Human Epidermal Growth Factor 2 (HER2) in Early Stage Uterine Serous Carcinoma: A Multi-Institutional Cohort Study

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Abstract

Background—Human epidermal growth factor receptor 2 (HER2) has emerged as an important prognostic and therapeutic target in advanced stage and recurrent uterine serous carcinoma (USC). The significance of tumoral HER2 expression in early-stage disease has not been established.

Methods—This multi-center cohort study included women with stage I USC treated from 2000–2019. Demographic, treatment, recurrence, and survival data were collected.

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Immunohistochemistry (IHC) was performed for HER2 and scored 0–3+. Equivocal IHC results (2+) were further tested with fluorescence in-situ hybridization (FISH). HER2 positivity was defined as 3+ IHC or FISH positive.

Results—One hundred sixty-nine patients with stage I USC were tested for HER2; 26% were HER2-positive. There were no significant differences in age, race, stage, adjuvant therapy, or follow-up duration between the HER2-positive and negative cohorts. Presence of lymph-vascular space invasion was correlated with HER2-positive tumors (p=0.003).

After a median follow-up of 50 months, there were 43 (25.4%) recurrences. There were significantly more recurrences in the HER2-positive cohort (50.0% vs 16.8%, p<0.001). HER2 positive tumors were associated with worse progression-free (PFS) and overall survival (OS) (p<0.001 and p=0.024). On multivariate analysis, HER2 positive tumors were associated with inferior PFS (aHR 3.50, 95%CI 1.84–6.67; p<0.001) and OS (aHR 2.00, 95%CI 1.04–3.88; p=0.039) compared to HER2-negative tumors.

Conclusions—Given its significant association with worse recurrence and survival outcomes, HER2 positivity appears to be a prognostic biomarker in women with stage I uterine serous carcinoma. These data provide support for clinical trials with anti-HER2-directed therapy in early-stage disease.

Introduction

Uterine serous carcinoma (USC) is a biologically aggressive, poor prognostic subtype of endometrial cancer associated with higher recurrence and mortality rates compared to other, more common epithelial endometrial cancer subtypes. USC represents only 10% of all endometrial cancers, but an astonishing 40% of endometrial cancer-related deaths (1). Among women with early-stage USC, the standard treatment is hysterectomy and surgical staging followed by platinum/taxane-based chemotherapy with or without vaginal brachytherapy in most cases. Even in those with uterine-limited disease who are treated with adjuvant therapy, cancer recurrences are observed in an estimated 11–22% of stage I cases (2–4). Most recurrences are systemic and not possible to salvage, highlighting the critical need for novel and improved therapies.

Advancements in understanding the genomic expression profiles of USC have driven the development of targeted therapeutic agents. One such molecular target is human epidermal growth factor receptor 2 (HER2), also known as ERBB2. HER2 is a receptor tyrosine kinase that regulates cell proliferation, survival, and differentiation. The oncogenic potential of HER2 protein overexpression and/or gene amplification is widely recognized in a variety of solid tumors, including breast, gastric, esophageal, head and neck, and gynecologic cancers (5–8). HER2 overexpression and/or amplification has been reported in 18–42% of USC (9–11). In 1998, trastuzumab, a monoclonal antibody directed at HER2, was the first drug approved by the U.S. Food and Drug Administration (FDA) for treating HER2-positive metastatic breast cancer. Since then, five additional HER2-targeting agents have been approved by the FDA (12).

HER2 has emerged as an important prognostic and therapeutic target in USC. Recent randomized data demonstrate the survival benefit of adding trastuzumab to platinum/taxane-

based therapy in women with advanced or recurrent, HER2-positive USC (13). The significance of tumoral HER2 overexpression or amplification in early-stage disease has not yet been established. Therefore, our study objective was to determine whether HER2 is a prognostic biomarker in women with Stage I USC.

Methods

Patient population

This was a multi-institutional, retrospective cohort study involving three U.S. tertiary academic centers: University of Minnesota (Minneapolis, MN, USA), Johns Hopkins School of Medicine (Baltimore, MD, USA), and Yale School of Medicine (New Haven, CT, USA). Institutional Review Board approval was obtained at each of the participating institutions. Patients were identified from pathology databases and through ICD-9/10 searches and were included if they had a diagnosis of stage IA or stage IB (FIGO 2009 staging) USC between the years 2000–2019. Patients were excluded if their tumor contained less than 20% serous histology. The medical record was queried for demographic information, including age, body mass index (BMI), race/ethnicity, and Eastern Cooperative Oncology Group (ECOG) performance status. Tumor characteristics collected from pathology reports included percent serous component, depth of invasion, tumor size, involvement of a polyp, lymph-vascular space invasion (LVSI), and the extent of surgical staging. Data on adjuvant treatment, recurrence, and survival were also collected.

Pathological analysis

Paraffin-embedded tumor blocks were collected from the original hysterectomy specimen. Pathology was reviewed based on hematoxylin and eosin (H&E) staining by experienced gynecologic pathologists at each institution to confirm the diagnosis of USC. Adjacent sections were then cut, and slides were submitted for HER2 immunohistochemistry (IHC) with or without dual-probe fluorescence in-situ hybridization (FISH) testing. For patients with mixed histology, testing was performed on the tumoral serous component. All IHC and FISH slides were scored by 2 pathologists using the modified 2007 ASCO/CAP guidelines for HER2 IHC (to include tumors showing a basolateral/ lateral membrane staining pattern) and FISH interpretation in breast carcinoma (14). This classification was used as it has been validated in the Fader et al, phase II USC trial (13, 15).

At Yale School of Medicine, IHC was performed using the DAKO HercepTest kit (DAKO, Carpinteria, CA). At the University of Minnesota, this was done using the Ventana PATHWAY anti-HER2 (4B5) platform (Ventana, Oro Valley, Arizona). At Johns Hopkins, both IHC methods and antibodies were used. Tumors were classified as HER2-negative if IHC staining was 0 or 1+, and as HER2-positive if IHC staining was 3+. In cases with a score of 2+, FISH was performed to determine whether *HER2* was amplified in the tumor.

Dual-probe FISH was performed using fluorescently labeled probes to centromere 17 (CEP17) and a probe to the *HER2* gene. At the Johns Hopkins School of Medicine and Yale School of Medicine, FISH was performed using the Abbott Molecular PathVysion Kit (Abbott Molecular, Abbott Park, IL, USA). At the University of Minnesota, this was done

using the Dako IQFISH pharmDx kit (DAKO, Carpinteria, CA). Results on enumeration of at least 20 interphase tumor cell nuclei from specified tumor areas were reported as the average *HER2* copy number per cell and as the ratio of average *HER2* copy number to that of CEP17. Tumors were classified as HER2-amplified in cases of a HER2/CEP17 ratio ≥ 2.0 or an average HER2 copy number/cell ≥ 6.0 (14).

Statistics

Patient demographics, clinical characteristics, and treatment variables were compared between the HER2-positive and HER2-negative cohorts. For categorical variables, comparisons were drawn using chi-square contingency tables and Fisher's exact tests where appropriate. Continuous variables were compared using a t-test for independent samples to test equality of means, or using the Wilcoxon rank-sum test to compare medians for non-normally distributed variables. Recurrence and survival outcomes were also compared based on HER2 status. Progression-free survival (PFS) was defined as the time from surgery to documented disease recurrence or progression, last follow-up or death. Overall survival (OS) was defined as time from surgery to last follow-up or death. PFS and OS were determined in the HER2-positive and HER2-negative groups using Kaplan-Meier analysis, and log-rank tests were used to compare survival functions.

Cox proportional hazards analyses were subsequently performed to determine predictors of PFS and OS. Univariate analyses for each of PFS and OS were initially performed to assess the effects of age, race, ECOG score ≥ 2, tumor substage, lymph-vascular space invasion, HER2 status, lymphadenectomy, omentectomy, and receipt of adjuvant chemotherapy (with or without radiation therapy). Afterwards, covariates for the final multivariate models were selected using forward stepwise regression with variable exclusion if $p ≥ 0.2$. Statistical analyses were performed using STATA/SE 15.1 (STATA, College Station, TX, USA).

Results

Demographic and clinical features

One hundred sixty-nine patients met inclusion criteria and had tumor slides available for pathological analysis and HER2 testing. Patient demographics, clinical characteristics, and treatment variables were compared between HER2-positive and HER2-negative cohorts (Table 1). The mean age for the overall cohort was $68.0 ± 8.0$ years. The distribution of patients by race and ethnic background was also similar in the HER2-positive and HER2-negative groups, with the majority of patients being white (67.4%), followed by African American/Black (25.4%). Age, race, and ECOG performance score were unassociated with HER2 status.

HER2 status was not associated with surgical staging or approach. Overall, 137 patients (81.1%) underwent comprehensive surgical staging, including both pelvic and para-aortic lymphadenectomy. Pelvic washings were collected in 140 women (82.8%), among whom 12 (8.6%) had positive peritoneal cytology. These proportions did not differ by HER2 status.

Comparing pathologic features of HER2-positive and HER2-negative groups, no significant differences were found in substage, carcinoma originating in a polyp, the proportions of pure

and mixed histologies, and the presence of myometrial invasion. Overall, 130 patients (76.9%) had stage IA disease, while 39 patients (23.1%) had stage IB disease. One hundred forty patients (82.8%) had pure serous histology, 24 (14.2%) had mixed serous-endometrioid histology, and 5 (3.0%) had mixed serous-clear cell histology. HER2-positive tumors were significantly more likely to exhibit lymph-vascular space invasion compared to HER2-negative tumors (40.9% versus 18.4%; $p = 0.003$). Adjuvant therapy did not differ between HER2 cohorts. Most patients (70.4%) received adjuvant platinum/taxane-based chemotherapy with or without radiation therapy.

HER2 testing results

In 169 tumor samples, 44 (26.0%) were HER2-positive. Ninety-nine patients (58.6%) had tumors with IHC scores of 0 or 1+ and were classified as HER2-negative whereas 28 patients (16.6%) had tumors with an IHC score of 3+ and were classified as HER2-positive (Figure 1). The remaining 42 patients (24.9%) had tumors with 2+ IHC scores (equivocal). Dual-probe FISH was performed on these cases and 16 (38.1%) of these demonstrated *HER2* amplification. Rates of HER2 positivity were similar across all 3 study sites (22.8%, 26.1%, 28.8%, p=0.75)

Recurrence and survival outcomes

Recurrence and mortality rates were analyzed by HER2 status. With a median follow-up interval of 50 months (IQR 22 – 91 months), 43 patients (25.4%) experienced disease recurrence. Recurrence was significantly associated with HER2 status, with 50.0% of those with HER2-positive tumors experiencing disease relapse compared with 16.8% of those with HER2-negative tumors ($p < 0.001$) (Table 2). On Kaplan-Meier analysis, PFS was significantly worse in women with HER2-positive tumors ($p < 0.001$) (Figure 2A). At 36 months, the proportion of patients progression free was 0.84 (0.75–0.90) in the HER2 negative cohort and 0.49 (0.32–0.63) in the HER2 positive cohort (p<0.001) Of the 43 recurrences, 16 (37.2%) were pelvic, 17 (39.5%) were intra-abdominal, and 10 (23.3%) were extra-abdominal, with no difference by HER2 status ($p = 0.24$).

Overall, 39 patients (23.1%) died; 30 (17.8%) died of disease, and 9 (5.3%) died from other causes (Table 2). All cause mortality rates were significantly higher in women with HER2-positive tumors compared to those with HER2-negative tumors (34.1% versus 19.2%, $p = 0.044$). Women with HER2-positive tumors experienced significantly worse OS (log rank $p = 0.024$) (Figure 2B).

Univariate Cox proportional hazards analyses were performed to assess the impact of variables on PFS and OS (Supplementary Table 1). On multivariate analysis, HER2 positivity remained a strong independent risk factor for recurrence (aHR 3.50, 95% CI 1.84 – 6.67, p <0.001) and overall survival (aHR 2.00, 95% CI 1.04 – 3.88, $p = 0.039$) (Table 3).

Analyses were also performed for patients with pure serous histology only (excluding all patients with mixed histology). Results were similar. Notably, recurrence rates were higher in patients with HER2 positive tumors (45.5% vs 15.9%, p<0.001) HER2 positive tumors were associated with an increased hazard of recurrence (HR 3.44, 95% CI 1.72–6.9, p=0.001) and death (HR 1.92, 95% CI 0.89–4.16, p=0.10).

Discussion

In this study of women with stage I uterine serous carcinoma, patients with HER2 overexpression and/or gene amplification experienced significantly worse recurrence and survival outcomes than those without HER2 overexpression/amplification. HER2 positivity was associated with a three-fold greater risk of disease recurrence, and on both unadjusted and adjusted analyses, a significantly worse progression-free and overall survival. The overall cohort recurrence rate of 25% and mortality rate of 23% demonstrate the poor overall outcomes of women with early-stage USC.

Recurrences in USC are largely distant, multisite, and notoriously difficult to salvage with currently available therapies. Therefore, defining better and more targeted treatment strategies is an unmet clinical need in women with USC of all stages. This is one of the first studies to suggest that HER2 is overexpressed in 1 in 4 women with early-stage USC and may be a meaningful prognostic biomarker in this cohort. Furthermore, this study provides rationale for exploration of anti-HER2 therapy in this patient cohort.

Rates of HER2 positivity have varied dramatically in the literature, likely as a result of variable testing and reporting methods, as well as heterogeneous patient cohorts. In prior studies of HER2 expression in USC, advanced-stage tumors have represented the majority of samples, while early-stage tumors have represented a small fraction of samples. Reported rates of overexpression have ranged from 18–42%, and rates of gene amplification have varied from 16–47% (9–11, 16). Because HER2 positivity appears to be a prognostic biomarker for poor survival outcomes, higher rates of HER2 positivity might be expected in advanced-stage tumors. However, in this study, we found the rate of HER2 positivity to be comparable to that described in prior studies of predominantly advanced-stage tumors.

The oncogenic potential of the HER2 receptor is well known, although the significance of HER2 overexpression in the pathogenesis of USC remains poorly understood. In our cohort, HER2-positive tumors were significantly more likely to exhibit lymph-vascular space invasion ($p = 0.003$), suggesting that HER2 signaling may promote tumor invasiveness. HER2/PI3K/Akt activation has been demonstrated to drive resistance to multiple chemotherapeutic agents in breast and gastric adenocarcinoma (17, 18). Prior in vitro studies have suggested that HER2 may similarly promote chemo-resistance in USC (19). Our findings appear to be consistent with this data, as evidenced by the 50% recurrence rate reported among women with HER2-positive tumors, despite 70% receiving platinum/taxane-based adjuvant therapy.

Identifying HER2 as a biomarker in this high-risk disease has implications beyond prognosis, given that HER2 is an actionable target. Multiple anti-HER2 therapies have been described (20–25). In a recent phase II randomized trial, Fader et al evaluated 58 patients with advanced or recurrent uterine serous carcinoma overexpressing HER2 (13). Patients received carboplatin and paclitaxel with or without trastuzumab. Patients who received trastuzumab demonstrated an improved PFS of 12.6 versus 8.0 months compared to those who received placebo ($p = 0.005$; HR 0.44; (90% CI 0.26 – 0.76)). When examining the subgroups, the greatest reduction in recurrence risk was seen in the patients receiving

primary treatment for stage III or IV disease ($p = 0.013$, HR 0.40, 90% CI 0.20 –0.80), suggesting that the greatest benefit of trastuzumab is in the upfront treatment of advanced stage disease. These encouraging results prompted changes in the National Comprehensive Cancer Network (NCCN) Uterine Cancer Guidelines to include trastuzumab in addition to platinum and taxane-based chemotherapy as the preferred regimen for women with advanced or recurrent HER2-positive USC (26). The findings in the current study support extending the investigation of HER2-targeted therapies to early-stage USC.

We chose to use the 2007 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) breast cancer HER2 algorithms, noting that more recent guidelines do exist (7, 14). Based on two pre-trial pathology studies, the 2007 breast guidelines were used with specific modifications in the phase II study by Fader et al. Tumors with intense complete or lateral/basolateral membranous HER2 immunostaining in more than 30% of tumor cells were assigned a 3+ score, and 2+ score was assigned when intense complete or lateral/basolateral membrane staining was seen in 30%, or weak to moderate staining in 10% of tumor cells. We felt it was important to remain consistent with the limited data in this rare disease (15, 27). Ultimately, validating HER2 testing in uterine cancer will require not only consistency among testing platforms, but also correlations between testing and outcomes of targeted therapy.

Study strengths include its relatively large sample size, inclusion of only early stage patients, that most patients were comprehensively surgically staged and received adjuvant therapy, and that experienced gynecologic pathologists and HER2 specialists reviewed and tested all cases. Limitations of this study include its retrospective nature with inherent limitations and its broad time range, which was necessary in order to achieve adequate power. Additionally, the integrity of paraffin embedded tissue does diminish overtime, which could have resulted in falsely negative IHC or FISH analyses. Adjuvant treatment recommendations have changed over this time period, creating potential unrecognized bias.

Decades of research have informed the utility of HER2 testing and HER2-targeted therapy in breast cancer. We have only begun to explore role of HER2 in uterine cancer. Emerging clinical trial data are now informing our understanding of HER2 overexpression and/or amplification as a likely poor prognostic biomarker in multiple cancers, and particularly in uterine serous carcinoma. Our study provides rationale for the exploration of anti-HER2 therapies in women with early-stage, HER2-positive uterine serous carcinoma. A cooperative group trial is planned to determine the role of HER2-targeted therapy in women with primary uterine serous carcinoma of all stages.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Twenty six percent of stage I uterine serous carcinoma tumors were HER2 positive

- HER2 positivity was associated with a 3 fold greater risk of disease recurrence

- HER2 is a potential prognostic biomarker for women with early stage disease
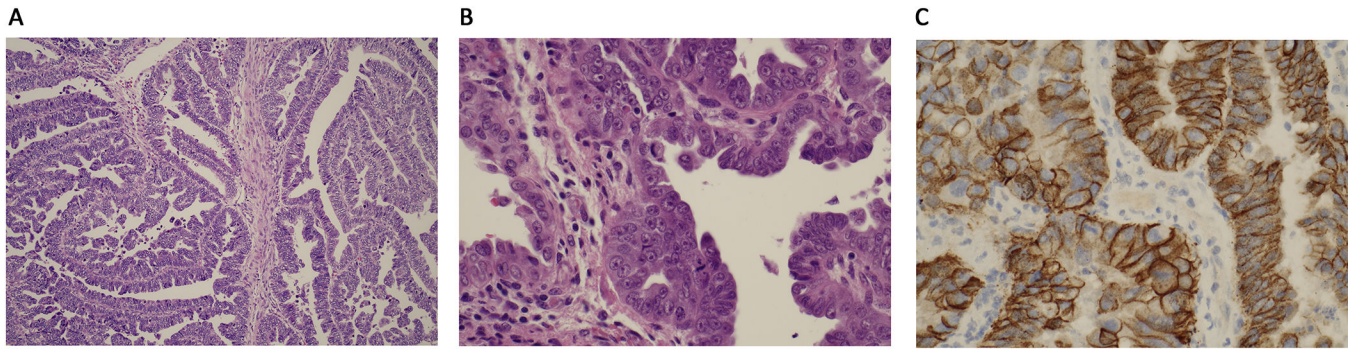
Figure 1:
Uterine serous carcinoma. a. papillary growth pattern b. malignant cells with prominent nucleoli and brisk mitotic activity c. HER2 immunohistochemical staining with 3+ staining pattern.
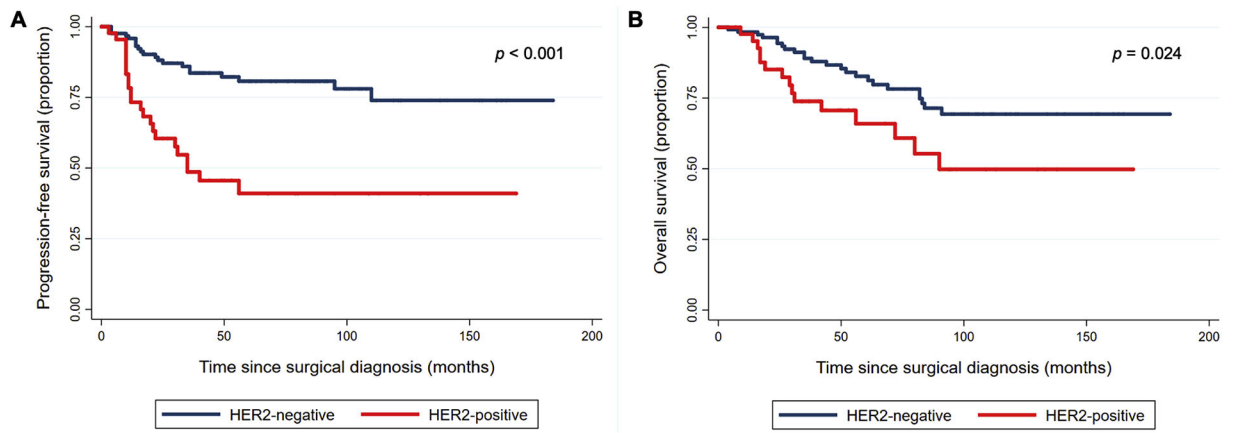
Figure 2:
Kaplan-Meier curves demonstrating (A) progression-free and (B) overall survival in women with stage I uterine serous carcinoma, stratified by HER2 status

Table 1:

Demographic and clinicopathologic characteristics of women with stage I uterine serous carcinoma stratified by HER2 status

	HER2-negative n = 125	HER2-positive n = 44	p-value
Mean Age (years)	67.9 ± 8.1	68.1 ± 7.7	0.86
Median BMI (kg/m^2)	32.0	28.7	0.13 [*]
Race/Ethnicity			
Caucasian/White	81 (64.8)	33 (75.0)	
Black/African American	34 (27.2)	9 (20.5)	
Asian	1 (0.8)	2 (4.5)	
Hispanic	4 (3.2)	0 (0.0)	
Other/decline to answer	5 (4.0)	0 (0.0)	
ECOG [†] performance status			0.43
0	96 (76.8)	33 (75.0)	
1	21 (16.8)	10 (22.7)	
2+	8 (6.4)	1 (2.3)	
History of breast cancer	22 (17.6)	4 (9.1)	0.23 [‡]
Surgical approach			
Minimally invasive (including robotic)	66 (52.8)	24 (54.6)	0.84
Laparotomy	59 (47.2)	20 (45.4)	
Omentectomy	94 (75.2)	34 (77.3)	0.78
Pelvic lymphadenectomy	114 (91.2)	43 (97.7)	0.15
Pelvic and para-aortic lymphadenectomy	102 (81.6)	35 (79.6)	0.77
Pelvic washings	102 (81.6)	38 (86.4)	0.47
Stage (FIGO 2009)			
IA	100 (80.0)	31 (70.4)	0.19
IB	25 (20.0)	13 (29.6)	
Originating in polyp	45 (36.0)	17 (38.6)	0.76
Histology			
Pure serous	107 (85.6)	33 (75.0)	0.27
Mixed serous-endometrioid	15 (12.0)	9 (20.4)	
Mixed serous-clear cell	3 (2.4)	2 (4.6)	
Myometrial invasion	75 (60.0)	30 (68.2)	0.34
Lymph-vascular space invasion	23 (18.4)	18 (40.9)	**0.003**
Positive peritoneal cytology (n=140)	9 (8.8)	3 (7.9)	1.00 [‡]
Adjuvant therapy			
None	31 (24.8)	11 (25.0)	0.99
Vaginal brachytherapy alone	6 (4.8)	2 (4.6)	
Chemotherapy alone	34 (27.2)	11 (25.0)	
Combined chemo-radiotherapy [**]	54 (43.2)	20 (45.4)	

	HER2-negative n = 125	HER2-positive n = 44	p-value
Median follow-up (months)	52 (22–95)	43 (19–80)	0.26 [*]

Data are mean ± SD, median (interquartile range), or n (%)

[*] p-value determined using Wilcoxon rank-sum test

[†] ECOG = Eastern Cooperative Oncology Group

[‡] p-value determined using Fisher's exact test

[**] 61 patients received brachytherapy, 6 patients pelvic radiotherapy, 7 patients brachytherapy + pelvic radiotherapy

Table 2:

Comparison of rates of disease recurrence and death according to HER2 status

	HER2-negative n = 125	HER2-positive n = 44	p-value
Recurrence	21 (16.8 %)	22 (50.0 %)	< 0.001
Death *	24 (19.2 %)	15 (34.1 %)	**0.044**

*
Deaths due to all causes. Nine patients died of non-uterine cancer causes including 8 in the HER2- negative cohort and 1 in the HER2-positive cohort.

Table 3:

Multivariate Cox proportional hazards analyses for predictors of progression-free and overall survival, with selection of covariates using stepwise forward selection (p<0.2)

Progression-free survival				Overall Survival			
Covariate	Adjusted Hazard Ratio (aHR)	95% Confidence Interval	p-value	Covariate	Adjusted Hazard Ratio (aHR)	95% Confidence Interval	p-value
Lymph-vascular space invasion	1.71	0.80 – 3.63	0.17	Age (years)	1.038	0.99 – 1.08	0.063
Stage IB	1.71	0.79 – 3.67	0.17	Stage IB	2.241	1.11 – 4.51	0.029
Omentectomy	0.45	0.23 – 0.87	0.018	Omentectomy	0.566	0.28 – 1.13	0.11
Adjuvant chemotherapy +/− radiation therapy	0.50	0.25 – 0.99	0.046	ECOG[*] score 2	3.099	1.18 – 8.14	0.022
HER2+	3.50	1.84 – 6.67	< 0.001	HER2+	2.00	1.04 – 3.88	0.039

[*] ECOG = Eastern Cooperative Oncology Group