low-energy CT scan can be performed just prior to emission PET scan (after completion of diagnostic CT) for attenuation correction of the PET images. In the alternative scenario described below, the low-dose CT scan must be performed prior to the PET scan if the diagnostic CT is to follow the PET imaging. The CT parameters for attenuation correction will be utilized according to imaging protocol at each center. We recommend effective mAs of 111, kVp of 130, 5-mm slice thickness and 4 –mm interval.

12.2.1 Diagnostic CT Imaging (06/09/08)(11/25/08)

General: All PET/CT (including the diagnostic CT part of PET/CT) scans must be performed on the same scanner immediately before or after the PET emission scan, depending on the CT option (see below). In either case, **the PET emission scan has to be performed approximately 60 minutes (+/- 10 minutes) after FDG injection.** It is recommended (but not obligatory) to use a breathing technique already in place to diminish respiratory artifacts. Typically, participants will be instructed to hold their breath while scanning the diaphragm.

First option: Diagnostic CT before PET (with optional low-dose CT in between).

1. Diagnostic CT imaging (with oral and intravenous contrast) per institutional standard of care will be done approximately 60 minutes (+/- 10 minutes) after the FDG injection (see section 12.2.4) beginning in a craniocaudal direction with the participant's upper neck.
2. An optional low-dose CT can be conducted immediately after the diagnostic CT without moving the participant. The low-dose CT will take a minute or so.
3. The PET scan should follow immediately after the CT without moving the participant.

Second option: The low-dose CT (with oral contrast) will be performed before PET emission scan and the diagnostic CT will be performed immediately after completion of PET emission scan.

1. The low-dose CT, starting at approximately 60 minutes (+/- 10 minutes) after FDG injection immediately before the PET emission scan in a craniocaudal direction starting with the participant's upper neck. The low-dose CT will take a minute or so.
2. The PET emission scan should then be initiated at 60 minutes (+/- 10 minutes) immediately after the low-dose CT scan.
3. Diagnostic (intravenous contrast) CT should be performed immediately after the PET scan without moving the participant (it will be about 75 to 90 minutes after the FDG injection).

Intravenous contrast: Intravenous contrast is required in participants with adequate intravenous access and no contradictions to it. A nonionic contrast agent (such as Optiray 350) will be administered intravenously according to the participant's weight:

- For participants <180 pounds, 125 mL of Optiray[®] 350 (Mallinckrodt Inc.) or equivalent will be given at the rate of 3 mL/sec with a 55-sec delay in imaging.
- For participants ≥180 to <250 pounds, 150 mL Optiray 350 will be given at the rate of 3 mL/sec with a 70-sec delay in imaging.
- For participants 250 to 300 pounds, 175 mL Optiray 350 will be given at the rate of 3 mL/sec with an 85-sec delay in imaging. **(09/09/08)**

Oral contrast: A water-soluble, iodinated oral contrast such as MD Gastroview[®] (Mallinckrodt Inc.) or equivalent is preferred over barium. Typically, a total dose of 600 mL of MD-Gastroview will be ingested prior to FDG injection.

MD-Gastroview (Diatrizoate Meglumine and Diatrizoate Sodium Solution) is a palatable lemon-vanilla flavored water-soluble iodinated radiopaque contrast medium for oral or rectal administration. Each ml contains 660 mg diatrizoate meglumine, 100 mg diatrizoate sodium, and approximately 4.8 mg sodium and 367 mg organically bound iodine. MD-Gastroview will be prepared according to the package insert – 25 ml of MD-Gastroview is diluted in 1L of tap water. A 600 mL dose is equal to 22.9 g of iodine.

12.2.2 PET Imaging

All participants will begin fasting 4 hours prior to the FDG-PET/CT imaging. If the participant is receiving total parenteral nutrition and/or intravenous fluids containing glucose, it also should be discontinued for at least 4 hours prior to the FDG-PET imaging. To exclude fasting hyperglycemia in all participants regardless of history of diabetes or nutritional status (such as total parenteral nutrition), the blood glucose level should be determined prior to the FDG administration. No diabetic medications should be administered within 4 hours prior to checking the glucose level. Participants with poorly controlled diabetes can have a small dose of short-acting insulin (with dose determined by the referring physician) with a light meal and then fast for 4 hours prior to the PET study. PET imaging should not be performed if the blood glucose level is >200 mg/dL.

An intravenous catheter (typically, a 20- or 22-gauge Angiocath) will be placed, typically in the antecubital fossa, for participant hydration, contrast, and FDG administration. 10-20 mCi of FDG (0.14-0.21 mCi/kg) will be administered intravenously as a bolus. A dose at a higher end of the range is recommended, with appropriate reduction in the per kilogram dose for heavier patients (in accordance with the manufacturer's recommendation). All participants will be well hydrated during the study (typically given an infusion of 500 mL 0.45% or 0.9% saline solution intravenously) or a minimum of 4 cups of water, if intravenous hydration is not possible (e.g., if it is difficult to establish intravenous access). To ensure adequate clearance of bladder activity (which might obscure structures adjacent to the bladder), all participants should void immediately prior to imaging.

12.2.3 Optional Diuretic Treatment:

Diuretics without Foley catheter: 20 mg of furosemide will be given before or at the time of FDG administration.

Diuretic with Foley catheter: 20 mg of furosemide will be given 20 minutes after FDG administration. Before the study, a Foley catheter (typically 16-french) will be placed using aseptic technique.

12.2.4 PET Technique(11/25/08)

Imaging will begin approximately 60 minutes (+/- 10 minutes) after FDG injection (see above in section 12.2.1 for the order options of diagnostic and low-dose CT and PET imaging). The participant will be positioned supine, with arms comfortably positioned above the head, whenever possible. To minimize lower back discomfort, one or two pillows may be placed under the participant's knees. The region imaged should extend from the participant's upper/mid-neck to the upper thigh.

If the acquisition of diagnostic CT data (see section 12.2.1 for CT technique) occurs prior to PET imaging, the imaging table will automatically be moved

further into the imaging system and PET imaging will be initiated, covering the same field of view as the CT, beginning in a caudocranial direction with the participant's upper thigh. A series of sequential emission scans (3-5 minutes' duration, depending on the participant's size) will be performed. Images will be corrected for scatter and reconstructed using iterative reconstruction algorithm. Emission PET images will be reconstructed with and without attenuation data. Low-dose and/or diagnostic CT data will be used for attenuation correction of the PET data per the options outlined in section 12.2.1 above. Image reconstruction will depend on the scanner manufacturer. We recommend an iterative reconstruction using OSEM algorithm in a 128 x 128 matrix with a Zoom of 1 and with a 5 mm Gaussian filter. Scatter, decay and deadtime correction, as provided by the manufacturer.

12.2.5 Image Submission to ACRIN(11/25/08)

All images collected from PET/CT, CT, and MRI are to be in digital format. All CT and MR images must be in the DICOM format. ACRIN has developed software that allows for electronic transmission of images to the Image Management Center (IMC) that have been scrubbed of all participant identifiers.

ACRIN can provide software (TRIAD, see www.triad.acr.org) for installation on a PC at your site that collects and submits image sets from your MRI computer or from your PACS. The images are "DICOM pushed" either from the MRI computer or from the PACS to the PC on which the software is installed. This software anonymizes, encrypts and non-destructively compresses the images as they are transferred by FTP to the ACRIN database in Philadelphia. For further information or questions, email imagearchive@phila.acr.org.

Image Submission Software PC Requirements:

1. Network capability to transmit data from a MR and PET scanner to a linked workstation or PC?
2. Do you have a PC available to transmit data (patient data, MR and PET image data) to ACRIN?
 - a. Operating System Windows XP Pro
 - b. Access to the Internet: Internet Explorer
 - c. Minimum of 50 GB available hard drive
 - d. At least 1 GB RAM
 - e. Ability to view PDF documents
3. Software utilities required to run image transmission software:
 - a. Windows Installer 3.1
 - b. Microsoft .NET framework 2.0
 - c. MDAC Type 2.8
 - d. MS SQL 2005 Express

Please contact ACRIN to arrange for installation of the TRIAD software prior to first participant accrual. Contact the TRIAD help desk by e-mailing Triad-Support@phila.acr.org or by calling 215-940-8820.

For Imaging Core lab image submission questions contact the lead technologist for this trial at imagearchive@phila.acr.org or 215-940-8880.

For submission on media, the media type must be limited to MOD, CD, or DVD. Media will not be returned unless specifically requested and unless return instructions and packaging are provided.

Send media to:

American College of Radiology
1818 market Street, 16th floor
Philadelphia, PA. 19103
ATTN: ACRIN 6671 – Core lab

Each site will be required to be qualified by ACRIN prior to participant accrual. For detailed information regarding site PET qualification and PET/CT requirements, visit the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

To better ensure image quality, the technical parameter charts should be distributed to the individual modalities to guarantee protocol compliance. These charts are available at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>.

12.2.6 Image Quality Review

A review of all imaging procedures will be performed to ascertain the quality of image processing at the contributing institutions for adequate quality. The first three (3) cases from each institution along with a continual random sampling of cases will be examined. The first three (3) MRI ferumoxtran-10 cases will be examined by Dr Mukesh Harisinghani from Massachusetts General Hospital to assure optimal quality. Continual random sample of remaining ferumoxtran-10 cases will be monitored by Drs. Mostafa Atri and Jelle Barentsz. The MRI images will be monitored for the compliance with the protocol parameters and interpretability of sequences especially T2* sequence with respect to the presence of artifacts, motion, and resolution. All sequences including repeat sequences will be included for the review both at the institution and for central reader study. In order to assure PET/CT image quality, the instructions for **PET/CT IMAGING QUALITY CONTROL STANDARDS** (Appendix X) must be followed for the duration of the study. The Quality Control Review of the PET/CT images for the initial three (3) cases, along with the continual random sampling, will be performed at ACRIN Headquarters. ACRIN will be monitoring all images that come in for the duration of the study.

12.2.7 PET/CT Review at Imaging Institutions

PET/CT images will be assessed by trained PET/CT readers blinded to the results of other imaging examinations and clinical data. Images will be evaluated

qualitatively for focal areas of abnormally increased FDG uptake in the nodal region and other organs, and data forms will be completed.

12.3 Central Reader Study

The primary analyses for evaluation of study objectives 3.1.1, 3.1.2, 3.2.1, 3.2.2 will be based on data obtained from two central reader studies.

In one reader study, seven (7) readers will all interpret PET scans alone and then fused PET/CT scans obtained on each of 120 women, 60 with pathology-proven metastases to abdominal lymph nodes and 60 without abdominal lymph node involvement. Scans will be presented to the participating readers in a randomized order. Readers will be aware of the inclusion criteria for participants in the protocol but will be blinded to all other clinical information about each case, any results of other tests and to information about the reference standard. Interpretation data for PET alone and PET/CT images will be recorded on separate data forms. In addition to addressing the primary question of presence of abdominal node metastasis, readers will use the CT images to assess the presence and size of primary cervical cancer, nodal, and extra-nodal metastases, and will record on a separate data form.

In the other reader study, seven (7) readers will all interpret ferumoxtran-10 MRI scans for each of the same 120 women. The procedures for scan presentation and the available information to the readers will be as described in the previous paragraph. The entire scan including suboptimal and repeat sequences will be included in the review session. All data, even data from original scans that are repeated, will be kept and evaluated by the on-site and central readers. The PET/CT and ferumoxtran-10 MRI will be read by different readers.

The central reader review could be conducted at the ACRIN HQ or the expert reviewer's institution. The central readers will be provided the training as electronic training aids.

12.4 PET/CT Review at Imaging Institutions

PET/CT images will be assessed by trained PET/CT readers blinded to the results of other imaging examinations and clinical data. Images will be evaluated qualitatively for focal areas of abnormally increased FDG uptake in the nodal region and other organs, and data forms will be completed.

13.0 DRUG INFORMATION

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14.0 CLINICAL STAGING AND LYMPHATIC EVALUATION

Participants will undergo clinical staging as permitted by FIGO rules, including examination under anesthesia, cystoscopy, and proctoscopy.

Participants will then undergo pelvic and abdominal lymph node sampling by either an extra-peritoneal or laparoscopic approach. Eight lymph node “regions” will be sampled independent of one another: left obturator, right obturator, left external iliac, right external iliac, left common iliac, right common iliac, right para-caval, and left para-aortic. The degree of sampling will be dictated by a combination of both the amount of lymphadenopathy and the investigator’s discretion. Non-suspicious lymph node regions must be removed completely in order to document them as negative. Overtly positive lymph node regions must be biopsy proven with intra-operative frozen section confirming metastatic disease unless a complete lymphadenectomy is to be performed. Each lymph node “region” is to be considered independently of one another. Therefore, even if a biopsy is positive in another region, a complete lymph node dissection is required in all other regions unless intra-operative confirmation of metastatic disease outside lymph nodes obviates the need for any other given region.

14.1 Lymph Node Sampling

14.1.1 Extra-peritoneal Pelvic and Abdominal Lymph Node Sampling: Pelvic and abdominal lymph node sampling must be completed through an adequate incision as outlined in Appendix V and the GOG Surgical Manual. Choice of incision

may include, but is not limited to, midline, para-median, double-“J” incision, and Pfannensteihl.

14.1.2 *Laparoscopic Pelvic and Abdominal Lymph Node Sampling (Appendix V)*: Pelvic and abdominal lymph node sampling may also be performed through a laparoscopic approach as outlined in Appendix V.

If the lymph node sampling cannot be completed successfully via a laparoscopic approach due to technical difficulties (i.e., inadequate exposure), an extra-peritoneal lymph node sampling must be attempted. If unresectable lymph nodes are encountered during the laparoscopic lymph node sampling, extra-peritoneal lymph node dissection is not required as long as tissue confirmation of each region has been obtained.

If the lymph node sampling cannot be accomplished due to retroperitoneal fibrosis/adhesions, which in the investigator’s opinion would alter an extra-peritoneal lymph node dissection, every reasonable attempt should be made to perform a biopsy of any available lymph nodes. An extra-peritoneal attempt at lymph node sampling is unnecessary and trans-peritoneal lymph node sampling will not be performed.

15.0 PATHOLOGY INFORMATION

15.1 Lymph node dissection will be performed in accordance with strict anatomic boundaries. Note that this differs from the standard GOG definitions. For details of the specific boundaries of dissection, see Section 8.2

15.2 Pathologic Evaluation of Lymph Nodes

15.2.1 Most lymph nodes are small enough (1.0 cm maximum long axis dimension) to permit bisection into two halves approximately 5 mm thick. The node should be cut from hilum to periphery if possible. A slide should be made from each section. If the lymph node is divided into smaller sections, one slide from each should be evaluated.

15.2.2 If a lymph node is larger than 1.0 cm in long axis, then the node should be sectioned in at least 5-mm intervals in a “bread loaf” fashion parallel to the short axis. Again, if more sections are made, then one slide from each should be evaluated.

15.2.3 Size of positive submitted lymph nodes and size of metastatic focus will be recorded by the local institutional pathologist.

15.2.4 Slides (or recuts) of all lymph node specimens and copies of all surgical pathology reports will be submitted to GOG for review at semi-annual meetings by the pathology committee. The review will consist of two pathologists who will confirm size of the largest positive submitted lymph nodes and size of largest metastatic focus.

16.0 ADVERSE EVENTS REPORTING

16.1 Definition of Adverse Event (NCI CTCAE v3.0) (06/09/08)

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory or physiological finding), symptom, or disease temporally associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Abnormal results of diagnostic procedures are considered to be adverse events (AEs) if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

16.2 Definition of Serious Adverse Event

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that:

- results in death, or
- is life-threatening (at the time of the event), or
- requires inpatient hospitalization or prolongation of an existing hospitalization, or
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect.

16.3 Adverse Event Grading

Grade denotes the severity of the adverse event. An AE is graded using the following categories:

- 1 – Mild
- 2 – Moderate
- 3 – Severe
- 4 – Life-threatening or disabling
- 5 – Fatal

16.4 Adverse Event Attribution

Attribution determines whether an adverse event is related to a study treatment or procedure. Attribution categories are:

- Definite – AE *is clearly related* to the study treatment or procedure.
- Probable – AE *is likely related* to the study treatment or procedure.
- Possible – AE *may be related* to the study treatment or procedure.
- Unlikely – AE *is doubtfully related* to the study treatment or procedure.
- Unrelated – AE *is clearly NOT related* to the study treatment or procedure.

16.5 Potential Expected and Unexpected Adverse Events

Adverse events may be **expected** or **unexpected**:

- An **expected AE** is one that is described in the protocol, the consent form, or the investigator’s clinical brochure.
- An **unexpected AE** is one that has not been described in the protocol, the consent form, or the investigator’s clinical brochure.

16.6 Expected Adverse Events

16.6.1 Adverse Events Associated with Lymph Node Sampling and Lymphadectomy:

Multiple series of patients undergoing pretreatment surgical staging for cervical cancer have been reported. Adverse events may be due to surgery alone or due to the combination of surgery followed by radiation or chemoradiation (13, 17, 23, 69).

Vascular Injury	2.3-3.5%
Wound Infection	2.3-10.1%
Lymphocyst	3.5-19.9%
Lymphocyst requiring intervention (drainage of laparotomy)	6.7%
Lymphedema	18.4%
Treatment Related Death (PE or post radiation bowel perforation)	1.1%

16.6.2 Adverse Events Associated with the Injection of Fluorodeoxyglucose (FDG):

FDG can cause allergic reactions when injected, such as mild itching or hives (small bumps on the skin). The injection can also cause bruising and infection at the site of the injection. Symptoms of a more serious allergic reaction include shortness of breath and swelling of the throat or other parts of the body.

16.6.3 Adverse Events Associated to the Oral and Intravenous Iodine Contrast

A history of contrast allergy or asthma excludes potential participants from this study. The injection may cause discomfort and irritation. The iodine-containing contrast used for PET/CT scanning may cause significant contrast reactions in about one in a thousand participants. Severe reaction is seen in as low as 4/10000

to as high as 2/1000 depending on the type of contrast used. Fatal reactions are exceedingly rare and have been reported in 1:170,000 irrespective of the type of contrast used. The most common reactions are nausea, vomiting, hives, or rash. The risk of death is less than 1 in 10,000.

16.6.4 Adverse Events Associated with Radiation Risks:

While the radiation dosage for PET/CT scanning varies with the part of the body being scanned, the exposure for this examination is approximately 2000-2800 millirems (*about 40-50% of recommended annual maximum exposure*). The radiation dose from the PET/CT has not been shown to have any adverse effects.

16.6.5 Reported Adverse Events and Potential Risks Associated with Ferumoxtran-10 (NSC #BLANK; IND #BLANK)

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16.6.6 Adverse Events Associated with MRI

While there are no significant risks from MRI, the participant may be uncomfortable due to the loud noise and/or feelings of claustrophobia during the MRI. If the participant experiences a sensation of claustrophobia while in the magnet, the MRI will be immediately stopped. Having a pacemaker or other electromagnetic device or vascular clip in the head excludes potential participants from this study. No serious biological effects have been reported from the magnetic fields used in clinical MRI. The FDA approved substance gadolinium is sometimes used for contrast in MRI. Although approximately two percent of participants experience some side effects, these are mostly mild (*nausea, headache, hives, temporary low blood pressure*). Serious side effects are almost unheard of.

16.6.7 Adverse Events Associated with PET/CT

Participants may experience discomfort or claustrophobia during the PET scan. CT requires the injection of contrast material, which may cause an allergic reaction (See section 16.6.3).

16.7 Reporting of Adverse Events

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. Anyone uncertain about whether a particular adverse event should be reported should contact GOG headquarters

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at 215-854-0770 or ACRIN headquarters at 215-574-3150 for assistance. Please refer to Appendix XIV for detailed reporting instructions. (06/09/08)

An adverse event should be reported if there is a reasonable suspicion that the AE is reasonably related to the protocol-specific medical treatment, investigational imaging contrast agent, and/or imaging procedures.

GOG will report all serious adverse events to NCI via electronic AdEERS. The ACRIN research associate will provide very detailed information on any imaging adverse event(s) and/or the investigative contrast agent AE(s) on the paper AdEERS to the GOG Data Manager (DM) for electronic AdEERS reporting.

All unresolved adverse events should be followed by the investigator or investigator-designee until the events are resolved, the participant is lost to follow-up, or the adverse events are otherwise explained. Any death or adverse event (e.g. development of cancer, congenital anomaly in conceived offspring) occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the protocol-specific medical treatment, investigational imaging contrast agent, and/or imaging procedures should be reported by the GOG Data Manager.

Assignment of grades and attribution for each AE/SAE must be completed by the site principal investigator or investigator-designee. All AEs/SAEs should be documented in the study participant's chart, AE form, and/or AdEERS expedited report. The ACRIN research associate (RA) will capture all imaging AEs and/or the investigative contrast agent AEs on the AE form and paper AdEERS expedited report and provide them to the GOG Data Manager. The expedited AdEERS reports must be submitted by the GOG Data Manager to NCI and GOG must keep a copy of the report on file at the site. Significant new info on the on-going SAE should be promptly reported to NCI/CIP and ACRIN by GOG.

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on adverse events through discussion and, as appropriate, by examination. Information on all serious and non-serious, expected and unexpected adverse events considered unrelated, unlikely, possibly, probably, or definitely related to the GOG-0233/ACRIN 6671 trial with the severity level of grades 1, 2, 3, 4, and 5 should be recorded immediately into the source document, e.g. adverse event log and/or progress notes of the study participant's chart, and retained at the site. These adverse events will also be recorded in the AE form and reviewed by the principal site investigator in real time to determine grade and attribution of the event and submitted to ACRIN/GOG.

All adverse events occurring during the study period must be recorded on the AE form. Each adverse event should be followed until resolution, stabilization, or until it has been determined that the study procedures or study participation is not the cause. All serious adverse events that are still ongoing at the end of the study must be followed up to determine the final outcome. Any serious adverse event that occurs after the study

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period and is considered to be **possibly related** to the study procedures or study participation should be recorded and reported immediately.

16.8 AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent: Ferumoxtran-10

Table D1: Reporting Requirements for Adverse Events that occur within 30 Days¹ of the Last Dose of the Investigational Agent (Ferumoxtran-10) on the Phase 2 and 3 Trials

<i>Attribution</i>	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days	7 Calendar Days	Not Required	24-Hour; 3 Calendar Days	7 Calendar Days
¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CIP IND require reporting as follows: AdEERS 24-hour notification followed by complete report within 3 calendar days for: <ul style="list-style-type: none"> Grade 4 and Grade 5 unexpected events with attribution of possible, probable, and definite AdEERS 7 calendar day report: <ul style="list-style-type: none"> Grade 2 unexpected events with attribution of possible, probable, and definite Grade 3 unexpected events with hospitalization or prolongation of hospitalization with attribution of unrelated and unlikely and possible, probable, and definite Grade 3 unexpected events without hospitalization or prolongation of hospitalization with attribution of possible, probable, and definite Grade 3 expected events with hospitalization or prolongation of hospitalization with attribution of unrelated and unlikely and possible, probable, and definite Grade 4 and 5 unexpected events with attribution of unrelated and unlikely Grade 4 and 5 expected events with attribution of unrelated and unlikely and possible, probable, and definite ² Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.									

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NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines:**
 - 24 Hours; 3 calendar days** – The GOG investigator or investigator-designee must initially report the AE via AdEERS within 24 hours of first knowledge of the event followed by a complete AdEERS report within 3 calendar days of the initial 24-hour report.
 - 7 calendar days** – A complete AdEERS report on the AE must be submitted within 7 calendar days of the GOG investigator or investigator-designee first knowledge of the event.
 - Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates **hospitalization* (or prolongation of existing hospitalization)** must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in **persistent or significant disability/incapacity, congenital anomaly, or birth defect** must be reported via AdEERS by GOG if the event occurs following treatment with an agent under a CIP IND.
- Expedited reporting is defined as immediate notification of NCI/CTEP by the GOG Data Manager within the specified timeframe outlined in the protocol. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting. Routine reporting requirements also apply.
- Use the NCI protocol number and the protocol-specific participant ID provided during trial registration on all reports.

* Hospitalizations are defined as lasting 24 hours or longer and these events must be reported via AdEERS.

16.9 When to Report for Ferumoxtran-10 Related Adverse Events

It is the responsibility of the GOG and ACRIN investigators or investigator-designees to document all Adverse Events (AEs), which occur during the course of the study. For each adverse event, the GOG and ACRIN investigator will evaluate and assign attribution and grade (see section 16.1 for definition). AEs not previously documented in the study will be recorded on the Adverse Event Log within the study participant's chart to identify any potentially related to any study procedures. The nature of each event, date, and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution will be recorded.

AEs already documented in the CRF (i.e., at a previous assessment) and designated as 'ongoing' should be reviewed at subsequent visits as necessary. If these have been resolved, the documentation in the CRF should be completed including an end date for the event and not the date of the visit. If an adverse experience increases in frequency or severity during a study period, an up to date record of the experience will be documented. The ACRIN RA will complete the AE form for any ferumoxtran-10 and/or imaging adverse events for both serious and non-serious and forward it to the GOG Data Manager for submission to the data center. The GOG Data Manager is responsible for reporting all adverse events that occur at the site level.

Routine reporting is defined as documentation of adverse events on source documents and AE CRF, and submission to GOG for preparation of a report for Data and Safety Monitoring Committee (DMC) review, quarterly reports to CDUS, FDA annual reports, and the final study report.

Expedited reporting is defined as immediate notification of NCI/CTEP by the GOG Data Manager within the specified timeframe outlined in the protocol. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting. Routine reporting requirements also apply.

16.9.1 Any adverse events associated with any primary study procedures in this protocol are ferumoxtran-10 administration, study-related imaging procedures, and surgical procedures. For this protocol, **all adverse events associated with**

the primary study procedures will be reported as adverse events to the data center and/or NCI, when appropriate, by the GOG Data Manager.

16.9.2 The reporting of AEs for the investigational contrast agent, ferumoxtran-10, in this protocol will conform to the following:

1. Grade 1 unexpected and expected adverse events that are unrelated, unlikely, possible, probable, or definite will be reported by **routine reporting procedures only**.
2. Grade 2 unexpected adverse events that are unrelated or unlikely will be reported by **routine reporting procedures only**.
3. Grade 2 unexpected adverse events that are possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
4. Grade 2 expected adverse events that are unrelated, unlikely, possible, probable, or definite will be reported by **routine reporting procedures only**.
5. Grade 3 unexpected adverse events with hospitalization that are unrelated, unlikely, possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
6. Grade 3 unexpected adverse events without hospitalization that are unrelated or unlikely will be reported by **routine reporting procedures only**.
7. Grade 3 unexpected adverse events without hospitalization that are possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
8. Grade 3 expected adverse events with hospitalization that are unrelated, unlikely, possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
9. Grade 3 expected adverse events without hospitalization that are unrelated, unlikely, possible, probable, or definite will be reported by **routine reporting procedures only**.

10. Grade 4 and 5 unexpected adverse events that are unrelated or unlikely require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply.**
11. Grade 4 and 5 unexpected adverse events that are possible, probable, and definite will be reported within a 24-hour time period via AdEERS by the investigator or investigator-designee. In addition, a complete AdEERS report is due within **3 calendar days** of the initial 24-hour report. **Routine reporting procedures also apply.**
12. Grade 4 and 5 expected adverse events that are unrelated, unlikely, possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply.**
13. Expedited adverse event reporting must be completed within **7 calendar days** of first knowledge of the event for all unexpected and expected Grade 4 and Grade 5 events, regardless of attribution. **Routine reporting procedures also apply.**
14. All fatal (Grade 5) adverse events should also be reported by telephone to NCI by the GOG Data Manager within 24 hours of first knowledge of the event. **Routine reporting procedures also apply.**

16.10 Adverse Event Reporting for Any Surgical and Imaging Procedures

Table D2: Expedited Reporting of Adverse Events occurring 30 Days of the Surgical Procedure: The following table summarizes the regulatory requirements for expedited reporting of AEs that occur within 30 days of the surgical procedure.

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected With Hospitalization	Without Hospitalization	Expected With Hospitalization	Without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	7 Calendar Days	Not Required	7 Calendar Days	Not Required	7 Calendar Days	7 Calendar Days

¹ Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after surgery require reporting as follows:
 AdEERS 7 calendar day report:
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization with attribution of unrelated/unlikely and possible, probable, and definite
 • Grade 3 expected events with hospitalization or prolongation of hospitalization with attribution of unrelated/unlikely and possible, probable, and definite
 • Grade 4 and 5 unexpected and expected events with attribution of unrelated/unlikely and possible, probable, and definite
 • **Grade 5:** All deaths within 30 days of the surgical procedure must be reported within 7 calendar days using expedited reporting regardless of causality

“See exceptions below under the section entitled, “Additional Instructions or Exceptions to Expedited Reporting Requirements for Surgical Trials.”

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All CTCAE v 3.0 expedited AEs must be reported by the GOG Data Manager. All expedited AE reports must be submitted by using the CTEP automated system for expedited reporting (AdEERS). Submitting a report through AdEERS serves as a notification to GOG, and satisfies the GOG requirements for expedited AE reporting. GOG may contact site PI for imaging or surgery depending on the nature of SAE.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to the surgical treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
 “7 calendar days”- A complete AdEERS report on the AE must be submitted within 7 calendar days of the investigator or investigator-designee first knowledge of the event.
- Any medical event equivalent to CTCAE grades 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities and/or incapacities must be reported via AdEERS by the GOG Data Manager if the event occurs following a protocol procedure.
- Use the NCI protocol number and the protocol-specific participant ID provided during trial registration on all reports.
- CTEP and GOG will then notify CIP and ACRIN of the expedited reporting.

16.10.1 Additional instructions or exceptions to AdEERS expedited reporting requirements for this protocol:

16.10.1.1 Adverse events associated with any primary study procedures: Lymph Node Sampling, any protocol-specific surgical procedures, PET/CT, and MRI procedures will be reported.

16.10.2 AdEERS reporting of all relevant SAEs will be entered into the electronic AdEERS by the GOG Data Manager. The reporting of surgical, commercial contrast agent, and imaging AEs for this protocol will conform to the following:

1. Grades 1 and 2 unexpected and expected adverse events that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite will be reported by **routine reporting procedures only**.
2. Grade 3 unexpected and expected adverse events with hospitalization that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.
3. Grade 3 unexpected and expected adverse events without hospitalization that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, or definite will be reported by **routine reporting procedures only**.
4. Grades 4 and 5 unexpected and expected adverse events that are unrelated (surgical **only**, not necessary for imaging), unlikely (surgical **only**, not necessary for imaging), possible, probable, and definite require a complete AdEERS report on the AE to be submitted within **7 calendar days** of the investigator or investigator-designee first knowledge of the event. **Routine reporting procedures also apply**.

5. Expedited adverse event reporting must be completed within 7 calendar days of first knowledge of all unexpected and expected Grade 5 events, regardless of attribution. Routine reporting procedures also apply.
6. All fatal/Grade 5 adverse events (Imaging procedures: only deaths with attributions of possible, probable, or definite) should also be reported by telephone to NCI by the GOG Data Manager within 24 hours of first knowledge of the event. Routine reporting procedures also apply.

The ACRIN research associate (RA) will complete an AE form and paper AdEERS expedited report, if appropriate, for ferumoxtran-10 and imaging adverse events and forward it to the GOG Data Manager for submission to NCI and GOG. The GOG Data Manager will be responsible for reporting all adverse events that occur at the site level.

16.10.3 Procedures for Expedited Adverse Event Reporting

Expedited reports are to be submitted using AdEERS, available at <http://ctep.cancer.gov>. The NCI guidelines for expedited event reporting requirements are also available at this site.

16.11 How to Report

- 16.11.1** Some adverse events require 24-hour notification (refer to Tables D1 and D2 in sections 16.8 and 16.10) via AdEERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to CIP by telephone at 301-496-0737 and CTEP by telephone at 301-897-1704. Once Internet connectivity is restored, a 24-hour notification that was phoned in must be entered electronically into AdEERS by the original GOG submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of first knowledge of the event specified in Tables D1 and D2 in sections 16.8 and 16.10. An expedited adverse event report requires submission to NCI/CTEP by the GOG Data Manager via the AdEERS system. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting.

16.11.2 AdEERS Reports Recipients: AdEERS Reports to the following:

To GOG:

Attention: Manager of Regulatory Affairs

Shawn Griffin: sgriffin@gog.org

RE: Adverse Event Report

GOG-0233/ACRIN 6671

4 Penn Center, 1600 JFK Blvd.

Suite 1020

Philadelphia, PA 19103

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To NCI/CIP:

Lalitha Shankar: shankarl@mail.nih.gov
Barbara Galen: bgalen@mail.nih.gov
Carl Jaffe: jaffec1@mail.nih.gov
Paula Jacobs: jacobsp@mail.nih.gov
James L. Tatum: tatumj@mail.nih.gov
RE: Adverse Event Report
Cancer Imaging Program
6130 Executive Blvd., MSC 7412
Room 6050
Bethesda, MD 20892-741

To AMAG Pharmaceuticals:

Gerard Wolf: gwolf@amagpharma.com
Jana Subramaniam: jsubramaniam@amagpharma.com
RE: Adverse Event Report
AMAG Pharmaceuticals, Inc.
125 Cambridge Park Drive
6th Floor
Cambridge, MA 02140

To ACRIN: (06/09/08)

Maria Oh: moh@phila.acr.org
Pamela Harvey: pharvey@phila.acr.org
Attention: ACRIN SAE Coordinator
Cornelia Tsikos: ctsikos@phila.acr.org
RE: Adverse Event Report
ACRIN Protocol 6671
1818 Market Street
Suite 1600
Philadelphia, PA 19103

To make a telephone report, contact NCI at (301) 496-0737, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time).

- 16.11.3** A copy of all expedited adverse event reports will be forwarded by GOG to NCI/CTEP. CTEP and GOG will then notify CIP and ACRIN of the expedited reporting at the email addresses provided above.
- 16.11.4** All fatal adverse events identified in the imaging and ferumoxtran-10 component of the study must be reported by telephone within 24-hours of the event. To make a telephone report call GOG at (215) 854-0770, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time). All fatal adverse events must also be reported to CIP by telephone at (301) 496-0737 and to GOG within 24-hours of the event and via AdeERS. All fatal

adverse events identified to the surgical component of the study must be reported to GOG through AdEERS, per GOG AE/SAE reporting policies.

16.11.5 All expedited adverse event reports should be sent to the local Institutional Review Board (IRB). Refer to the IRB policies and procedures for adverse event reporting.

16.11.6 For automated CDUS reporting for studies using investigational agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through AdEERS will also be included with the quarterly CDUS data submissions.

17.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice [International conference of Harmonization (ICH) guidelines], applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB) for a formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to ACRIN before implementation of the study. The investigator will provide ACRIN with the institution's assurance number, along with the IRB approval letter.

All study participants in this study will be provided a consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix II for a copy of the sample informed consent form). This consent form will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB approved consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

18.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN policies and applicable federal, state, and local laws and regulations.

19.0 PUBLICATION POLICY

Neither complete nor partial study results will be published or passed on to any third party without the formal consent of the ACRIN Publication Committee and GOG Publication

Committee. Investigators will follow both the ACRIN Publication Policy (ACRIN website at <http://www.acrin.org/ADMINISTRATION/ADMINISTRATIVEPOLICIES/tabid/292/Default.aspx>) and GOG Publication Policy (<http://gogmember.gog.org/>). (06/09/08)

20.0 INSTITUTIONAL AUDITS

The investigator will permit study-related auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, AMAG Pharmaceuticals, and ACRIN/GOG. The investigator will ensure the capability for inspection of all participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct these visits. ACRIN will conduct audits for the imaging component of the trial per standard regulatory guidelines indicated in the ACRIN Audit Manual. This manual is available online at www.acrin.org. GOG will conduct audits for the surgical component of the trial. The guidelines can be found in the GOG Data Management Manual.

Institutional on-site audits will be completed within 18-36 months after first participant enrollment of each site's enrollment. Subsequent audits will be scheduled per the outcome of the initial audit. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI or CTEP. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN/GOG. IRB procedures, approvals, and consent forms will also be reviewed at the time of the audit visit.

To help sites prepare for audits and assure that the investigator and the research staff maintain records appropriately, the ACRIN data management and auditing departments will offer training to sites. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

20.1 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents must verify the eligibility criteria and data submitted on all case report forms (CRFs).

Research records for each case should contain source documents for the data reported to ACRIN/GOG. If data are abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. However, every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol at the time of the audit visit. This

will prevent any discrepancies and the inability to verify the document and the data reported.(11/25/08)

20.2 Case Report Forms

Case report forms (CRFs) are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank because the procedure was not done or the question was not asked, “N/D” must be noted. If the item is not applicable to the individual case “N/A” must be noted. All entries must be printed legibly in black ink on the paper case report forms. In the event of any entry errors, corrections must be made by drawing a single straight line through the incorrect entry, writing the initials of the person making the correction, recording the date when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the case report forms (CRFs) will be audited against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires may be documented on the CRF. The image interpretation data required by the study that is a more detailed extraction of information from the image and is not typically documented in the standard radiology report may be recorded on the CRF and is accepted as source documentation if signed by the Investigator. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date on which the exam took place from the medical record. Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, MR, etc.).

Any use of CRFs as source documentation when the protocol has designated the source data will be medical record documentation will be considered a deficiency.

20.3 Institutional Review Board

Sites must obtain local IRB initial approval. Prior to participant registration, a copy of the IRB approval letter for the protocol and the informed consent form must be sent to ACRIN (see section 6.2), along with a copy of the IRB approved informed consent form. ACRIN/GOG investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s). Copies of IRB documentation will also be forwarded to the GOG Regulatory Affairs department for their files.

21.0 STATISTICAL CONSIDERATIONS

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REFERENCES

1. CA: A Cancer Journal for the Clinician 1996; 46(1).
2. American Cancer Society, *Cancer Facts and Figures 2007*. Atlanta: American Cancer Society; 2007
3. Trends in Cancer Incidence and Mortality, WHO International, IARC Scientific Publication, Lyon 1993, pp. 433.
4. Adams S, Baum RP, Stuckensen T, Bitter K, Hor G. Prospective comparison of 18F-FDG PET with conventional imaging modalities (CT< MRI< US) in lymph node staging of head and neck cancer. Euro J Nucl Med 1998; 25:1255-60.
5. Amendola MA, Hricak H, Mitchell DG et al, Utilization of diagnostic studies in the pretreatment evaluation of invasive cervical cancer in the United States: results of intergroup protocol ACRIN 6651/GOG 183. JCO 2005;23:7454-59.
6. Antoch G, Saoudi N, Kuehl H, Dahmen G, Mueller SP, Beyer T, Bockisch A, DebatinJF, Freudenberg LS. Accuracy of whole body dual modality fluorine-18-2-fluoro-2-deoxy D-glucose positron emission tomography and computed tomography (FDG-PET/CT) for tumor staging in solid tumors: comparison with CT and PET. J Clin Oncol 2004; 22:4357-4368.
7. Antoch G, Vogt FM, Freudenberg LS, Nazaradeh F, Goehde SC, Barkhausen J, Dahmen G, Bockisch A, Debatin JF, Ruehm SG. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. JAMA 2003; 290:3199-206
8. Anzai Y, Piccoli CW, Outwater EK, et al. Evaluation of neck and body metastases to nodes with ferumoxtran 10-enhanced MR imaging: phase III safety and efficacy study. Radiology 2003; 228:777-788.
9. Averette HE, Dudan RC, Ford JH. Exploratory celiotomy for surgical staging of cervical cancer. Am J Obstet Gynecol 1972; 11:1090
10. Ballon SC, Berman ML, Lagasse LD, Petrilli ES, Castaldo TW. Survival after extraperitoneal pelvic and paraaortic lymphadenectomy and radiation therapy in cervical carcinoma. Obstet Gynecol 1981; 57:90-5.
11. Bellin MF, Roy C, Kinkel K, et al. Lymph node metastases: safety and effectiveness of MR imaging with ultrasmall superparamagnetic iron oxide particles--initial clinical experience. Radiology 1998; 207:799-808
12. Benedet JL, Bender H, Jones H 3rd, Ngan HY, Pecorelli S. FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers. FIGO Committee on Gynecologic Oncology. Int J Gynaecol Obstet. 2000;70:209-62.

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13. Berman ML, Lagasse LD, Ballon SC, Watring WG, Tesler A. Modification of Radiation therapy following operative evaluation of patients with cervical carcinoma. *Gynecologic Oncology*, 1978; 6: 328-332.
14. Carl UM, Bahnsen J, Wiegel T. Radiation therapy of paraaortic lymph nodes in cancer of the uterine cervix. *Acta Oncol* 1993; 32:63-7.
15. Choi JY, Lee KH, Shim YM, Lee KS, Kim JJ, Kim SE, Kim BT. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. *J Nucl Med* 2000; 41:808-15.
16. Chung CK, Nahhas WA, Stryker JA, Curry SL, Abt AB, Mortel R. Analysis of factors contributing to treatment failures in stages IB and IIA carcinoma of the cervix. *Am J Obstet Gynecol* 1980; 138:550-6.
17. Cosin JA, Fowler JM, Chen MD, Paley PJ, Carson LF, Twiggs LB. Pretreatment surgical staging of patients with cervical carcinoma: the case for lymph node debulking. *Cancer* 1998; 82:2241-8.
18. Deserno WM, Harisinghani MG, Taupitz M, et al. Urinary bladder cancer: preoperative nodal staging with ferumoxtran-10-enhanced MR imaging. *Radiology*. 2004;233:449-56.
19. Downey GO, Potish RA, Adcock LL, Prem KA, Twiggs LB. Pretreatment surgical staging in cervical carcinoma: therapeutic efficacy of pelvic lymph node resection. *Am J Obstet Gynecol* 1989; 160:1055-61.
20. Fine BA, Hempling RE, Piver MS, Baker TR, McAuley M, Driscoll D. Severe radiation morbidity in carcinoma of the cervix: impact of pretherapy surgical staging and previous surgery. *Int J Radiat Oncol Biol Phys* 1995; 31:717-23.
21. Fletcher GH. Lucy Wortham James Lecture: subclinical disease. *Cancer* 1984; 53:1274-84.
22. Gallup DG, King LA, Messing MJ, Talledo OE. Paraaortic lymph nodes sampling by means of an extraperitoneal approach with a supraumbilical transverse "sunrise" incision. *Am J Obstet Gynecol* 1993; 169:307-11.
23. Goff BA, Muntz HG, Paley PJ, et al. Impact of surgical staging in locally advanced cervical cancer. *SGO* 1999 Abstract #4.
24. Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm). *Chest* 2000; 117:773-8.
25. Harisinghani MG, Barentsz J, Hahn PF, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. *N Engl J Med* 2003; 348:2491-2499.

CONFIDENTIAL

26. Harisinghani MG, Saini S, Weissleder R, et al. MR lymphangiography using ultrasmall superparamagnetic iron oxide in patients with primary abdominal and pelvic malignancies: radiographic-pathologic correlation. *AJR Am J Roentgenol* 1999; 172:1347-1351.
27. Harisinghani MG, Saksena MA, Hahn PF et al. Ferumoxtran-10-enhanced MR lymphangiography: does contrast-enhanced imaging alone suffice for accurate lymph node characterization? *AJR Am J Roentgenol*. 2006;18:144-148.
28. Havrilesky LJ, Kulasingam SL, Matchar DB, Myers ER. FDG-PET for management of cervical and ovarian cancer. *Gynecol Oncol* 2005; 97:183-91.
29. Heller PB, Malfetano JH, Bundy BN, Barnhill DR, Okagaki T. Clinical-pathologic study of stage IIB, III, and IVA carcinoma of the cervix: extended diagnostic evaluation for paraortic node metastasis – a Gynecologic Oncology Group study. *Gynecol Oncol* 1990; 38:425-30.
30. Horiot JC, Pigneaux J, Pourquier H, et al. Radiotherapy alone in carcinoma of the intact uterine cervix according to G. H. Fletcher guidelines: a French cooperative study of 1383 cases. *Int J Radiat Oncol Biol Phys* 1988; 14:605-11.
31. Hricak H, Gatsonis C, Chi DS et al, Role of imaging in pretreatment evaluation of early invasive cervical cancer: results of the intergroup study American College of Radiology Imaging Network 6651-Gynecologic Oncology Group 183. *JCO* 23:9329-39, 2005.
32. A. Hudgins PA, Anzai Y, Morris MR, Lucas MA. Ferumoxtran-10, A Superparamagnetic Iron Oxide as a Magnetic Resonance Enhancement Agent for Imaging Lymph Nodes: A Phase 2 Dose Study. *AJNR Am J Neuroradiol* 2002;23(4):649-56.
33. Ishwaran H and Gatsonis C. A general class of hierarchical ordinal regression models with applications to correlated ROC analysis. *Canadian Journal of Statistics*, 2000; 28, 731-750.
34. Jolles CJ, Freedman RS, Hamberger AD, Horbelt DV. Complications of extended-field therapy for cervical carcinoma without prior surgery. *Int J Radiat Oncol Biol Phys* 1986; 12:179-83.
35. Kademian MT, Bosch A. Is staging laparotomy in cervical cancer justifiable? *Int J Radiat Oncol Biol Phys* 1972; 2:1235.
36. Kataoka M, Kawamura M, Yasuyuki N, Hamamoto K, Hamada KI, Iketani H, et al. Patterns of failure and survival in locally advanced carcinoma of the uterine cervix treated with high dose-rate intracavitary irradiation system. *Int J Radiat Oncol Biol Phys* 1991; 22:31-5.
37. Kinney WK Hodge DO, Egorshin EV, Ballard DJ, Podratz KC. Surgical treatment of patients with stages IB and IIA carcinoma of the cervix and palpably positive pelvic lymph nodes. *Gynecol Oncol* 1995; 57:145-9
38. Kosary CL. FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecologic system: an analysis of 1973-87 SEER

CONFIDENTIAL

- cases of cancer of the endometrium, cervix, ovary, vulva, and vagina. *Semin Surg Oncol* 1994; 10:31-46.
39. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 Pattern of Care studies. *Int J Radiat Oncol Biol Phys* 1991; 20:667-76.
 40. Larsson EM, Sunden P, Olsson CG, et al. MR venography using an intravascular contrast agent: results from a multicenter phase 2 study of dosage. *AJR Am J Roentgenol* 2003; 180:227-232.
 41. Leiner T, Ho KY, Ho VB, et al. Multicenter phase-II trial of safety and efficacy of NC100150 for steady-state contrast-enhanced peripheral magnetic resonance angiography. *Eur Radiol* 2003; 13:1620-1627.
 42. Mack MG, Balzer JO, Straub R, Eichler K, Vogl TJ. Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. *Radiology* 2002; 222:239-244.
 43. Michel SC, Keller TM, Frohlich JM, et al. Preoperative breast cancer staging: MR imaging of the axilla with ultrasmall superparamagnetic iron oxide enhancement. *Radiology* 2002; 225:527-536.
 44. Morrow CP, Curtain JP, Townsend DE. *Synopsis of gynecologic oncology*. 4th edition. New York: Churchill Livingstone, 1993.
 45. NF, Wain GV, Nicklin JL. Resection of bulky positive lymph nodes in patients with cervical carcinoma. *Int J Gynecol Cancer* 1995; 5:250-6.
 46. Obuchowski N. Multi-Reader multi-modality ROC studies: Hypothesis testing and sample size estimation using an ANOVA approach with dependent observations. *Academic Radiology*, 1995; 2:S22-S29.
 47. Pannu HK, Wang KP, Borman TL, Bluemke DA. MR imaging of mediastinal lymph nodes: evaluation using a superparamagnetic contrast agent. *J Magn Reson Imaging* 2000; 12:899-904.
 48. Perez CA, Fox S, Lockett MA, et al. Impact of dose on outcome of irradiation alone in carcinoma of the uterine cervix: analysis of two different methods. *Int J Radiat Oncol Biol Phys* 1991; 21:885-98.
 49. Podczaski E, Stryker JA, Kaminski P, Ndubisi B, Larson J, DeGeest K, et al. Extended-field radiation therapy for carcinoma of the cervix. *Cancer* 1990; 66:251-8.
 50. Reinhardt M, Ehrhrit-Braun D, Vogelgesang D, et al. Metastatic lymph nodes in patients with cervical cancer: detection with MR imaging and FDG PET. *Radiology*. 2001;218: 776-782.
 51. Rockall AG, Sohaib SA, Harisinghani MG, Babar SA, Naveena S, Jeyarajah AR, Oram DH, Jacobs IJ, Shepherd JH, and Reznick RH. Diagnostic Performance of Nanoparticle-Enhanced Magnetic Resonance Imaging in the Diagnosis of Lymph Node Metastases in Patients with Endometrial and Cervical Cancer. *Journal of Clinical Oncology*, 2005; 23, 2813-2821.

CONFIDENTIAL

52. Rose PG, Adler LP, Rodriguez M, et al. Positron emission tomography for evaluating para-aortic nodal metastasis in locally advanced cervical cancer before surgical staging: a surgicopathologic study. *J Clin Oncol*. 1999; 171:41-5
53. Rotman M, Pajak TF, Choi K, Clery M, Marcial V, Grigsby PW, et al. Prophylactic extended-field irradiation of paraaortic lymph nodes in stages IIB and bulky IB and IIA cervical carcinomas: ten-year treatment results of RTOG 79-20. *JAMA* 1995; 274:387-93.
54. Rutter C. and Gatsonis C. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Statistics in Medicine*, 2001; 20: 2865-2884
55. Scheidler J, Hricak H, Yu KK, Subak L, Segal MR. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. *JAMA* 1997; 278:1096-1101.
56. Sharma R, Saini S, Ros PR, et al. Safety profile of ultrasmall superparamagnetic iron oxide ferumoxtran-10: phase II clinical trial data. *J Magn Reson Imaging* 1999; 9:291-294.
57. Sigal R, Vogl T, Casselman J, et al. Lymph node metastases from head and neck squamous cell carcinoma: MR imaging with ultrasmall superparamagnetic iron oxide particles (Sinerem MR) -- results of a phase-III multicenter clinical trial. *Eur Radiol* 2002; 12:1104-1113.
58. Sironi S, Buda A, Picchio M, Perego P, Moreni R, Pellegrino A, Colombo M, Mangioni C, Messa C, Fazio F. *Lymph node metastasis in patients with clinical early-stage cervical cancer: detection with integrated FDG PET/CT*. *Radiology* 2006; 238:272-9
59. Stehman FB, Bundy BN, DiSaia PJ, et al. Carcinoma of the cervix treated with radiation therapy: a multivariate analysis of prognostic variables in the Gynecologic Oncology Group. *Cancer* 1991; 67:2776-85.
60. Stehman FB, Perez CA, Kurman RJ, Thigpen TJ. Uterine Cervix. In Hoskins WJ, Perez CA and Young RC (eds): *Principles and Practice of Gynecologic Oncology*, 2nd ed., Philadelphia, Lippincott 1996, pp. 785-860.
61. Stets C, Brandt S, Wallis F, Buchmann J, Gilbert FJ, Heywang-Kobrunner SH. Axillary lymph node metastases: a statistical analysis of various parameters in MRI with ferumoxtran-10. *J Magn Reson Imaging* 2002; 16:60-68.
62. Sugawara Y, Eisbruch A, Kosuda S, et al. Evaluation of FDG PET in patients with cervical cancer. *J Nucl Med* 1999; 40:1125-31.
63. Taupitz M, Hamm BK, Barentsz JO, et al. Enhanced MR imaging compared to plain MR imaging in evaluating lymph-node metastasis from urologic and gynecologic cancers [abstract] *RSNA* 1999:387

CONFIDENTIAL

64. Taylor AM, Panting JR, Keegan J, et al. Safety and preliminary findings with the intravascular contrast agent NC100150 injection for MR coronary angiography. *J Magn Reson Imaging* 1999; 9:220-227.
65. Thomas G, Dembo AJ. Carcinoma of the cervix. In London HA and Arnold E (eds) *Combined Radiotherapy and Chemotherapy in Clinical Oncology* 1993, pp. 150-61.
66. Vasilev SA. A modified incision and technique for total retroperitoneal access and lymph node dissection. *Gynecol Oncol* 1995; 56:226-30.
67. Vigliotti AP, Wen BC, Hussey DH, Doornbos JF, Staples JJ, Jani SK, et al. Extended field irradiation for carcinoma of the uterine cervix with positive periaortic nodes. *Int J Radiat Oncol Biol Phys* 1992; 23:501-9.
68. Von Schulthess, GK. Integrated modality imaging with PET-CT and SPECT-CT: CT issues. *Eur Radiol* 2005; 15 Suppl 4:D121-6
69. Weiser EB, Bundy BN, Hoskins WJ, Heller PB, Whittington RR, DiSaia PJ, et al. Extraperitoneal versus transperitoneal selective paraaortic lymphadenectomy in the pretreatment surgical staging of advanced cervical carcinoma (a Gynecologic Oncology Group study). *Gynecol Oncol* 1989; 33:283-9.
70. Weissleder R, Elizondo G, Wittenberg J, Lee AS, Josephson L, Brady TJ. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymph nodes with MR imaging. *Radiology* 1990; 175:494-498.
71. Wharton JT, Jones HW III, Day TG Jr., Rutledge FN, Fletcher GH. Preirradiation celiotomy and extended field irradiation for invasive carcinoma of the cervix. *Obstet Gynecol* 1977; 49:333-8.
72. Zhou X-H, Obuchowski N, and McClish D. (2002) Statistical methods in diagnostic medicine. Chapter 9.2.. Wiley , New York.

APPENDIX I
CLINICAL STAGING - CARCINOMA OF THE CERVIX UTERI
FIGO CLASSIFICATION

PRE-INVASIVE CARCINOMA

STAGE 0: Carcinoma in situ, intraepithelial carcinoma.

(Cases of Stage 0 should not be included in any therapeutic statistics)

INVASIVE CARCINOMA

STAGE I: Carcinoma strictly confined to the cervix.

STAGE IA: Invasive cancer identified only microscopically. (All gross lesions, even with superficial staging, are stage IB cancers)

Invasion is limited to measured stromal invasion with maximum depth of 5.0 mm and no wider than 7.0 mm.¹

STAGE IA1: Measured invasion of stroma no greater than 3.0 mm in depth and no wider than 7.0 mm.

STAGE IA2: Measured invasion of stroma greater than 3 mm and no greater than 5 mm and no wider than 7 mm.

STAGE IB: Clinical lesions confined to the cervix or pre-clinical lesions greater than stage IA.

STAGE IB1: Clinical lesions no greater than 4.0 cm in size.

STAGE IB2: Clinical lesions greater than 4 cm in size.

STAGE II: The carcinoma extends beyond the cervix but has not extended on to the pelvic wall. The carcinoma involves the vagina, but not the lower third.

STAGE IIA: No obvious parametrial involvement.

STAGE IIB: Obvious parametrial involvement.

STAGE III: The carcinoma has extended on to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydro-nephrosis or non-functioning kidney.

STAGE IIIA: No extension on to the pelvic wall.

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STAGE IIIB: Extension on to the pelvic wall and/or hydro-nephrosis or non-functioning kidney.

STAGE IV: The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allotted to Stage IV.

STAGE IVA: Spread of the growth to adjacent organs.

STAGE IVB: Spread to distant organs.

Notes on Staging

Stage IA carcinoma should include minimal microscopically evident stromal invasion as well as small cancerous tumors of measurable size. Stage IA should be subdivided into those lesions with minute foci or invasion visible only microscopically as Stage IA1 and the macroscopically measurable microcarcinomas as Stage IA2 in order to gain further knowledge of the clinical behavior of these lesions. The term IB occult should be omitted.

The diagnosis of both Stage IA1 and IA2 should be based on microscopic examination of removed tissue, preferably a cone, which must include the entire lesion. As noted above, the lower limit of Stage IA2 should be that it can be measured macroscopically (even if dots need to be placed on the slide before measurement) and the upper limit of IA2 is given by measurement of the two largest dimensions in any given section. The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The second dimension, the horizontal spread, must not exceed 7 mm. Vascular space involvement, either venous or lymphatic, should not alter the staging but should be specifically recorded as it may affect treatment decisions in the future.

Lesions of greater size should be staged as IB.

As a rule, it is impossible to estimate clinically whether a cancer of the cervix has extended to the corpus. Extension to the corpus should therefore be disregarded.

A patient with a growth fixed to the pelvic wall by a short and indurated, but not nodular, parametrium should be allotted to Stage IIB. It is impossible at clinical examination to decide whether a smooth and indurated parametrium is truly cancerous or only inflammatory. Therefore, the case should be placed in Stage III even if according to the other findings the case should be allotted to Stage I or Stage II.

The presence of the bullous edema as such should not permit a case to be allotted to Stage IV. Ridges and furrows into the bladder wall should be interpreted as signs of submucous involvement of the bladder if they remain fixed to the growth at palpation (i.e., examination from the vagina or the rectum during cystoscopy). A cytological finding of malignant cells in washings from the urinary bladder requires further examination and a biopsy from the wall of the bladder.

1 The depth of invasion should be no more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.

APPENDIX II

GOG-0233/ACRIN 6671

SAMPLE CONSENT FOR RESEARCH STUDY

Protocol Title:

UTILITY OF PREOPERATIVE FDG-PET/CT AND FERUMOXTRAN-10 MRI SCANNING PRIOR TO PRIMARY CHEMORADIATION THERAPY TO DETECT RETROPERITONEAL LYMPH NODE METASTASIS IN PATIENTS WITH LOCOREGIONALLY ADVANCED (IB2, IIA \geq 4 CM, IIB-IVA) CARCINOMA OF THE CERVIX

[Note: ACRIN does not monitor compliance with the Health Insurance Portability and Accountability Act (HIPAA); that is the responsibility of local IRBs].

You are being asked to be in this trial because you have cervical cancer. This is a clinical trial (a type of research study) run by the American College of Radiology Imaging Network (ACRIN), the Gynecologic Oncology Group (GOG), and funded by the National Cancer Institute (NCI). Clinical trials include only participants who choose to take part. Please take your time to make your decision.

You may discuss this research study with your family and friends. You are being asked to volunteer because you meet the study requirements. Your participation is voluntary, which means you can choose whether or not you want to be in this study.

This study will evaluate two types of tests, often called “scans.” The scans are a PET/CT scan and an MRI scan using an investigative contrast drug. Both scans are described in detail below. Researchers hope to learn the following:

- if the scans can find cancer that may have spread to your lymph nodes and,
- if the investigative contrast drug, ferumoxtran-10, helps MRI scans locate cancer in lymph nodes.

These questions are important to answer for treatment of patients with cervical cancer. Cancer that has spread to lymph nodes is treated differently than cancer that has not spread. This study may help determine if these scans along with the investigative contrast drug can locate cancer that has spread, so that patients can receive appropriate treatment.

Before you make a decision you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will be asked to do in this study. The research team is going to talk to you about the study and you will be given this consent form to read. You can discuss it with your family, friends, or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or research staff about this form or if you have any questions. If you decide to do this study, you will be asked to sign and date this form.

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WHY IS THIS STUDY BEING DONE?

The purpose of this study is to learn if one or both of these two scans, PET/CT and MRI using an investigative contrast agent , can find cancer that may have spread to your lymph nodes.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

About 325 people will take part in this study at a number of cancer centers in the United States and Canada. Forty of these 325 participants will consent to participate in the optional arm of the study.

WHAT AM I BEING ASKED TO DO IN THE STUDY?

Before you begin the study...

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests, or procedures may be 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.

- Physical examination
- Medical history, including pregnancy test,
- Tumor measurement (part of qualifying for trial),
- Blood tests,
- Chest X-Ray,
- ECG,
- Obtain signed consent,
- Gather Fast Fact Sheet.

During the study...

If the exams, tests, and procedures show that you can be in the study, and you choose to take part, then you will have the following as part of the research study:

- PET/CT,
- MRI with a special contrast drug,
- Surgery.

DESCRIPTION OF THE PET/CT SCAN

Positron emission tomography scan (PET) is a diagnostic procedure in which a small amount of radioactive glucose (sugar) called FDG (Fluorodeoxyglucose) is injected into a vein. You will have the injection 50 minutes before the scan. Then a scanner is used to make detailed, computerized pictures of areas inside the body where the glucose is used. Because cancer cells often use more glucose than normal cells, the pictures can be used to find cancer cells in the body. Computed tomography (CT) is a diagnostic procedure that uses special x-ray equipment to obtain cross-sectional pictures of the body. Combined PET/CT scanning joins these tests into one procedure.

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DESCRIPTION OF THE MRI SCAN

Magnetic resonance imaging (MRI) uses a powerful magnet to create radio frequency signals that a computer uses to make detailed pictures of areas inside the body without the use of radiation.

For the MRI scan you will receive an injection of an MRI contrast drug. Some participants (40 total) will have the choice to receive an MRI before receiving the special contrast drug. The contrast drug helps to make any abnormal lymph nodes easier to see on the MRI scan. You will have the injection between 24 and 36 hours before the MRI scan. In rare cases, this may be done up to 48 hours. The investigational agent that is being studied is called ferumoxtran-10.

AFTER YOU HAVE THE SCANS THAT ARE PART OF THE RESEARCH STUDY

Results of the scan will be explained to you prior to surgery/biopsies since the results determine the procedure. After reviewing the scan results and the results of other tests, certain lymph nodes will be removed and biopsied. Biopsies are the removal of a sample of tissue for examination. Other biopsies may be necessary if your scan shows that cancer may have spread to areas other than your abdominal and pelvic lymph nodes. Once your nodes have been checked for cancer cells, you will receive appropriate treatment with chemotherapy and radiation therapy (chemoradiation) for your cancer. Your treatment will be determined by the results of the biopsy. Your treatment will not be determined by the MRI scans, which are part of the study.

OVERVIEW OF TIMELINE AND PROCEDURES ASSOCIATED WITH STUDY:

Day	Exams, tests, procedures and scans	What happens in standard care
You are diagnosed with cervical cancer, stages IB2, IIA \geq4cm, IIB-IVA		
Prior to starting study	<ul style="list-style-type: none">• Tumor measurement (part of qualifying for trial),• Medical history including pregnancy test,• Blood tests,• Chest X-Ray,• ECG.	<ul style="list-style-type: none">• Medical history,• Blood tests,• Chest X-Ray,• ECG.
Day 1	<ul style="list-style-type: none">• Fast (no food or drink) for 4 hours prior to the FDG-PET/CT imaging,• Injection of FDG 50 minutes prior to scan,• Drink oral contrast drug prior to CT,• Urine pregnancy test• PET/CT scan of abdomen, pelvis and chest,• Inject contrast drug ferumoxtran-10 for the MRI scan.	The CT and combined PET/CT scans are part of standard of care.
Day 2	<ul style="list-style-type: none">• MRI scan 24-36 hours after injection of MRI drug (This may be done up to 48 hours in rare cases).	MRI scan in some centers is standard, but not with the contrast drug ferumoxtran-10
Prior to surgery	<ul style="list-style-type: none">• Biopsy of any disease identified by the PET scan outside the abdomen, if feasible	This procedure is standard of care

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Day 3-15	<ul style="list-style-type: none">● Lymph node examination, by surgery, laparoscopy or appropriate biopsy of lesions outside lymph glands.	The procedure is part of standard care at some centers
Within 28 days	<ul style="list-style-type: none">● Begin appropriate treatment with chemoradiation, as defined by standard treatment guidelines for your diagnosis, your physician and you'	This is standard care
Within 6 weeks post-op	<ul style="list-style-type: none">● Physical examination,	This is standard care
6 months after enrolling	<ul style="list-style-type: none">● Medical history,● CT scan or PET/CT if a finding is visible on PET/CT and was not able to be biopsied,	Medical history is standard care. The CT or PET/CT scan is part of the standard of care at some centers.
Every 3 months for 2 years	<ul style="list-style-type: none">● Routine blood tests and medical exams and x-rays at doctor's discretion,	These procedures are standard care
Every 6 months for 3 additional years	<ul style="list-style-type: none">● Routine blood tests and medical exams and x-rays at doctor's discretion,	These procedures are standard care

WHAT HAPPENS WHEN I HAVE A PET/CT SCAN?

You will have the CT scan first, and then a PET scan, in the same room and on the same table. You will be told not to eat or drink for 4 hours before the PET/CT scan. When you arrive to have the PET/CT scan, you will have an intravenous (IV) line inserted into a vein and a blood sample taken. Then, a small amount of radioactive glucose (sugar) called FDG (Fluorodeoxyglucose) will be injected into the IV line. The chemical is a “radioactive tracer” and is called FDG. Approximately 50 minutes after the injection of FDG, you will be asked to drink about 2 cups of an oral contrast drug.

You will then be asked to change into a hospital gown and will have a chance to go to the bathroom (urinate). You will be brought to the scanning room, and you will lie on your back on a scanning table. Your arms will be placed above your head, and pillows may be placed under your knees and back to make you more comfortable. The scans will take approximately 45-60 minutes. A second contrast drug will be injected into your IV line. The injection does not hurt. The contrast drug may cause you to feel warm, and may create a pressure in your pelvic area. This will go away.

During the CT scan you lie very still. The table slowly passes through the center of a large x-ray machine. You might hear whirring sounds during the procedure, and you may be asked to hold your breath. After the CT scan is complete, the table will automatically pass into the PET scan system. You will continue to lie still and you may be asked to hold your breath again.

PET/CT scans do not cause any pain. However, lying in one position during the procedure may be slightly uncomfortable.

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ARE THERE RISKS ASSOCIATED WITH A PET/CT SCAN?

The radiation exposure from a PET/CT scan is no higher than what you would experience with a normal CT scan. This can be higher than the radiation exposure from a regular x-ray. Approximately 1 person in 1000 may have an allergic reaction from the contrast drugs. These reactions are temporary and treatable. Allergic reactions may include:

- mild itching or hives (small bumps on the skin) and,
- shortness of breath and swelling of the throat or other parts of the body.

People should tell the technologist immediately if they experience any of these symptoms so they can be treated promptly.

WHAT HAPPENS WHEN I HAVE A MRI SCAN?

The day before you arrive for the MRI scan you will be injected with an experimental contrast drug called ferumoxtran-10. (See next question for details regarding this drug.) When you arrive to have the MRI, you will change into a hospital gown and an MRI technologist will help you lie on your back on the scanning table. The technologist will insert an IV line into your vein so that a drug to help relax your bowel can be injected into the line. The drug will help obtain a better image.

The technologist will place a piece of equipment called a “coil” that is made of curved hard plastic bands over your pelvic area. The coil helps to increase the radio frequency signals sent to the computer to produce good MRI images.

The table will slide into a tube-like machine that contains the MRI magnet. The technologist will talk with you through a special sound system to make sure you are comfortable. You will hear loud “knocking” noises during the scan. These noises are normal. The entire MRI scan will take about 30-40 minutes.

You will have to lie very still during this time. MRI scans do not cause any pain. However, lying in one position during the procedure may be slightly uncomfortable. A padded table will be used to keep you from becoming too uncomfortable.

WHAT IS FERUMOXTRAN-10?

Ferumoxtran-10 is an experimental MRI contrast drug. It was developed so that lymph nodes with cancer could be more clearly seen on MRI scans. Other studies have shown that it may help to find cancer in lymph nodes, which helps determine the best treatment for patients. In a recent study, Rockall et al. (51) evaluated 44 women with cervical cancer with ferumoxtran-10 prior to removal of the lymph nodes.

ARE THERE RISKS ASSOCIATED WITH FERUMOXTRAN-10?

Ferumoxtran-10 has been used in approximately 2000 people in the United States and Europe. It is not approved for general use. Most participants who receive ferumoxtran-10 do not have side effects.

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The side effects reported are usually mild and temporary. That means the side effects will stop once the drug is discontinued. Side effects in this category include:

Likely:

- flushing (3.3%),
- rash (3.0%)
- back pain (2.4%),

Less Likely:

- itching (2.2%),
- hives (1.7%),
- shortness of breath (1.3%).

Rare:

- nausea (1.2%)
- chest pain (1.1%),
- pain (0.8%),
- sweating (0.7%),
- headache (0.6%),

Ferumoxtran-10 has caused a rare, but serious allergic reaction. Your chance of having this type of reaction is less than 2 in 1000. 1 of the 2000 participants who have received ferumoxtran-10 worldwide had an allergic reaction that resulted in death. This death was due to a severe allergic reaction to the administrative method of the drug. This method of administration is no longer used. Participants with other known allergies and liver disease may be more likely to react to ferumoxtran-10.

You should tell the study doctor and/or technologist immediately if you experience any of these symptoms so they can be treated promptly.

WHAT IS THE PROCEDURE FOR INJECTING FERUMOXTRAN-10?

Ferumoxtran-10 will be injected slowly through an intravenous (IV) line (a small plastic tube) placed in a hand or arm vein over 30-45 minutes. You will be observed at the hospital for 2 to 3 hours after the ferumoxtran-10 is injected to see if you experience any side effects. If you do, you will be treated immediately. The next day (after 24 hours) you will return for a MRI scan. The time between injection and the MRI scan allows the ferumoxtran-10 to reach your lymph nodes. **(11/25/08)**

ARE THERE RISKS ASSOCIATED WITH THIS KIND OF MRI?

MRI scans have been used worldwide for many years, and have no known harmful effects in participants without metal in their body. The MRI uses radio waves and strong magnets to make images of the body. Anything that can be affected by a magnet should not be taken into the MRI scanning area. This includes credit cards with magnetic strips. In addition, if you have any metal implants in your body

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(e.g. aneurysm clips, metal plates) you should not be in this study. If you have any questions please notify your doctor.

During the MRI you will hear loud noises. The procedure may lead to some anxiety because of the noise of the MRI scanner and its enclosed space. Earplugs or headphones may help decrease the sound. These will be supplied to you.

Finally, you must lie still in a confined area, which may make you feel claustrophobic. If you find the procedure for the MRI intolerable the study will be stopped or you may be sedated. Being immobilized for 45 minutes for the scan may lead to mild stiffness and discomfort.

You may develop a bruise or have bleeding at the needle site where the IV is placed. Occasionally, an infection may develop which can be treated with antibiotics. In rare instances, a person feels faint when a needle is inserted into a vein.

WHAT IS A LYMPH NODE DISSECTION? WHAT IS THE PROCEDURE?

Lymph nodes are areas in the body that help to fight the spread of infection and cancer. If your cancer has spread to your lymph nodes, the treatment for your cancer may be modified. In this study, certain lymph nodes will be removed and examined to see if cancer has spread. Lymph node dissection is part of standard treatment at some but not all medical centers, so you may have lymph nodes dissected whether or not you participate in this study.

Lymph nodes lie along the blood vessels deep in your abdomen or pelvis. They can be removed surgically, (using either one large incision) or laparoscopically (using multiple small incisions).

Once the incision (or incisions) reach the lymph nodes, a portion of the group of the nodes will be cut away and sent to a pathologist who will help to determine whether or not your cancer may have spread to them.

For this study, the lymph nodes to be removed and checked are the left and right pelvic lymph nodes (called external iliac, obturator, and common iliac lymph nodes) and the lower abdominal lymph nodes (called para-aortic and para-caval lymph nodes).

Following surgery, you will remain in the hospital until you have recovered from your surgery, usually about 1 to 3 days. Although it is not anticipated that you will have any long term complications, the following is a list of the possible side effects.

WHAT ARE THE RISKS ASSOCIATED WITH THIS TYPE OF SURGERY?

As with all operations, the lymph node sampling has risks and discomforts that include the following:

Hematologic: injury to arteries and veins with potentially heavy bleeding could occur. Blood transfusions may be necessary. Shock with damage to other organs may develop. Death is possible.

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Urinary: injury to the urinary bladder or ureter (the tube carrying urine from the kidney to the bladder) may occur and require surgical repair.

Gastrointestinal: injury to the intestines may occur and require surgical repair.

Neurological: injuries to nerves in the operative areas may occur resulting in loss of sensation or function. Usually these are temporary but could be permanent.

Skin: a hernia (protrusion of an organ or body part) can form in the areas of incision and may need further surgery to repair them. Cancer cells may be deposited in the incision and begin to grow there.

Pulmonary: blood clots can form in large veins and pass into the lungs, causing breathing failure and possibly death.

Infection: infection may occur and will require further treatment.

Lymphedema: swelling in the leg(s) because fluid in your lymph nodes is not draining properly and builds up. This can lead to trouble moving your limb(s), infection, and/or hardening of the skin around the limb(s). Lymphedema cannot be cured, but it can be treated. **(11/25/08)**

Other unknown side effects can occur but are rare and will be monitored.

You will sign a separate consent form for your surgery. Your doctor has discussed with you possible risks of the surgery you will be undergoing, and will be able to answer questions you may have.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS OF THE STUDY?

Risks and discomforts that may occur during the scans or surgery have been discussed above. You may have side effects while on the study and receiving treatment for your cancer. There are risks associated with surgery, lymph node sampling and chemoradiation used to diagnose and treat cervical cancer.

Everyone taking part in the study will be watched carefully for any side effects. However, doctors do not 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 taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

ARE THERE REPRODUCTIVE RISKS?

If you are pregnant or nursing you cannot take part in this research study. The effects on the fetus are unknown; breast-feeding baby, or mother-to-be, and this study may cause harm. Because the MRI contrast drug and FDG chemical used for the PET/CT scan in this study can affect a baby. Also, you should not nurse your baby while on this study.

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Ask about counseling and more information about preventing pregnancy. For more information about risks and side effects, ask your study doctor. During the study, you need to take safety measures to avoid pregnancy.

HOW LONG WILL I BE IN THE STUDY?

After you are finished with the scans and treatment for your cancer, the study doctor will ask you to visit the office for follow-up exams for 5 years. This is the same follow-up that you would receive if you were not in the trial.

This study is expected to end after all study participants have completed the visits and all the information has been collected. This study may be stopped at any time by your study doctor, GOG, ACRIN, Food and Drug Administration (FDA), or National Cancer Institute (NCI) without your consent in the following situations:

- For your health or safety
- For not following study instructions
- For study administrative decision by ACRIN, GOG, the study doctor, FDA or NCI

These actions do not require your consent, but you will be informed of any of these decisions if such a decision is made.

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 to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART IN THIS STUDY?

Taking part in this study may or may not make your health better. The information from this study will help study doctors learn whether PET/CT and MRI scans using ferumoxtran-10 will help identify cancer that has spread to lymph nodes. This knowledge will help doctors decide on the best treatment for patients with cervical cancer, which will benefit women with cervical cancer in the future. In some participants, a change in treatment that will better treat their cancer is predicted.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

You may choose not to participate in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. Your doctor can tell you the different available treatments for your cervical cancer.

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WHAT ABOUT CONFIDENTIALITY?

You understand that every attempt will be made by the investigators to keep all the information collected in this study strictly confidential, including your personal information. Absolute confidentiality can not be guaranteed. Records of your progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) and Gynecologic Oncology Group (GOG). All data sent to ACRIN/GOG over the Internet will be coded so that other people cannot read it. Your personal information may be disclosed if required by law.

You further understand that authorized representatives of ACRIN/GOG, the Food and Drug Administration (FDA), AMAG Pharmaceuticals (manufacturer of ferumoxtran-10), the National Cancer Institute (NCI), the Institutional Review Board (IRB) of <<*Institution*>> and other groups or organizations that have a role in this study will have access to and may copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner in which you cannot be identified.

Your images will be kept permanently on file at ACRIN/GOG and may be used for future research. All personal identifiers are removed and replaced with a unique identifying number.

WILL I HAVE TO PAY FOR ANYTHING?

During the study, you will undergo imaging examinations as well as ferumoxtran-10 administration. You will not be responsible for the costs of any study-related examinations and treatments. ACRIN and the individual insurance carriers will assume responsibility for the financial burden of the study. In regards to co-pays, you and/or your health plan/insurance company may need to pay for some or all of the costs of treating your cancer in this study. The Division of Cancer Treatment and Diagnosis, NCI, will provide you with the ferumoxtran-10 free of charge for this study.

Every effort to prevent injury as a result of your participation will be taken. It is possible, however, that you could develop complications or injuries as a result of participating in this research study. In the event of injury resulting from this research, emergency medical treatment is available but will be provided at the usual charge. You and/or your insurance will be responsible for the cost of the medical care of that illness or injury. There is no financial compensation that has been set aside to compensate you in the event of injury.

WILL I BE PAID FOR BEING IN THIS STUDY?

You will receive no payment for taking part in this study.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

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Taking part in this study is voluntary. You may choose not to take part in the study. If you decided to participate, you are free to leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled. Your decision to participate in this study will not interfere with your future care.

During the study, more information that could be important to you may be discovered. A Data Safety and Monitoring Board, an independent group of experts, will review the data from this research throughout the study. This includes information that might cause you to change your mind about being in the study. If information becomes available from this or other studies that may affect your health, welfare, or willingness to stay in this study, you will be contacted about it as soon as possible.

At any time, the study doctor may discontinue your participation in this study. The study doctor may decide to take you off this study if it is determined that the treatment is further intensifying the disease and endangers the participant.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

This document explains your rights as a study participant. If you have any questions regarding your participation in this research study or you have any questions regarding your rights as a research participant, do not hesitate to speak with your study doctor or anyone listed below.

For additional information about your health or medical emergency, you may contact: *Usually the name of the local hospital information is provided with instructions to study participants to inform the ER doctor of their participation in a clinical trial.*

Name

Telephone Number

For information about this study, you may contact:

Name

Telephone Number

For information about your rights as a research subject, you may contact <<*Institution Name*>> Institutional Review Board (a group of people who review the research to protect your rights): *(Provide the name of local IRB contact person)*

Name

Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at:
1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

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APPENDIX III
PARTICIPATING INSTITUTIONS

A minimum of ten (10) participating institutions, Site Principal Investigators will be identified upon review and approval of completed ACRIN Protocol Specific Application (PSA).

APPENDIX IV
EXTRAPERITONEAL LYMPHADENECTOMY

PURPOSE

- 1) Histologic evaluation of pelvic and periaortic nodes.

INDICATION

- 1) Surgical staging of gynecologic malignancy.

CONTRAINDICATION

- 1) Evidence of extra-abdominal and extra-nodal METASTASES by cytology, radiographic, or histologic parameters.
- 2) Poor surgical risk.

CONTENT OF PROCEDURE

- 1) The skin incision may be of the surgeon's choosing including midline vertical, transverse, and lateral vertical.
- 2) The peritoneum is exposed and may be opened before or after retroperitoneal exploration if biopsies and cytologic washings are indicated.
- 3) The retroperitoneum is exposed by rolling the peritoneum medially until psoas muscle and iliac vessels are visualized.
- 4) The aorta, vena cava and iliac vessels on the side of entry are exposed.

NOTE: The ureter should be left attached to the peritoneum on the side of entry.

- 5) Proceed with abdominal lymphadenectomy:
 - a) The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery, the ureters and duodenum should be identified.
 - b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
 - c) The nodal tissue around the distal vena cava from the level of the inferior mesenteric artery to the mid right common iliac artery is removed.
 - d) The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
 - e) Ligation of the proximal and distal nodal tissue is recommended. It is also recommended that bilateral retroperitoneal drains should be placed in each of the lymph node beds upon completion of the lymphadenectomy.

- f) Dissection cephalad to the inferior mesenteric artery is restricted to those cases with palpably suspicious nodes above that level.

6. Proceed with pelvic lymphadenectomy.

- a) Identify the bifurcation of the common iliac, external iliac, hypogastric arteries and veins and the ureters, bilaterally.
- b) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- c) The nodal tissue from the distal one-half of each common iliac artery should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas to the ureter medially.
- d) The nodal tissue along the external iliac vessels should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas medially to the ureter including the hypogastric artery and vein, distally to the circumflex iliac vein. This will be sent as External Iliac Lymph Nodes.
- e) The nodal tissue anterior to the obturator nerve and deep to the external iliac vessels should be removed from the obturator fossa and sent as Obturator Lymph Nodes.
- f) Ligation of the proximal and distal attachments of the nodal tissue is recommended. Unresectable nodes should be outlined with clips.

APPENDIX V
LAPAROSCOPIC PELVIC AND ABDOMINAL LYMPHADENECTOMY

PURPOSE

- 1) Histologic evaluation of pelvic and periaortic nodes.
- 2) Reduction of nodal tumor bulk.
- 3) Surgical-pathologic staging of gynecologic malignancy.
- 4) Provide guidelines for subsequent therapy.

INDICATION

- 1) Surgical staging of gynecologic malignancy.

CONTRAINDICATION

- 1) Evidence of extra-abdominal and extra-nodal METASTASES by cytology, radiographic, or histologic parameters.
- 2) Medical inoperability.

CONTENT OF PROCEDURE

A) Pelvic Lymphadenectomy

- 1) Identify the bifurcation of the common iliac, external iliac, hypogastric arteries and veins and the ureters, bilaterally.
- 2) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- 3) The nodal tissue from the distal one-half of each common iliac artery should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas to the ureter medially.
- 4) The nodal tissue along the external iliac vessels should be removed and the iliac vessels skeletonized; laterally from the mid portion of the psoas medially to the ureter including the hypogastric artery and vein, distally to the circumflex iliac vein. This should be sent as External Iliac Lymph Nodes.
- 5) The nodal tissue anterior to the obturator nerve and deep to the external iliac vessels should be removed from the obturator fossa and sent as Obturator Lymph Nodes.
- 6) Ligation of the proximal and distal attachments of the nodal tissue is recommended.

B) Abdominal

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- 1) The bifurcation of the aorta, the inferior vena cava, the ovarian vessels, the inferior mesenteric artery, the ureters and duodenum should be identified.
- 2) Any enlarged or suspicious nodes will be excised or biopsied if unresectable.
- 3) The nodal tissue around the distal vena cava from the level of the inferior mesenteric artery to the mid right common iliac artery is removed.
- 4) The nodal tissue between the aorta and the left ureter from the inferior mesenteric artery to the left mid common iliac artery is removed.
- 5) Ligation of the proximal and distal nodal tissue is recommended.
- 6) Dissection cephalad to the inferior mesenteric artery is restricted to those cases with palpably suspicious nodes above that level.

APPENDIX VI
GUIDELINES FOR LAPAROSCOPIC SURGERY

Preparation of the Patient

1. Liquid diet for 48 hours prior to the procedure.
2. Magnesium Citrate 8 oz, 36 hours and 12 hours prior to procedure.
3. Fleet enemas in the a.m. of the procedure.
4. General anesthesia.
5. Nasogastric tube.
6. Pulse oximeter.
7. Arms tucked to the side.
8. Low dorsal lithotomy position.
9. Vaginal prep and placement of a sponge stick in the vagina if appropriate.

Instrumentation

1. High flow electronic insufflator, high intensity light source, high resolution camera, 2 monitors, coagulation source, 4 forceps and dissecting scissors.
2. 10-11 mm operating laparoscope inserted at the umbilicus.
3. 10-11 mm trocar in the midline above the pubic symphysis.
4. 5 mm trocars in the right and left mid-abdomen.

Aortic Lymphadenectomy

1. Steep Trendelenburg's position.
2. Posterior peritoneum incised medial to the right ureter from the common iliac artery to the level of the inferior mesenteric artery.
3. Retract the ureter laterally.

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4. Retract the inferior mesenteric artery and its branches superiolaterally.
5. Remove the para-caval and para-aortic lymph nodes. Nodes judged to be unresectable by laparoscopy should be biopsied.

Pelvic Lymphadenectomy

1. The peritoneum between the round ligament and the ovarian pedicle is incised over the psoas muscle.
2. The ureter and ovarian vessels retracted medially.
3. The umbilical artery is identified and retracted medially.
4. Remove the pelvic lymph nodes.
5. Nodes judged to be unresectable by laparoscopy should be biopsied.

APPENDIX VII
CREDENTIALING PROCEDURES FOR PET/CT IMAGING FOR THIS STUDY

ACRIN's standard operating procedure (SOP) for credentialing PET/CT imaging can be found on the ACRIN web site at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>. (06/09/08)

Credentialing Procedures for MRI Images: It is a requirement for this study to submit one (1) test MRI case. Information on the technical parameters that should be utilized and how to submit these images can be found at: <http://www.acrin.org/PROTOCOLSUMMARYTABLE/PROTOCOL6671/6671ImagingMaterials/tabid/417/Default.aspx>. Data from this case will be reviewed centrally and each site will receive feedback regarding the test case before finalizing the first study participant. (06/09/08)

APPENDIX VIII
FERUMOXTRAN-10 DOSING CHART (09/09/08)
(Dose 2.6 mg Fe/kg)

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APPENDIX IX
SAMPLE DATA COLLECTION SHEETS

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APPENDIX X
PET/CT IMAGING QUALITY CONTROL STANDARDS

Detailed criteria/specifications for performance of PET and CT imaging are described in **Appendix VII**.

1. FDG-PET/CT imaging will be performed using “state-of-the-art” equipment. The PET/CT unit should have a multislice CT (> 1-slice) and BGO (Bismuth Germinate Oxide), LSO (Lutetium Oxyorthosilicate) and GSO, which will have the following:
 - A field of view appropriate for body imaging (> 10 cm)
 - High intrinsic spatial resolution at transaxial plane ($FWHM \leq 6.5$ mm at the center) and high sensitivity
 - Post-injection transmission capability using CT. (Please note that intrinsic resolution is usually better than the reconstructed resolution which is heavily dependent on the type of filter used. The intrinsic resolution at transverse plane typically is in the range of 4.2-6.3 mm at the center).
(09/09/08)

2. **PET Scanner Quality Assurance:** Daily and monthly steps will be taken to assure quantitative accuracy of PET/CT imaging studies and reliable imaging results at all performance sites. Daily quality assurance includes a simplified chi-square test to assure consistent sensitivity and uniformity of the PET component of the camera. The calculation provides a quantitative means of monitoring drift of the scanner electronics with time. A liquid-filled or standardized sealed-source cylinder phantom is used monthly to validate the quantitative accuracy of the images against a dose calibrator. The dose calibrator is itself calibrated daily against standards for constancy and annually for accuracy using NIST-traceable standards. Each month, fine gain calibration of all detectors in the PET system will be performed, followed by recalculation of the sensitivity normalization factors for the scanner. Quality assurance tests should also be performed on the CT component of the PET/CT camera. Such test may include daily scanning of a standardized phantom to validate the CT number calibration and the slice thickness.

CT scan will be used for attenuation correction of PET data with CT data from a combined PET/CT scanner, in accordance with manufacturer’s recommendations). An algorithm to correct for activity in the field of view should be used for processing of the post-injection transmission images, if provided by the vendor. Then the corresponding emission images, each at least 5 minutes per bed position for BGO, LSO and GSO systems operated in the 2-D mode; at least 3 minutes per bed position for BGO, LSO, and GSO systems operated in the 3-D mode; and at least 6 minutes per bed position for NaI systems. The PET images will be reconstructed by standard vendor-provided reconstruction algorithms. We recommend an iterative reconstruction using OSEM algorithm in a 128 x 128 matrix with a Zoom of 1 and with a 5 mm Gaussian filter. Scatter, decay and deadtime correction, as provided by the manufacturer. The emission images will be reconstructed both with and without attenuation correction.

3. SUV Calculation: To enable accurate and meaningful SUVs to be calculated, the following information must be recorded for each scan:

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- Injection time
- Tracer dosage
- Tracer dosage assay time
- Start-of-scan time
- Scan duration
- Patient height (to be measured on the day of scan)
- Patient weight (to be measured on the day of scan)
- Blood glucose level prior to scan

**APPENDIX XI
MRI TECHNIQUE CHART**

GE MRI Scanners

Scan Name	Plane	Sequence	TR	TE	Flip	FOV	Matrix	Averages	Slice Thickness	Slice Gap	ETL
			(ms)	(ms)		(cm)		(NEX)	(mm)	(mm)	
Localizer	3-plane										
T2	Axial	FSE	4500 - 5500	80-100	180°	24-40	256 x 256	2-4	3	0	8 to 16
T2	Sagittal	FSE	4500 - 5500	80-100	180°	24-40	256 x 256	2-4	3	0	8 to 16
T2*	Axial	GRE	2000 - 2100	12 and 21	60-70	24-40	256 x 128	2-4	3	0	
T2*	Left Obturator	GRE	2000 - 2100	12 and 21	60-70	22-30	256 x 128	2-4	3	0	
T2*	Right Obturator	GRE	2000 - 2100	12 and 21	60-70	22-30	256 x 128	2-4	3	0	
T1	Axial	FSPGR	175	1.8	80°	22-30	256 x 128	2-4	3	0	
T1	Coronal	FSPGR	175	1.8	80°	22-30	256 x 128	2-4	4	0	
T1 3D	Axial	FAME	4.5-13	1.4-5	8° to 15°	24-40	256 x 256	2-4	1-2	0	

Siemens MRI Scanners

Scan Name	Plane	Sequence	TR	TE	Flip	FOV	Matrix	Averages	Slice Thickness	Slice Gap	Turbo Factor
			(ms)	(ms)		(cm)		(Acq)	(mm)	(mm)	
Localizer	3-plane										
T2	Axial	TSE	5000 - 6000	80-100	160°	24-40	256 x 256	2-4	3	0	8 to 12
T2	Sagittal	TSE	5000 - 6000	80-100	160°	24-40	256 x 256	2-4	3	0	8 to 12
T2*	Axial	GRE	3000	12	75°	24-	256 x	2-4	3	0	

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			- 3500	and 21		40	256				
T2*	Left Obturator	GRE	3000 - 3500	12 and 21	75°	22- 30	256 x 256	2-4	3	0	
T2*	Right Obturator	GRE	3000 - 3500	12 and 21	75°	22- 30	256 x 256	2-4	3	0	
T1	Axial	FLASH	175	1.8	80° to 90°	22- 30	256 x 256	2-4	3	0	
T1	Coronal	FLASH	175	1.8	80° to 90°	22- 30	256 x 256	2-4	4	0	
T1 3D	Axial	VIBE	4.5- 13	1.4-5	8° to 15°	24- 40	256 x 256	2-4	1-2	0	

Philips MRI Scanners

Scan Name	Plane	Sequence	TR (ms)	TE (ms)	Flip	FOV (mm)	Matrix	Aver ages (NSA)	Slic e Thi ckn ess (m m)	Slic e Gap (mm)	Tur bo Fa cto r
Localiz er	3-plane										
T2	Axial	FSE	4500 - 5500	80- 100	180°	24- 40	256 x 256	2-4	3	0	8 to 16
T2	Sagittal	FSE	4500 - 5500	80- 100	180°	24- 40	256 x 256	2-4	3	0	8 to 16
T2*	Axial	FFE	3000 - 3500	12 and 21	20° to 30°	24- 40	256 x 128	2-4	3	0	
T2*	Left Obturator	FFE	3000 - 3500	12 and 21	20° to 30°	22- 30	256 x 128	2-4	3	0	
T2*	Right Obturator	FFE	3000 - 3500	12 and 21	20° to 30°	22- 30	256 x 128	2-4	3	0	
T1	Axial	T1 FFE	175	1.8	80° to 90°	22- 30	256 x 128	2-4	3	0	
T1	Coronal	T1 FFE	175	1.8	80° to 90°	22- 30	256 x 128	2-4	4	0	
T1 3D	Axial	THRIVE	4.5- 13	1.4-5	8° to 15°	24- 40	256 x 256	2-4	1-2	0	

APPENDIX XII DATABASE ARCHIVING

The Archived Images Database will be set up utilizing Microsoft SQL Server 7.0 running under Microsoft NT Server 2000 Enterprise Edition with clustering and full fault tolerance enabled. Image storage will be maintained on multiple servers connected to a distributed Level 5 RAID architecture, which will have sufficient capacity to handle the required number of diagnostic images anticipated for this trial. Backup will be performed on a DAT tape server with backup sets maintained both on and off site. Digitally acquired images will be received from the institutions where possible via the Web via a dedicated T3 link. The proprietary software utilized for acquisition and transmission has been developed by the ACR specifically for use in direct digital image acquisition for ACRIN trials. The digitally acquired images will be maintained in their original DICOM format and stored as individual files in the archive.

The archive environment will be set up utilizing a central SQL image database that will maintain the indexing of all the image series files sorted by study, case, exam, and image type. The software developed for management of the archive also includes a DICOM compliant viewer capable of retrieval and display of both digitally acquired and scanned film images. The viewing package includes the ability to pan and zoom as well as window/level the images for enhanced viewing and review purposes. There is a separate remote client image acquisition package that will be installed at the institution with connections to both the internal DICOM network as well as to the Web for purposes of image transmission. This software is Windows XP compatible and is set up on a PC that then becomes a node on the DICOM network. When images are “pushed” by the modality to this workstation the technician will be notified that there are received images ready for forwarding to the central archive in our Philadelphia office. Using the client software the technician will identify the study and case number whereupon the software will automatically scrub the DICOM image file headers of all identifying information and replace selected tags with study and case ID. The images are then encrypted and transmitted to the secure FTP site in Philadelphia. Once received the central management software will automatically import the images through the firewall into the permanent database and image archive. The images may then be made available for review either through web based retrieval or via media for review and other approved research activities.

The following includes detail on the Server and RAID configurations typically used throughout the ACR for all projects as exemplified here with our clinical server configuration.

Server Setup:

Reliable-Fault-Tolerant Configuration

Mirror Set

The boot and the system partition are mirrored to significantly reduce the amount of time needed to get the Windows NT Server back up if there is a problem with the hard disk containing the operating system. The mirrored disks are identical to the original disk in size, number of tracks, and cylinders.

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RAID

The Database resides on a Redundant Array of Independent Disks (RAID) system. RAID is a method of combining several disk drives into a single logical storage unit. RAID provides real-time data recovery when a disk drive fails, increasing system uptime and network availability. RAID also increases system performance when multiple drives work together.

RAID level 5 distributes parity information among each drive in the array in such a way that the data can be reconstructed on the fly in the event of a drive failure without bringing the server down.

Clustering Server:

The Cluster Services in each node of a cluster are in constant communication with each other. Services in a Windows XP cluster are exposed as *virtual servers*. Client Workstations believe they are connecting with a physical system, but are in fact, connecting to a service, which is provided by either Clinical_Server (Production) or the Clinical_Backup. Clients create a TCP/IP session with a service in the cluster using a known IP address. This address appears to the cluster software as a resource in the same group as the application providing the service. In the event the Production Server fails the cluster service moves the entire group to another system. This provides higher availability of the service. Clinical Application uses transactions to guarantee that the client request has been committed to the server database to gain fault tolerant semantics.

APPENDIX XIII
COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)/CLINICAL TRIALS AGREEMENT (CTA)

The study agent will be provided via NCI Pharmaceutical Branch under the CIP/DCTD/NCI Clinical Trials Agreement with AMAG Pharmaceuticals Inc.

The agent used in this protocol, which is supplied by CIP/ DCTD/NCI, is provided to the NCI under a Clinical Trials Agreement (CTA) between the Pharmaceutical Company(ies) [hereinafter referred to as "Collaborator"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" contained within the terms of award, will apply to the use of the Agent in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a Participant participating on the study or Participant's family member, the individual should sign a confidentiality agreement.
2. Only one investigational agent will be used in this study. Therefore, there is to be no "Multi-Party data."
3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.
4. Any manuscripts reporting the results of this clinical trial will be provided to CIP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts will be provided to CIP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations will also be forwarded to CIP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation will be sent to:

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Molecular Imaging Branch, CIP, DCTD, NCI
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APPENDIX XIV
GOG-0233/ACRIN 6671 RESPONSIBILITIES AND ROLES FOR REPORTING OF ADVERSE
EVENTS AND SERIOUS ADVERSE EVENTS

Adverse Event Reporting – Serious and Non-Serious Assessed at the Time of Study Procedure(s) or Reported by Study Participant to ACRIN RA and/or GOG Data Manager

ACRIN RA Responsibilities:

Non-Serious Imaging AE – Routine Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the imaging AE (see sections **16.10** – Table D2 and **16.10.2**);
4. Complete the AE form with all the information reported or assessed;
5. Have the PI sign and date the AE form;
6. Submit the completed AE form to the GOG data manager for data entry and submission into the clinical database.

Non-Serious Combidex (ferumoxtran-10) AE – Routine and Expedited Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the IND (see sections **16.8** – Table D1 and **16.9.2**);
4. Complete the AE form and paper template of AdEERS, if applicable (only unexpected grade 2 require expedited reporting) with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. For AEs that require expedited reporting, provide documentation of the report/assessment and the completed paper AE form and paper template of AdEERS to the GOG data manager for data entry and submission to the clinical database and electronic AdEERS within the appropriate timeframe to ensure meeting the regulatory reporting timeframe;
7. For routine reporting of AEs, only the AE form will need completion. The completed AE form will be provided to the GOG data manager for data entry and submission to the clinical database.

Serious Imaging AE – Routine and Expedited Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
4. Have the PI sign and date the AE form and paper template of AdEERS;

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5. Submit the completed AE form to the GOG data manager for data entry and submission into the clinical database and the electronic AdEERS.

Serious Combix (ferumoxtran-10) AE – Routine Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the IND (see sections **16.8** – Table D1 and **16.9.2**);
4. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. For expedited AE reporting, provide documentation of the report/assessment and the completed paper AE form and AdEERS form to the GOG data manager for data entry and submission to the clinical database and electronic AdEERS within the appropriate timeframe to ensure meeting the regulatory reporting timeframe.

GOG Data Manager Responsibilities:

Non-Serious Imaging AE – Routine Reporting

1. Review the documentation and completed AE form for the imaging AE forwarded by ACRIN RA to ensure forms are completed;
2. Data enter and submit the AE into the clinical database.

Non-Serious Combix (ferumoxtran-10) AE – Routine and Expedited Reporting

1. Review the documentation and completed AE form and paper template of AdEERS, if applicable (only unexpected grade 2 require expedited reporting per sections **16.8** – Table D1 and **16.9.2**) for the ferumoxtran-10 AE forwarded by the ACRIN RA for completion;
2. Data enter and submit the AE form into the clinical database and the AdEERS information into the electronic AdEERS, if applicable, within the specified regulatory reporting timeframe.

Serious Imaging AE – Routine and Expedited Reporting

1. Review the documentation and completed AE form and paper template of AdEERS (see sections **16.8** – Table D1 and **16.9.2**) for the imaging AE forwarded by the ACRIN RA to ensure forms are completed;
2. Data enter and submit the AE form into the clinical database and the AdEERS information into the electronic AdEERS within the specified regulatory reporting timeframe.

Serious Combix (ferumoxtran-10) AE – Routine and Expedited Reporting

1. Review the documentation and completed AE form and paper template of AdEERS (see sections **16.8** – Table D1 and **16.9.2**) for the imaging AE forwarded by the ACRIN RA to ensure forms are completed;
2. Data enter and submit the AE form into the clinical database and the AdEERS information into the electronic AdEERS within the specified regulatory reporting timeframe.

Non-Serious Surgical AE – Routine Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Determine the regulatory reporting requirements for the surgical AE (see sections **16.10** – Table D2 and **16.10.2**);
4. Complete the AE form with all the information reported or assessed;
5. Have the PI sign and date the AE form and the paper template of AdEERS;
6. Data enter and submit the AE information into the clinical database.

Serious Surgical AE – Routine & Expedited Reporting

1. Document the report of or the assessment of the AE in the participant's study chart/file;
2. Have the PI evaluate the AE to determine grade and attribution, as well as expected or unexpected;
3. Complete the AE form and paper template of AdEERS with all the information reported or assessed;
4. Have the PI sign and date the AE form and paper template of AdEERS;
5. Data enter and submit the AE information into the clinical database and the electronic AdEERS.