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Using machine learning to create prognostic systems for endometrial cancer

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HIGHLIGHTS

- This novel machine learning algorithm demonstrates improved prognostic prediction for patients with endometrial cancer.
- Using machine learning for endometrial cancer allows for the integration of multiple clinical factors into staging.
- A machine learning for endometrial cancer allows for development of a precision prognostication system.

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ABSTRACT

Objective. We used a novel machine learning algorithm to develop a precision prognostication system for endometrial cancer.

Methods. The Ensemble Algorithm for Clustering Cancer Data (EACCD) unsupervised machine learning algorithm was applied to women with endometrioid endometrial cancer in the Surveillance, Epidemiology, and End Results database from 2004 to 2015. The prognostic system was created based on TNM stage, grade, and age. The concordance (C-index) was used to cut dendrograms and create prognostic groups. Kaplan-Meier cancer-specific survival was employed to visualize the survival function of EACCD-based prognostic groups and AJCC groups.

Results. A total of 46,773 women were identified. Using the machine learning algorithm with TNM stage, grade, and three age groups, eleven prognostic groups were generated with a C-index of 0.8380. The five-year survival rates for the eleven groups ranged from 37.9–99.8%. To simplify the classification system further, using visual inspection of the data we created a modified EACCD grouping, and combined the top six survival groups into three new prognostic groups. The new five-year survival rates for these eight modified prognostic groups included: 99.1% for group 1, 96.5% for group 2, 92.2% for group 3, 84.8% for group 4, 72.7% for group 5, 61.1% for group 6, 52.6% for group 7, and 37.9% for group 8. The C-index for the modified eight prognostic groups was 0.8313.

Conclusion. This novel machine learning algorithm demonstrates improved prognostic prediction for patients with endometrial cancer. Using machine learning for endometrial cancer allows for the integration of multiple factors to develop a precision prognostication system.

1. Introduction

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) established staging criteria for uterine cancer based on surgical staging, including lymphadenectomy. This staging system was developed in line with the results of Gynecologic Oncology Group (GOG) protocol 33 which described the pathologic spread of endometrial cancer [1]. In line with the American Joint Committee on Cancer (AJCC), FIGO

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staging utilizes the TNM nomenclature to create various staging groups based on the extent of the local tumor (T stage), nodal involvement (N stage), and metastatic (M stage) spread. Since the introduction of the 1988 FIGO staging criteria, the treatment of uterine cancer in the U.S. has evolved. In 2009, the FIGO staging criteria were updated to classify women with endometrial confined disease and superficial myometrial invasion into a single substage (stage IA) [2–5].

While the majority of women with endometrial cancer do well and are cured from their disease, a subset of patients are at higher risk for recurrence and death [6]. To improve prognostication and help guide adjuvant therapy, a number of risk stratification systems have been proposed [7–10]. These risk stratification systems have used a variety of factors including age, grade, histology, and lymphovascular space invasion to more precisely quantitate risk [7–10]. For example, both GOG-99 and PORTEC 1 created low-risk, intermediate-risk, and high-risk stratification systems to help further stratify risk and estimate the benefit of adjuvant therapy [7,8].

While available risk stratification systems are informative, most of these schemas were created using relatively small, homogenous populations of women. As such, these systems are often based on insufficient data for smaller subsets of patients and aggregate relatively large groups of subjects into prognostic groups. Recently, machine learning algorithms have evolved to help develop risk stratification systems with greater precision [11,12]. Machine learning algorithms utilize unsupervised clustering to classify prognostic groups based on disease specific risk factors. When applied to population-based data, these algorithms can generate prognostic groups with similar outcomes with more precision than traditional staging algorithms [11,12]. Machine learning algorithms have been used successfully applied for a number of tumor types [11,12]. With the growing complexity of cancer prognostication prediction systems and the larger number of risk factors considered, machine learning offers an opportunity to "systematically consider any variable, present and future, to find groups of cancer cases with similar outcomes." [11] Endometrial cancer is particularly well suited to the development of a machine learning algorithm given that patients with heterogenous outcomes are currently grouped into each stage in the currently available staging algorithms. We therefore utilized a novel machine learning algorithm to develop a risk stratification schema based on clinical and pathologic characteristics for women with stage I-III endometrial cancer.

2. Materials and methods

2.1. Data source and study cohort

The Surveillance, Epidemiology, and End Results (SEER) database was utilized for the analysis. SEER is a population-based cancer registry that includes data on approximately 34% of the United States population and captures information on patient demographics, cancer characteristics, and cancer-specific or overall survival [13]. Exemption from the Columbia University Institutional Review Board was obtained.

This analysis was restricted to women who were diagnosed with endometrioid endometrial cancer from 2004 to 2015 with T1a to T3b and any regional nodes stage ($N = 0$ or $N = 1$). We chose to include stages T1-T3 as these typically encompass the stages in which decisions about adjuvant therapy are often uncertain. Patients with metastases to distant site ($M = 1$) were excluded. Women who did not undergo hysterectomy and those who did not have complete information on vital status, cancer grade, and age were also excluded. Patients in which the T stage was classified as not otherwise specified (T1NOS) were excluded. AJCC 6th staging from 2004 to 2009 were converted to AJCC 7th for the classification of T, N, and M stage and the summary stage.

In this analysis, four prognostic factors were included T stage, N stage, cancer grade, and age categories. A combination of prognostic factors serves as a subset of the data that corresponds to one level of each selected factors. Two analyses were performed. Analysis 1 consisted of 46,773 endometrial cancer patients with 10 combinations based on stage T and stage N ($5 \times 2 = 10$). The events of death were observed in all 10 combinations. Analysis 2 consisted of 46,466 patients with 68 combinations according to TNM stage, cancer grade, and three age categories (18–49, 50–69, ≥70 years old). From dataset 1 to dataset 2, we removed 307 patients with 22 rare combinations where no events were observed.

2.2. Ensemble algorithm for clustering cancer data (EACCD)

The Ensemble Algorithm for Clustering Cancer Data (EACCD) is an unsupervised machine learning algorithm designed to build prognostic systems for cancer based on survival data [11,12]. Three main steps are included: (1) Defining initial dissimilarities: this step computes the initial dissimilarity in survival functions between pair-wise combinations. (2) Computing learned dissimilarities: this step uses initial dissimilarities and a machine learning process to obtain learned dissimilarities in survival between combinations based on the data-driven process. (3) Applying hierarchical clustering analysis: this step clusters the combinations by the learned dissimilarities and a linkage method to create a dendrogram visualizing the relationship between survival and prognostic factors. A detailed description of each step is outlined.

In step 1 [12], we defined the initial dissimilarity between any two combinations using hazard ratios from Cox proportional hazards models assuming the proportional hazards assumption holds for the populations represented by any two combinations. The hazard ratio is an effect-size based measure independent of the sample size. It can generate robust results on clustering with respect to the data size of each combination and has a better performance than log-rank test [14]. There are 2 ratios for each pair (one is the reciprocal of the other). The larger ratio is used as the initial dissimilarity between two combinations.

In step 2, we utilize the initial dissimilarities in step 1 to compute learned dissimilarities. The two-phase Partitioning Around Medoids (PAM) algorithm of Kaufman and Rousseeuw is a partitioning method operating on the initial dissimilarity matrix [15]. PAM is used to partition available combinations into k clusters, where k ranges from 1 to n (the total number of combinations), that is 1 to 10 in our analysis set 1 and to 68 in analysis set 2. For each k, we define $\delta_k(i,j) = 1$ if combinations i and j are not assigned into the same cluster and $\delta_k(i,j) = 0$ otherwise [12,16]. The learned dissimilarity between combinations i and j is defined as the ratio $\sum_{k=1}^{n}\delta k(i,j)$ to n, which is the percentage of the times i and j are not placed into the same cluster by the PAM algorithm. The learned dissimilarities, which are between 0 and 1, are more data-driven than the initial dissimilarities.

In step 3, we employed a hierarchical clustering process to cluster the combinations using the learned dissimilarities and a complete linkage method [12]. The output of a linkage method is often summarized into a dendrogram where the nested clusters are graphically represented as a tree. The branches in the tree represent clusters. Two clusters merge at a height among a dissimilarity axis that is equal to the dissimilarity between two clusters. The dendrogram is the primary output of EACCD that provides a graphical summary of patients' survival based on clusters.

2.3. Prognostic systems

The dendrogram produced in EACCD can be cut horizontally based on C-index to generate prognostic groups. The C-index is an estimate of the probability that a patient in our study who died in an earlier time had a shorter predicted time than a patient who died at a later time. The C-index can be computed in Cox proportional hazard model that indicates a statistically predictive accuracy. A higher C-index implies a higher accuracy in survival prediction. In general, the curve of the C-index versus the number of groups increases for relatively small numbers of groups and then quickly plateaus as more groups are

generated. The optimal level of stratifying the dendrogram is achieved when the minimum number of groups yields the maximum value of the C-index or a C-index approximates the maximum where extra groups would not significantly increase the C-index. The final prognostic system is a collection of the dendrogram, the group assignment, the C-index, and the survival curves for the prognostic groups [11].

2.4. Statistical analysis

Cancer specific survival curves are estimated by the Kaplan-Meier method. A non-parametric approach was used to compare two correlated C-indices with right-censored survival outcome [17]. Clinical relevance of the survival categories was based on subject-matter medical knowledge and visual inspection of the data. All analyses were conducted with SAS 9.4 (SAS Institute Inc., Cary, North Carolina) and R 3.5.1 (Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Prognostic system based on TNM stage

A total of 46,773 patients with endometrial cancer were identified (Table 1). Using the TNM staging system results in six stage groups (IA-IIIC) (Panel A in Fig. 1.) Using the EACCD machine learning algorithm to determine a prognostic system on the basis of TNM alone, five groups were generated in dendrogram (Panel B in Fig. 1) with five-year survival rates of: 98.1% (95% CI, 97.9–98.3%) for group 1 (T1aN0M0), 95.8% (95% CI, 95.5–96.2%) for group 2 (T1bN0M0), 89.1% (95% CI, 87.9–90.2%) for group 3 (T1aN1M0 and T2N0M0), 81.6% (95% CI, 79.8–83.2%) for group 4 (T1bN1M0 and T3aN0M0), and 60.3% (95% CI, 57.8–62.8%) for group 5 (T2N1M0, T3aN1M0, T3bN0M0, and T3bN1M0) (Panel C in Fig. 1). The C-index for the EACCD generated five prognostic groups was 0.7705, compared to 0.7682 for the TNM prognostic grouping.

Table 1
Clinical and demographic characteristics of the study cohort.

	N	%
Age (years)		
18–49	7228	15.5
50–69	30,680	65.6
≥70	8865	19.0
Stage		
IA	25,192	53.9
IB	13,828	29.6
II	3062	6.6
IIIa	1744	3.7
IIIb	359	0.8
IIIc	2588	5.5
Grade		
Well differentiated	25,745	55.0
Moderately differentiated	15,224	32.6
Poorly differentiated and undifferentiated	5804	12.4
Year of Diagnosis		
2004	2620	5.6
2005	2894	6.2
2006	3002	6.4
2007	3353	7.2
2008	3448	7.4
2009	3648	7.8
2010	4621	9.9
2011	4746	10.2
2012	4707	10.1
2013	4494	9.6
2014	4748	10.2
2015	4492	9.6
Race		
White	39,002	83.4
Black	3146	6.7
Other	4625	9.9
Marital Status		
Married	25,256	54.0
Single	19,364	41.4
Unknown	2153	4.6
Registry area		
West	21,996	47.0
Central	11,108	23.8
Eastern	13,669	29.2

3.2. Prognostic system based on TNM stage, grade, and age

Prognostic grouping for endometrial cancer often relies on inclusion of age based on three age categories (18–49 years, 50–69 years, and ≥ 70 years) and grade [7,8]. Using the EACCD machine learning algorithm to determine a prognostic system on the basis of TNM, grade, and age results in eleven groups with a C-index of 0.8380 (Fig. 2A). The dendrogram and survival curves for the EACCD based classification are shown in Fig. 2.

3.3. Modified EACCD grouping

To simplify the classification system, we sought to further refine the EACCD classification based on TNM stage, grade, and age. Given that survival was >90% for six of the original eleven groups in the classification schema, we generated a modified EACCD eight group system by collapsing these six groups into three unique prognostic groups by visual inspection of the data. The five-year survival for Groups 1–6 were the following: 99.8%, 98.9%, 97.6%, 95.6%, 93.3%, and 91.9%. By visual inspection of these 6 five-year survival groups, combining Groups 1 and 2, Groups 3 and 4, and Groups 5 and 6, leads to a more differentiated prognostication system. The modified eight group EACCD prognostic system is displayed in Table 2.

The five-year survival for these new eight prognostic groups were: 99.1% for Group 1, 96.5% for Group 2, 92.2% for Group 3, 84.8% for Group 4, 72.7% for Group 5, 61.1% for Group 6, 52.6% for Group 7, and 37.9% for Group 8 (Fig. 2C). Traditional AJCC TNM stage varied within these modified eight prognostic groups and are demonstrated in Table 2. For example, group 1, the most favorable prognostic group, including women age 18–49 years of age, with T1a or T1b, N0, grade 1 or 2 tumors and women age 50–69 years with T1a or T1b, N0, grade 1 tumors. In contrast, group 8, the poorest prognosis group, include women age 50–69 years, with T3a or T3b, grade 3 tumors and women >70 years of age with T3aN1 grade 2 or 3 tumors, T3bN0 or N1 grade 3 tumors. The C-index for these modified eight prognostic groups was 0.8313 which was slightly higher than moving to eight prognostic groups within EACCD solely (C-index = 0.8307).

4. Discussion

These data demonstrate that application of a machine learning algorithm to endometrial cancer can result in a staging classification schema with improved prognostic capability. In addition to nodal status and depth of invasion, the classification schema incorporates readily available clinical data such as age and grade.

Since the recognition of the importance of surgical staging for endometrial cancer in 1988, various risk scoring systems have incorporated clinical characteristics into traditional staging criteria to more precisely stratify patients, predict outcomes, and assist in adjuvant treatment decision making. Most notably are the risk stratification systems of GOG-99 and PORTEC-1, which divide patients into low-, intermediate-, and high-risk groups based on stage and prognostic factors such as grade, age, and the presence of lymphovascular space invasion [7,8].

Despite the frequent clinical use of these risk stratification systems, their discriminatory abilities have been poorly tested in many cases. Bendifallah and colleagues assessed the ability of five commonly used stratification systems, PORTEC-1, GOG-99, SEPAL, ESMO, and ESMO-modified to discriminate nodal metastases and recurrence free survival

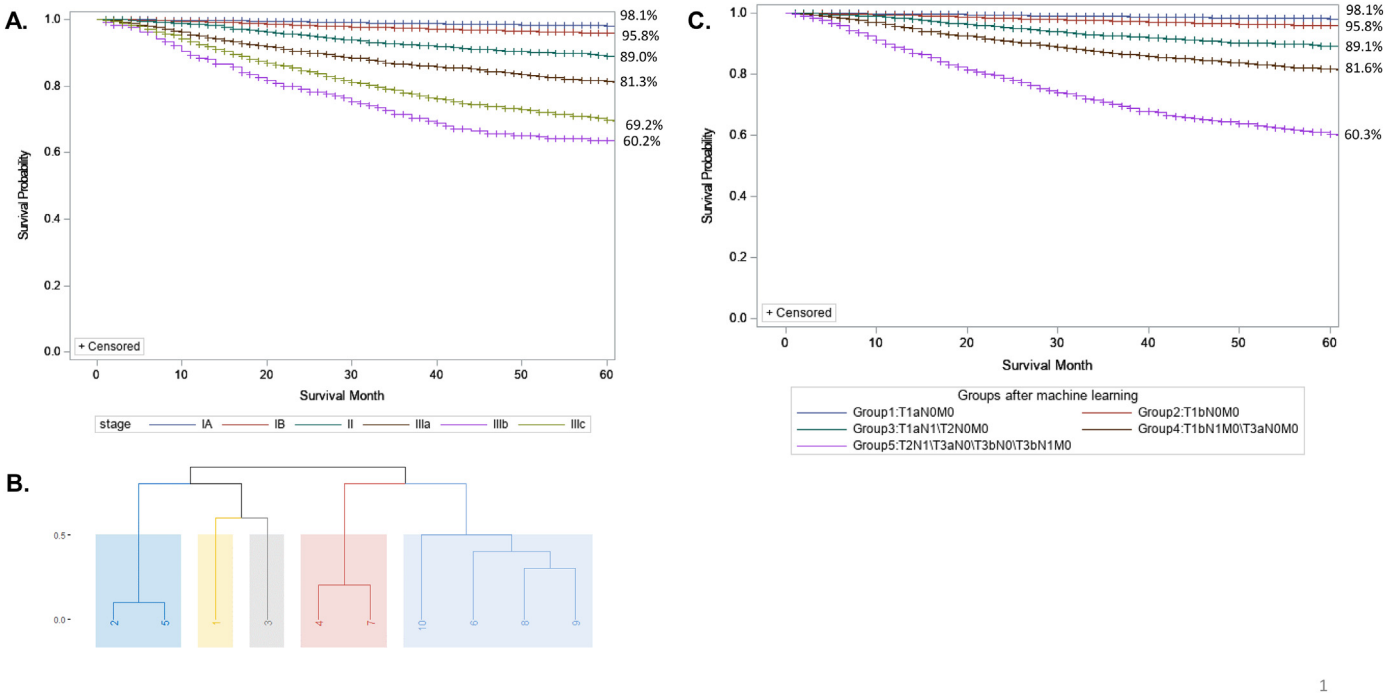

Fig. 1. Comparison of TNM (C-index = 0.7682) (1A), dendogram (1B) and EACCD based (C-index = 0.7705) (1C) prognostication for women with endometrial cancer.

[9,10,18–21]. The authors noted that none of the risk stratification systems showed high accuracy in stratifying risk [19]. The benefit of our machine learning algorithm is that it allows precise grouping of smaller subsets of patients to more accurately classify groups of patients with similar prognoses.

The EACCD machine learning algorithm has been successfully utilized in several other solid tumors [11,12,22]. These studies have concluded that integrating additional prognostic factors into the traditional AJCC TNM system, improves the stratification of patients and accuracy in treatment decision making and outcomes [11,12,22]. For example, a study of patients with colon and rectal cancer noted that adding age, carcinoembryonic antigen and location improved the predictive accuracy of traditional scoring approaches using only tumor factors, nodal status and metastases [22]. Similarly, A recent study used DeepSurv (a deep learning survival neural network) to create more precise prognostic evaluation and treatment recommendations with respect to non-small cell lung cancer [23]. We noted similar findings when applying the EACCD machine learning algorithm to endometrial cancer. Using the EACCD machine learning algorithm for endometrial cancer, we demonstrated an improved discriminatory

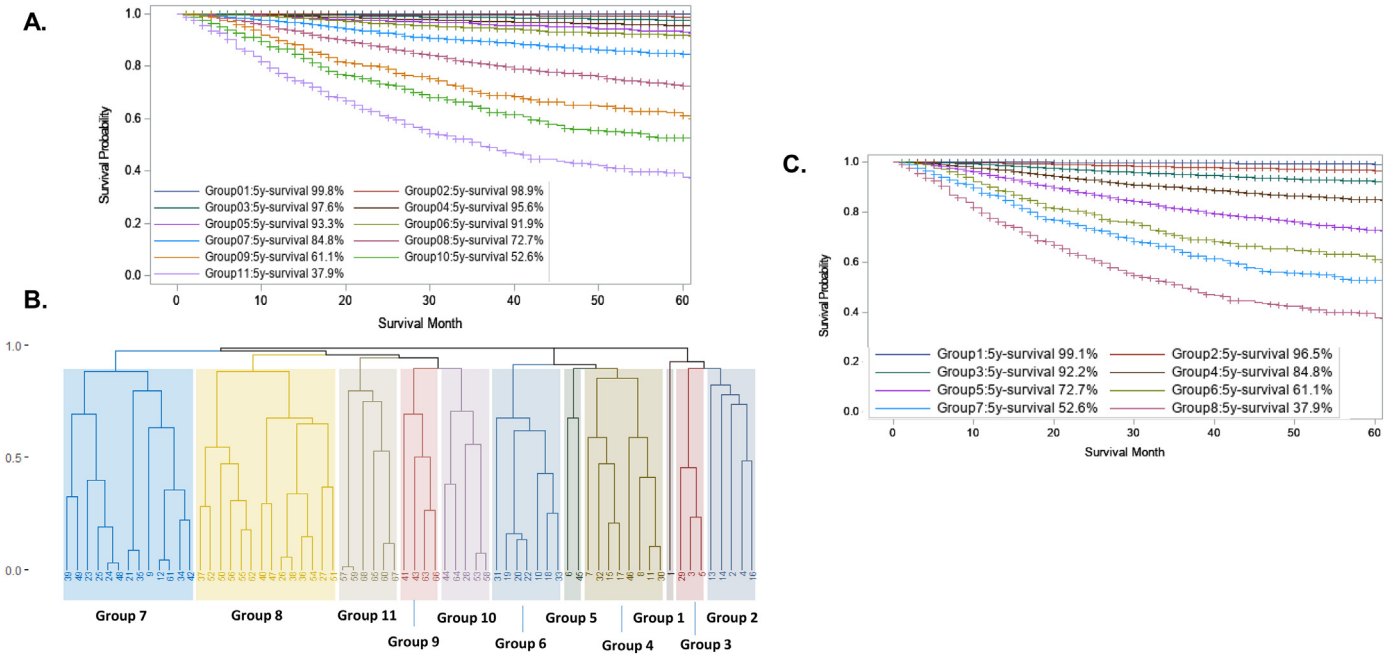

Fig. 2. EACCD classification into 11 groups (C-index = 0.838) with Kaplan-Meier curve (2A) and dendogram (2B) and EACCD classification into 8 groups (C-index = 0.8307) (2C).

Table 2
Five-year survival rates based on machine learning and AJCC staging algorithms based on 68 combinations of TNM, grade, and age.

T	N	Grade	Age	AJCC 7th	EACCD prognostic group ($N = 11$)†	5-year survival % (95% CI)	Modified EACCD prognostic group ($N = 8$)‡	5-year survival % (95% CI)
T1a	0	1	18–49	IA	1	99.8 (99.5–99.9)	1	99.1 (98.9–99.2)
T1a	0	1	50–69	IA	2	98.9 (98.7–99.1)	1	
T1a	0	2	18–49	IA	2		1	
T1b	0	1	18–49	IB	2		1	
T1b	0	1	50–69	IB	2		1	
T1b	0	2	18–49	IB	2		1	
T1a	0	1	>70	IA	3	97.6 (97.2–98.0)	2	96.5 (96.1–96.8)
T1a	0	2	50–69	IA	3		2	
T2	0	1	18–49	II	3		2	
T1a	0	3	18–49	IA	4	95.6 (95.0–96.1)	2	
T1a	0	3	50–69	IA	4		2	
T1a	1	2	50–69	IIIc	4		2	
T1b	0	1	>70	IB	4		2	
T1b	0	2	50–69	IB	4		2	
T2	0	1	50–69	II	4		2	
T2	0	2	18–49	II	4		2	
T3a	0	1	50–69	IIIa	4		2	
T1a	0	2	>70	IA	5	93.3 (91.4–94.7)	3	92.2 (91.4–93.0)
T3a	0	1	18–49	IIIa	5		3	
T1a	1	1	50–69	IIIc	6	91.9 (90.9–92.8)	3	
T1b	0	2	>70	IB	6		3	
T1b	0	3	18–49	IB	6		3	
T1b	0	3	50–69	IB	6		3	
T2	0	1	>70	II	6		3	
T2	0	2	50–69	II	6		3	
T1a	0	3	>70	IA	7	84.8 (83.1–86.3)	4	84.8 (83.1–86.3)
T1a	1	3	50–69	IIIc	7		4	
T1b	0	3	>70	IB	7		4	
T1b	1	1	>70	IIIc	7		4	
T1b	1	2	18–49	IIIc	7		4	
T1b	1	2	50–69	IIIc	7		4	
T2	0	2	>70	II	7		4	
T2	0	3	18–49	II	7		4	
T2	1	2	18–49	IIIc	7		4	
T2	1	3	18–49	IIIc	7		4	
T3a	0	2	18–49	IIIa	7		4	
T3a	0	2	50–69	IIIa	7		4	
T3b	0	1	50–69	IIIb	7		4	
T1b	1	2	>70	IIIc	8	72.7 (70.4–74.8)	5	72.7 (70.4–74.8)
T1b	1	3	50–69	IIIc	8		5	
T2	0	3	50–69	II	8		5	
T2	0	3	>70	II	8		5	
T2	1	1	50–69	IIIc	8		5	
T2	1	2	50–69	IIIc	8		5	
T3a	0	1	>70	IIIa	8		5	
T3a	0	2	>70	IIIa	8		5	
T3a	0	3	18–49	IIIa	8		5	
T3a	0	3	50–69	IIIa	8		5	
T3a	1	1	50–69	IIIc	8		5	
T3a	1	2	18–49	IIIc	8		5	
T3a	1	2	50–69	IIIc	8		5	
T3b	0	2	50–69	IIIb	8		5	
T2	1	2	>70	IIIc	9	61.1 (54.4–67.1)	6	61.1 (54.4–67.1)
T2	1	3	50–69	IIIc	9		6	
T3b	0	2	>70	IIIb	9		6	
T3b	1	2	50–69	IIIc	9		6	
T1b	1	3	>70	IIIc	10	52.6 (46.9–57.9)	7	52.6 (46.9–57.9)
T2	1	3	>70	IIIc	10		7	
T3a	0	3	>70	IIIa	10		7	
T3a	1	3	18–49	IIIc	10		7	
T3b	0	3	50–69	IIIb	10		7	
T3b	0	3	>70	IIIb	11	37.9 (32.8–42.9)	8	37.9 (32.8–42.9)
T3a	1	2	>70	IIIc	11		8	
T3a	1	3	50–69	IIIc	11		8	
T3a	1	3	>70	IIIc	11		8	
T3b	1	3	50–69	IIIc	11		8	
T3b	1	3	>70	IIIc	11		8	

Note: Each combination has greater than 25 patients and at least one event (death). 22 rare combinations (25 patients or less) accounting for 307 patients were removed. † Concordance index = 0.8380, ‡Concordance index = 0.8313.

ability for survival compared to traditional TNM staging. Improvements in predictive ability were noted based on reclassification of existing pathologic variables as well as with inclusion of other factors including tumor grade and age in the model. These systems can be readily applied to clinical practice.

A major concern for using machine learning algorithms for cancer prognostication is the increase in complexity these systems add to conventional staging. Accuracy of the risk stratification system must be balanced against the number of prognostic factors included as well as in the number of groups produced. In our analysis, simplifying the prognostic system to a modified eight groups by merging the top six groups into three new groups maintained a C-index >0.8. The machine learning algorithm in combination with clinical knowledge can be used with a variety of factors to generate as many or as few groups as desired to optimize its utility in the clinical setting. Our proposed eight group risk stratification scoring system relies on commonly utilized, readily available clinical factors, and generates a manageable and improved prognostication system.

While machine learning inevitably introduces more complexity into the clinical practice for endometrial cancer, it also allows the incorporation of many clinical, pathologic, and now molecular characteristics of a patient's tumor. In the past five years, molecular and genetic characterization of endometrial tumors has significantly changed the landscape of our knowledge of endometrial cancers and treatment implications [24–27]. Machine learning algorithms readily allow for the incorporation of molecular changes into staging schemas.

While our study benefits from the inclusion of a large number of women, we recognize a number of important limitations. First, the SEER database does not include data on some clinical covariates that may be of prognostic significance, most notably, lymphovascular space invasion [28]. Second, similar to prior studies, our EACCD algorithm requires at least 100 patients or one event in a given prognostic group to provide adequate data on outcomes [11,12,22]. As such, some uncommon groupings lacked a sufficient number of patients or events to provide accurate estimates. Third, similar to clinical practice, not all patients underwent nodal evaluation. Staging was assigned based on available pathologic data. Fourth, data on use of adjuvant therapy was not included in our analysis. The use of adjuvant therapy for both early and advanced endometrial cancer remains an area of controversy and we believe any bias would be minimal. Finally, our analysis is based on cancer specific survival. We acknowledge that cause of death may have been misclassified in a very small number of subjects.

Our novel risk stratification system demonstrated improved prognostic prediction for patients with endometrial cancer compared to traditional staging algorithms. A useful risk stratification system should be valid, reliable, and practical and aid in prognosis prediction, evaluation of results, and treatment decision making [29,30]. Using machine learning to create prognostic systems for endometrial cancer allows for the integration of multiple factors to develop a precision prognostication system. While this machine learning algorithm and our study did not incorporate adjuvant therapy, future studies and investigations using machine learning may elucidate more precise adjuvant therapies for women with endometrial cancer. Importantly, the risk stratification system is flexible and allows the addition of additional prognostic factors if needed. This is particularly important for endometrial cancer as additional biologic and pathologic markers become available.

Contribution of authorship

Praiss: study conception and planning, statistical analysis, interpretation of results, manuscript drafting, final approval of manuscript.

Huang: study conception and planning, statistical analysis, interpretation of results, manuscript drafting, final approval of manuscript.

Melamed: interpretation of results, final approval of manuscript.

Tergas: interpretation of results, final approval of manuscript.

Khoury-Collado: interpretation of results, final approval of manuscript.

Hou: interpretation of results, final approval of manuscript.

St. Clair: interpretation of results, final approval of manuscript.

Hu: interpretation of results, final approval of manuscript.

Hur: interpretation of results, final approval of manuscript.

Hershman: interpretation of results, final approval of manuscript.

Wright: study conception and planning, statistical analysis, interpretation of results, manuscript drafting, final approval of manuscript.

Declaration of Competing Interest

Dr. Wright has served as a consultant for Clovis Oncology and received research funding from Merck. Dr. Hur has served as a consultant for Kite Pharmaceuticals and has equity in Cambridge Biomedical Economic Consulting Group. No other authors have any conflicts of interest or disclosures.

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