

Summer 5-2019

THE USE OF NEOADJUVANT BRACHYTHERAPY IN ENDOMETRIAL CANCER

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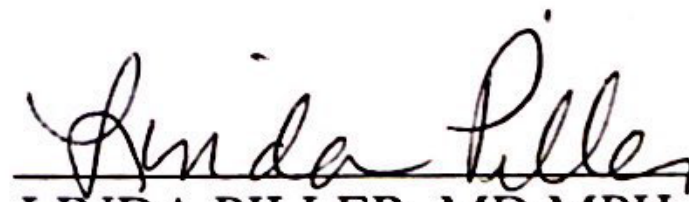
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THE USE OF NEOADJUVANT BRACHYTHERAPY IN ENDOMETRIAL CANCER

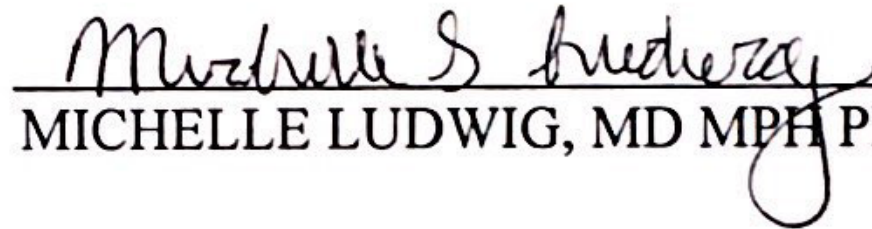
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2019

THE USE OF NEOADJUVANT BRACHYTHERAPY IN ENDOMETRIAL CANCER

by

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BS CHEMICAL ENGINEERING, Washington University in St. Louis, 2011

Presented to the Faculty of The University of Texas

School of Public Health

in Partial Fulfillment

of the Requirements

for the Degree of

MASTER OF PUBLIC HEALTH

THE UNIVERSITY OF TEXAS
SCHOOL OF PUBLIC HEALTH

Houston, Texas

May, 2019

THE USE OF NEOADJUVANT RADIATION IN ENDOMETRIAL CANCER

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Abstract

Uterine cancer is the most common gynecologic malignancy in the United States with almost 62,000 cases expected in 2019. In general, treatment consists of primary surgery possibly followed by adjuvant radiation and/or chemotherapy. However, in cases with cervical involvement or when the patient is a non-surgical candidate, neoadjuvant treatment can be employed; specifically, neoadjuvant radiation with or without brachytherapy and/or chemotherapy. There have not been any large-scale studies looking at the addition of brachytherapy to external beam radiation in the neoadjuvant setting and whether or not its addition improves outcomes.

In order to analyze this, the National Cancer Database was used to study women diagnosed with uterine cancer who were treated with neoadjuvant radiation with or without brachytherapy followed by hysterectomy. Univariate and multivariate cox regression survival analysis was done to look at overall survival (OS) between the group that received brachytherapy and the group that did not. Logistic regression was performed to analyze the association between the use of brachytherapy and negative margins upon surgical resection. Both cox regression analysis and logistic regression analysis were done for the entire cohort and for each histological subtype.

There were 1009 women treated with neoadjuvant radiation followed by external beam, the majority of whom did not receive brachytherapy (n=640, 63.4%). Women who did receive brachytherapy were more likely to be stage II ($p<0.001$), and were less likely to have been treated at a community cancer center ($p=0.045$). They were also less likely to have received a radical hysterectomy ($p=0.009$). The addition of brachytherapy was not associated with improved OS on univariate or multivariate analysis (HR=0.831, $p=0.073$; HR=0.868, $p=0.179$, respectively). This relationship remained across all histologies (all $p>0.05$). In addition, the use of brachytherapy was not associated with margin status on surgical resection in univariate or multivariate analysis (both $p>0.05$).

The addition of brachytherapy to external beam radiation in the neoadjuvant setting did not affect survival in this cohort of uterine cancer patients. However, its use was associated with decreased utilization of radical hysterectomies, which is an important clinical finding as radical hysterectomies can be much more morbid than total hysterectomies.

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BACKGROUND

Literature Review

Endometrial cancer is the most common gynecologic malignancy in the United States, and the fourth most common malignancy in women ("SEER Cancer State Facts: Uterine Cancer"). With the prevalence of major risk factors for uterine cancer increasing, including diabetes and obesity, the medical community has seen an increase in the incidence of uterine cancer, up from 40,100 patients diagnosed in 2008 to 61,880 expected in 2019 (Corzo, Barrientos Santillan, Westin, & Ramirez, 2018; Jemal et al., 2008; "Key Statistics for Endometrial Cancer" 2019).

Treatment guidelines for uterine cancer consist of multiple modalities depending on stage. The general treatment paradigm is primary surgery possibly followed by adjuvant therapy, though this is dependent on a patient's ability to undergo a surgical procedure. Adjuvant therapy can consist of external beam radiation, chemotherapy, vaginal cuff brachytherapy, or a combination of these. Patients with early-stage disease are treated with hysterectomy followed by adjuvant radiotherapy only if adverse risk factors are present (most often vaginal cuff brachytherapy). Those with later stage disease may have hysterectomies with adjuvant therapy or chemoradiation alone depending on risk factors and suitability for surgery ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms").

Locally advanced uterine cancer with cervical and/or parametrial extension comprises less than 10-15% of all endometrial cancer cases (Ahmad et al., 1989; Vargo et al., 2014). In part due to its low incidence, there is not a consensus on how to best treat these patients. The National Comprehensive Cancer Network (NCCN) details multiple approaches as

appropriate ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms"). For patients who are surgical candidates, either radical or total hysterectomy followed by adjuvant therapy or neoadjuvant (preoperative) radiation followed by total hysterectomy are suitable approaches. Oftentimes, radical hysterectomies are required for patients with cervical or parametrial involvement, as these include removal of the upper 1/3 of the vagina and parametrium in addition to the uterus and cervix. This is in contrast to a total hysterectomy, where only the uterus and cervix are removed. For those who are not able to undergo immediate surgery, either radiation or chemotherapy followed by surgery if they are rendered an operable candidate is acceptable. Neoadjuvant radiation is a category 2B recommendation by the NCCN, or based on "lower-level evidence," in part due to the lack of studies looking at its effectiveness.

Neoadjuvant (preoperative) therapy is frequently employed in patients who are obese or have other comorbidities that make a radical hysterectomy difficult, as total hysterectomies are shorter surgeries with fewer complications and risks than a radical hysterectomy (Shukla et al., 2011). Neoadjuvant radiation therapy can also be used to increase the likelihood of negative margins on surgical resection (Boisen et al., 2017). Pre-operative radiation therapy consists of external beam radiation with or without brachytherapy (or intracavitary radiation). The use of brachytherapy as an adjunct to external beam radiation has not been adequately studied. Most studies examining the use of neoadjuvant radiation have been small retrospective case series, and have included only included patients who received brachytherapy (Boisen et al., 2017; Iheagwara et al., 2019; Vargo et al., 2014). However, the NCCN states that one "could consider adding" brachytherapy to neoadjuvant

radiation ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms"), and there have been no large-scale studies showing whether or not the addition of brachytherapy improves outcomes in these patients.

This proposal is to study survival differences between patients treated with different neoadjuvant modalities for non-metastatic endometrial cancer. Specifically, this study will look at patterns of care and survival for patients treated with neoadjuvant radiation with or without brachytherapy. In addition, it will look at surgical margins and evaluate whether the use of brachytherapy improves the odds of having a negative surgical margin at time of hysterectomy.

Public Health Significance

It is still unknown as to whether or not patients who have uterine cancer being treated with neoadjuvant radiation should receive intracavitary radiotherapy. Neoadjuvant treatment is not widely utilized; however, it is used for patients with cervical involvement as well as those who are not candidates for immediate surgery. While cervical involvement of uterine cancer without occult lymph node involvement is rare, and only comprises 10-15% of all endometrial cancer cases, with approximately 62,000 uterine cancer cases total per year in the United States alone this is still a large population of women. In addition, due to the link between obesity, metabolic syndrome, and endometrial cancer, it is not uncommon for women to be ineligible for immediate surgery upon diagnosis (Shaw, Farris, McNeil, & Friedenreich, 2016). It is important to understand how to best treat this disease to improve survival for all of these women.

Hypothesis, Research Question, Specific Aims or Objectives

As cervical involvement of uterine cancer is rare, and the use of neoadjuvant radiation even rarer, the use of a national database is a reasonable approach to maximize the number of cases. The research question that this proposal aims to answer is whether the use of brachytherapy in neoadjuvant radiation improves overall survival (OS) and/or margin status. In order to do so, the patterns of care and outcomes for all patients in the NCDB who received neoadjuvant radiation will be discussed. Then, the difference between patients who received neoadjuvant brachytherapy and those who did not will be analyzed. Finally, whether the use of brachytherapy in neoadjuvant radiation has an impact on margin status will be assessed.

Objective 1: To describe the patterns of neoadjuvant radiation treatment, including sequencing with surgery and/or chemotherapy, and the use of brachytherapy, for uterine carcinomas treated with hysterectomy.

Objective 2: To assess for differences in survival between patients who received neoadjuvant external beam and those who received neoadjuvant external beam plus brachytherapy for uterine carcinoma.

Objective 3: To assess for differences in margin status for patients who received neoadjuvant external beam and those who received neoadjuvant external beam plus brachytherapy.

METHODS

Study Design

This is a retrospective study using a nationally available database, the National Cancer Database (NCDB).

Study Subjects

Women between ages 18 and 100 who were diagnosed with endometrial cancer and whose information is available in the NCDB were included. Participants were eligible for analysis if their disease characteristics were available (histology, stage), treatment characteristics were available (treatment sequence, radiation information and use of brachytherapy, chemotherapy information), and if they had available follow-up information. Participants who received neoadjuvant radiation followed by hysterectomy were analyzed. To eliminate death due to surgical complications, patients were excluded if they died within 30 days of surgery. In addition, participants with more than one cancer diagnosis, carcinoma-in-situ, or diagnosis at time of autopsy were excluded from analysis.

Data Collection

The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The NCDB collects data from more than 1,5000 Commission-accredited cancer programs in the United States and Puerto Rico, which comprises approximately 70% of all new cancer diagnosis. Data is collected at each individual accredited institution and then submitted to the NCDB using nationally standardized data items and coding definitions.

Data Analysis

All variables were decoded per NCDB guidelines, and all patients treated between 2004 and 2014 were queried for analysis. First, the database was filtered to include only patients who received neoadjuvant radiation. Patients were then deemed eligible if they had a confirmed malignant uterine carcinoma and were between the ages of 18 and 100. Patients with benign disease, in-situ disease, or sarcomas were excluded. In addition, patients with missing vital status, those who died within 30 days of surgery, or who had fewer than 30 days of follow-up were excluded.

Next, patients with stage I-III disease were included in the cohort for analysis. AJCC clinical staging was used as the analysis is looking at the effect of neoadjuvant treatment, so clinical staging was deemed the most appropriate. Clinical stage was unavailable in 186 patients, so pathologic stage was used. The cohort was then filtered to only those who were treated with both neoadjuvant radiation therapy followed by surgery as part of treatment. Specifically, all patients must have received a hysterectomy as part of their surgical management. Those with a subtotal resection or exenteration were excluded. Patients who received either neoadjuvant external beam or external beam plus brachytherapy were included, while patients receiving brachytherapy only were excluded (Figure 1).

After obtaining only subjects who fulfilled all inclusion and exclusion criteria, patients were categorized by whether or not they received brachytherapy as a part of their neoadjuvant treatment course. Demographics and disease characteristics between groups were compared. Chi-square analysis was used to compare all variables except age and tumor

size, for which independent T-test analysis was done. Survival was compared initially using Kaplan-Meier log rank tests.

Univariate cox regression survival analysis was performed to analyze variables that could significantly affect OS. Multivariate cox regression survival analysis was then completed to control for confounding variables. Variables that could be associated with both the exposure variable of interest (the use of brachytherapy) and the outcome (OS) that were not deemed to be in the causal pathway between the two were considered for inclusion in the model (Dunkler, Plischke, Leffondre, & Heinze, 2014). A backwards stepwise selection algorithm was used for the multivariate cox regression model. The variables were eligible for inclusion in the multivariate cox regression if their significance level from the univariate analysis was <0.25 . Variables continued to be eligible for the model if their significance level remained <0.05 . For categorical variables with more than two options, if any significance value for the variable was <0.05 they remained in the model. Variables with subjects per variable of less than 20 were excluded from analysis (Green, 1991). The use of brachytherapy remained in the model regardless of significance value as this was the variable of interest. In the event of co-linearity between variables in the multivariate model, the variable that is deemed to be more likely causal of the event of interest (OS) will be included.

A stratified analysis was then done for each histological sub-type to assess for innate biological differences. The histologies were broken down as follows: grade 1-2 endometrioid endometrial cancer was designated low-grade endometrioid disease, grade 3 endometrioid endometrial cancer was designated high-grade endometrioid disease, and all other histologies (serous cell, clear cell, and mixed histologies) were designated non-endometrioid histologies.

Univariate and multivariate cox regression survival analysis were performed. The same backwards stepwise algorithm was employed for each multivariate analysis with the same inclusion and exclusion significance and subject per variable criteria. Models were run separately for each analysis, allowing for different variables to be significant in each model. Another univariate and multivariate cox regression survival analysis was done for only patients with stage II disease, as these are the ones most often treated with neoadjuvant radiation.

In addition, binary univariate and multivariate logistic regression was performed to assess for whether or not neoadjuvant brachytherapy improved odds of negative margins at time of surgical resection. Only patients with known margin status were included in this analysis. The multivariate model was again built using a backwards stepwise algorithm with significance levels of <0.25 to enter the model and <0.05 required to remain in the model. In the event of co-linearity between variables in the multivariate model, the variable that is deemed to be more likely causal of the event of interest (margin status) was included. The logistic regression was also repeated after stratifying by histological subtypes, low-grade endometrioid, high-grade endometrioid, and non-endometrioid histologies.

Human Subjects Considerations

Per the University of Texas Health Science Center at Houston Committee for the Protection of Human Subjects Office, this project did not qualify as human subject research as it is a de-identified database.

JOURNAL ARTICLE

Title of Journal Article: The use of neoadjuvant brachytherapy in endometrial cancer: an NCDB analysis

Name of Journal Proposed for Article Submission: Brachytherapy

Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, and the fourth most common malignancy in women ("SEER Cancer State Facts: Uterine Cancer"). With the prevalence of major risk factors for uterine cancer increasing, including diabetes and obesity, the medical community has seen an increase in the incidence of uterine cancer, up from 40,100 patients diagnosed in 2008 to 61,880 expected in 2019 (Corzo et al., 2018; Jemal et al., 2008; "Key Statistics for Endometrial Cancer" 2019).

Treatment guidelines for uterine cancer consist of multiple modalities depending on extent of the tumor burden. Patients with early-stage disease are treated with surgery and adjuvant radiotherapy (most often vaginal cuff brachytherapy), while those with later stage disease may have hysterectomies with adjuvant therapy or chemoradiation alone ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms"). Adjuvant therapy, or treatment after primary surgery, can consist of external beam radiation, chemotherapy, brachytherapy, or a combination of these.

There are occasionally indications for neoadjuvant treatment. These include, though are not limited to; stage II disease (or uterine cancer with cervical involvement), comorbidities that make surgery difficult, or bulky disease where the surgeon is concerned

about their ability to fully remove the tumor with negative margins (Shukla et al., 2011). Pre-operative therapy can consist of radiation alone (which itself can be external beam and/or intracavitary radiation), concurrent chemoradiation, or systemic therapy alone. The use of brachytherapy as an adjunct to external beam in neoadjuvant radiation has not been adequately studied. Most studies examining the use of neoadjuvant radiation have been small retrospective series that have only included patients who received brachytherapy (Boisen et al., 2017; Iheagwara et al., 2019; Vargo et al., 2014). However, the NCCN is not clear on this issue and states that one “could consider adding” brachytherapy to neoadjuvant radiation to reduce the chance of positive margins ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms"), and there have been no large-scale studies showing whether or not the addition of brachytherapy improves outcomes in these patients.

This analysis utilized the National Cancer Database (NCDB) in order to better understand the utility of neoadjuvant brachytherapy in treating uterine cancer, and to examine whether its use increased survival or the odds of negative surgical margins. The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. It captures approximately 70% of all new cancer diagnosis in the United States, and is a hospital-based registry.

Materials/Methods:

We queried the NCDB for all women treated for uterine cancer between 2004 and 2014. First, the database was filtered to include only patients who received neoadjuvant radiation. Patients were then deemed eligible if they had a confirmed uterine carcinoma and were between the ages of 18 and 100. Patients with benign disease, in situ disease, or

sarcomas were excluded. In addition, patients with missing vital status, those who died within 30 days of surgery, or who had less than 30 days of follow-up were excluded. Next, patients with stage I-III disease were included in the cohort for analysis. AJCC clinical staging was used as we are looking at the effect of neoadjuvant treatment, so clinical staging was deemed the most appropriate. Clinical stage was unavailable in 186 patients, so pathologic stage was used. The cohort was then filtered to only those who were treated with both neoadjuvant radiation therapy followed by surgery as part of treatment. Specifically, all patients must have received a hysterectomy as part of their surgical management. Those with a subtotal resection or exenteration were excluded. Patients who received either neoadjuvant external beam or external beam plus brachytherapy were included, while patients receiving brachytherapy only were excluded (Figure 1).

Patients were separated into groups depending on whether or not they received brachytherapy as a part of their neoadjuvant treatment. Demographics and disease characteristics between groups were compared. Chi-square analysis was used to compare all variables except age and tumor size, for which independent T-test analysis was done. Univariate cox regression analysis was performed to assess for disease and treatment variables that had an effect on overall survival (OS). Multivariate cox regression was then done to control for confounding variables. A backwards stepwise algorithm was used with a significance level of <0.25 from the univariate analysis required to enter into the model, and <0.05 to stay in the model. This did not apply for the use of brachytherapy as it was the main exposure variable of interest. Univariate and multivariate analysis was repeated for each histological subtype separately in order to analyze the effect of brachytherapy on different

histologies. The histologies were broken down as follows: grade 1-2 endometrioid endometrial cancer was designated low-grade endometrioid disease, grade 3 endometrioid endometrial cancer was designated high-grade endometrioid disease, and all other histologies (serous cell, clear cell, and mixed histologies) were grouped as non-endometrioid histologies. In addition, a univariate and multivariate survival analysis was done limited to only stage II patients, as these are the patients who are most often treated with neoadjuvant radiation.

Binary logistic regression was performed to assess whether or not the use of brachytherapy or any other variable had an impact on margin status. Only patients with known margin status were included. Multivariate logistic regression was also done to control for confounding variables.

Results:

After querying the NCDB and applying all inclusion and exclusion criteria, 1009 women were eligible for analysis. Of these, 640 women received external beam radiation only for their disease, while 369 received neoadjuvant external beam and brachytherapy. Mean age was 62 years old, and the majority of patients were non-Hispanic white (n=776, 76.9%). Almost all patients were insured (n=937, 92.9%), and had good functional status with Charleson-Deyo score less than 2 (n=946, 93.8%). Median follow-up time was 62.4 months (95%CI 57.9-66.9 months) for the entire cohort.

There were considerably fewer women treated with brachytherapy at community cancer programs, with only 17% of patients treated at these facilities receiving brachytherapy (p=0.045). This is compared to comprehensive community cancer programs, academic or research programs, or integrated network cancer centers, where 34%, 39%, and 37% of their

patients received brachytherapy respectively (see Table 1). There were no differences in the percentage of women who received brachytherapy as a part of their neoadjuvant treatment across race/ethnicities, insurance status, Charlson-Deyo score, or histology. Significantly more patients with stage II disease received brachytherapy compared to those with stage I or III disease ($p<0.001$). Women were less likely to receive a modified radical or extended hysterectomy after the addition of brachytherapy to their radiation treatment ($p=0.009$). There was no difference in the percentage of women who received neoadjuvant or adjuvant chemotherapy between the external beam radiation only and external beam radiation plus brachytherapy groups (22% and 21%, respectively, $p=0.056$). However, there was a significant difference in the type of chemotherapy these women received. For women who were treated with neoadjuvant chemotherapy, those who received external beam radiation only were significantly more likely to be treated with multi-agent chemotherapy ($n=54$, 38.6%) as compared to those who received external beam radiation with brachytherapy ($n=16$, 20.8%; $p=0.001$). Median survival for patients treated with brachytherapy was 106.8 months compared to 88.6 months for those without ($p=0.073$, Figure 2).

On univariate analysis non-Hispanic black women had significantly worse OS than other race and ethnic groups (Table 2). The type of surgical procedure had no effect on OS, though residual tumor after surgical resection was associated with worse survival (HR 2.250, $p<0.001$). Stage III patients did significantly worse than stage I or II patients (HR=1.900, $p<0.001$), and high-grade endometrioid adenocarcinoma or serous, clear cell, or mixed histologies were associated worse OS than those with low-grade endometrioid carcinoma (HR=2.010, $p<0.001$; HR=2.227, $p<0.001$, respectively).

The addition of brachytherapy did not affect OS on univariate analysis (HR=0.831, $p=0.073$). The presence of any chemotherapy was significantly associated with survival in that those who received chemotherapy had worse OS than those who did not (HR=1.220, $p=0.046$). Specifically, patients who received adjuvant chemotherapy after surgery did significantly worse than other groups (HR =1.444, $p=0.015$).

To control for confounding variables, a multivariate analysis was done (Table 3). Age, Charlson-Deyo score, histology, stage, the presence of any chemotherapy, and the addition of brachytherapy were the final variables included in this model. After controlling for these variables, the addition of brachytherapy was still not associated with OS (HR=0.868, $p=0.179$). Increasing age, the presence of comorbidities, high-risk histologies (high-grade endometrioid and non-endometrioid), higher stage, and unknown status of chemotherapy delivery remained significantly associated with OS. Patients with unknown chemotherapy status did better than those who did not receive any (HR=0.367, $p=0.016$), however there was no difference between patients who received chemotherapy and those who did not (HR=1.128, $p=0.285$) after controlling for other variables. Again, patients with low-grade endometrioid cancer had significantly improved OS compared to those with high-grade endometrioid disease (HR=1.600, $p<0.001$) and non-endometrioid histologies (HR=1.801, $p<0.001$).

Sub-analyses were done across each histological subtype. The use of brachytherapy was associated with improved OS in univariate analysis in non-endometrioid histologies only (HR=0.659, $p=0.017$, Appendix A). However, this association disappeared on multivariate analysis, and brachytherapy was not associated with OS for any histology (all $p>0.05$).

Increasing age was the only variable to remain significantly associated with worse OS in each multivariate model (all $p \leq 0.001$, Appendix B). In both low- and high-grade endometrioid histologies, stage III disease was associated with worse OS (both $p < 0.05$), though stage was not a significant factor in non-endometrioid patients. Caucasian patients did better than non-Hispanic black patients with non-endometrioid histologies (HR=0.585, $p=0.005$). In the sub-analysis limited to only stage II patients, brachytherapy again did not affect OS in either univariate or multivariate analysis (Appendix C).

Binary logistic regression was done to assess for the effect of brachytherapy and other variables on margin status. The addition of brachytherapy was not associated with margin status ($p=0.237$, Table 4). However, increased stage and high-risk histologies were both associated with decreased odds of negative margins on surgical resection. On multivariate logistic regression, stage II and stage III disease remained associated with decreased odds of negative margins on resection (OR=0.284, $p=0.012$; OR=0.254, $p=0.006$, respectively). Histology was no longer associated with negative margins once stage and the use of chemotherapy were accounted for. The use of neoadjuvant chemotherapy did not alter the odds of negative margins compared to no chemotherapy (OR=0.821, $p=0.593$). After stratifying the analysis by histology, the use of brachytherapy did not affect the odds of the patient having negative margins on resection for any histology (all $p > 0.05$, Appendix D).

Discussion:

This analysis of NCDB data examined whether or not the addition of brachytherapy to neoadjuvant radiation treatment for endometrial cancer was associated with an improvement in OS. Per NCCN guidelines, neoadjuvant radiation can be employed for

uterine cancer in cases where there is gross evidence of cervical involvement (which is known as stage II disease), or when patients are not initially surgical candidates ("NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms"). There are not strict guidelines on when or how brachytherapy should be employed for neoadjuvant radiation. Some reports have detailed the practice of only adding brachytherapy when there was evidence of gross cervical disease, and otherwise have just utilized external beam radiation (Reisinger, Staros, Feld, Mohiuddin, & Lewis, 1992). Oftentimes, neoadjuvant brachytherapy is added to external beam for stage II disease in every case (Boisen et al., 2017; Iheagwara et al., 2019; Shukla et al., 2011). However, there have been no randomized trials looking at whether or not the addition of brachytherapy improves outcomes for these patients; whether they have stage II disease and have gross cervical involvement, or if they are being treated with radiation as the first-course of treatment in hopes to prepare them for surgery. This is likely due to the fact that neoadjuvant radiation is rarely utilized in endometrial cancer.

In this retrospective analysis, the addition of brachytherapy to neoadjuvant radiation for the treatment of endometrial cancer was not significantly associated with OS. This result was seen both when analyzing the entire cohort and after stratifying by histology. A previous study looking at adjuvant radiation for stage II patients was able to show a benefit in disease-free survival when treating with external beam plus brachytherapy compared to brachytherapy alone; however, they did not show any improvement in OS. Importantly, they did not compare external beam alone plus brachytherapy (Ozgul et al., 2018).

Previous studies have reported that neoadjuvant radiation can improve the chance of negative margins on surgical resection, particularly in high-risk histologies (Iheagwara et al.,

2019). However, to our knowledge there have not been any large-scale studies that looked at whether or not the addition of brachytherapy to external beam radiation improved these chances. This analysis indicates that the addition of brachytherapy does not improve the odds of negative margins on surgical resection when compared to external beam radiation alone. Again, this remained constant across all histological sub-types.

Notably however, the addition of brachytherapy was associated with a significant decrease in the utilization of radical hysterectomies in this cohort. This is important because radical hysterectomies have increased incidence of major complications when compared to total hysterectomies (Mariani, Webb, Keeney, Calori, & Podratz, 2001). One of the main reasons neoadjuvant radiation is utilized for endometrial cancer is that it can debulk the initial disease allowing surgeons to remove the tumor with a total hysterectomy instead of a radical hysterectomy, thus hoping to reduce surgical complications (Boisen et al., 2017; Iheagwara et al., 2019). If the addition of brachytherapy can allow a surgeon to perform a total hysterectomy instead of a radical hysterectomy, this can render its addition an important part of the treatment paradigm. Due to its retrospective nature it is not possible in this study to look at whether or not patients with who were treated with brachytherapy were candidates for total hysterectomy after their external beam radiation but before their brachytherapy treatment. We also cannot look at the toxicity profile of neoadjuvant treatment with brachytherapy followed by total hysterectomy as compared to neoadjuvant external beam only followed by radical hysterectomy. Both of these are important and should be investigated in a prospective nature.

There are significant limitations to the study. Most notably, as it is a retrospective database study, we cannot examine the reasons as to why the physician chose whether or not to add brachytherapy to the radiation treatment. They may have been concerned for local recurrence based on physical exam, image findings, or other factors that we cannot examine in this study. Additionally, some of the physicians may have chosen to exclude brachytherapy based on patient factors such as inability to tolerate treatment, but these cannot be determined either. Another important limitation of this study is that we can only examine OS, and cannot look at either local control or disease-free survival. Radiation is utilized for local control, and unfortunately, we cannot examine whether or not the addition of brachytherapy helped to increase local control in this cohort. Lastly, we cannot look at toxicity or quality of life information. As most uterine cancer patients have a good prognosis, long-term toxicities are very important to consider when deciding on treatment plans.

While there are limitations, this study does have many advantages. First, it is the only study we know of that looks directly at whether or not the addition of brachytherapy to external beam radiation in the neoadjuvant setting improves survival or the odds of negative margins in endometrial cancer patients. Additionally, it has a very large cohort for a rare treatment, as neoadjuvant radiation is not commonly employed for endometrial cancer. The ability to stratify the analysis by histological type is also an advantage of this study, as there are innate biological differences between histologies that are important when looking at prognostic factors. A prospective study looking at the addition of brachytherapy to neoadjuvant radiation treatment for uterine cancer is recommended to fully examine how we should be treating these patients.

Table 1: Patient demographics and treatment characteristics

		No Brachytherapy		Brachytherapy		p-value
		Number of Patients (n)	(%)	Number of Patients (n)	(%)	
Total (n)		640	63%	369	37%	
Mean age at diagnosis (yrs)		62.9	11.8	61.1	11.8	0.016
Facility Type						0.045
	Community Cancer Program	29	5%	6	2%	
	Comprehensive Community Cancer Program	251	40%	130	37%	
	Academic/Research Program	269	43%	174	49%	
	Integrated Network Program	72	12%	42	12%	
	Unknown	19	3%	17	5%	
Race						0.633
	Non-Hispanic Black	90	14%	43	12%	
	Hispanic	38	76%	19	79%	
	Other	28	6%	15	5%	
	Non-Hispanic White	484	4%	292	4%	
Insurance Status						0.696
	Un-insured	40	6%	19	5%	
	Insured	591	92%	346	94%	
	Unknown	9	1%	4	1%	
Charleson-Deyo Score						0.315
	0	444	69%	266	72%	
	1	152	24%	84	23%	
	2	35	5%	18	5%	
	3	9	1%	1	0%	
Stage						<0.001
	I	168	26%	61	17%	
	II	207	32%	162	44%	
	III	265	41%	146	40%	
Histology/Grade						0.517
	Grade 1-2 endometrioid	317	50%	169	46%	
	Grade 3 endometrioid	142	22%	89	24%	
	Non-endometrioid histologies	181	28%	111	30%	
Surgical Margins						0.298
	Negative	524	82%	316	86%	
	Positive	48	8%	21	6%	
	Unknown	68	11%	32	9%	
Surgical Procedure						0.009
	Total Hysterectomy	541	85%	333	90%	
	Modified radical or extended hysterectomy	56	9%	14	4%	
	Hysterectomy, NOS	43	7%	22	6%	
Received Chemotherapy						0.068
	No	332	52%	173	47%	
	Yes	290	45%	191	52%	
	Unknown	18	3%	5	1%	
Chemotherapy Sequence						0.056
	None	332	52%	173	47%	
	Neoadjuvant	140	22%	77	21%	
	Adjuvant	77	12%	42	11%	
	Other/Unknown	91	14%	77	21%	

Table 2: Univariate cox regression survival analysis comparing neoadjuvant radiation with and without brachytherapy

	HR	LL 95% CI	UL 95% CI	p-value
Mean age at diagnosis (yrs)	1.04	1.032	1.049	<0.001
Facility Type				
Community Cancer Program	1			ref
Comprehensive Community Cancer Program	1.027	0.605	1.744	0.922
Academic/Research Program	0.982	0.580	1.664	0.946
Integrated Network Program	1.234	0.696	2.187	0.472
Race				
Non-Hispanic Black	1			ref
Hispanic	0.649	0.500	0.842	0.001
Other	0.403	0.231	0.705	0.001
Non-Hispanic White	0.441	0.239	0.815	0.009
Insurance Status				
Un-insured	1			ref
Insured	1.583	0.960	2.610	0.072
Unknown	---	---	---	---
Charleson-Deyo Score				
0	1			ref
1	1.068	0.847	1.348	0.577
2	1.494	1.025	2.178	0.037
3	---	---	---	---
Stage				
I	1			ref
II	1.045	0.788	1.387	0.758
III	1.900	1.458	2.475	<0.001
Histology/Grade				
Grade 1-2 endometrioid	1			ref
Grade 3 endometrioid	2.010	1.574	2.566	<0.001
Non-endometrioid histologies	2.227	1.774	2.796	<0.001
Surgical Procedure				
Total hysterectomy	1			ref
Modified radical or extended hysterectomy	1.074	0.735	1.568	0.713
Hysterectomy, NOS	0.898	0.603	1.337	0.595
Surgical Margins				
No residual tumor	1			ref
Residual	2.250	1.631	3.104	<0.001
Unknown	1.306	0.961	1.773	0.088
Radiation				
External Beam	1			ref
External Beam + Brachytherapy	0.831	0.679	1.018	0.073
Received Chemotherapy				
No	1			ref
Yes	1.045	0.834	1.309	0.701
Unknown	0.353	0.155	0.803	0.013
Chemotherapy Sequence				
None	1			ref
Neoadjuvant	1.110	0.855	1.442	0.434
Adjuvant	1.444	1.073	1.943	0.015
Other/Unknown	1.100	0.843	1.436	0.483

*--- indicates that there were not enough subjects per variable to be included in analysis (Green, 1991)

Table 3: Multivariate cox regression survival analysis comparing neoadjuvant radiation with and without brachytherapy

		HR	LL 95% CI	UL 95% CI	p-value
Age		1.040	1.031	1.050	<0.001
Charleson-Deyo Score					
	0	1			ref
	1	1.049	0.831	1.324	0.688
	2	1.607	1.093	2.363	0.016
Stage					
	I	1			ref
	II	1.073	0.798	1.444	0.639
	III	1.751	1.315	2.330	<0.001
Histology/Grade					
	Grade 1-2 endometrioid	1			ref
	Grade 3 endometrioid	1.600	1.243	2.060	<0.001
	Non-endometrioid histologies	1.801	1.417	2.288	<0.001
Radiation					
	External Beam	1			ref
	External Beam + Brachytherapy	0.898	0.705	1.067	0.179
Received Chemotherapy					
	No	1			ref
	Yes	1.128	0.904	1.408	0.285
	Unknown	0.367	0.161	0.832	0.016

*--- indicates that there were not enough subjects per variable to be included in analysis (Green, 1991)

Table 4: Univariate and Multivariate binary logistic regression analyzing factors associated with negative margin status on surgical resection

		Univariate		Multivariate	
		OR	p-value	OR	p-value
Facility Type					
	Community Cancer Program	1	ref	---	---
	Comprehensive Community Cancer Program	1.528	0.511	---	---
	Academic/Research Program	1.258	0.718	---	---
	Integrated Network Program	0.867	0.835	---	---
Race					
	Non-Hispanic Black	1	ref	---	---
	Hispanic	0.932	0.900	---	---
	Other	1.255	0.737	---	---
	Non-Hispanic White	1.276	0.484	---	---
Stage					
	I	1	ref	1	ref
	II	0.290	0.013	0.284	0.012
	III	0.189	0.001	0.254	0.006
Histology/Grade					
	Grade 1-2 endometrioid	1	ref	1	ref
	Grade 3 endometrioid	0.465	0.017	0.533	0.056
	Non-endometrioid histologies	0.448	0.007	0.597	0.100
Surgical Procedure					
	Total hysterectomy	1	ref	---	---
	Modified radical or extended hysterectomy	0.464	0.210	---	---
	Hysterectomy, NOS	0.489	0.211	---	---
Radiation					
	External Beam	1	ref	1	ref
	External Beam + Brachytherapy	1.378	0.237	1.642	0.076
Chemotherapy Sequence					
	None	1	ref	1	ref
	Neoadjuvant	0.676	0.278	0.821	0.593
	Adjuvant	0.246	0.000	0.335	0.003
	Other/Unknown	0.370	0.003	0.472	0.036

*--- indicates that there were not enough subjects per variable to be included in analysis (Green, 1991)

Figure 1: Cohort Selection

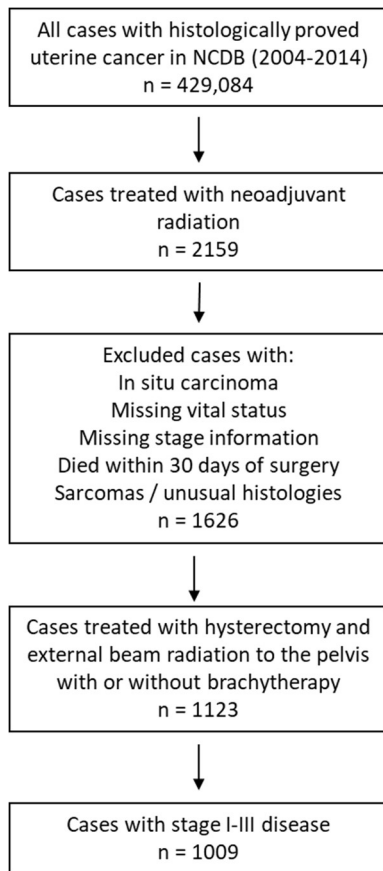
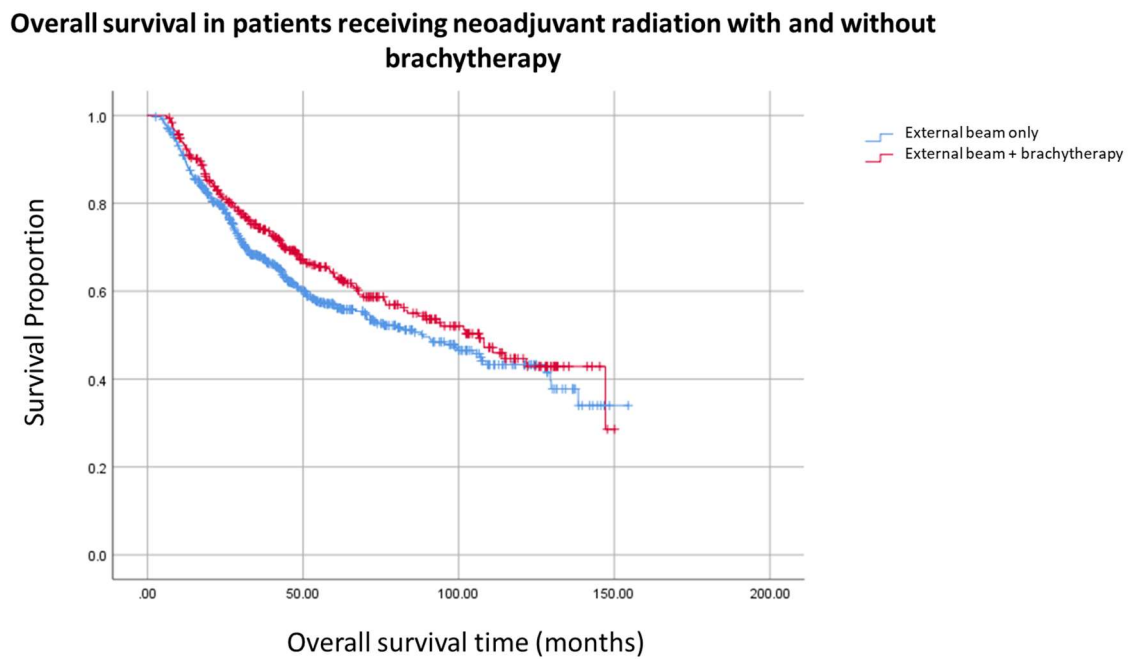


Figure 2: Kaplan-Meier comparing survival in patients treated with neoadjuvant radiation with or without brachytherapy, $p=0.073$



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doi:10.1016/j.ygyno.2014.09.001

CONCLUSION

In this retrospective NCDB analysis, the use of brachytherapy in neoadjuvant radiation for uterine cancer was not significantly associated with OS or with increased odds of negative margins on surgical resection when compared to external beam radiation alone. These findings remained constant across all histological sub-types. Notably however, the addition of brachytherapy was associated with a significant decrease in the utilization of radical hysterectomies, a much more morbid surgery than a total hysterectomy. If the addition of brachytherapy can allow a surgeon to perform a total hysterectomy instead of a radical hysterectomy, this can render its addition an important part of the treatment paradigm. Due to its retrospective nature it is not possible in this study to look at factors leading physicians towards choosing to add brachytherapy to external beam, or toxicities. However, this is one of the largest studies of patients undergoing neoadjuvant radiation for uterine cancer to date. We also cannot look at the toxicity profile of neoadjuvant external beam with brachytherapy followed by total hysterectomy as compared to neoadjuvant external beam only followed by radical hysterectomy. While neoadjuvant radiation for uterine cancer is rare, it is becoming increasingly important to examine all treatment paradigms with the increasing incidence of uterine cancer. A prospective study looking at the addition of brachytherapy to neoadjuvant radiation treatment for uterine cancer is recommended to fully examine how we should be treating these patients.

APPENDICES

Appendix A: Univariate cox regression survival analysis stratified by histology

Low-grade endometrioid endometrial cancer

		No. cases	HR	LL 95% CI	UL 95% CI	p-value
	Total (n)	486				
Mean age at diagnosis (yrs)			1.035	1.021	1.050	<0.001
Facility Type						
	Community Cancer Program	172	1			ref
	Comprehensive Community Cancer Program	216	1.454	0.525	4.023	0.471
	Academic/Research Program	50	1.467	0.534	4.031	0.457
	Integrated Network Program	172	2.458	0.849	7.117	0.097
Race						
	Non-Hispanic Black	39	1			ref
	Hispanic	37	0.540	0.184	1.583	0.261
	Other	21	0.721	0.226	2.301	0.581
	Non-Hispanic White	389	1.246	0.654	2.372	0.504
Insurance Status						
	Un-insured	33	1			ref
	Insured	6	---	---	---	---
	Unknown	447	0.926	0.471	1.821	0.825
Charleson-Deyo Score						
	0	340	1			ref
	1	117	1.115	0.753	1.653	0.587
	2	25	2.412	1.372	4.238	0.002
	3	4	---	---	---	---
Stage						
	I	132	1			ref
	II	196	1.054	0.684	1.623	0.812
	III	158	1.771	1.154	2.717	0.009
Surgical Procedure						
	Total Hysterectomy	427	1			ref
	Modified Radical or extended hyst	28	1.108	0.563	2.178	0.766
	Hysterectomy, NOS	31	0.661	0.309	1.415	0.287
Surgical Margins						
	No residual tumor	426	1			ref
	Residual	22	1.344	0.657	2.749	0.417
	Unknown	38	1.253	0.721	2.179	0.423
Radiation						
	External Beam	317	1			ref
	External Beam + Brachytherapy	169	1.004	0.718	1.403	0.982
Received Chemotherapy						
	No	286	1			ref
	Yes	190	1.094	0.780	1.536	0.602
	Unknown	10	---	---	---	---
Chemotherapy Sequence						
	None	286	1			ref
	Neoadjuvant	106	0.935	0.589	1.483	0.775
	Adjuvant	38	1.275	0.712	2.286	0.414
	Other/Unknown	56	1.035	0.637	1.681	0.891

High-grade endometrioid endometrial cancer

	No. cases	HR	LL 95% CI	UL 95% CI	p-value
Total (n)	231				
Mean age at diagnosis (yrs)		1.025	1.008	1.042	0.003
Facility Type					
Community Cancer Program	8	---	---	---	---
Comprehensive Community Cancer Program	101	1			ref
Academic/Research Program	98	0.938	0.639	1.378	0.745
Integrated Network Program	22	0.386	0.154	0.965	0.042
Race					
Non-Hispanic Black	35	1			ref
Hispanic	10	---	---	---	---
Other	8	---	---	---	---
Non-Hispanic White	178	0.785	0.486	1.269	0.323
Insurance Status					
Un-insured	11	---	---	---	---
Insured	4	---	---	---	---
Unknown	216	---	---	---	---
Charleson-Deyo Score					
0	168	1			ref
1	49	1.051	0.665	1.660	0.832
2	12	---	---	---	---
3	2	---	---	---	---
Stage					
I	40	1			ref
II	82	0.966	0.523	1.785	0.913
III	109	2.215	1.262	3.885	0.006
Surgical Procedure					
Total Hysterectomy	197	1			ref
Modified Radical or extended hyst	20	1.186	0.618	2.278	0.607
Hysterectomy, NOS	14	---	---	---	---
Surgical Margins					
No residual tumor	180	1			ref
Residual	20	2.929	1.681	5.103	0.000
Unknown	31	1.463	0.878	2.439	0.144
Radiation					
External Beam	142	1			ref
External Beam + Brachytherapy	89	0.753	0.514	1.104	0.146
Received Chemotherapy					
No	113	1			ref
Yes	116	1.146	0.792	1.658	0.469
Unknown	2	---	---	---	---
Chemotherapy Sequence					
None	113	1			ref
Neoadjuvant	51	0.928	0.560	1.537	0.771
Adjuvant	26	1.412	0.783	2.548	0.252
Other/Unknown	41	1.158	0.712	1.882	0.555

Non-endometrioid endometrial cancer

		No. cases	HR	LL 95% CI	UL 95% CI	p-value
	Total (n)	292				
Mean age at diagnosis (yrs)			1.045	1.030	1.061	<0.001
Facility Type						
	Community Cancer Program	7	---	---	---	---
	Comprehensive Community Cancer Program	108	1			ref
	Academic/Research Program	129	1.030	0.717	1.481	0.873
	Integrated Network Program	42	1.473	0.919	2.361	0.108
Race						
	Non-Hispanic Black	59	1			ref
	Hispanic	10	---	---	---	---
	Other	14	---	---	---	---
	Non-Hispanic White	209	0.570	0.392	0.828	0.003
Insurance Status						
	Un-insured	15	---	---	---	---
	Insured	3	---	---	---	---
	Unknown	274	---	---	---	---
Charleson-Deyo Score						
	0	202	1			ref
	1	70	1.078	0.742	1.565	0.694
	2	16	---	---	---	---
	3	4	---	---	---	---
Stage						
	I	57	1			ref
	II	91	1.068	0.666	1.713	0.784
	III	144	1.339	0.867	2.067	0.188
Surgical Procedure						
	Total Hysterectomy	250	1			ref
	Modified Radical or extended hyst	22	0.830	0.436	1.579	0.569
	Hysterectomy, NOS	20	0.962	0.520	1.781	0.902
Surgical Margins						
	No residual tumor	234	1			ref
	Residual	27	2.010	1.235	3.270	0.005
	Unknown	31	1.030	0.601	1.763	0.916
Radiation						
	External Beam	181	1			ref
	External Beam + Brachytherapy	111	0.659	0.468	0.928	0.017
Received Chemotherapy						
	No	106	1			ref
	Yes	175	1.021	0.731	1.426	0.904
	Unknown	11	---	---	---	---
Chemotherapy Sequence						
	None	106	1			ref
	Neoadjuvant	60	1.224	0.801	1.870	0.350
	Adjuvant	55	1.064	0.679	1.667	0.787
	Other/Unknown	71	0.789	0.508	1.226	0.291

Appendix B: Multivariate cox regression survival analysis stratified by histology

		Low-grade endometrioid		High-grade endometrioid		Non-endometrioid	
		HR	p-value	HR	p-value	HR	p-value
Mean age at diagnosis (yrs)		1.037	<0.001	1.030	0.001	1.043	<0.001
Race							
	Non-Hispanic Black	---	---	---	---	1	ref
	Hispanic	---	---	---	---	---	---
	Other	---	---	---	---	---	---
	Non-Hispanic White	---	---	---	---	0.585	0.005
Charleson-Deyo Score							
	0	1	ref	---	---	---	---
	1	1.034	0.867	---	---	---	---
	2	2.641	0.001	---	---	---	---
	3	---	---	---	---	---	---
Stage							
	I	1	ref	1	ref	---	---
	II	1.074	0.754	0.958	0.895	---	---
	III	1.787	0.010	1.981	0.021	---	---
Radiation							
	External Beam	1	ref	1	ref	1	ref
	External Beam + Brachytherapy	1.136	0.469	0.789	0.237	0.806	0.241

Appendix C: Univariate and multivariate cox regression survival analysis for stage II patients only

Univariate cox regression analysis for stage II disease

		No. cases	HR	LL 95% CI	UL 95% CI	p-value
Total (n)		369				
Mean age at diagnosis (yrs)			1.047	1.031	1.063	<0.001
Facility Type						
	Community Cancer Program	10	---	---	---	---
	Comprehensive Community Cancer Program	120	1			ref
	Academic/Research Program	167	0.908	0.612	1.348	0.633
	Integrated Network Program	51	1.137	0.678	1.907	0.626
Race						
	Non-Hispanic Black	53	1			ref
	Hispanic	18	---	---	---	---
	Other	15	---	---	---	---
	Non-Hispanic White	283	0.555	0.359	0.858	0.008
Insurance Status						
	Un-insured	19	---	---	---	---
	Insured	3	---	---	---	---
	Unknown	347	---	---	---	---
Charleson-Deyo Score						
	0	254	1			ref
	1	83	1.357	0.904	2.036	0.141

	2	30	1.698	0.978	2.947	0.060
	3	2	---	---	---	---
Histology						
Grade 1-2 endometrioid	196	1				ref
Grade 3 endometrioid	82	1.575	1.017	2.441	0.042	
Non-endometrioid histologies	91	2.300	1.548	3.419	0.000	
Surgical Procedure						
Total Hysterectomy	324	1				ref
Modified Radical or extended hyst	25	1.353	0.709	2.583	0.359	
Hysterectomy, NOS	20	0.211	0.052	0.854	0.029	
Surgical Margins						
No residual tumor	310	1				ref
Residual	25	1.948	1.071	3.545	0.029	
Unknown	34	1.354	0.788	2.327	0.273	
Radiation						
External Beam	207	1				ref
External Beam + Brachytherapy	162	0.777	0.549	1.102	0.157	
Received Chemotherapy						
No	213	1				ref
Yes	150	1.423	1.006	2.014	0.046	
Unknown	6	---	---	---	---	
Chemotherapy Sequence						
None	213	1				ref
Neoadjuvant	76	1.264	0.787	2.031	0.333	
Adjuvant	36	2.476	1.519	4.038	0.000	
Other/Unknown	44	0.916	0.524	1.601	0.758	

Multivariate cox regression analysis for stage II disease

	HR	LL 95% CI	UL 95% CI	p-value
Mean age at diagnosis (yrs)	1.044	1.028	1.060	<0.001
Histology				
Grade 1-2 endometrioid	1			ref
Grade 3 endometrioid	1.262	0.807	1.973	0.308
Non-endometrioid histologies	2.134	1.428	3.189	<0.001
Radiation				
External Beam	1			ref
External Beam + Brachytherapy	0.773	0.543	1.100	0.152

Appendix D: Univariate and multivariate binary logistic regression stratified by histology

Low-grade endometrioid endometrial cancer

		Univariate		Multivariate	
		OR	p-value	OR	p-value
Facility Type					
	Community Cancer Program	1	ref	---	---
	Comprehensive Community Cancer Program	1.467	0.728	---	---
	Academic/Research Program	1.253	0.835	---	---
	Integrated Network Program	1.022	0.985	---	---
Stage					
	I	1	ref	---	---
	II	0.432	0.209	---	---
	III	0.341	0.113	---	---
Surgical Procedure					
	Total hysterectomy	1	ref	---	---
	Modified radical or extended hysterectomy	1.206	0.858	---	---
	Hysterectomy, NOS	0.603	0.513	---	---
Radiation					
	External Beam	1	ref	1	ref
	External Beam + Brachytherapy	1.153	0.762	1.281	0.605
Chemotherapy Sequence					
	None	1	ref	1	ref
	Neoadjuvant	0.401	0.108	0.400	0.108
	Adjuvant	0.264	0.063	0.264	0.063
	Other/Unknown	0.176	0.003	0.171	0.003

High-grade endometrioid endometrial cancer

		Univariate		Multivariate	
		OR	p-value	OR	p-value
Facility Type					
	Community Cancer Program	1	ref	---	---
	Comprehensive Community Cancer Program	1.464	0.736	---	---
	Academic/Research Program	1.175	0.886	---	---
	Integrated Network Program	1.071	0.958	---	---
Race					
	Non-Hispanic Black	1	ref	---	---
	Hispanic	---	---	---	---
	Other	---	---	---	---
	Non-Hispanic White	2.145	0.182	---	---
Stage					
	I	1	ref	1	ref
	II	0.276	0.242	0.241	0.198
	III	0.160	0.083	0.148	0.072
Radiation					
	External Beam	1	ref	1	ref
	External Beam + Brachytherapy	2.192	0.145	2.327	0.121
Chemotherapy Sequence					
	None	1	ref	---	---
	Neoadjuvant	1.290	0.713	---	---
	Adjuvant	0.613	0.492	---	---
	Other/Unknown	0.542	0.306	---	---

*surgical procedure excluded due to low n

Non-endometrioid endometrial cancer

		Univariate		Multivariate	
		OR	p-value	OR	p-value
Facility Type					
	Community Cancer Program	1	ref	---	---
	Comprehensive Community Cancer Program	1.917	0.569	---	---
	Academic/Research Program	1.417	0.756	---	---
	Integrated Network Program	0.778	0.830	---	---
Race					
	Non-Hispanic Black	1	ref	---	---
	Hispanic	1.021	0.985	---	---
	Other	1.404	0.764	---	---
	Non-Hispanic White	1.129	0.807	---	---
Stage					
	I	1	ref	1	ref
	II	0.147	0.073	0.133	0.060
	III	0.123	0.045	0.115	0.039
Radiation					
	External Beam	1	ref	1	ref
	External Beam + Brachytherapy	1.273	0.575	1.491	0.359
Chemotherapy Sequence					
	None	1	ref	---	---
	Neoadjuvant	0.800	0.739	---	---
	Adjuvant	0.218	0.005	---	---
	Other/Unknown	0.667	0.500	---	---

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