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Classification and Regression Tree (CART) Analysis of Endometrial Carcinoma: Seeing the Forest for the Trees

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Abstract

Objective—To evaluate which clinicopathologic factors influenced overall survival (OS) in endometrial carcinoma and to determine if the surgical effort to assess para-aortic (PA) lymph nodes (LNs) at initial staging surgery impacts OS.

Methods—All patients diagnosed with endometrial cancer from 1/1993-12/2011 who had LNs excised were included. PALN assessment was defined by the identification of one or more PALNs on final pathology. A multivariate analysis was performed to assess the effect of PALNs on OS. A form of recursive partitioning called classification and regression tree (CART) analysis was implemented. Variables included: age, stage, tumor subtype, grade, myometrial invasion, total LNs removed, evaluation of PALNs, and adjuvant chemotherapy.

Results—The cohort included 1920 patients, with a median age of 62 years. The median number of LNs removed was 16 (range, 1-99). The removal of PALNs was not associated with OS (P=0.450).

Using the CART hierarchically, stage I vs. stages II-IV and grade 1-2 vs. grade 3 emerged as predictors of OS. If the tree was allowed to grow, further branching was based on age and myometrial invasion. Total number of LNs removed and assessment of PALNs as defined in this study were not predictive of OS.

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Conclusion—This innovative CART analysis emphasized the importance of proper stage assignment and a binary grading system in impacting OS. Notably, the total number of LNs removed and specific evaluation of PALNs as defined in this study were not important predictors of OS.

Keywords

classification and regression tree analysis; CART analysis; endometrial cancer; lymph nodes; staging; overall survival

Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the Western world, with a generally favorable 5-year overall survival rate of 80-85% [1], but there are still many controversies with regard to extent of staging and treatment. The International Federation of Gynecology and Obstetrics (FIGO) endometrial cancer staging system was changed from a clinical to surgical system in 1988, and was most recently updated in 2009 [2-4]. It is well accepted that surgical staging should include a hysterectomy and bilateral salpingo-oophorectomy, but the role and extent of lymph node dissection is highly debated [5]. Do all patients require lymphadenectomy? Should pelvic and para-aortic lymph nodes be excised? If lymph node dissection is not therapeutic, can it guide adjuvant treatment decisions? How do grade and tumor subtype impact survival or the need to perform a lymph node dissection? Who if anyone needs adjuvant therapy?

Classification and regression tree (CART) analysis is an innovative and powerful statistical technique with significant clinical utility [6]. CART analysis is a tree-building technique in which several “predictor” variables are tested to determine how they impact the “outcome” variable, such as overall survival. It has many advantages over more traditional methods, such as multivariate regression; it is inherently non-parametric, can handle highly skewed data, and does not require much input or categorization of the data, as is needed for other multivariate modeling methods. The resulting trees from CART analysis are clear and easy to interpret. Given the many controversies in endometrial cancer, CART analysis provides a promising statistical technique that can assist in identifying important predictors of overall survival and homogeneous subsets of patients with regards to outcome.

Our primary objectives were to evaluate what clinicopathologic factors influenced overall survival in women with endometrial carcinoma undergoing primary surgical staging and to determine if the surgical effort to assess para-aortic lymph nodes at staging surgery impacted overall survival. In other words, where is the value added to the patient beyond a total hysterectomy and adnexectomy when it comes to staging?

Methods

After institutional review board approval, we identified all patients diagnosed with endometrial cancer at Memorial Sloan-Kettering Cancer Center from January 1993 through December 2011 who had lymph nodes excised at the time of surgical staging and evaluated by pathology. Removal of lymph nodes was at surgeon discretion, and stage assignment was based on all available pathologic information. Tumor types included: endometrioid adenocarcinoma, carcinosarcoma, clear cell, serous, and other. Tumor grading was determined as per FIGO definitions, and carcinosarcoma, clear cell, and serous tumors were assigned grade 3. All pathologic evaluations were performed by expert gynecologic pathologists. Standard demographic and clinical data were extracted. The primary endpoint for our study was overall survival. Overall survival was calculated from date of staging

surgery to date of last follow-up or death. Standard Kaplan-Meier methods and log-rank test were performed in the univariate setting. A subset analysis of the effect of para-aortic lymph node assessment by stage was performed.

Patients were divided into two groups based on whether para-aortic lymph nodes were assessed, as defined by the identification of one or more para-aortic lymph nodes on final pathology. The decision to excise para-aortic lymph nodes is specific to each patient's characteristics and based on the surgeon's discretion.

We performed multivariate analyses to evaluate which clinicopathologic factors influenced overall survival in endometrial carcinoma. Using the entire cohort, a form of recursive partitioning called CART analysis was performed. Variables included in the CART analysis included: age, FIGO 1988 stage, tumor subtype, final FIGO grade, depth of myometrial invasion, total lymph node count removed, evaluation of para-aortic lymph nodes (yes/no), and adjuvant chemotherapy (yes/no) with or without adjuvant external radiation therapy or brachytherapy. Total lymph nodes were defined as the sum of pelvic and para-aortic lymph nodes removed. Lymphovascular invasion was not included in the CART variables because of missing results in a substantial number of cases (Table 1). Moreover, radiation therapy was not separately studied because randomized trials have not demonstrated an overall survival advantage.

The CART method was used to separate patients into different homogeneous risk groups and to determine predictors for survival [6]. The algorithm selects the predictor that provides the best or "optimal" split, such that each of the two subgroups is more homogeneous with respect to outcome. Each subgroup is further dichotomized into smaller and more homogeneous groups by choosing the variable that best splits the subgroup. To prune the tree and minimize overfitting, a cost complexity parameter of 0·022 was used using the one minus standard error rule [7,8]. The complexity parameter reflects the tradeoff between the tree complexity and how well the tree fits the data. All analyses were performed using RPART library in R2.13.2 [6], which is an established computational software for implementing CART. We followed the manual in technical reports by Therneau and Atkinson [7,8].

Results

During the study period, 1920 patients met inclusion criteria and had surgically staged endometrial carcinoma including evaluation of at least one lymph node (Table 1); 880 patients were excluded because lymph nodes were not sampled. The median age was 62 (range, 21-92). FIGO (1988) stage distribution was as follows: stage I, 1313; stage II, 114; stage III, 397; and stage IV, 96. The majority of patients (1433) had endometrioid adenocarcinoma histology, but we also included carcinosarcoma, 128; clear cell, 71; serous, 259; and other tumor types, 29. The median number of total lymph nodes removed per patient for the entire cohort was 16 (range, 1-99). Sixty-three percent of patients also had para-aortic lymph nodes excised. Among those patients with para-aortic lymph nodes assessed, the median number excised was five (range, 1-67). Adjuvant therapy was variable, but for the purposes of this report on overall survival, adjuvant therapy was divided into chemotherapy vs. no chemotherapy, with or without radiation in either group. Twenty-eight percent of patients received adjuvant chemotherapy with or without pelvic radiation or vaginal brachytherapy. The median follow-up time was 42 months (range, 0·1-226 months).

On univariate analysis, age, stage, tumor subtype, grade, and total number of lymph nodes removed were significantly associated with overall survival ($P<0.001$). The removal of para-aortic lymph nodes was not associated with overall survival ($P=0.450$). Figure 1 illustrates

the Kaplan-Meier survival curves demonstrating no difference in overall survival for patients who had para-aortic lymph nodes assessed as defined in this study. On subset analysis within different stages, the assessment of para-aortic lymph nodes remained insignificant.

However, a test for differences between patients who did and did not have para-aortic lymph nodes removed and various clinical factors demonstrated that patients who had para-aortic lymph nodes assessed were significantly more likely to have advanced-stage disease, non-endometrioid adenocarcinoma histology, high-grade disease, deep myometrial invasion, and positive lymphovascular space invasion. Because of the significant association of para-aortic lymph node evaluation with high-risk features, we sought to evaluate the impact of para-aortic lymph node assessment on overall survival in a multivariate analysis.

Three patients were excluded from the analysis cohort due to missing information on myometrial invasion, leaving 1917 patients for analysis. Using the CART method, stage I vs. stages II-IV and grade 1-2 vs. grade 3 (a binary grading system of low vs. high-grade) emerged as predictors of overall survival (Figure 2).

If the tree was allowed to grow past the one minus standard error rule, which is highlighted in green in Figure 3, further branching in grey was based on age and myometrial invasion. For stage I patients, the tree divided at age 68 followed by myometrial invasion for younger patients. For stage II-IV patients who were grades 1-2, age divided at 78 was predictive of overall survival. For stage II-IV patients who were grade 3, the tree split at stage II-III vs. stage IV, followed by dividing by age 48 for stage II-III patients.

Even when the tree was allowed to grow for exploratory purposes beyond the recommended level, total lymph nodes removed, assessment of para-aortic lymph nodes, and tumor subtype were not found to be predictive of overall survival. One explanation for the fact that tumor subtype did not appear as an independent factor is that the grade 3 tumors (high grade) encompassed all the high-risk histologies as defined in this study (carcinosarcoma, clear cell, and serous) and appeared as a more important predictor of overall survival compared to tumor subtype.

Discussion

In an effort to see the big picture and determine what truly matters in overall survival of women with endometrial carcinoma undergoing primary staging surgery, this innovative CART analysis emphasized the importance of proper stage assignment category (I-IV) and grade (a binary system of low-grade [1-2] vs. high-grade [3], which included all serous carcinomas, clear cell carcinomas, and carcinosarcomas) in impacting overall survival. The surgical staging of all patients in this study included the evaluation of lymph nodes. Notably, the total number of lymph nodes removed and specific evaluation of para-aortic lymph nodes at surgical staging were not important predictors of overall survival by CART, further emphasizing that we need some lymph node evaluation to properly assign patients to node-positive stage IIIC disease but the use of a traditional anatomic template dissection and radical lymphadenectomy may not be necessary or add value to the patient when it comes to overall survival.

After the results from two randomized controlled trials on pelvic lymph node dissection demonstrated no therapeutic benefit from it, the importance and extent of lymph node dissection has come into question. A Study in the Treatment of Endometrial Cancer (ASTEC) included over 1400 patients randomized to pelvic lymph node dissection and found no difference in overall survival [9]. ASTEC has been heavily criticized as an intention-to-treat study in which almost half of patients in the pelvic lymph node dissection

arm had no nodes or ≤9 nodes excised; furthermore, many patients were secondarily randomized to radiation without taking surgical pathology into account. The randomized trial by Panici *et al.* required a minimum of 20 lymph nodes and had similar adjuvant therapy in both groups but still showed no difference in overall survival [10]. Our study supports the notion that there is no total number of excised lymph nodes that is therapeutic but highlights the importance of accurate surgical staging.

An objective of this study was to determine if the surgical effort to assess para-aortic lymph nodes at staging surgery impacted overall survival. A limitation of our study is that the median number of para-aortic nodes examined per patient was five. The Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer (SEPAL) study was a retrospective analysis of intermediate- and high-risk patients who had a complete, systematic pelvic lymph node dissection vs. combined pelvic and para-aortic lymph node dissection [11]. SEPAL reported that overall survival was significantly improved in the patients undergoing pelvic and para-aortic lymph node dissection; but it is worth noting that the pelvic and para-aortic lymph node group had a median of 59 pelvic lymph nodes and 23 para-aortic lymph nodes removed. This is dramatically higher than the number of lymph nodes excised in most studies and higher than the median number of para-aortic lymph nodes in this single-institution study. It is also unclear whether the difference in overall survival reported in the SEPAL study was due to adjuvant therapy rather than the actual removal of para-aortic lymph nodes. Forty-seven percent of the pelvic and para-aortic lymphadenectomy group received adjuvant chemotherapy compared to 27% in the pelvic lymphadenectomy group, a difference that is statistically significant.

Although there are retrospective studies that have shown a survival advantage for para-aortic lymph node dissection, its therapeutic role is not well accepted or well documented in prospective, randomized trials. The actual importance of para-aortic lymph node status may be in guiding adjuvant therapy, particularly extended-field radiation. Thus, it is important to know the rate of isolated positive para-aortic lymph nodes. Previous publications have cited a 1-3% rate of isolated positive para-aortic lymph nodes with negative bilateral pelvic lymph nodes [3,12]. In the current study, assessment of para-aortic lymph nodes was not found to be significantly associated with overall survival on univariate analysis or CART analysis. Until future trials demonstrate an overall survival advantage to women undergoing para-aortic lymph node dissection, we argue that the decision to proceed with a para-aortic lymph node dissection should be left to the surgeon's discretion.

Our results did not find the total number of lymph nodes removed or the specific evaluation of para-aortic lymph nodes to be important predictors of overall survival in lymph node excised endometrial carcinoma; a potential compromise in the spectrum of no lymph node dissection to systematic pelvic and para-aortic lymph node dissection is sentinel lymph node (SLN) mapping. The prospective SENTI-ENDO study reported a sensitivity of 84%, negative predictive value of 97%, and false-negative rate of 16% [13]. Barlin *et al.* found that the false-negative rate dropped from 15% to 2% after implementation of an SLN algorithm in which any suspicious nodes are removed regardless of mapping and a side-specific pelvic lymph node dissection is performed if there is no mapping on a hemi-pelvis [14]. SLN mapping may be a middle ground that spares most patients from undergoing complete bilateral pelvic lymph node dissection and provides a reasonably low false-negative rate.

In addition to proper surgical stage assignment, grade 1-2 vs. grade 3 (a binary grading system) was a significant predictor of overall survival in our CART analysis. The landmark trial by Creasman *et al.* established grade in combination with myometrial invasion as risk factors for nodal metastasis [3]. Notably, tumor subtype was not predictive in our CART

analysis, but grade and tumor subtype are intimately connected in our design, as the high-risk histologies of serous, clear cell, and carcinosarcoma are all considered grade 3. Voss *et al.* proposed that grade 3 endometrioid endometrial carcinoma should be considered a type 2 endometrial carcinoma based on clinical and pathological evaluation [15]. The disease-specific and recurrence-free survivals were similar among grade 3 endometrioid endometrial carcinomas, serous carcinomas, and clear cell carcinomas. Our CART analysis emphasizes the importance of high grade on overall survival. Thirty-six percent of patients in our cohort were grade 3 compared to 25% reported by Creasman *et al.* [3]. The higher percentage of grade 3 patients in our study was likely due to the exclusion of patients with no lymph nodes excised, who were predominantly low grade.

We decided to divide adjuvant therapy into chemotherapy or no chemotherapy because although adjuvant radiation has been shown to decrease locoregional recurrence, it has not been shown to improve overall survival [1,16,17]. A randomized phase III trial by Randall *et al.* of whole abdominal radiation vs. doxorubicin and cisplatin reported a superior overall survival in the chemotherapy arm [18]. However, that study has been criticized because the difference in overall survival was only significant after adjusting for stage because the stage distribution was not balanced after randomization. In our study, adjuvant chemotherapy was examined in the CART analysis by applying landmark analysis at 8 weeks post surgery. Adjuvant chemotherapy was not selected in the CART analysis. Further trials specifically investigating the impact of adjuvant therapy on overall survival in endometrial cancer are ongoing and will clarify the role of chemotherapy and radiation in this disease.

Although this study is retrospective, it has significant strengths, including the large cohort of over 1900 patients, all of whom had at least one lymph node evaluated; the standardized expert gynecologic pathology review; the novel CART analysis in this setting, which provides several advantages over other multivariate analyses in which subgroups need to be defined upfront; and the broad objective of attempting to determine what really impacts overall survival in endometrial carcinoma.

Conclusions

In the midst of several ongoing controversies in the staging and treatment of endometrial carcinoma, our CART analysis is an innovative attempt at seeing the forest for the trees. Utilizing commonly available clinicopathologic variables and limiting investigator selection bias of variables and cut-offs, we have found that what really matters in endometrial cancer overall survival is stage assignment category (I-IV) and final grade (a binary system of low grade [1-2] vs. high grade [3], with the high-risk histologies being considered grade 3 by default) at initial surgery. Between these, the only factor that can be controlled by the gynecologic surgeon is stage assignment. This depends on what we do in the operating room and how pathologists evaluate the specimens harvested from the patient. The total number of lymph nodes excised and the assessment of para-aortic lymph node status were not important predictors of overall survival based on CART analysis, further emphasizing the role of a more accurate surgical nodal staging procedure that adds value to the patient (the surgeon finding the nodes most likely to harbor disease and the pathologist detecting microscopic nodal disease) and not purely relying on total nodal count numbers and predetermined anatomic templates. These data argue for the continued practice of the SLN mapping algorithm for the surgical staging of women with endometrial cancer.

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Highlights

1. Classification and regression tree (CART) analysis is an innovative form of recursive partitioning that provides multivariate analysis.
2. CART analysis emphasized the importance of proper stage assignment and a binary grading system in impacting survival in endometrial cancer.
3. Number of lymph nodes removed and specific evaluation of paraaortic nodes were not important predictors of overall survival.

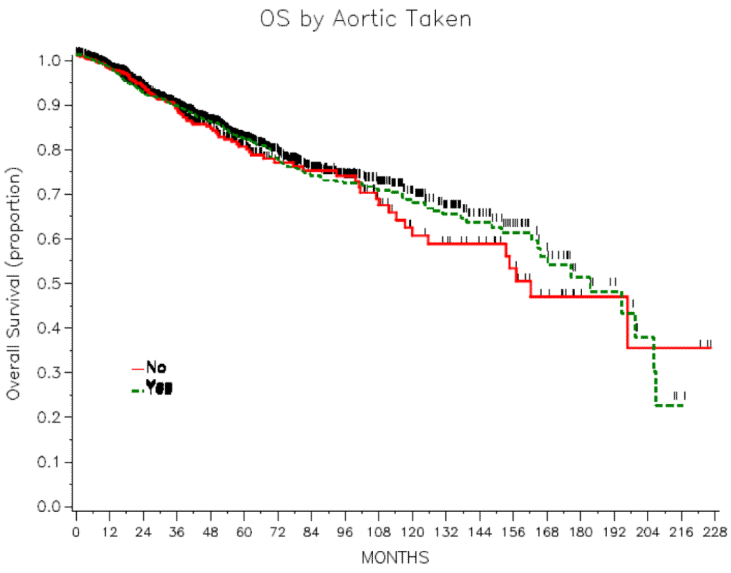

Figure 1.
Kaplan-Meier analysis demonstrating no difference in overall survival for patients with para-aortic nodes removed (*P*=0.450).

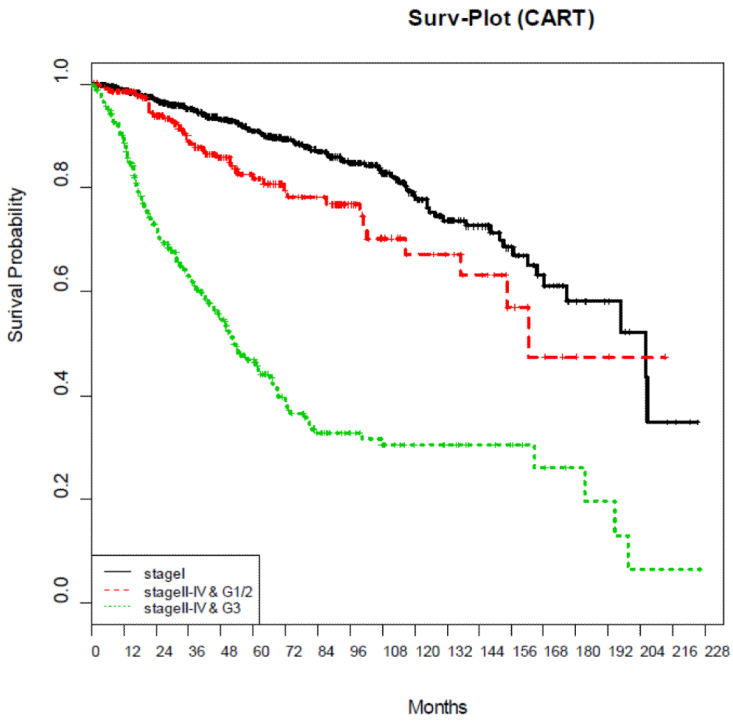

Figure 2.

Kaplan-Meier analysis for the optimal classification and regression tree subgroups. Five-year overall survival rates were: 90.9% (95% CI: 88.6-92.7%) for stage I patients, 82.6% (95% CI: 76.2-87.4%) for stage II-IV & grade 1/2 patients, and 46.9% (95% CI: 40.6-52.9%) for stage II-IV & grade 3 patients.

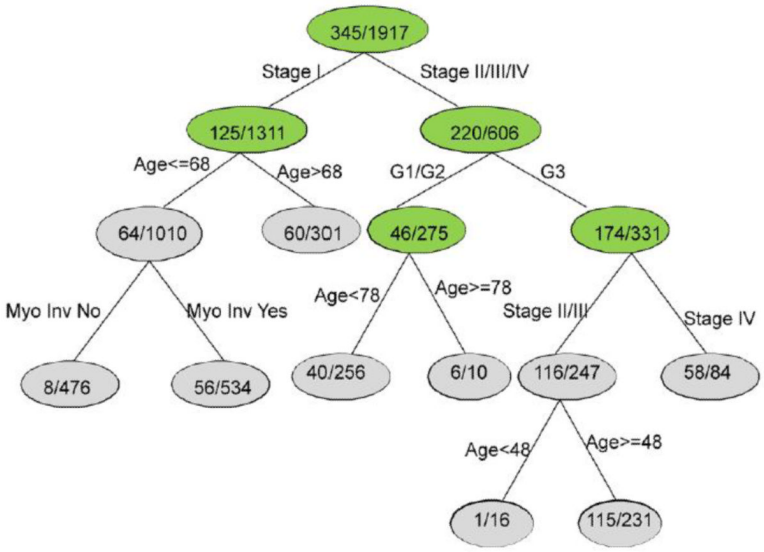

Figure 3.

Classification and regression tree results using the following variables: age, stage, tumor subtype, grade (G), myometrial invasion (Myo Inv), total lymph nodes removed, and evaluation of para-aortic lymph nodes. Complexity parameter (CP) =0.022 for the green highlighted tree; CP=0.0071 for the tree shown. The numerators indicate number of deaths, and the denominators indicate total number of cases in the subcategory.

Table 1

Patient Demographics

Variable	No. of Patients	%
All	1920	
Vital Status		
AWD	119	6.2
NED	1456	75.8
DOD	233	12.1
DOO	84	4.4
DUN	28	1.5
Age at Diagnosis, years		
Median (Mean)	62 (61.3)	
Range	21-92	
Weight at Diagnosis, kg (62 missing)		
Median (Mean)	74 (7 7.8)	
Range	39.2-208.6	
Height at Diagnosis, cm (77 missing)		
Median (Mean)	160 (1 60.1)	
Range	118-188	
BMI, kg/m ^{2} (92 missing)		
Median (Mean)	29·1 (30.4)	
Range	16·7-84.1	
Uterine Weight, g (486 missing)		
Median (Mean)	120 (1 76.6)	
Range	15-3024	
FIGO 1988 Stage		
IA	589	30.7
IB	559	29.1
IC	165	8.6
IIA	39	2
IIB	75	3.9
IIIA	156	8.1
IIIB	1	0.05
IIIC	240	12.5
IVA	7	0.4
IVB	89	4.6
Tumor subtype		
Endometrioid adenocarcinoma	1433	74.6
Carcinosarcoma	128	6.7

Variable	No. of Patients	%
Clear Cell	71	3.7
Serous	259	13.5
Other	29	1.5
Final FIGO Grade		
G1	740	38.5
G2	492	25.6
G3	688	35.8
Myometrial Invasion		
None	659	34.3
<50%	838	43.7
≥50%	420	21.9
Missing	3	0.2
Lymphovascular Invasion		
No	1078	56.2
Yes	500	26
Missing	342	17.8
Washings		
Negative	1304	67.9
Positive	165	8.6
Suspicious	50	2.6
Unavailable/Missing	401	20.9
Total Nodes Taken		
Median(Mean)	16 (17.9)	
Range	1-99	
Total Pelvic Node		
Median (Mean)	13 (1 3.9)	
Range	0-53	
Total Aortic Nodes		
Median (Mean)	3 (4 .0)	
Range	0-67	
No. of Pts with Aortic Nodes Taken		
No	715	37.2
Yes	1205	62.8
Among the 1205 pts:		
Aortic Nodes Taken		
Median (Mean)	5 (6 .4)	
Range	1-67	
No. of Pts with Pelvic Nodes Taken		
No	68	3.54
Yes	1852	96.5

Variable	No. of Patients	%
Among the 1852 pts:		
Pelvic Nodes Taken		
Median (Mean)	13 (1 4.4)	
Range	1-53	
Chemotherapy		
No	1350	70.3
Yes	534	27.8
Missing	36	1.9
Radiation		
Pelvic	208	10.8
Intracavitary	651	33.9
Both	52	2.7

NED, no evidence of disease; AWD, alive with disease; DOD, dead of disease; DOO, dead of other; DUN, dead of unknown reason; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics