Young Onset CRC: What's New about Biology and Treatment in Advanced Disease?

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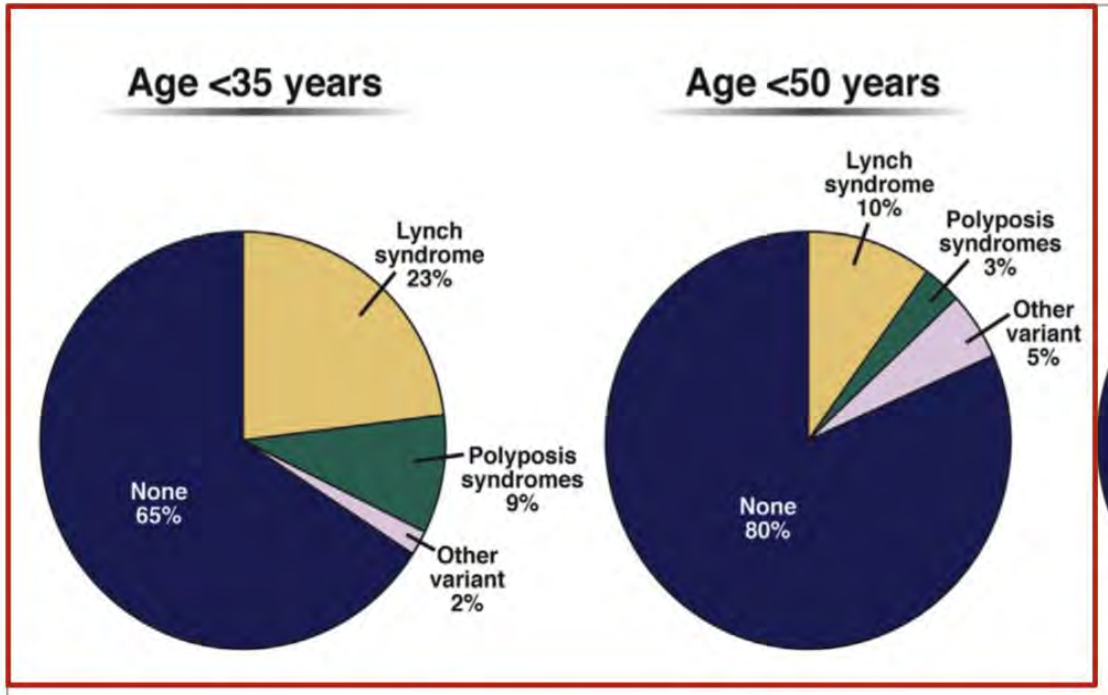
AGENDA

1. *Biology*
2. *Treatment*
3. *Circulating tumor DNA & Minimal Residual Disease*
4. *Conclusions*

KEY BIOLOGIC ASPECTS OF YOCRC

Genes of YOCRC



Lynch syndrome	Polyposis syndromes	Other pathogenic variants	
		High penetrance	Moderate/low penetrance
MLH1	*APC*	*BRCA1*	*CHEK2*
MSH2	*MUTYH*	*BRCA2*	*ATM*
MSH6	*SMAD4*	*TP53*	*NBN*
PMS2	*BMPR1A*	*PALB2*	*BARD1*
	PTEN	*CDKN2A*	*BRIP1*
	POLE		

~70-80% unknown

Sporadic YOCRC!

Stoffel and Murphy, Gastroenterology' 2020

MDACC Dataset + AACR GENIE

>36,000 pts

	MDACC Molecular Cohort	MDACC Tumor Registry Cohort	AACR Project GENIE Cohort	CMS Cohort
Patient Information	• N=1877 • Seen at MDACC from January 1, 2012 to September 1, 2016	• N=32507 • Seen at MDACC from January 1, 1980 to present	• N=1868 • Excluded patients from MDACC to prevent duplication of data	• Total N=626 • N=448 from TCGA N=178 from MDACC
Clinical Data	• Baseline clinical and pathologic characteristics	• Baseline clinical and pathologic characteristics	• Limited clinical and pathologic characteristics	• Limited clinical and pathologic characteristics
Molecular Data	• Mutational data available from 46- or 50-gene CLIA next-generation sequencing panel	• Unavailable	• Mutation data available from AACR Project GENIE database, which includes a mixture of next-generation sequencing platforms	• RNA expression data. • For TCGA patients, data were publicly available. • For MDACC patients, data were obtained with Affymetrix RNA expression arrays.
Cancer Stage(s)	• Stage IV	• Stages I-IV	• Majority stage IV	• Stages I-IV
Additional Data	• Comorbid predisposing condition information available for patients < 50 years			• Classification by CMS subtype

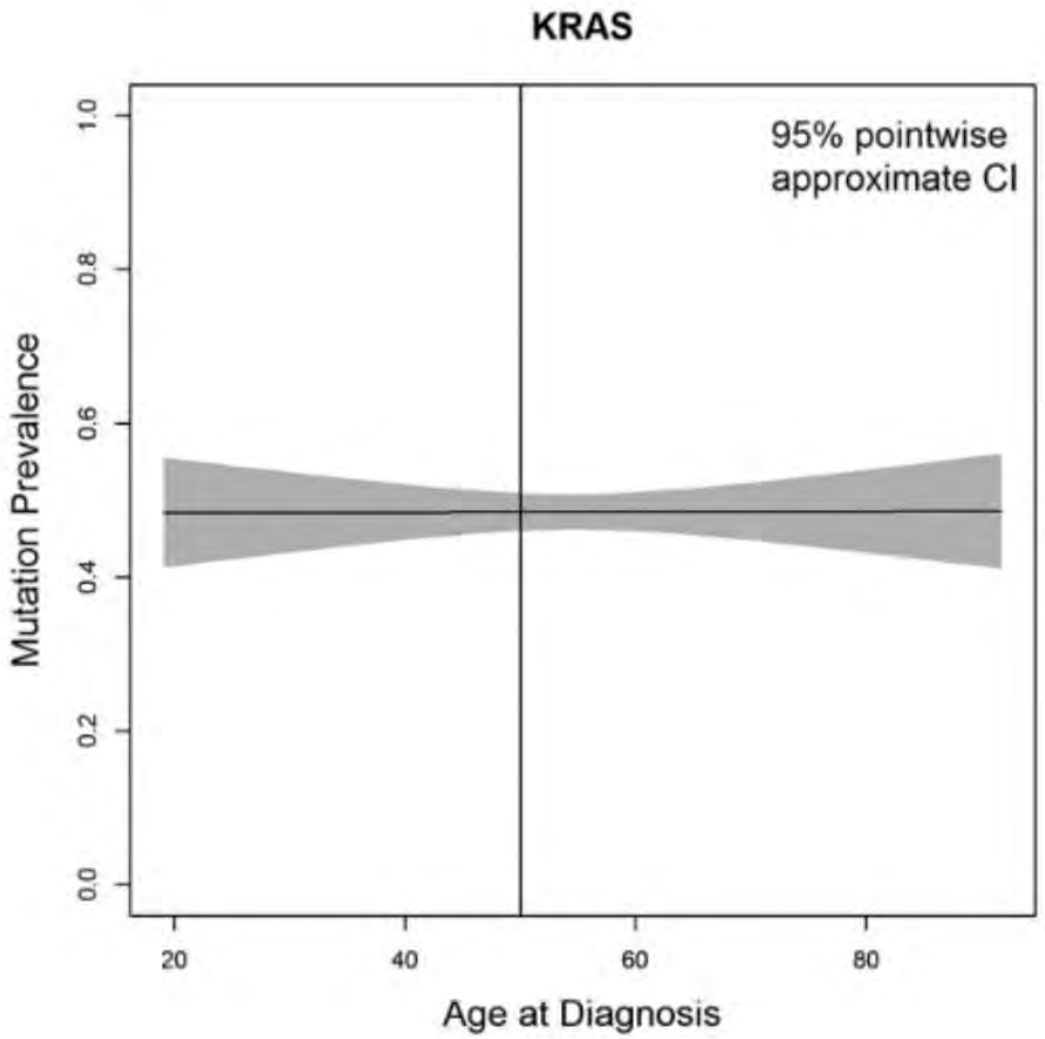
Foundation Medicine

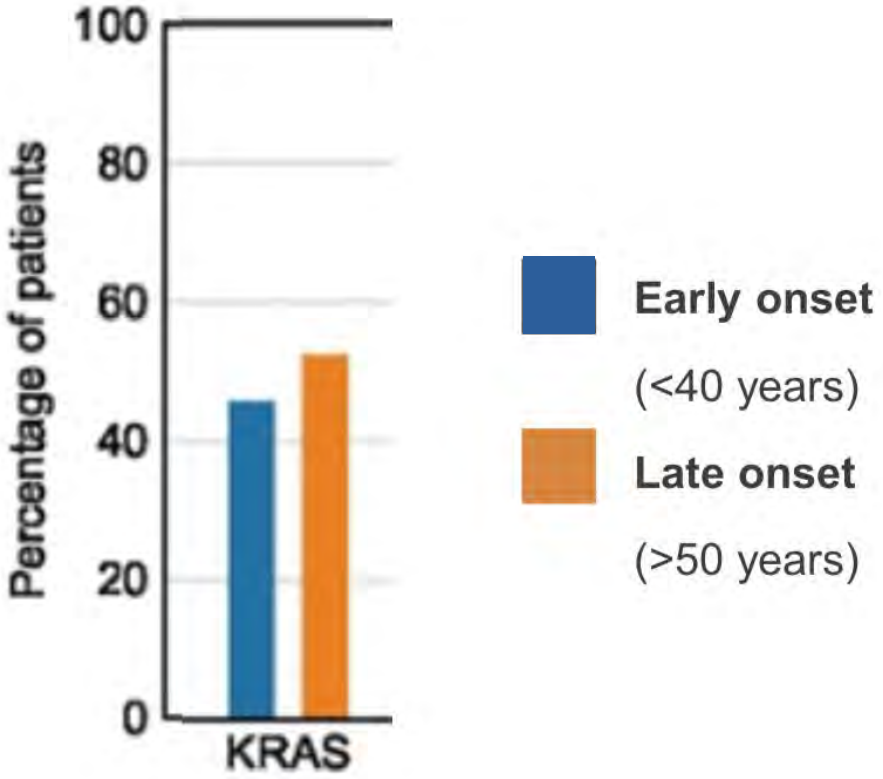
18,218 total patients

- 1,420 patients under the age of 40
- 3,248 between 40 and 49
- 13,550 age 50 and older

Willauer et al Cancer ’19, Lieu et al CCR ‘19

No significant difference in *KRAS*, *NRAS* mutations





Willauer et al Cancer '19, Lieu CCR

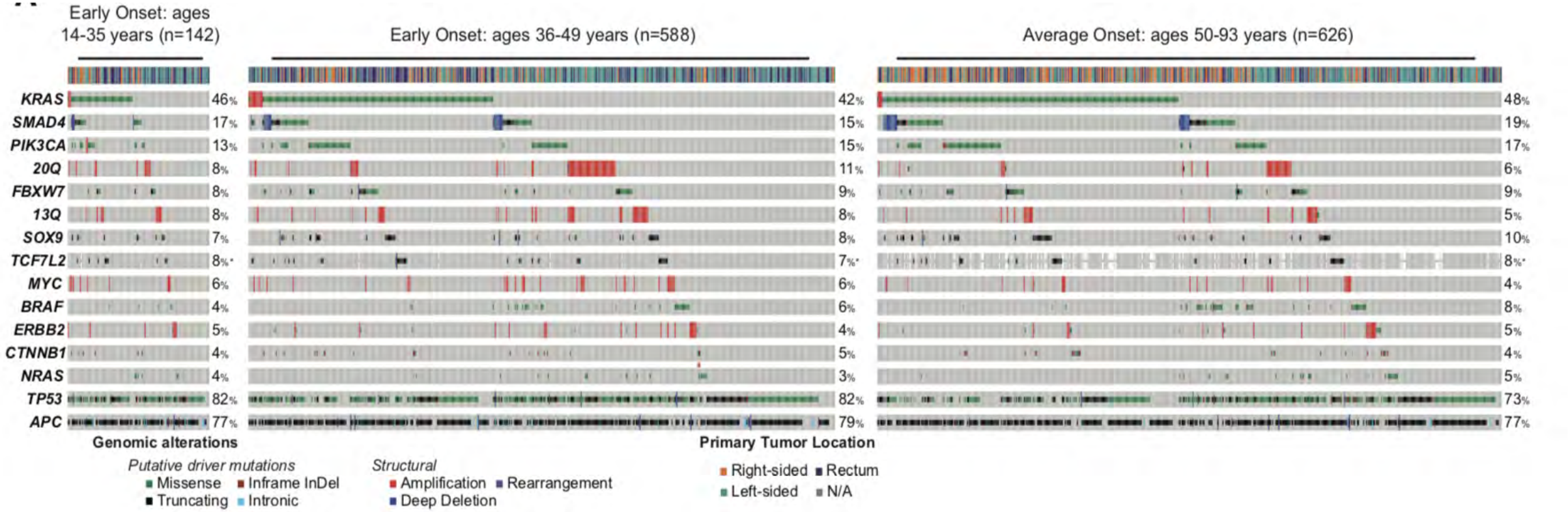
Foundation One molecular testing → *CTNNB1, TP53*

Table 1. Significant alterations and alterations in genes of interest between cohorts using false discovery rate (FDR) in MSS colorectal cancer (CRC) and MSI-H colorectal cancer

	Alteration rates in the MSS cohort		
Gene	**Rate observed in under 40 group (%)**	**Rate observed in 50 and over group (%)**	**FDR**
TP53	82.3	76.7	1.56E−05
APC	65.8	79.7	4.84E−26
KRAS	45.6	52.4	1.56E−05
PIK3CA	14.1	17.5	0.002959601
CTNNB1	4	2.7	0.013488987
BRAF	5.2	7.7	0.002067048
FAM123B	2	6.8	1.35E−12
NRAS	3.7	4.6	0.171847712

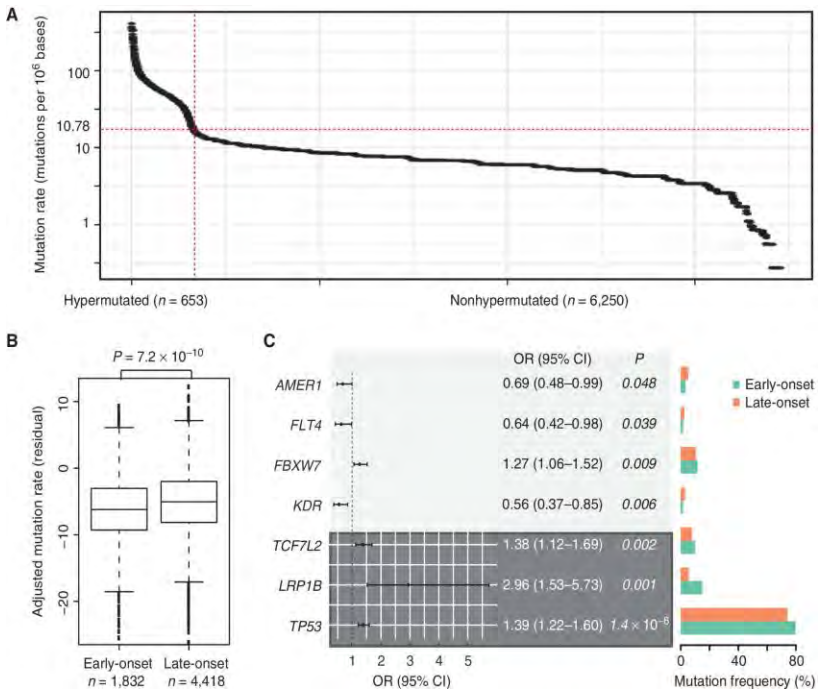
Lieu et al CCR '19

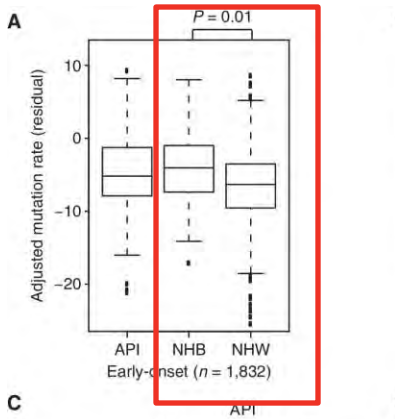
Real world data @MSKCC: No major genomic differences between YOCRC and average onset CRC

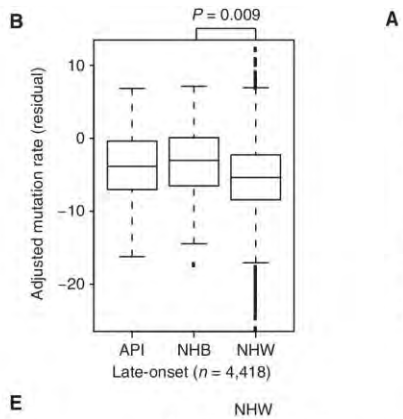


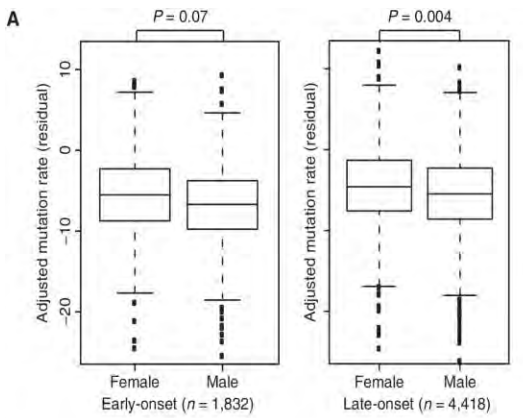
Cercek et al, JNCI 21'

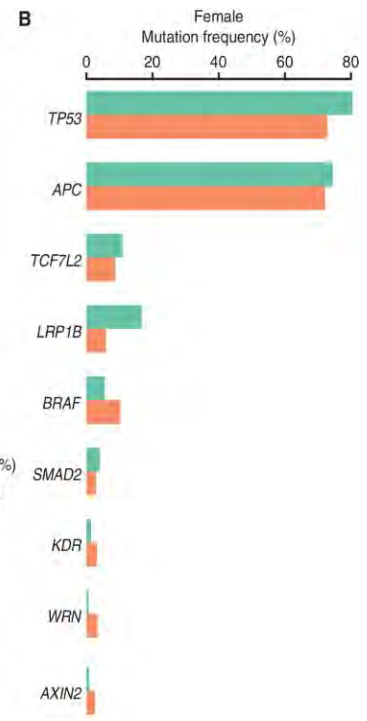
YOCRC Biology differs based on race and sex; n=6903 pts (NHW, NHB, API)

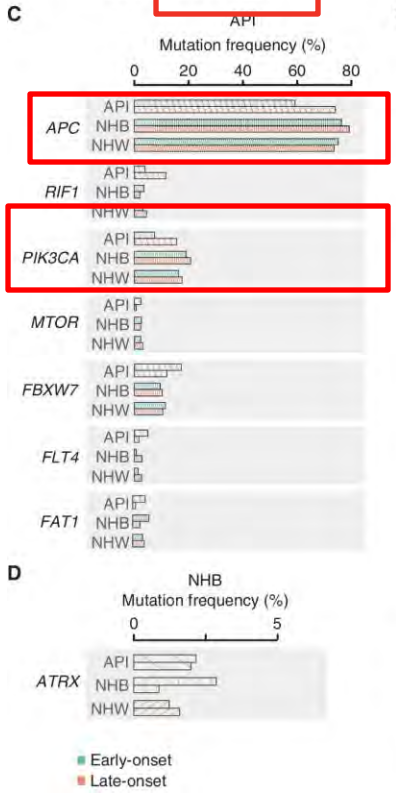


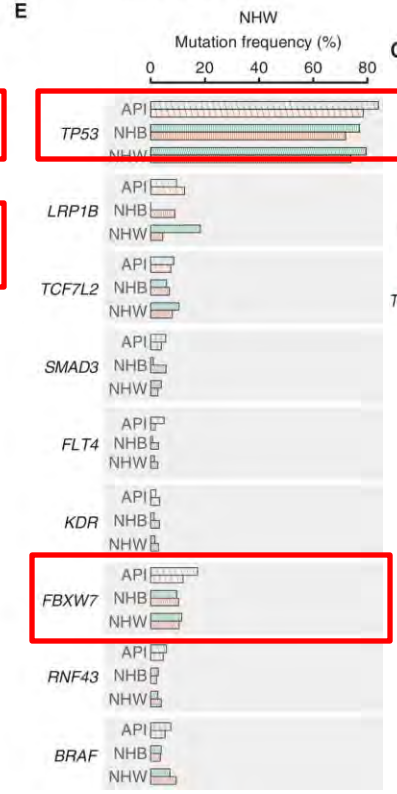


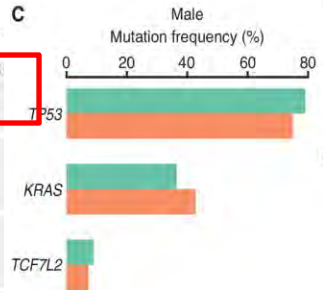


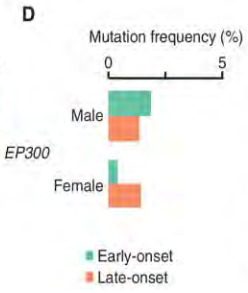












Young patients (n=1832) with sporadic CRC had significantly higher odds of presenting with nonsilent mutations in *TP53, LRP1B, TCF7L2, and FBXW7*

NHBs, but not APIs, with early-onset sporadic colorectal cancer had higher adjusted tumor mutation rates versus NHWs.

Differences for FLT4, FBXW7, RNF43, LRP1B, APC, PIK3CA, and ATRX mutation rates between racial/ethnic groups and EP300, KRAS, AXIN2, WRN, BRAF, and LRP1B mutation rates by sex.

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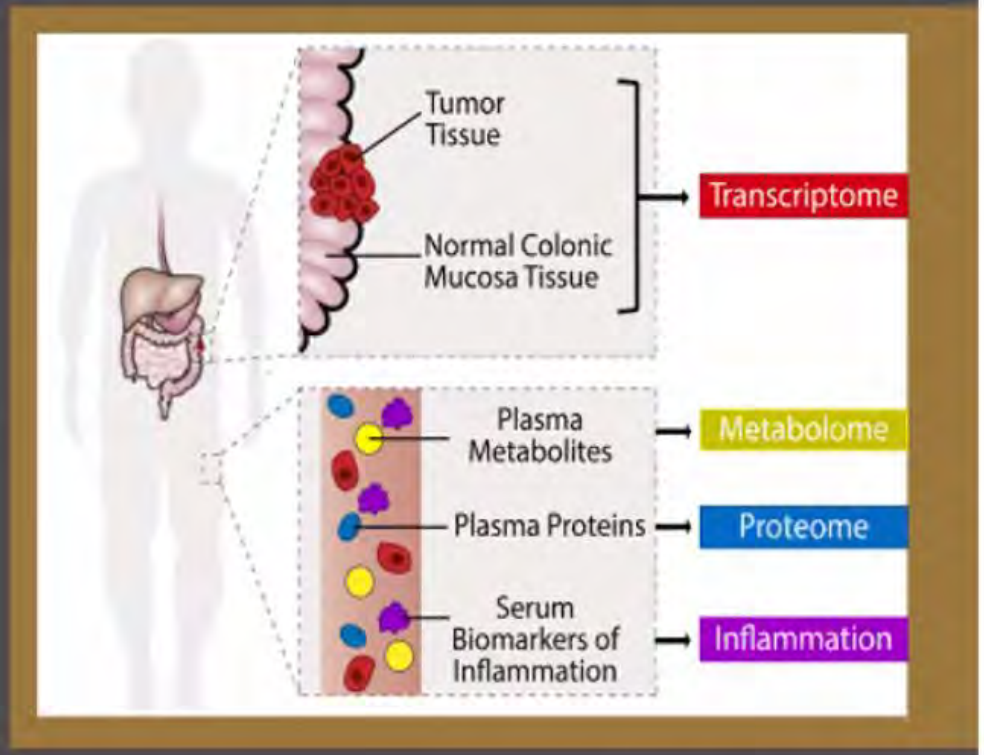
Holowatyj et al Cancer Discov 2023

Deregulated redox homeostasis is a distinct molecular hallmark of early-onset sporadic CRC

Integrated, multi-omics analysis implicate perturbations in:

- *NRF2*-mediated oxidative stress response,
- glutathione metabolism, and
- the *CXCL12-CXCR4* signaling axis,

as a molecular phenotype distinct to early-onset sporadic CRC.

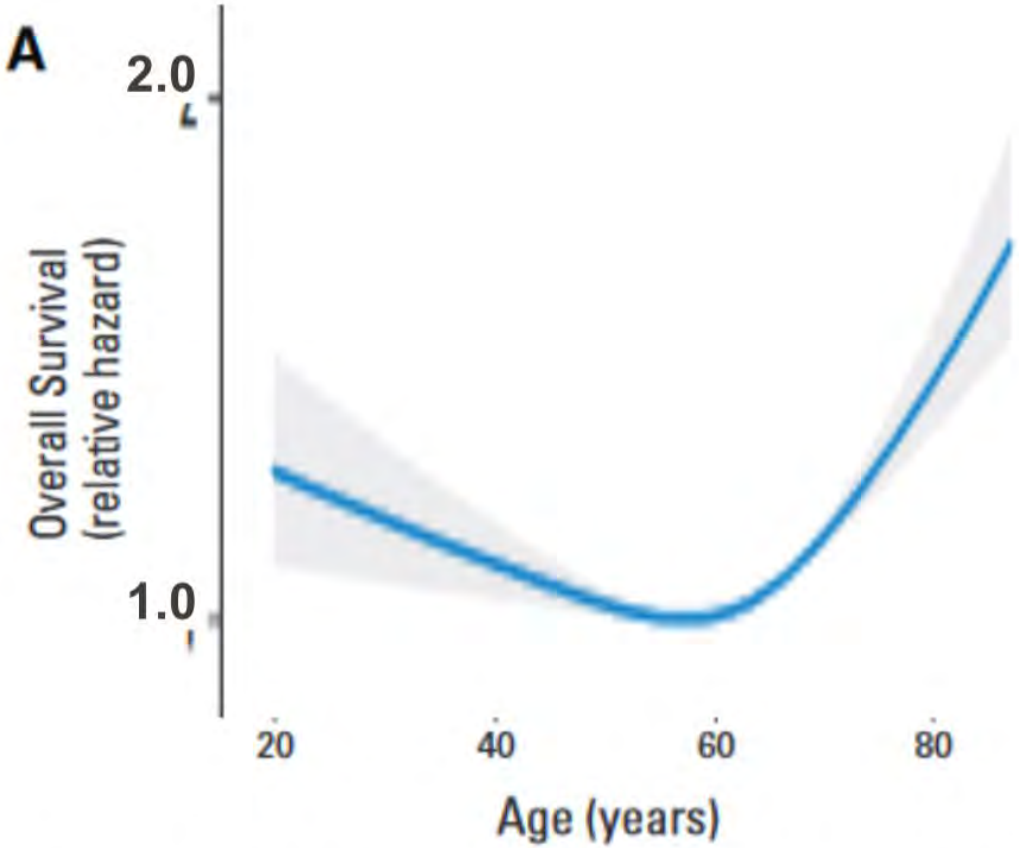


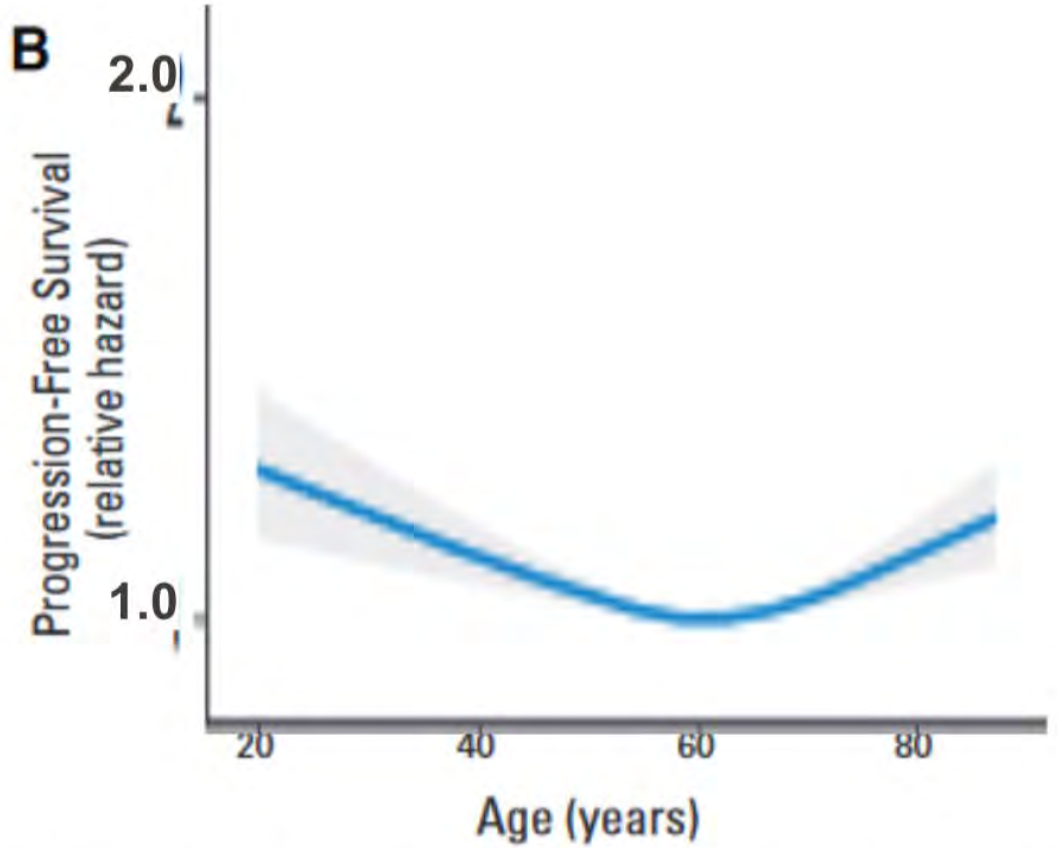
Holowatyj et al. *Gastroenterology*. 2020.

Imbalance in glutathione metabolism

TREATMENT FOR YOCRC & NEW DEVELOPMENTS

Overall survival and progression-free survival from diagnosis of mCRC is worse for EOCRC patients





20,003 patients from 24 first line studies of mCRC (ARCAD database)

Lieu et al JCO '14

YOCRC: Warrants more ‘aggressive’ therapy?…

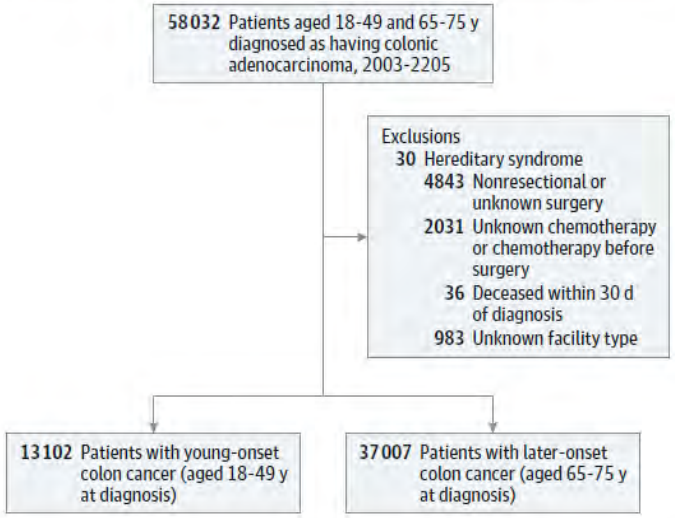
More chemotherapy must be better.

Original Investigation

Overtreatment of Young Adults With Colon Cancer
More Intense Treatments With Unmatched Survival Gains

Peter J. Kneuertz, MD; George J. Chang, MD, MS; Chung-Yuan Hu, MPH, PhD; Miguel A. Rodriguez-Bigas, MD; Cathy Eng, MD; Eduardo Vilar, MD, PhD; John M. Skibber, MD; Barry W. Feig, MD; Janice N. Cormier, MD, MPH; Y. Nancy You, MD, MHSc

Figure 1. Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers



The patients were treated between January 1, 2003, and December 31, 2005, and were reported to the National Cancer Data Base.

More Surgery must be better.

The prognostic impact of *RAS* on overall survival following liver resection in early versus late-onset colorectal cancer patients

Alexandre A. Jácome[1], Timothy J. Vreeland[2], Benny Johnson[1], Yoshikuni Kawaguchi[2], Steven H. Wei[2], Y. Nancy You[2,3], Eduardo Vilar[1,4], Jean-Nicolas Vauthey[2] and Cathy Eng[1,5]

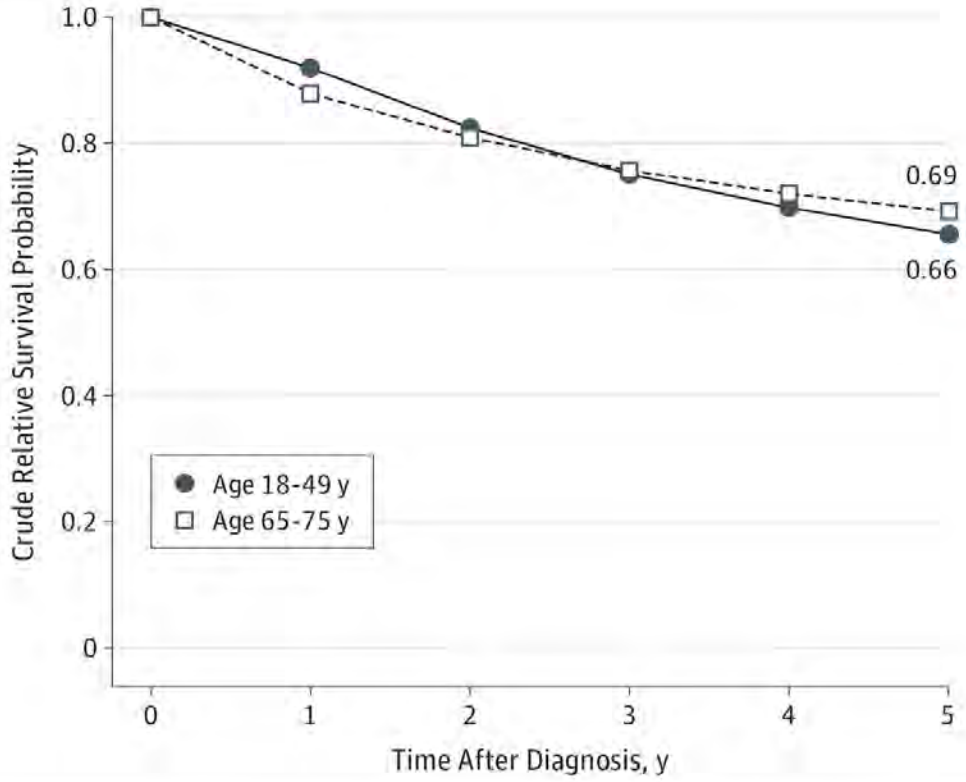
Table 1. Baseline characteristics of the overall population by the timing of onset of colorectal cancer ($n = 573$).

Characteristic	Early-onset ($n = 192$)	Late-onset ($n = 381$)	*P* value
Median age at diagnosis (range), y	42 (22–49)	59 (50–81)	**<0.001**
Sex			
Male	99 (52)	236 (62)	**0.019**
Female	93 (48)	145 (38)	
RAS *status*			
Mutated	77 (40)	178 (47)	0.154
Wild-type	115 (60)	203 (53)	
BRAF *status*			
Mutated	5 (3)	4 (1)	0.294
Wild-type	163 (97)	293 (99)	
MSI status			
MSS	150 (98)	204 (97)	0.739
MSI-H	3 (2)	6 (3)	
Tumour location			
Ascending colon	29 (15)	93 (25)	**0.012**
Transverse colon	8 (4)	16 (4)	0.527
Descending colon	9 (5)	32 (8)	0.122
Rectosigmoid	146 (76)	240 (63)	**0.001**
Sidedness			
Right	37 (19)	109 (29)	**0.015**
Left	155 (81)	272 (71)	
CEA level > 10 ng/mL			
Yes	40 (22)	101 (27)	0.213
No	143 (78)	271 (73)	
Bilobar disease			
Yes	39 (21)	28 (26)	0.389
No	149 (79)	82 (75)	
≥2 liver lesions			
Yes	92 (48)	182 (49)	1
No	98 (52)	193 (51)	

More intensive chemotherapy for YOCRC – did not translate to survival benefits

Patients Who Received Chemotherapy	Any Chemotherapy, No. (%)	Odds Ratio for Receiving Chemotherapy (95% CI)	Multiagent Regimens, No. (%)	Odds Ratio for Receiving Multiagent Regimen (95% CI)
Stage I				
Ages 65-75 y (n = 8991)	162 (1.8)	1 [Reference]	52 (43.0)	1 [Reference]
Ages 18-49 y (n = 1926)	109 (5.7)	2.88 (2.21-3.77)	43 (48.3)	1.38 (0.71-2.68)
Stage II Overall				
Ages 65-75 y (n = 11 011)	2748 (25.0)	1 [Reference]	773 (41.7)	1 [Reference]
Ages 18-49 y (n = 3083)	1732 (56.2)	3.93 (3.58-4.31)	670 (54.9)	1.71 (1.48-1.97)
Stage II Low Risk				
Ages 65-75 y (n = 4822)	923 (19.1)	1 [Reference]	313 (39.6)	1 [Reference]
Ages 18-49 y (n = 1636)	826 (50.5)	4.22 (3.70-4.81)	388 (52.5)	1.67 (1.34-2.09)
Stage II High Risk				
Ages 65-75 y (n = 6189)	1825 (29.5)	1 [Reference]	677 (42.7)	1 [Reference]
Ages 18-49 y (n = 1447)	906 (62.6)	3.69 (3.23-4.20)	454 (57.0)	1.77 (1.46-2.14)
Stage III				
Ages 65-75 y (n = 11 202)	8175 (73.0)	1 [Reference]	4209 (59.4)	1 [Reference]
Ages 18-49 y (n = 4780)	4132 (86.4)	2.42 (2.18-2.68)	2590 (71.5)	1.75 (1.58-1.93)
Stage IV				
Ages 65-75 y (n = 5803)	3652 (62.9)	1 [Reference]	2567 (80.4)	1 [Reference]
Ages 18-49 y (n = 3313)	2710 (81.8)	2.74 (2.44-3.07)	2136 (88.6)	1.90 (1.60-2.26)

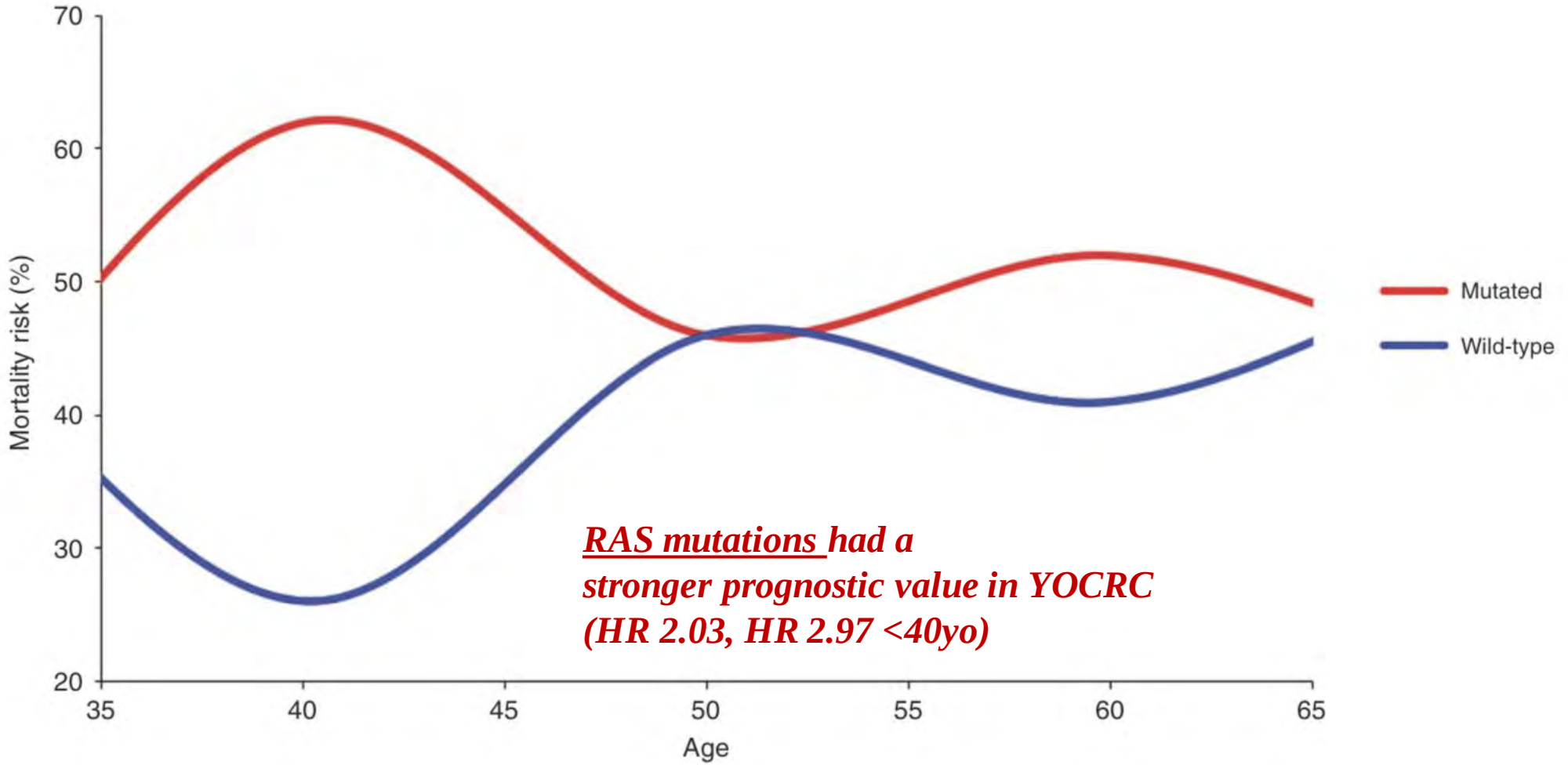
Figure 2. Crude Relative Survival of Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers



The unadjusted survival analysis showed slightly inferior 5-year relative survival for the young adults (0.66 vs 0.69, $P < .001$).

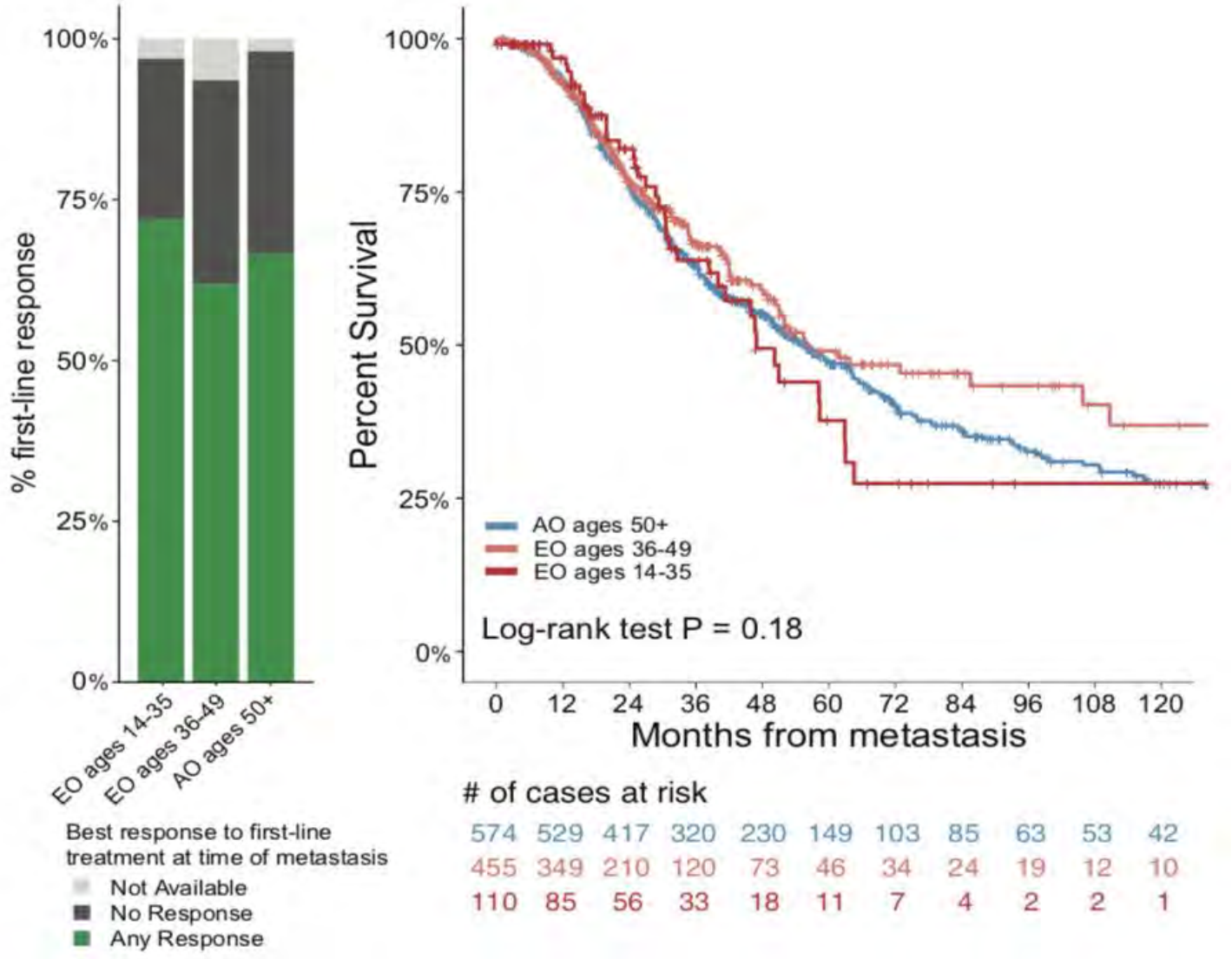
Kneuertz et al. JAMA Surgery 2015

Surgical Outcomes in mCRC: Prognostic impact of *RAS* mutation status CLM in YOCRC



Jacome et al. BJC 2020

Sporadic YOCRC with very similar response to 1L chemotherapy & survival as average age population



Cercek et al JNCI 21'

FOLFOXIRI in mCRC

Triplet/bev vs doublets/bev in mCRC

Pooled analysis; n = 1697

Primary Endpoint: OS

	Triplet/bev	Doublet/bev*	p
ORR (%)	64.5	53.6	p < 0.001
Median OS(mos)	28.9	24.5	p < 0.001
Median PFS (mos)	12.2	9.9	p < 0.001
5-year OS (%)	22.3%	10.7%	P < 0.001

*70% FOLFOX/bev; 30% FOLFIRI/bev

Triplet/bev vs doublets/bev in mCRC

Secondary analyses of survival in resected pts

Trial / Endpoint	Triplet/bev	Doublet/bev*	HR (95% CI)
OLIVIA / RFS (mos)	17.1	8.1	0.31 (0.12 – 0.75)
Cremoloni et al, OS (mos)	64	52.6	0.79 (0.5 – 1.24)

Cremoloni et al, Abs 4015, ASCO 2020

How I treat a patient with Advanced Young Onset CRC

1. Establish **goals** of therapy & highlight **supportive services** (oncofertility, social work, integrative medicine, supportive care)

2. All pts: **Precision** : **Expanded molecular profiling** - tissue NGS or ctDNA testing

3. **Early** surgical consultation in stage IV with potential resectable liver or lung metastases; careful use of triplet chemotherapy for conversion (FOLFOXIRI/BEV)

4. **1L** - FOLFOX / FOLFIRI +/- BEV or anti-EGFR (if left sided colon cancer, RAS wt) ; Immunotherapy if Lynch syndrome/MSI-H ; 3 drug chemo if very symptomatic → *Clinical trial enrollment*

5. **2L** – opposite chemotherapy backbone + appropriate biologic / targets (HER2 amp; BRAFV600E; KRAS G12C) / → *Clinical trial enrollment*

6. **3L** – TAS-102/BEV or Regorafenib → *Clinical trial enrollment*

Paradigm Shifts in CRC with impact for Young Onset

1. **Expanded NGS/ctDNA testing** → Key biologic subgroups w/ FDA approved targeted therapies available:
   - ***MSI-H / BRAFV600E / RAS/RAF wt / HER2 amplification / NTRK fusions***

2. '**Watch and Wait**' in rectal cancer for cCR after upfront chemotherapy/radiation

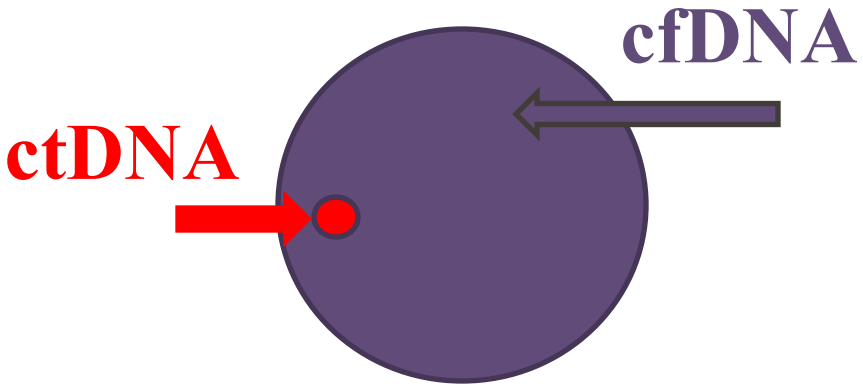
3. **Emergence of ctDNA** – the future: guided/personalization of therapy in **stage II and III** CRC to avoid toxicity from oxaliplatin based chemotherapy (DYNAMIC, ongoing COBRA & CIRCULATE-US)

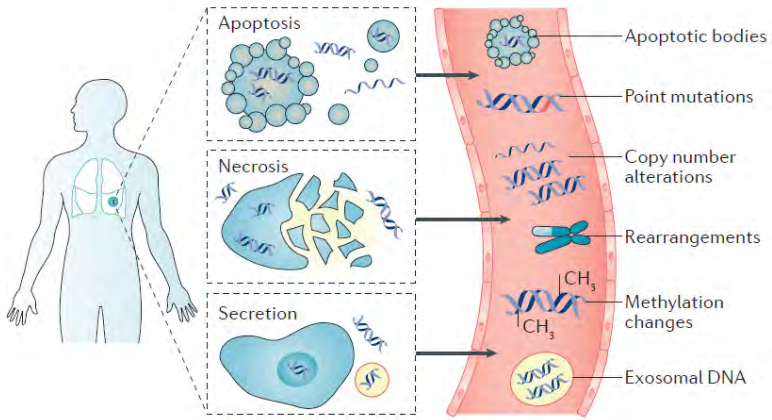
4. Immunotherapy alone for **dMMR/MSI-H** locally advanced rectal cancer- (avoidance of chemotherapy/radiation/surgery) (n=12; 100% cCR) – Caveat: **applies to only a small subset of pts**

5. **Clinical Trial/Emerging targets** – *KRAS G12C combo;* neoantigen vaccine approaches, TCR therapy; **MRD trials**

Habr-Gama A, Ann Surg 2004; Tie NEJM 2022; Cercek NEJM 2022

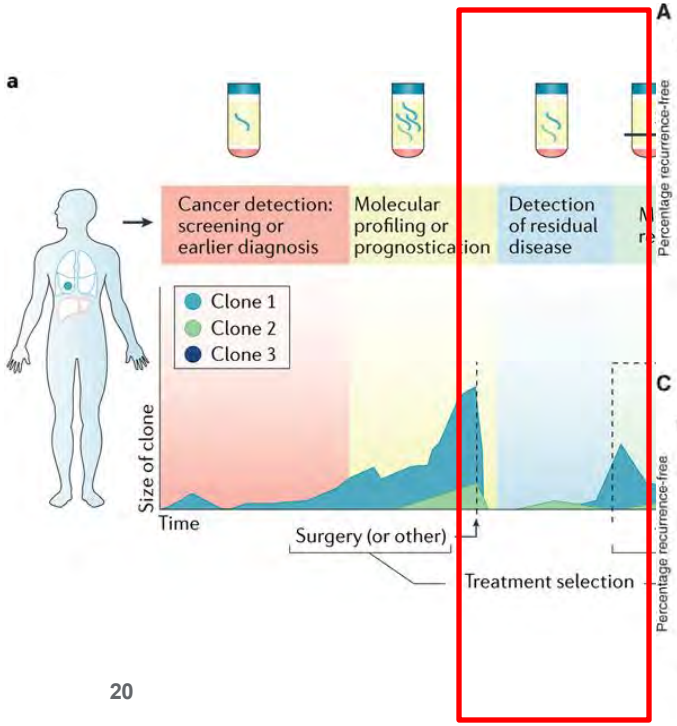
Circulating tumor DNA (ctDNA) & Minimal Residual Disease (MRD) in Colorectal Cancer

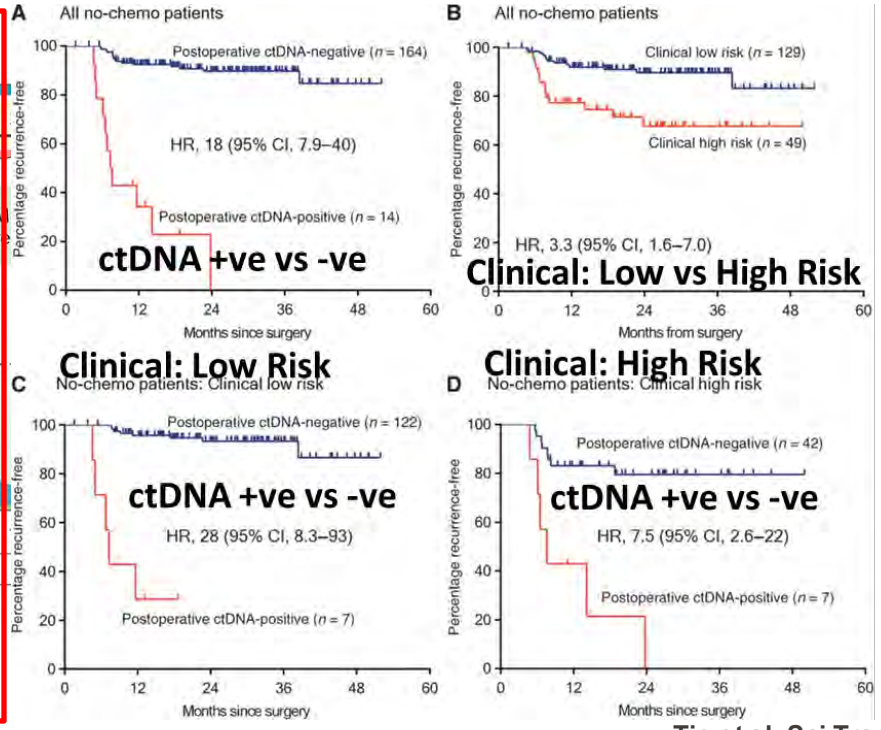


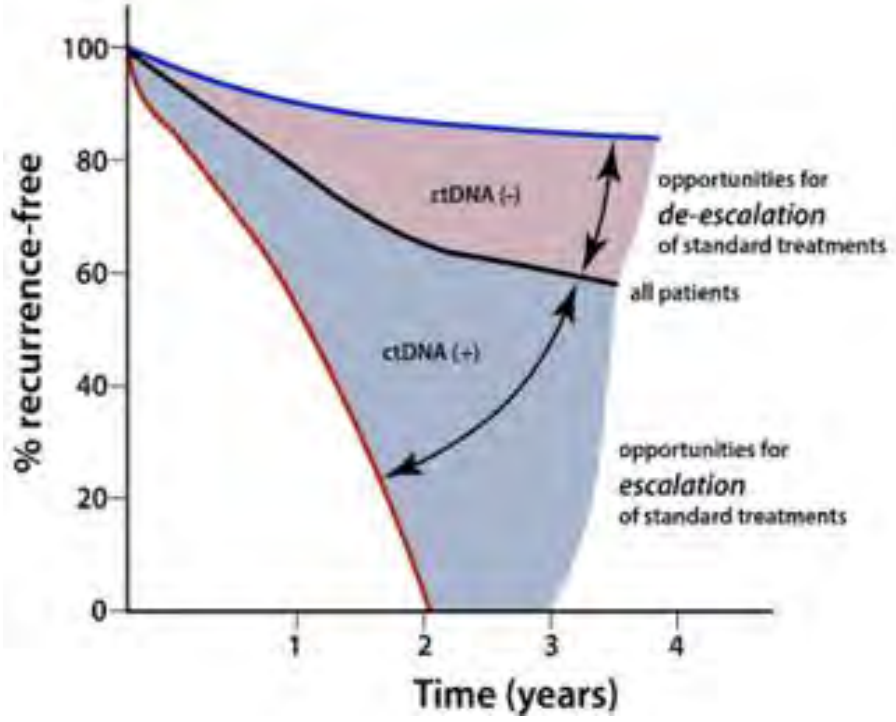


- ctDNA can be detected in the blood following release from tumor cells,
- Fragment size: cfDNA ~167 bp; ctDNA ~20-30 bp shorter
- "real time" analysis; t ½ ~ 2 – 3 hours

cfDNA described > 70 years ago;
ctDNA described > 40 years ago







Tie et al, Sci Tran Med, 2016; Reinart et al, JAMA Onc 2019; Dasari et al, Nat Rev Clin Onc, 2020

Protocols at MDACC: Targeting CRC MRD with novel approaches

Intervention (INTERCEPT Study Lead)	Setting
COBRA NRG (Dr. Van Morris)	Stage II, immediate post op
CIRCULATE US– NRG / SWOG (Dr. Arvind Dasari)	Stage III / ctDNA+ stage II, immediate post op
BioNTech RNA vaccine (Dr. Van Morris / Dr. Scott Kopetz)	Stage II, III, immediate post op
Chemo de-escalation (Dr. Timothy Newhook)	Stage IV, immediately post op
KRAS vaccine (Dr. Shubham Pant)	Any stage
Cetuximab + NK Cell therapy (Dr. Pia Morelli)	Any stage
Lifestyle Bootcamp (Dr. Alisha Bent)	Any stage
TAS-102 (Dr. Arvind Dasari / Dr. Alisha Bent)	Any stage
CXCR1/2 inhibitor + anti-PD-1 (Dr. Benny Johnson)	Any stage

Conclusions

- No major differences in frequency of traditional mutations of interest (*KRAS, NRAS, BRAF*, HER2 amplification, etc) in YOCRC.
- There are clues to underlying **genomic differences** noted in sporadic YOCRC biology – that may be related to **ethnicity & sex**.
- YOCRC treatment should incorporate **precision** regarding **key molecular drivers**, **goals** of therapy – essentially **personalized** for each patient.
- **Clinical trial enrollment** should be a part of the cancer journey for **all patients** with YOCRC.
- Novel de-escalation/escalation & monitoring strategies utilizing **circulating tumor DNA (ctDNA)** have relevant implications for YOCRC treatment & survivorship.

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Thank you!
Any questions? – bjohnson6@mdanderson.org
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