The Heterogeneic Molecular Landscape of Cervical Cancer Metastases (CCM)

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Background:

- Cervical Cancer (CC) is a heterogenous disease with multiple histological sub-types.
- Early screening has led to a significant reduction in disease related mortality, but a significant number of patients present with or progress to advanced disease.
- Studies between the molecular and immune alterations in CC primaries (CCP) and CC metastases (CCM) are needed to interrogate potential therapeutic strategies.

Methods:

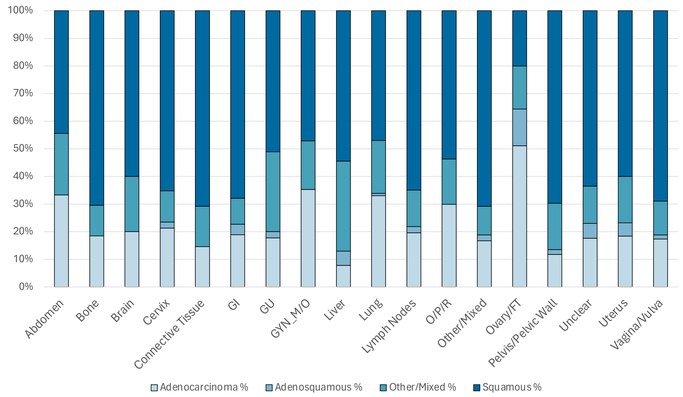
- Relationships of CCM and alterations detected by NGS (592, NextSeq; WES, NovaSeq) were investigated in 2,668 (1,393 primary Cervix samples, 383 local metastatic GYN samples, and 892 distant metastatic samples) CC samples (Caris Life Sciences, Phx, AZ)
- PD-L1+ was tested by IHC (22c3, ≥1%). Tumor mutational burden (TMB) was measured by summing somatic mutations per tumor (H: ≥10 mt/MB)
- Immune infiltrates estimated by deconvolution of WTS data (NovaSeq) using Quantiseq.
- Statistical significance determined by chi-square and Mann-Whitney U and adjusted for multiple comparisons (q<0.05).

A. Basic Demographics

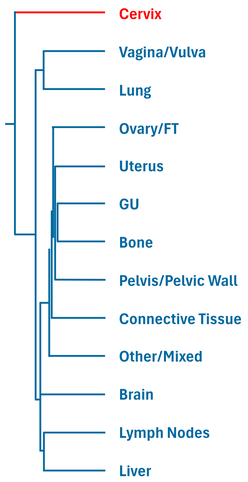
	Primary/Local					Distant Metastases											
	Cervix	Vagina/Vulva	Ovary/FT	Uterus	GYN_M/O	Lymph Nodes	P/PW	Lung	Liver	O/P/R	GI	Other/Mixed	C/ST	GU	Bone	Abdomen	Brain
N	1393	196	45	125	17	265	119	115	77	67	53	48	48	45	27	18	10
Age, median (range)	51 (19 - >89)	54 (29 - >89)	44 (32 - 86)	56 (21 - 89)	59 (35 - 77)	53 (22 - 88)	49 (27 - 88)	55 (27 - 87)	54 (30 - >89)	53 (30 - 78)	58 (27 - 82)	58 (30 - 82)	49 (30 - 77)	54 (32 - 86)	47 (26 - 72)	54 (26 - 73)	54 (38 - 70)

- Ovary/FT: *Ovary/Fallopian Tube*
- GYN_M/O: *GYN Mixed/Other*
- GI: Gastrointestinal Organs
- GU: Genito-urinary organs
- C/ST: *Connective/Soft Tissue*
- O/P/R: *Omentum/Peritoneum/Retroperitoneum*
- P/PW: *Pelvis/Pelvic Wall*

B. Histology by Site



C. Clustering metastatic sites by mutational profile similarity



***TP53*-mt:**
- *6.6% vs 14.7%*

***ARID1A*-mt:**
- *4.53% vs 8.27%*

***BRCA1*-mt:**
- *3.03% vs 0.87%*

Median TMB (range):
- 6 (0-101) vs 5 (0-460)

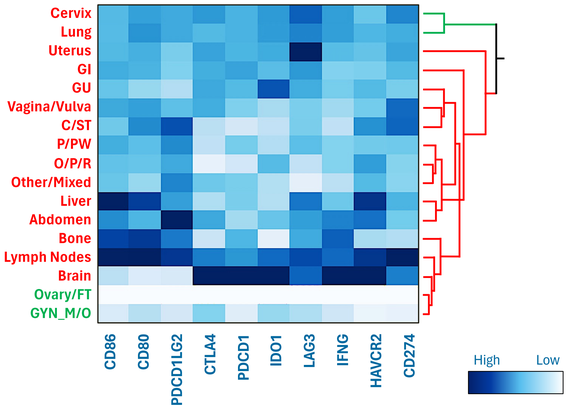
HPV 16/18+ Rate:
- 81.2% vs 66.8%,

***BRCA1*-mt:**
- 6.67% vs 0.87%

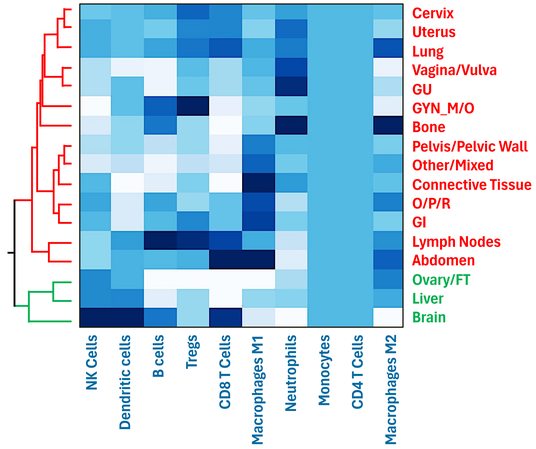
***ASXL1*-mt:**
- 8.47% vs 2.96%

***APC*-mt:**
- 4% vs 0.65%

D. Immune Checkpoint Gene Expression of CCP vs CCM

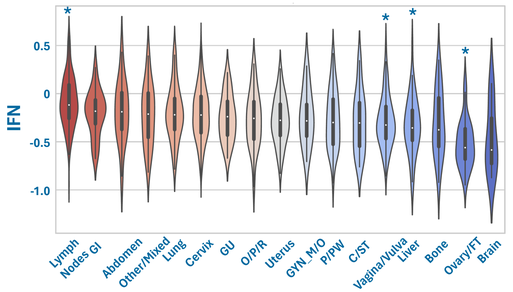


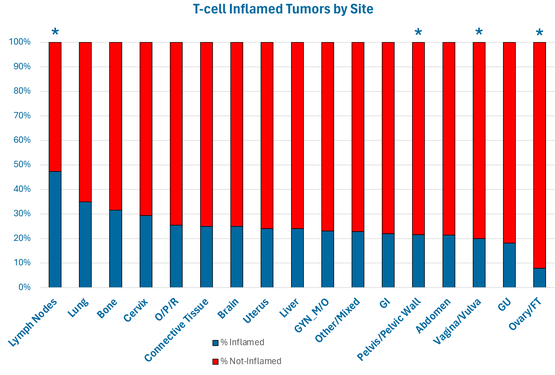
E. Immune Cell Infiltration of CCP vs CCM



F. IFN score and T-cell Inflamed Score in CCM compared to CCP

(* significant compared to CCP of Cervix)





- CCM to Liver had lower expression of *CTLA4* compared to CCP (1.67-fold decrease), similarly, Ovary/FT had significantly lower expression of immune checkpoint (IC) gene expression (*CD80*, *CD86*, *CD274*, *PDCD1*, *PDCD1LG2*, *CTLA4*, *HAVCR2*, *IDO1*, *LAG3*, *IFNG*: 2.23-4.66-fold decrease) (q<0.05)
- While Lymph Nodes had higher expression of the IC genes compared to CCP (1.30-1.49-fold, q<0.05)
- CCM to Liver and Ovary/FT had lower median infiltration of immune cells while Lymph Nodes had higher compared to CCP of Macrophage M1 (2.7% vs 1.03% vs 3.35% vs 3.1%), B cells (3.7% vs 3.5% vs 5.6% vs 4.3%), CD8 T cells (0% vs 0% vs 1.01% vs 0.75%), and Tregs (1.6% vs 0.74% vs 2.86% vs 2.5%) (q<0.05).
- CCM to Liver and Ovary/FT had lower median IFN score while Lymph Nodes had higher median IFN score (q<0.05) compared to CCP, similarly, Ovary/FT had a lower % of T-cell inflamed tumors with Lymph Nodes having higher T-cell inflamed tumors compared to CCP (7.89% vs 47.4% vs 29.3%, q<0.05).
- CCM to Lymph Nodes and Liver had the most distinct molecular and immune landscape compared to CCP while Ovary/FT had a similar molecular profile but a distinctively cold immune profile compared to CCP.
- *Additional studies will be needed to further evaluate potential therapeutic opportunities.*

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