

Young Onset Colorectal Cancer

Afsaneh Barzi, MD, PhD

Associate Professor of Oncology

Medical Director of Value and Quality AccessHope



Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed <u>Assembly Bill (AB) 1195</u>, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed <u>AB 241</u>, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

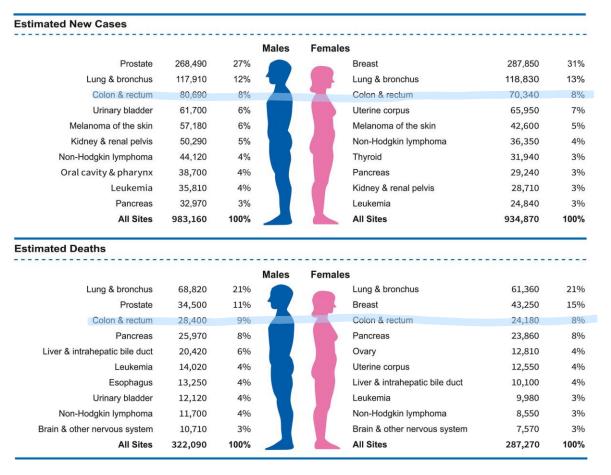
EXEMPTION:

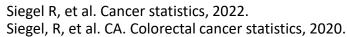
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

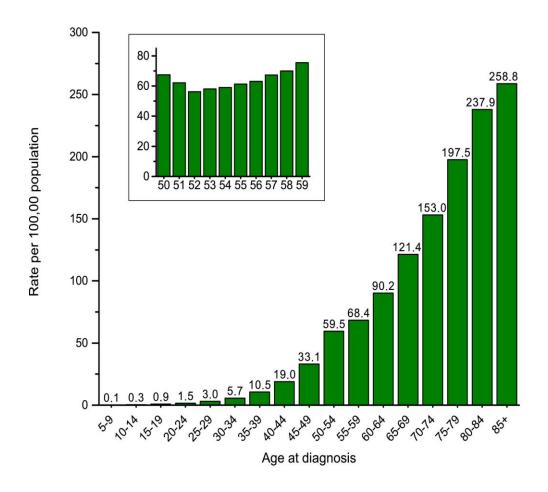
The following CLC & IB components will be addressed in this presentation:

- Young adults have a special need for attention to fertility issues and certain survivorship issues are more relevant to this population.
- Lack of personalization of care to the needs of this population.

Epidemiology

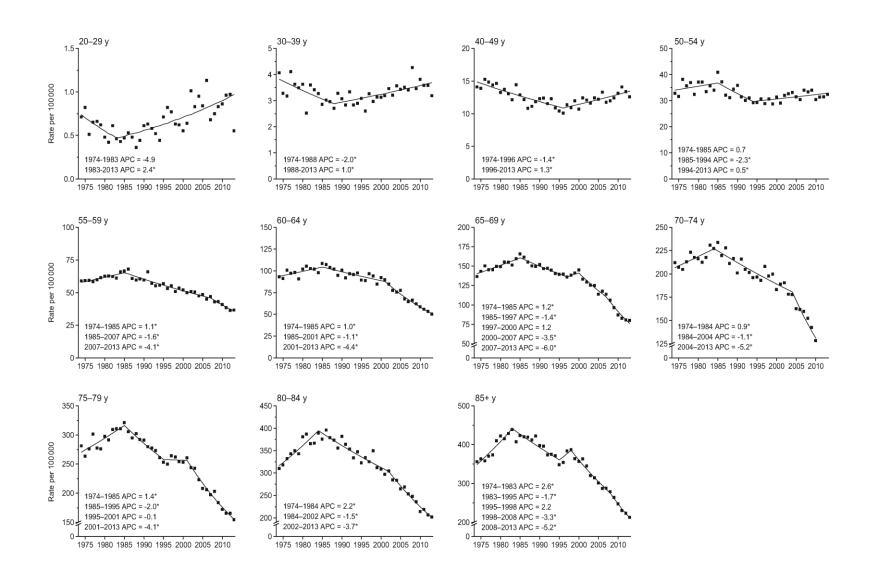




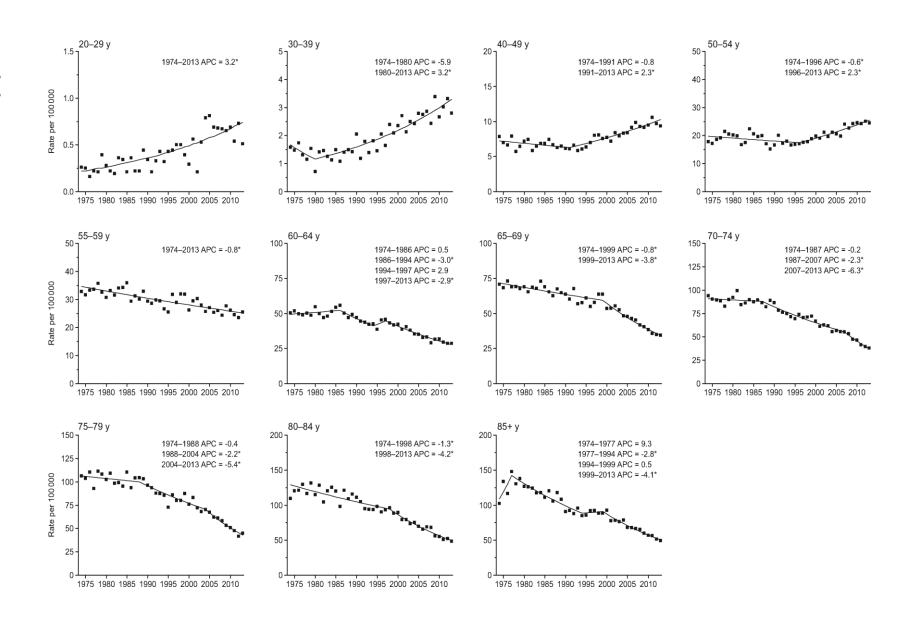


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Changing Epidemiology: Colon Cancer



Changing Epidemiology: Rectal Cancer



Disparities in Changing Epidemiology

	2001-2002 TO 2017 – 2018 (% increase)
NHW	1.62*
Black	0.05
Hispanic	1.10*
AIAN	3.13*
Asian	0.37

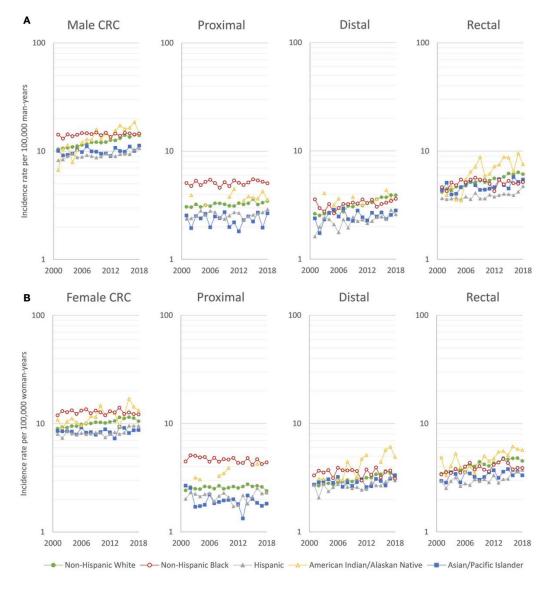
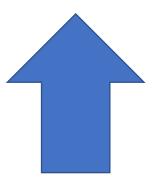


FIGURE 1 | Age-adjusted early-onset (20-49 years of age) colorectal cancer incidence rates per 100,000 person-years in (A) men and (B) women, US Cancer Statistics 2001-2018.

Shift in the Median Age

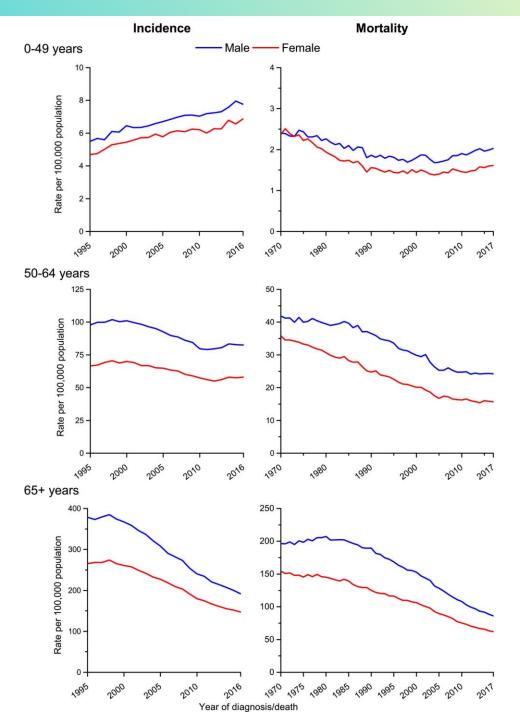
The median age of CRC patients went from **72 years during 2001-2002** to **66 years during 2015-2016**



The number of CRC in older patients is declining
The number of CRC in younger patients increasing

Not Just rising incidence, but *rising* mortality in young adults





More Aggressive Treatment

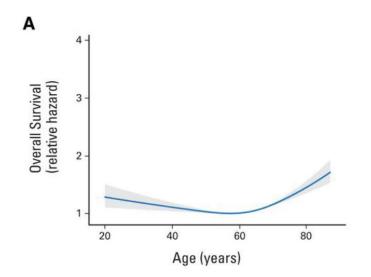
Higher utilization of treatment

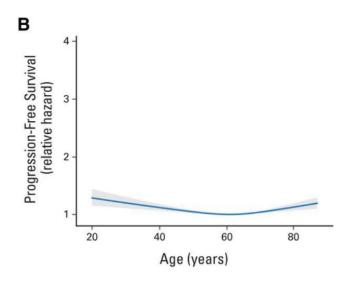
Stage of Disease	Receipt of Cancer-Directed Surgery		Receipt of Cancer-Directed Radiation			
	Age <50 Years	Age ≥50 Years	Age <50 Years	Age ≥50 Years		
Localized	95.8%	94.9%	36.2%	29.7%		
Regional	97.7%	97.1%	82.4%	77.7%		
Distant	70.8%	66.6%	49.1%	41.9%		

Abdelsattar, Z., et al. Cancer, 2016.

HOPE Young Onset Colorectal Cancer

Poorer Survival on 1st Line Clinical Trials



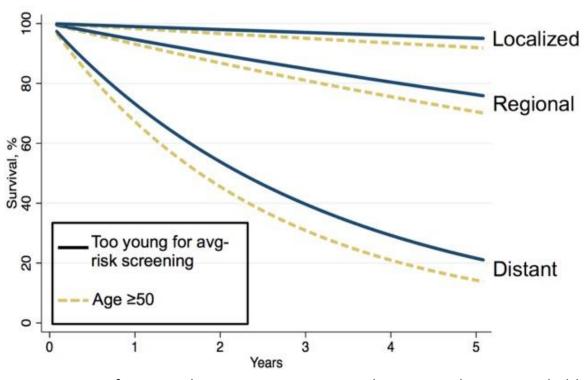


Lieu, C., et al. JCO, 2014.

CITY OF HOPE Young Onset Colorectal Cancer

Cancer Specific Survival

Adjusted Cancer-Specific Survival



The 5-year cancer-specific survival rate patients younger than 50 vs. those 50 and older was 95.1% versus 91.9% (P<.001) for localized disease, 76% versus 70.3% (P<.001) for regional disease, and 21.3% versus 14.1% (P<.001) for distant disease, respectively. Adjusted for sex, race/ethnicity, marital status, tumor location, stage at diagnosis, receipt of cancer-directed surgery or radiation, and year of diagnosis

Abdelsattar, Z., et al. Cancer, 2016.

Over-utilization of Treatment for Stage II

Table 2. Likelihood of Receiving Postoperative Systemic Chemotherapy and Multiagent Regimens for Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers^a

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)

Kneuertz, P., et al. JAMA Surgery, 2015.

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Over-treatment, no Associated Survival Benefit

Surgery Plus Postoperative Systemic Chemotherapy Surgery Adjusted Adjusted 5-Year Adjusted Adjusted 5-Year **Relative Risk** Relative Relative Risk Relative **Patients** No. (%) (95% CI) Survival, % No. (%) (95% CI) Survival, % Stage I 8829 (98.2) NA Ages 65-75 y (n = 8991) 1 [Reference] 96.8 NA NA Ages 18-49 y (n = 1926) 1817 (94.3) 0.49 (0.29-0.85) 98.4 NA NA NA Stage II Overall Ages 65-75 y (n = 11 011) 8263 (75.0) 1 [Reference] 82.3 2748 (25.0) 1 [Reference] 90.2 1732 (56.2) 0.90 (0.69-1.17) Ages 18-49 y (n = 3083)1351 (43.8) 0.72 (0.58-0.88) 86.9 91.1 Stage II Low Risk Ages 65-75 y (n = 4822) 3899 (80.9) 1 [Reference] 89.2 923 (19.1) 1 [Reference] 95.4 Ages 18-49 y (n = 1636) 810 (49.5) 0.60 (0.41-0.87) 93.3 826 (50.5) 1.03 (0.53-2.00) 95.2 Stage II High Risk

74.6

78.9

39.1

54.7

Table 3. Relative Survival of Young Adults (Ages 18-49 Years at Diagnosis) vs Older Adults (Ages 65-75 Years at Diagnosis) With Colon Cancers^a

Kneuertz, P., et al. JAMA Surgery, 2015.

Ages 65-75 y (n = 6189)

Ages 18-49 y (n = 1447)

Ages 65-75 y (n = 11 202)

Ages 18-49 y (n = 4780)

Stage III

4364 (70.5)

541 (37.4)

3027 (27.0)

648 (13.6)

1 [Reference]

1 [Reference]

0.64 (0.55-0.74)

0.80 (0.63-1.02)

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1825 (29.5)

906 (62.6)

8175 (73.0)

4132 (86.4)

1 [Reference]

1 [Reference]

0.85 (0.64-1.13)

0.89 (0.81-0.97)

85.8

87.7

71

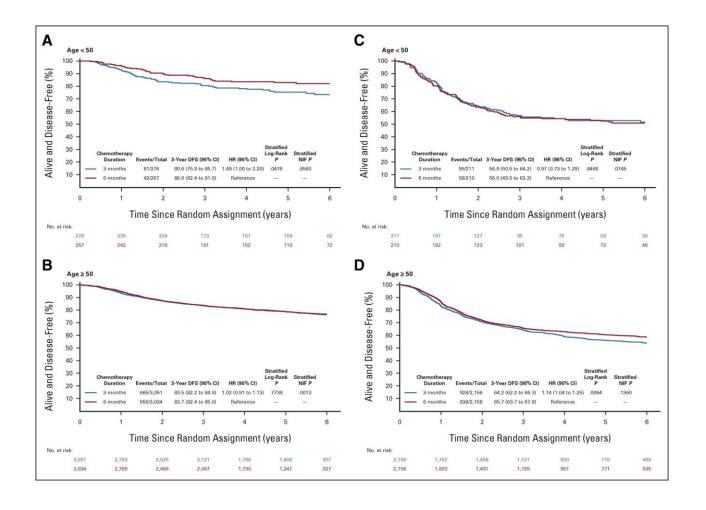
73.7

IDEA: Recommendation for Stage III

3-year DFS rate (%) and HR	Regimen										
by regimen and risk group	САРОХ	CAPOX			FOLFOX			CAPOX/FOLFOX combined			
	3-year DFS, % (95% CI)		HR (95% CI)	3-year DFS, % (95% CI)		HR (95% CI)	3-year DFS, % (95% CI)		HR (95% CI)		
	3 months	6 months		3 months	6 months		3 months	6 months			
Risk group											
Low-risk (T1–3/N1) ~60% High-risk	85.0 (83.1 to 86.9)	83.1 (81.1 to 85.2)	0.85 (0.71–1.01)	81.9 (80.2 to 83.6)	83.5 (81.9 to 85.1)	1.10 (0.96–1.26)	83.1 (81.8 to 84.4)	83.3 (82.1 to 84.6)	1.01 (0.90–1.12)		
(T4 and/or N2) ∼40%	64.1 (61.3 to 67.1)	64.0 (61.2 to 67.0)	1.02 (0.89–1.17)	61.5 (58.9 to 64.1)	64.7 (62.2 to 67.3)	1.20 (1.07–1.35)	62.7 (60.8 to 64.4)	64.4 (62.6 to 66.4)	1.12 (1.03–1.23)		
Risk groups combined	75.9 (74.2 to 77.6)	74.8 (73.1 to 76.6)	0.95 (0.85–1.06)	73.6 (72.2 to 75.1)	76.0 (74.6 to 77.5)	1.16 (1.06–1.26)	(<i>P</i> -value interaction Regimen: 0.0061 Risk group: 0.11)		1.07 (1.00–1.15)		
Key for 'non-inferiority' of 3 vers	sus 6 months of adjuv	ant therapy:									
		No	on-inferior	Not proven	Inf	erior					
CAPOX, capecitabine plus oxali	olatin; CI, confidence	interval; DFS, disease	e-free survival; FOL	FOX, infusional 5-fluc	prouracil, leucovorin	and oxaliplatin; HR	, hazard ratio; N, node	e; T, tumour.			
			·			, ,	. ,				

Sobrero, A. Annals of Oncology, 2018.

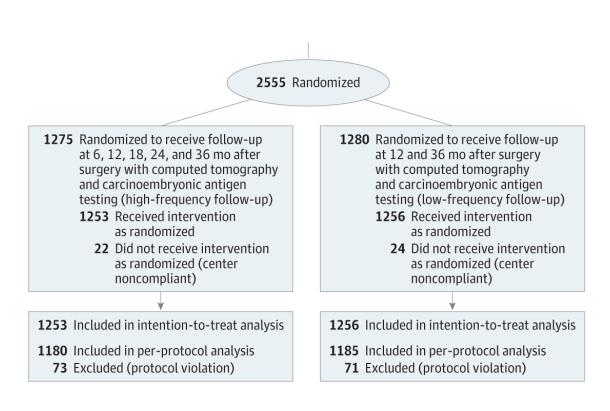
Adjuvant Therapy for Stage III, undertreatment?

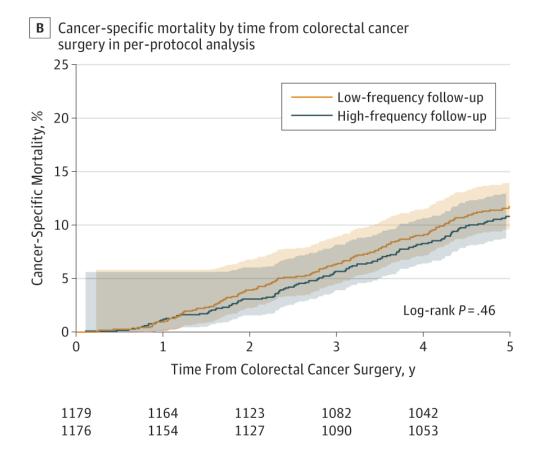


Fontana, E., et al. JCO, 2021.

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Surveillance: Annual CT scan





Wille-Jorgensen, P., JAMA, 2018.

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Actionable Molecular Alteration

	MDACC Molecular Cohort			AACR Project GENIE Cohort											
	18-29 y	30-39 y	40-49 y	50-59 y	60-69 y	≥70 y	P	18-29 y	30-39 y	40-49 y	50-59 y	60-69 y	≥70 y	P	Combined P
Patients, No. (%)	46 (2)	177 (9)	411 (22)	605 (32)	454 (24)	184 (10)		31 (2)	126 (7)	371 (20)	518 (28)	510 (27)	312 (17)		
Mutation, No. (%)															
APC	12 (26)	71 (40)	181 (44)	287 (47)	208 (46)	88 (48)	.059	18 (58)	81 (64)	245 (66)	338 (65)	303 (59)	196 (63)	.33	.096
AKT1	1 (2)	3 (2)	1 (0)	4 (1)	4 (1)	1 (1)	.25	1 (3)	2 (2)	6 (2)	2 (0)	9 (2)	8 (3)	.067	.085
ATM	0 (0)	1 (1)	7 (2)	23 (4)	9 (2)	1 (1)	.037	6 (19)	5 (4)	25 (7)	31 (6)	23 (5)	31 (10)	.004	.001
BRAF	2 (4)	8 (5)	27 (7)	36 (6)	50 (11)	21 (11)	.006	4 (13)	16 (13)	33 (9)	46 (9)	59 (12)	55 (18)	.004	<.001
BRAF V600	2 (4)	5 (3)	17 (4)	30 (5)	43 (9)	18 (10)	.001	0 (0)	11 (9)	21 (6)	31 (6)	45 (9)	42 (13)	.001	<.001
CDKN2A	1 (2)	2 (1)	1 (0)	2 (0)	3 (1)	3 (2)	.11	0 (0)	3 (2)	10 (3)	7 (1)	11 (2)	10 (3)	.51	.22
CTNNB1	0 (0)	7 (4)	8 (2)	5 (1)	10 (2)	0 (0)	.020	4 (13)	9 (7)	10 (3)	23 (4)	23 (5)	18 (6)	.054	.008
ERBB2	0 (0)	2 (1)	3 (1)	7 (1)	4 (1)	4 (2)	.71	3 (10)	5 (4)	12 (3)	16 (3)	17 (3)	11 (4)	.53	.74
ERBB4	0 (0)	1 (1)	4 (1)	12 (2)	4 (1)	1 (1)	.55	3 (10)	7 (6)	20 (5)	18 (3)	27 (5)	14 (4)	.40	.55
FGFR3	1 (2)	2 (1)	3 (1)	3 (0)	2 (0)	0 (0)	.37	2 (6)	3 (2)	11 (3)	9 (2)	10 (2)	13 (4)	.15	.22
FBXW7	2 (4)	8 (5)	34 (8)	50 (8)	29 (6)	19 (10)	.26	2 (6)	10 (8)	33 (9)	57 (11)	46 (9)	41 (13)	.36	.31
GNAS	0 (0)	1 (1)	5 (1)	10 (2)	9 (2)	5 (3)	.61	2 (6)	6 (5)	17 (5)	8 (2)	23 (5)	11 (4)	.031	.094
KDR	0 (0)	1 (1)	5 (1)	6 (1)	4 (1)	3 (2)	.91	3 (10)	3 (2)	13 (4)	10 (2)	18 (4)	10 (3)	.18	.46
KIT	0 (0)	1 (1)	5 (1)	5 (1)	2 (0)	0 (0)	.68	1 (3)	0 (0)	14 (4)	8 (2)	11 (2)	4 (1)	.071	.19
KRAS	17 (37)	89 (50)	207 (50)	292 (48)	210 (46)	94 (51)	.46	12 (39)	47 (37)	161 (43)	244 (47)	239 (47)	148 (47)	.30	.41
MET	1 (2)	1 (1)	1 (0)	5 (1)	3 (1)	1 (1)	.52	1 (3)	5 (4)	12 (3)	7 (1)	4 (1)	8 (3)	.023	.065
NRAS	3 (7)	8 (5)	14 (3)	22 (4)	24 (5)	8 (4)	.61	1 (3)	5 (4)	15 (4)	20 (4)	26 (5)	17 (5)	.87	.87
PIK3CA	4 (9)	27 (15)	66 (16)	80 (13)	72 (16)	38 (21)	.16	8 (26)	29 (23)	67 (18)	102 (20)	94 (18)	58 (19)	0.71	.36
PTEN	2 (4)	2 (1)	14 (3)	6 (1)	16 (4)	6 (3)	.017	1 (3)	8 (6)	28 (8)	23 (4)	28 (5)	14 (4)	0.42	.042
RB1	1 (2)	1 (1)	6 (1)	2 (0)	4 (1)	2 (1)	.24	2 (6)	4 (3)	12 (3)	11 (2)	12 (2)	7 (2)	0.53	.39
RET	0 (0)	1 (1)	4 (1)	7 (1)	2 (0)	2 (1)	.85	3 (10)	4 (3)	12 (3)	6 (1)	11 (2)	6 (2)	.036	.14
SMAD4	9 (20)	24 (14)	53 (13)	66 (11)	58 (13)	23 (13)	.58	5 (16)	14 (11)	51 (14)	63 (12)	72 (14)	41 (13)	.88	.85
SMARCB1	0 (0)	0 (0)	4 (1)	4 (1)	6 (1)	1 (1)	.71	2 (6)	2 (2)	6 (2)	4 (1)	2 (0)	8 (3)	.010	.042
SMO	0 (0)	0 (0)	4 (1)	5 (1)	6 (1)	1 (1)	.77	4 (13)	6 (5)	12 (3)	12 (2)	9 (2)	7 (2)	.020	.080
STK11	0 (0)	1 (1)	2 (0)	8 (1)	1 (0)	2 (1)	.36	0 (0)	1 (1)	2 (1)	3 (1)	12 (2)	4 (1)	.14	.20
TP53	28 (61)	120 (68)	265 (64)	398 (66)	280 (62)	123 (67)	.62	18 (58)	91 (72)	269 (73)	347 (67)	326 (64)	204 (65)	.06	.16
MAPK summary	22 (48)	102 (58)	239 (58)	349 (58)	274 (60)	120 (65)	.27	15 (48)	71 (56)	211 (57)	303 (58)	321 (63)	217 (70)	.004	.008

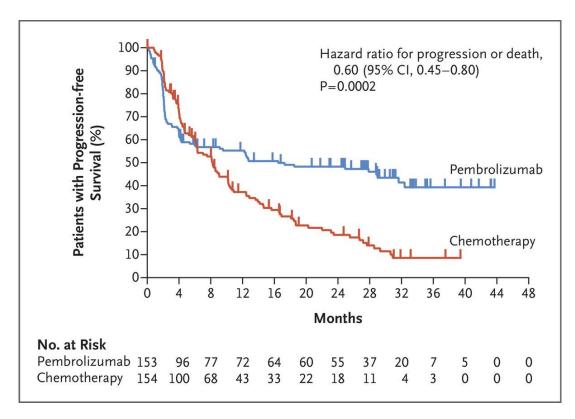
Willauer, A, et al. Cancer, 2019.

Molecular Landscape of Young Patients

	Onset <50 years, n = 24	Onset >70 years, n = 17	P-values
Mean number of mutations per patient	1.04	1.47	0.14
Median number of regions with copy number aberration per patient	43.29	26.88	0.02
Median percentage of normal copy number per patient	71.72	77.23	0.66

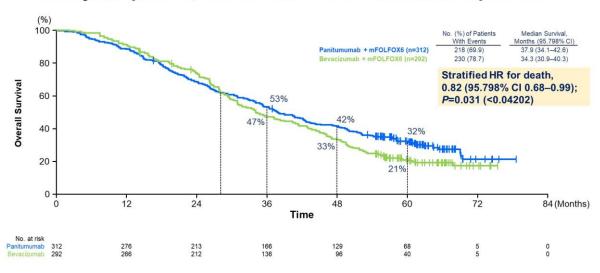
Median number of mutations per patient (= gene mutation index) is based on data from analyses of KRAS, BRAF, PIK3CA, PTEN and TP53. Median number of regions with copy number aberrations (= genomic complexity) and median percentage of normal copy number per patient are based on results from aCGH analysis. doi:10.1371/journal.pone.0013978.t002

Know the Biomarker: Role in Selection of 1st Line



André, T., et al. N Engl J Med, 2020.

Primary Endpoint-1; Overall Survival in Left-sided Population



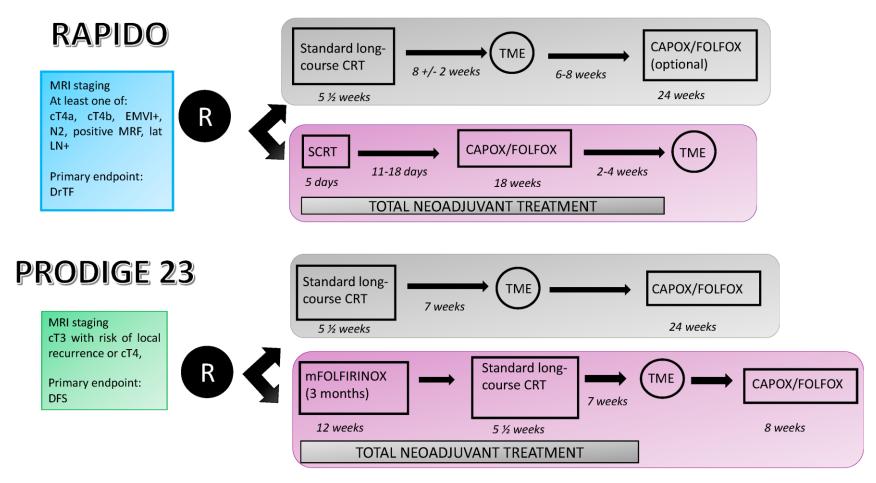
Yoshini, T. et al. ASCO 2022.

OPE Young Onset Colorectal Cancer 20

Treating Young Onset Rectal Cancer

Approximately 30% of rectal cancers are diagnosed in patients younger than age 55

TNT



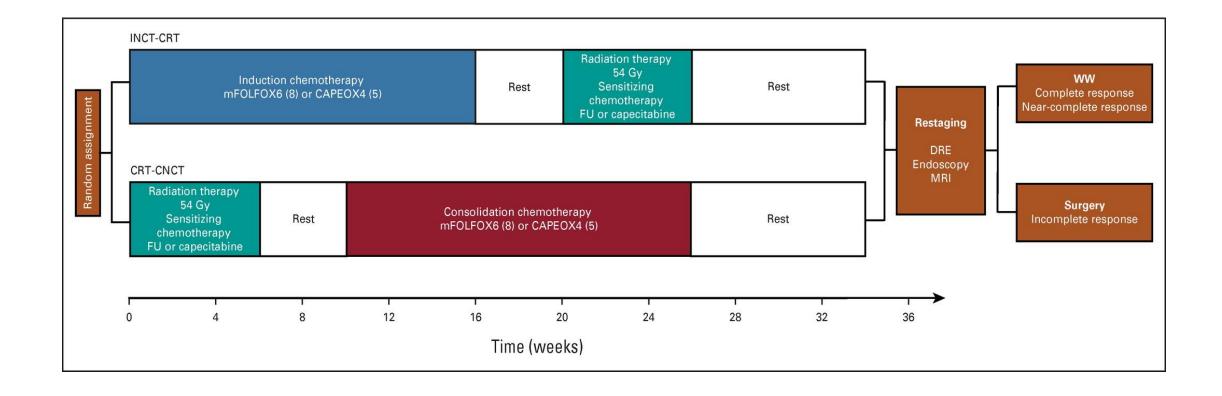
Bahadoer, R., et al. Lancet Oncol, 2021. Conroy, T., et al. Lancet Oncol, 2021. Papaccio, F. et al. Cancers, 2020.

Reason to Intensify

RAPIDO (TNT vs. CRT)	PRODIGE 23 (TNT vs. CRT)
61 yrs vs. 61 yrs	61 yrs vs. 62 yrs
462 vs. 450	231 vs. 230
30.4% vs. 31.8%	17.8% vs. 15.6%
68% vs. 68%	Not stated
32% vs. 28%	Not stated
62% vs. 60%	26% vs. 27.7%
	(TNT vs. CRT) 61 yrs vs. 61 yrs 462 vs. 450 30.4% vs. 31.8% 68% vs. 68% 32% vs. 28%

	Outcomes	RAPIDO	PRODIGE 23
	Outcomes	(TNT vs. CRT)	(TNT vs. CRT)
-	Median FU	4.6 yrs	3.8 yrs
	Primary endpoint	3-yrs DrTF	3-yrs DFS
	Timary enuponii	23.7% vs. 30.4% (HR 0.75 [95%	75.7% vs. 68.5% (HR 0.69 95%
		CI $0.60-0.96$]; $p = 0.019$)	[CI $0.49-0.97$]; $p = 0.034$)
	3-year MFS	80% vs. 73.2%	78.8% vs. 71.7%
	pCR rate	28.4% vs. 14.3%	27.5% vs. 11.7%
	Local relapse	8.7% vs. 5.4%	4.8% vs. 7%
, 2020.	3-year OS	89.1% vs. 88.8%	90.8% vs. 87.7%

OPRA Trial



Non-operative Management in Young Patients?

	Five-year OS	DSS
WW (113 patients)	73% (60-89%)	90% (81-99%)
PCR (136 patients)	94% (90-99%)	98% (95-100%)

Selecting the Goal

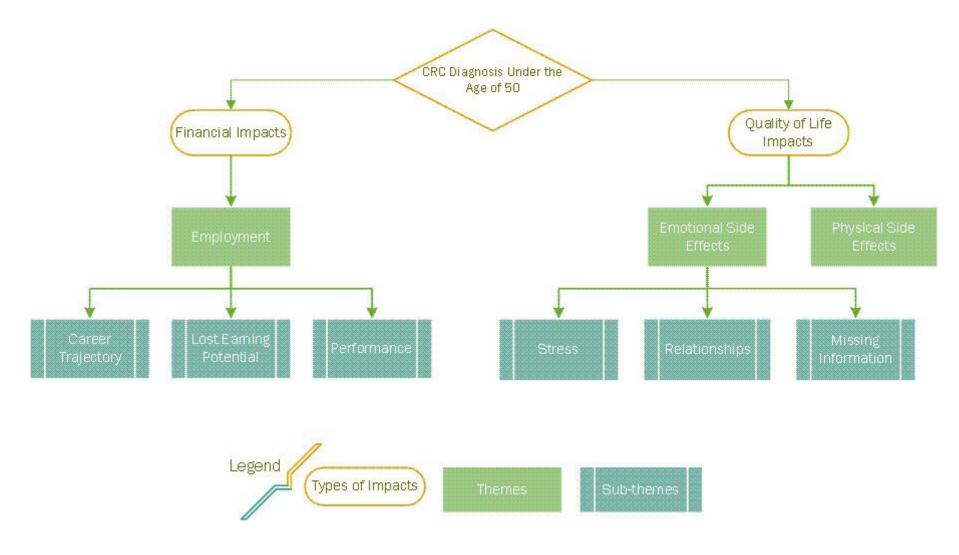
• TNT

- Extended survival?
- Better QOL?
- Time commitment?
- Organ preservation
- Surgical approach >>> sexual functioning

Caution

- Identify the goal
- Avoid longer than needed or intensified chemotherapy
- Discuss the need for follow up care if WW pursued

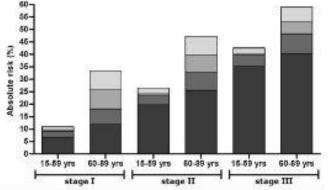
Care for the Patient, not the Cancer



Health Expectations, Volume: 22, Issue: 5, Pages: 1050-1057, 2019.

Changing Needs for Care

A Absolute risks for different causes of death A. 0-5 years follow-up



Proportional distribution causes of death for patients who died during follow-up									
Other	11%	23%	9%	16%	5%	10%			
CVD	7%	23%	3%	10%	1%	8%			
Other ca	21%	18%	13%	15%	11%	14%			
CRC	61%	38%	75%	54%	63%	68%			

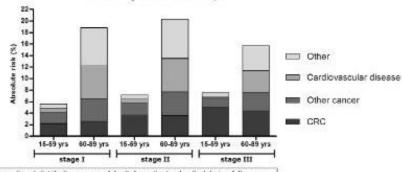
B Absolute risks for different causes of death B. 6-10 years follow-up

Other

CRC

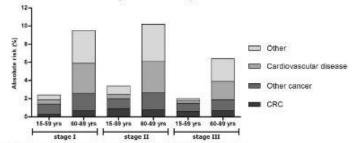
Cardiovascular disease

Other cancer



Other	12%	35%	11%	33%	9%	27%
CVD	14%	30%	10%	29%	3%	25%
Other pa	34%	21%	27%	20%	21%	20%
CRC	40%	14%	62%	18%	67%	28%

C Absolute risks for different causes of death C. 11-15 years follow-up

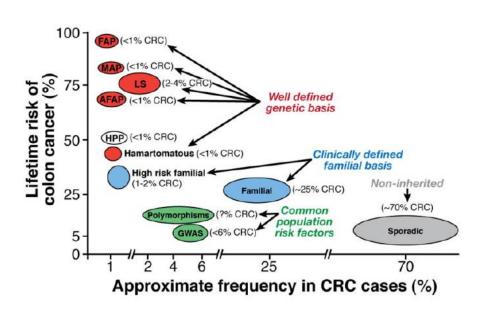


Other	20%	39%	25%	41%	8%	39%
CVD	21%	34%	19%	33%	15%	31%
Other ca	48%	20%	31%	18%	45%	18%
CRC	11%	7%	25%	8%	32%	12%

Van Erning, F N, et al. EJC, 2014.

Genetics of colorectal cancer

5% of patients have hereditary cancer syndrome



16% of young adults have hereditary cancer syndrome

Gene	Associated Syndrome or Cancer(s)	Overall Penetrance	Patients With Mutation, No. (%)	(95% CI)
Any pathogenic or likely pathogenic mutation			72 (16)	(12.8-19.8)
Genes associated with colon cancer			59 (13.1)	(10.2–16.7)
MLH1	Lynch syndrome	High	13 (2.9)	(1.6-5.0)
MSH2	Lynch syndrome	High	16 (3.6)	(2.1-5.8)
MSH2/monoallelic MUTYH	Lynch syndrome/colon cancer	High/low	1 (0.2)	(0.01-1.4)
MSH6	Lynch syndrome	Moderate	2 (0.4)	(0.08-1.8)
PMS2	Lynch syndrome	Moderate	5 (1.1)	(0.4-2.7)
APC	Familial adenomatous polyposis (FAP)	High	5 (1.1)	(0.4-2.7)
APC p.11307K	Colon cancer	Low	4 (0.9)	(0.3-2.4)
MUTYH				
Biallelic	MUTYH-associated polyposis (MAP)	High	4 (0.9)	(0.3-2.4)
Monoallelic	Colon cancer	Low	7 (1.6)	(0.7-3.3)
SMAD4	Juvenile polyposis syndrome	High	1 (0.2)	(0.01-1.4)
APC/PMS2	FAP/Lynch syndrome	High/moderate	1 (0.2)	(0.01-1.4)
Genes not traditionally associated with colon cancer			13 (2.9)	(1.6-5.0)
BRCA1	Hereditary breast-ovarian cancer syndrome	High	2 (0.4)	(0.08-1.8)
BRCA2	Hereditary breast-ovarian cancer syndrome	High	4 (0.9)	(0.3-2.4)
ATM	Breast cancer, pancreatic cancer	Moderate	3 (0.7)	(0.2-2.1)
ATM/CHEK2	Breast cancer, pancreatic cancer	Moderate	1 (0.7)	(0.01-1.4)
PALB2	Breast cancer, pancreatic cancer	Moderate	2 (0.4)	(0.08-1.8)
CDKN2A	Melanoma, pancreatic cancer	High	1 (0.2)	(0.01-1.4)

Conclusion

- Young onset colorectal cancer may not be a different disease. Yet, patients have different needs.
 - Discussion about long- and short-term toxicities
 - Expectations of treatment
 - Germline testing and genetic counseling
 - Sexual functioning and fertility remains an area in need of attention in this population
 - Expanding the horizons of multidisciplinary care beyond its traditional definition
- Data shows a more aggressive management approach in these young patients
 - Avoid over and under treatment and adhere to the available high-quality data
 - Sparing young patients from long term toxicities is detrimental to health of this population

CITY OF HOPE