Leids Universitair
Medisch Centrum

Ovariumcarcinoom: van proeflaparotomie via stadiering naar debulking en HIPEC…

Cor de Kroon
Gynaecoloog oncoloog
LUMC

Agenda…

Anatomie

Epidemiologie

Erfelijkheid

Diagnostiek ovariumcyste

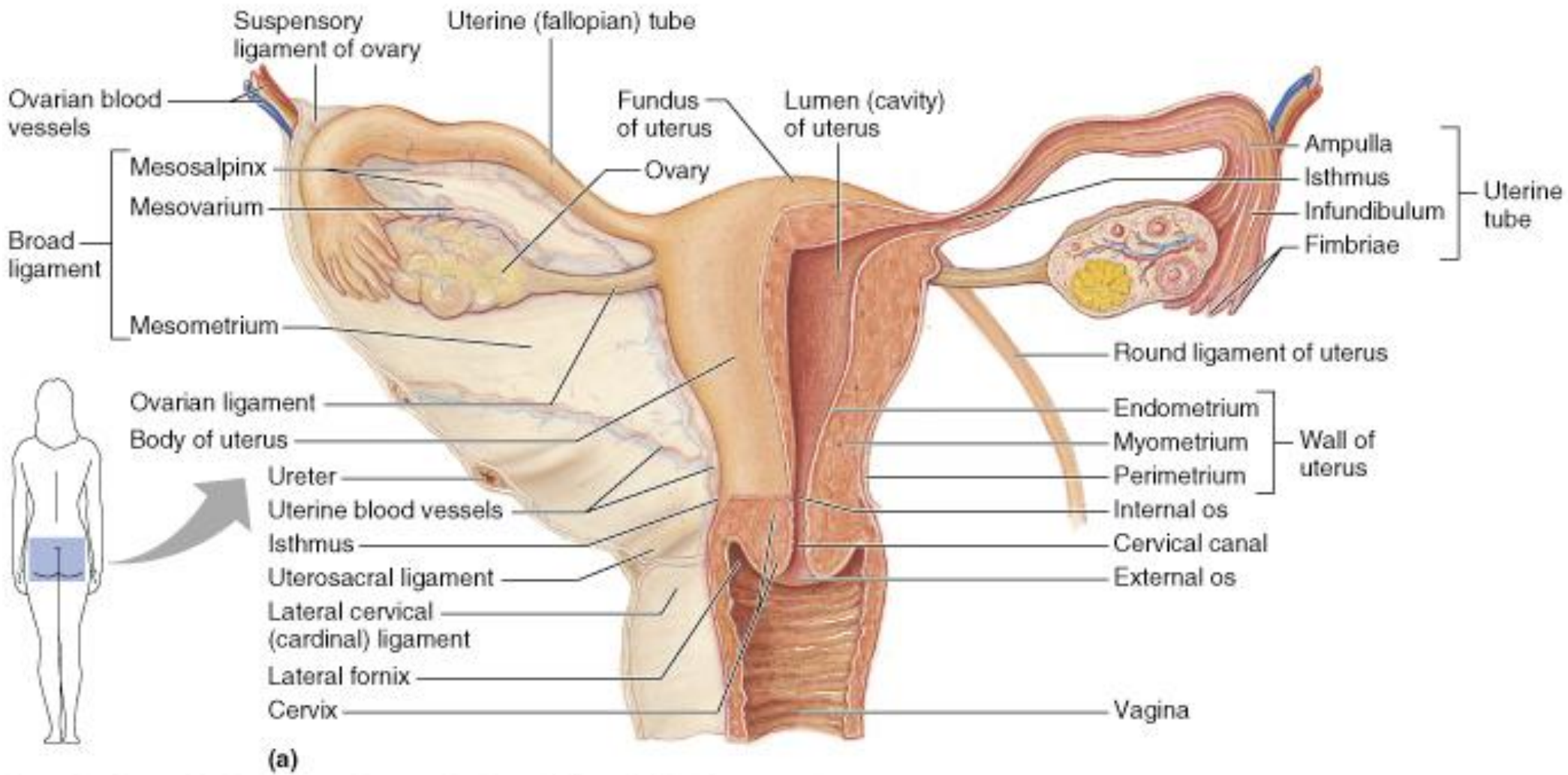
Stadiering

Primaire debulking versus intervaldebulking

HIPEC

…

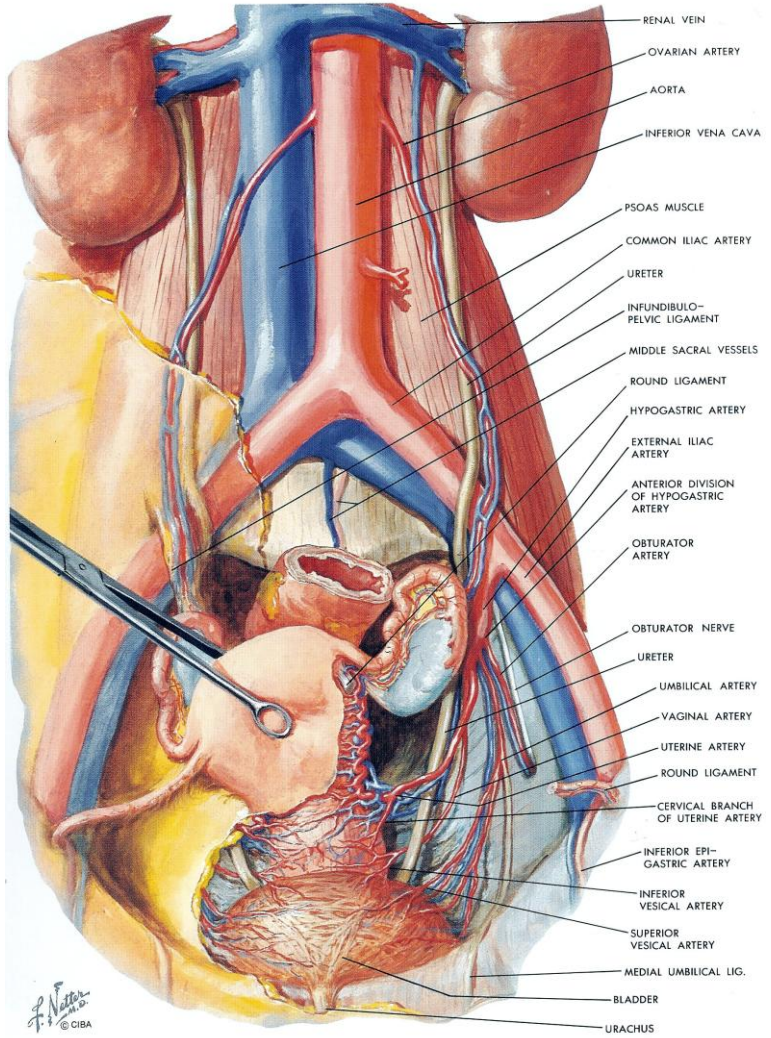
Uterus en adnexen



Uterus en adnexen

Maar hoe ziet dat er nou in het echt uit?

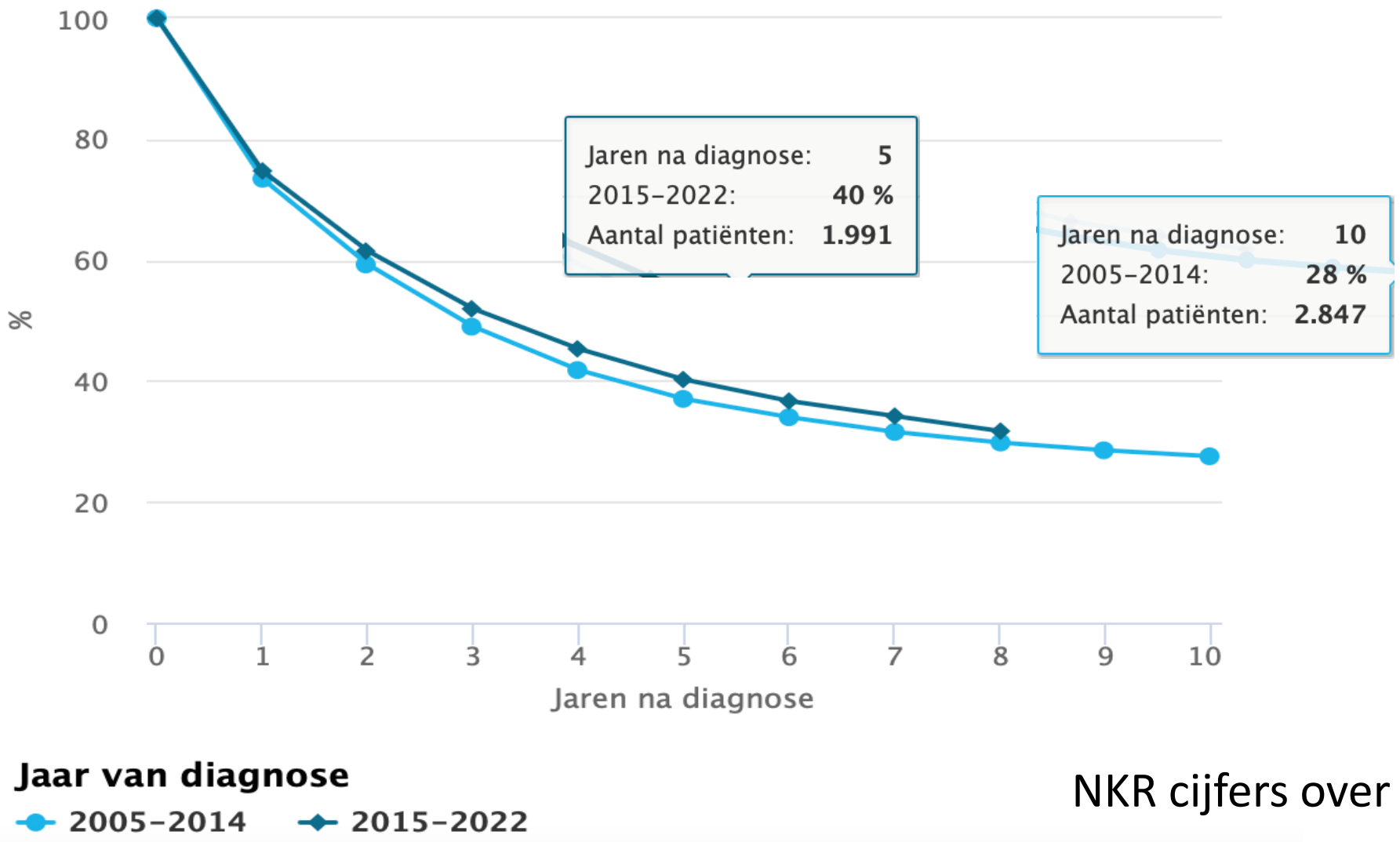
https://www.youtube.com/watch?v=h3mUMhtIZ_A&t=8s



ovariumcarcinoom

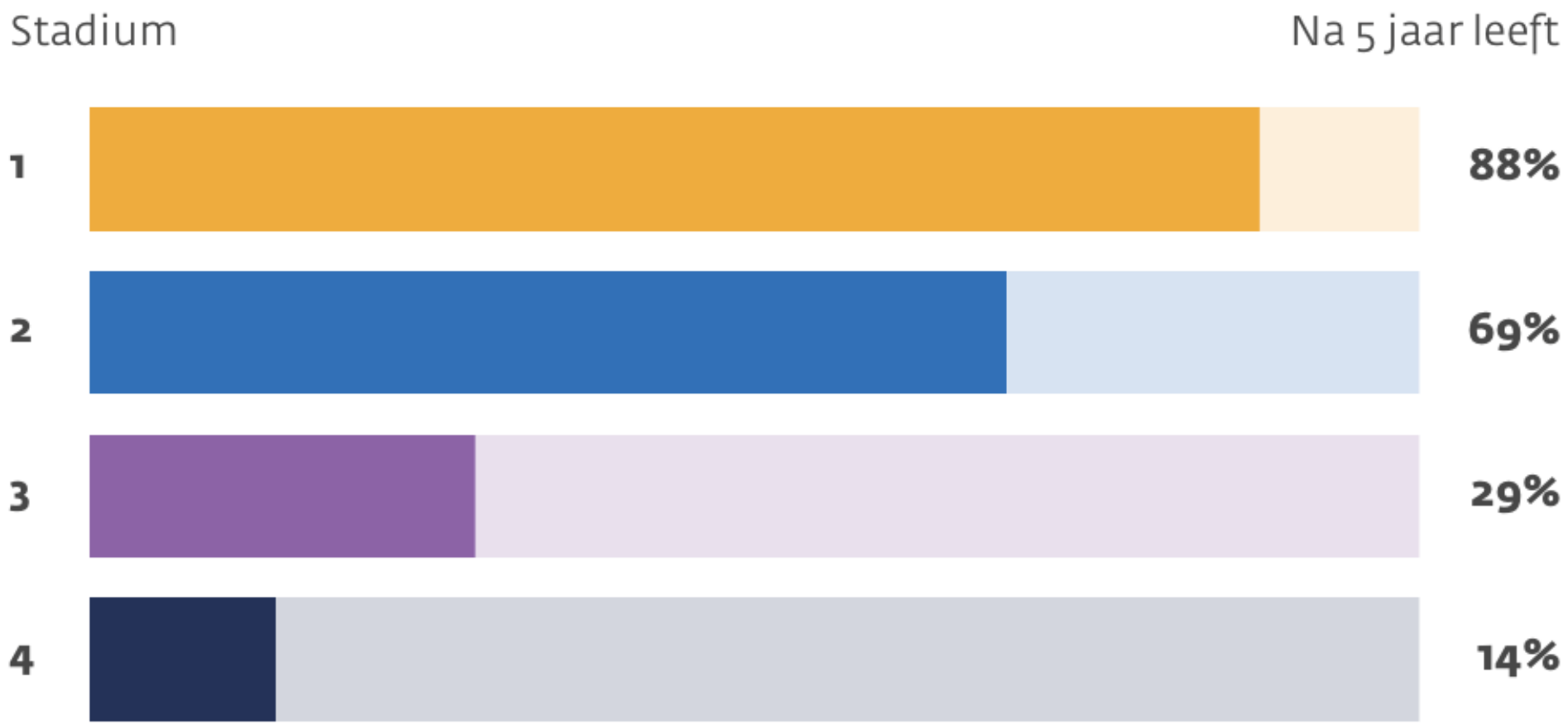
- NL 1400 /jaar
- circa 75% diagnose hoog stadium
- merendeel stadium III (buikholte verspreid)
- mediane leeftijd 65 jaar
- lifetime risico 1.3%, 1 op 78

overleving ovariumcarcinoom (alle stadia)



NKR cijfers over kanker

5 jaars overleving ovariumcarcinoom per stadium



NKR cijfers over kanker

Erfelijkheid

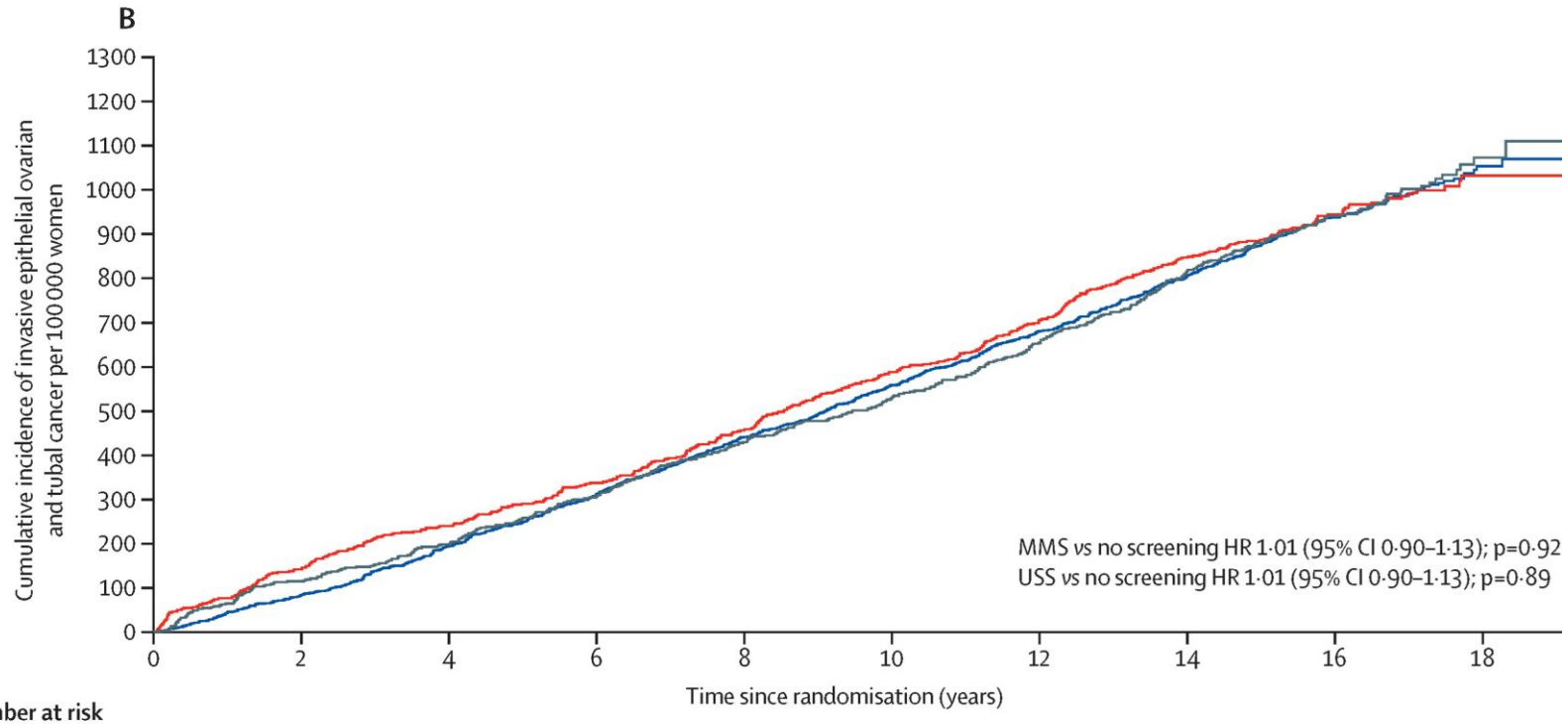
sporadisch ovariumcarcinoom: circa 90 % **(= niet erfelijk**)

erfelijk:

- circa 10-15 % van de ovariumcarcinomen heeft BRCA 1/2 mutatie
  - BRCA1 (chromosoom17): 39% risico ov ca (begint vanaf 35 jaar)
  - BRCA2 (chromosoom13): 16 % risico ov ca (begint vanaf 40 jaar)
  - Nog aantal andere mutaties (CHEK2, BRIP,…) met lagere risico's

(Lynch syndroom: erfelijk verhoogd risico colon, endometrium, ovariumcarcinoom)

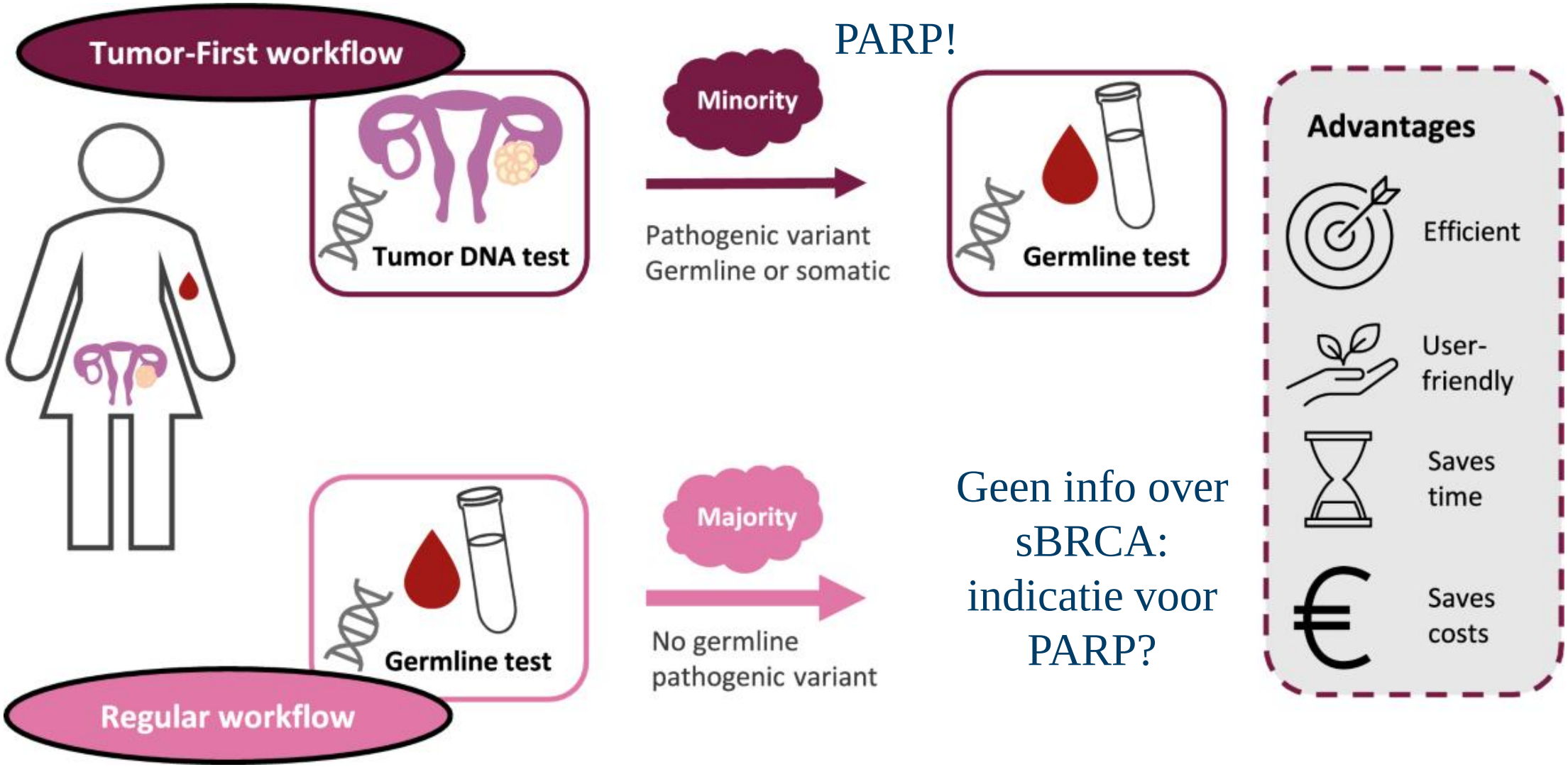
Screening?



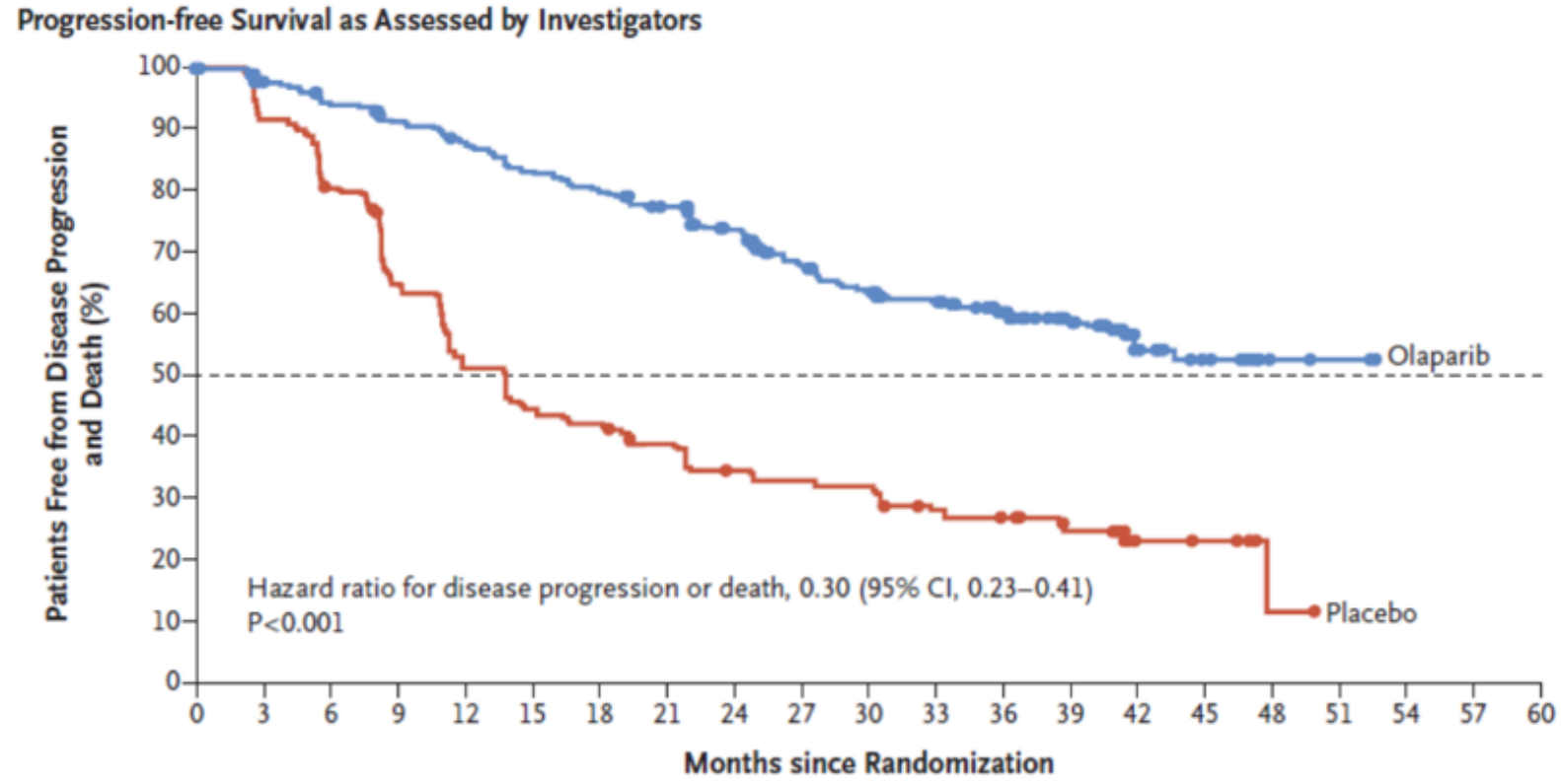
Number at risk (number censored)																			
No screening	101297	(83)	100339	(110)	98911	(116)	97202	(126)	95311	(111)	92414	(111)	88732	(108)	85151	(102)	56370	(37)	9992
MMS	50618	(71)	50046	(49)	49277	(48)	48322	(57)	47219	(62)	45752	(53)	43994	(61)	42257	(36)	27837	(15)	4947
USS	50614	(57)	49199	(41)	48295	(52)	47350	(58)	46241	(45)	44858	(56)	43238	(68)	41534	(47)	27405	(20)	4912

Menon et al 2021

Alle vrouwen met ovariumcarcinoom testen op BRCA mutatie



PARP werkt écht heel goed!



No. at Risk

Olaparib	260	240	229	221	212	201	194	184	172	149	138	133	111	88	45	36	4	3	0	0	0
Placebo	131	118	103	82	65	56	53	47	41	39	38	31	28	22	6	5	1	0	0	0	0

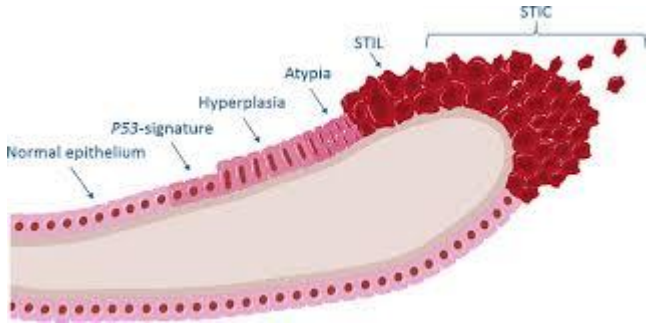
From the New England Journal of Medicine, Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. DOI: 10.1056/NEJMoa1810858. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

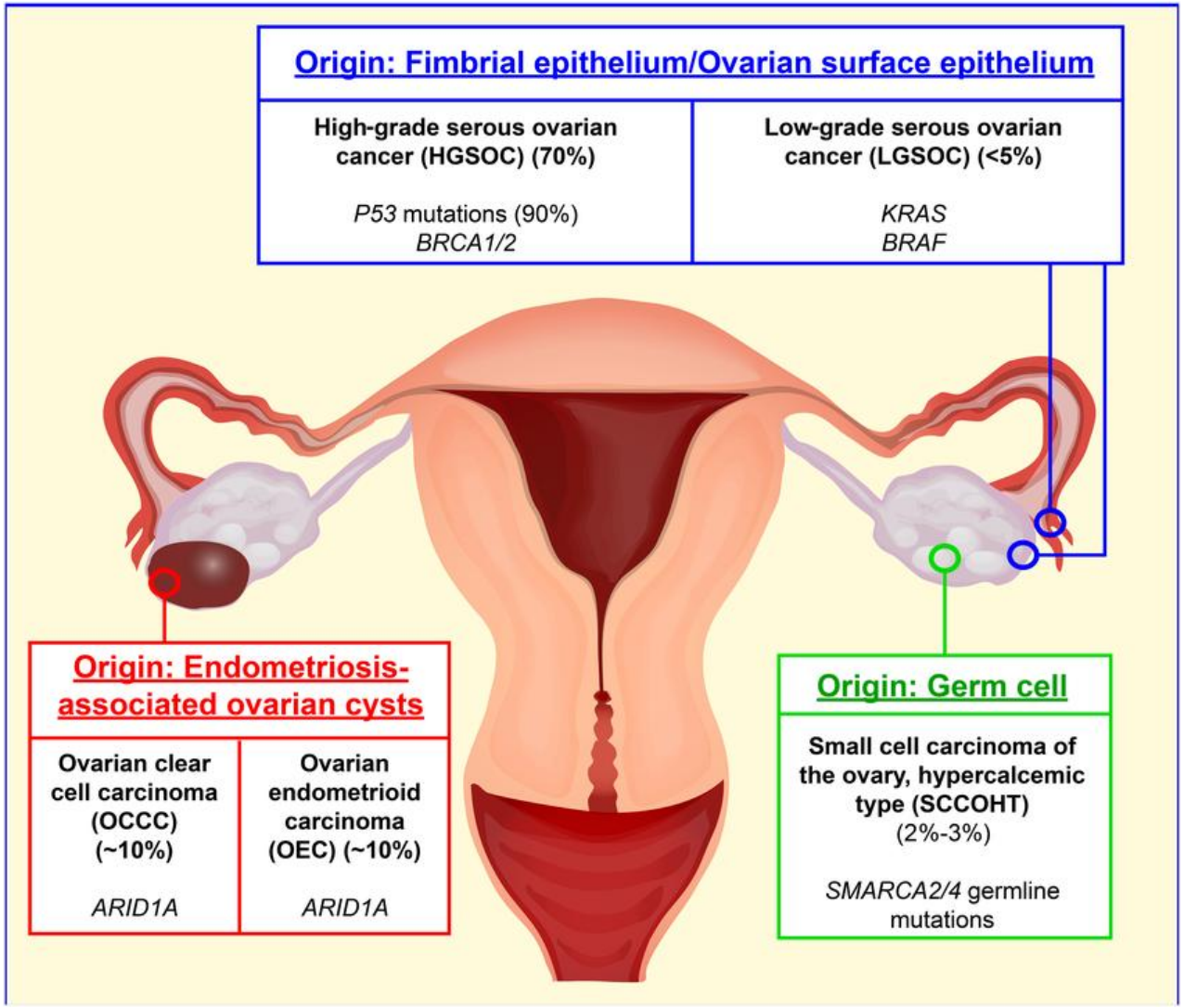
Ovariumcarcinoom

Aspecifieke klachten (via internist)

- Malaise en anorexia
- Vage gastro-intestinale klachten
- Opgezette buik
- Passage stoornissen darmen
- Mictieklachten
- …

Preventie?

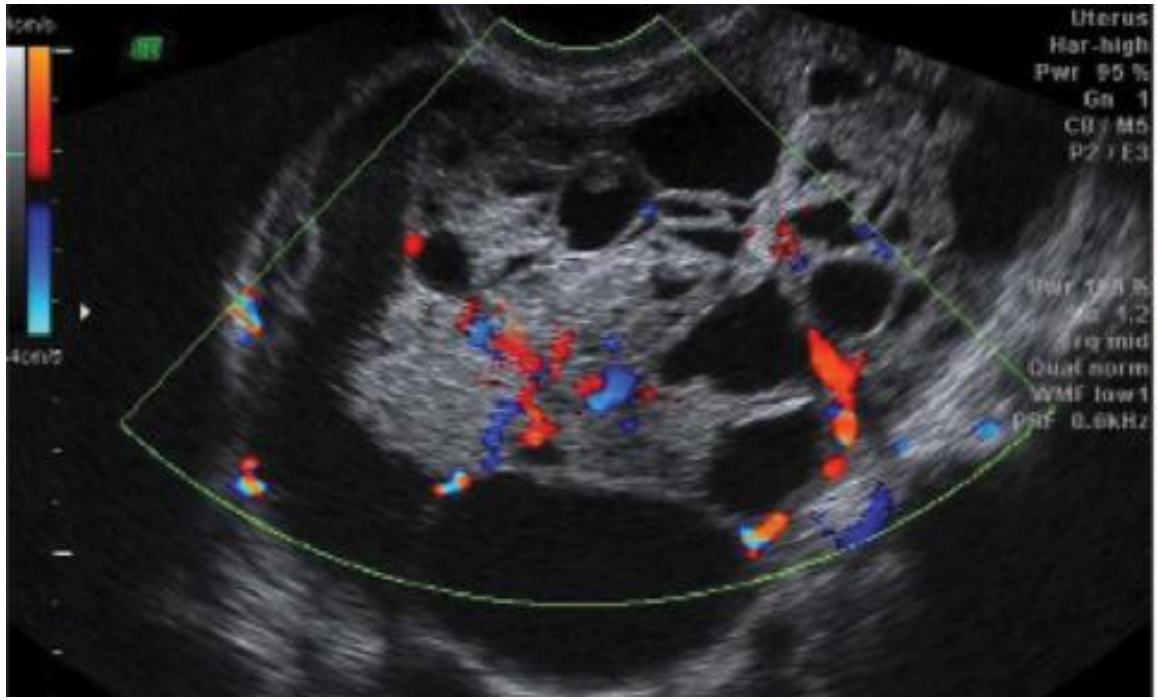

STIC
STIL
Atypia
Hyperplasia
P53-signature
Normal epithelium


Origin: Fimbrial epithelium/Ovarian surface epithelium
High-grade serous ovarian cancer (HGSOC) (70%)
P53 mutations (90%)
BRCA1/2
Low-grade serous ovarian cancer (LGSOC) (<5%)
KRAS
BRAF
Origin: Endometriosis-associated ovarian cysts
Ovarian clear cell carcinoma (OCCC) (~10%)
ARID1A
Ovarian endometrioid carcinoma (OEC) (~10%)
ARID1A
Origin: Germ cell
Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) (2%-3%)
SMARCA2/4 germline mutations

Ovariumcarcinoom

Lichamelijk onderzoek:

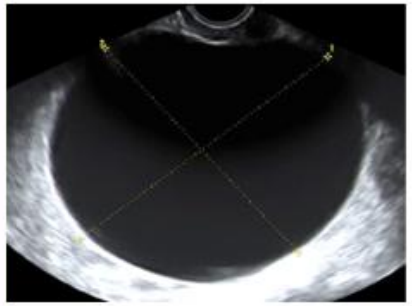
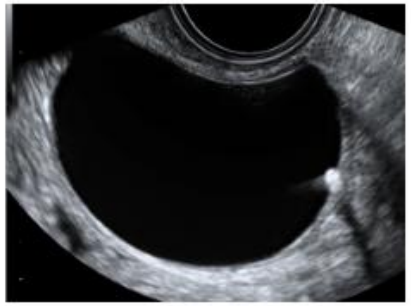
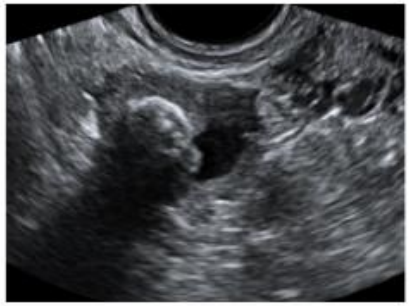
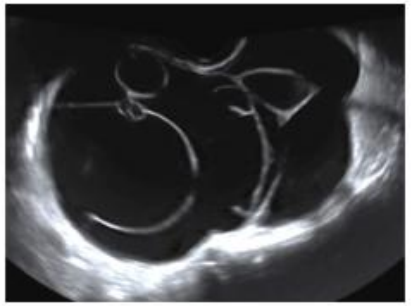
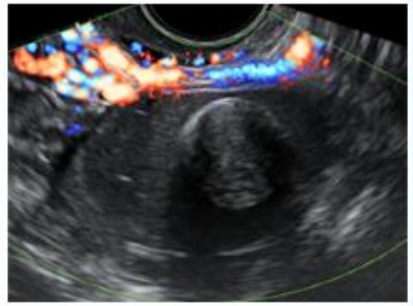
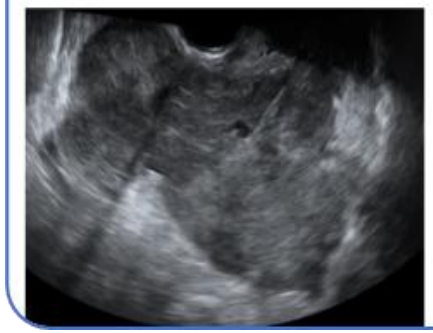
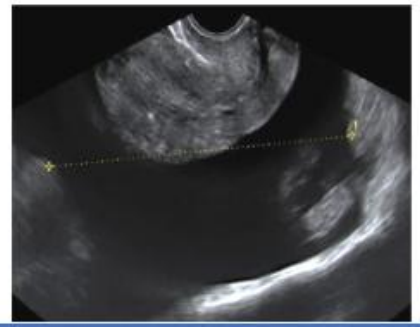
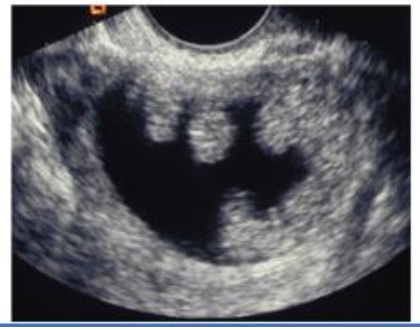
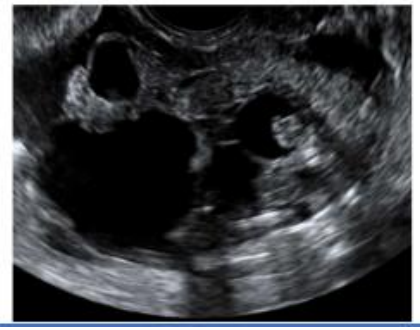
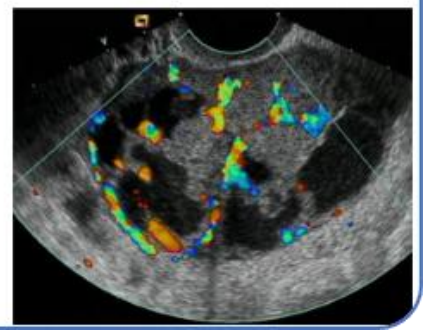
- RIP kleine bekken
- ascites
- vergrote supraclaviculaire lymfklier (Virchow)



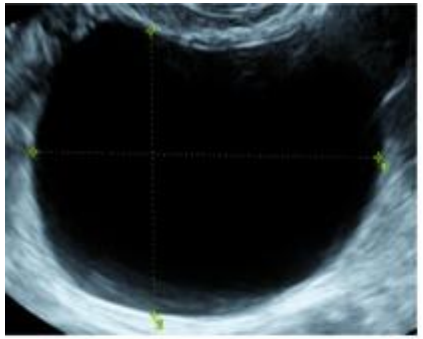
- Transvaginale echografie:
  - afwijkend ovarium, vrij vocht

- bloedonderzoek
  - CA125, CEA, hematologie, nierfunctie

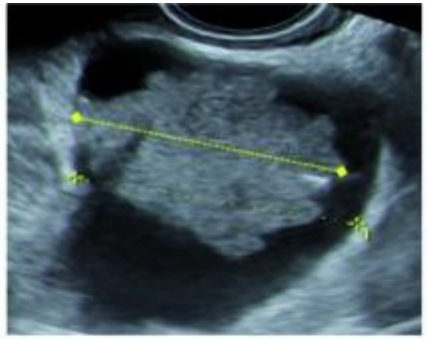
IOTA simple rules

B1 Unilocular	B2 Presence of solid components with largest diameter < 7 mm	B3 Presence of acoustic shadows	B4 Smooth multilocular tumor with largest diameter < 100 mm	B5 No blood flow (color score 1)
				
M1 Irregular solid tumor	**M2 Presence of ascites**	**M3 At least 4 papillary structures**	**M4 Irregular multilocular-solid tumor with largest diameter ≥ 100 mm**	**M5 Very strong blood flow (color score 4)**
				

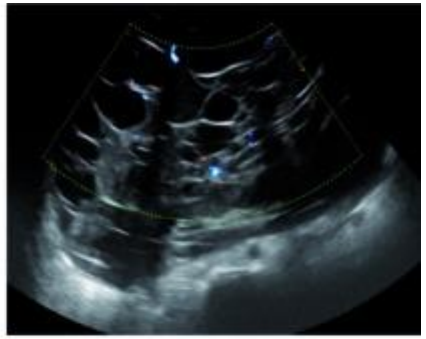
IOTA adnex model



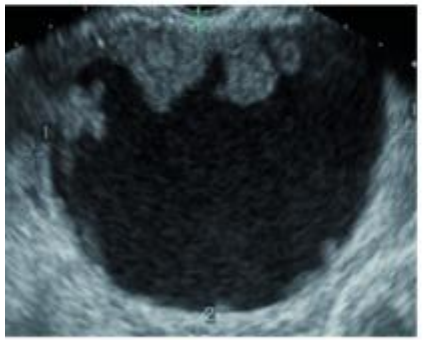
(1) maximum diameter of lesion (mm)



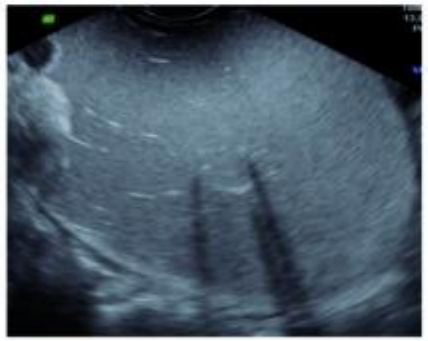
(2) proportion of solid tissue



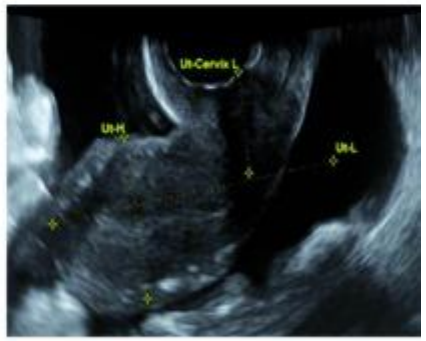
(3) more than 10 cyst locules (yes vs no)



(4) number of papillary projections (0, 1, 2, 3, more than 3)



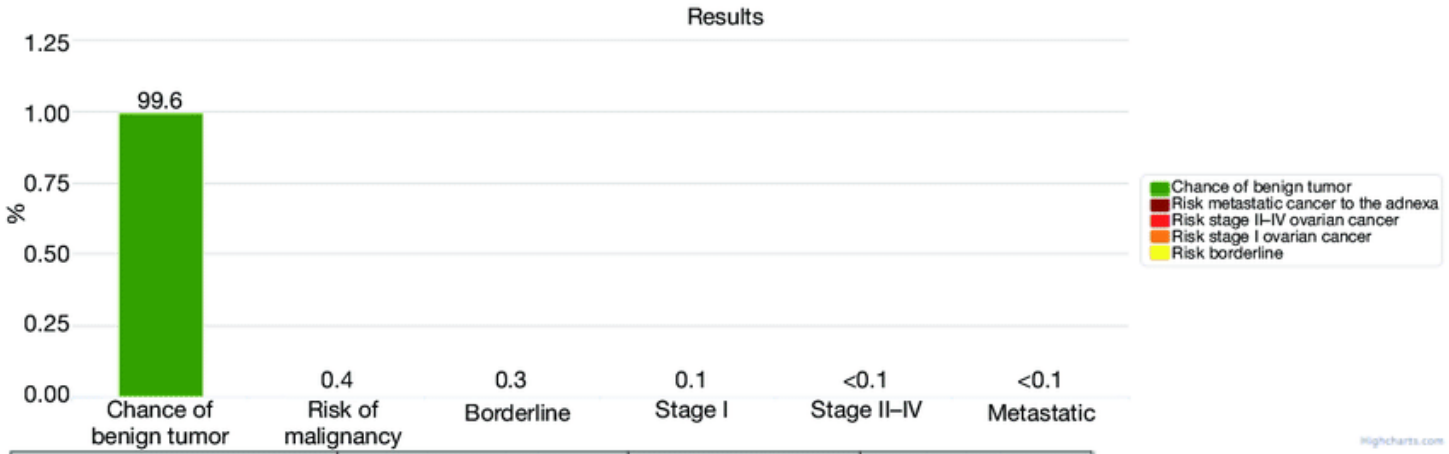
(5) acoustic shadows (yes vs no)



(6) ascites (yes vs no)

IOTA adnexmodel

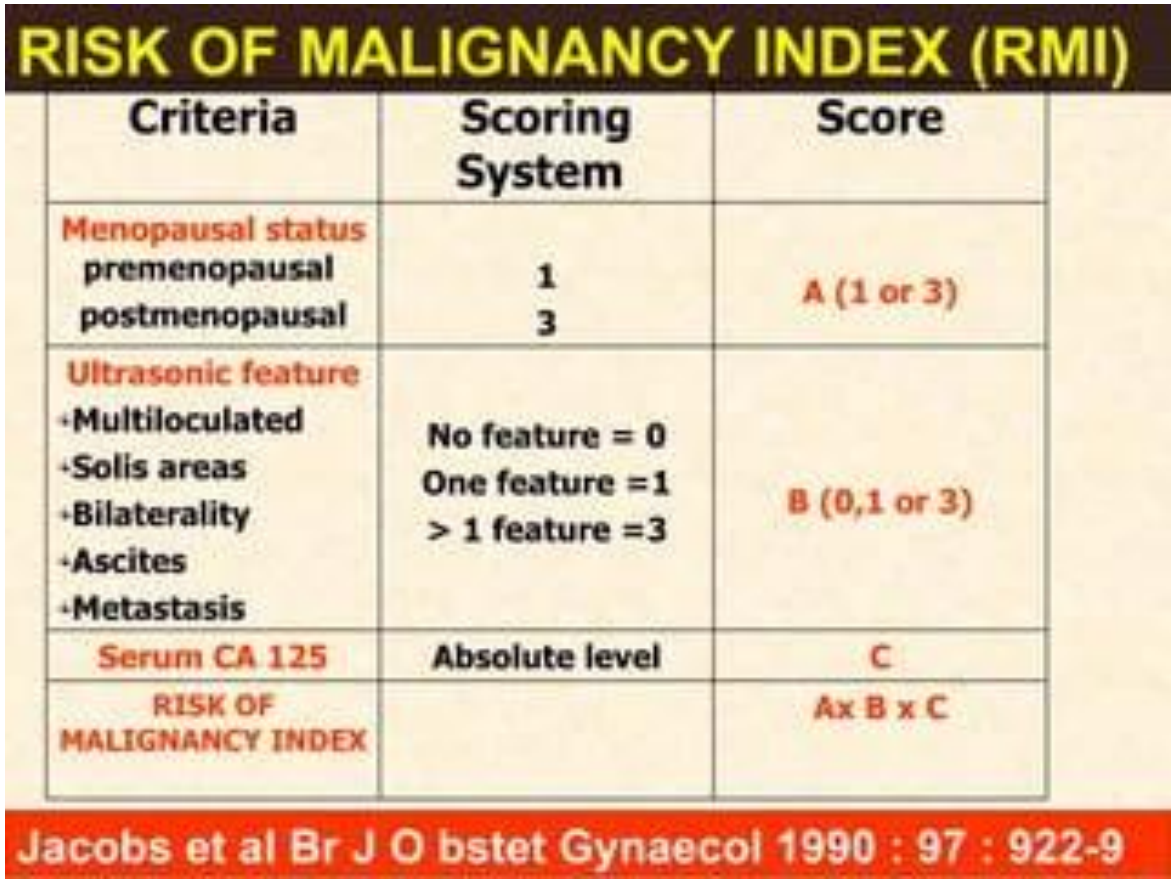
1. Age of the patient at examination (years) 53
2. Oncology center (referral center for gyn-oncol)? no
3. Maximal diameter of the lesion (mm) 55
4. Maximal diameter of the largest solid part (mm) 3
5. More than 10 locules? no
6. Number of papillations (papillary projections) one
7. Acoustic shadows present? yes
8. Ascites (fluid outside pelvis) present? no
9. Serum CA-125 (U/ml) 7.8



	Patient Specific Risk	Relative Risk	Baseline Risk
CHANCE OF BENIGN TUMOR	99.6 %	1.5	68.2%
RISK OF MALIGNANCY	0.4 %	0	31.8 %
->Risk borderline	0.3 %	0	6.3 %
->Risk stage I ovarian cancer	0.1 %	0	7.5 %
->Risk stage II-IV ovarian cancer	<0.1 %	0	14.1 %
->Risk metastatic cancer to the adnexa	<0.1 %	0	4.0 %

Transvaginale echo

Risk of malignancy index (RMI)



RISK OF MALIGNANCY INDEX (RMI)

Criteria	Scoring System	Score
Menopausal status premenopausal postmenopausal	 1 3	A (1 or 3)
Ultrasonic feature •Multiloculated •Solis areas •Bilaterality •Ascites •Metastasis	No feature = 0 One feature =1 > 1 feature =3	B (0,1 or 3)
Serum CA 125	Absolute level	C
RISK OF MALIGNANCY INDEX		Ax B x C

Jacobs et al Br J O bstet Gynaecol 1990 : 97 : 922-9

Ovariumcarcinoom: CT scan

CT Thorax-abdomen

Waar let je op?

RIP

Omental cake

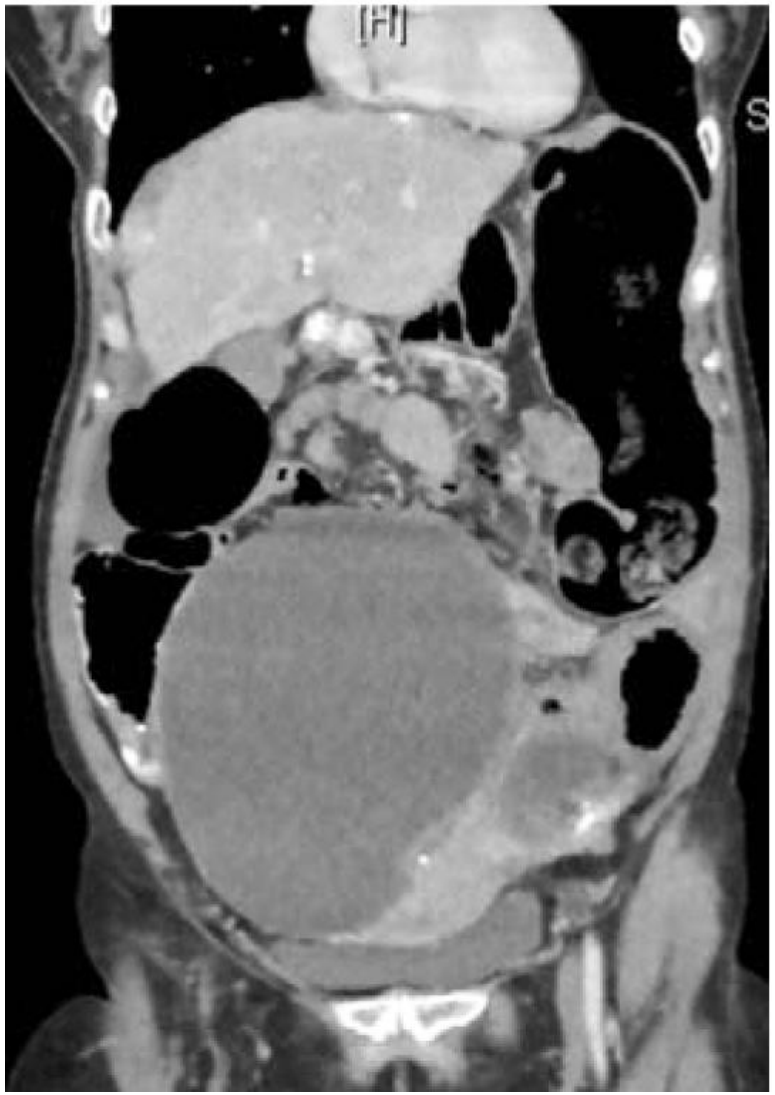
Ascites

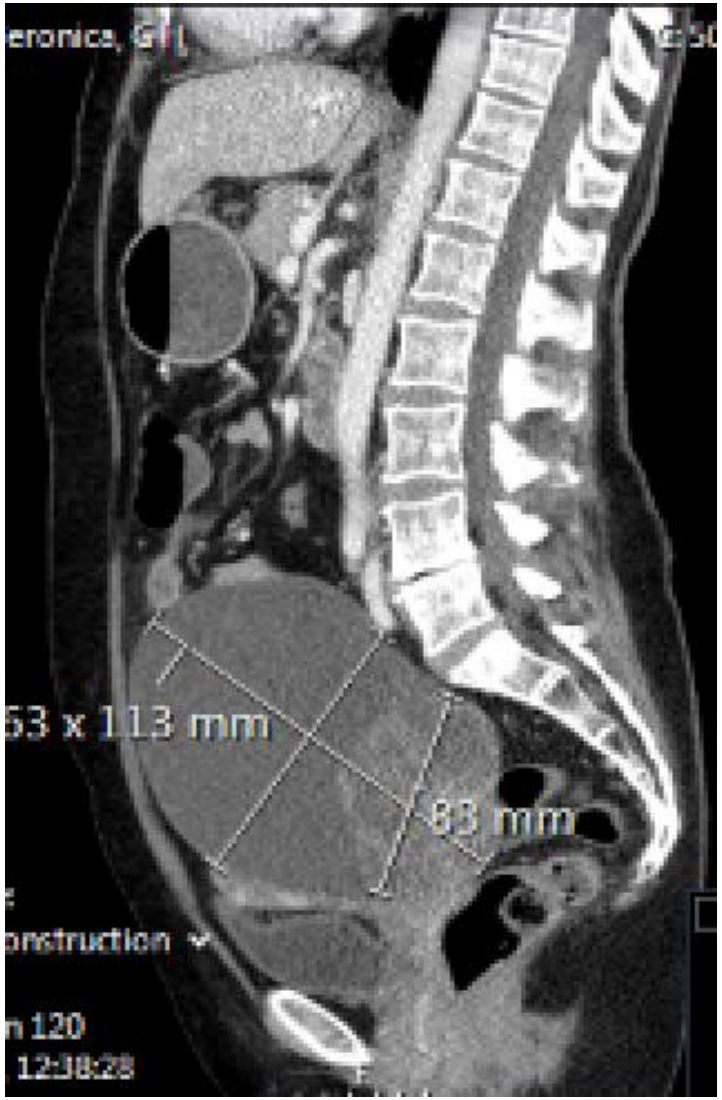
Lever/ milt metastasen

Peritoneale deposities

Retroperitoneale klieren

Pleuravocht





In de praktijk….

Ovariumcyste ZONDER aanwijzingen voor metastasen:

Op basis van RMI / IOTA laag risico: expectatief vs laparoscopische adnexextirpatie

Op basis van RMI / IOTA hoog risico: ‘proeflaparotomie’ met vriescoupe

(Op basis van RMI / IOTA hoog risico: laparoscopische adnexextirpatie ‘zonder spill’

Laag stadium ovariumcarcinoom: proeflaparotomie

In de praktijk….

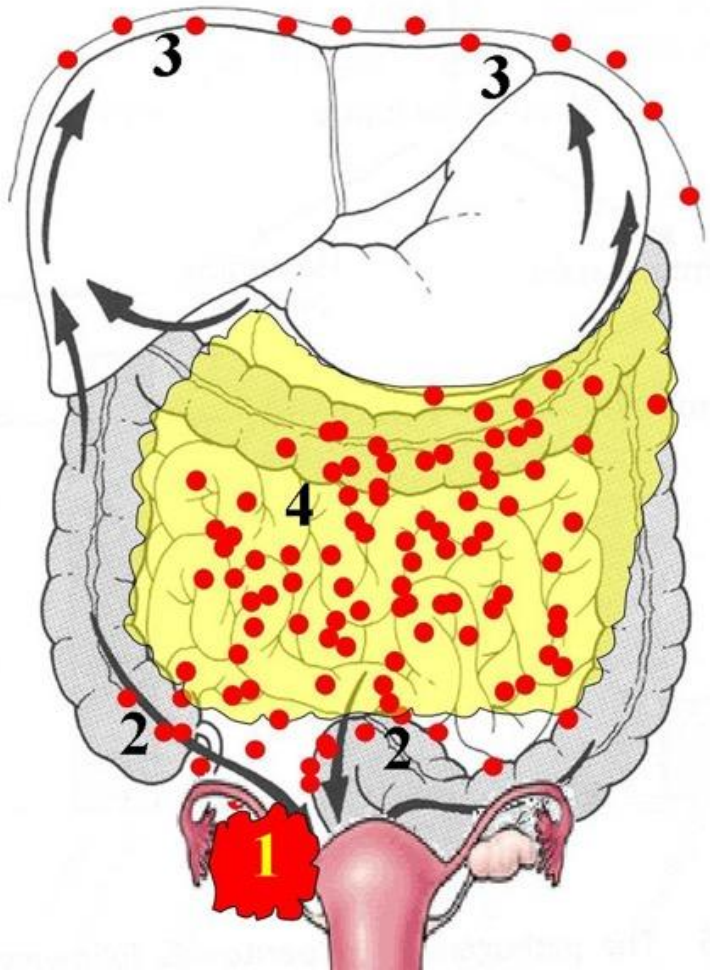
Ovariumcyste die maligne blijkt te zijn…

Als geen adhesies: op zoek naar occulte metastasen (en dan chemotherapie)

Als adhesief met omliggende structuren beschouwen als hoog stadium? Dus chemotherapie?
Als adhesief met omliggende structuren adequaat ‘gedebulkt’? (omentum? Andere ovarium?...)

Metastasering ovariumcarcinoom

- contralaterale ovarium
- directe doorgroei in uterus of tuba
- **intra-abdominale verspreiding**:
  - ascites
  - omentum
  - peritoneum
- lymfogeen: pelviene en para-aortale klieren
- hematogeen (2-3%): in lever, in pleuravocht
- zelden: hersenen, subcutaan



Laag stadium ovariumcarcinoom stageren

Doel stageren:

- Detectie van occult hoger stadium
- Daarmee indicatie voor chemotherapie
- Kans upstaging stadium = 12-19 %
- Kans positieve klieren = 4-8%

methode stageren:

- laparoscopisch of laparotomie

Ovariumcarcinoom stadiëring bij klinisch laag stadium

spoelvocht of ascites

uterus + adnexextirpatie

biopten peritoneum

infracolische) omentectomie

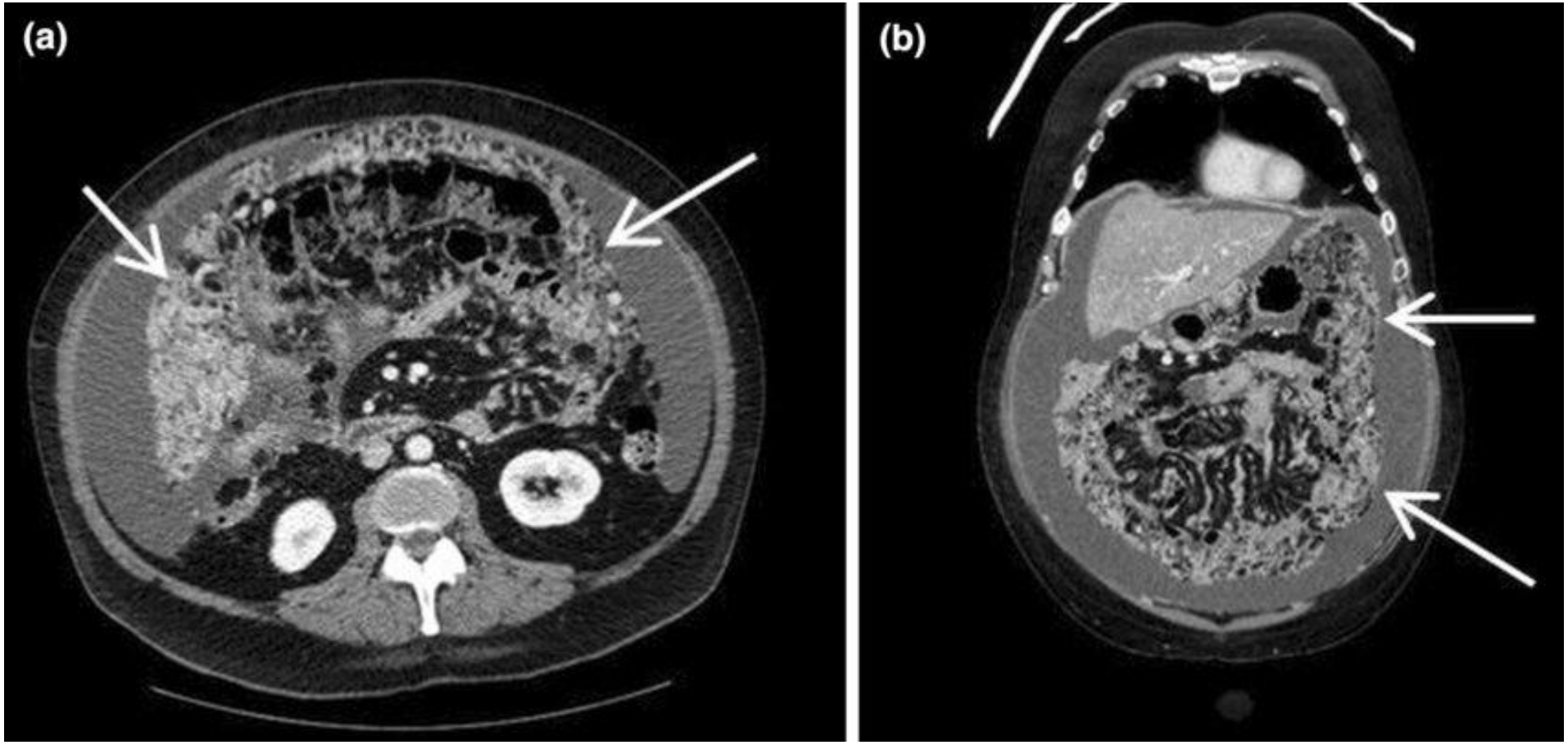
Darminspectie (meckelen)

Indien geen metastasen zichtbaar

dan para-aortaal en pelviene lymfeklieren

sampling/adenectomie

Maar heel vaak hoog stadium bij diagnose…



Hoog stadium ovariumcarcinoom

Hoog stadium ovariumcarcinoom

Omental cake

Mesenterium met tumordeposities

Hoog stadium ovariumcarcinoom behandelstrategie

Primaire debulking

OK  → IV CHEMO

HIPEC in studieverband

6 kuren carboplatin + paclitaxel i.v.
Evt ook intraperitoneaal via catheter

NACT gevolgd door intervaldebulking

IV CHEMO → OK  → IV CHEMO

3 kuren om de 3 weken
of wekelijks schema

Evt + HIPEC 

adjuvant 3 kuren

Debulking

Doel: complete debulking (geen zichtbare tumorrest)

(optimaal <1cm, incompleet >1cm)

Uterus- en adnexextirpatie,

omentum, metastasen

Indien nodig voor complete resectie:

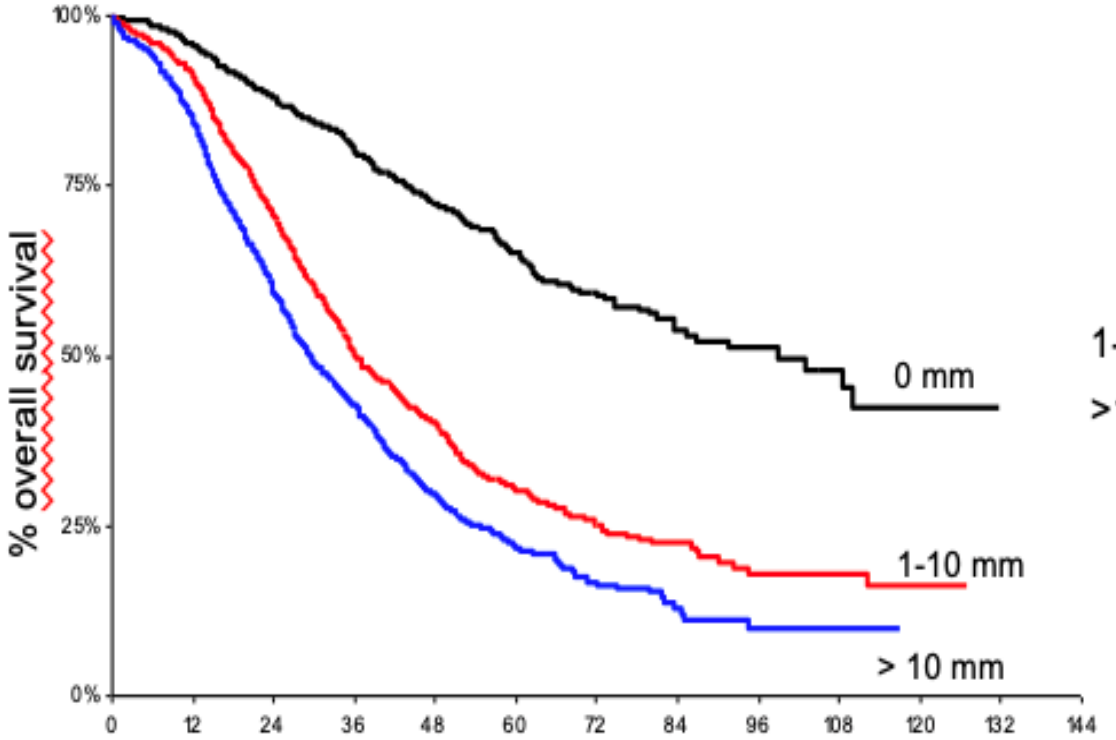
darmresectie met anastomose/stoma

Evt miltextirpatie

Evt strippen diaphragma

Streven naar complete debulking

Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials (n=3126) **(Du Bois et al., Cancer, 2009)**



	HR (95%CI)
1-10 mm vs. 0 mm:	2.70 (2.37; 3.07)
>10 mm vs. 1-10 mm:	1.34 (1.21; 1.49)

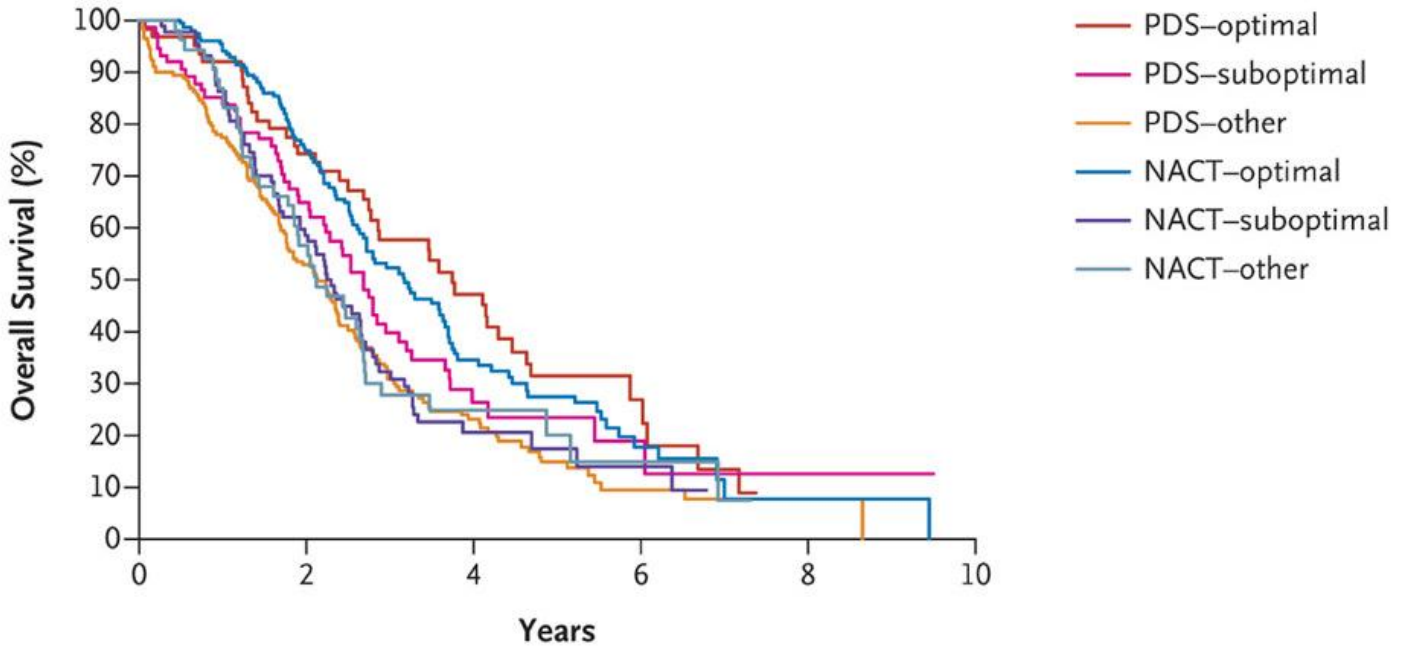
log-rank: p < 0.0001

Stadium IIB en hoger

Het grote dilemma: ‘NACT of PDS’

PDS sub-optimal vs NACT optimal…

B Per-Protocol Analysis



	No. of Events	No. of Patients at Risk				
PDS–Optimal	42	62	46	22	6	0
PDS–Suboptimal	52	74	46	11	3	1
PDS–Other	136	169	86	29	5	1
NACT–Optimal	100	152	110	30	8	2
NACT–Suboptimal	67	87	49	9	3	0
NACT–Other	41	53	29	6	2	0

Vergote, 2010

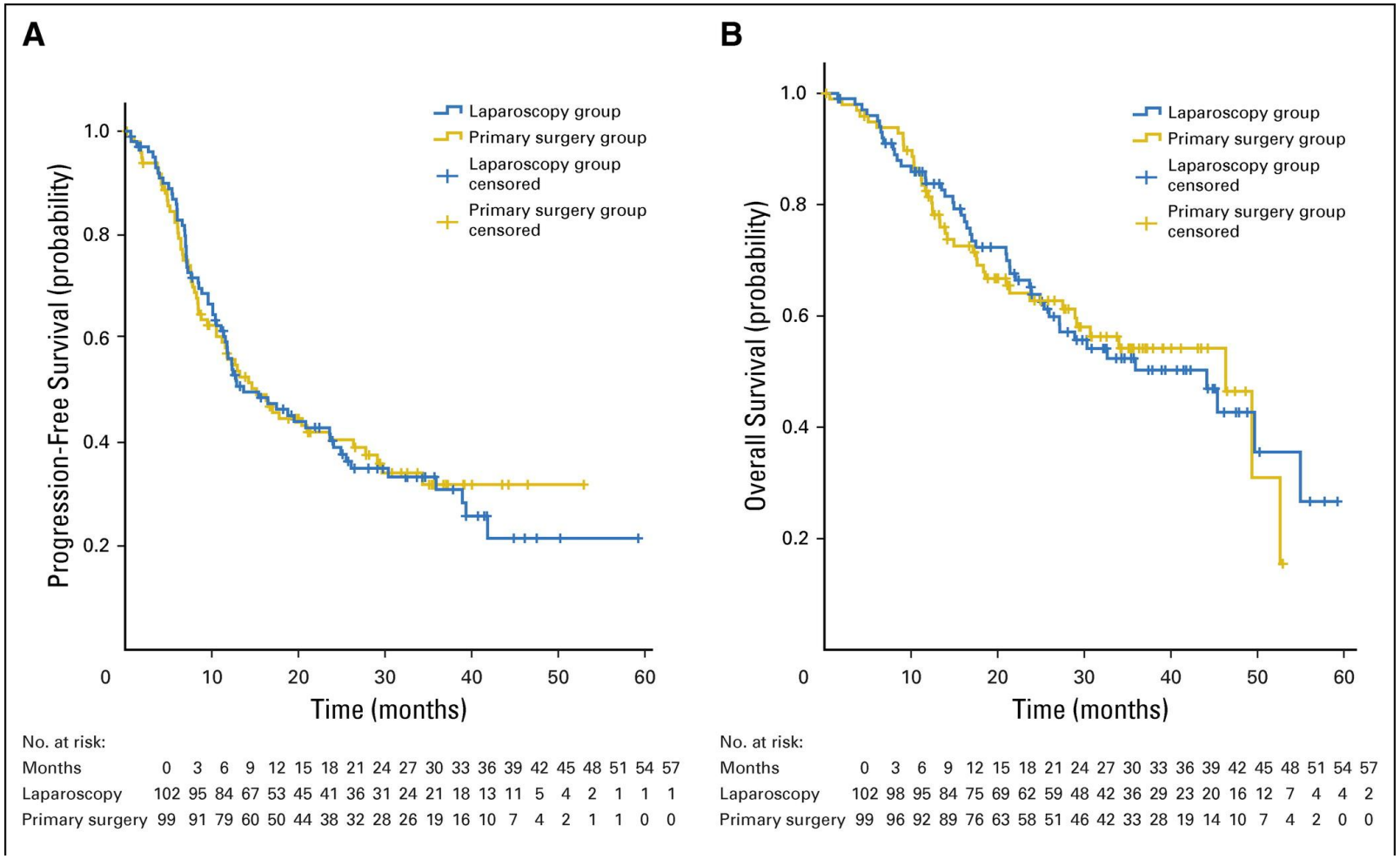
Laparoscopie om 'debulkbaarheid' te beoordelen

Table 3. Primary Outcome (futile laparotomies per treatment arm [intention-to-treat analysis]) and Secondary Outcome (patients who underwent zero, one, or two laparotomies per intervention arm) for All Patients and for Patients With Histologically Confirmed Stage IIIC or IV Ovarian Cancer

Outcome	Laparoscopy Before Surgery, No. (%)	Primary Surgery, No. (%)	RR (95% CI)	*P*
All patients	102	99		
Futile laparotomy*	10 (10)	39 (39)	0.25 (0.13 to 0.47)	< .001
Futile laparotomy any residual disease†	27 (27)	56 (57)	0.47 (0.32 to 0.68)	< .001
No. of laparotomies				
0	4 (4)	1 (1)		< .001
1	94 (92)	70 (71)		
2	4 (4)	28 (28)		
No. in FIGO stage IIIC or IV	71	69		
Futile laparotomy*	6 (8)	32 (46)	0.18 (0.08 to 0.41)	< .001
Futile laparotomy any residual disease†	20 (28)	47 (68)	0.41 (0.28 to 0.62)	< .001
No. of laparotomies in FIGO stage IIIC or IV				
0	3 (4)	1 (1)		< .001
1	64 (90)	46 (67)		
2	4 (6)	22 (32)		

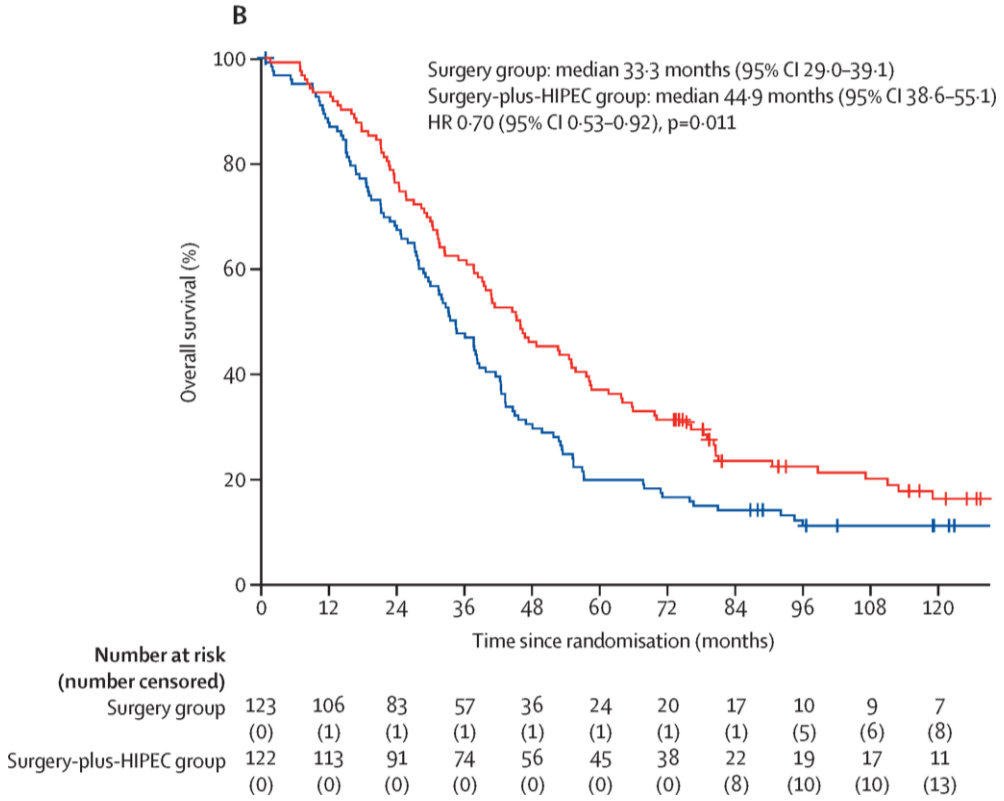
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; RR, relative risk.
*> 1 cm of residual disease after primary cytoreductive surgery.
†> 0 cm of residual disease after primary cytoreductive surgery.

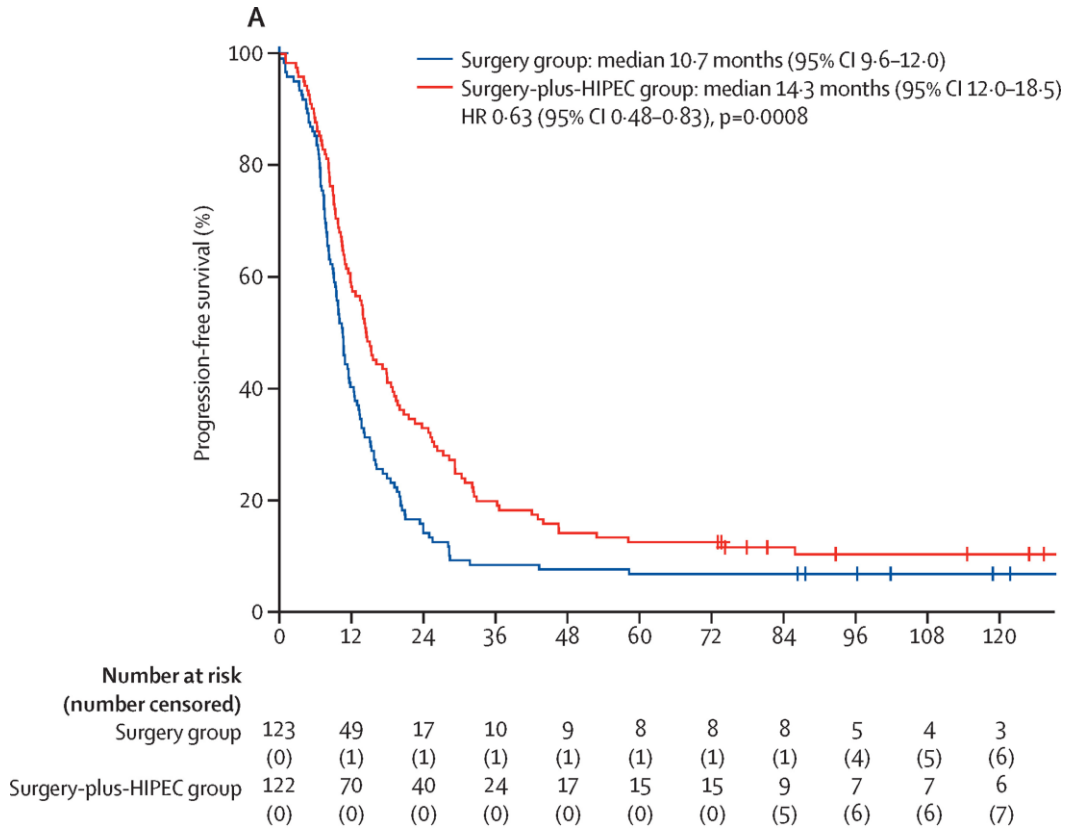
Laparoscopie om debulkbaarheid te beoordelen



Steeds vaker NACT en IDB….

HIPEC…

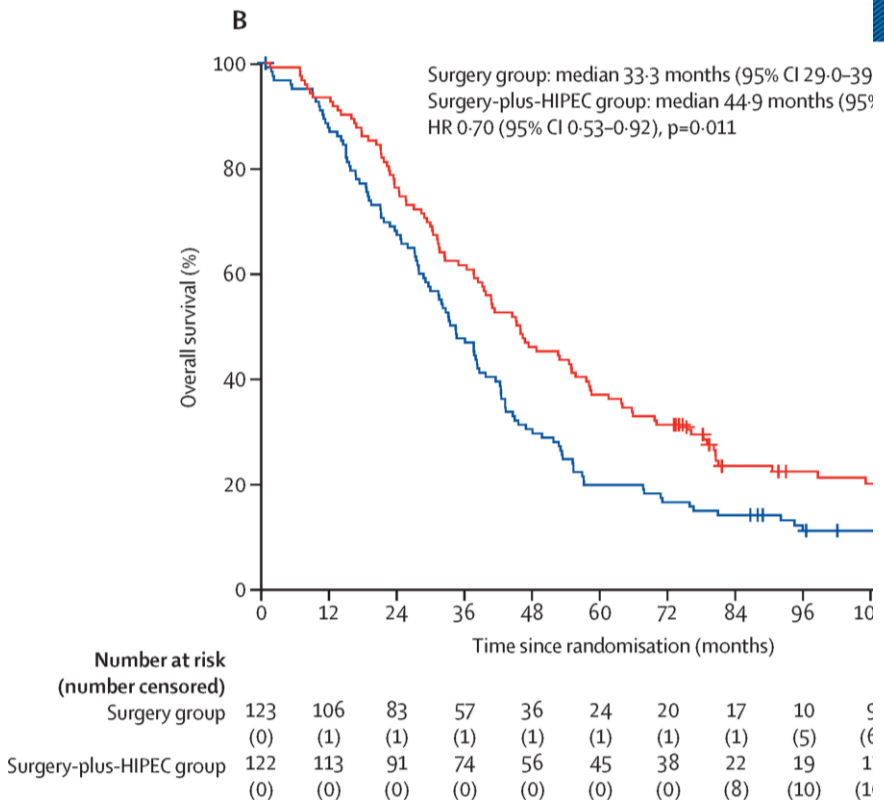


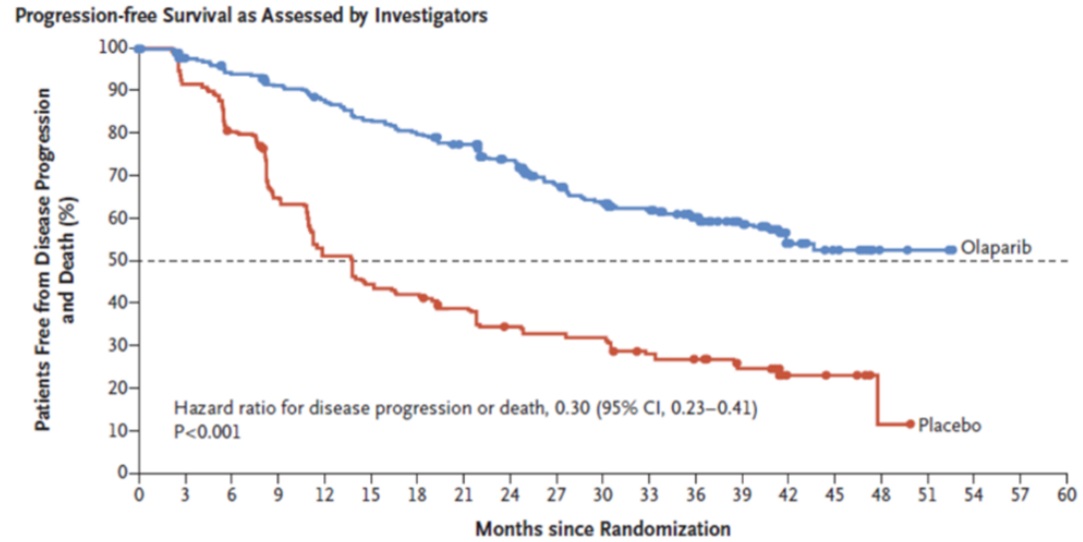


v Driel 2018

HIPEC…

PARP werkt écht heel goed!





From the New England Journal of Medicine, Moore K, Colombo N, Scambia G, et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. N Engl J Med. DOI: 10.1056/NEJMoa1810858. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

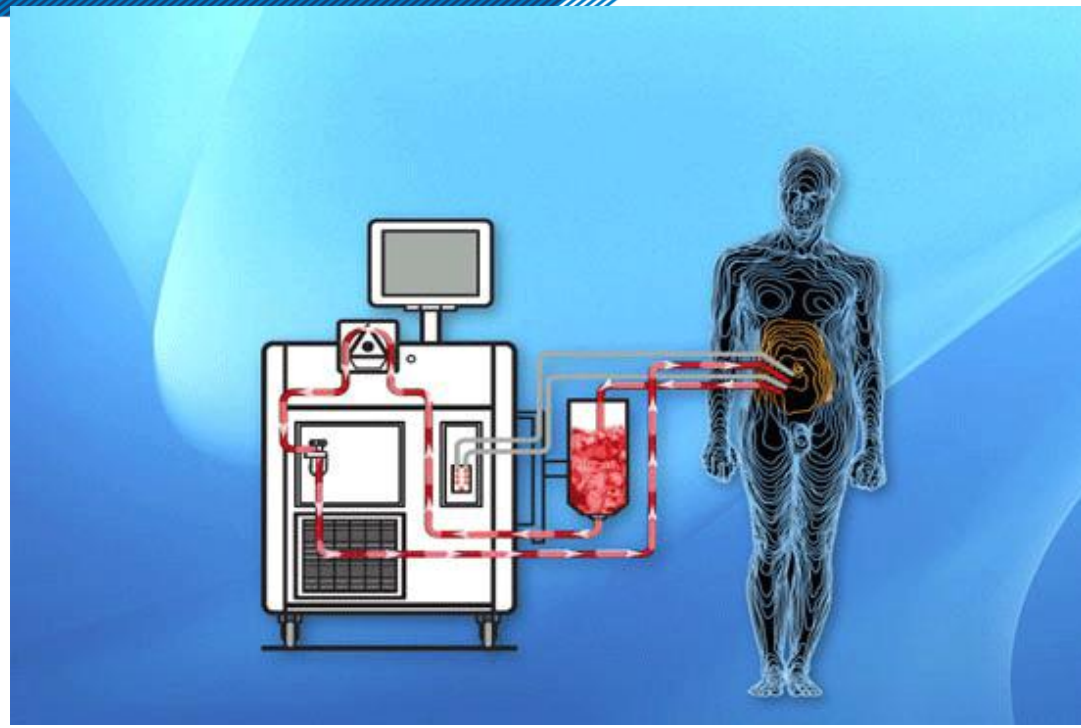
Hypertherme IntraPeritoneale Chemotherapie -HIPEC

tijdens intervaldebulking

continue circulatie Cisplatinum 100 mg/m^2

40 - 41^o C

90 minuten perfusie



Maar…

PFS primaire eindpunt ipv OS

Randomisatie voor operatie

245 patiënten, 10 jaar, 8 centra (3 centra 75% inclusions)

70% vd patiënten ‘maar’ 0-5 regio’s betrokken

‘maar’ 80% R0 na operatie, snijtijd ‘maar’ verdubbeld in HIPEC groep

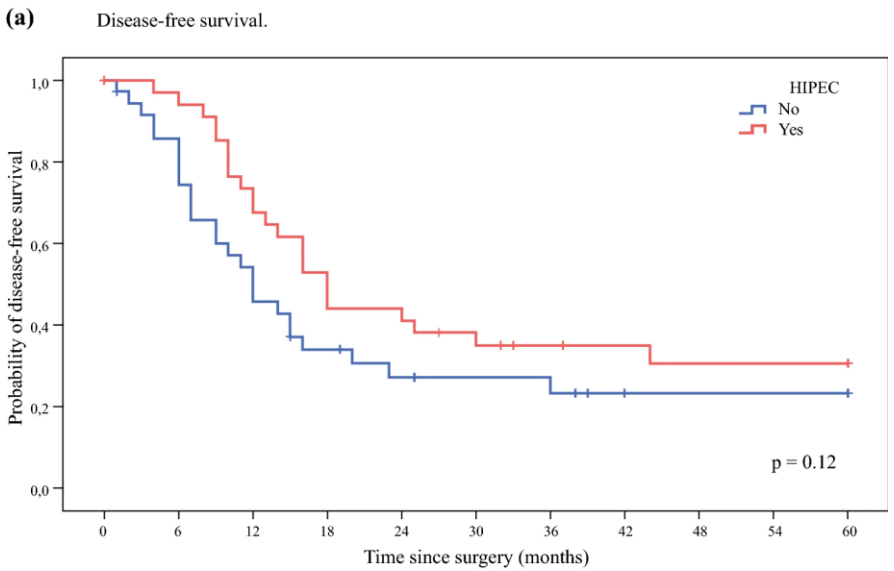
3.5 vs 12.0 mnd voordeel van HIPEC PFS vs OS

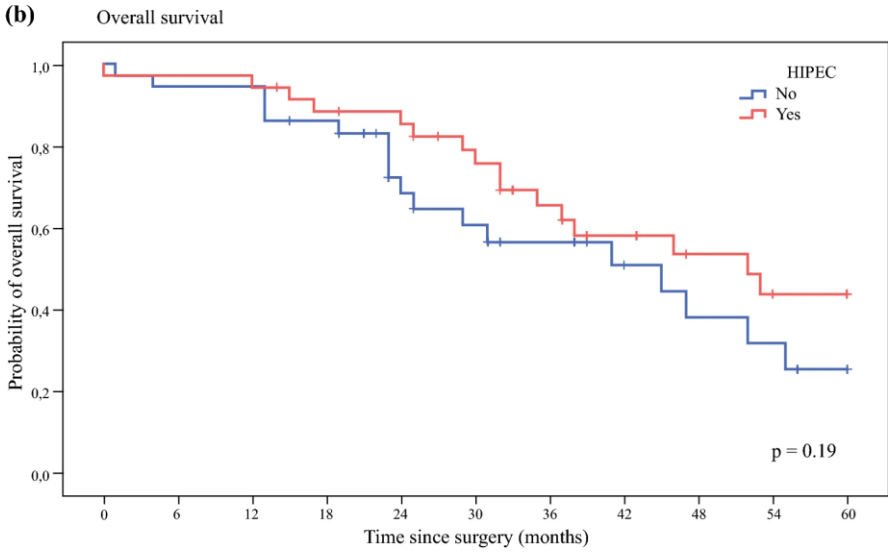
Vergelijkbare toxiciteit

Heel veel studies zonder voordeel van IP chemo

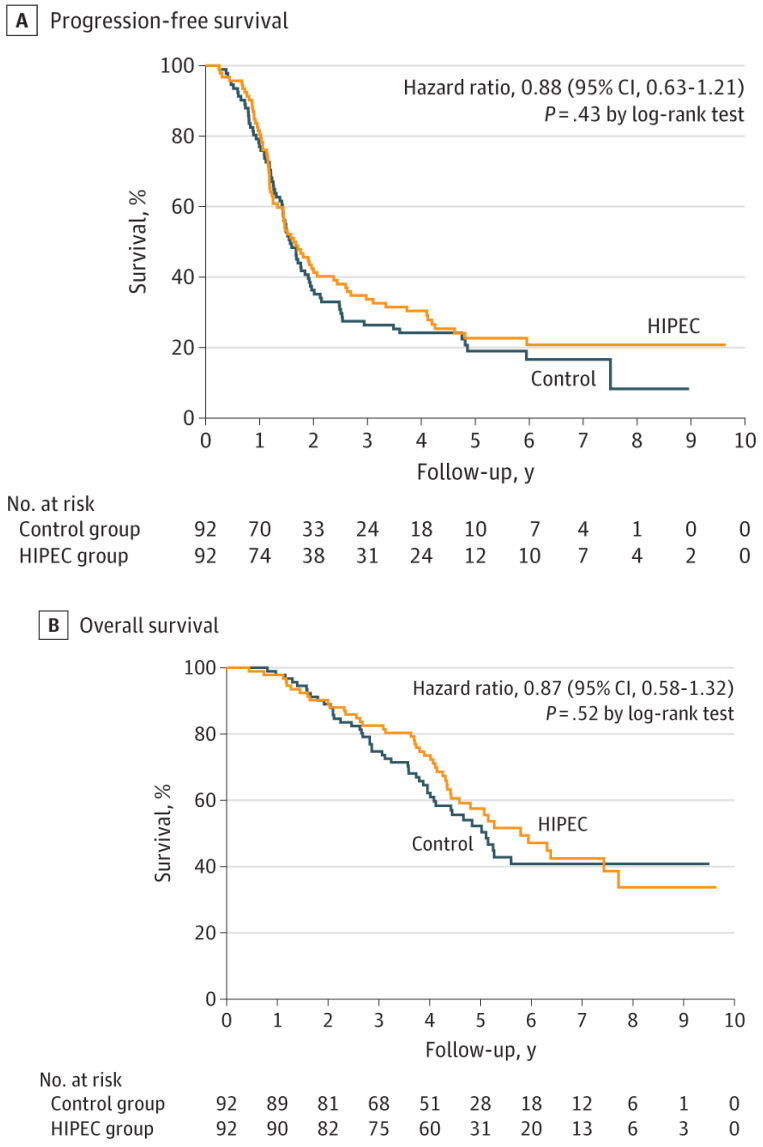
Fotopoulou, Ann Oncol, 2018

Maar…





Antonio Ann Surg Oncol 2021



Lim JAMA Surg 2022

complicaties chirurgie

bloedvatletsel, bloeding > 1000 cc

ureter laesie

blaas laesie

darm laesie

postoperatief ovariumcarcinoom

- pijn, misselijk
- anemie (aanvullende chemo!)
- maaghevel: ileus (braken, elektrolyten)
- naadlekkage darmen (peritonitis beeld, ziek, koorts, pijn)
- wondinfectie, wonddehiscentie
- fistels (darm-vagina, darm-blaas)
- Diagnose!

Take home messages ovariumcarcinoom

- Erfelijkheid, sBRCA vs gBRCA, screening, preventie
- 75% diagnose hoog stadium
- silent lady killer: 70% recidief < 5 jaar
- Diagnostiek ovariumcyste

- **laag stadium**: stagering (detectie occulte tumor)

- **hoog stadium**: combinatie chirurgie + i.v. chemotherapie
    - debulking: primair of interval-streven naar complete debulking
    - chemotherapie: standaard i.v. 6 kuren (q 3 weken of wekelijks)
    - optie intra-peritoneaal chemotherapie (HIPEC)

Websites en info

- Kanker.nl
- Olijf.nl patientenvereniging
- Inloophuizen
- Richtlijnen: NVOG richtlijnen database
  https://richtlijnendatabase.nl/
- Landelijke studies gyn oncologie: DGOG
  https://www.nvog.nl/organisatie/pijler-oncologie/dgog/