Study Protocol

STUDY TITLE: Prospective evaluation of quality of life and treatment-related side effects of women undergoing multimodality treatment for advanced stage endometrial carcinoma

1. STUDY AIM, BACKGROUND, AND DESIGN ABSTRACT

Purpose: To prospectively determine patients' quality of life (QOL) and treatment-related toxicity outcomes with adjuvant multimodality treatment (chemotherapy and radiation treatment) in women with advanced endometrial carcinoma after surgical staging.

Specific Aim:

1. To prospectively determine QOL after adjuvant treatment using the prospectively-validated FACT questionnaires at baseline, 3, 6, 12, and 24 months after surgical staging
2. To prospectively determine the rate of any grade 2 or higher treatment-related side effects: mainly bone marrow suppression, lymphedema, diarrhea, and others. Additionally, we will collect information about the rate of completion of planned adjuvant treatment (number of chemotherapy cycles, dose reduction or chemotherapy delay, radiation treatment interruption, etc.).
3. To prospectively collect survival outcome endpoints after adjuvant treatment (recurrence-free, disease-specific and overall survival).

Introduction and Rationale: Endometrial cancer is the most common gynecologic malignancy in the United States and ranks second in gynecologic cancer mortality following only ovarian cancer. More than 84% of patients present with International Federation of Gynecology and Obstetrics (FIGO) stage I-II disease. By definition, patients with advanced-stage uterine carcinoma (FIGO stages III-IV) are those with extrauterine disease and are at significant risk of dying from uterine cancer. They constitute a very heterogeneous group of patients with varying risk factors yielding highly variable clinical outcomes. Within the same FIGO stage, patients with disease involving multiple extrauterine sites fare worse compared to patients with involvement of a single site[1].

Postoperatively, patients with advanced stage disease often require adjuvant therapy(s) to reduce the chance of tumor recurrence with the potential to improve survival. However, the optimal adjuvant therapy is yet to be established with several options available for adjuvant treatment.

Rationale for multimodality treatment with chemotherapy and radiation treatment (CMT)

Current treatment recommendations for advanced stage endometrial cancer consist of multiple approaches including chemotherapy alone, radiotherapy (RT) alone, or combined modality treatment (CMT)[2].

GOG 122 study, which was a phase III trial, randomized patient with advanced endometrial carcinoma to adjuvant chemotherapy alone versus whole abdomen RT (WART). Outcomes of this study showed that the chemotherapy arm had an improved 5-year progression-free survival (PFS) and overall survival (OS) compared to RT alone. However, this trial showed that if chemotherapy is given alone, that rate of local recurrence approaches 20%[3].

The safety of CMT with concurrent chemotherapy and RT (chemoRT) was explored in RTOG 9708, which was a phase II trial that evaluated outcomes in patients receiving concurrent chemoRT. All patients received adjuvant pelvic RT (45 Gy) concurrent with cisplatin followed by four additional cycles of cisplatin and paclitaxel. The 4-year OS and PFS for patients with stage III disease were 77% and 72%, respectively. Rates

of grade 1 toxicity were found in 16% of patients, grade 2 in 41%, grade 3 in 16%, and grade 4 in 5%. This study demonstrated that concurrent chemoRT is safe with excellent local control[4].

More recent studies have sought to compare chemoRT to chemotherapy or radiation alone. PORTEC-3 was a phase III randomized trial comparing adjuvant RT alone to concurrent chemoRT. The RT dose was 48.6 Gy in 27 fractions and chemotherapy was concurrent cisplatin followed by an additional 4 cycles of carboplatin and paclitaxel. For women with stage III disease, the addition of chemotherapy to radiation treatment showed benefit in terms of improvement in FFS. An analysis of toxicity outcomes found that 60% of patients in the chemoRT arm experienced a grade 3 or greater adverse event compared to 12% in the RT alone arm ($p<0.0001$)[5].

GOG 258 study was recently published and was similar to PORTEC-3 except that it compared concurrent chemoRT to adjuvant chemotherapy alone. Patients were randomized to receive concurrent chemoRT (45 Gy in 25 fractions concurrent with cisplatin followed by 4 cycles of carboplatin and paclitaxel) or chemotherapy alone. The results of this study showed that chemoRT was associated with a lower 5-year incidence of vaginal and regional lymphatic recurrence. However, distant recurrence rates were higher in the chemoRT arm compared to chemotherapy alone[6].

The above studies helped to establish concurrent chemoRT with cisplatin followed by adjuvant carboplatin/paclitaxel as a valid adjuvant treatment approach for women with advanced endometrial carcinoma.

A retrospective review from Washington University included 51 women with stage III-IV endometrial carcinoma who received CMT with carboplatin/paclitaxel-based regimen concurrent with RT and assessed survival and toxicity outcomes. The chemotherapy regimen given was carboplatin/paclitaxel for 4-6 cycles and RT was 48-51.2 Gy. Patients also received a vaginal brachytherapy boost. They found that 48 patients (94%) completed chemotherapy and 16 patients (30%) required chemotherapy dose-reduction. Thirty-four patients experienced grade 3-4 toxicities, most of which were hematologic. Over 80% of patients required leukocyte growth factor injections. There were seven late grade 3-4 toxicities (4 GI, 2 GU, and 1 ongoing neuropathy). They found a median PFS of 42.8 months, median OS of 44.9 months, and 3-year OS of 80%[7]. This study suggests that concurrent chemoRT using a carbotaxol-based regimen has favorable outcomes, a tolerable side effect profile, and the potential to reduce overall treatment duration.

Building off of the results of the above retrospective study as well as the aforementioned randomized trials, we wish to PROSPECTIVELY assess outcomes of women with advanced endometrial carcinoma who receive the same concurrent chemoRT with a carboplatin/paclitaxel-based regimen.

2. SUBJECT POPULATION AND ELIGIBILITY

A total of 60 patients with FIGO stage III uterine carcinoma will be prospectively enrolled in this study. All patients will have undergone hysterectomy and should be eligible candidates for the standard multimodality treatment with the standard doses and frequency of administration (radiation treatment and chemotherapy). Patients will be identified during gynecologic oncology physician consult. Study eligibility will be determined from the treating physician chart review. Vulnerable population will not be targeted for this study; however, women with low educational attainment and low income status may still be enrolled if they meet eligibility criteria. Eligibility/exclusion will be documented in the legal medical record. Considering our current volume of

patients, it would take about 24 months to enroll these patients in the study. The study would not compete with other local or national studies.

3. STUDY PROCEDURES

All patients will undergo surgical staging with TAH/BSO and lymph node dissection. As stated above, patients with surgically-staged FIGO stage III uterine carcinoma (all histological types including carcinosarcoma) will be enrolled in the study.

Following surgical staging and enrollment in the study, chemotherapy and RT will start approximately 4 weeks following the date of surgery. For chemotherapy administration, patients will receive the standard 6 cycles of both carboplatin (AUC 6) and paclitaxel (175 mg/m^2). All women will receive growth factor injections as clinically indicated while undergoing treatment in order to reduce the risk of severe hematologic toxicity. Chemotherapy dose-reduction will be at the discretion of the treating gynecologic oncologist.

Radiation treatment will start within 7-10 days of the first chemotherapy cycle and will be given during cycles 1-3. Prior to the start of RT a CT simulation will be performed for each patient using a Philips Brilliance Big Bore CT scanner (Philips Medical Systems, Andover, MA) with a slice thickness of 3 mm. Following simulation, external beam radiation will be given via intensity-modulated RT (IMRT) in once-daily fractions of 1.8-2.0 Gy for a total dose of 44-45 Gy to the pelvis (vaginal cuff, pelvic LN, and para-aortic lymph nodes). If there is grossly visible nodal disease seen at the time of treatment planning, a boost to 54 Gy will be given to the gross disease. If the patient is found to have cervical stromal invasion, we will recommend that she receive a brachytherapy boost of 21 Gy in 3 fractions prescribed to the upper 4.0 cm of the vaginal surface using a vaginal cylinder applicator. The patient will be fitted for the cylinder (0.5, 1.0, or 1.5 cm diameter depending on the size of the vaginal vault) in the final weeks of RT. Cylinder treatments are given approximately every other day of the week. A separate simulation process will be performed near the end of the EBRT course for the cylinder treatment.

Patients will be followed as per the standard of care and data will be collected on OS and PFS endpoints. Data will also be collected on treatment toxicity (diarrhea, dysuria, anemia, leukopenia, etc). We will also evaluate patients' quality of life with a series of questionnaires (Appendix A) at baseline, 3, 6, 12, and 24 months after surgical staging. These are prospectively validated questionnaires and include FACT-G (physical and functional well-being sections), FACT-En (additional concerns section), FACT/GOG-NTX-4 (additional concerns section), and FACT-C (items C3 and C5).These sections will be combined into one single form for ease of completion for the patients (a total of 36 items).

This data will be stored in a secure database/spreadsheet. Patient questionnaires will be kept in a binder. Once the patient has completed the study, these data points will be entered into the spreadsheet, and the paper copies will be destroyed. Please see Figure 1 below for clinical flow of the study as well as Table 1 regarding experimental vs standard of care components of the study.

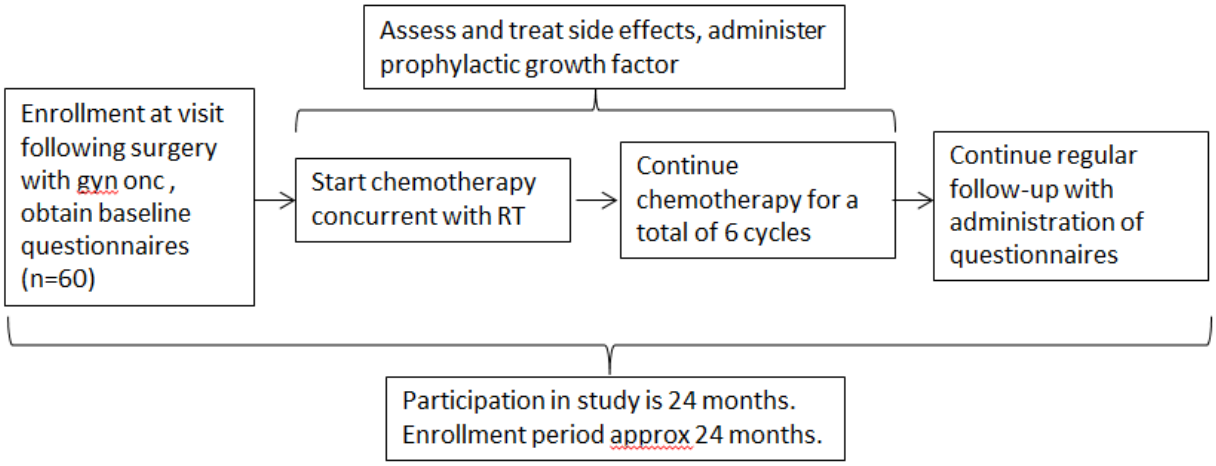

Figure 1. Clinical workflow and time frame of the study

Experimental Components	Standard Components
QoL questionnaire at baseline, 3, 6, 12, and 24 months	Combined modality treatment (chemo and RT), growth factor administration/treatment of side effects

Table 1. Comparison of experimental and standard of care components

Data analysis:

After data collection, we will pursue statistical analysis of the data using the appropriate software in our department. If further biostatistical consultation is required, Charlotte Burmeister MS will help with the analysis.

Because this is a simple exploratory study, a total of 60 patients were felt to be adequate. We will collect data for OS, PFS, toxicity outcomes, and quality of life metrics using the aforementioned questionnaires. The variables will be analyzed as continuous variables (mean, standard deviation, minimum, median, and maximum). Categorical variables will be also analyzed (count and percent). Kaplan-Meier survival estimates will be calculated for local control and survival end points. Each patient, disease characteristic and adjuvant treatment will be placed in a simple logistic regression models on predicting survival endpoint. A multivariate analysis will be performed for exploratory purposes. Hazard ratios and 95% confidence intervals for the hazard ratios will be reported. Tests will be considered significant at $p < 0.05$. All analyses will be performed using SAS 9.4.

4. ANTICIPATED RISKS

The chemotherapy therapy regimen and the radiation treatment will be delivered as per the standard of care to this protocol. Concurrent carbotaxol-based chemotherapy and radiation carries the risks of GI toxicity (diarrhea, nausea/vomiting leading to dehydration and weight loss, hematochezia), GU toxicity (dysuria, frequency, hematuria), hematologic toxicity (leukopenia leading to infection/sepsis, anemia, thrombocytopenia leading to bleeding), and neuropathy. Late effects can manifest as well including scarring of pelvic tissues leading to small bowel obstruction, persistent hematuria and GI bleeding, vaginal dryness/stenosis that may result in dyspareunia, and persistent neuropathy. These toxicities may result in death. Some toxicities including diarrhea and dysuria can be managed symptomatically with OTC medications. In order to prevent immunosuppression and severe hematologic toxicity, we will prophylactically administer growth factors during

treatment whenever there are signs of marrow suppression. If toxicities become severe, interruptions in treatment or dose-reduction in chemotherapy/radiation will be determined by the treating physicians. Regular follow-up with the treating physicians will help to identify and treat these side effects that may occur.

There is a low risk of breach of confidentiality on this study. Questionnaires with any identifying patient information on them will be entered into a database following completion of trial and immediately destroyed.

5. ANTICIPATED BENEFITS

There is the possibility that this regimen will improve the patient's outcomes in term of OS and disease recurrence. This study will also help us to determine QoL and toxicity patterns in patients receiving this therapy.

6. RENUMERATION/COMPENSATION

No payment will be provided for participation in the study.

7. COSTS

Patients will not incur any costs associated with this study. Patients are not compensated for their participation.

8. ALTERNATIVES

The alternative to the study is not participating in this trial. If the patient does not wish to participate, then she will be recommended to receive the standard of care at Henry Ford Cancer Institute, which involves combined modality treatment with radiation and chemotherapy with the sequence either a "sandwich" technique of 3 cycles of carboplatin/paclitaxel followed by external beam RT +/- brachytherapy followed by an additional 3 cycles of chemotherapy or concurrent chemotherapy and radiation with cisplatin following by several cycles of carboplatin/paclitaxel.

9. CONSENT PROCESS AND DOCUMENTATION

Gynecology oncology physicians will obtain consent during the first post-op visit. Patient will be given the opportunity to ask questions.. The consent form will be explained to the patient, and the purpose, duration, procedures, and risks will be made clear. Patient will be made aware of alternatives to participating in the study, and they will be told that not participating will have no impact on the quality of care they receive. If non-English speaking patients are enrolled, a translator will be used during the consent process. If patient agrees to participate and signs consent, this will be documented in the legal EMR. The consent form will be scanned and stored in a folder on the HFHS shared drive.

Patients will also be provided with the HIPAA authorization form for prospective studies. Regarding data collected during the study process, questionnaires will have patient label information on these forms so that data can be organized during input into the computer. These data will also be saved on a secure HFHS shared drive. Following entering these data into the computer, these documents will be destroyed. This data will be maintained indefinitely as this data may be used for future studies following completion of this trial.

10. WITHDRAWAL OF SUBJECTS

Patients will be withdrawn from the trial if they exhibit poor tolerance and severe toxicity to the therapy. These situations include hematologic toxicity refractory to growth factor injections and transfusions or the

development of sepsis requiring hospitalization. Patient may also be terminated from the study if they develop any acute grade 4 toxicity.

11. PRIVACY AND CONFIDENTIALITY

All patient data and identifiers will be stored in a secure file and drive on the HF network. Only staff associated with the trial will have access to the data including nursing, physicians, statisticians, and others involved in the project. The only identifiable data will be patient stickers on the questionnaires. These questionnaires will be destroyed (by shredding) following patient's completion of the study and once data has been entered. Authorization for PHI access for screening purposes will be obtained at physician visit before enrollment in trial is performed.

12. DATA AND SAFETY MONITORING PLAN

The PI of the study will meet at least twice a month with other co-investigators and nurse teams to objectively evaluate adherence to the protocol and patient compliance with the study protocol. An update to the group will be conducted at the time of the weekly gynecologic oncology tumor board.
The group will decide whether or not any amendment to the protocol is needed.
If an unexpected event is encountered, the PI of the study will report it immediately to the IRB and other co-investigators.

13. QUALIFICATIONS OF THE INVESTIGATOR(S)

The PI of the study is a well-established national researcher with more than 200 published abstracts and peer-reviewed manuscripts in endometrial cancer. Charlotte Burmeister has been conducting statistical analysis for our work for more than 7 years now.

14. REFERENCES

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4. Greven K, Winter K, Underhill k et al. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin/paclitaxel chemotherapy following surgery for patients with high-risk endometrial cancer. *Gynecol Oncol*. 2006;103:155-159
5. De Boer SM, Powell ME, Mileshkin L el al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3):final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19:295-309
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7. Wilkinson-Ryan I, Binder PS, Pourabolghasem S et al. Concomitant chemotherapy and radiation for the treatment of advanced-stage endometrial cancer. *Gynecol Oncol*. 2014;134:24-28

APPENDIX A-QUALITY OF LIFE QUESTIONNAIRE

FACT-G (Version 4-Physical and Functional Well-Being)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4

GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-En (Version 4-Additional Concerns Section)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-**	**Quite a bit**	**Very much**
O1	I have swelling in my stomach area	0	1	2	3	4
O3	I have cramps in my stomach area	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area.....	0	1	2	3	4
ES6	I have vaginal bleeding or spotting.....	0	1	2	3	4
ES4	I have vaginal discharge	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
ES1	I have hot flashes/hot flushes.....	0	1	2	3	4
ES2	I have cold sweats	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
ES8	I have pain or discomfort with intercourse.....	0	1	2	3	4
En1	I have trouble digesting food	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
Cx6	I am bothered by constipation	0	1	2	3	4
BL2	I urinate more frequently than usual.....	0	1	2	3	4
En2	I have discomfort or pain in my pelvic area	0	1	2	3	4

FACT/GOG-NTX-4 (Version 4)

Below is a list of statements that other people with your illness have said are important**.**
Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands.....	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet.....	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4

FACT-C (Version 4, Items C3 and C5)

C3	I have control of my bowels	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4