CANCER GENETICS

Clinical Implications of Genomic Loss of Heterozygosity in Endometrial Carcinoma

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PURPOSE Homologous recombination deficiency, identified by homologous recombination deficiency gene alterations or high percentage of genome-wide loss of heterozygosity (gLOH), is associated with improved prognosis, platinum sensitivity (PS), and poly (ADP-ribose) polymerase inhibitor response in high-grade ovarian cancer. Since the copy number–high (CN-H) endometrial cancer molecular subtype (EC-MS) shares molecular features with high-grade ovarian cancer, our aim was to assign EC-MS on the basis of comprehensive genomic profiling (CGP) results and evaluate the gLOH status with clinical behavior of EC.

METHODS Eighty-two epithelial EC tumor tissues were sequenced by hybrid capture–based CGP, and results were used to assign EC-MS (ultramutated, microsatellite instability–high, CN-low; CN-high). Retrospective chart review established clinical characteristics, including PS. Relationships of PS, EC-MS, gene alterations, and gLOH were assessed statistically.

RESULTS PS and EC-MS of CN-H showed statistically significant difference in overall survival (OS). Most notably, when the CN-H EC-MS was subcategorized by gLOH status, there was a significant difference in OS with gLOH-H being associated with longer survival. Cox semi-proportional hazard modeling showed that gLOH, stage, and race were significant in modeling OS.

CONCLUSION The method of assigning EC-MS by CGP demonstrates similar clinical features to previous reports of EC-MS assigned by other methods. CGP can also assess gLOH status with gLOH-H most commonly seen in CN-H tumors. CN-H, gLOH-H patients showed significantly improved OS (hazard ratio, 0.100 [0.02-0.51 95% CI]). Thus, gLOH status may be a meaningful prognostic biomarker within the CN-H tumors and possibly across EC-MS.

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INTRODUCTION

Emerging data suggest that *BRCA1/2* mutations and homologous recombination deficiency (HRD) may play a role in the pathogenesis of a subset of endometrial carcinomas. Homologous recombination is a high-fidelity DNA repair mechanism that repairs double-stranded DNA breaks. Platinum-based chemotherapeutics cause intrastrand links in DNA and have shown particular efficacy in killing HRD cancer cells, which are less able to repair this type of DNA damage. Because poly (ADP-ribose) polymerase inhibitors (PARPi) inhibit the secondary single-strand base excision repair process, platinum-sensitive (PS) HRD tumors treated with PARPi experience synthetic lethality in their ability to repair DNA damage: one DNA repair mechanism is lost to somatic or hereditary mutation and the second repair mechanism blocked by targeted therapy leads to irreversible cell damage and death.[1]

Loss of heterozygosity (LOH) is the irreversible loss of one parental allele of a gene and each instance can be detected by DNA sequencing of tumor tissue. A genome-wide LOH (gLOH) percentage can be assigned by assessing the ratio of affected DNA segments to unaffected segments across the tumor genome. High gLOH (gLOH-H) is observed in high-grade ovarian cancer (HGOC) with homozygous *BRCA1/2* mutations, can be an indicator of HRD, and has been associated with PARP inhibitor sensitivity.[2,3] The ARIEL 2 and 3 trials showed that a gLOH-H could identify a population of patients without *BRCA1/2* mutations who might be HRD because of other mechanisms. Patients with *mutBRCA* or *wtBRCA,* gLOH-H (≥ 16%), and platinum-sensitive ovarian carcinomas treated with rucaparib demonstrated longer progression-free survival compared with patients with *wtBRCA* gLOH-L carcinomas. These results suggest that gLOH can be used to identify patients with *wtBRCA* ovarian cancers who might benefit from rucaparib because of an HRD-associated process.[4,5] Recently, patients with *mutBRCA1/2* pancreas, prostate,

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

High genomic loss of heterozygosity (gLOH-H) is a known marker of sensitivity to platinum-based chemotherapy and poly (ADP-ribose) polymerase inhibitors in high-grade serous ovarian cancer. This retrospective study examined whether gLOH-H status had prognostic and/or predictive correlation to clinical behavior in epithelial endometrial cancer. Additionally, it evaluated the clinical value of assigning the endometrial cancer molecular subtype by comprehensive genomic profiling parameters.

Knowledge Generated

Among the copy number–high (CN-H) patients, gLOH-H status was associated with prolonged OS. Endometrial cancer molecular subtype can be assigned by comprehensive genomic profiling results, with similar clinical outcomes as compared with subtyping by other methods.

Relevance

The CN-H molecular subtype of endometrial cancer is associated with the worst prognosis of the four groups, but high gLOH can identify a subset of these patients with better prognosis. Further studies on the basis of this biomarker should be pursued to discover potential differential responses to treatments.

and breast adenocarcinoma have also demonstrated responsiveness to PARPi therapy suggesting that synthetic lethality in the double-strand DNA break repair pathway may be a relevant therapeutic approach if one can appropriately identify HRD tumors.[6,7] A pan-cancer analysis has identified an association between biallelic *BRCA1/2* mutation and an HRD signature in tumors regardless of the site of tissue origin and predicted a gLOH cutoff that ranged between 14% and 17% for most cancers.[8] In this study, approximately 70% of biallelic *mutBRCA1/2* and about 16% of *wtBRCA1/2* endometrial cancers (ECs) had a gLOH $\geq$ 16%.

Analysis of The Cancer Genome Atlas (TCGA) EC whole-exome and whole-genome sequence data identified four distinct molecular subtypes of endometrial cancer (EC-MS) with differing clinical outcomes: two characterized by high tumor mutation burden (TMB) distinguished by the mutational mechanisms, and two with low TMB but distinguished by their levels of genomic instability. Microsatellite-unstable tumors (microsatellite instability–high [MSI-H]) have a high TMB from insertion and deletion events related to mismatch repair deficiency. Ultramutated ECs are microsatellite-stable (MSS) but demonstrate an even higher TMB because of DNA polymerase epsilon (*POLE*) mutations and are associated with the best prognosis. Copy number–high (CN-H) ECs have low TMB and were characterized by extensive DNA segment copy number variability similar to ovarian serous carcinoma, usually had high-grade histology, and were associated with the worst prognosis. Finally, the copy number–low (CN-L) subtype comprised ECs with low TMB and without genomic instability of the CN-H ECs.[9]

Talhouk et al proposed a TCGA-like EC-MS categorization strategy that did not require whole-exome or whole-genome sequencing but instead used mismatch repair protein immunohistochemistry, *POLE* single-gene mutational analysis, and p53 immunohistochemistry as a surrogate for copy number status. This study showed similar clinical outcomes as the TCGA analysis for each of the molecular subtypes when combined with clinicopathologic type (stage, histotype, grade, and lymphovascular invasion).[10]

Our study investigates the relationship between clinical features of advanced epithelial EC and the combination of TCGA-like EC-MS and gLOH status determined by comprehensive genomic profiling (CGP) results. In particular, we hypothesized that patients with CN-H EC may show an HRD phenotype similar to HGOC, which may predict platinum responsiveness and affect prognosis.

METHODS

In this retrospective analysis, EC tumor samples with predominantly aggressive histology, advanced stage, or recurrent disease were submitted from a single institution to Foundation Medicine for next-generation sequencing to inform clinical decision making. Tumor tissue collected from 117 uterine malignancies at our institution, of which 103 were epithelial, were analyzed between March 2013 and May 2020 (Fig 1). All classes of genomic alterations were identified by hybrid-capture, next-generation sequencing of exons and select introns from up to 324 genes in a Clinical Laboratory Improvement Amendments–certified, College of American Pathologists–accredited laboratory (Foundation Medicine, Cambridge, MA). In brief, $\geq$ 50 ng DNA was extracted from 40 microns of tumor samples and assayed using adaptor ligation and hybrid capture and sequenced using Illumina technology to a mean exon coverage depth of $>$ 500×, with resulting sequences analyzed as previously described.[11]

TMB was calculated as mutations per megabase (muts/Mb) using the number of somatic base substitution or

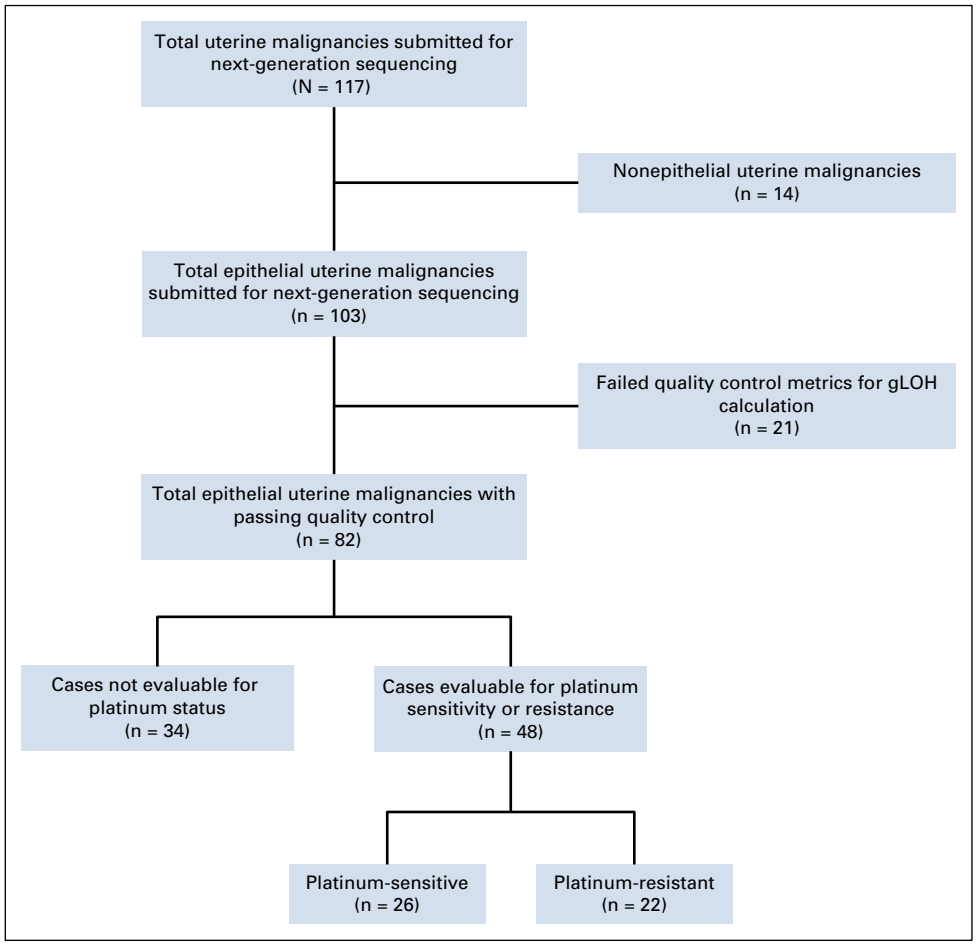

FIG 1. Schematic of database creation with entire cohort equaling 82 patients, with 48 patients evaluable for platinum sensitivity or resistance. gLOH, genome-wide loss of heterozygosity.

insertion and deletion alterations excluding known somatic and deleterious mutations on 0.8- to 1.1-Mb sequenced DNA as previously described, and microsatellite instability was determined at 95-114 loci as previously described.[12,13]

Genomic LOH was calculated by quantifying LOH at > 3,500 sequenced SNPs excluding whole chromosome arm losses (defined as > 90% loss of the arm) and SNPs with ≥ 40% mutant allele frequency as previously described and analytically validated in ovarian cancer samples.[14] To pass quality control (QC) metrics for reporting, specimens required ≥ 35% computed tumor purity for gLOH and determinable tumor ploidy and copy number calls. Only patients with specimens that passed all QC criteria were included in our final analysis (n = 82). Scores were reported as percentage gLOH, and ≥ 16% was used to define the high-gLOH group on the basis of the threshold previously established in ovarian cancer.[14]

The entire cohort of epithelial endometrial carcinoma cases with passing QC metrics were assigned molecular subtypes (EC-MS) using microsatellite status, TMB, and the presence or lack of *TP53* alterations. MSI-H subtype was assigned if microsatellite status is MSI-H with any TMB score and *wtTP53* or *mutTP53*; CN-H subtype if MSS, any TMB score, and *mutTP53*; and CN-L subtype if MSS, TMB < 20 muts/Mb, and *wtTP53*. No ultramutated and *POLE* (MSS, TMB > 20 muts/Mb) cases were identified in the cohort. After obtaining institutional review board (IRB) approval, retrospective chart review established clinical characteristics for these patients (n = 82), including response to platinum adjuvant treatment (n = 48). Thirty-four cases were not evaluable for platinum status as they did not receive platinum-based systemic treatment, no follow-up data after platinum-based treatment was available, or patient had not reached interval of time (≥ 6 months) after completion of platinum to make determination of without relapse to meet definition of PS. PS was defined as progression-free survival ≥ 6 months per the ovarian cancer literature. Platinum-resistant (PR) patients included those who progressed on platinum therapy or progressed within 6 months after conclusion of platinum adjuvant therapy. Twelve patients were excluded from the recurrence-free survival (RFS) analysis as they presented at an advanced stage, underwent primary systemic therapy, never reached a disease-free state, and progressed on therapy. These 12 patients were included in the overall survival (OS) analysis.

Relationships of PS, gene alterations, EC-MS, and gLOH were assessed using *t* test or Wilcoxon rank-sum test for

continuous variables and chi-square and Fisher's exact test for categorical variables. Kaplan-Meier nonparametric product-limit function was used to construct and estimate the RFS and OS in the current data set. Log-rank nonparametric test was used to compare the distribution of survival outcomes between groups of patients. To model survival outcomes by clinical variables, Cox semi-proportional hazard (Cox PH) model was used, and stepwise selection method was used to eliminate insignificant variables to the model. Hazard ratios and 95% CIs for the hazard ratios were provided for variables included in the Cox PH survival models.

RESULTS

Of the 82 patients with epithelial EC with evaluable QC criteria, 16 patients were MSI-H, 16 patients CN-L, and 50 patients CN-H molecular subtype. The demographics table (Table 1) reviews characteristics of the entire cohort and also compares the CN-H patients (column 3) with the non–CN-H subtypes (MSI-H and CN-L combined, column 2). There was a statistically significant difference in histotype between EC-MSs, with a preponderance of carcinosarcoma and serous cases within CN-H and lower-grade endometrioid cases falling within MSI-H and CN-L. Similarly, 98% of the CN-H cases were classified as grade 3, whereas the other EC-MSs showed a wider distribution of grade (25% grade 1, 22% grade 2, and 53% grade 3) (Table 1). Although there was no statistically significant difference in stage between CN-H and other molecular subtypes within this cohort, CN-H patients were more likely to undergo adjuvant chemotherapy (85% of CN-H cases compared with 48% of other molecular subtypes). Of the evaluable cases, 48 received platinum adjuvant chemotherapy, with 26 cases showing platinum-sensitive (PS) and 22 PR responses. There were no statistically significant differences in demographics between PS and PR groups (Appendix Table A1). However, recurrence rates were similar in both CN-H and the other EC-MSs (91% *v* 84%) reflecting the clinical selection criteria of advanced, aggressive, or recurrent disease used for pursuing CGP testing. Targeted therapy was used to treat the CN-H patients with about the same frequency as the other molecular subtypes (30% *v* 35%). Hormonal treatment was used in 40% of the MSI-H and CN-L patients and zero CN-H patients (Table 1).

When examining the relationship between gLOH-H status and EC-MS, there was a statistically significant association using a cutoff of 16% ($P = .013$) as has been applied in ovarian cancer, as well as a lower cutoff of 14% ($P = .002$). There was a higher proportion of gLOH-H within the CN-H cases, and the majority of MSI-H and CN-L cases were found to be gLOH-L (97%) (Table 1).

Kaplan-Meier curves for RFS showed statistical significance when stratified by either molecular subtype or platinum status. When stratifying by EC-MS, CN-H patients fared the worst, MSI-H had the longest RFS, and CN-L demonstrated intermediate RFS. Platinum-sensitive patients had significantly improved RFS. OS by EC-MS was not statistically significant ($P = .076$), but OS by platinum status was significant ($P < .0001$) (Fig 2). When CN-H cases were compared with the other molecular subtypes, they had significantly shorter RFS intervals ($P < .0001$). OS curves were statistically significant when comparing CN-H with other subtypes ($P = .023$) (Fig 3).

When assessing OS by gLOH, there was no statistically significant difference between gLOH-H (≥ 16%) and gLOH-L patients in the overall cohort ($P = .074$). However, when CN-H subtype cases were subclassified by gLOH status, CN-H gLOH-H patients had significantly improved OS compared with CN-H gLOH-L patients ($P = .013$) (Fig 4).

Cox semi-proportional hazard modeling of RFS and OS was performed using gLOH first as a categorical variable (gLOH high ≥ 16% and gLOH low < 16%) (Table 2) and then as a linear variable (Appendix Table A2). The gLOH both as a categorical variable and a linear variable was significant in modeling OS, along with stage IV and Black race. Linear modeling of gLOH suggests that as gLOH increases incrementally, there is a concordant increase in OS. Stage III and CN-H category were significant in modeling RFS (Table 2).

Finally, particular gene alterations were assessed for association with gLOH and platinum status. In all patients with CN-L and CN-H subtypes, patients with gLOH-H (> 16%) were enriched for alterations in *FGFR1* ($P = .04$) and *WHSC1L1* ($P = .02$). Platinum-sensitive patients with a CN-L or CN-H tumor types were enriched for alterations in *KRAS* ($P = .05$) compared with PR patients. There were three cases in the cohort with alterations in *BRCA1/2*. One patient harbored a homozygous, germline *BRCA1* E1053* alteration and was gLOH-H (32.86%). Another had a homozygous, germline *BRCA2* S1982fs*22 and was also gLOH-H (20.62%). A third case had a *BRCA2* rearrangement predicted to result in a truncated protein and had a gLOH score categorized as low but was near the threshold (13.95%). All three patients were platinum-sensitive.

DISCUSSION

This study confirmed the validity of defining EC-MS by CGP characteristics, by comparing this surrogate for TCGA molecular subtype with clinical outcomes. Additionally, we aimed to extend our understanding by interrogating the relationship of EC-MS with gLOH status and platinum responsiveness. We found CGP-defined EC-MS showed similar clinical behavior of the three subtypes as previously observed in the TCGA analysis. Our cohort analysis validates the observation that compared with other molecular subtypes, CN-H serous-like tumors have significantly worse PFS as originally reported by Levine et al[9] and a worse RFS as reported in the follow-up study by Talhouk et al,[10] despite our cohort representing predominantly advanced or recurrent ECs of other molecular subtypes. The EC-MS was

TABLE 1. Demographic Data of Entire Patient Cohort and by TCGA Status

Characteristic	Entire Cohort (N = 82)	MSI-H and CN-L (n = 32)	CN-H (n = 50)	*P*
Age, years	65 (61-71)	61.5 (53-68)	66.5 (64-71)	.0077
Race, n (%)				
Asian and others	16 (20.0)	8 (25.0)	8 (16.7)	.067
Black	24 (30.0)	5 (15.6)	19 (39.6)	
White	40 (50.0)	19 (59.4)	21 (43.8)	
Histology, n (%)				
Endometrioid	25 (30.5)	22 (68.8)	3 (6.0)	< .001
Serous	30 (36.6)	2 (6.2)	28 (56.0)	
Carcinosarcoma	13 (15.9)	1 (3.1)	12 (24.0)	
Clear cell	8 (9.8)	5 (15.6)	3 (6.0)	
Others[a]	6 (7.3)	2 (6.2)	4 (8.0)	
Grade, n (%)				
G1	8 (9.8)	8 (25.0)	0 (0.0)	< .001
G2	7 (8.5)	7 (21.9)	0 (0.0)	
G3	67 (81.7)	17 (53.1)	50 (100.0)	
Stage, n (%)				
I	26 (31.7)	11 (34.4)	15 (30.0)	.175
II	3 (3.7)	3 (9.4)	0 (0.0)	
III	30 (36.6)	10 (31.2)	20 (40.0)	
IV	23 (28.0)	8 (25.0)	15 (30.0)	
Therapies				
Adjuvant chemotherapy, n (%)				
Yes	56 (71.8)	14 (48.3)	42 (85.7)	.001
Targeted therapy, n (%)				
Yes	19 (32.2)	7 (35.0)	12 (30.8)	.775
Hormonal therapy, n (%)				
Yes	9 (15.3)	9 (45.0)	0 (0.0)	< .001
Recurrence, n (%)				
Yes	62 (75.6)	21 (65.6)	41 (82.0)	.443
No	8 (9.8)	4 (12.5)	4 (8.0)	
Not evaluable[b]	12 (14.6)	7 (21.9)	5 (10.0)	
gLOH 16, n (%)				
Low < 16%	69 (84.1)	31 (96.9)	38 (76.0)	.013
High ≥ 16%	13 (15.9)	1 (3.1)	12 (24.0)	
gLOH 14, n (%)				
Low < 14%	65 (79.3)	31 (96.9)	34 (68.0)	.002
High ≥ 14%	17 (20.7)	1 (3.1)	16 (32.0)	

NOTE. Graphic compares the demographics of MSI-H and CN-L (column 3) versus CN-H (column 4). Please see Appendix Table A1 for demographics of platinum-sensitive versus platinum-resistant subgroups.

Abbreviations: CN-H, copy number–high; CN-L, copy number–low; gLOH, genome-wide loss of heterozygosity; MSI-H, microsatellite instability–high; RFS, recurrence-free survival; TCGA, The Cancer Genome Atlas.

[a]Histologies within the others category include undifferentiated, dedifferentiated, and poorly differentiated mullerian.

[b]Patients with advanced disease at time of diagnosis with no disease-free period were deemed not evaluable for recurrence and excluded from RFS analysis.

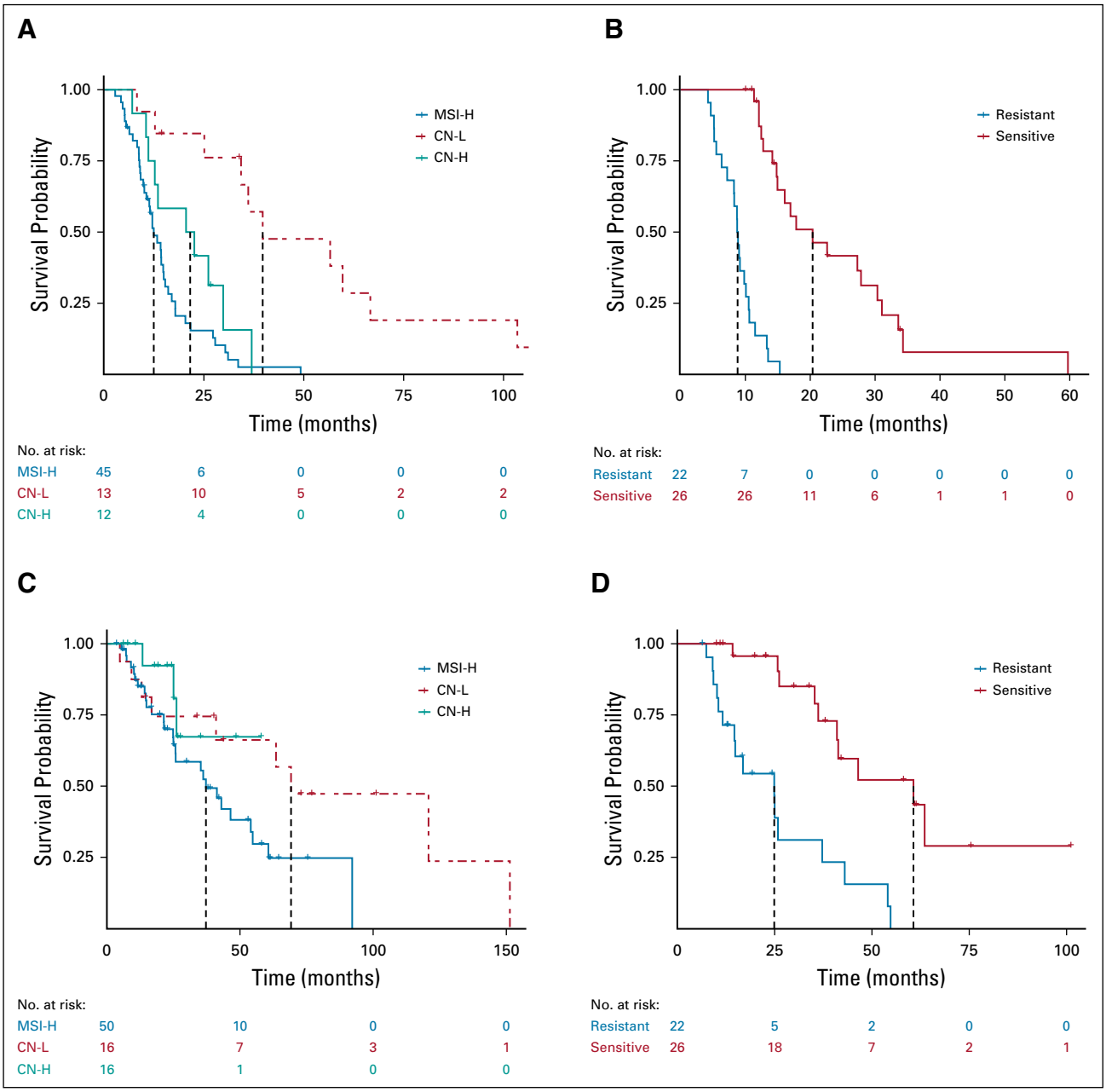

FIG 2. RFS and OS by EC-MS and platinum sensitivity. (A) RFS by EC-MS, $P < .0001$. (B) RFS by platinum sensitivity, $P < .0001$. (C) OS by EC-MS, $P = .076$. (D) OS by platinum sensitivity, $P < .0001$. CN-H, copy number–high; CN-L, copy number–low; EC-MS, endometrial cancer molecular subtype; MSI-H, microsatellite instability–high; OS, overall survival; RFS, recurrence-free survival.

also a significant predictor for OS, when comparing CN-H subtype with the others. Again, seeing significance in the OS analysis maintain in this cohort is particularly interesting, since there was inherent selection bias by clinicians for ordering next-generation sequencing for patients with clinically more aggressive tumors or for those who had already recurred on standard treatment and needed alternative therapy options. Consistent with this, our cohort did not have any *POLE* ultramutated subtype, which has been observed to have the best outcome and is less likely to recur.[15] Despite the cohort bias, statistical significance was maintained in OS analysis for PS and our analysis recapitulated established poor clinical outcomes for PR patients. As next-generation sequencing becomes more ubiquitous in patient care and molecular tumor subtyping of EC moves into the diagnostic workup of a patient to inform treatment decisions, a greater separation of OS curves will likely be observed.

Previous studies of HGOC have shown that HRD, irrespective of *BRCA1/2* alteration status, is associated with better outcomes for patients treated with platinum

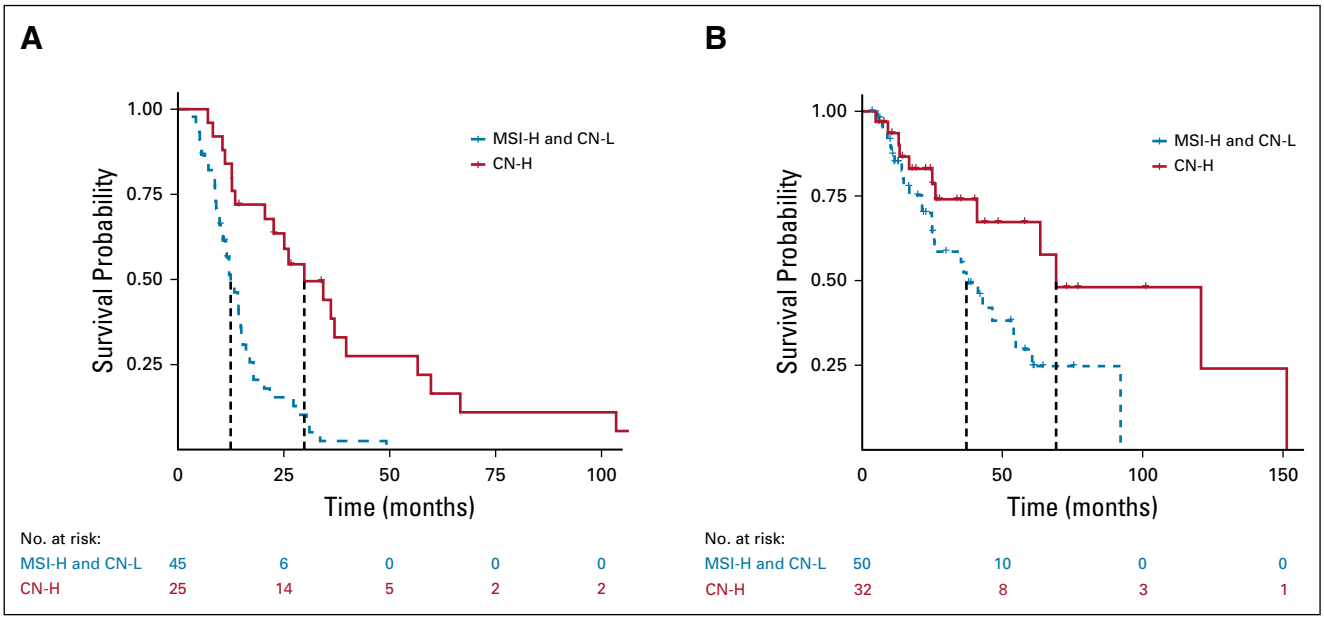

FIG 3. CN-H RFS and OS compared with the other EC-MSs. (A) RFS compared between CN-H and other molecular subtypes (MSI-H and CN-L), $P < .0001$. (B) OS compared between CN-H and other molecular subtypes (MSI-H and CN-L), $P = .023$. CN-H, copy number–high; CN-L, copy number–low; EC-MS, endometrial cancer molecular subtype; MSI-H, microsatellite instability–high; OS, overall survival; RFS, recurrence-free survival.

agents.[16,17] In this cohort of advanced ECs using gLOH-H status with > 16% threshold as a proxy for HRD, we found no statistically significant correlation between gLOH-H and PS, RFS, or OS when including all TCGA categories. However, similar to what has been described in HGOC, when we restricted the gLOH analysis to the most aggressive EC molecular subtype of the CN-H tumors, there was a significant difference in OS associated with gLOH status, with the gLOH-H patients living longer ($P = .013$) compared with the CN-H patients with gLOH-L. gLOH-H was also shown to be a significant predictor of OS by Cox semi-proportional hazard modeling. By comparison, in this cohort, the histologic category (endometrioid *v* other histologies) was not associated with RFS or OS benefit in the multivariate analysis. This observation adds to prior studies that have reported inconsistent associations of histologic

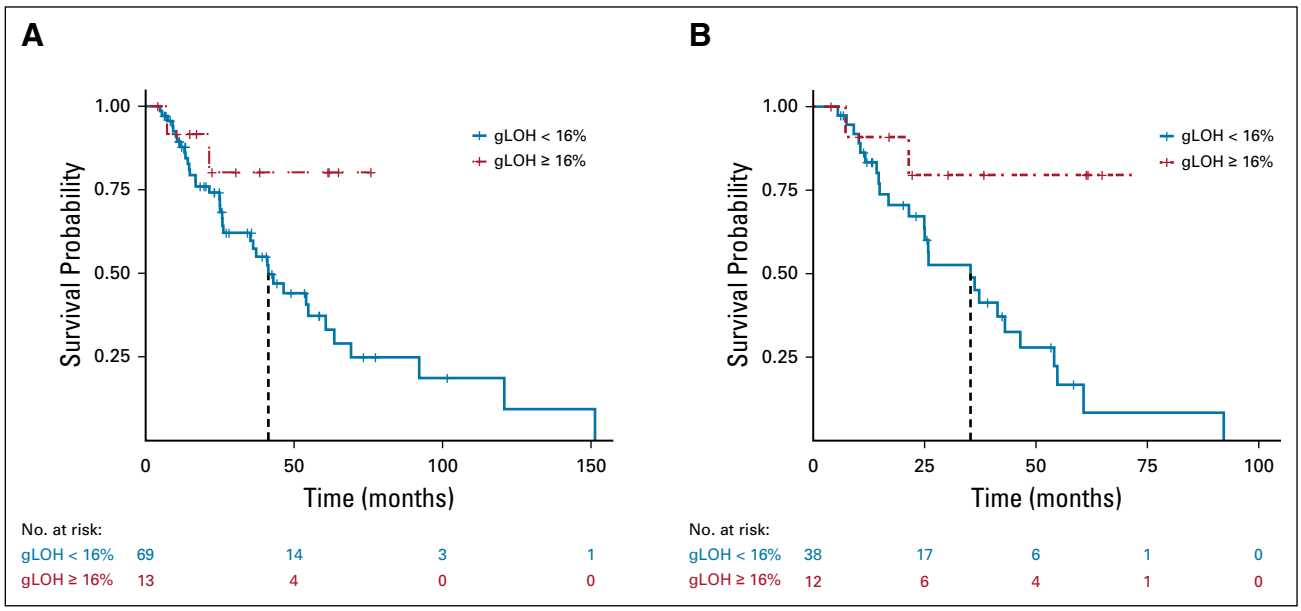

FIG 4. OS by gLOH 16% within entire cohort, then within CN-H molecular subtype. (A) OS within entire cohort by gLOH 16%, $P = .074$. (B) OS within CN-H cases, by gLOH 16%, $P = .013$. CN-H, copy number–high; gLOH, genome-wide loss of heterozygosity; OS, overall survival.

TABLE 2. Cox Regression Modeling for RFS and OS by gLOH as a Categorical Variable (gLOH High ≥ 16%, Compared With gLOH Low < 16%)

Characteristic	RFS (n = 70)	OS (N = 82)
gLOH ≥ 16%	0.60 (0.25-1.41)	0.10*** (0.02-0.51)
Age, years	0.99 (0.96-1.03)	1.01 (0.97-1.05)
BMI	0.99 (0.94-1.04)	0.97 (0.91-1.04)
Stage III	2.98*** (1.38-6.47)	3.09** (1.18-8.10)
Stage IV	2.41* (0.93-6.29)	3.92*** (1.44-10.66)
Black race	1.72 (0.77-3.87)	3.37** (1.23-9.28)
CN-H	5.87*** (2.01-17.18)	1.82 (0.51-6.46)
Endometrioid histology	0.46 (0.16-1.38)	0.88 (0.26-3.01)

NOTE. See Appendix Table A2 for Cox regression modeling for RFS and OS by gLOH as a linear variable. *$P < .05$, **$P < .01$, ***$P < .001$.

Abbreviations: BMI, body mass index; CN-H, copy number–high; gLOH, genome-wide loss of heterozygosity; OS, overall survival; RFS, recurrence-free survival.

subtypes in high-grade disease with patient outcomes.[18-20] For example, although Alkushi et al demonstrated survival advantage for endometrioid carcinomas, studies by Voss et al and Soslow et al both showed no difference in disease-specific survival between histologic subtypes. Given the ambiguous predictive value of histologic characterization, the results of our study support the additional utility of comprehensive genomic information to support more accurate disease classification as EC-MS that can better predict patient outcomes.

In trials of PARP inhibitors, *BRCA1/2* alteration status and HRD as established by gLOH-H or other methods independent of *BRCA* alterations have demonstrated efficacy as biomarkers of therapy response.[4,21] The utilization of a cutoff of 16% for gLOH-H in this study was based upon the results of the ARIEL 3 trial for ovarian cancer. Additionally, a recent study by Sokol et al demonstrated that gLOH-H cutoff of 14%-16% had adequate sensitivity and specificity as a genomic phenotype for stratifying biallelic *mutBRCA* alterations from *wtBRCA*, non-HRD tumors in ECs[8] and supports our selection of a 16% threshold for this retrospective, correlative study. Consistent with the Sokol study, two of the three patients in our EC cohort with *BRCA1/2* mutations were gLOH-H and the third had a score close to the threshold (13.96%) and notably all were platinum-sensitive.

This study has several limitations. As mentioned above, there was inherent selection bias for patients submitted for tumor genomic sequencing to have overwhelmingly presented with advanced disease or had already recurred on standard therapy. Additionally, the study has inherent weaknesses associated with the retrospective nature of review with some patients lost to follow-up or missing data. Finally, the sample size with evaluable platinum status was limited with 26 PS and 22 PR patients. Moreover, this study has important strengths. To our knowledge, it is the first study to investigate the relationship between clinical prognosis and percent genomic LOH in EC. Additionally, this study provides further evidence that defining EC molecular subtypes from comprehensive tumor genomic profiling results obtained during the course of clinical care yields prognostic information about clinical outcomes comparable with the more labor-intensive technique used by TCGA.

In summary, these results suggest gLOH may be an additional meaningful biomarker of prognosis beyond molecular subtype in EC, especially within the CN-H tumors. Further studies will focus on determining if gLOH-H predicts benefit or duration of response from platinum-based therapy. Additionally, prospective trials that include molecular subtype and HRD status assessment are needed to further optimize and validate a gLOH cutoff for both prognosis and to investigate the relevance of PARPi therapy in EC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

TABLE A1. Demographic Data of Patients Evaluable for Platinum Status, With Platinum-Resistant Versus Platinum-Sensitive Patients Compared

Characteristic	Platinum-Resistant (n = 22)	Platinum-Sensitive (n = 26)	*P*
Age, years	67.5 (63-71.8)	66 (60-67.8)	.5289
Race (%)			
Asian and others	4 (19.0)	6 (24.0)	.299
Black	10 (47.6)	6 (24.0)	
White	7 (33.3)	13 (52.0)	
Histology (%)			
Endometrioid	3 (13.6)	3 (11.5)	.767
Serous	8 (36.4)	14 (53.8)	
Carcinosarcoma	6 (27.3)	5 (19.2)	
Clear cell	3 (13.6)	3 (11.5)	
Others	2 (9.1)	1 (3.8)	
Grade (%)			
G1	0 (0.0)	0 (0.0)	1
G2	1 (4.5)	2 (7.7)	
G3	21 (95.5)	24 (92.3)	
Stage (%)			
I	5 (22.7)	9 (34.6)	.655
II	0 (0.0)	0 (0.0)	
III	11 (50.0)	12 (46.2)	
IV	6 (27.3)	5 (19.2)	
Status at last follow-up (%)			
No evidence of disease	0 (0.0)	6 (23.1)	.019
Alive with disease	6 (27.3)	10 (38.5)	
Died of disease	16 (72.7)	10 (38.5)	
Recurrence (%)			
No	0 (0.0)	6 (23.1)	.025
Yes	22 (100.0)	20 (76.9)	
Therapies			
Targeted therapy (%)			
Yes	5 (29.4)	6 (31.6)	1
Hormone therapy (%)			
Yes	1 (5.9)	1 (5.3)	1
TCGA (%)			
MSI-H	2 (9.1)	2 (7.7)	.324
CN-L	1 (4.5)	5 (19.2)	
CN-H	19 (86.4)	19 (73.1)	
gLOH 16 (%)			
< 16%	21 (95.5)	19 (73.1)	.055
≥ 16%	1 (4.5)	7 (26.9)	
gLOH 14 (%)			
< 14%	19 (86.4)	19 (73.1)	.307
≥ 14%	3 (13.6)	7 (26.9)	

Abbreviations: CN-H, copy number–high; CN-L, copy number–low; gLOH, genome-wide loss of heterozygosity; MSI-H, microsatellite instability–high; TCGA, The Cancer Genome Atlas.

TABLE A2. Cox Regression Modeling for RFS and OS by gLOH as a Linear Variable

Characteristic	RFS (n = 70)	OS (N = 82)
gLOH linear variable	0.96 (0.92-1.01)	0.88*** (0.82-0.95)
Age, years	0.99 (0.96-1.03)	1.01 (0.97-1.06)
BMI	0.98 (0.94-1.03)	0.97 (0.91-1.03)
Stage III	3.05*** (1.41-6.58)	2.92** (1.10-7.77)
Stage IV	2.76** (1.05-7.27)	6.75*** (2.29-19.88)
Black race	1.73 (0.77-3.87)	3.78** (1.34-10.68)
CN-H	6.78*** (2.25-20.39)	2.83 (0.70-11.50)
Endometrioid histology	0.53 (0.17-1.63)	1.08 (0.29-3.97)

NOTE. *$P < .05$, **$P < .01$, ***$P < .001$.

Abbreviations: BMI, body mass index; CN-H, copy number–high; gLOH, genome-wide loss of heterozygosity; OS, overall survival; RFS, recurrence-free survival.