Prospective Evaluation of Lymph Node Metastasis at the time of Surgical Staging for High Risk Endometrial Cancer

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1.0 Objectives

1.1 Primary Objective:

1.1.1 To estimate the false negative rate of PET/CT and/or sentinel lymph node mapping in the detection of positive lymph nodes in women with high risk endometrial cancers.

1.2 Secondary Objectives:

1.2.1 To estimate the sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT and/or sentinel lymph node mapping in the detection of positive lymph nodes in women with high risk endometrial cancer.

1.2.2 To determine if a molecular panel of estrogen-induced genes that we have previously identified from retrospective studies correlate with extra-uterine spread including lymph node metastasis at the time of surgical staging for endometrial cancer.

1.2.3 To prospectively identify patterns of lymphatic spread of endometrial cancer.

1.2.4 To correlate CA-125 and HE4 levels with disease metastasis at the time of surgical staging and to explore the use of other serum biomarkers to predict recurrence

1.2.5 To prospectively collect morbidity and mortality data related to performing lymph node dissection including intra-operative and postoperative complications.

1.2.6 To determine whether metabolic parameters of the primary endometrial tumor on PET including tumor intensity (maximum SUV and peak SUV), metabolic tumor volume (obtained at a threshold of 40% of maximum and at a threshold of SUV=3), and total lesion glycolysis (expressed average SUV over the metabolic tumor volume) are predictive of locoregional or metastatic spread, and whether these parameters correlate with CA-125 and HE4 levels

2.0 Background

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) adopted a surgically based staging system for endometrial cancer[1]. This paradigm shift from clinical to surgical staging was based on prospective studies conducted by the Gynecologic Oncology Group (GOG)

demonstrating a relationship between prognosis and surgically determined risk factors[2]. Surgical management of endometrial cancer typically includes exploratory laparotomy, pelvic washings, hysterectomy, bilateral salpingo-oophorectomy, selective biopsies of suspicious areas, and lymph node sampling in patients at risk for extra-uterine disease. Complete surgical staging is not only prognostic but also facilitates targeted therapy to maximize survival while minimizing morbidity by reducing both under- and over-treatment. Unfortunately, patients with endometrial cancer are often poor surgical candidates due to obesity, diabetes, and hypertension which are common risk factors for this disease.

A complete staging procedure for all women with endometrial cancer including lymphadenectomy continues to remain controversial. According to GOG 33, the overall risk of lymph node metastasis in women with clinical stage I or occult stage II disease was 11% [2]. More recent data from the Mayo Clinic identified a subset of women with endometrial cancer who are at "low risk" for lymph node spread. In their study, women with a grade 1 or 2 endometrioid adenocarcinoma with less than 50% myometrial invasion and a tumor size of less than 2 cm in size on intra-operative frozen section had no risk of lymph node involvement. In their patient population 27% of all women with endometrial cancer (all histologies) met these criteria and did not require surgical staging. Of those with endometrioid tumors, 33% of patients met these criteria. The conclusion from these studies was that "low risk" patients could safely be treated with total hysterectomy and bilateral salpingo-oophorectomy alone [3].

In larger, multi-institutional studies, including GOG 33, the risk of lymph node involvement was been based on final tumor histology and depth of myometrial invasion. These data, however, are not available to the surgeon until the operation has been completed and the pathologist has carefully evaluated the surgical specimens. As a proxy for these, a multitude of pre-operative techniques including endometrial biopsy, trans-vaginal ultrasound, CT scan, and pre-operative CA125 have been evaluated and shown to be ineffective in predicting extra-uterine spread or lymph node metastasis [4-6]. While many current algorithms, including the algorithm used at the Mayo Clinic, base the decision for complete surgical staging on intra-operative frozen section, this is not universally available and is not always reliable [7]. In addition, the reproducibility of the diagnosis of endometrial cancer and endometrial hyperplasia among gynecologic pathologists is not always accurate [8].

For the above reasons, the gynecologic oncologists at Mayo Clinic recently re-evaluated the staging algorithm for endometrial cancer. After careful review of their consecutive endometrial cancer

cases over a thirteen year period (1984-1996), they have developed the following algorithm.

Mayo Surgical Guidelines for the treatment of endometrial cancer

Treatment includes hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, bilateral pelvic and paraaortic lymphadenectomy (up to the renal vessels).

The lymphadenectomy can be omitted if:

- All of the following: no myometrial invasion, endometrioid histology, grade 1 or 2, no evidence of tumor outside the corpus (independent of tumor grade or tumor diameter).
- All of the following: endometrioid histology, grade 1 or 2, less than 50% myometrial invasion, tumor diameter less than or equal to 2 cm, and no evidence of tumor outside the corpus.
- Endometrioid histology (grade 3) with no myometrial invasion, tumor diameter less than or equal to 2 cm, and no evidence of gross tumor outside the uterus.

If non- endometriod histology (serous, clear cell) add complete omentectomy, appendectomy, and peritoneal biopsies.

The ultimate goal of this research is to determine if either PET/CT and or sentinel lymph node mapping can better predict which patients are at high risk for lymph node metastasis and would therefore benefit from the full staging procedure. PET/CT would allow us to pre-operatively assess risk for lymph node involvement and therefore eliminate any uncertainty at the time of frozen section. Sentinel lymph node mapping could potentially help identify patients that need adjuvant therapy without putting patients with limited risk through a full staging procedure.

In addition, as a secondary endpoint we will evaluate a panel of molecular markers performed on a pre-operative tissue samples to determine if they correlate with final pathology. This would be a second model to assist in the decision to perform a complete surgical staging on women diagnosed with endometrial cancer. The clinical benefit of identifying women, who are at high risk for advanced disease preoperatively, could significantly decrease the number of patients who require a complete surgical staging and therefore limit the morbidity and mortality of such a procedure without compromising overall care. All of these modalities, including PET/CT, lymphatic mapping and a molecular panel could help standardize the current practices among gynecologic oncologist in both the university setting and the community where frozen section may not be available.

3.0 Patient Eligibility and Exclusions

3.1 Inclusion Criteria:

3.1.1 Histologically confirmed high grade endometrial cancer including grade 3 endometrioid, serous, clear cell, MMMT or any mixed tumor containing one of these cell types

3.1.2 Patients with a grade 1/2 tumors and evidence of deep myometrial invasion or cervical involvement on preoperative imaging or physical exam

3.1.3 Candidate for surgery.

3.1.4 No evidence of peritoneal disease on preoperative imaging

3.1.5 Negative pregnancy test if of child-bearing age

3.1.6 No preoperative treatment for endometrial cancer including radiation or chemotherapy

3.1.7 Previous hormonal therapy is allowed

3.2 Exclusion Criteria:

3.2.1 Medical co-morbidities making surgery unsafe, as determined by the primary treating physician

3.2.2 Any contraindications to PET/CT or lymph node mapping (inability to control serum glucose to a value of </= 200 mg/dl for FDG-PET/CT)

3.2.3 Does not meet histologic criteria

3.2.4 Evidence of peritoneal or distant metastasis on preoperative imaging

3.2.5 Baseline creatinine (necessary for imaging studies)

4.0 Research Plan/Methods

4.1 **Patient Identification**

All patients with a preoperative diagnosis of endometrial cancer, confirmed on the pathology report that meet the above eligibility criteria will be asked to participate in this study. They will be approached prior to surgery by the research nurse, study coordinator, or primary treating physician. If they agree to participate in the study and informed consent is obtained, patients will undergo a pre-operative evaluation by their primary physician to include. We will enroll up to 150 patients in order to accrue 100 evaluable patients. Patients will be considered evaluable if they have an attempt at sentinel lymph node mapping (i.e. cervical injection) and a full lymphadenectomy.

- Pre-operative informed consent

- Pre-operative laboratory assessment including CBC, electrolytes, bun, cr, CA125 and future research testing (as outlined in objective 1.2.4). Samples to be collected through this protocol or through the GYN Tumor Bank Protocol.
- Pre-operative CXR
- Pre-operative MRI or CT scan as per the primary surgeon
- Histologic confirmation of the pre-operative biopsy

4.2 Treatment Plan

If the patient is deemed eligible for the study, the following tests and procedures will take place:

- PET/CT (see details 5.0) prior to surgery
- Surgical approach as determined by the primary surgeon
- At the time of surgery, intra-operative lymphatic mapping with blue dye, radioactive colloid, or indocyanine green will be performed. Including a superficial and deep cervical injection at 3 and 9 o'clock will be performed.
- If peritoneal disease or other contraindications to IOLM are detected at the time of surgery, mapping and lymphadenectomy will be performed at the discretion of the surgeon.
- Sentinel lymph nodes will be removed and labeled as blue, green, and/or hot. These nodes will be processed separately.
- Full Lymphadenectomy will then be performed and labeled as follows:
    a. External iliac nodes– right and left
    b. Obturator nodes – right and left
    c. Common iliac nodes – right and left
    d. Paraaortic nodes – below IMA
    e. Paraaortic nodes – above IMA

The final pathologic findings in the lymph nodes will be compared to both the pre-operative PET/CT results as well as the pathologic results of the sentinel lymph nodes.

5.0 PET/CT Performance and Interpretation

Presurgical positron emission tomography scanning with integrated computed tomography (PET/CT) will be performed using ^{18}F-fluorodeoxyglucose (FDG) per standard clinical protocol. Patients will fast for at least 6 hours prior to injection with radiotracer, and the serum blood

glucose will be measured at the time of injection and confirmed to be ≤200 mg/dl. Following radiotracer injection, patients will rest quietly for at least 60 minutes to allow for radiotracer distribution and localization. PET/CT scanning will then be performed, typically from the level of the orbits to the proximal thighs, although the precise scan extent may vary based on individual patient parameters. PET acquisition parameters are based on body mass index, and CT will be performed using tube current modulation for dose reduction purposes.

FDG-PET/CT scans will be interpreted clinically. Subsequently, PET/CT data will be reviewed by two experienced Nuclear Medicine physicians, who will be blinded to the results of surgery. Readers will denote the presence or absence of nodal hypermetabolism in the pelvis and retroperitoneum (using the same anatomic definitions described in the Treatment Plan below), with a confidence scale of 1-4 for each site: 1=no disease, 2=suspected no disease, 3=suspected disease, 4=definite disease. Discordancy in interpretation between the readers will be resolved by consensus. Any visible nodes on PET/CT will be assessed as to their bidimensional measurements and intensity (using maximum Standardized Uptake Value, SUV).

For the primary endometrial tumor, separate analysis of the PET/CT data will be performed. Parameters measured will include tumor intensity (maximum SUV and peak SUV), metabolic tumor volume (obtained at a threshold of 40% of maximum and at a threshold of SUV=3), and total lesion glycolysis (expressed average SUV over the metabolic tumor volume). Tumors will be categorized as being confined to the uterus, abutting the uterine serosa, or extending beyond the myometrium. Additional findings such as parametrial invasion, hydronephrosis, etc. will be noted, if present.

6.0 **Sentinel Lymph Node Mapping**

6.1 Agents for Sentinel Lymph Node Mapping

The three agents used in this protocol (lymphazurin, technetium-99 radiocolloid, and indocyanine green) are all FDA-approved for intradermal injection. There will be no direct mixing of any agents. All open, laproscopic, or robotic cases will use Blue Dye (Isosulfan or Methylene) and/or Green dye (Indocyanine) and/or Technetium99 for Lymphatic Mapping.

One percent isosulfan blue (Lymphazurin; U.S. Surgical Corporation, Norwalk, CT) is a patent blue dye that is used in lymphatic mapping. Its use is standard-of-care for lymphatic mapping in patients with breast cancer and melanoma and has been used in protocols mapping essentially all solid tumors.

Methylene Blue, USP is a sterile solution of methylene blue (methylene blue injection) in water for injection suitable for parenteral administration. It is also used as a dye or staining agent to make certain body fluids and tissues easier to view during surgery or on an x-ray or other diagnostic exam.

Technetium-99 radiocolloid is a gamma-emitting isotope with a short half-life (6 hours). Its use is standard-of-care for lymphatic mapping in patients with breast cancer and melanoma and has been used in protocols mapping essentially all solid tumors.

Indocyanine green (ICG, IC-Green) is a water soluble, tricarbocyanine dye which has a half-life of 180 seconds. Once injected, ICG takes 1 to 10 minutes to transfer to the sentinel lymph node. ICG can be detected using near-infrared guidance. This agent has been utilized in sentinel lymph node mapping studies for multiple solid tumors including breast, gastric, colorectal, anal, and skin cancer. The robotic platform has a fluorescence imaging application ("Firefly") for use in partial nephrectomy that is now being explored for sentinel node detection.

6.2 Injection of Agents

· The patient must be positioned, prepped and draped so that a speculum examination can be performed during the procedure.

· The patient will be injected with 2.0 mCi to 2.5 mCi of radiolabeled Tc-99 sulfur microcolloid in four divided doses into the cervix at 3 o'clock and 9 o'clock positions, superficial and deep, within one hour of the lymph node dissection.

· The injection of isosulfan or methylene blue is performed after the abdomen is entered, explored, and the surgeon is ready to perform the sentinel lymph node biopsy.

· Clamps should not be placed on the uterus that might interfere in any way with distribution of the dye.

- After the abdomen has been entered, a speculum will be placed into the vagina and 3 ml of 1% isosulfan or methylene blue (Lymphazurin; U.S. Surgical Corporation, Norwalk, CT) will be injected into the cervix at 3 o'clock and 9 o'clock positions, superficial and deep. Use the approximate sites injected with the radionuclide.
- Allow approximately 5 minutes for the blue dye to reach the sentinel nodes.

- A tenaculum may be used to manipulate the cervix while injecting blue dye.
- Avoid spillage of blue dye into the vagina by using a narrow gauge needle (21-25 gauge) under low pressure. A needle extender, spinal needle, or control grip syringe may be used if needed.
- For minimally invasive surgery, the uterine manipulator can be placed after this injection.

6.3 Identification of Sentinel Nodes

- When using the Tc-99 sulfur microcolloid, the hand-held or laparoscopic gamma counter should be used. Cover the gamma counter with a sterile sleeve. While waiting for distribution of blue dye, the hand held gamma counter can be used to identify "hot" nodes. The gamma probe should be fitted with a collimator if available. If using the ICG, the Firefly fluorescence imaging system for the robotic system should be utilized.
- Incise the peritoneum lateral to the infundibulopelvic ligament and bluntly explore the retroperitoneum with care so that the afferent lymphatic channels are not transected. The afferent lymphatic channel is commonly seen adjacent to the uterine artery near the site where it passes over the ureter.
- All blue nodes (lymphazurin) or green nodes (ICG) are to be considered sentinel. If a blue/green channel leads directly to a lymph node but the lymph node itself is not blue/green, it should still be considered sentinel.
- When using Tc-99, the "hottest" lymph node in situ will be considered a sentinel node. The probe counts for the first lymph node in situ must be at least twice the background count in the pelvis to be considered a sentinel node.
- The background counts in the pelvis are determined by holding the gamma counter over the sacrum pointed away from the cervix.
- Following removal of the sentinel node, it should be separated from extraneous material or other non-sentinel nodes and moved off the surgical field. The gamma counter is used to determine if the node is "hot".
- Subsequent "hot" nodes must be at least 10% of the "hottest" node ex vivo to be considered an additional sentinel node. If using ICG, all green nodes may be considered sentinel nodes.
- If two sentinel nodes are adjacent to each other they should be separated and labeled as separate specimens.

- Following completion of the lymphadenectomy as described above, the operative field is inspected with the gamma probe to see if there are any remaining "hot" or blue/green nodes.
- The half-life of the radionucleotide is much longer than the blue or green dye and therefore is more likely to be transported to second echelon lymph nodes. For this reason there may be more "hot" nodes than "blue" or "green"nodes. The sentinel node usually retains higher counts than second echelon nodes, however this may be difficult to distinguish intraoperatively. Therefore, all "hot" nodes that are at least 10% of the "hottest" node in ex vivo counts, should be submitted as sentinel.

6.4 Labeling Sentinel Node Specimens

- Careful description of sentinel nodes in the operating room is vital part of this study. Pathologists will enter all these data into the pathology report. The amount of radioactivity will be entered in terms of counts per second. This will allow determination of the most radioactive nodes in an individual and will not be used for comparison between patients.
- A sentinel node that is blue but not hot will be labeled "blue sentinel node".
- A sentinel node that is hot but not blue will be labeled "hot sentinel node".
- A sentinel node that is both blue and hot will be labeled "blue/hot sentinel node".
- A sentinel node that is green will be labeled "green sentinel node".
- Sentinel nodes should be labeled by location using the following categories and definitions:
    - Para-aortic: Sentinel nodes between the origin of the inferior mesenteric artery and bifurcation of the aorta. In addition, these nodes will be labeled right, left, or inter-aortic (between the inferior vena cava and aorta). Retroaortic or retrocaval locations are also acceptable for labeling the nodes resected from behind these vessels.
    - Common iliac: Sentinel nodes between the bifurcation of the aorta and bifurcation of the common iliac artery. Sentinel nodes will be labeled "right" or "left". Retroiliac nodes can be specified if appropriate.
    - External iliac: Any sentinel node in contact with the external iliac vein or artery. Sentinel nodes will be labeled "right" or "left".
    - Obturator: Any sentinel node that is apparent after the obturator space is opened and is in close proximity to the obturator nerve. Sentinel nodes will be labeled "right" or "left".

6.5 Sentinel Lymph Node Surgical Pathology

Sentinel nodes will be classified according to a modification of the AJCC staging for axillary nodes from breast cancer as follows: 1) metastases present – tumor greater than 2.0 mm in diameter; 2) micrometastases present – tumor cell aggregates between 0.2 and 2.0 mm in diameter; 3) isolated tumor cells – individual tumor cells or aggregates that are less than 0.2 mm in diameter, usually detected by immunohistochemistry; or 4) tumor absent – no tumor cells identified in H&E (or immunohistochemically, if applicable) stained sections. Non-sentinel lymph nodes will simply be reported as positive or negative for metastases based upon routine sectioning and examination of a single H&E stained section.

Most SLN's are small enough (0.5 cm maximum dimension) to permit bisection into two halves about 3 mm thick. The node should be cut from hilum to periphery if possible.

If the SLN is larger than 0.5 cm, the node should be sectioned at 2-mm intervals in a "bread loaf" fashion.

One section for H&E should be obtained from each paraffin block. A second unstained section is cut, which is to be used for IHC if all H&Es are negative.

IHC using a pan-cytokeratin stain should be performed on the sentinel nodes in all cases in which there is no evidence of metastasis on the H and E.

7.0 Estrogen Induced Genes

Previously, we identified a cadre of genes with strong expression induced by estrogen in the human endometrium[10]. Briefly, in collaboration with Wyeth Research, baseline and 3 month post-treatment endometrial biopsies were obtained from women enrolled in a large clinical trial of hormone replacement therapy. Microarray analyses were performed on pooled samples, and qRT-PCR was used to verify microarray results. We focused on genes in pathways which are important for growth regulation in the uterus as well as one novel gene of unknown function (EIG121). As estrogen exposure has been epidemiologically linked to early stage EC, we hypothesized estrogen-induced genes could be used as markers to predict final stage and recurrence. Using the results for all 72 tumors, we performed an unsupervised cluster analysis using the 6 genes. This analysis resulted in a definitive two group cluster with an agglomerative coefficient of 0.79. Thirteen of the patients had tumor recurrence by 2 years post-hysterectomy. Ten of these patients segregated to cluster 1, including 2 patients with grade 1 endometrioid tumors. Interestingly, the cluster with

low expression of the estrogen-induced genes had a recurrence rate 4.35 times that of cluster with high expression (p=0.02)[10].

We plan to asses this panel of genes in the tumors obtained on pre-operative tissue samples to determine if the findings will correlate with risk of recurrence from endometrial cancer. Any residual blood and tissue will be banked in the Gynecologic Tissue Bank. Further, we will determine if this panel can be utilized to determine presence of lymph node metastasis and would therefore benefit from the full staging procedure. The performance of the panel will be compared to results from sentinel lymph node mapping to potentially help identify patients that need adjuvant therapy without putting patients with limited risk through a full staging procedure. Ultimately, we hope to standardize the care of endometrial cancer for gynecologic oncologists in both the university setting and the community where frozen section may not be available.

8.0 **Statistical Considerations**

The primary outcome for this study is the false negative rate of PET/CT and/or sentinel lymph node mapping for detecting positive lymph nodes in women with high risk of endometrial cancers as compared with pathological findings as the gold standard.

We will also estimate the concordance, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each method (PET/CT and sentinel lymph node mapping), as well as the combination of the 2 methods.

Futility Monitoring

We will enroll 100 evaluable patients. We will monitor the false negative rate for the sentinel lymph node mapping procedure using the method described by Thall et al. [9], and we will stop using the sentinel lymph node mapping procedure if we have reason to believe that the false negative rate for this procedure is more than 10%. However, we will continue to use the PET/CT procedure for detecting positive lymph nodes for all patients.

We will monitor the false negative rate only for those patients with positive lymph nodes. We expect about 25% of patients will have positive lymph nodes, and we expect the false negative rate to be at most 10%, therefore, we expect about 70 patients will test negative for positive lymph nodes.

Formally, we will assume a uniform prior distribution for the false negative rate, and we will stop using the sentinel lymph node mapping procedure if Pr(false negative rate > 10% | data) > 0.95. That is, if there is more than a 95% chance that the false negative rate is more than 10% we will stop using the sentinel lymph node mapping procedure. We will evaluate the monitoring rule after each cohort of 5 patients with positive lymph nodes. This decision rule gives the following stopping rule.

Stop using the sentinel lymph node mapping procedure if

[# of patients with false negative finding] / [# of patients with positive lymph nodes]

≥ 2/5, 3/10, 4/15, 5/20, 5/25, 6/30, 7/35.

The operating characteristics of this stopping rule are shown in the table below and are based on 1,000 simulations.

Table 1. Operating Characteristics of Futility Stopping Rule

False Negative Rate	Probability of Stopping Early	Sample Size P_{25}	Sample Size P_{50}	Sample Size P_{75}
25.0%	0.701	5	10	25
20.0%	0.530	5	20	25
15.0%	0.314	15	25	25
10.0%	0.139	25	25	25
5.0%	0.032	25	25	25

Sample Size

If we complete the study with 1 false negative with the sentinel lymph node mapping procedure among 25 patients with positive lymph nodes, then a 90% credible interval for the false negative rate for that procedure will be 1.4% to 13.8%.

With a sample size of 100 evaluable patients we will be able to estimate the concordance between either of the 2 procedures, or the combination of the 2 procedures, and pathologic findings with a 95% confidence bound of at most 10%. We expect approximately 25% of patients will be found to have positive lymph nodes. The table below illustrates a possible study outcome with an 8% false negative rate with 25% of patients with positive lymph nodes.

Table 2. 100 Patients, 25% Lymph Node Positive, 10% False Negative

		Lymph Nodes		Total
		Negative	Positive	
Test	Positive	7	23	30
	Negative	68	2	70
	Total	75	25	100

For the study outcome illustrated in Table 2 we would have the following results:

Sensitivity = 92% (95% CI 72% - 99%),

Specificity = 91% (95% CI 81% - 96%),

PPV = 77% (95% CI 57% - 89%),

NPV = 97% (95% CI 89% - 99%).

Analysis

We will use descriptive statistics to summarize demographic and clinical characteristics of patients.

Once the trial is complete we will estimate the false negative rate for each procedure (PET/CT, sentinel lymph node mapping) and for the combination of the 2 procedures with 90% credible intervals. We will also report the posterior probability that the false negative rate is > 10% for each procedure and for the combination of the 2 procedures.

We will also estimate with 95% confidence intervals the concordance, sensitivity, specificity, PPV, and NPV for each procedure and for the combination of the 2 procedures using pathologic findings as the gold standard.

We will use logistic regression methods to model the logit of the probability of metastatic disease at the time of surgical staging as a function of CA-125 level, HE4 level, and other metabolic parameters including tumor intensity, metabolic tumor volume, and total lesion glycolysis. And we will estimate the odds ratio of the association between these factors and metastatic disease with a 95% confidence interval. We will similarly model the logit of the probability of locoregional spread as a function of these factors. We will also estimate the correlations among these factors.

We will tabulate morbidity and mortality data, including intra-operative and post-operative complications.

9.0 Data Confidentiality

The data will be collected from medical records. Study data will be collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at MD Anderson. [10] REDCap (www.project-redcap.org) is a secure, web-based application with controlled access designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless downloads to common statistical packages; and 4) procedures for importing data from external sources. In the case of multi-center studies REDCap uses Data Access Groups (DAGs) to ensure that personnel at each institution are blinded to the data from other institutions. REDCap (https://redcap.mdanderson.org) is hosted on a secure server by MD Anderson Cancer Center's Department of Research Information Systems & Technology Services. REDCap has undergone a Governance Risk & Compliance Assessment (05/14/14) by MD Anderson's Information Security Office and found to be compliant with HIPAA, Texas Administrative Codes 202-203, University of Texas Policy 165, federal regulations outlined in 21CFR Part 11, and UTMDACC Institutional Policy #ADM0335. Those having access to the data file include the study PI and research team personnel. All protected health information (PHI) will be removed from the data when it is exported from REDCap for analysis. Information will be reported at a group level. All dates for a given patient will be shifted by a randomly generated number between 0 and 364, thus preserving the distance between dates. Dates for each patient will be shifted by a different randomly generated number.

Informed consent is to be obtained by Principal Investigator or Primary Care Provider.

10.0 References

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