Genomic and immunohistochemical characterization of NSMP endometrial cancer: a novel approach to estrogen receptor positivity

Alexander C. Cohen[1], Sharon Wu[2], Ninad Kulkarni[2], Matthew J. Oberley[2], Premal H. Thaker[3], Thomas J. Herzog[4], Matthew A. Powell[3], Britt K. Erickson[5], Michael D. Toboni[6]

[1]Division of Gynecologic Oncology, RUSH University Medical Center, Chicago, IL; [2]Caris Life Sciences, Phoenix, AZ; [3]Division of Gynecologic Oncology, Washington University, St. Louis, MO; [4]University of Cincinnati Cancer Center; Cincinnati, OH; [5]Division of Gynecologic Oncology, University of Minnesota, Minneapolis, MN; [6]Division of Gynecologic Oncology, University of Alabama, Birmingham, AL

SGO ANNUAL MEETING ON WOMEN'S CANCER SEATTLE, WA • 2025

Objective

We aimed to describe the genomic and clinical characteristics of the no specific molecular profile (NSMP: *POLE*-WT, MSS, and *TP53*-WT) endometrial cancer (EC) tumor cohort and to clarify the utility of estrogen receptor (ER) status.

Methods

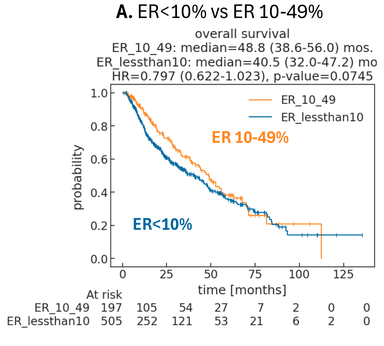
- 4162 NSMP EC tumors were analyzed by NGS (NextSeq, 592 genes or NovaSeq, WES) (Caris Life Sciences, Phoenix, AZ).
- Survival data were obtained from insurance claims data and calculated from first treatment to last contact for molecularly defined cohorts.
- Survival and mutation enrichment were compared among several IHC thresholds (regardless of staining intensity):
  - <1% or <10% (ER-neg)
  - 1-49% or 10-49% (ER-low)
  - ≥50% (ER-H)
- Hazard ratios (HR) were calculated by Cox proportional hazards, with p-values determined by log-rank tests. Statistical significance was assessed using chi-square analysis.

Results

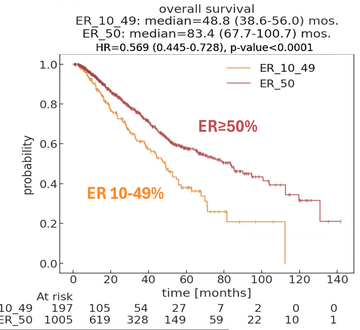
How should estrogen receptor negativity be determined?

Fig 1. Should we use ER<10%? (In all figures, survival is measured from first treatment with carboplatin to last contact.)

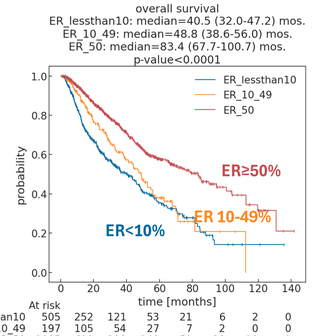
A. ER<10% vs ER 10-49%



B. ER 10-49% vs ER≥50%



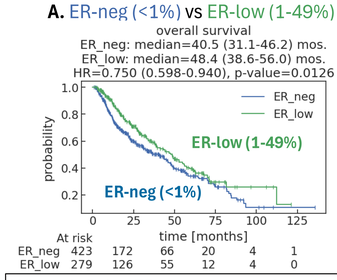
C. ER<10% vs ER 10-49% vs ER≥50%



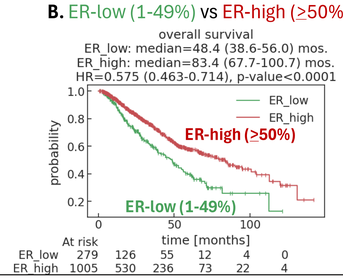
There is no significant difference in post-carbo survival in patients that are ER <10% vs ER 10-49% (p=0.0745).

Fig 2. What about ER<1%?

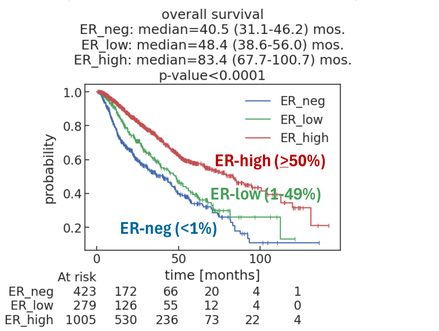
A. ER-neg (<1%) vs ER-low (1-49%)



B. ER-low (1-49%) vs ER-high (≥50%)



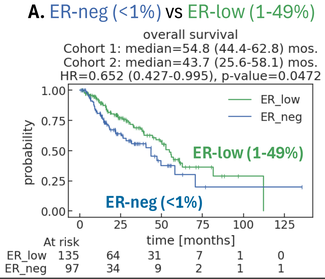
C. ER-neg (<1%) vs ER-low (1-49%) vs ER-high (≥50%)



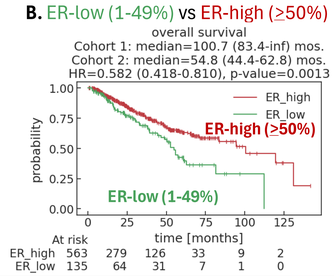
When defining ER-neg as <1%, there is a significant difference in post-carbo survival between ER-neg and ER-low tumors (p=0.0126). Similarly, we see improved survival in ER-high compared to ER-low patients (p<0.0001).

Fig 3. Examining ER spectrum in Endometrioid Tumors

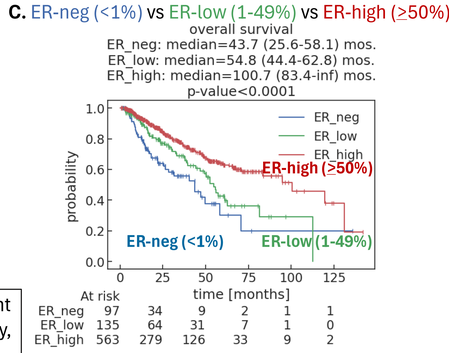
A. ER-neg (<1%) vs ER-low (1-49%)



B. ER-low (1-49%) vs ER-high (≥50%)



C. ER-neg (<1%) vs ER-low (1-49%) vs ER-high (≥50%)

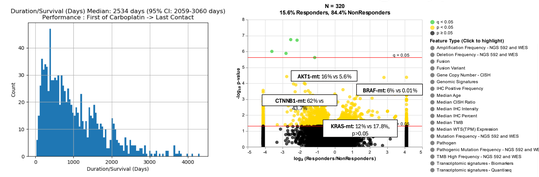


Limiting analysis to Endometrioid tumors and defining ER-neg as <1%, there is a significant difference in post-carbo survival between ER-neg and ER-low tumors (p=0.0126). Similarly, we see significant improved survival in ER-high compared to ER-low patients (p<0.0001).

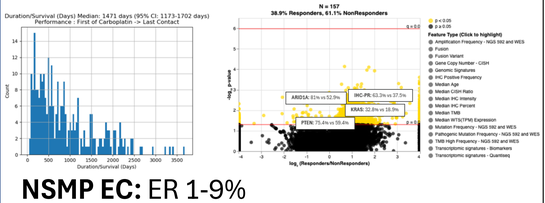
Results

Mutation Enrichment Analysis

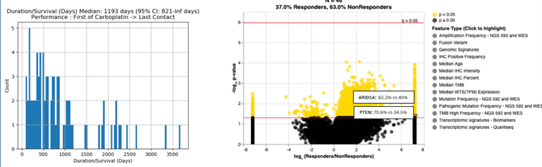
NSMP EC: ER 50%+, all histologic types



NSMP EC: ER 1-49%, all histologic types



NSMP EC: ER 1-9%



- *Among tumors with longer post-carbo survival, KRAS-MT were enriched in the ER-neg (42.9% vs 22.9%, p<0.001) and ER-low (36.4% vs 19.4%, p=0.047) tumors but not in ER-high tumors (12% vs 17.8%, p=0.316).*
- *Progesterone receptor (PR)+ IHC (79.6% vs 50.8%, p=0.002) and ARID1A-MT (83.3% vs 55.2%, p=0.01) were enriched among ER-low tumors with longer post-carbo survival.*
- *CTNNB1-MT were enriched in ER-H tumors (62% vs 43.7%, p=0.02) with longer post-carbo survival but not in other cohorts.*

Table 1. Characteristics of NSMP EC by ER staining

Characteristic	NSMP ER<1%	NSMP ER 1-9%	NSMP ER<10%	NSMP EC 10-49%	NSMP EC ER+ 50%
N	900 (21.6)	189 (4.54)	1089 (26.1)	499 (12)	2574 (61.8)
Age, median (range)	65 (25-90+)	65.5 (17-90+)	65 (17-90+)	62 (22-90+)	63 (24-90+)
Site, N (%)					
Primary	611 (68.1)	137 (72.5)	748 (68.7)	424 (85)	1775 (69)
Metastatic	281 (31.1)	46 (24.3)	327 (30)	71 (14.2)	776 (30.1)
Unclear	8 (0.88)	6 (3.17)	14 (1.29)	4 (0.8)	23 (0.89)
Histology, N(%)					
Carcinosarcoma	104 (11.5)	28 (14.8)	132 (12.1)	23 (4.61)	46 (1.79)
Clear Cell	128 (14.1)	12 (6.35)	140 (12.9)	12 (2.4)	10 (0.39)
Endometrioid	201 (22.1)	65 (34.4)	266 (24.4)	299 (59.9)	1587 (61.7)
Serous	47 (5.18)	7 (3.70)	54 (4.96)	23 (4.61)	59 (2.29)
Other/Mixed	420 (46.3)	77 (40.7)	497 (45.6)	142 (28.5)	872 (33.9)
Race, N (%)					
AAPI	38 (5.46)	5 (3.25)	43 (5.06)	17 (4.5)	90 (4.46)
B/AA	146 (21)	26 (16.9)	172 (20.2)	51 (13.5)	240 (12)
White	474 (67.5)	112 (72.7)	582 (68.5)	287 (75.9)	1556 (77.5)
Other	42 (6.03)	11 (7.14)	53 (6.24)	23 (6.08)	122 (6.08)
Ethnicity, N (%)					
Hispanic/Latino	89 (13.4)	21 (13.9)	110 (13.5)	42 (11.6)	270 (13.8)
Not Hispanic/Latino	573 (86.6)	130 (86.1)	703 (86.5)	319 (88.4)	1686 (86.2)

Conclusions

- NSMP tumors with ER>50% have good prognoses.
- ER<10% and ER 10-49% tumors have similar prognoses. But NSMP ER<1% tumors have worse survival than ER 1-49%.
- Mutation enrichment analysis of our ER-low cohort was distinct from ER-neg
- These observations remain even after excluding clear cell tumors.
- 27% of our ER 1-49% cohort would be classified as "ER negative" using a <10% threshold.
- Using a <1% and 1-49% thresholds (ER-neg and ER low) should be considered.