Surgical Management of Colonic Neoplasms in Lynch Syndrome

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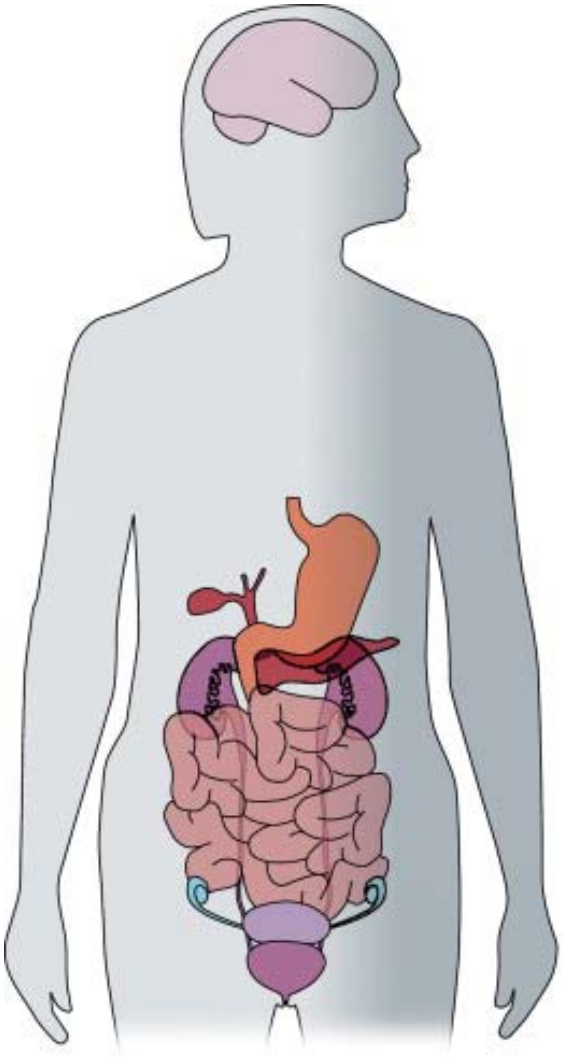
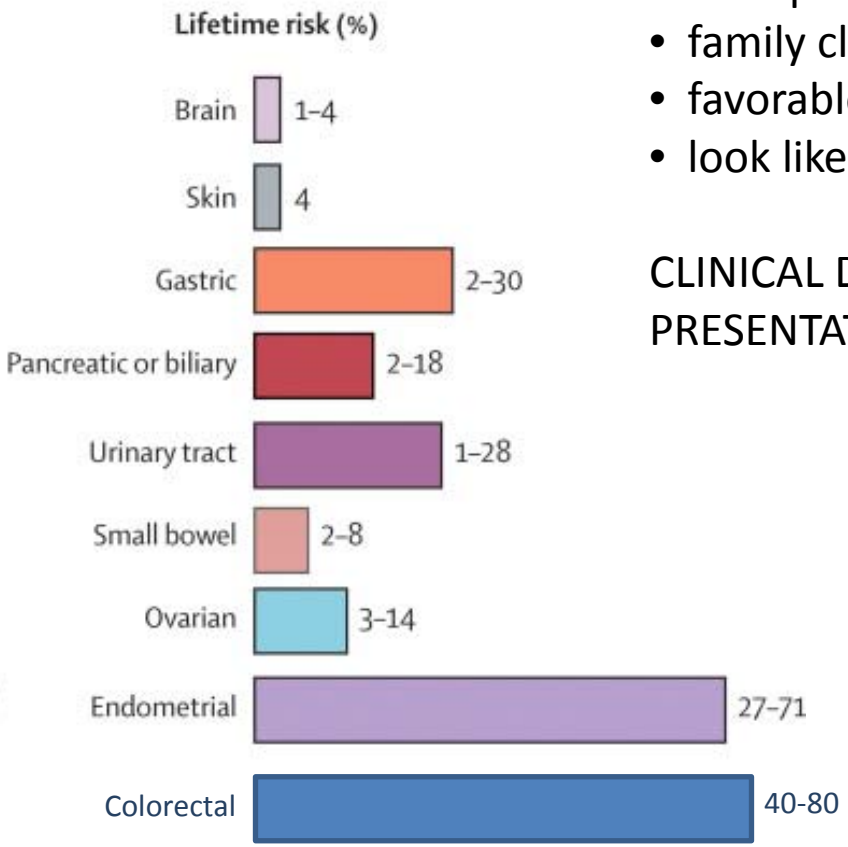
Lynch Syndrome





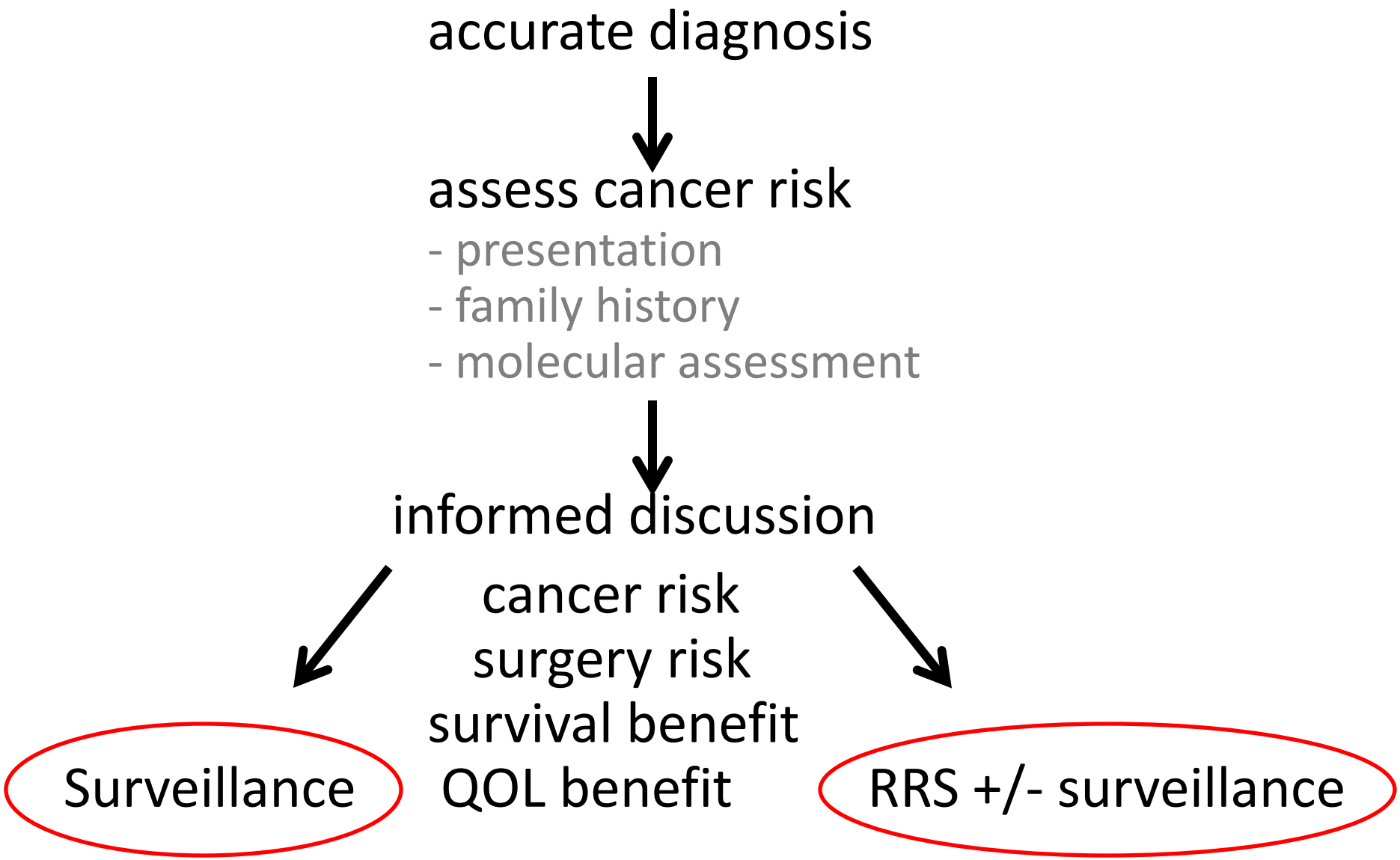
- early onset
- multiple tumors
- family clustering
- favorable prognosis
- look like sporadic cancers

CLINICAL DIAGNOSIS AT PRESENTATION IS DIFFICULT.

Lynch Syndrome Cancers

- early onset CRC
  - 40-80% penetrance
  - med age 45 years (20 – 80)
  - accelerated carcinogenesis
  - right sided CRC (70% proximal to SF)
  - ↑↑ synchronous / metachronous CRC
  - favorable prognosis
- early onset EC
  - 30-70% penetrance
  - median age 45-50 years
  - favorable prognosis
- other cancers
  - gastric (19%), urinary (18%), ovarian (9%)
  - skin, small bowel, biliary, brain (1-4%)

Principles of Risk-Reducing Surgery



Surgical Mgmt of CRC in LS

Presentations

- Newly diagnosed colon ca
- Newly diagnosed rectal ca
- History of segmental resection for colon ca
- Mutation carrier with adenoma
- Metastatic CRC

Treatment Issues

- Extent of colectomy
  - Segmental colectomy
  - Extended colectomy
- Prophylactic colectomy?
- Prophylactic TAH/BSO

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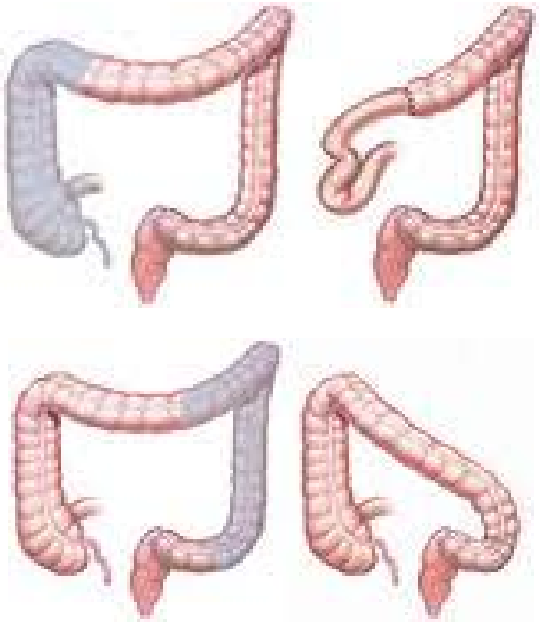
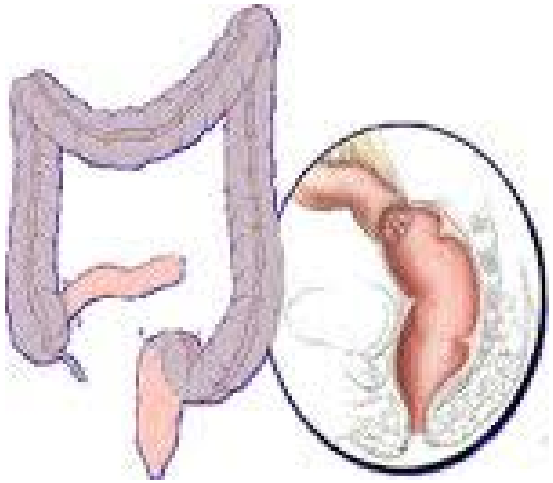
Surgical Options for LS patient with Colon Ca

Segmental Colectomy



Right colectomy
Transverse colectomy
Left Colectomy
Sigmoid colectomy

Extended Colectomy



Subtotal colectomy / ileosigmoid
Total colectomy / ileorectal

Segmental Colectomy for Colon Cancer

Risk of metachronous cancer following segmental colectomy
Dutch Lynch Syndrome Family Registry
114 families under surveillance
35 metachronous cancers detected with med fup 9 years

Segmental colectomy	15.7% (CI 4.1 – 27.3%)
Extended colectomy	3.4%

Dukes Stage of Met CRC	
Surveillance q 1-2 yrs	A 4 / B 11 / C 1
Surveillance > 2 years	A 3 / B 10 / C 6

De Vos et al. DCR 2002: 45:1588-1594.

Surgery for Colon Cancer in LS

	segmental colectomy	extended colectomy
Bowel function	√	
Quality of life	√	
Metachronous CRC		√
Endosc surveillance		√
Survival	?	

Decision Analysis: Segmental vs Ext Colectomy

Markov model based on data from Dutch LS Registry
assumes: 10 year risk met CRC (segm 16%, ext 4%)
stage CRC / survival I 98%, II 80%, III 60%

Life expectancey gains from Extended Colectomy:

colectomy at age 27	2.3 years
age 47	1.0 year
age 67	0.3 year

Concl: extended colect most likely to benefit younger patient with early stage index CRC.

De Vos tot Nederveen Cappel, Gut 2003; 52:1752-1755.

Extended Colectomy Reduces Metachronous CRC

International Colon Cancer Family Registry 1997 – 2007
382 mutation carriers (MLH1 172, MSH2 167, MSH6 23, PMS2 20)
median fup 9 years after colectomy (range 1 – 40)

	Segmental	Extended	
patients	N = 332	N = 50	
age	med 46y	med 45y	
MetachronCRC	**74 (22%)**	**0**	
Inc per 1000 person-yrs	23.6 CI 18.8-29.7	0 CI 0.0 – 7.2	P<0.001
Survival 5yr	98%	98%	
Survival 10yr	97%	98%	

Parry et al, Gut 2011; 60:950-957.

Extended Colectomy Reduces Metachronous CRC

Colon Cancer Family Registry 1997 – 2007

	Segmental	Extended	
patients	N = 332	N = 50	
Metachr CRC	74 (22%)	0	
CRC stage	I 54%		
	II 35%		
	III 18%		
Surveillance	1yr 57%	1yr 67%	P = 0.16
	2yr 20%	2yr 22%	
	3yr 1%	3yr 3%	
	none 20%	none 14%	
bowel resected (+/- sd)	26.1cm (14.6cm)	71.4cm (20.9cm)	

Parry et al, Gut 2011; 60:950-957.

Metachronous CRC after Segmental Colectomy Multivariate Correlates of Risk

	Multiv HR (CI)		P
MLH1 mut	1.00		
MSH2 mut	1.21	(.62 – 2.35)	0.58
MSH6 mut	0.84	(.22 – 3.24)	0.80
PMS2			
Australasia	1.00		
Canada	5.00	(2.04 – 12.29)	<0.001
USA	2.71	(1.21 – 6.06)	0.02
Length of bowel removed (per 10cm)	0.69	(.54 - .88)	0.002

Parry et al, Gut 2011; 60:950-957.

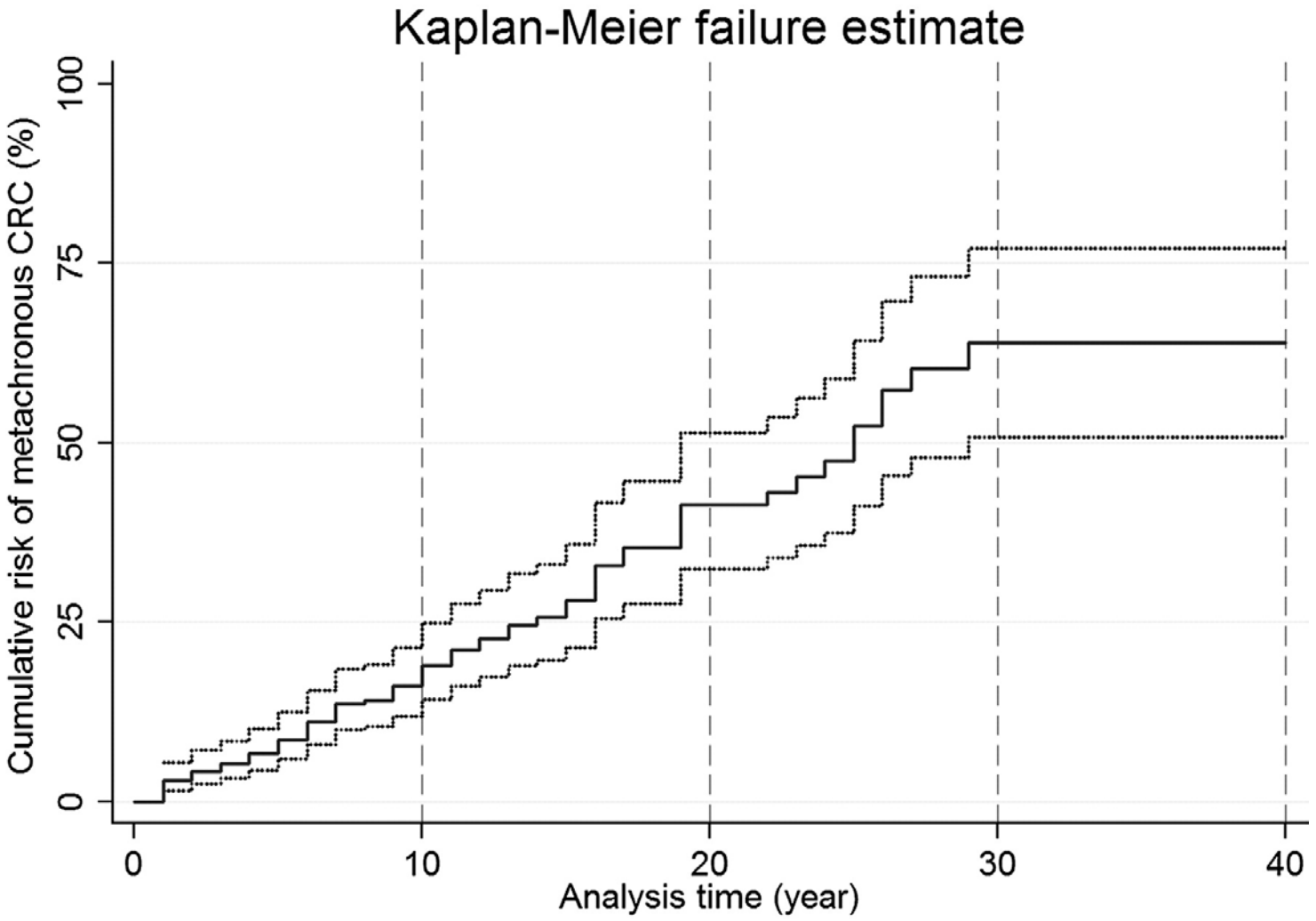
Extended Colectomy Reduces Metachronous CRC

Risk of metachronous CRC after segmental colectomy

10 yr	16%	10-25% (95% CI)
20 yr	41%	30-52%
30 yr	62%	50-77%

Parry et al, Gut 2011; 60:950-957.

Kaplan–Meier hazards estimation curve for the risk of metachronous colorectal cancer (CRC) following segmental colon resection for the first diagnosis of colon cancer.

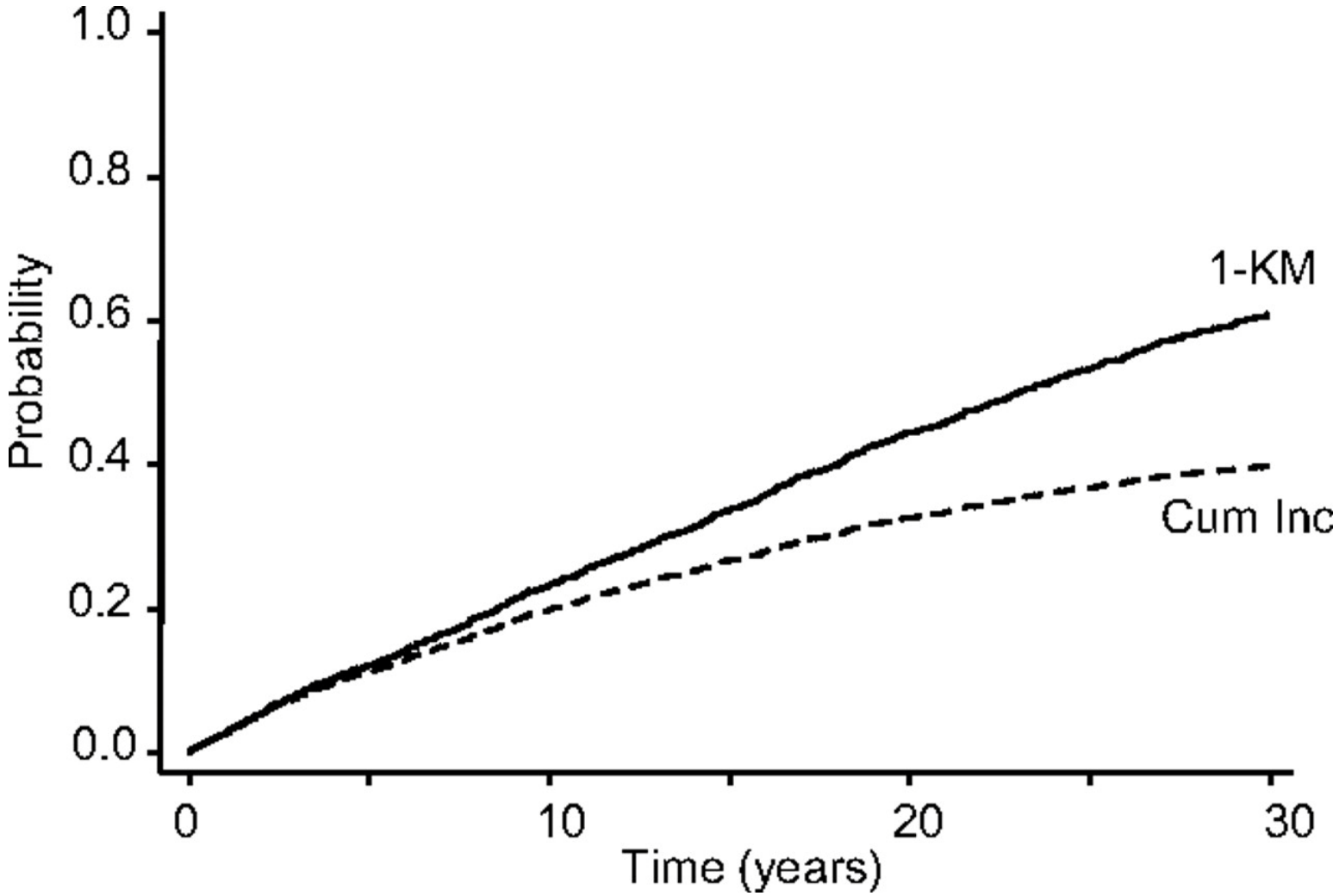


Parry S et al. Gut 2011;60:950-957

Limitations

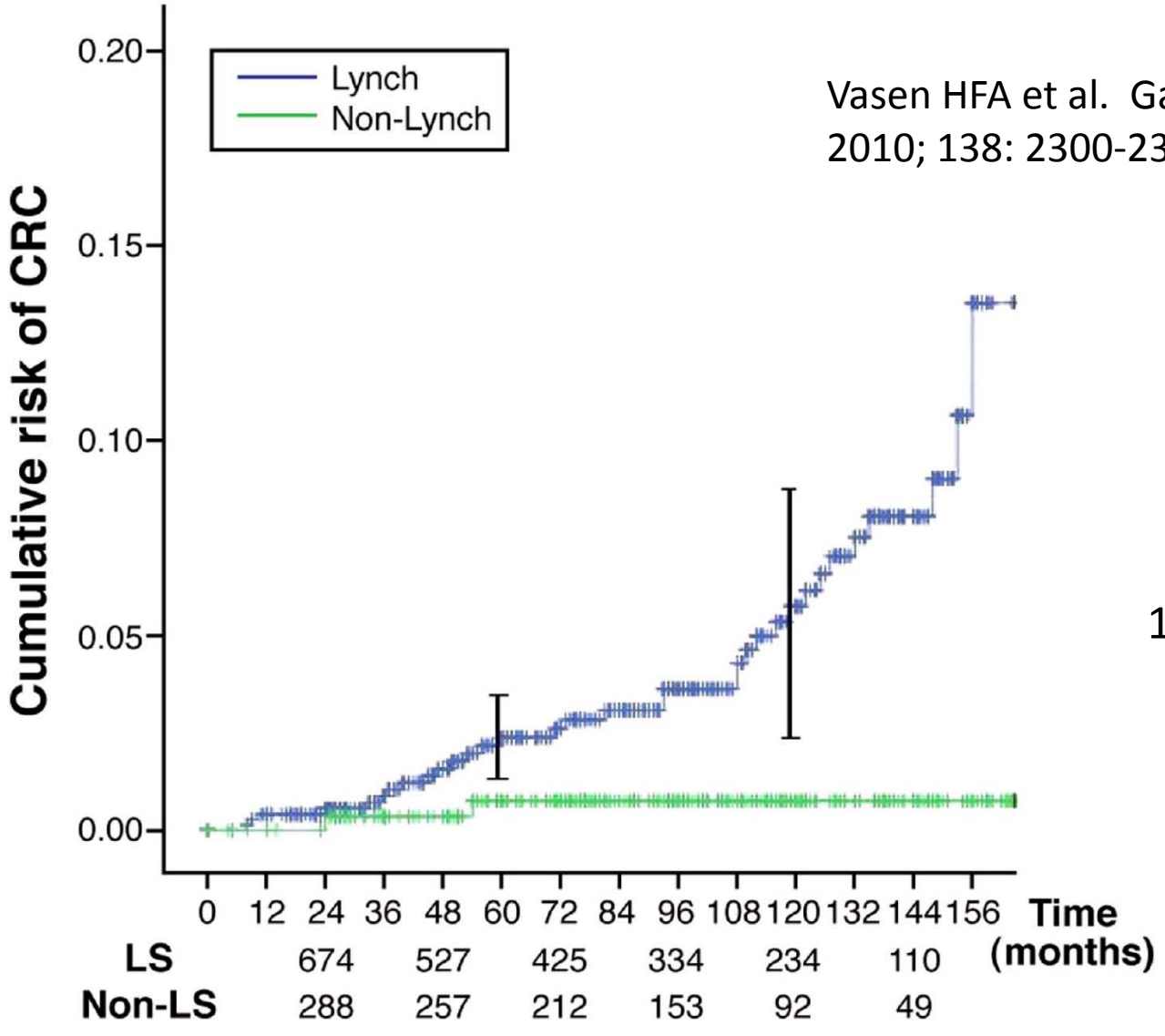
- Small number of ext colectomy cases
- Limited information on frequency and quality of endoscopic followup. Many cases from 1990s before value of frequent endoscopic followup fully appreciated.
- Possible selection bias in registry toward families / patients with high penetrance of CRC.

Simulated models for metachronous CRC illustrating differences between rates estimated using Kaplan–Meier (1-KM) versus cumulative incidence (Cum Inc) estimated using competing risk analyses.



Renehan A G Gut 2012;61:783-783

Benefit of Surveillance Colonoscopy
Results from Dutch LS Registry
Colonoscopy interval = 1-2 years



Vasen HFA et al. Gastroenterology 2010; 138: 2300-2306.

10 year risk = 6%

Risk of Interval CRC During Surveillance Results from Dutch LS Registry

Colonoscopy interval = 1-2 years

Conclusion

Surveillance intervals of 1-2 years in family members with Lynch syndrome lowers the risk of developing CRC compared to surveillance intervals of 2-3 years.

Vasen HFA et al. Gastroenterology 2010; 138: 2300-2306.

Quality of Life after Colectomy for LS?

study from Dutch Lynch Syndrome Registry

288 LS patients sent questionnaires

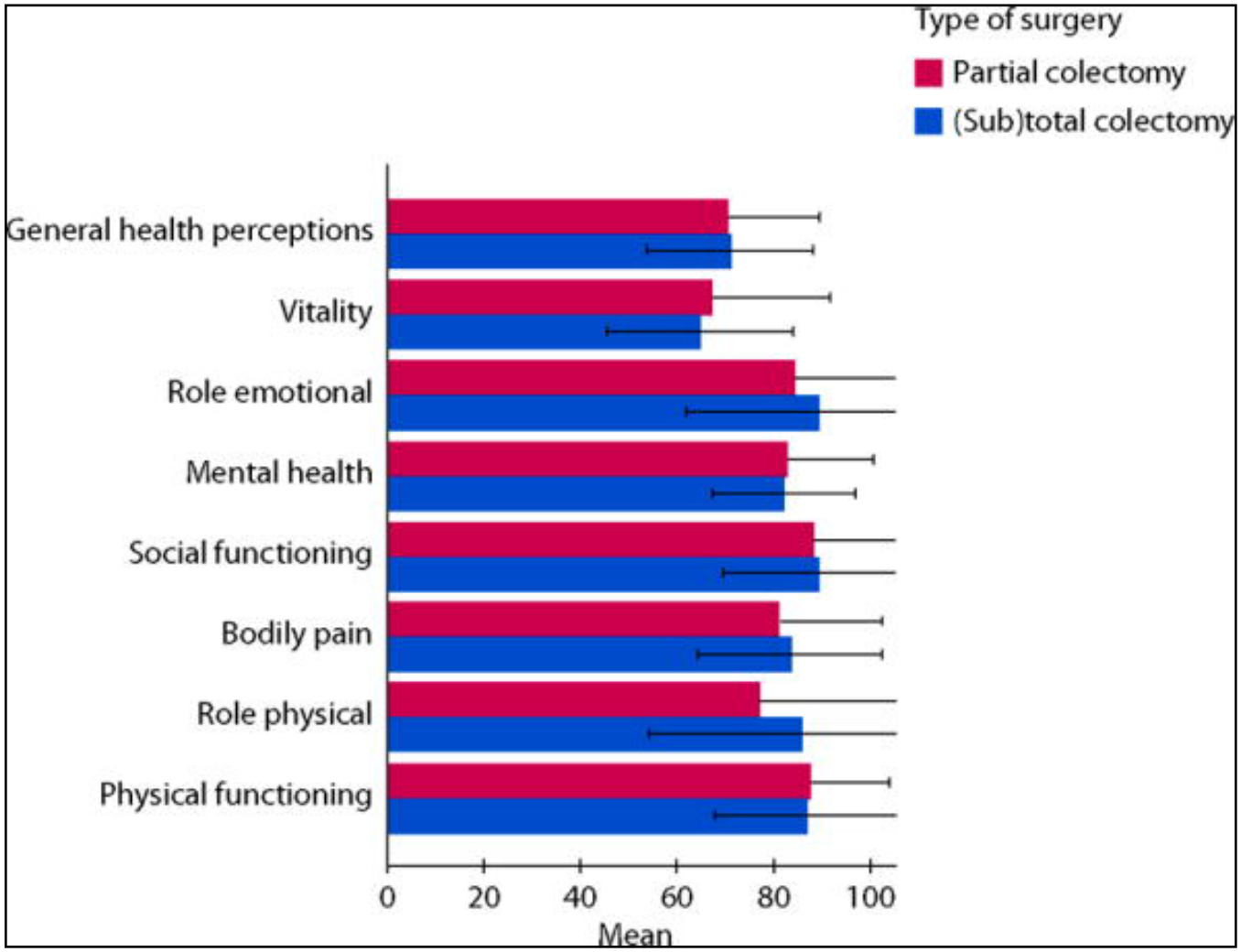
Evaluable pts:	partial colectomy	51	(fup 12.7yr)
	subtotal colectomy	53	(fup 9.2 yr)

Assessment:	SF36	general QOL
	EORTC CR38	QOL for CRC pts
	COREF	bowel function

Response: 71%

Haanstra et al, DCR 2012; 55(6): 653 -659.

SF 36 General QOL



Results SF-36. A higher score represents a higher level of functioning. Error bars, +/-1 SD. SF-36 = Short Form-36 health survey.

Haanstra et al, DCR 2012; 55(6): 653 -659.

EORTC QLQ CR-38: QOL for CRC Patients

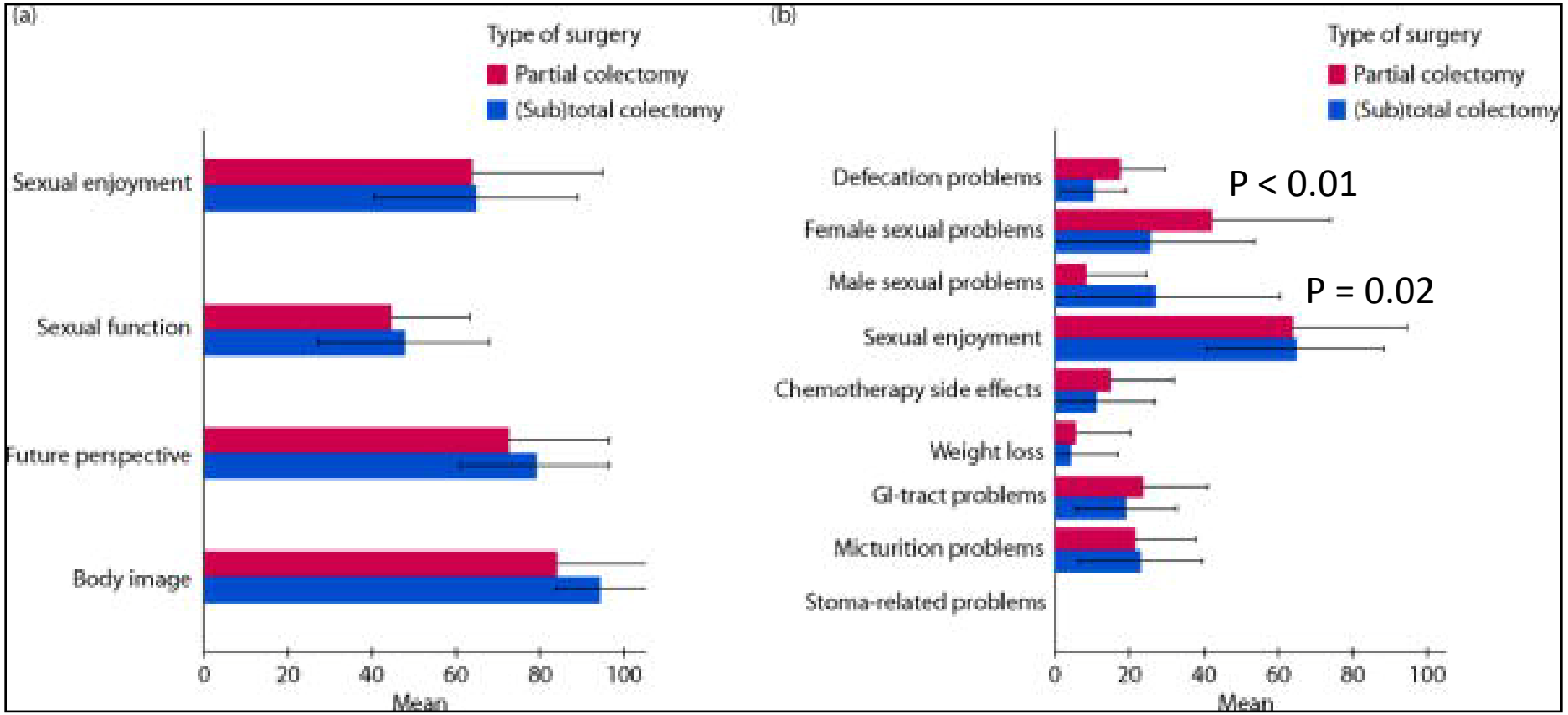


FIGURE 3 . Results EORTC QLQ CR-38. A, Functional scales and single items (sexual enjoyment and future perspective): A higher score indicates better functioning. Error bars, +/-1 SD. B, Symptom scales and the single item weight loss: A higher score indicates a higher level of symptomatology. Error bars, +/-1 SD. EORTC QLQ CR-38 = European Organization for Research and Treatment of Cancer Colorectal Cancer-specific Quality of Life Questionnaire Module.

Haanstra et al, DCR 2012; 55(6): 653 -659.[2]

COREFO: Bowel Function

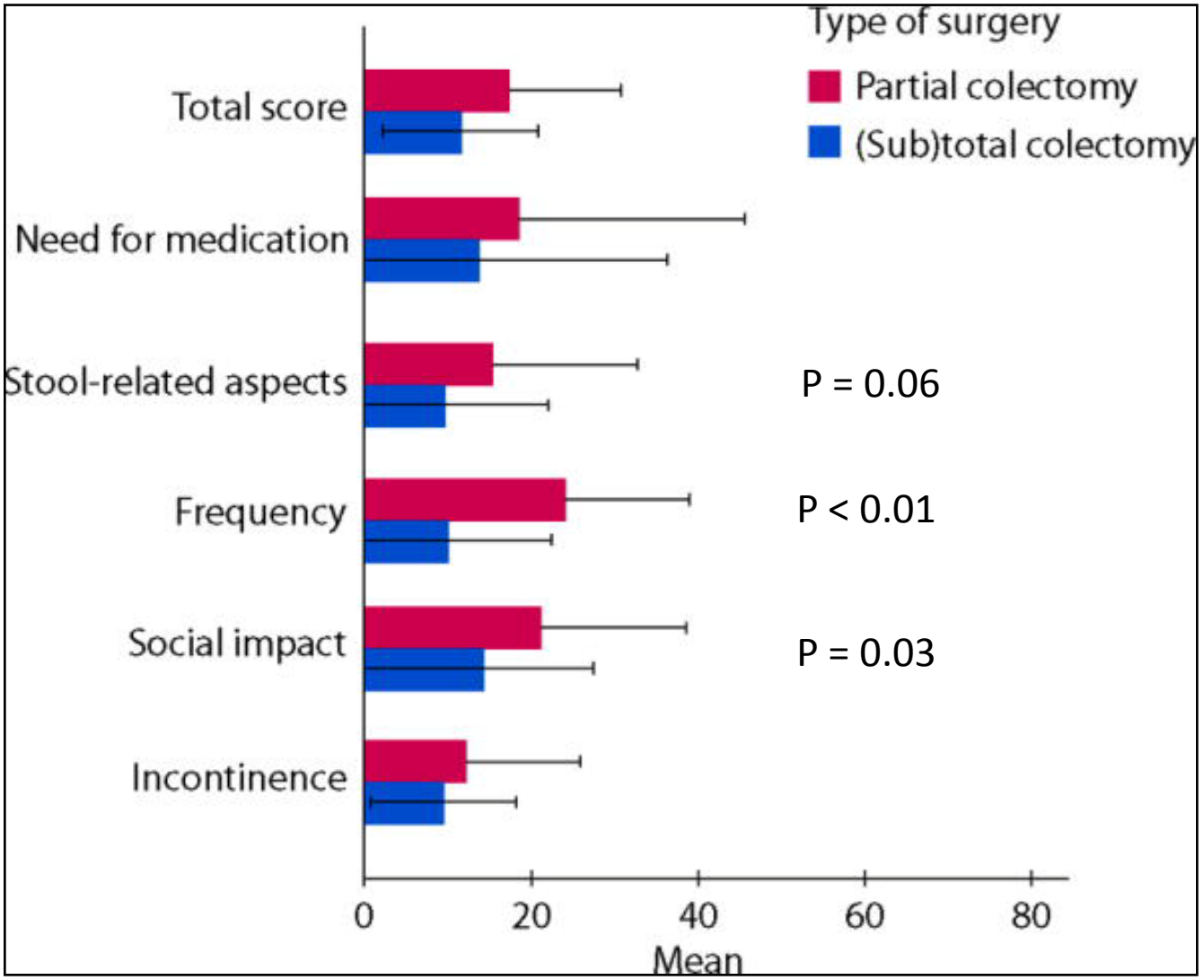


FIGURE 4 . Results COREFO. Higher scores represent a higher level of symptomatology. Error bars, +/-1 SD. COREFO = Colorectal Functional Outcome.

Haanstra et al, DCR 2012; 55(6): 653 -659.

QOL CONCLUSIONS
Segmental vs Extended Colectomy

- Functional outcome of extended colectomy is worse, due to increased stool frequency and problems with defecation.
- Overall quality of life does not differ.

Haanstra et al, DCR 2012; 55(6): 653 -659.

Extended vs. Segmental Colectomy Summary

- Extended colectomy for treatment of first CRC in LS patients significantly reduces risk of metachronous CRC.
- No survival benefit can be demonstrated from available published data.
- Extent of risk reduction appears to correlate with length of bowel resected.
- Quality of life is reduced by extended colectomy due to stool frequency and difficulties with defecation.
- Surgical treatment should be tailored to clinical presentation including age and stage of index cancer and to patient preference after informed discussion.

Prophylactic Colectomy for Mutation Carriers in LS

Rationale: remove at risk mucosa
eliminate risk of CRC
maintain bowel function and QOL

Problem: colonoscopic surveillance effective
(60% reduction cancer risk)
small mortality risk for colectomy
extended colectomy reduces QOL

Annals of Internal Medicine
Established in 1927 by the American College of Physicians

From: Benefits of Colonoscopic Surveillance and Prophylactic Colectomy in Patients with Hereditary Nonpolyposis Colorectal Cancer Mutations

Strategy	Life Expectancy	Life Expectancy Benefit Compared with No Surveillance	Life Expectancy Benefit Compared with Surveillance	Quality-Adjusted Life Expectancy	Quality-Adjusted Life Expectancy Benefit Compared with No Surveillance	Quality-Adjusted Life Expectancy Benefit Compared with Surveillance
	← y →			← QALY →		
Immediate prophylactic protocolectomy	52.2	15.6	2.1	46.4	10.9	−3.1
Immediate prophylactic subtotal colectomy	51.9	15.3	1.8	49.2	13.7	−0.3
Surveillance from 25 to 40 years of age, proctocolectomy at 40 years of age	50.8	14.2	0.7	46.6	11.1	−2.9
Surveillance from 25 to 40 years of age, subtotal colectomy at 40 years of age	50.7	14.1	0.6	48.6	13.1	−0.9
Surveillance from 25 to 50 years of age, proctocolectomy at 50 years of age	50.5	13.9	0.4	47.2	11.7	−2.3
Surveillance from 25 to 50 years of age, subtotal colectomy at 50 years of age	50.4	13.8	0.3	48.7	13.2	−0.8
Surveillance and proctocolectomy if adenoma is found	50.6	14.1	0.6	47.3	11.8	−2.2
Surveillance and subtotal colectomy if adenoma is found	50.5	13.9	0.5	48.8	13.3	−0.7
Surveillance and proctocolectomy if cancer is found	50.1	13.5	0.0	48.9	13.4	−0.6
Surveillance and subtotal colectomy if cancer is found	50.1	13.5	0.0	49.2	13.7	−0.3
Surveillance and segmental resection if cancer is found	50.1	13.5	–	49.5	14.0	–
No surveillance and segmental resection if cancer is found	36.6	–	–	35.5	–	–

* QALY = quality-adjusted life-year.

Syngal Ann Int Med, 1999.

Prophylactic Gynecologic Surgery in LS

	Lifetime Risk US population	Lifetime Risk Lynch Syndrome
Endometrial Ca	1%	40 - 60%
Ovarian Cancer	1.5%	10 – 12%
Surveillance	endometrial bx tranvaginal US CA125	avoid surgery preserve hormone fx
Prophylactic Surgery	laparoscopic TAH/BSO	↓↓ cancer risk

Efficacy of Prophylactic GYN Surgery in LS

Retrospective case control study

314 women with LS (MLH1 137; MLH2 174; MSH6 3)

	Endometrial Cancer		Ovarian Cancer	
	TAH	no surgery	BSO	no surgery
N	61	210	47	223
age	41y		41y	
fup	13.3y	7.4y	11.2y	10.6y
cancers	0	69 (33%)	0	12 (5%)
age		46y		42y
risk/yr		4.5%/yr		0.5%/yr

Schmeler et al, NEJM 2006; 354:261-269.

Surgical Treatment of CRC in LS

- Extended colectomy for treatment of first CRC in LS patients significantly reduces risk of metachronous CRC. No survival benefit.
- Quality of life is reduced by extended colectomy due to stool frequency and difficulties with defecation.
- Prophylactic TAH/BSO is highly effective in preventing cancer. Woman requiring colon resection should be referred to Gynecology specialist for consideration of prophylactic surgery at time of colectomy.
- Surgical treatment should be tailored to patient presentation and preference after informed discussion.