



Risico op peritoneale metastasen bij T4 coloncarcinoom

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Gepubliceerde incidentie metachrone PM pT4 coloncarcinoom

- Willett, 1984: 32/395 8%
- Shepherd, 1997: 45/242 19%
- Jayne, 2002: 25/193 13%
- Luna-Pérez, 2002: 8/28 pT4b 29%
- Fujii, 2009: 1/6 17%
- Hompes, 2012: 7/14 pT4a 50%
- Hompes, 2012: 1/5 pT4b 20%
- Segelman BJS 2012: 17%
- Van Santvoort, 2014: 33/154 21%
- no difference between pT4a / pT4b
- Klaver, 2017: 25/89 28%



Incidentie peritoneale metastasen coloncarcinoom

- Exacte incidentie onbekend
- (vroeg) detectie moeilijk



Interpretatie van de literatuur

- Incidentie metachrone peritoneaal metastasen:
 - routine follow-up (CT / echo abdomen / CEA)
 - Abdominale exploratie voor benigne indicaties (bijv. littekenbreuk) of ander recidief (lever metastase)
 - Obductie

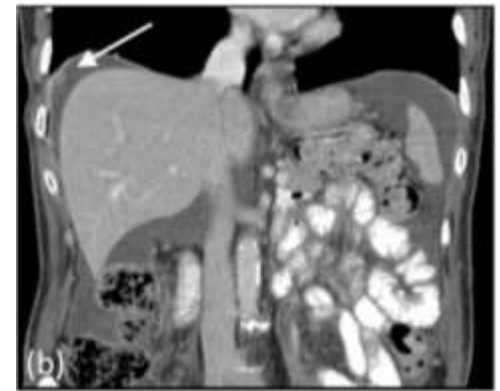


TABLE 2. Incidence of Local Recurrence or Peritoneal Carcinomatosis After Resection of Colorectal Cancer

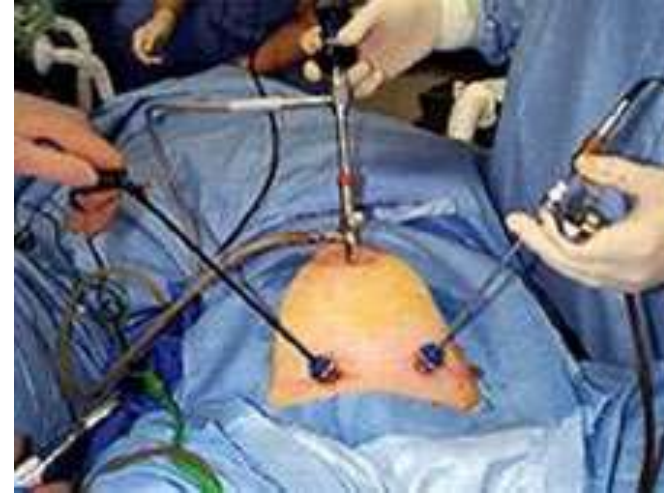
Reference	No. of Patients	No.		% LR		% PC		
		Colon Cancer	Rectal Cancer	Total	Colon Cancer	Total	Colon Cancer	Rectal Cancer
Clinical series								
Malcolm et al ²⁴	285	217	68	3.9%	5%	13%	12%	19%
Cass et al ²¹	280	129	151	23%	18%	28%	8%	2%
Russell et al ²⁸	94	94	0	7%	7%	12%	12%	NA
Mendenhall et al ²⁵	140	0	140	29%	NA	3%	NA	3%
Olson et al ²⁷	281	214	67	9%	7%	—	—	—
Minsky et al ²⁶	294	294	0	9%	9%	4%	4%	NA
Gilbert et al ²³	31	25	6	36%	—	3%	—	—
Jayne et al ³³	2756	1289	1467	—	—	4.9%	4.8%	5.0%
Reoperation series								
Gunderson et al ²⁹	91	91	0	48%	48%	21%	21%	NA
Tong et al ³⁰	64	64	0	48%	48%	44%	44%	—
Autopsy series								
Russell et al ³¹	53	53	0	38%	38%	36%	36%	NA
Gilbert et al ²³	45	25	20	67%	—	40%	—	—

LR indicates local recurrence; PC, peritoneal carcinomatosis; NA, not applicable.

Koppe, Ann Surg 2006



Geen 'gouden standaard'



Abdominale exploratie op verschillende tijdsintervallen tijdens follow-up



Pathologisch vaststellen T4 stadium

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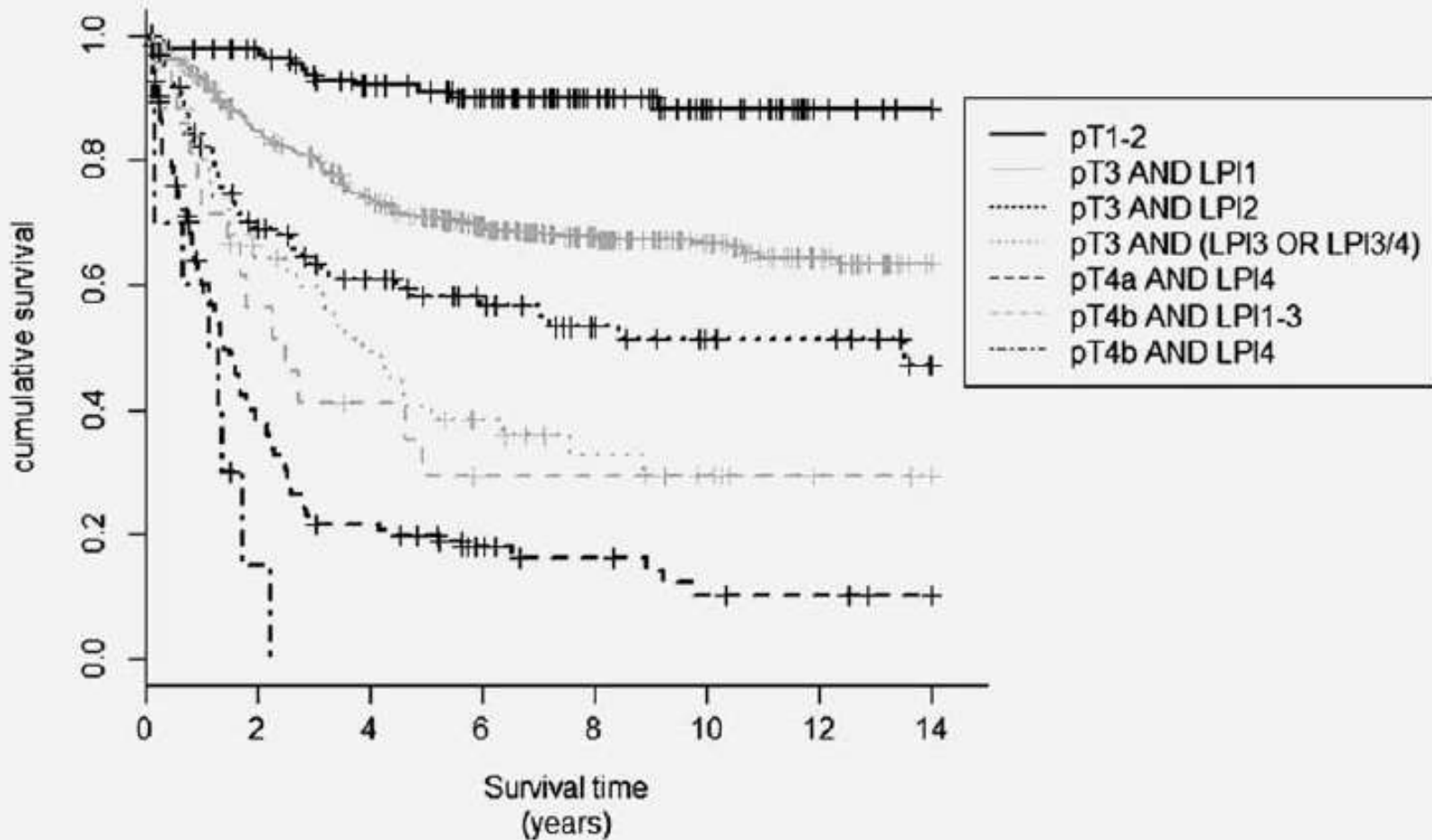


Shepherd classification

Category	Definition
1	Tumour well clear of closest peritoneal surface
2	Mesothelial inflammatory and/or hyperplastic reaction with tumour close, but not at, the peritoneal surface
3	Tumour present at peritoneal surface with inflammatory reaction, mesothelial hyperplasia, and/or ulceration
4	Tumour cells shown free in peritoneum and evidence of adjacent ulceration



Cancer-specific survival as a function of pT and LPI



Snaebjornsson Int J Cancer 2014

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Interobserver variabiliteit bij T4 diagnose onder pathologen

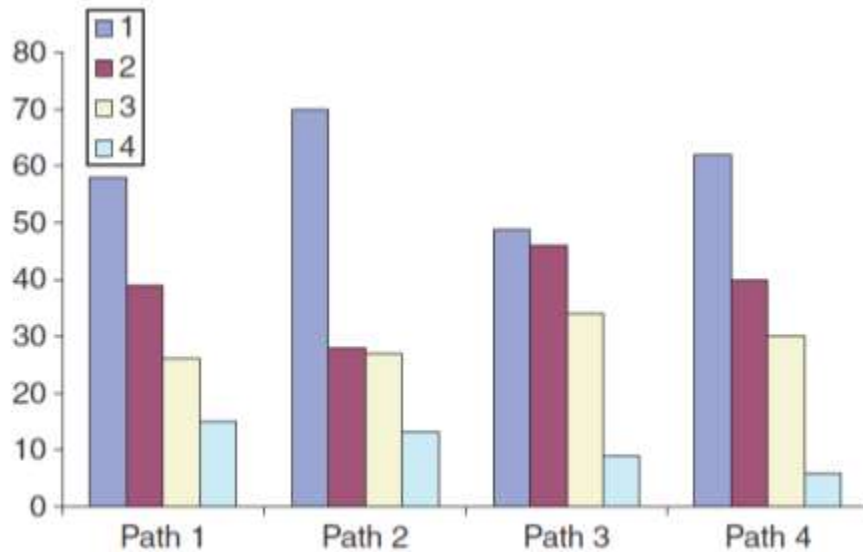
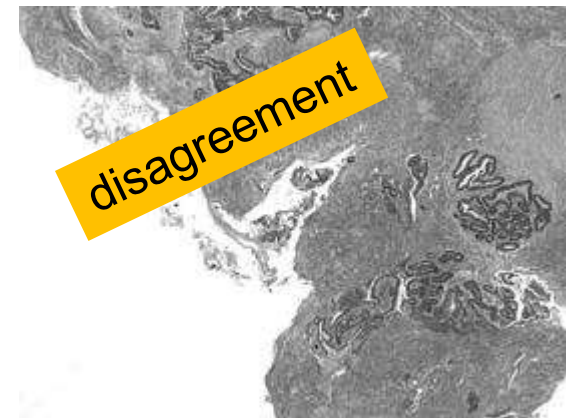


Figure 1. Frequencies of reporting LPI categories 1-4.

LPI=local peritoneal involvement

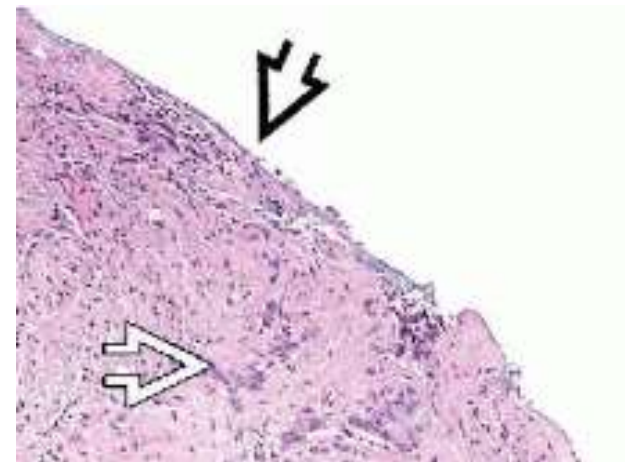


Littleford , Histopathology 2009



Peritoneale reactie versus penetratie associatie met peritoneale metastasen

- Cohort coloncarcinoom UZ Leuven Jan 2010-Juli 2013
- Systematische bepaling van:
 - Peritoneale reactie met tumor cellen tot 1 mm afstand van het peritoneale oppervlakte
 - Peritoneale penetratie door tumorcellen (T4a)



Klaver Ann Surg Oncol 2017

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Risico op peritoneale metastasen

	Metachrone PM
Peritoneale reactie	5 (13%)
Peritoneale penetratie	25 (28%)

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Risico op peritoneale metastasen

Multivariabele analyse

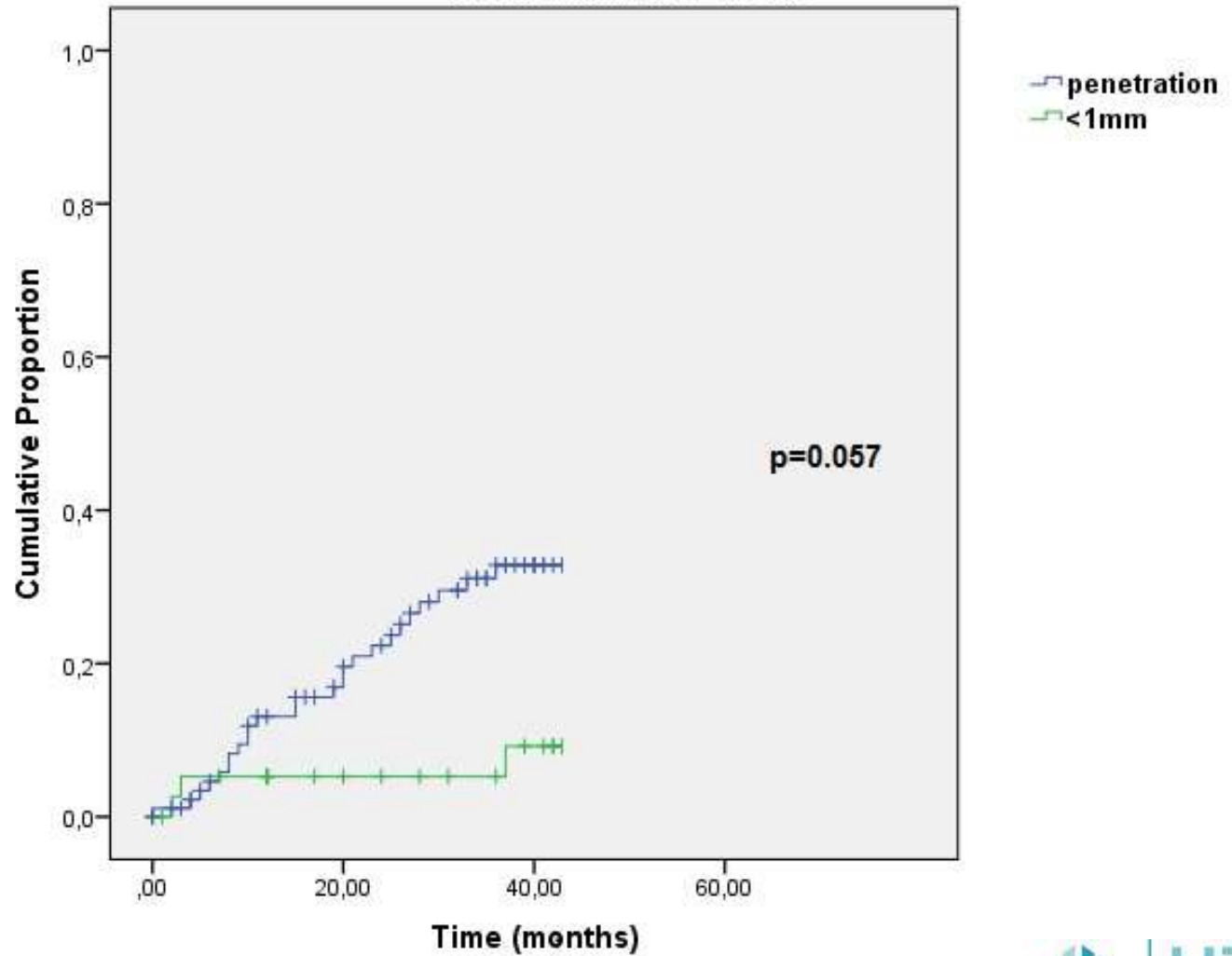
- Peritoneale penetratie:
 - OR 2.518 (1.038-6.111)
- N-status:
 - N1: OR 1.572 (0.651-3.797)
 - N2: OR 4.046 (1.549-10.569)

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Metachronous PMCRC

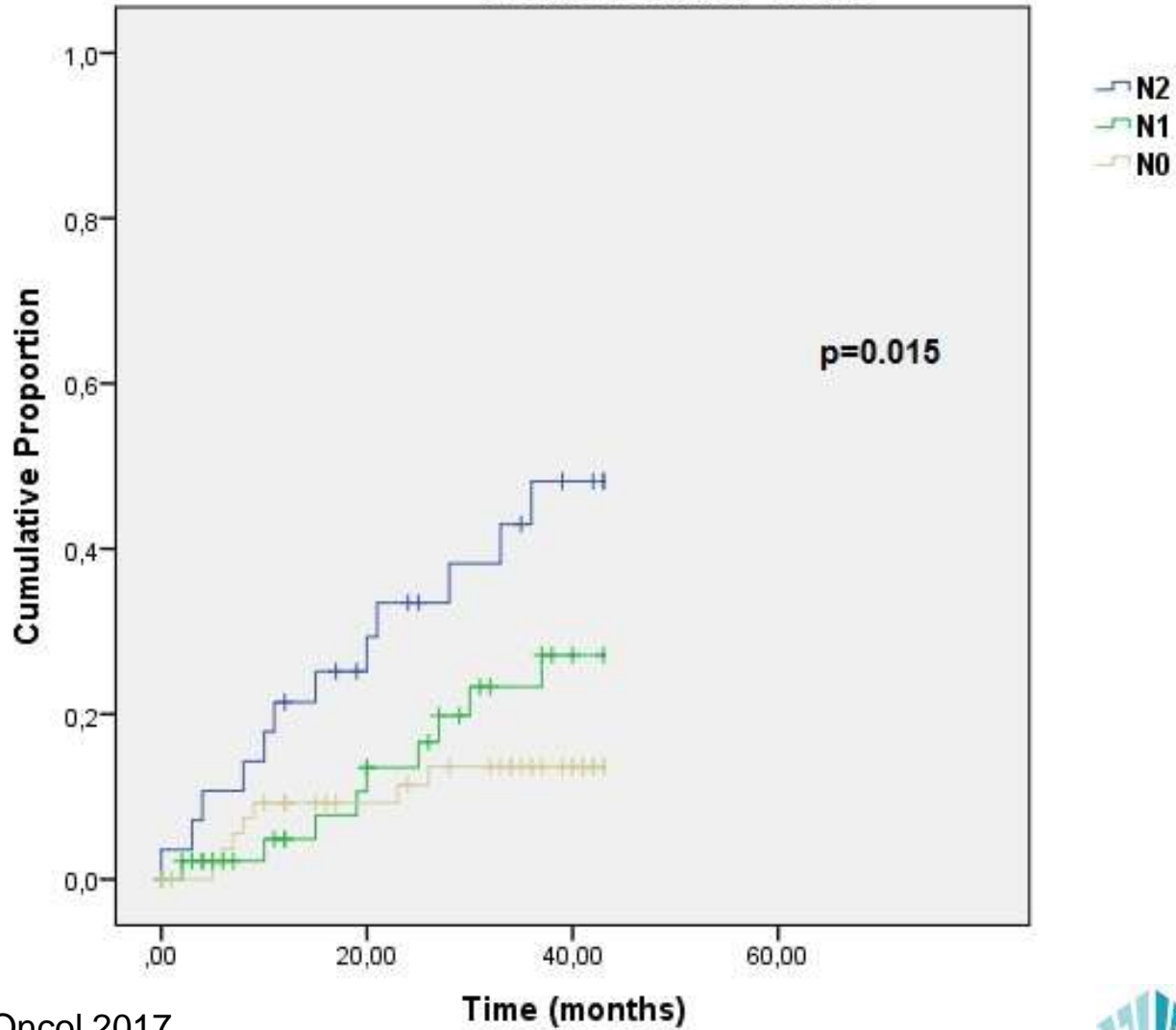


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Metachronous PMCR



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Waarom is N-status voorspellend?

Hypothese

1. 'Agressief' biologisch gedrag (parallele metastaserings routes)
2. Tumorcellen die 'in transit' zijn; lekkage van tumorcellen tijdens mesenteriale transectie



Clinicopathologische predictiemodellen

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Incidence, prevalence and risk factors for peritoneal carcinomatosis from colorectal cancer

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Incidence metachronous PM: 4.2% (447 / 10,646 stage I-III CRC patients)

Segelman BJS 2012



	Incidence PM	HR multivariable
Age > 70	4.0%	HR 0.69
Right colon	6.3%	HR 1.77
T3	4.9%	HR 3.82
T4	16.8%	HR 9.98
N1 (≥ 12)	5.1%	HR 2.15
N1 (<12)	7.7%	HR 3.76
N2 (≥ 12)	11.8%	HR 4.66
N2 (<12)	12.7%	HR 7.41
Emergency	11.5%	HR 2.11
R1	13.8%	HR 1.96
R2	14.3%	HR 2.75
Adjuvant chemotherapy	10.1%	HR 0.73

Segelman BJS 2012



Individualized prediction of risk of metachronous peritoneal carcinomatosis from colorectal cancer

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N=8044 stage I-III CRC

Segelman Col Dis 2014



Characteristic	Score points for colon cancer	Score points for rectal cancer
Age	-0.01*	-0.03*
Primary site		
Left colon	-	-
Right colon	0.21	-
Transverse colon	-0.08	-
pT stage		
T0-T2	-	-
T3	1.88	1.32
T4	2.97	1.86
pN stage		
N0	-	-
N1	0.76	0.88
N2	1.51	1.46
Number of examined lymph nodes		
≥ 12	-	-
0-11	0.50	0.61
Radicality		
R0	-	-
R1	0.40	1.35
R2	0.84	1.42
Type of surgery		
Elective surgery	-	-
mergency surgery	0.74	-
Preoperative radiotherapy		
No	-	-
Yes	-	-1.03
Adjuvant chemotherapy†		
No	-	-
Yes	-0.33	-0.19

	Probability of metachronous peritoneal carcinomatosis (%)		
	1 year	2 years	3 years
Colon cancer total score			
0	0.4	0.8	1.1
0.5	0.7	1.3	1.8
1.0	1.1	2.1	2.9
1.5	1.8	3.5	4.8
2.0	2.7	5.5	7.5
2.5	4.5	9	12.2
3.0	7.3	14.3	19.1
3.5	11.9	22.6	29.7
4.0	17.9	32.9	42.2
4.5	28.6	49.4	60.7
Rectal cancer total score			
0	1.6	3.3	4.3
0.5	2.6	4.8	6.8
1.0	4.3	7.9	11.1
1.5	7.0	12.7	17.6
2.0	11.1	19.9	27.1
2.5	17.5	30.4	40.3
3.0	25.4	42.4	54.4
5.0	43.7	68.5	79.4



External validation of models predicting the individual risk of metachronous peritoneal carcinomatosis from colon and rectal cancer

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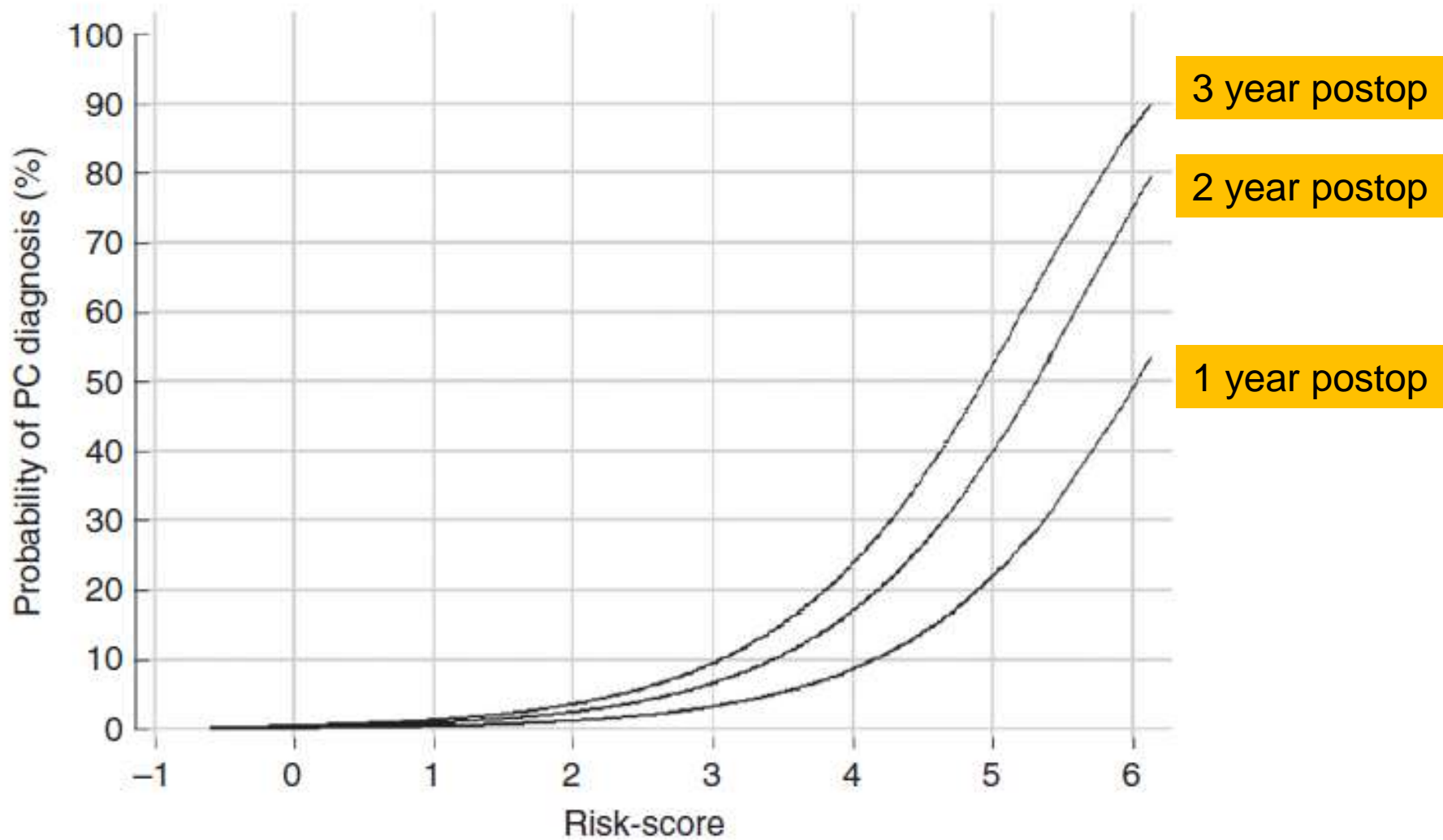
Segelman Col Dis 2016



	Score point	HR multivariable
Age > 70	-0.01	HR 0.99
Right colon	0.22	HR 1.25
T3c/d	1.73	HR 5.62
T4a (peritoneal penetration)	2.83	HR 10.76
T4b (invasion adjacent organ)	1.45	HR 4.26
N1	0.86	HR 2.37
N2	1.72	HR 5.61
mucinous	0.69	HR 1.99
Emergency	0.80	HR 2.22
R1	0.36	HR 1.43
R2	1.19	HR 3.27
Adjuvant chemotherapy	-0.59	HR 0.55

Segelman Col Dis 2016





Clinical implications?

Adjuvante intraperitoneale behandeling

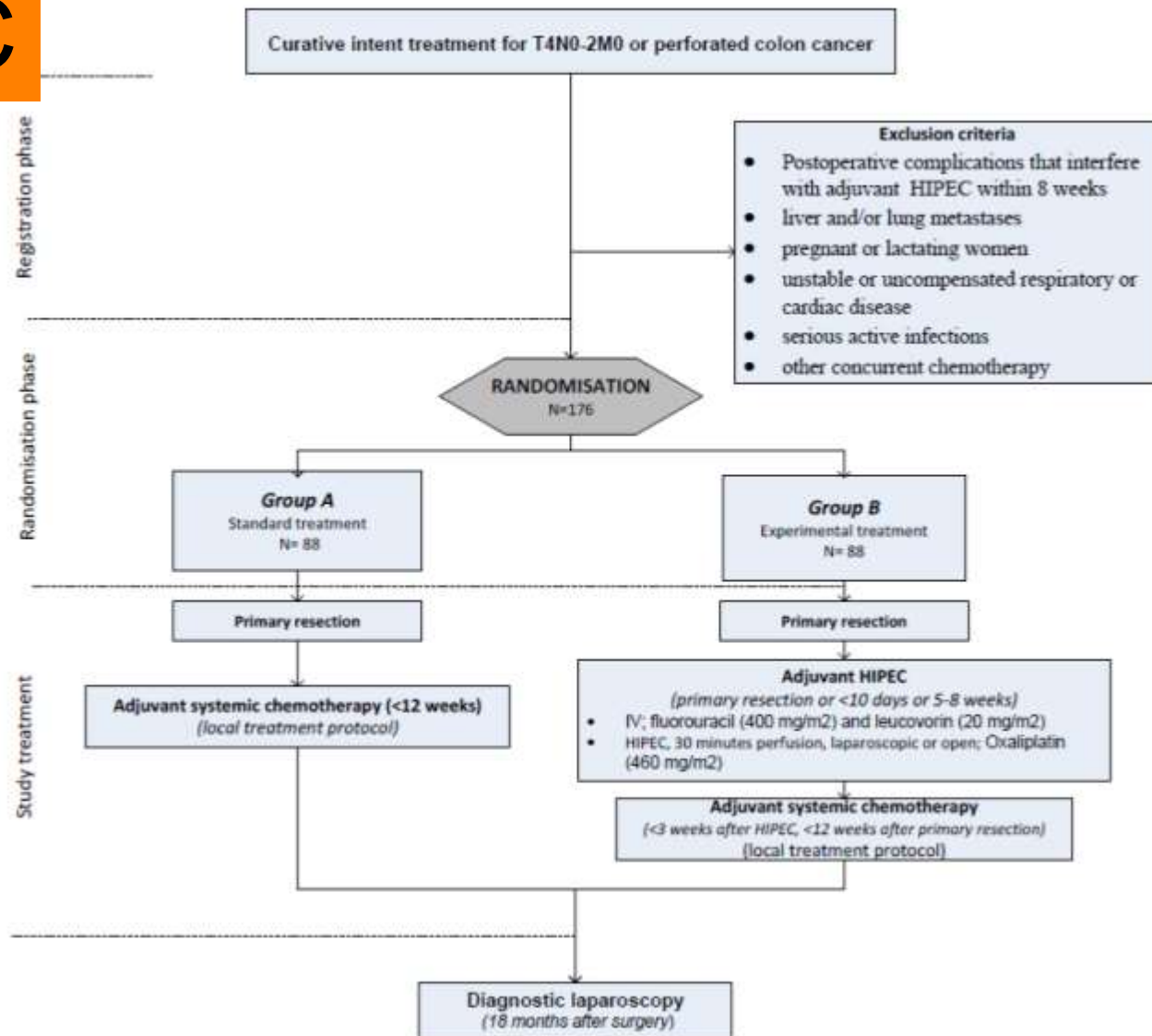
- Adjuvante HIPEC

Vroege detectie bij hoog risico groepen

- ‘second look’ laparoscopie / laparotomie



COLOPEC

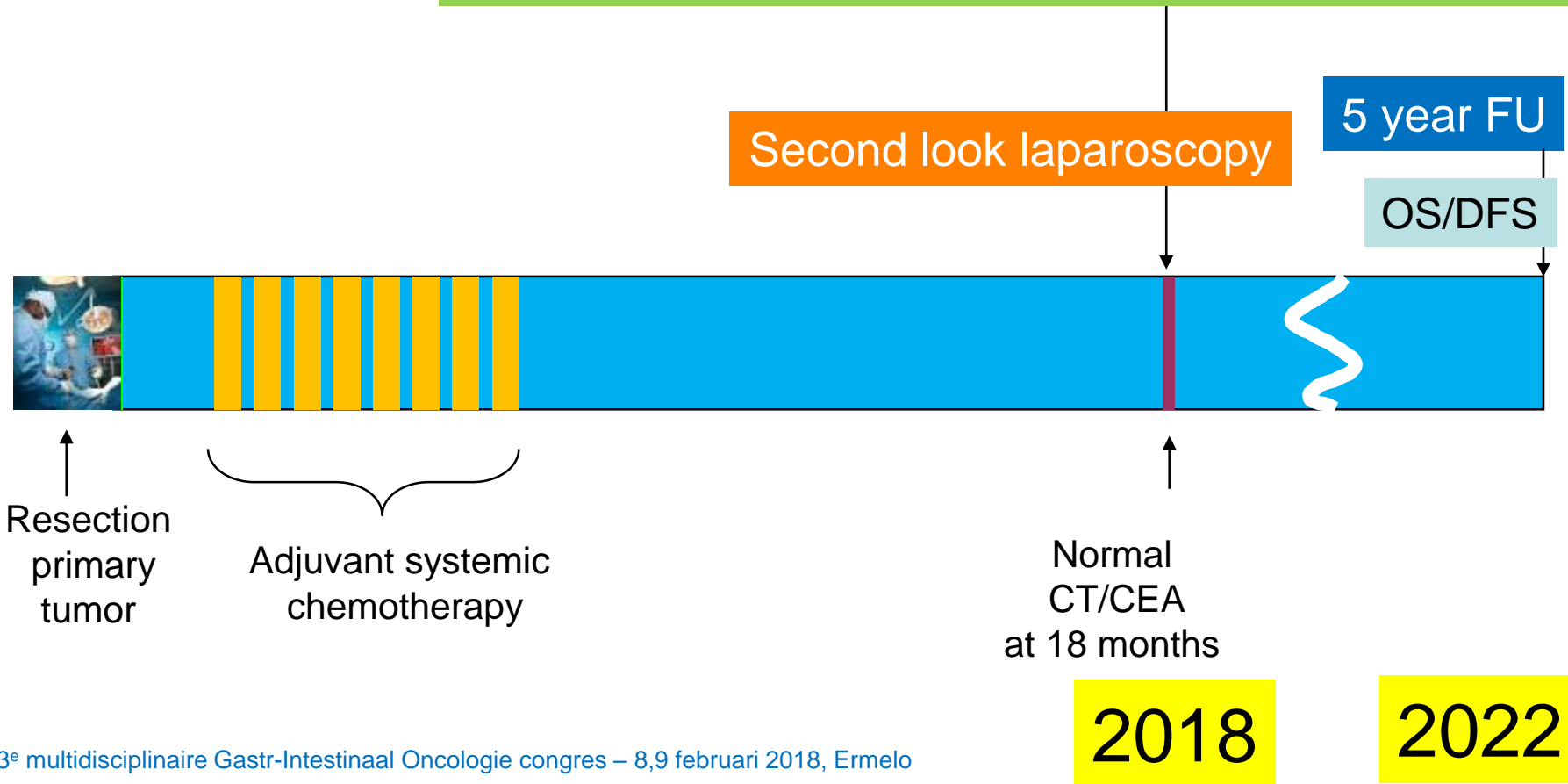


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COLOPEC

Peritoneal recurrence at 18 months



Andere relevante trials

- (French ProphyloCHIP trial (NCT01226394))
- **PROMENADE trial (NCT02974556), start 1-1-2018, cT3cd/T4 colon cancer (by CT imaging)**
 - experimental arm: simultaneous adjuvant HIPEC (oxaliplatin) and target organ resection (omentectomy, bilateral adnexectomy in post-menopausal patients, appendectomy and hepatic round ligament resection) + adjuvant systemic chemotherapy if indicated based on definitive pathology
 - control group with only adjuvant systemic chemotherapy.
- **Spanish multicentre study (NCT02614534), accrual started 2015, cT4a/b (by CT imaging)**
 - experimental arm: simultaneous adjuvant HIPEC (MMC) and target organ resection + adjuvant systemic chemotherapy
 - control group with target organ resection + adjuvant systemic chemotherapy



Vroege detectie bij hoog risico groepen

– ‘second look’ laparoscopie / laparotomie

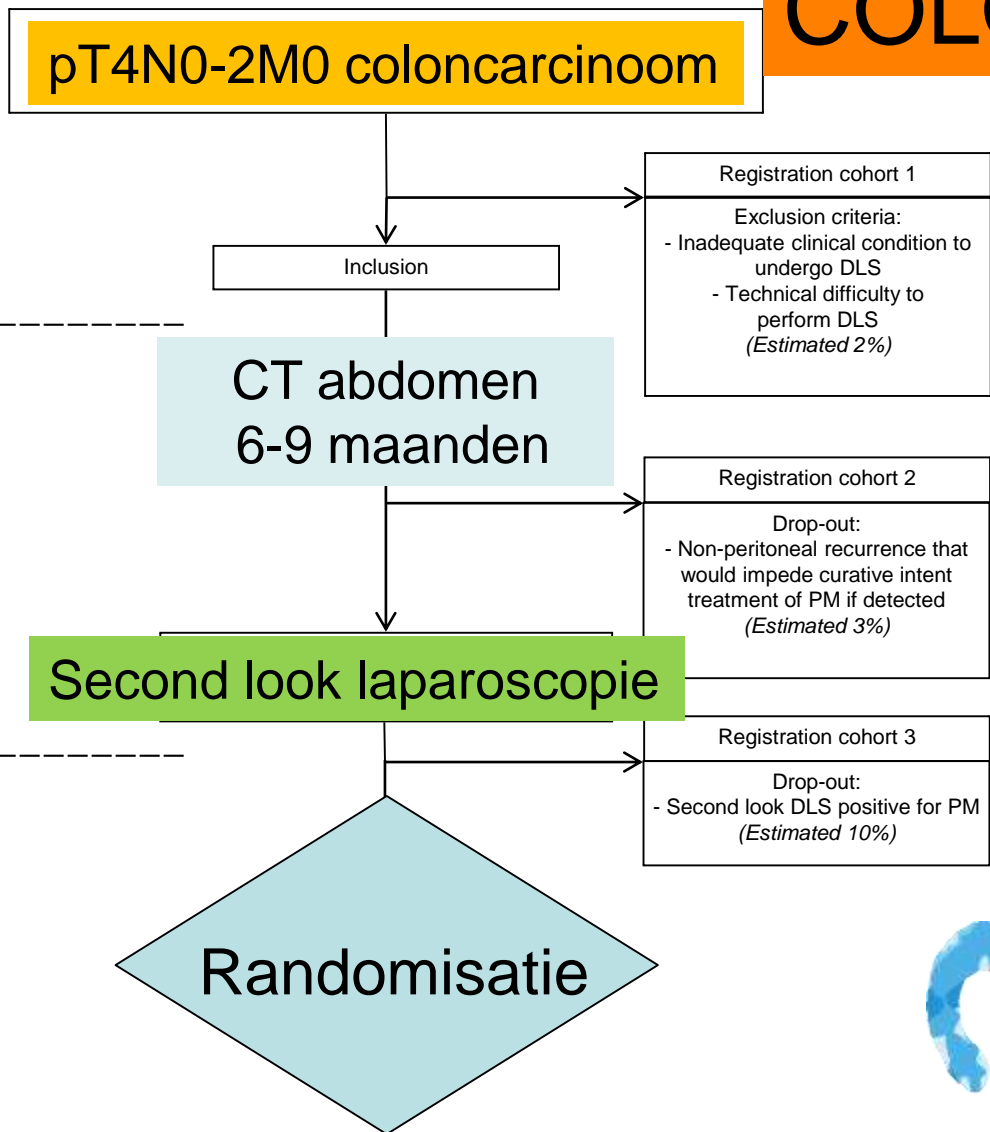
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COLOPEC 2

Registration phase

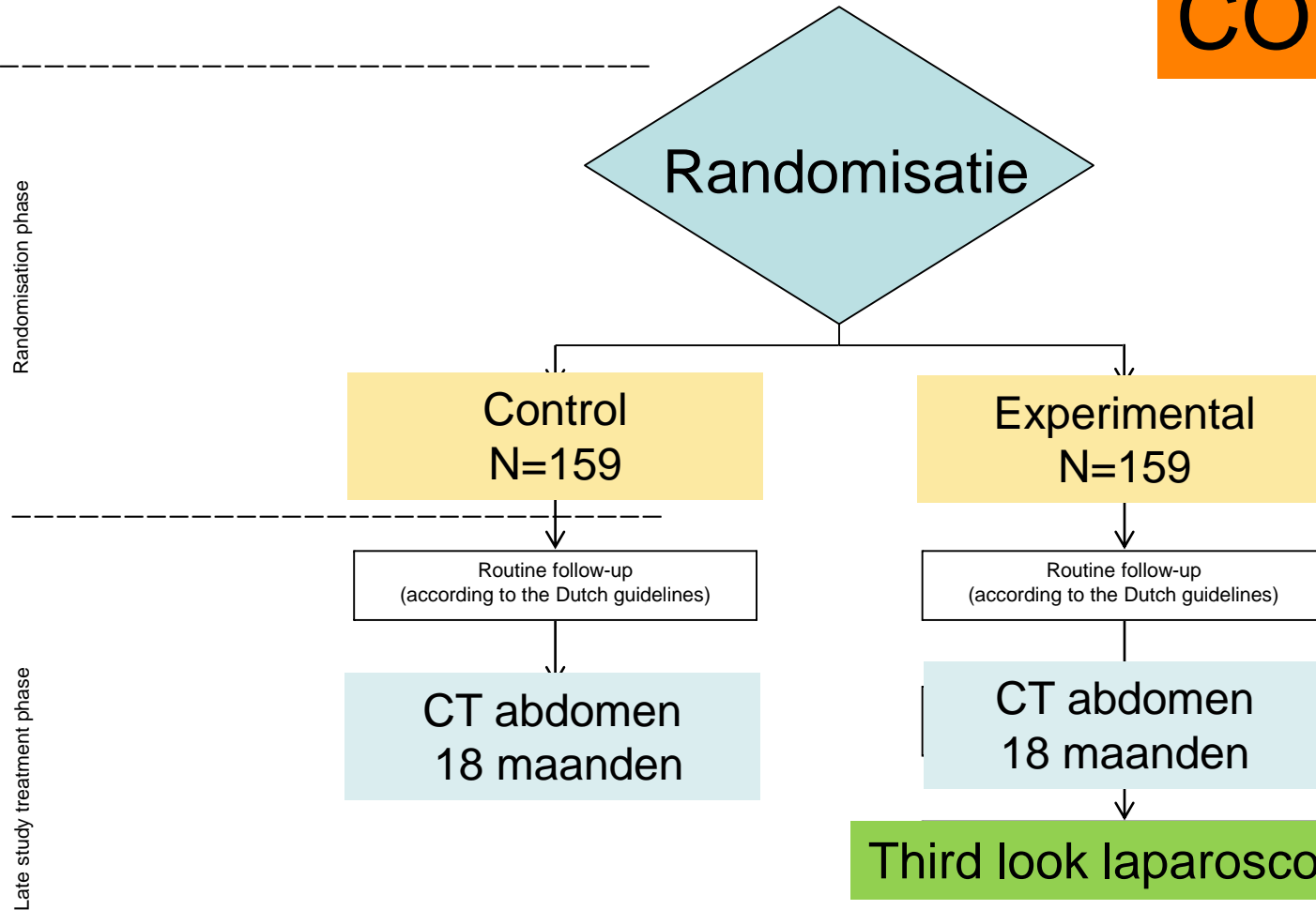
Early study treatment phase



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COLOPEC 2



Side studies: ctDNA at 6 and 18 months, intraoperative tumour specific fluorescence



Andere trials

Italian study, currently recruiting:

- randomized trial investigating the role of second look surgery six months postoperatively in mucinous CRC (NCT01628211)



Samenvatting

- T status en N status zijn de belangrijkste risicofactoren voor peritoneaal recidief na curatieve resectie van coloncarcinoom
- Ware incidentie van metachrone peritoneale metastasen onbekend
- Belang van prospectieve studies naar vroege detectie van metachrone peritoneale metastasen: laparoscopie (+NIR imaging?), ctDNA
- Lopende trials naar preventieve / adjuvante HIPEC

