IRB#: 08-092A(1)

Evaluation of Thermal Spread into the Interstitial Portion of the Fallopian Tubes Using the Ligasure Device at Time of Hysterectomy

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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	Douglas A. Levine, M.D.	Surgery: Gynecology
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	John Diaz, M.D.	Surgery: Gynecology
	Lisa Dos Santos M.D.	Surgery: Gynecology
	Fady Khoury-Collado M.D.	Surgery: Gynecology
	Karin Shih M.D.	Surgery: Gynecology

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: Evaluation of thermal spread into the interstitial portion of the fallopian tubes using the LigaSure device.

Background: Women who are high risk for ovarian cancer will often undergo a salpingo-oophorectomy defined as removal of the ovaries and fallopian tubes in order to decrease their risk developing ovarian cancer. These women also may have an increased risk of developing fallopian tube and primary peritoneal cancer. Therefore, removal of the both the right and left fallopian tube along with the right and left ovary (termed bilateral salpingo-oophorectomy) is necessary. Anatomically, a portion of the fallopian tube extends into the myometrium of the uterus, which is termed the intersitial or intramural portion. Women undergoing a risk reducing bilateral salpingo-oophorectomy (BSO) will often have this procedure performed without removal of the uterus. There is a theoretical concern that this remaining intersitial portion of the fallopian tube may be a site for future development of neoplasia. These remaining tubal cells may be at risk of malignant transformation and therefore, it is critical that our surgical technique ensures that all the fallopian tube tissue is excised or electrosurgically coagulated.

Objective: This study is designed to evaluate the thermal spread of the vessel sealing electrocautery device, the LigaSure (Valley Lab), into the interstitial portion during a salpingectomy (removal of fallopian tubes). The objective of this study is to determine if the LigaSure device, which we routinely use for removal of tubes and ovaries, is effective at destroying all tubal cells comprising the fallopian tube including those cells within the cornu of the uterus.

Patient Population: The population to be studied will include women who are undergoing a total hysterectomy with removal of the ovaries and fallopian tubes for either benign or malignant conditions that do not involve the fallopian tube. Those being treated by either by laparotomy or laparoscopy can be enrolled into the study since the same technique with the same instruments is applied.

Study Design: We will intend to enroll a total of 60 patients planned to undergo a total hysterectomy and bilateral salpingo-oophorectomy. The first 30 patients will be enrolled into group A. In this group, the surgeon will be instructed to perform a right salpingectomy in the following manner: the LigaSure will be used with a single application on the fallopian tube at the closest point to the cornua and the fallopian tube will be sealed and divided. The next 30 patients will be enrolled into group B. In this group, the surgeon will be instructed to perform a right salpingectomy in the following manner: the first application of the LigaSure will be the same as in group A. The surgeon will place the LigaSure on the portion of the fallopian tube closest to the cornua to seal and divide the tube. Then the LigaSure will be applied using the coagulation mode only a second time to the remaining medial portion of the tubal stump

on the uterine cornua. The surgeon will use this second application to coagulate the tissue at the cornua without dividing it. The purpose of this extra step is to evaluate if further proximal coagulation is needed to ensure all the tubal tissue is destroyed. The tissue specimen with be sent to pathology where it will be evaluated histologically in a standard fashion. The pathologists will have the ability to evaluate the hysterectomy specimen for viable fallopian tube cells. The cornua will be serially sectioned by the pathologist as described in section 10.0.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

The objective of this study is to determine if the LigaSure device, which we routinely used for removal of tubes and ovaries, is effective at destroying all tubal cells comprosing the fallopian tube including those cells within the cornua of the uterus.

- Histologically evaluate whether viable fallopian tube cells remain in the uterus after electrocautery excision with the LigaSure. Determine if the additional cautery step compared to the one step standard destroys all fallopian tube cells present in the intersitial portion of the uterus.

3.0 BACKGROUND AND RATIONALE

Women who are known to have an increased risk of both ovarian and fallopian tube cancer are offered surgical intervention to remove the ovaries and fallopian tubes since screening for ovarian cancer even in high-risk women has a low predictive value. These women undergo a bilateral salpingo-oophorectomy (BSO) to remove both ovaries and fallopian tubes. This procedure has been shown to decrease risk of ovarian cancer and fallopian tube cancer by approximately 95%[1].

Occult ovarian cancers and fallopian tube cancers are found at the time of bilateral salpingo-oophorectomy (BSO) at varying rates. In one large series of 98 mutation carries, three (3%) occult cancers were found at the time of the prophylactic surgery (two ovarian and one fallopian tube)[2]. There is also a risk of developing primary peritoneal cancer (PPC) after undergoing a bilateral salpingo-oophorectomy. PPC is morphologically similar to ovarian cancer and the prognosis and long term outcomes are also similar to ovarian cancer. The rate of developing PPC after undergoing a prophylactic BSO has been reported to be 2-11% in the literature[3]. The exact area of origin of this cancer is not known. However, one needs to consider the relationship between the increased risk of fallopian tube cancers with the increased risk of PPC. If we speculate that fallopian tube epithelial cells may be the point of origin for peritoneal cancer, then it is crucial that the risk reducing surgery completely removes the entire ovary as well as the entire fallopian tube.

Anatomically, the fallopian tubes are adjacent to the ovary and end in the posterosuperior aspect if the uterus termed the cornua of the uterus (Figure 1). The total length of the fallopian tube is approximately 9-11cm. A small portion of the tube, 1cm, extends into the myometrium of the uterus and then opens into the endometrial cavity (Figure 2). On histologic evaluation. epithelial cells continue to line this interstitial or intramural portion of the fallopian tube[5].

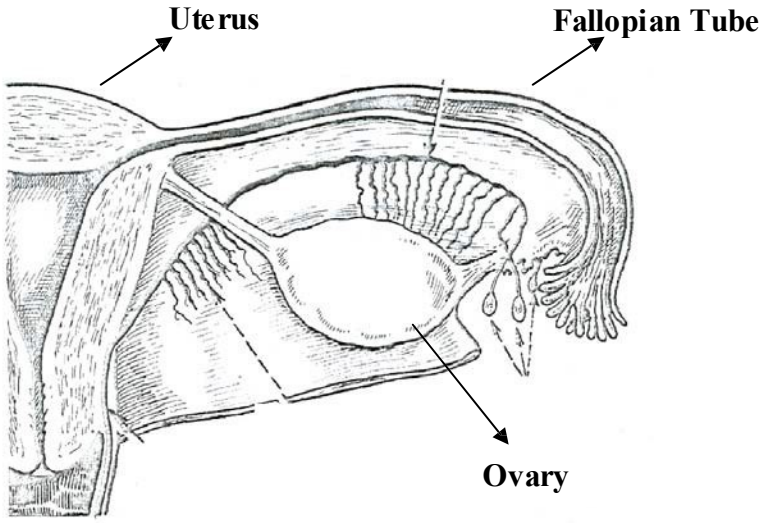


Figure 1: Relationship of ovary, fallopian tube and uterus.

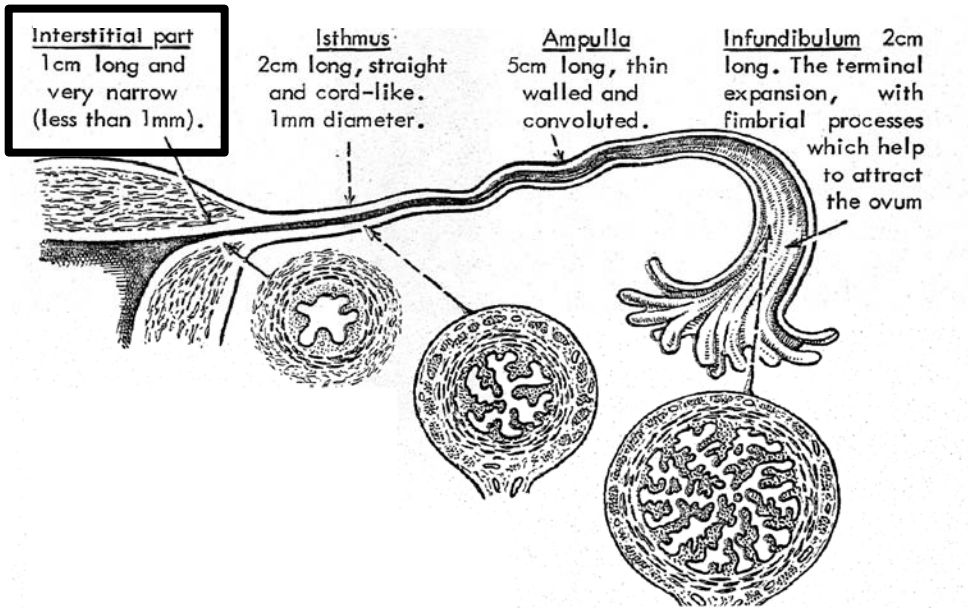


Figure 2: Histology of the fallopian tube
The tube extends into the cornua of the uterus and is lined with ciliated fallopian tube cells.

Illustrations from **Pathology of the Female Reproductive Tract**[5]

Currently, the standard method for prophylactic BSO is to ligate the tube and uteroovarian ligament at their insertion into the uterus with one single cut. It is not the standard of care to perform a hysterectomy in those women undergoing a prophylactic BSO. Therefore, the anatomy of the fallopian tube needs to be considered when performing a prophylactic surgery so that there are no viable fallopian tube epithelial cells remaining at the end of the procedure since part of the fallopian tube remains in situ after prophylactic BSO[6]. In one study that examined hysterectomy specimens from standard hysterectomy procedures, the mean length of intramural portion of fallopian tube remaining in the uterus was 11.3mm[6].

It is known that in those women who are mutation carriers or those with a strong family history, meticulous gross inspection and microscopic examination is encouraged. Protocols have been created to address the type of histologic evaluation performed on the surgical specimen. Currently, detailed serial sectioning of the specimen is performed to attempt to detect microscopic cancers[4]. However, there is no defined standard operative protocol and currently varying techniques as well as a number of different instruments are used to excise the fallopian tube. The optimal type of prophylactic surgery has not been determined.

Our goal is to test the ability of electrocautery using the LigaSure device to thermally destroy the fallopian tube epithelial cells within the myometrium. The destructive effect of cautery on residual fallopian tube cells within the uterus to remove the tubes has not been studied. The results of this study may lead us to alter our surgical approach and perhaps change the recommendations for what procedure is performed for high risk women undergoing prophylactic surgery.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

All female patients who are already scheduled to undergo a total hysterectomy with bilateral salpingo-oophorectomy (BSO) will be asked to participate in this trial. Patients will be eligible if they are undergoing a total abdominal hysterectomy (TAH) with a BSO performed through an open incision. Patients who are having either a total laparoscopic hysterectomy (TLH) or a laparoscopically assisted vaginal hysterectomy (LAVH) along with a BSO will also be eligible. Patients will be eligible whether they are undergoing

surgery for benign or malignant disease. These patients will consent to allow their surgeon to remove the fallopian tubes from the uterus first and then proceed with removal of the uterus. Those very rare cases who are suspected to have fallopian tube cancer prior to their surgery will not be eligible.

The skin incisions will be performed as the surgeon has planned for the procedure and will not be altered by the study. As standard protocol for gynecologic surgery, the entire pelvis will be inspected. The anatomy of the fallopian tubes and uterine fundus will be viewed in detail. If there are no anatomic abnormalities in the proximal fallopian tube, the surgeon will proceed to remove the fallopian tube from the cornua of the uterus with the specified procedure to which the patient has been assigned. This detailed surgical procedure will be explained in detail in section 9.0.

4.2 Intervention

The patients will already be undergoing a total hysterectomy with removal of the tubes and ovaries for a specific indication diagnosed or defined by their surgeon. If the patient is suitable to proceed by the surgeon, then he/she will perform a right salpingo-oophorectomy with the LigaSure device. The 10mm LigaSure is a standard instrument used in our gynecologic surgery and other surgical specialties for a variety of procedures on a daily basis (Figure 3). The LigaSure is a vessel sealing device that causes vessels to seal using pressure and energy, a high current, low voltage output. It uses this energy to allow tissue to be ligated with only a thermal spread of approximately 2mm.

Figure 3: LigaSure vessel sealing system; Valley Lab

There will be two techniques compared in this protocol. Group A will have the right tube removed with one application of the LigaSure. The LigaSure will be placed and the most proximal portion of the right fallopian tube adjacent to the uterine cornua and will be used to coagulate and cut the tube. Group B will have the tube ligated in the same fashion as group A however an additional step will be added once the fallopian tube has been removed. The LigaSure will be used to cauterize the remaining medial tissue on the cornua region of the uterus. This procedure is described in detail in Section 9.0.

The fallopian tube as well as the uterus will be labeled for the pathologist. The pathologist will then perform a thorough evaluation of the uterus with serial section of the right cornua to determine the amount of remaining viable fallopian tube cells. Please refer to Section 10.0 for detailed explanation of the histologic review of the submitted tissue.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

All interventions and instruments are standardly used for this surgical technique therefore all supplies will be obtained through the regular supply source at Memorial Sloan-Kettering. The LigaSure is a vessel sealing device that causes vessels to seal using pressure and energy, a high current, low voltage output. It uses this energy to allow tissue to be ligated with only a thermal spread of approximately 2mm. There will not be any experimental instruments or agents used in this protocol.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- Women undergoing a non-emergent total hysterectomy with removal of the tubes and ovaries by the gynecologic service for benign or malignant conditions-uterine, cervical or early ovarian cancer.
- Patients will undergo either a laparotomy, total laparoscopy or laparoscopically assisted vaginal hysterectomy
- Patients will be 21 years and older

6.2 Subject Exclusion Criteria

- Patients with abnormal fallopian tubes seen preoperatively by radiologic exam or intraoperatively by visual inspection
- Patients who are suspected to have fallopian tube cancer prior to their surgery
- Patients who have had any type of prior tubal surgery

- Patients who have had prior radiation therapy
- Patients who are undergoing a Robotically Assisted procedure

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

Surgeons within the department of gynecologic oncology will participate in this trial and ultimately decide if the patient is a candidate for the protocol. They will assess which patients are eligible for the trial in the outpatient setting while seeing routine visits and scheduling surgeries. The primary surgeon will then discuss the study with the potential subject and facilitate the enrollment in the research study. The consents will be obtained in the outpatient setting when the patient is signing consent for the medically indicated surgical procedure.

8.0 PRETREATMENT EVALUATION

Patients will be seen and evaluated by a gynecologic oncology surgeon at MSKCC. The standard pretreatment evaluation for any surgical patient will be performed including the following:

- Thorough history including all past operative procedures performed
- Physical examination
- Radiologic tests as ordered by the primary surgeon (there will be no specific tests or radiologic exams needed for entry into the study

There are no specific additional pretreatment tests necessary to enroll into the study.

9.0 TREATMENT/INTERVENTION PLAN

If the surgeon assesses during the time of surgery that the patient is a candidate to continue in the protocol, then he/she will proceed with the removal of the tube. The standard open total abdominal hysterectomy is usually performed with the surgeon initially placing a Kelly clamp on the right and left cornua to manipulate the uterus. This clamp on the cornua causes trauma to the tissue and will alter our analysis. The only alteration the surgeon will have to make is to place an atraumatic clamp in the middle fundus to avoid destruction of the tissue at the cornua. The surgeon will use the familiar instruments, either a Collin or Buxton uterine clamp, which are available routinely in our

operating rooms, to grasp the middle of the uterus for manipulation as he proceeds with the hysterectomy (see Figure 4).

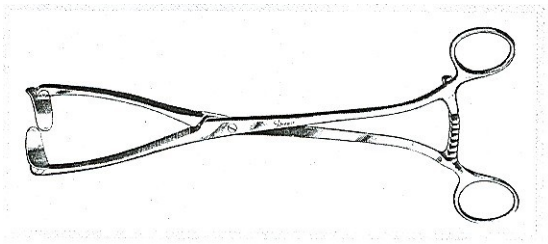
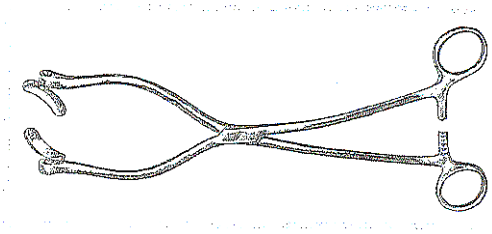


Figure 4a: Collin Uterine Clamp



4b: Buxton Uterine Clamp

The surgeon will then proceed with removal of the right fallopian tube with the LigaSure. The first 30 patients (group A) will have the right salpingectomy performed with only one application of the LigaSure. The LigaSure will be applied onto the fallopian tube adjacent to the cornua and the fallopian tube will be cauterized and ligated. The next 30 patients (group B) will have a right salpingectomy performed as those in group A (LigaSure cauterizing and ligating the right tube at the cornua insertion) and then the LigaSure will be applied an additional time to the portion remaining on the cornua. The surgeon will use this second application to coagulate (without cutting) the tissue at the cornua. The labeled fallopian tube specimen with be sent to pathology where it will be evaluated histologically in a described standard fashion.

GROUP A:

LigaSure applied at line 1 to coagulate and cut right FT.

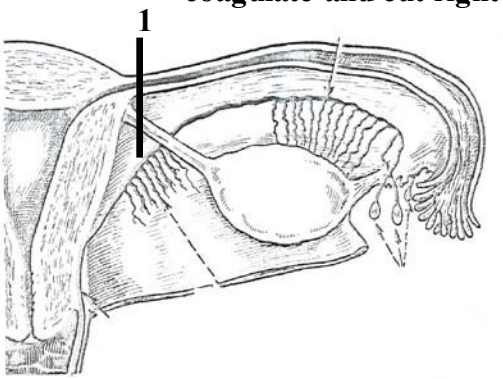


Figure 5a

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GROUP B: **LigaSure applied at line 1 to coagulate and cut right FT and then applied to line 2 to coagulate only.**

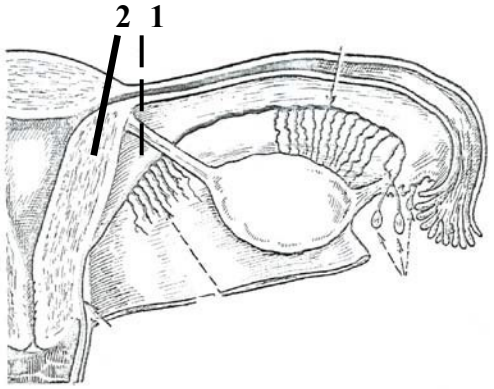

Figure 5b

If there is additional bleeding noted at the cornua in either group A or B, then additional coagulation of the area will be performed to achieve hemostasis. This patient will be removed from the study and not be incorporated in the data analysis.

The surgeon will continue with the rest of the surgery including the hysterectomy and further surgical procedures as needed in the fashion that the surgeon chooses. The labeled uterus will be sent to the pathologists who will evaluate the hysterectomy specimen for viable fallopian tube cells. The cornua will be serially sectioned by the pathologist as described later in this section.

The fallopian tube as well as the uterus will be labeled for the pathologist. The pathologist will then perform a thorough evaluation of the uterus with serial section of the right cornua to determine the amount of remaining viable fallopian tube cells. Please refer to Section 10.0 for detailed explanation of the histologic review of the submitted tissue.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Histologic Protocol for sectioning the intramural portion of the fallopian tube

The fallopian tube (FT) is divided into 4 anatomic segments: intramural, isthmus, ampulla and infundibulum. Each FT is approximate 11-12 cm in length, but can vary from patient to

patient. The intramural portion begins at the funnel-like uppermost recess of the uterine cornu and ends where the tube emerges from the uterine wall. The course of this approximately 0.8 cm long segment can vary from straight to highly convoluted and tortuous. The following protocol delineates the method by which this intramural portion of the FT will be examined in pathology.

The uterus is received fresh from the operating room with the protocol number and directed to the attention of Dr. Kay Park or Dr. Robert Soslow.

The external appearance of the uterus will be examined for any gross abnormalities, including tumor, hemorrhage, disruption of the surface integrity, etc. and noted in the gross description with all measurements recorded. Any gross abnormalities that distort the anatomy of the uterus, especially at the cornual ends, will disqualify the specimen from the study. This will be at the discretion of the surgeon and pathologist.

The insertion of the fallopian tube will be identified on the side where the adnexa have been previously removed (right side). Starting at the point of fallopian tube insertion, the cornual myometrium will be serially sectioned vertically at 2-3 mm intervals in the sagittal plane, up to 1.0 cm or until the endometrial cavity is reached (in cases where 1.0 cm is insufficient to reach the endometrial cavity). Each section will be grossly examined to identify the intramural portion of the fallopian tube, if possible, and any gross findings will be recorded. All of these sections will be submitted for histologic review with a designation of "IFT" for "intramural fallopian tube."

The uterus will then be bivalved in the coronal plane to examine the endometrial cavity and to assure that portions of the intramural FT are not missed. Additional sections of the cornu will be submitted as deemed necessary by the examiner.

All histologic sections from the cornu will be examined by the pathologist and the presence or absence of tubal epithelium will be recorded. The pathologist will not be blinded to which patient has received the second application of the LigaSure and therefore additional cautery. Any pathologic findings relevant to clinical management will be included in the final pathology report.

There will be no specific follow-up for these patients. The follow-up will be as the surgeon plans for postoperative assessment and evaluation. The protocol does not require any other patient data or involvement once the procedure has been completed.

11.0 TOXICITIES/SIDE EFFECTS

The risks that are associated with this intervention are the same risks described to the patient regarding surgical intervention. There are no additional risks expected based on the surgical procedure described as the LigaSure is an instrument used routinely and this procedure is performed by our gynecologic oncologists. For the patients in group B, there are no expected additional risk with a second application of the LigaSure. There are no expected side effects.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

This study will compare histologic specimens for viable fallopian tube cells. This study is designed to provide baseline data to an unanswered question at this time. This question is whether one application or simply one ligation on the tube is adequate to destroy all fallopian tube cells in the uterus. This evaluation will be done by the pathologist and will not have any impact on the patient time or recovery. The primary outcome of this discovery trial is to allow us to histologically identify how many patients will have viable fallopian tubes cells in the uterus after two different surgical methods of removing the fallopian tubes. Once we have this baseline data, we can then decide what type or if an additional study needs to be created.

This study will provide baseline information. We have no previous data looking at the standard method compared to a minimally altered method. Therefore there is no specific number of positive or negative cases needed. The results will either allow us to feel confident in our current method of prophylactic surgery or will help us define a more appropriate technique to achieve our goal for this surgery. If there are fallopian tube cells found in the uterus in both arms, then we have data to support defining a different surgical approach for those undergoing this surgery to decrease the risk of ovarian and fallopian tube cancers. We would then need to address the recommendation of hysterectomy for these women at the time of surgery. If there are no viable fallopian tube cells found in either group, then we can report that our current surgical technique is adequate and provide an answer to those who are concerned about the possibility of remaining fallopian cells based on the anatomy. If group B is shown to have no fallopian tube cells, then this provides evidence to surgical oncologists as well as benign gynecologists to slightly alter the current prophylactic technique to address the issue of viable cells within the remaining uterus.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If there are visible abnormalities of the fallopian tubes or uterine cornua/fundus, the surgeon will proceed with an appropriate procedure and the patient will no longer be a participant in our study. The surgeon has the right to choose not to proceed with the study if he/she feels that it would not be appropriate for the patient given the findings at the time of laparotomy or

laparoscopy. We do not expect this event to be common (1 in 20 patients). These patients will be replaced and the description of the abnormality will be reported.

If at anytime the patient develops unacceptable toxicity he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

The goal of this study is to obtain histologic data from pathology specimens and to compare two techniques to answer a yes/no question. The question is whether there are viable fallopian tubes cells in the uterine cornua after the fallopian tube is removed from the uterus.

We aim to evaluate if the technique of bilateral salpingo-oophorectomy using a two-step cautery procedure with the LigaSure device is feasible. The outcome is binary; whether there are any viable fallopian tube cells in the uterine cornua after the fallopian tube is removed from the uterus based on the pathologist's review that is described in section 10.0. We will not be performing any statistical comparison of these histologic findings as this is a study to provide us with baseline surgery data. The data we will collect is whether each technique removes all viable fallopian tube cells within the uterus. The surgery is effective (successful) if the pathologist can not identify any viable fallopian tube cells in the uterus. We plan to accrue two groups of 30 patients: group A will undergo the single step procedure whereas group B will undergo the two-step procedure. Assuming binomial proportions, 30 patients in each group can provide an estimate of the success probability +/- 18%. If at any point, we observe at least five patients in Group A with any viable fallopian tube cells in the uterus we will consider this method a failure and we will close accrual for Group A. At this point, accrual for Group B will be initiated. In the rare event where all patients in Group A have no residual fallopian tube cells, then we will not proceed with Group B, since the observed rate of 0/30 will provide sufficient evidence that the two-step procedure is not required.

The probability of closing accrual for Group A (i.e. stopping early) given the true probability of finding any viable fallopian tube cells (FTC) within the uterus is given in the table below:

True probability of	0.10	0.15	0.20	0.25	0.30

finding any viable FTC					
Probability of early stopping	0.18	0.48	0.74	0.90	0.97

We expect to enroll 15 patients per month, so the study is expected to complete within four months.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

The following person(s) can obtain informed consent:

Richard R. Barakat, M.D.
Nadeem R. Abu-Rustum, M.D.
Dennis Chi, M.D.
Carol Brown, M.D.
Yukio Sonoda, M.D.
Douglas A. Levine, M.D.
Mario Leitao, M.D.
Siobhan M. Kehoe, M.D.
Sharyn Lewin, M.D.
John Diaz, M.D

Lisa Dos Santos M.D.
Fady Khoury-Collado M.D.
Karin Shih M.D.

Confirm in the electronic medical record that the patient has received the Notice of Privacy Practice. This must be obtained before the eligibility confirmation and obtaining of the research informed consent.

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in section entitled Informed Consent Procedures.

All particpants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the informed consent form, the completed signature page of the Research Authorization and a completed Eligibility Checklist must be faxed to PPR.

During the registration process registering individuals will be required to answer specific eligibility questions and provide the following information:

Registering Individual	[Last, First Name]
Notice of Privacy Status	[Yes, No, N/A]
Research Authorization	[Date]
MSKCC IRB Protocol#	
Attending of Record (if applicable)	[Last, First Name]
Consenting Professional	[Last, First Name]
Informed Consent Date	
Participant's Full Name	[Last, First Name]
Participant MRN	

15.2 Randomization

There will be no randomization in this protocol. The first 15 patients enrolled will be assigned to group A and the next 15 to group B. We will continue to enroll patients until we have completed the surgical procedure successfully for 15 patients in each of the groups.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: *http://mskweb2.mskcc.org/irb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for it's level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

17.0 PROTECTION OF HUMAN SUBJECTS

The decision to treat a patient's diagnosis with surgery will be made independently by the surgeon. Only after the decision for surgery is made will the patients be offered enrollment in the study. The treatment options will not be changed or altered by this study. The patients will be explained the risk of surgery by their surgeon at the time of signing consent for surgery. There are no expected additional risks from participating in the study.

Patients will not be paid to participate in this study. Patients will not be billed for the expenditures for this study. The costs for this study include pathology fees for the additional cut sections for evaluation which will be paid for by philanthropic research grant money within the department of gynecologic oncology.

The decision to enroll in this study is completely voluntary and patients can decide to withdraw from the study at anytime before the surgery.

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

It is the responsibility of the Research Staff to ensure that protocol subjects received the Center's Notice of Privacy Practices. If the subject has not received one, MSK personnel must provide a Notice of Privacy Practices and obtain acknowledgment before the subject participates in the study.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB as soon as possible but no later than 5 calendar days. The IRB requires a Clinical Research Database (CRDB) AE report to be delivered

to the Institutional SAE Manager (307 East 63rd Street, 1st Floor) containing the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

18.0 INFORMED CONSENT PROCEDURES

Attending surgeons of the Gynecology Service will be qualified to consent patients for this protocol. The patients who are considered eligible for this study will be offered this protocol at the time they are being counseled for surgery. Those patients that agree to participate in our study will sign three copies of the consent. One copy will be given to the patient, one copy will be placed in the patient's medical record and the third copy will be placed in the research file. The informed consent procedure will be conducted in accordance with our institutional policy and National guidelines.

18.1 Research Authorization

Procedures for obtaining Research Authorization: Before any protocol-specific procedures are carried out, investigators and/or designated staff will fully explain the

details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization component of the informed consent form. The Research Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

19.0 REFERENCE(S)

References

1. Guillem JG, Wood WC, Moley JF et al. ASCO/SSO review of current role of risk-reducing surgery in common hereditary cancer syndromes. 2006 J Clin Oncol 24: 4642-60.
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4. Powell CB et al. Risk-reducing salpingo-oophorectomy in BRCA Mutation Carriers: Role of Serial Sectioning in the Detection of Occult Malignancy. 2005 J Clin Oncol 23:127-132.
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6. Gerritzen LHM, Grefte JMM, Hoogerbrugge N, et al. A substantial part of the fallopian tube is left after standard prophylactic bilateral salpingo-oophorectomy. 2006 International Journal of Gynecologic Cancer 16: 1940-1944.