Award Number: W81XWH-05-2-0065

TITLE: Gynecologic Cancer Center for Racial Disparities

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REPORT DATE: August 2008

TYPE OF REPORT: Annual Addendum

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
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There are significant health-related disparities in outcome among women in the U.S. with different types of gynecologic cancer. HYPOTHESIS: Poor outcome among minorities with gynecologic cancer exists because of biological differences in tumors related to race and ethnicity; cultural, social and psychological barriers to accessing care; less than optimal screening services and prevention strategies, and unequal provision of quality health care and tailored therapeutics. SPECIFIC AIMS: 1: An analysis of the genomic and proteomic expression of gynecologic cancers will be undertaken to determine if there are molecular differences that partially account for the poor outcome among minority patients with gynecologic cancer. This analysis will be expanded in future years to include larger under-served cohorts and comprehensive epidemiological data that will facilitate more detailed genetic and epigenetic analysis. 2: Epidemiological surveys will be used to identify demographic and behavioral differences that lead to poor outcome. We will preliminarily evaluate the use of psychosocial intervention on decreasing morbidity among minorities. 3: Development of Vaccine strategies and specific antibody reagents for the detection of unique targets that are differentially expressed between the African Americans and Caucasians with endometrial cancer. SIGNIFICANCE The incidence, severity, and overall burden of cancer in the U.S. vary by race, ethnicity or other demographic features. This project will focus on identifying the reasons underlying poor outcome among minority groups with gynecologic malignancy so that education, screening, prevention and treatment algorithms can be tailored to high risk populations in an effort to have the greatest impact on reducing morbidity and mortality among the underserved.
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INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The GCC program project is a collaborative effort between Ohio State University Cancer Center and Walter Reed Army Medical Center with programmatic oversight provided by the Telemedicine and Advanced Technology Research Center of the United States Army Medical Research and Material Command. Improved gynecologic health, particularly among the female active duty population and minority groups, is critically important for the maintenance of readiness among a military force that is composed of an expanding female and minority component. The Gynecologic Cancer Center is a partnership between Walter Reed Army Medical Center and the Department of Defense with Ohio State University Cancer Center to provide optimal unbiased care to gynecologic cancer patients and improve our understanding of racial disparities in outcome that exist for gynecologic cancer. The purpose of the Gynecologic Cancer Center is to identify the etiology of racial disparities in gynecologic cancer incidence and outcome. Tumors and data collected from consenting female military health care beneficiaries are being forwarded to a central data and tissue repository at Walter Reed Army Medical Center. A separate tissue and data acquisition process is being performed for non-DOD beneficiaries at OSU. The information and collected from both types of healthcare systems allows investigators to measure the incidence and prevalence of gynecologic cancer within different racial and ethnic groups and to identify risk factors that may be associated with racial disparities in outcome. Tissues collected within the military and civilian healthcare systems are being analyzed using high throughput molecular analysis (i.e. tissue and oligonucleotide microarray, proteomics, comparative genomic hybridization, etc) to characterize genetic variation and identify molecular profiles and biomarkers that may be associated with poor outcome in specific racial or ethnic groups. In addition, we are investigating the epidemiologic barriers to care and treatment inequalities that can lead to racial disparities in survival as well as quality of life for minority patients with gynecologic cancer. Using the information obtained from our initial activities, we will implement screening programs for racial and ethnic groups that are at high risk for each type of gynecologic cancer and well as develop novel chemopreventive agents and therapeutics that could be specifically targeted to the risk status of the individual. Currently, the GCC program is operational in a “no cost extension status” and the components of this annual report reflect work that is both ingoing and incomplete in nature.

BODY:

Aim I: Genetics (Morrison)

To identify disparities in genetic and proteomic profiles of minority patients and other groups with health disparities.

Project 1: Oligonucleotide microarray techniques will be used by Walter Reed investigators to analyze the genomic expression pattern of African American and Caucasian patients in an effort to identify genetic origins associated with the racial disparity in outcome that is found among African American women with endometrial cancer. These results will be complemented by both methylation specific array and genomic hybridization array of additional endometrial cancer specimens that will be performed at Ohio State University. (Months 1-12). This analysis will be extended to include similar analysis of ovarian and cervix cancer in the future (Months 8-48).

- Oligonucleotide Array Analysis: To date, we have completed LCM dissection of 50 pairs of African American and Caucasian patients with endometrial cancer matched for tumor stage, grade and histology. These sample sets were provided by collaborators at Sloan Kettering Memorial Hospital and Duke University.
  - Last year, our group completed oligonucleotide microarray analysis using Affymetrix 133 A+B on a test set of 23 matched pairs (Race Set I) as well as a Affymetrix U133plus2.0 on a validation set of 26 pairs (Race Set II). Over the past 12 months, we have evaluated these data independently as well as in combination. In the unsupervised analysis of Race Set I, we found clustering according to African
American and Caucasian status for both early stage and Advanced stage endometrial cancer (Figure 1A and 2A). Supervised analysis

**Figure 1:** top: Unsupervised analysis of gene expression in stage I endometrial cancers from African American and Caucasian women with tumors matched by stage, grade and histology. bottom, quantitative PCR validation of select transcripts differentially expressed on microarray

PSPH was overexpressed in endometrial cancers from Black women compared to normal endometrium from Blacks as well as cancers and normal endometrium from White women. The array data for PSPH also indicated that this gene was the most differentially expressed in our microarray study, being expressed more than 9 fold higher on average in the published study and more than 6 fold in the study of North Carolina samples. However, the real-time PCR data for PSPH gene did not show results consistent with the microarray data (Figure 2). We examined the Affymetrix probes designed to detect PSPH in more detail and found they also could detect the related phosphoserine phosphatase like (PSPHL) gene, perhaps explaining our finding. The two genes share extensive homology in the first coding exon but subsequently diverge. Only 2 deposited mRNAs exist for PSPHL and the locus was only recently recognized as distinct from
PSPH despite the fact that PSPH is located on chromosome 7P and PSPHL on 7Q. We subsequently have examined the shorter isoform of PSPHL on a limited set of endometrial cancers using a real-time PCR assay specific for this isoform (Figure 3). This preliminary data suggests that PSPHL and not PSPH is the racially differentially expressed gene identified in our 2 microarray findings.

Figure 3: Real time PCR gene expression analysis of the PSPHL gene in endometrial Cancers. A. Weighted Averages for Caucasians(C) and African American (AA) endometrial Cancers. B. Real-time PCR values for individual cancers and normal endometrial epithelial samples.

A.

B.

We have confirmed by RT-PCR and sequencing analysis that at least two isoforms of PSPHL are expressed in some endometrial cancers. These forms differ by alternative splicing. These forms are predicted to encode peptides of 72 or 91 amino acids. Examination of the gene databases suggest that a third form is likely based on an additional Pan troglodytes isoform represented by multiple deposited mRNAs. Examination of these other forms in normal and malignant tissues is warranted.

The second set of gene expression data from 27 matched pairs (Race Set II) was similarly analyzed in order to further confirm global differences in gene expression between Blacks and Whites. In this experiment, specimens were microdissected using laser capture microscopy prior to double round amplification and analysis using oligonucleotide array. In addition, we chose to use Affymetrix U133 plus 2 chips since our other experiments with endometrial cancer had transitioned to this new chip system. In the second analysis, only 30 genes were found to be differentially expressed at p<0.001, a finding that could occur by chance (p=0.58). The six transcripts (i.e. GBP5, NARG1, PSPHL, IGFR1, and MUC20) validated using quantitative PCR in the test set of matched pairs (Figure 2A and 2B), were not observed as having differential expression according to racial designation in the validation set of array that were performed. Although we did not validate global differences in gene expression in the second set of 27 matched pairs, we did identify 14 genes that were differentially expressed in both comparisons at p<0.001. In an effort to determine if perhaps differences in methodology lead to different results, we processed “Race Set II” using gross dissection techniques (instead of LCM) as well as the Affymetrix U133A plus B GeneChip System. However, we still did not find differences in global gene expression between African American and Caucasians with endometrial cancer. In recent discussion with a genetic epidemiologist, Dr Lara Suscheston, we have begun to speculate that there may be differences in the African Americans that is part comprised Race Set II. Approximately half of the African American used in this set were collected at Memorial Sloan Kettering in New York City while the remaining samples in Race Set II as well all of the African American samples from Race Set I were collected from patients treated at Duke University in North Carolina. Dr Sucheston has pointed out that there are subgroups of African American that can be classified according to haplotypes based on mitochondrial DNA polymorphisms. Our group is currently working
with the Gynecologic Oncology Group to obtain a set of 200 African Americans and 200 Caucasians that we plan to analyze for testing 120 polymorphisms and correlate with clinical and pathologic data. Once we have identified subgroups of African Americans that are associated with poor prognosis, we will further pursue identification of global gene expression patterns that are associated with poor prognosis among African American with endometrial cancer.

To further evaluate a potential biologic difference between endometrial cancers from African Americans and Caucasians, we also have also used LC/MS-MS methods of proteomic analysis in an attempt to identify differentially expressed proteins between the two groups. This work was performed using resources from the Gynecologic Disease Program. The significance of differentially expressed proteins between two groups was studied using the Mann-Whitney rank sum test with the significance level set as \( p \) value equal or less than 0.05. Significant differentially distributed proteins were utilized in the further hierarchical cluster analysis. Eleven different methods were used to calculate distance between the samples for finding similarities between observations, and then seven different methods were used to measure the linkage. The cluster trees were verified by calculating the cophenetic correlation coefficient. (Figure 14)

These pilot data further show that there appear to not only be differentially expressed genes associated with endometrial cancers from African Americans, there also appear to be unique proteins. Better designed studies to further investigate a biological origin for racial disparities are underway.

- **CGH-Array Analysis:** We have conducted a preliminary analysis of 66 samples (17 white-early stage, 15 black-early stage, 16 white-late stage, 17 black-late stage, and 1 black-stage IIB). Fourteen samples are pending completion of aCGH. Figure 1 provides the mean log2 Tumor/Control signatures for the 4 groups under consideration. The x-axes for the plots correspond to genomic location and the y-axes correspond to the average of the log2 tumor/control values across samples. Note that differences in the average profiles exist across both stage and race. A formal test of that hypothesis will be conducted upon the collection of the final 20 log2 Tumor/Control profiles. Figure 2 contains a heatmap of the aCGH profiles for chromosome arm 17p across the 66 samples. The columns of the visualized data matrix correspond to samples arranged by race and stage. The rows correspond to the BAC assays. The visualized data is colored such that green corresponds to evidence for copy number loss and red corresponds to evidence for copy number gain.
Figure 1: Mean log2 Tumor/Control signatures for the 4 groups under consideration
While we have more formal analysis and additional samples to complete our preliminary results support that genomic changes are more associated with race than stage. This is quite surprising but illustrated in the heat map plot (Figure 2) for chromosome 17p which clearly shows changes on this chromosome arm are for the most part restricted to African American patients.

- **Methylation Specific Array:** For this experiment, we used 22 endometrial cancer samples prepared using LCM. These samples were collected from 11 African American and 11 Caucasian patients matched for
stage, histology, and grade. DMH microarray data in to identify regions/loci that were differentially methylation between AA and C. We used the Wilcoxon test to avoid any distributional assumptions.

1. Methylation data: 11 arrays in each of those two groups: African American (AA) and Caucasian (CC). Using the following four criteria, we attempted to identify methylated CpG islands that might have relevance to endometrial cancer.
   - LM Model p-value <0.05
   - Permutated p-value <0.05
   - QR75 or QR25 model p-value <0.05
   - At the promoter region (Agilent definition)

We developed a list of 120 differentially expressed CpG islands according to the first 3 criteria. Among them, 59 are in the promoter region of some genes (according to Agilent’s annotation). Several of the 59 genes that revealed differential methylation between African Americans and Caucasians have been previously described in association with cancer. As an example, PKP1 has a binding for the MYC oncogene and is overexpressed in several types of solid tumors.

PKP1

We are currently screening several endometrial cancer cell lines (i.e. AN3CA, ECC-1, HEC-1-A, Ishikawa, KLE, RL-95-2, and SK-UT-1B) to confirm that these genes are associated with endometrial cancer prior to validation of differentially expressed methylation patterns in the original sample set using COBRA.
2. Integration of methylation specific array data with oligonucleotide array data: 8 arrays were available for each group from Race Set I (see oligonucleotide array section above). The preprocessing and the probe summary were performed using RMA (Bioconductor package).

3. The 59 differentially methylated CpG islands (DM) were associated with 69 unique genes. The goal of this data integration was to find how many of those 69 genes were differentially expressed.

4. Then for each probe set of each of those 69 genes, we performed t-test to check if there was gene expression difference between two groups. We used the following criteria to find differentially expressed (DE) genes:

   1) For one particular gene, there is at least one probe set (if it has more than one corresponding probe set) with t-test p-value < 0.05
   2) For one particular gene, there is at least one probe set (if it has more than one corresponding probe set) with t-test p-value < 0.01

   Using the first criteria, we get 27 DE genes.
   Using the second criteria, we get 16 DE genes.

   They are:

   27 DE genes based on criteria 1)
   "RPS7" "MYCN" "KCNJ3" "BHLHB2" "PGRMC2" "CALN1"
   "PNPLA8" "EN2" "NUP188" "SOHLH1" "GRIN1" "ADAM8"
   "ZNF215" "PRMT8" "RNF41" "TDRD3" "OXGR1" "KLHDC1"
   "SEMA4B" "FLJ35848" "ARMCh7" "ZNF135" "CSRP2BP" "RBM39"
   "LOC440836" "RPLP2" "OBFC2B"

   16 DE genes based on criteria 2)
   "MYCN" "KCNJ3" "BHLHB2" "PGRMC2" "PNPLA8" "EN2"
   "SOHLH1" "GRIN1" "ADAM8" "PRMT8" "RNF41" "OXGR1"
   "KLHDC1" "FLJ35848" "ZNF135" "RBM39"

   The above selection was done without any multiple test correction. Those 16 DE genes may be more reliable.

Notes and comments about the results of those 16 genes.
1. As we can see that 35 out of 69 genes have more than one probe sets, and sometimes the results of different probe sets may not agree with each other.
2. It seems that the expression level of these genes are a bit low, for example, the log(expression) is below 5 or even below 4, this may be real expression, may just the background of the arrays.
3. We may claim that each gene is up or down regulated and the promoter CpG island is hypermethylated or hypomethylated based on the test results. However, we are currently screening several endometrial cancer cell lines to confirm that these genes are associated with endometrial cancer prior to validation of differentially expressed methylation patterns in the original sample set using COBRA.
Project 2: Tissue microarray analysis will be used to validate protein expression patterns suggested by the oligonucleotide array, methylation specific array and genomic hybridization array analysis of gynecologic cancers. Construction and/or analysis of tissue microarrays will be performed at Ohio State University and at Walter Reed in conjunction with the Armed Forces Institute of Pathology (Months 1-48). The focus during Months 1-12 will be on validating abnormal expression of targeted proteins associated with endometrial cancer that may explain the observed racial disparity in outcome associated with this disease.

In our last annual report, we provided data investigating racial disparities in expression of select proteins (CAV1, CAV2, IGF1, IGF2, IGFR1R, etc). Despite our best efforts, the number of African American represented on this TMA (<30), provided insufficient power to make definitive conclusions regarding racial disparities in expression once we had accounted for other potentially confounding variables. This prompted us to collaborate with the Gynecologic Oncology Group (GOG) who has agreed to construct a TMA from paraffin blocks corresponding to the frozen specimens used for our CGH array. In addition, an independent set of endometrial cancers from African American and Caucasian patients will also be represented. In total, we plan to create a TMA with endometrial cancer specimens from 200 African Americans and 200 Caucasians using tissue from the GOG 210 Endometrial Cancer Repository. We expect this TMA to be completed in 2008 and this resource should facilitate our future research.

Aim II: Epidemiology and Psychology (Anderson)
To identify social, cultural, demographic and psychological barriers for optimal care of gynecologic cancer among minority patients and other groups with health disparities

Project 1: Epidemiologic Origins of Disparities in Outcome for African Americans
Data collected from gynecologic cancer patients at Walter Reed Army Medical Center, Ohio State University and other collaborating institutions will be used to identify social, environmental, and behavioral risk factors that could partially account for the differences in outcome among minorities with gynecologic cancer (Months 1-48).

Research Accomplishments 2007-2008
After an extremely prolonged approval of the master protocol by multiple primary IRBs and 3 second level review organizations (Ft Detrick, USUHS, and CIRO), tissue and data collection is underway. Personnel involved in enrollment and data collection have optimized collection efforts and developed detailed standard operating procedures. The collection is underway but it is unlikely that we will have an adequate sample size to facilitate a conclusive analysis of data prior to the completion of this grant. However, we have obtained supplemental funding from the Stewart Trust and the Rippel Foundation and have intentions to apply for continued funding of this network within an application for a NCI Specialized Program of Research Excellence award. The network that has taken 4 years to build and we will continue to add to the collection of data as we find alternate options of funding for these investigative activities.

Project 2: Energy Balance
A pilot study focused on endometrial cancer will be performed during Months 1-12, since this is the most common gynecologic cancer type and should provide adequate data for preliminary analysis. In this study, we will analyze the association between energy balance and endometrial cancer to determine if differences in diet can partially explain the racial disparity in outcome for endometrial cancer patients. These differences in diet will also be correlated with serum levels of IGF factors and other mediators associated with obesity.
This aim was not initiated because of delays encountered in the activation of the Data and Tissue Acquisition Network that is provided by Core B (Data Acquisition) and Core C (Tissue Banking). Collection of specimens and tissues will enable future research using other sources of funding.

Project 3: Psychologic Origins or Health Disparities
A pilot study will test the effectiveness of psychosocial intervention to reduce stress, enhance coping, and prevent sexual functioning morbidity for women with gynecologic cancer. (Months 1-12). The preliminary data will be used to implement a larger intervention trial during months 13-48.

Research Accomplishments 2007-2008
Data collected from gynecologic cancer patients at Walter Reed Army Medical Center, Ohio State University and other collaborating institutions seeks to identify social, environmental, and behavioral risk factors that could partially account for the differences in outcome among minorities with gynecologic cancer (Months 1-48).
In this third year, we continued our analysis of patients collected during the first two fiscal years of the program. A description of the data was previously provided in last year’s report. We have provided references to the two published manuscripts from this study in the research outcomes section of the annual report. There will not be any continued research for this project in the no cost extension.

Aim 3: Treatment (Kaumaya)
Development of Vaccine strategies and specific antibody reagents for the detection of unique targets that are differentially expressed between the African Americans and Caucasians with endometrial cancer
This Aim was previously closed as noted in a prior annual report

Cores B and C:
The Tissue Data Acquisition Activity study involves the prospective collection and banking of biological specimens from patients undergoing surgical operation (surgical procedure or surgery) for suspected gynecologic disease. In addition, the study involves the collection of epidemiological information that will aid us in better understanding (that will assist us with increasing our understanding) and developing better treatments (promote the development of improved treatments) and services for patients with gynecologic disease. The banking of biological specimens with clinical, epidemiological, and psychosocial information from patients diagnosed with a suspected gynecologic disease, will provide researchers with an invaluable repository of information from which future gynecological disease research studies can be conducted. The network established by the partnered institutions relies on local tissue banking at the respective institutions with the forwarding of data to a centralized data warehouse.

Due to the nature of the study, whereby patients’ biological specimens and clinical data are to be collected and stored indefinitely for future genomic and proteomic research experiments that are yet to be determined, USAMRMC was extremely diligent in their review in order to ensure that patient confidentiality is protected. In addition, given the vast amounts of data that will be collected from patients and stored indefinitely for future research activities, both local IRBs and USAMRMC extensively reviewed the questionnaires that will be administered to the patients. As a result, the cumulative review time for each site’s protocol at both the local and 2nd level IRB was extremely prolonged, averaging 12 months per site, thus significantly delaying our ability to begin enrolling patients in the study.

IRB approvals both primarily and at the second level review
Walter Reed Army Medical Center: January 10, 2006
Washington Hospital Center: August 7, 2006
Windber Research Institute: February 12, 2007
Delays in the approval process of the Tissue and Data Acquisition protocol at the H. Lee Moffitt Cancer Center & Research Institute (Moffitt) were encountered, whereupon, it was ultimately decided by their leadership that our protocol competed with a pre-existent protocol. Consequently, Moffitt has decided to decline the invitation to participate as a partner in this research endeavor.

In addition to addressing the regulatory aspects of the Tissue and Data Acquisition activity, we have also had to focus on establishing the infrastructure that will support this endeavor. This has involved hiring a research nurse who has had to undergo training on the various questionnaires that will be administered to the subjects. We have also worked on creating Standard Operating Procedures (SOPs) for this complex study which involves coordinating activities with pathology (separation of tissue for diagnosis and research purposes); the United States Military Cancer Institute (processing and freezing of the specimens and maintaining the tissue bank); the GDC histopathologist (responsible for DNA, RNA, and protein extractions from tissue and serum); the research nurse (responsible for consenting, administering questionnaires, drawing blood samples, and follow-up of patients); and, the regulatory affairs coordinator (responsible for submitting protocols to the IRBs). In addition, a number of critical pieces of equipment to support this project were purchased and a Memorandum of Understanding (MOU) was also established between the GDC and USMCI that outlines specific responsibilities associated with this project. Finally, because GDC research staff will be administering the study and processing the specimens of all subjects enrolled at Washington Hospital Center (WHC), we finalized the logistical issues involved in running the study at a second site.

In order to enhance the opportunities for data and tissue collection particularly for patients with endometrial cancer, we were able to successfully acquire funding to facilitate the support of additional sites for data and tissue collection activities (i.e. Duke University, Wayne State University, and Ohio State University). The additional sites use the same standard operating procedures as are approved for the Gynecologic Disease Program. In addition, quality assurance of the questionnaires and the storage of data at the Windber Research Center are independently supported by these grants outside of GDP funded activities.

Overall, we have found that logistical hurdles at each of the sites have made (caused) the enrollment and collection of tissue and data from consented patients (to be) challenging. We are continuing to develop strategies for improving this process at each of the participating sites, particularly those that are just being activated.

To date (7/14/2008) over 400 patients have been consented for this study. The pre and post operative data has successfully been collected on almost all patients and corresponding tissue samples have been collected. The “Barriers to Care” questionnaires have been completed in approximately 100 patients. We have developed strategies to enhance completion of these modules for the upcoming year.

Data Transfer to the WRI Repository
WRI has lead several teleconferences to straighten out technical issues related to data transfer from UPCI and OSU for the GDP. WRI has specified an XML data transfer format for OSU and UPitts to send data to WRI. The three parties have agreed on the principles. Three documents have been prepared and reviewed by the three parties. Both the WRI team and InforSense team continue to work on the clinical data model development.

Research Plans for 2008-2009
Based on current operations, we expect that the following patient accrual goals will be more realistic. We have also elected to primarily focus on collection of endometrial cancer specimens in order to enhance the collection of a large set of well annotated samples that are from the same disease site.
- Walter Reed Army Medical Center: 20 patients/year
- Washington Hospital Center: 40 patients/year
- Ohio State University: 75 patients/year
- University of Pittsburgh: 100 patients/year
- Windber Research Institute: 0 patients/year (data repository)
- Duke University: 75 patients/year
- Wayne State: 75 patients/year

KEY RESEARCH ACCOMPLISHMENTS (2007-2008)

- Completed an independent as well as combined biostatistical analysis of gene expression using two samples sets (Race Set I and Race Set II).
- Repeated gene expression analysis on Race Set II using the same pre-analytical conditions and array chip that was used for Race Set I.
- Further analysis of a subset of cases from Race Set I using methylation specific arrays and initiation of validation of differentially methylated CPG islands.
- Correlation of gene expression findings with methylation specific array findings in a subset of cases in Race Set I.
- Correlation of protein expression (provided using LC/MS-MS) and gene expression in a subset of cases from Race Set II.
- Completion of CGH-array for a sample set of endometrial cancers from African American and Caucasians provided by the Gynecologic Oncology Group.

REPORTABLE OUTCOMES (2007-2008): Provide a list of reportable outcomes that have resulted from this research to include:

Manuscripts
Chemotherapy: A Combined Analysis of Gynecologic Oncology Group Clinical Trials. (Manuscript in review)

Presentations
   a. Armed Forces District of the American College of Obstetricians and Gynecologists, Portsmouth, 2008
   b. Society of Gynecologic Oncologists, Tampa, 2007

We expect that following completion of the work during the no cost extension, our group will have multiple papers and presentations to provide as deliverables for this program project.

CONCLUSIONS: Our work for this final fiscal year is continuing under a “no cost extension”. Deliverables are provided at a reduced rate given the small amount of funding that is being spent at a reduced rate to facilitate collection of tissue specimens and data. Final conclusions will be provided with the final report.

REFERENCES: List all references pertinent to the report using a standard journal format (i.e. format used in Science, Military Medicine, etc.).

APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.