Treatment-induced decrease of tumor Chromosome Y is associated with poor prognosis.

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Background

Loss of chromosome Y (LOY) in cancer has been linked to increased mortality. Since tumors that are not completely eradicated often harbor additional molecular changes which may alter biological behavior, here we sought to examine if therapy has any impact on tumor chromosome Y content and if so, the relevance this has on patient outcome. Changes in chromosome Y content with therapy would impact clinical decision making in patients with persistent or recurrent tumors since tumors with LOY have also been shown to be more responsive to specific therapies.

Methods

- Male patients with > = 2 sequential tumor samples profiled at Caris Life Sciences (Phoenix, AZ) who received systemic therapy between collections were included.
- RNASeq was performed using NovaSeq platform. Chromosome Y score (YChr score) was calculated using ssGSEA (log-rank normalization) based on a previously published 9-gene signature (Nature 2025).

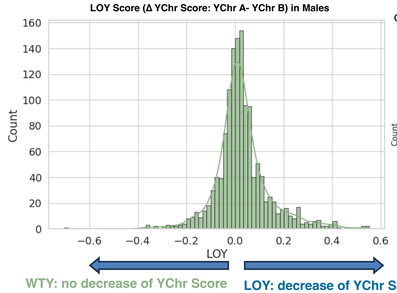
➢ **Ychr Score:** DDX3Y, UTY, KDM5D, USP9Y, ZFY, RPS4Y1, TMSB4Y, EIFAY, NLGN4Y

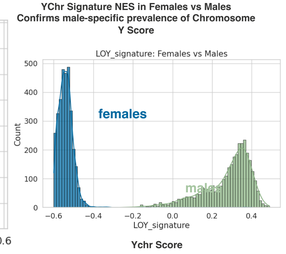
- Change in YChr score between pre and post treatment paired samples (ΔYChr) was computed per patient. A decrease in YChr score in post sample compared to pre sample was defined as ΔYChr ≥0.029 (cohort mean) and called progressive LOY (pLOY) while the remainder were called no-pLOY.
- Real-world clinical data were obtained from insurance claims. Overall survival (OS) was defined from first sample collection to last contact. Hazard ratios (HRs) were estimated using Cox proportional hazards models, with log-rank p values reported.

Results

1. Distribution of Ychr Score:

- LOY Score (Δ YChr Score) was calculated by YChr Score at biopsy A – YChr Score at biopsy B
- Due to the nearly normal distribution, a mean cut-off for LOY score was used to determine LOY and WTY (mean: 0.029384)
  - Everything >= mean is LOY whereas; everything <mean is WTY.





2. Patient characteristics

		LOY	WTY	Total
	N	552 (41%)	791	1343
All Cancer	Median Age	64	65	64
	Age IQR	(54-71)	(55-72)	(54.5-72)
Cancer type	CRC	124 (44.13)	157 (55.87)	281
	NSCLC	100 (42.74)	134 (57.26)	234
	Prostate Cancer	55 (52.38)	50 (47.62)	105
	High Grade Glioma	28 (27.45)	74 (72.55)	102
	EEJC	42 (45.65)	50 (54.35)	92
	Bladder Cancer	26 (38.81)	41 (61.19)	67
	Pancreatic Cancer	23 (41.82)	32 (58.18)	55
	Sarcoma	13 (25.0)	39 (75.0)	52
	H&N	18 (36.73)	31 (63.27)	49
	Melanoma	17 (38.64)	27 (61.36)	44
	Kidney Cancer	12 (37.5)	20 (62.5)	32
	Gastric Cancer	13 (44.83)	16 (55.17)	29
	NET	7 (25.0)	21 (75.0)	28
	Cholangiocarcinoma	6 (22.22)	21 (77.78)	27
	Cancer of Unknown Primary	14 (60.87)	9 (39.13)	23
	Other***	54 (43.9)	69 (56.1)	123

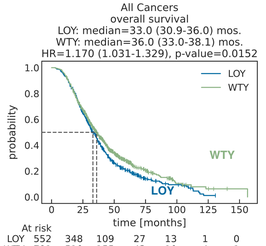
[***] Cancers with a N<20 were combined as 'Other', those include: GIST, Salivary Gland, Appendiceal Cancer, Small Bowel, Meningioma, Thyroid, SCLC, Squamous Cell Skin, Breast, Bone Cancer, Thymoma/Thymic, Lymphoma, Testicular Cancer, None of These Apply, Anal Carcinoma, Medulloblastoma, Low Grade Glioma, Hepatocellular Carcinoma, MPM, Pituitary Carcinomas, Penile Cancer, Peripheral Nervous System

- **EEJC:** Esophageal/Esophagogastric Junction Carcinoma
- **NSCLC:** Non-Small Cell Lung Cancer
- CRC: Colorectal Cancer
- **H&N:** Head and Neck Cancers
- **NET:** Neuroendocrine Tumors

Results

3. Overall Survival in patient with LOY vs WT.

A.



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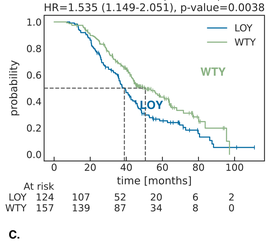

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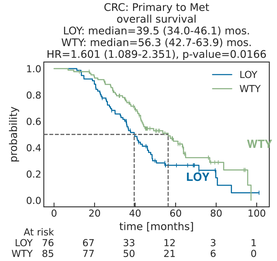


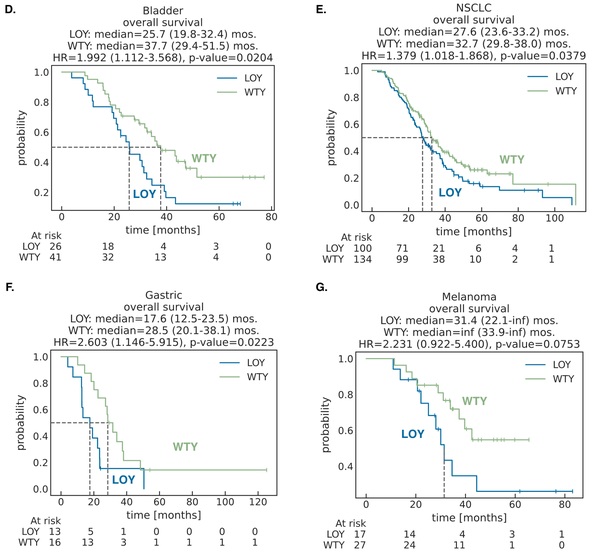
- All Cancers (A), CRC (B), Primary/Met pairs in CRC (C), Bladder (D.) NSCLC (E), Gastric Cancer (F) and Melanoma (G). A dotted line box suggests significant difference
- While a poor survival is evidently associated with LOY in the pan-cancer cohort and various cancer-specific cohorts, Cancer types including H&N, Kidney, Pancreatic, EEJC, NET, HGG, Sarcoma, Prostate and Cholangiocarcinoma didn't show significance, likely due to low N

CRC: Biopsy Site Breakdown		
A (1st specimen)	B (2nd Specimen)	N (%)
Metastatic	Metastatic	75 (26.7)
Metastatic	Primary/Local	13 (4.63)
Primary/Local	Metastatic	161 (57.3)
Primary/Local	Primary/Local	32 (11.4)

Cancer Type	CRC			
Treatment	WTY		LOY	
Antibody-Drug Conjugate	0	0.00%	0	0.00%
Chemo Combo	102	65.0%	83	66.9%
Chemotherapy	126	80.3%	102	82.3%
Hormone Therapy	6	3.82%	9	7.26%
Immune Checkpoint Inhibitors	7	4.46%	2	1.61%
Immunotherapy	0	0.00%	0	0.00%
Monoclonal Antibody	72	45.9%	57	46.0%
Other	87	55.4%	82	66.1%
Radiation Therapy	79	50.3%	56	45.2%
Radiopharmaceuticals	0	0.00%	0	0.00%
Small Molecule Inhibitors	11	7.01%	8	6.45%
Tumor Treating Field	1	0.64%	0	0.00%
Total Patients	157		124	

- As the largest cancer type, the CRC cohort were investigated further. While the entire CRC cohort is compromised of a mixture (upper table), the vast majority were from a primary/local site then a subsequent metastatic site (KM shown in C).
- Treatment given between specimen collections is shown in lower table, no significant imbalance was observed.

Results



Conclusions

- In a large real-world clinico-genomic cohort, longitudinal decrease in Chromosome Y score is independently associated with poor prognosis across multiple cancer types
- Our results support further investigation into the biological and clinical relevance of Y chromosome loss and providing insights on novel treatment selection strategies.
- Our next steps include Investigation into the liquid biopsy samples and investigate the impact of treatments on Chromosome Y score changes and the association with outcome

References

Nature volume 642, pages1041–1050 (2025)
Nature volume 619, pages624–631 (2023)

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