A Retrospective Analysis of Colorectal Cancer in Adolescents and Young Adults

A report from the Surgical Committee of the Children's Oncology Group

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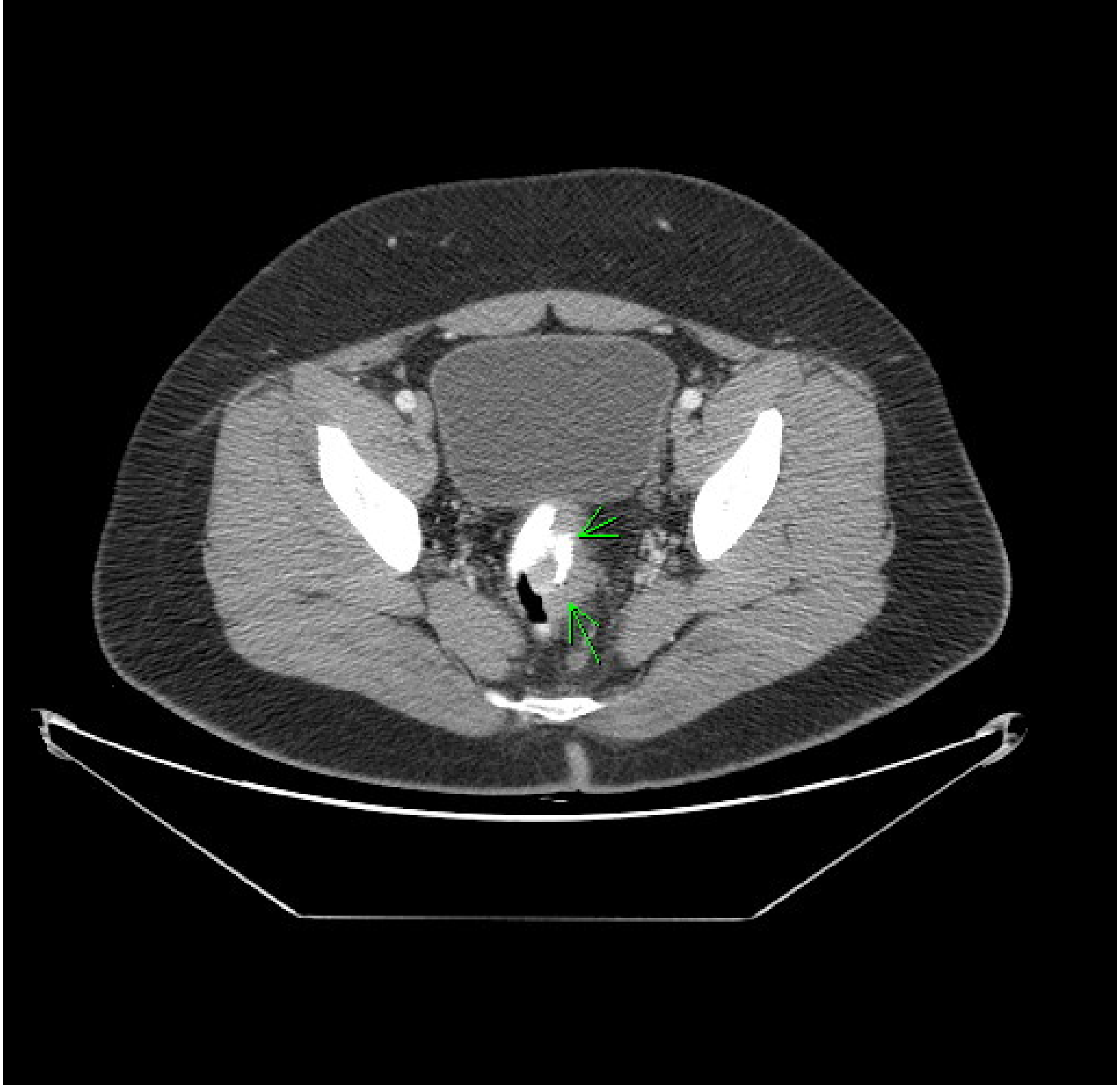
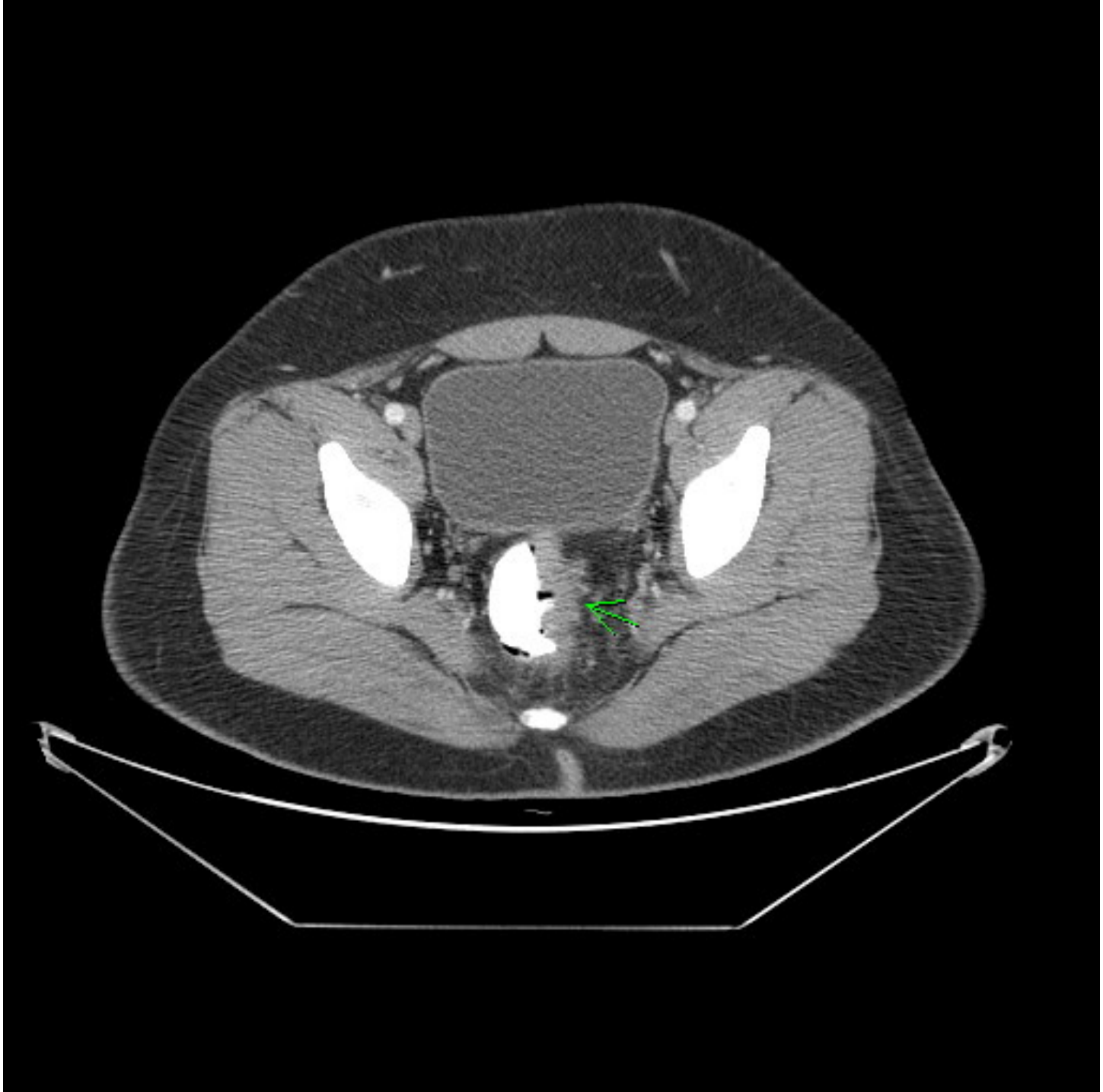
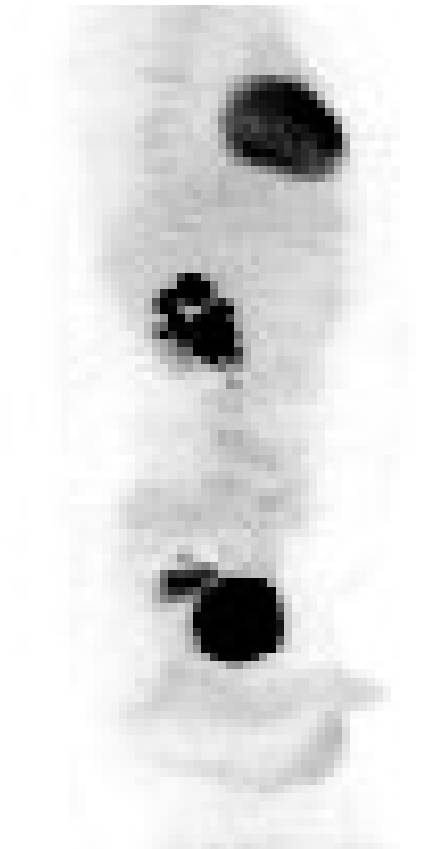


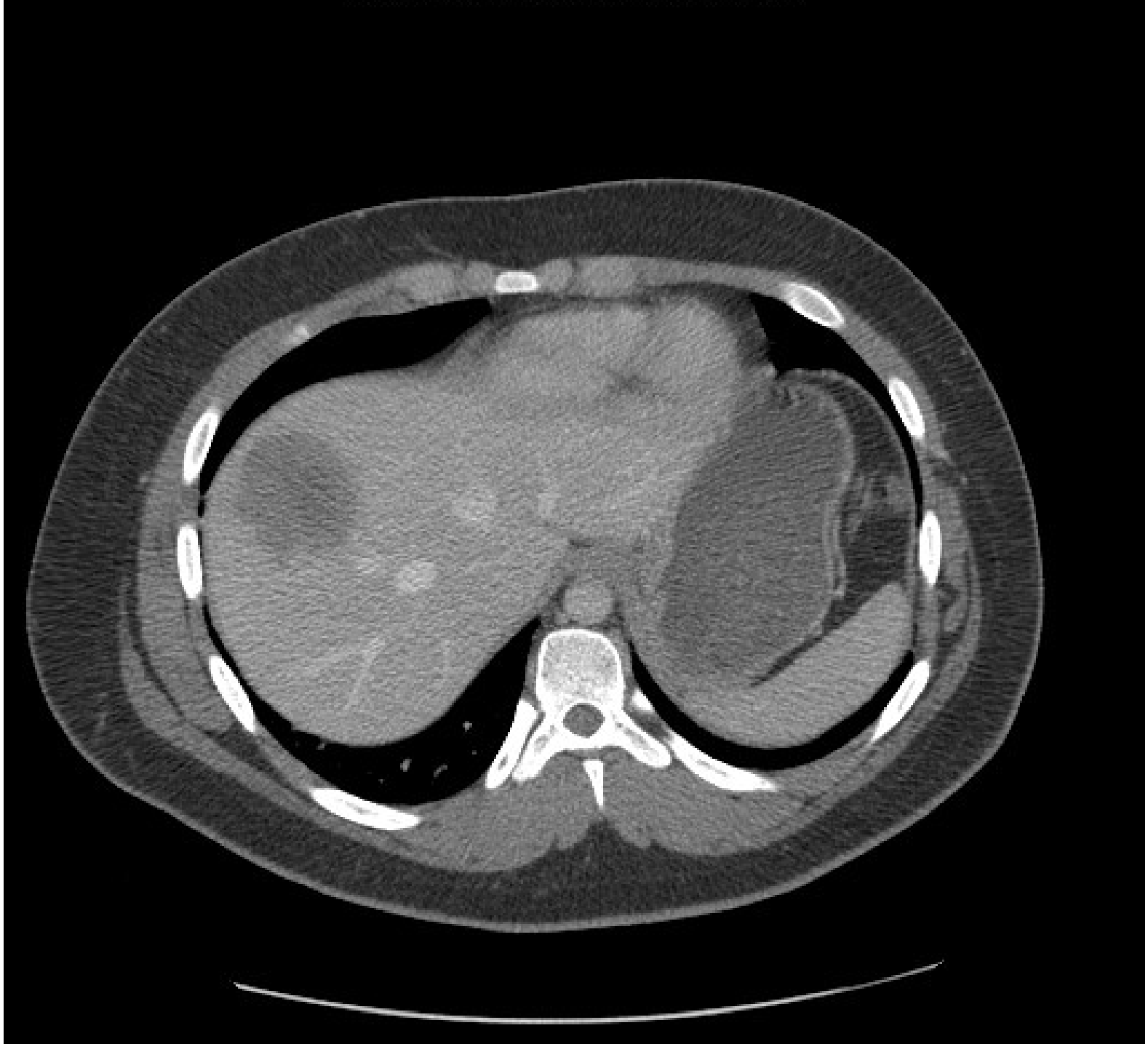


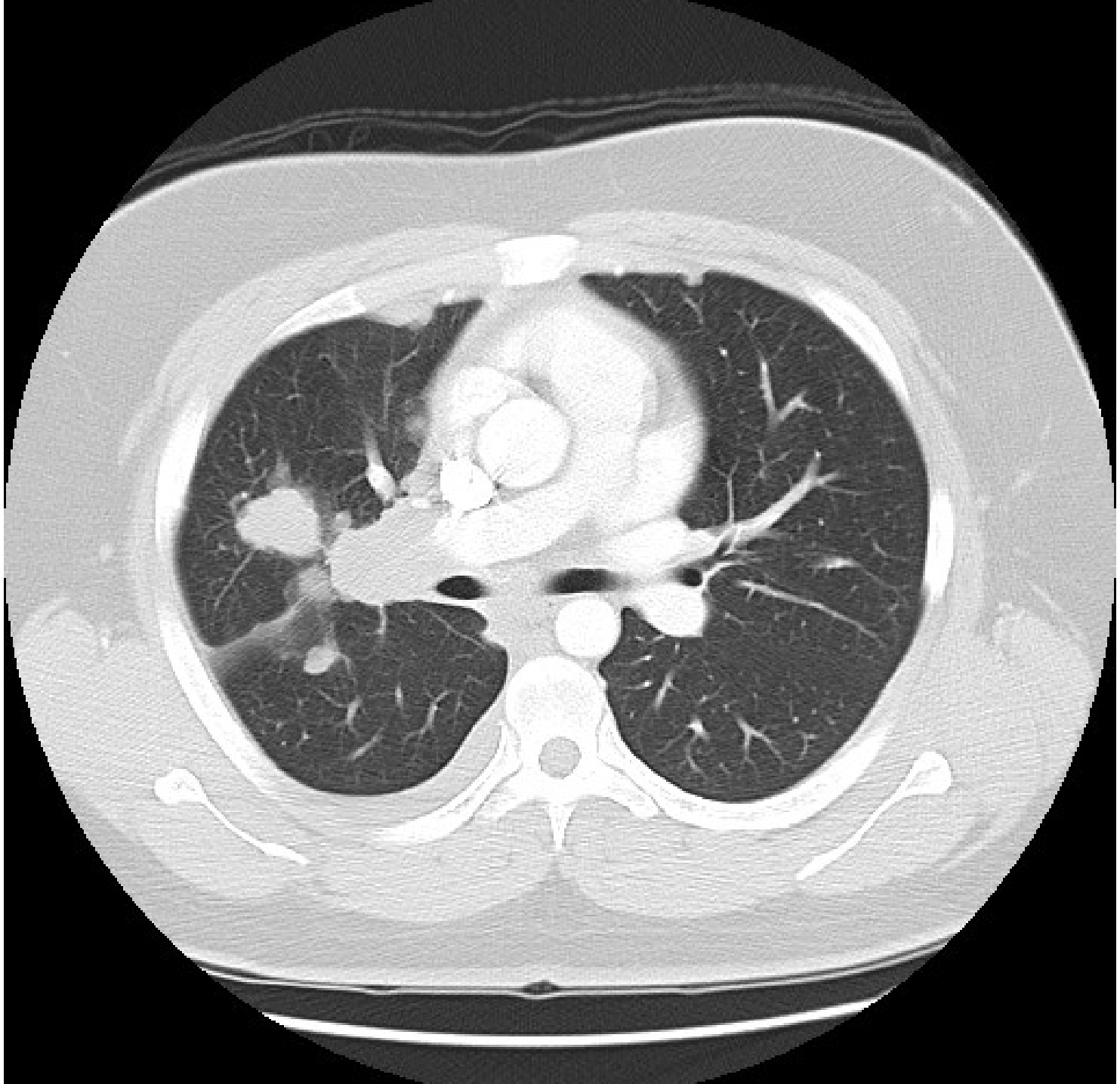
Comparison Of PET scans before and after Neoadjuvant Therapy



Pre-chemotherapy

Post-chemotherapy





Age-Specific Incidence of CRC in USA (SEER/Census)

Age Range (years)	Incidence (per 100,000)	Estimated Cases Per Year
10-14	0.0683	525
15-19	0.2192	
20-24	0.6603	
25-29	1.6190	
30-34	3.4004	2,000
35-39	6.9042	
40-44	13.0117	8,600
45-49	25.2359	
50-54	48.6546	145,000
55-59	80.0381	
60-64	127.2594	
65-69	189.7135	
70-74	255.3637	
75-79	327.2912	

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Colorectal Cancer in the Very Young: A Comparative Study of Tumor Markers, Pathology and Survival in Early Onset and Adult Onset Patients

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Early Onset CRC
A Unique Disease?

- Clinical study: 29 Patients age ≤ 21 years
  - Sporadic cancer = 76%
  - 3-year survival = 28%
  - Advanced stage upon presentation = 82%
  - High grade tumors = 69%
- Molecular analysis: 13 patients age ≤ 21 years
  - Microsatellite instability (MSI+) cancers = 46%
  - Microsatellite stability (MSS+) cancers = 54%

LaQuaglia MP *et al.* J Pediatr Surg,1992
Datta RV, Paty PB, *et al*. NEJM 2000

Molecular Features of Adult CRC

	Hereditary MSI	Sporadic MSI	Sporadic MSS
% of All CRCs	4%	12%	84%
Genomic Instability	Slippage mutation	Deregulated methylation	Chromosomal instability
Mismatch Repair (MMR) Genes	MLH1 MSH2 MLH6 PMS2	MLH1	-
***K-ras* Mutations**	40%	15%	40%
***B-raf* Mutations**	Absent	35%	4%

Clinical and Histological Features of Adult CRC

	Hereditary MSI	Sporadic MSI	Sporadic MSS
Age Onset (yrs)	30 - 60	55 - 90	55 - 90
Family History of Cancer	Amsterdam II	Not major	Not major
Histology	Poorly diff Lymph infilt	Poorly diff Lymph infilt	Variable

Study Questions

- Is the genetic spectrum of early onset CRC similar or different compared to adult onset CRC?

- Can a distinct class of CRC be defined within the early onset group?

Study Design

Study Group

Children Oncology Group (COG) and MSKCC:

- **CRC Diagnosed ≤30 years old**

↓

167 cases: Clinical Information Available

↓

96 Cases: Tumor Blocks Available And DNA successfully extracted

↓

94 Cases: ≤30 Years Old

Control Group

MSKCC: Operated by CR Service between 1991-2005

↓

Frozen Tissue Prepared from OR

↓

345 Cases: DNA Successfully Extracted

↓

275 Cases: ≥50 Years Old

1. **MSI status: (PCR-electrophoresis)**
2. ***K-ras* codon 12/13 mutation: (PCR-LDR)**
3. ***B-raf* V600E mutation: (PCR-LDR)**
4. **MMR presence: (IHC)**

Clinical Characteristics

		Age ≤30 (N=94)	Age ≥50 (N=275)	P
Median Age (y)		27	67	-
Sex	*M*	48%	53%	NS
	F	52%	47%	
Location	*Proximal*	34%	35%	NS
	Distal	66%	65%	
Stage	*III/IV*	76%	51%	<0.0001
Histology	*Poorly differentiated*	37%	8%	<0.0001
	Signet Ring	13%	<1%	<0.0001

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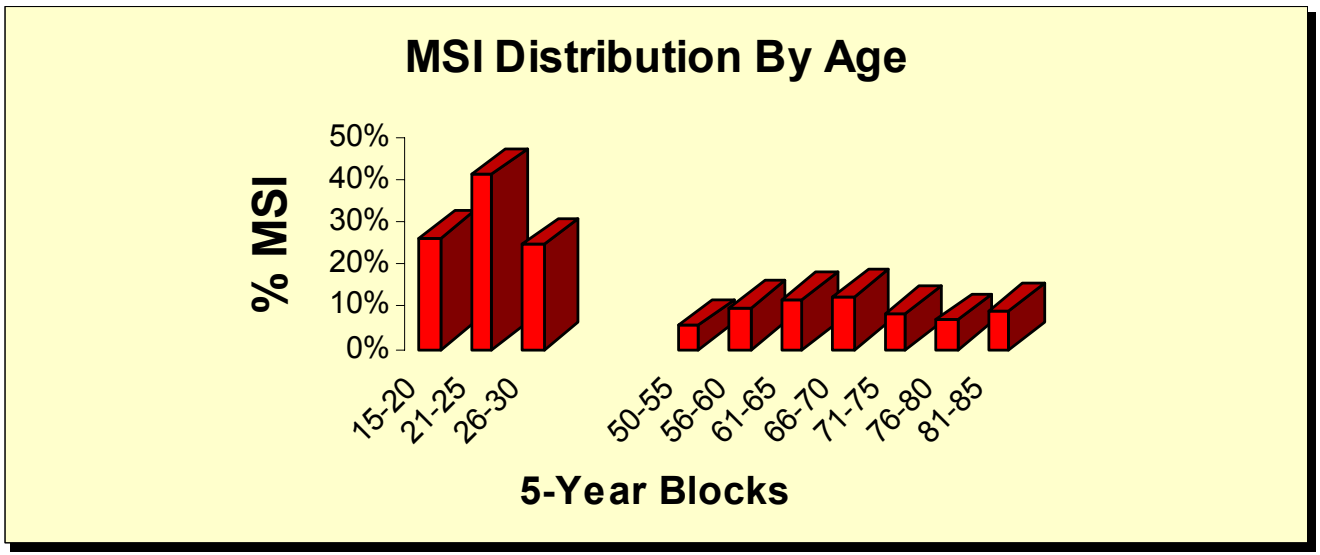
Frequency of Genetic Markers

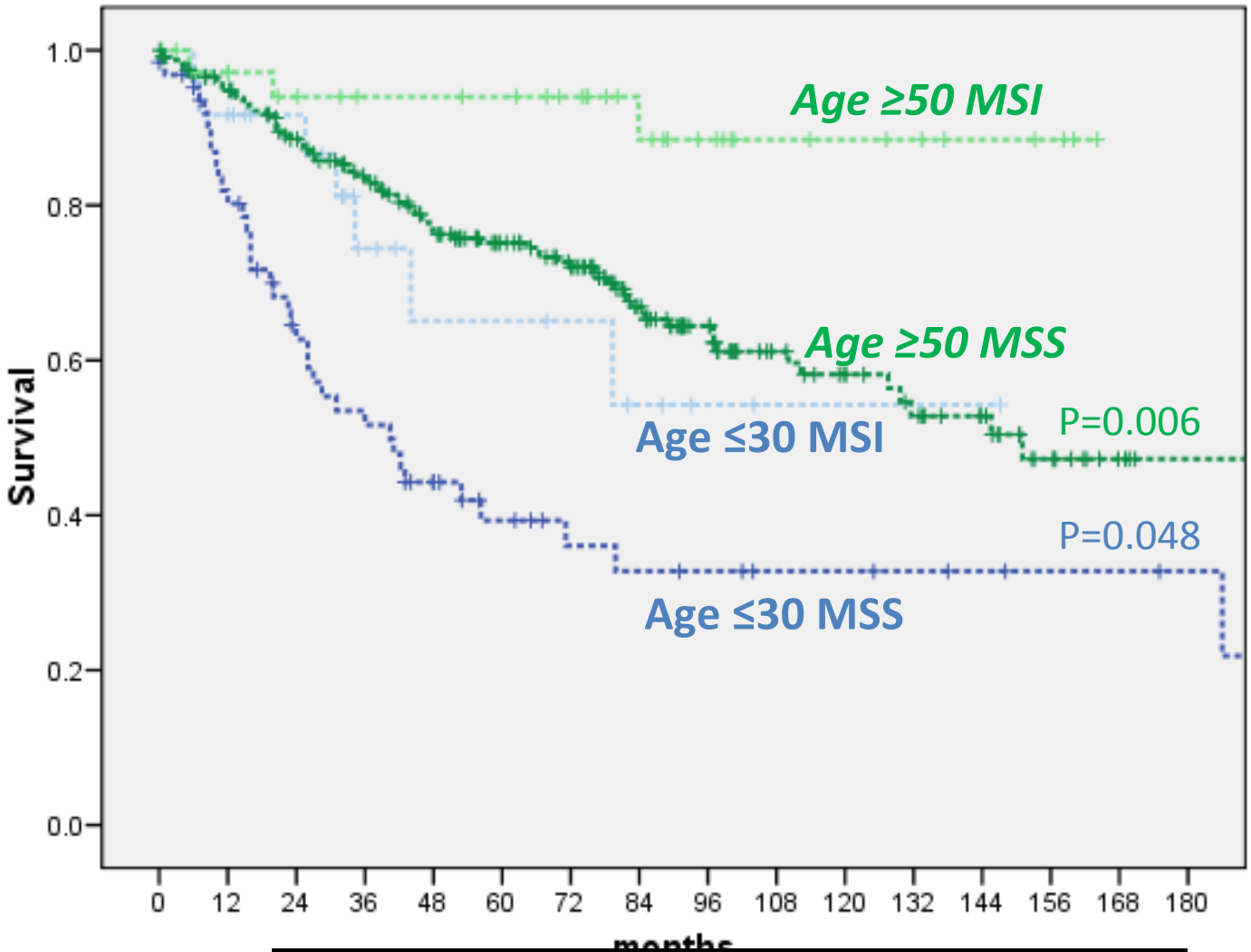
	Age ≤30 (N=94)	Age ≥50 N=275	P
B-raf V600E Mutation	9%	8%	NS
K-ras Codon 12/13 Mutation	28%	36%	NS
MSI	27%	13%	<0.01



Clinical Features of MSI/MSS tumors

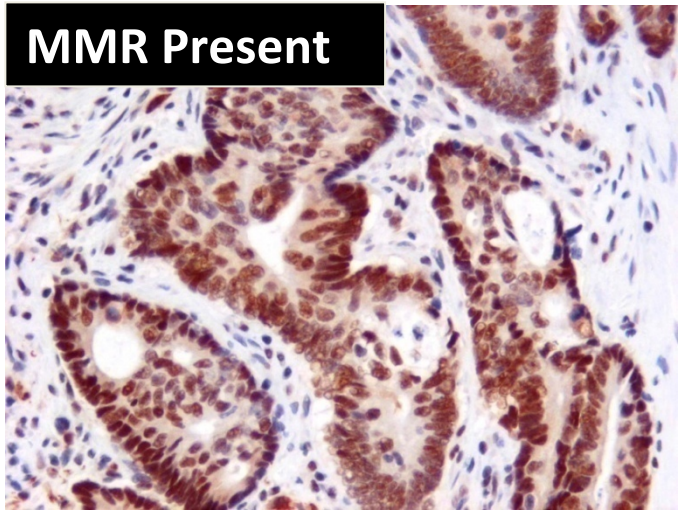
	Early Onset (N=94)	P	Adult Onset (N=275)	P
Right-sided Tumor	39% / 32%	0.78	65% / 30%	<0.0001
Tumor Grade	29% / 40%	0.33	23% / 5%	<0.0001
Early Stage (I +II)	29% / 22%	0.59	78% / 45%	<0.0001
5-year Survival	65% / 39%	0.048	94% / 75%	0.006
Amsterdam II	7% / 5%	0.80	0% / 1%	0.73

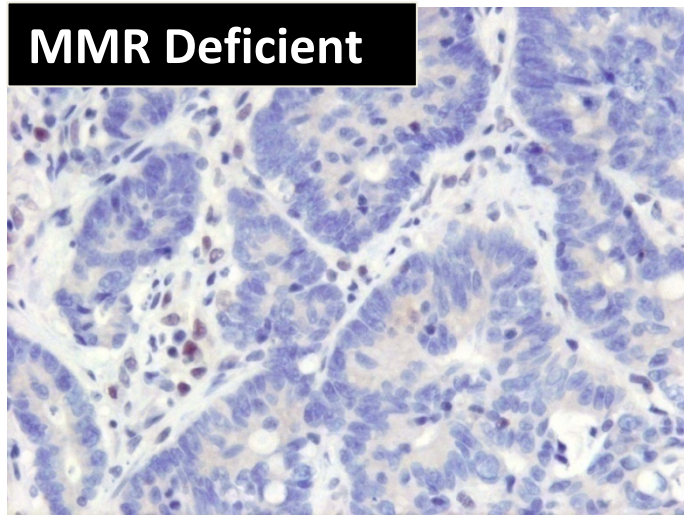
MSI Cancer
Favorable Disease-Specific Survival



MSI Tumors

A Different Distribution of MMR Gene Expression





MMR Gene	Early Onset (N=13)	Adult Onset (N=28)
MLH1	47%	79%
MSH2	29%	0%
MSH6	6%	5%
PMS2	18%	16%

95%

MSI Tumors

Absence of an Favorable Genotype

Prevalence of *B-raf Mutations* in MSI Tumors			
	Early Onset (N=25)	Adult Onset (N = 37)	P
B-raf V600E mutation	0%	38%	<0.01

	Early Onset	Adult Onset
MSI+ *B-raf* Mut	N = 0 (0%)	N = 14 (38%)
Stage I - II	-	93%
5-year DSS	-	100%
MSI + *B-raf* WT	N = 25 (27%)	N = 23 (62%)
Stage I - II	28%	65%
Median DSS	65%	90%

MSS Tumors

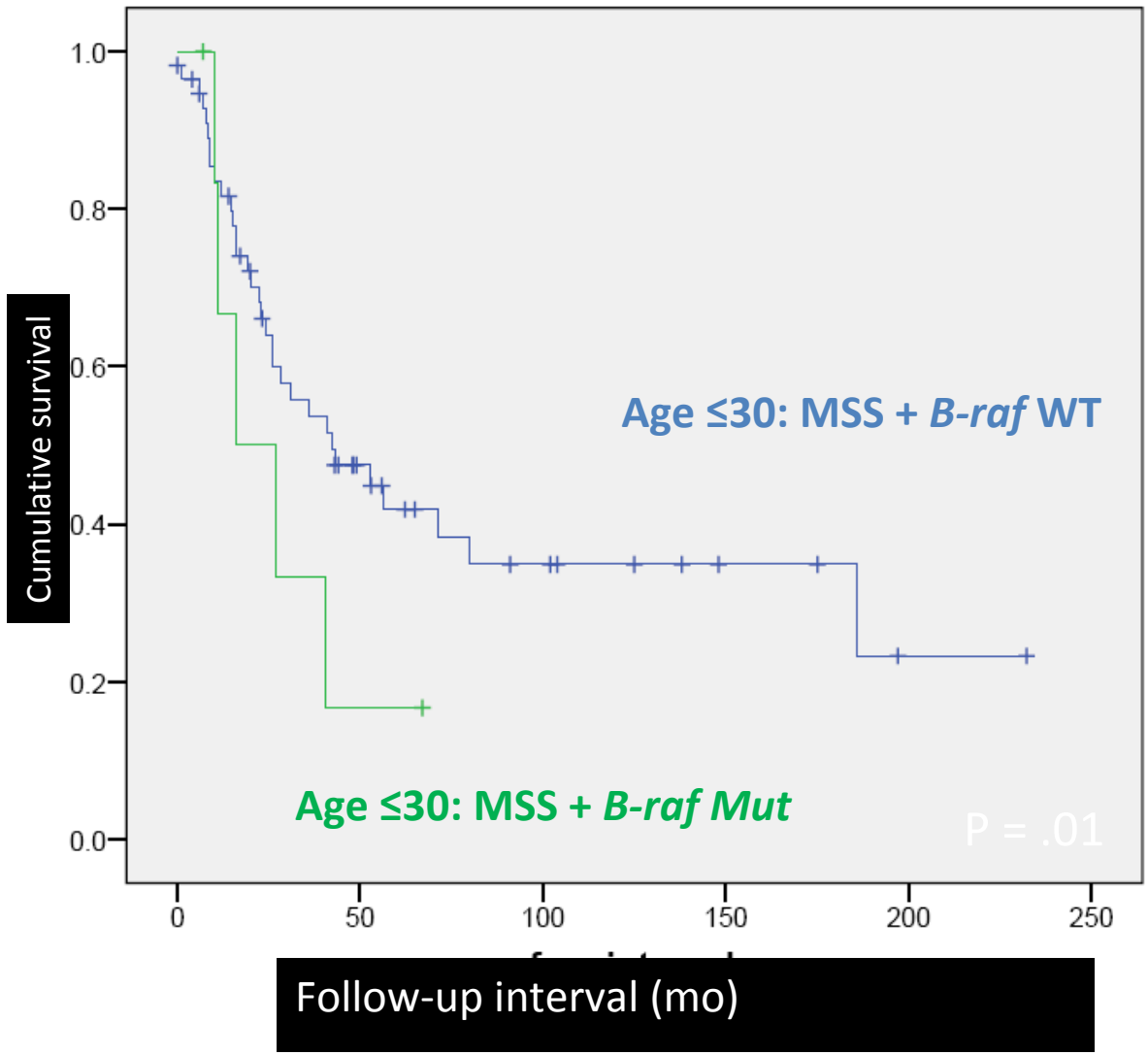
Enrichment Of An Aggressive Genotype

Prevalence of *B-raf* Mutations in MSS Tumors			
	Early Onset (N = 69)	Adult Onset (N = 237)	P
MSS + *B-raf mut*	9%	3%	<0.01

	Early Onset	Adult Onset
MSS + *B-raf* Mut	N = 8 (9%)	N = 8 (3%)
Stage III-IV	100%	100%
5-year DSS	16 mo	75%
MSS + *B-raf* WT	N = 61 (91%)	N = 230 (97%)
Stage III-IV	72%	53%
5-year DSS	56 mo	75%

MSS + *B-raf* Mutation

A Marker For Poor Disease-Specific Survival



Summary – Early Onset CRC

- High grade tumors, advanced stage and poor survival compared to adult onset CRC
- Enriched for MSI tumors (27%)
- Genetic subtypes:
  - ABSENT indolent MSI/*B-raf* mutant group
  - ENRICHED aggressive MSS/*B-raf* mutant group
- Among MSI tumors, MMR gene staining pattern and absence of *B-raf is* similar to HNPCC

Hypothesis: Early Onset CRC

- De novo germline mutations of genes in the p53 pathway are a cause for early onset colorectal cancer

Prevalence of Early Onset Colorectal Cancer in 397 Patients With Classic Li–Fraumeni Syndrome

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A Single Nucleotide Polymorphism in the *MDM2* Promoter Attenuates the p53 Tumor Suppressor Pathway and Accelerates Tumor Formation in Humans

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Elisabeth E. Bond,[2] Harlan Robins,[1]
Stuart G. Lutzker,[2] Nicoleta C. Arva,[7]
Jill Bargonetti,[7] Frank Bartel,[4] Helge Taubert,[4]
Peter Wuerl,[5] Kenan Onel,[6] Linwah Yip,[3]
Shih-Jen Hwang,[3] Louise C. Strong,[3]
Guillermina Lozano,[3] and Arnold J. Levine[1,2,*]

Introduction

The tumor suppressor protein, p53, is activated upon cellular stresses such as DNA damage and oncogene activation and initiates a transcriptional program which leads to DNA repair, cell cycle arrest, and in some cases, apoptosis (Jin and Levine, 2001). The p53 stress re-

Wong, Syngal et al, Gastroenterology 2006
Bond, Levine et al, Cell 2004

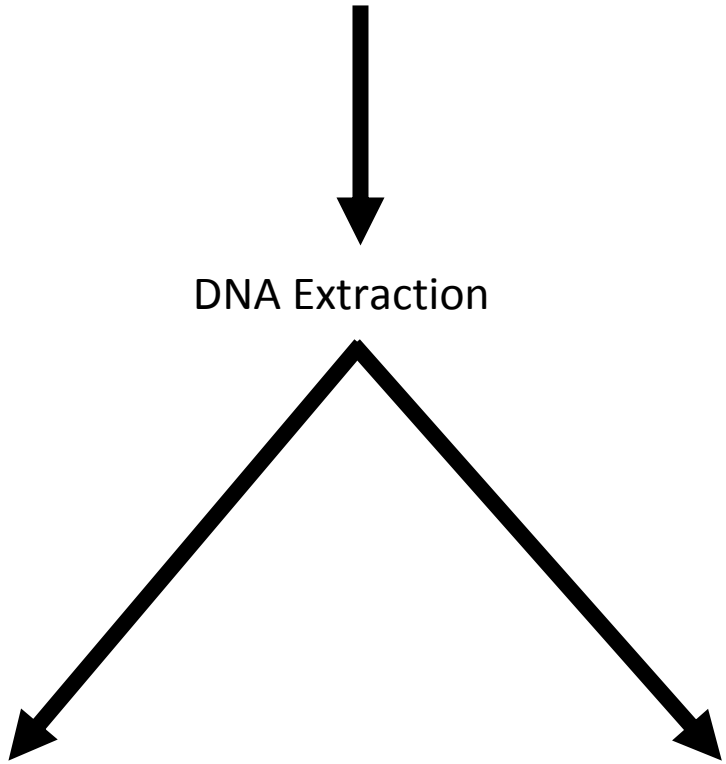
Li-Fraumeni Syndrome
A Rare Cause of CRC

- Li-Fraumeni Syndrome (LFS):
  - Classic: Sarcoma, breast, adrenal, brain cancer
  - Rare: Colon Cancer (2-3%)
  - Genetic alteration: germline p53 mutation (more common), Chk2 mutation
- Germline p53 Mutations:
  - Range of phenotypic expression not fully known
  - No population based studies
  - LFS versus rare phenotypes: ascertainment bias

http://www-p53.iarc.fr
Olivier M. Cancer Res. 2003;63(20):6643-50

Study Design: Molecular Characteristics of Germline Tissue in Early Onset CRC

35 Cases – Frozen Peripheral Blood Leukocytes
With CRC Diagnosed ≤30 years old

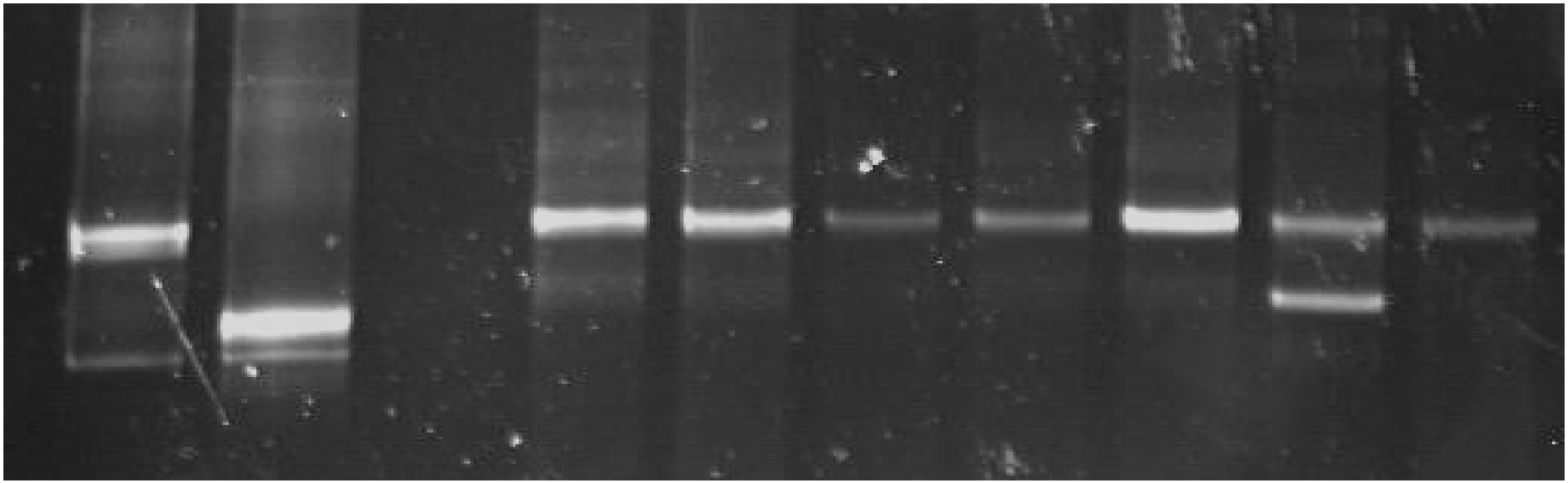


DNA Extraction

p53 Screen: PCR/TTGE Exons 4 -10
(sequencing of aberrant bands)

MDM2 SNP309: PCR/LDR

TTGE Gel for TP53 Exon 6



Patient 7

Patient 6

Patient 5

Patient 4

Patient 3

Patient 2

Patient 1

BxPC3 (Mut control)

LoVo (WT control)

MDM2 SNP309 Genetic Analysis

	T/T	T/G	G/G	P-value
Median Age at Diagnosis	28	28	27	-
Number of Cases	11	19	3	-
Percent	33%	58%	9%	NS
Adult Prevalence*				
CRC	34%	48%	18%	NS
Population	30%	53%	17%	NS

*Alhopuro, J of Med Gen 2005

Conclusion

- Genetic variants in P53 and MDM2 SNP309 in germline tissue are not associated with early onset CRC

Khan SA, Idrees K, Paty PB et al, submitted for publication, 2007

Future Directions

- Targetted agents (ie. Inhibitors of B-raf)
- Prospective molecular profiling and clinical database
- Inclusion of cases in Cancer Genome Anatomy Project
  - **Fresh frozen tissue**
  - **White cells or buccal mucosal cells**
  - **Detailed family Hx**