



Leids Universitair
Medisch Centrum

Ovariumcarcinoom: van proeflaparotomie via stadiering naar debulking en HIPEC...

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LUMC



Komt een vrouw bij de dokter...

Aspecifieke klachten (via internist)

- Malaise en anorexia
- Vage gastro-intestinale klachten
- Dikker wordende buik
- Passage stoornissen darmen
- Mictieklachten
- Gewichtsverlies
- ...



Lichamelijk onderzoek:

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

- Transvaginale echografie:
 - afwijkend ovarium, vrij vocht

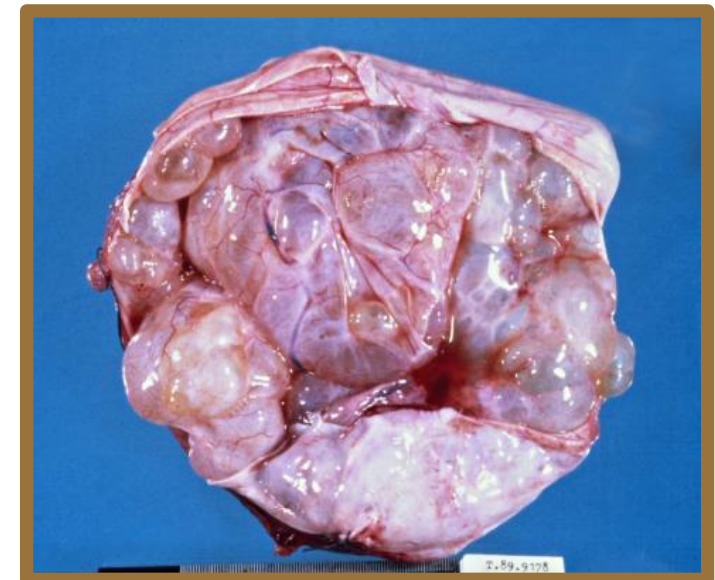
- Bloedonderzoek
 - CA125, CEA, hematologie, nierfunctie

Ovariumtumoren

Benigne tumoren

Borderline tumoren van het ovarium

Maligne tumoren



Transvaginale echo: Risk of Malignancy Index

Index = CA 125 (U/ml) x menopauze status x echoscore

Menopauze status:

- Premenopauze = 1
- Postmenopauze = 3

Echoscore:

0 indien geen van onderstaande

1 indien een van onderstaande

3 indien twee of meer van onderstaande kenmerken:

- Multiloculair
- Solide partijen
- Bilateraal
- Intra abdominale metastasen

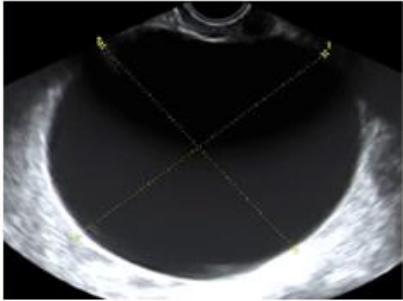
Bij een cutoff van 200:

Sensitiviteit 71-97%

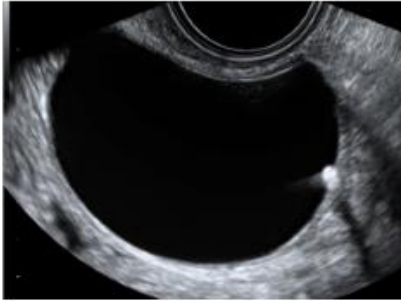
Specificiteit 85-92%

IOTA simple rules

B1 Unilocular



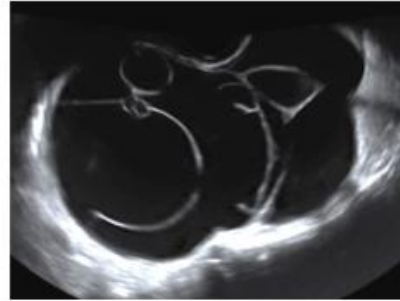
B2 Presence of solid components with largest diameter < 7 mm



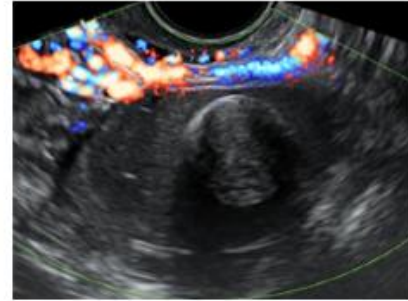
B3 Presence of acoustic shadows



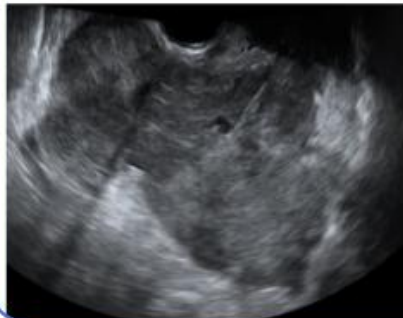
B4 Smooth multilocular tumor with largest diameter < 100 mm



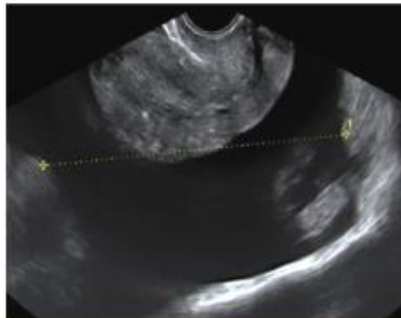
B5 No blood flow (color score 1)



M1 Irregular solid tumor



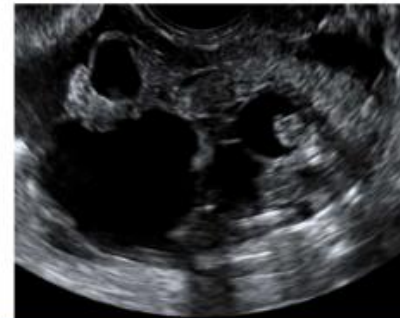
M2 Presence of ascites



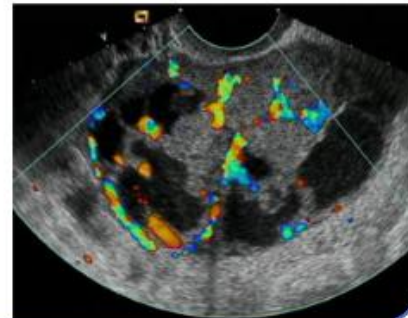
M3 At least 4 papillary structures



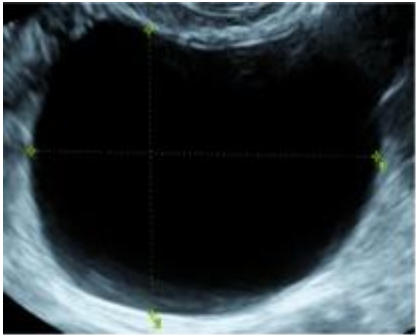
M4 Irregular multilocular-solid tumor with largest diameter ≥ 100 mm



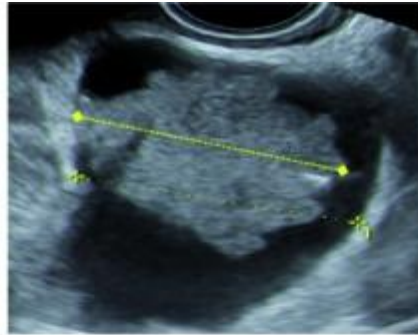
M5 Very strong blood flow (color score 4)



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)

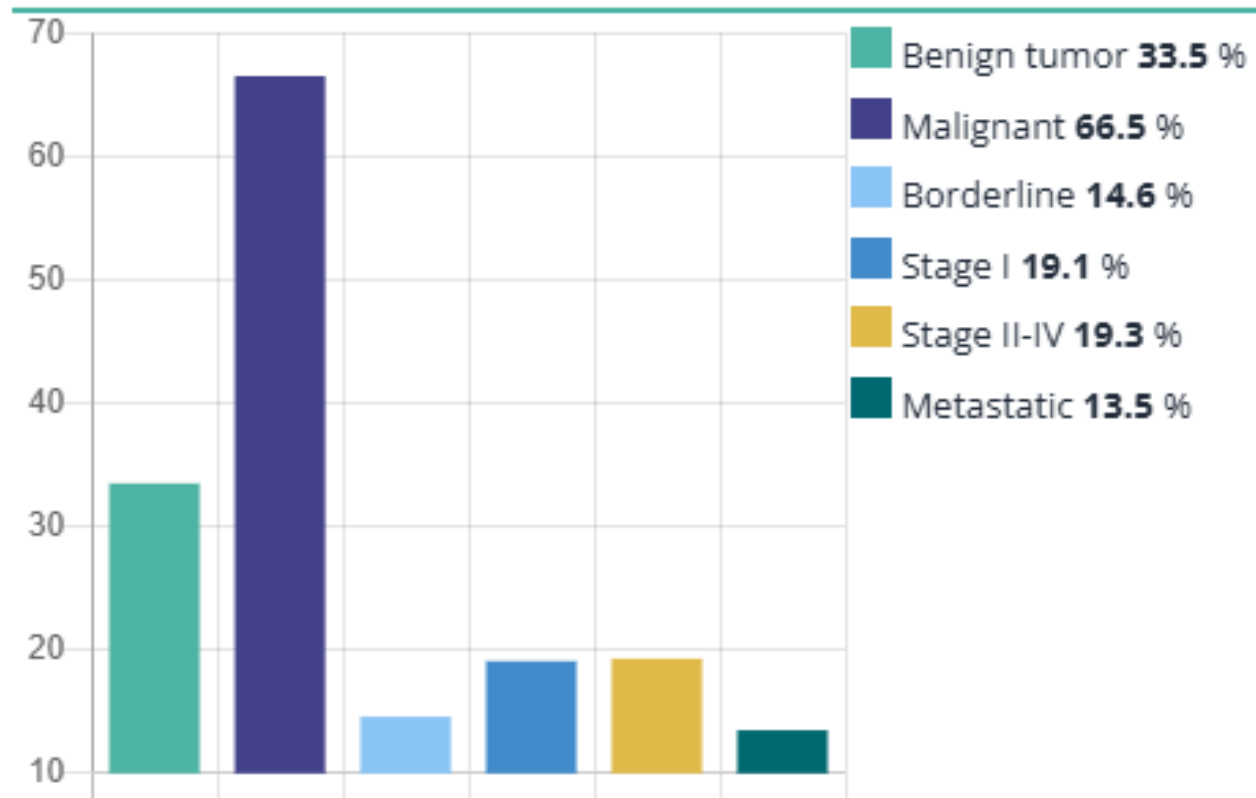


(5) acoustic shadows (yes vs no)



(6) ascites (yes vs no)

IOTA adnex model



Ovariumcarcinoom: CT scan

CT Thorax-abdomen

Waar let je op?

RIP

Omental cake

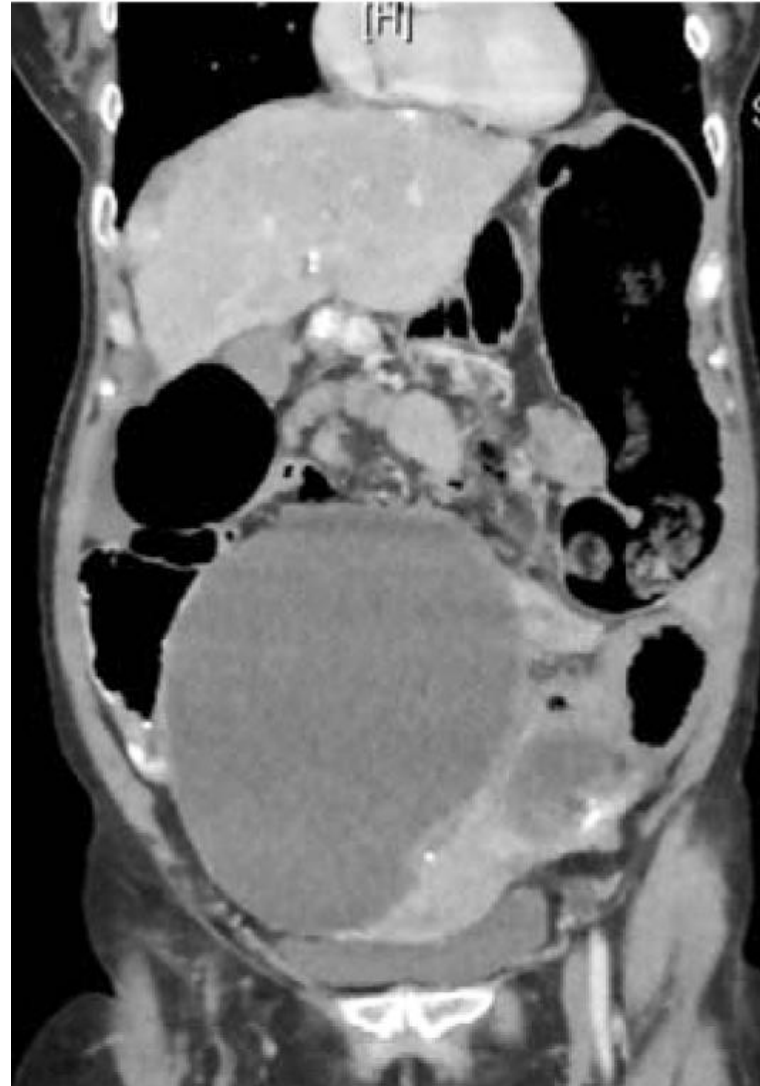
Ascites

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

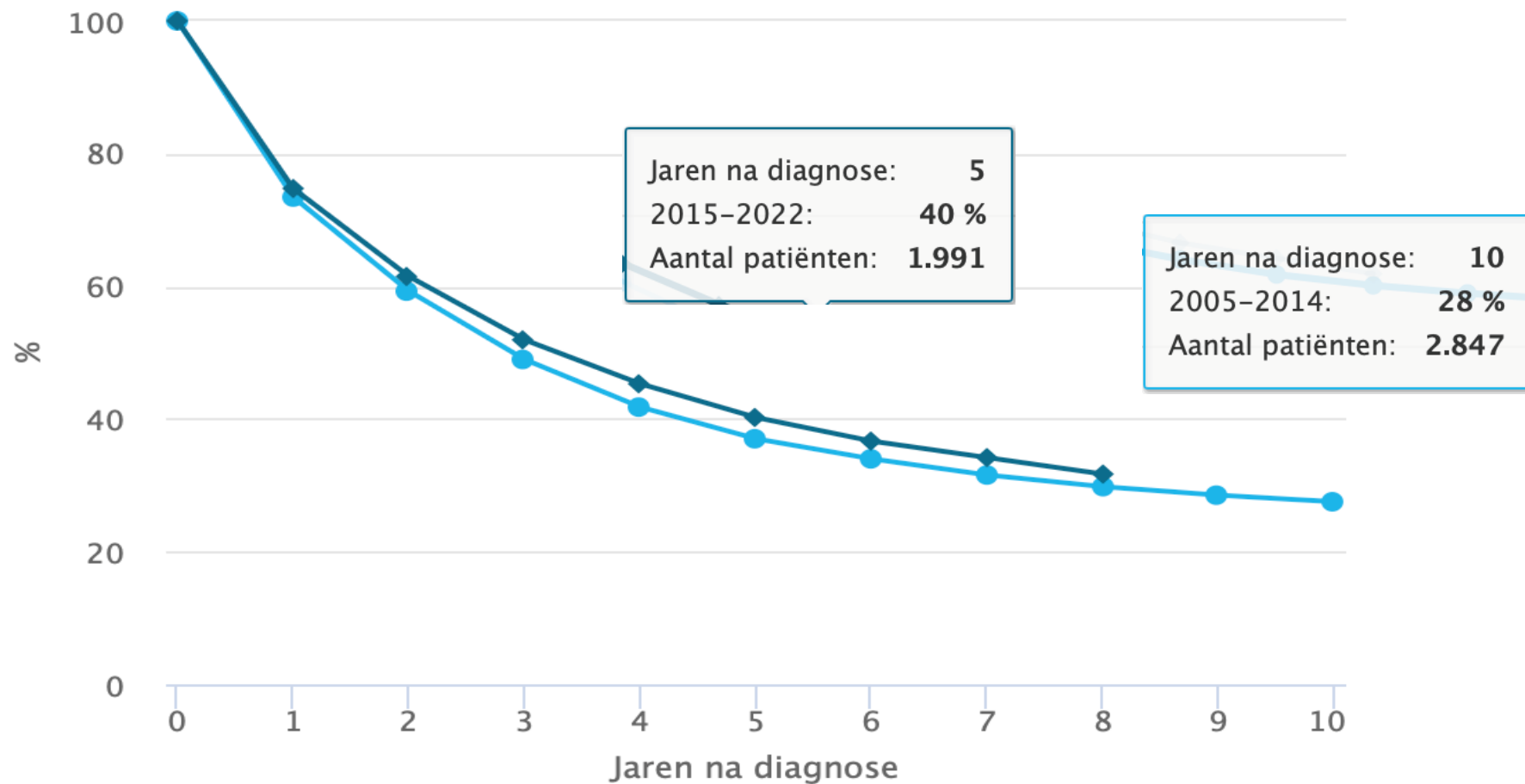
(Op basis van RMI / IOTA hoog risico: laparoscopische adnexextirpatie 'zonder spill')

→ Durante OK verder beleid bepalen

Ovariumcarcinoom → 'Silent lady killer'

- 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)

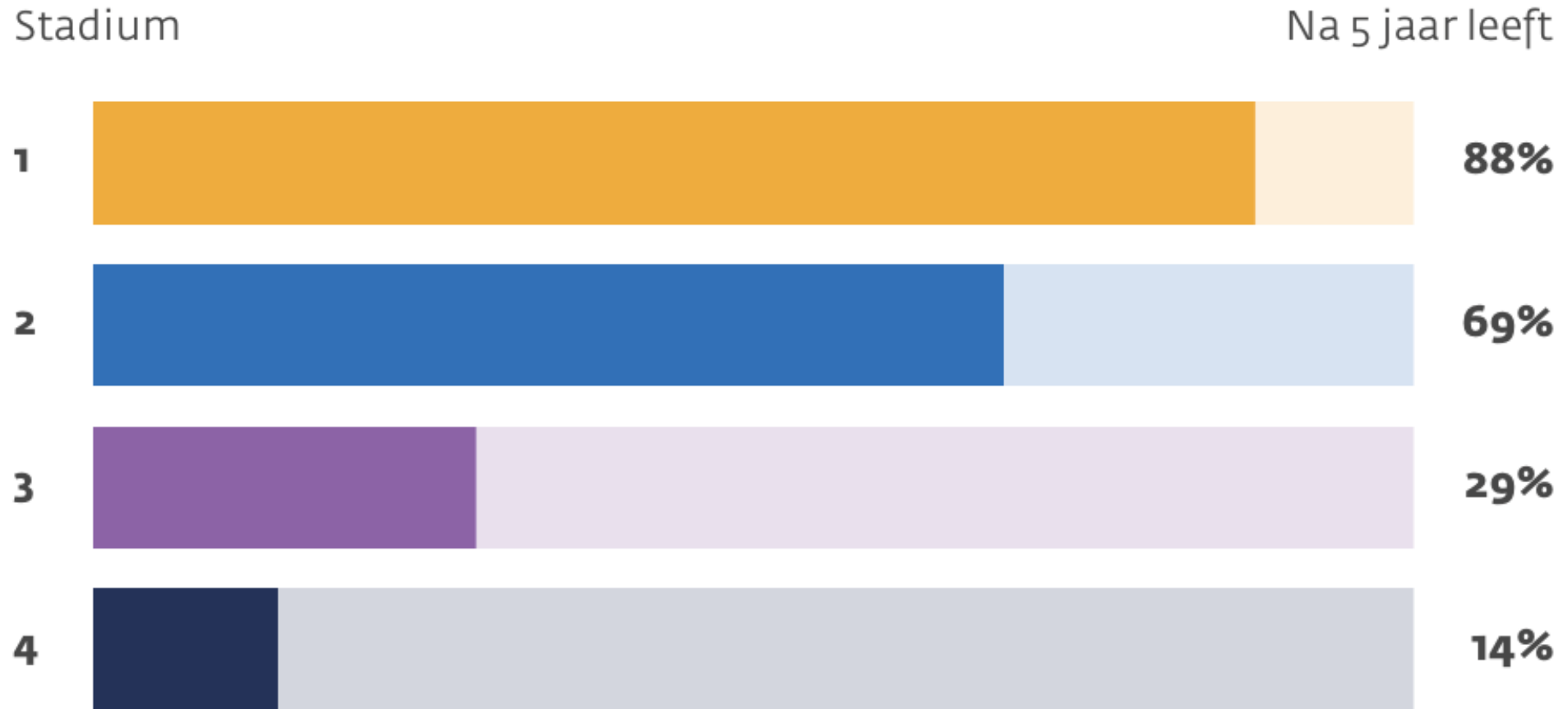


Jaar van diagnose

● 2005-2014 ◆ 2015-2022

NKR cijfers over kanker

5-jaars overleving ovariumcarcinoom per stadium



NKR cijfers over kanker



Reproductieve factoren:

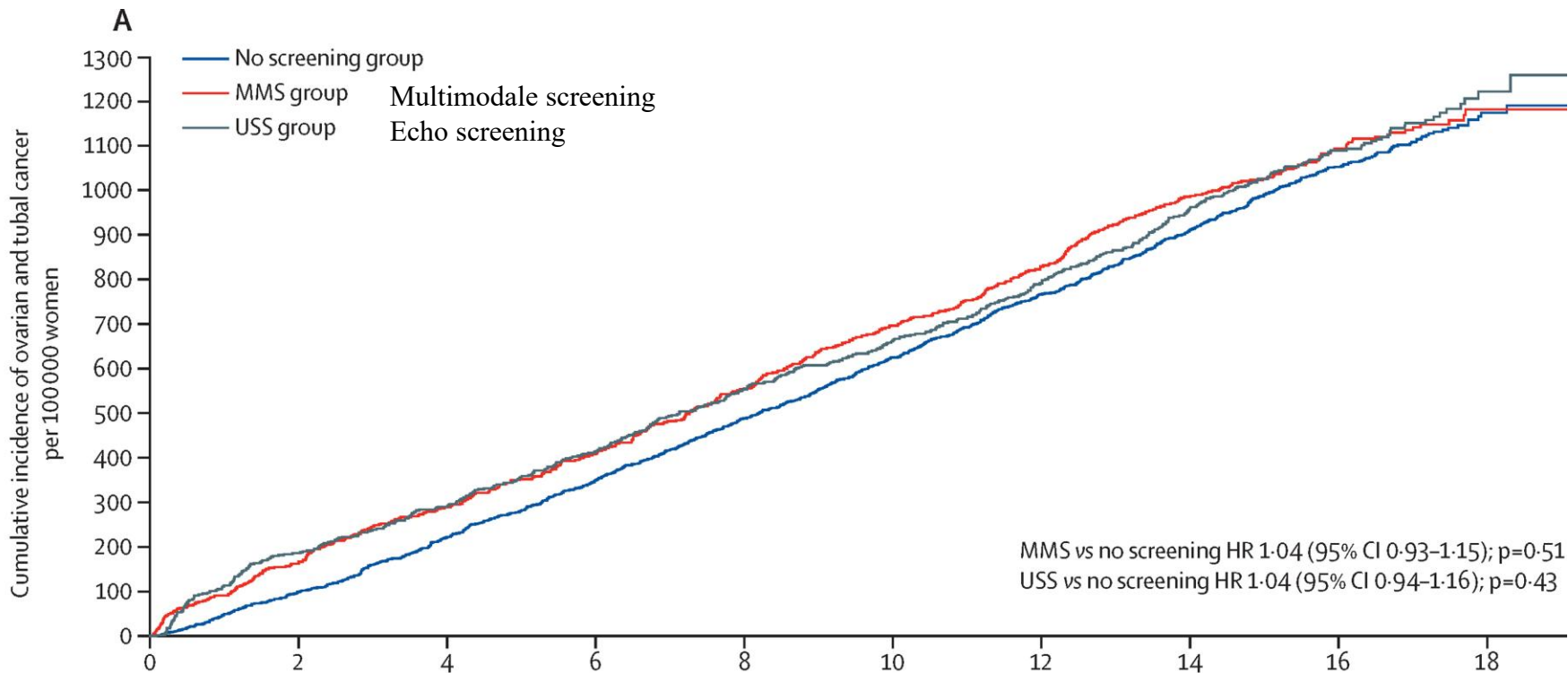
- Geen of een laag aantal kinderen verhoogt de kans op een ovariumcarcinoom
- De kans op een ovariumcarcinoom wordt met 30 tot 50% verlaagd door het gebruik van > 3 jaar ovulatieremmers of meerdere zwangerschappen.

Genetische factoren (10% - 15 % vd ovariumcarcinomen)



- 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

Screening?



Menon et al 2021

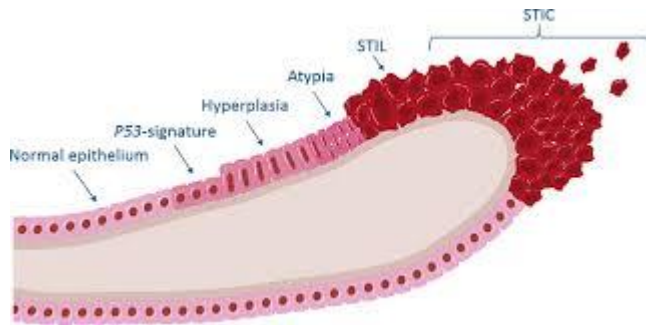
Number at risk
(number censored)

No screening	101297 (99)	100339 (122)	98911 (126)	97202 (135)	95311 (129)	92414 (129)	88732 (125)	85151 (110)	56370 (39)	9992
MMS	50618 (82)	50046 (63)	49277 (58)	48322 (70)	47219 (67)	45752 (60)	43994 (68)	42257 (39)	27837 (15)	4947
USS	50614 (93)	49199 (51)	48295 (59)	47350 (66)	46241 (49)	44858 (58)	43238 (71)	41534 (49)	27405 (20)	4912

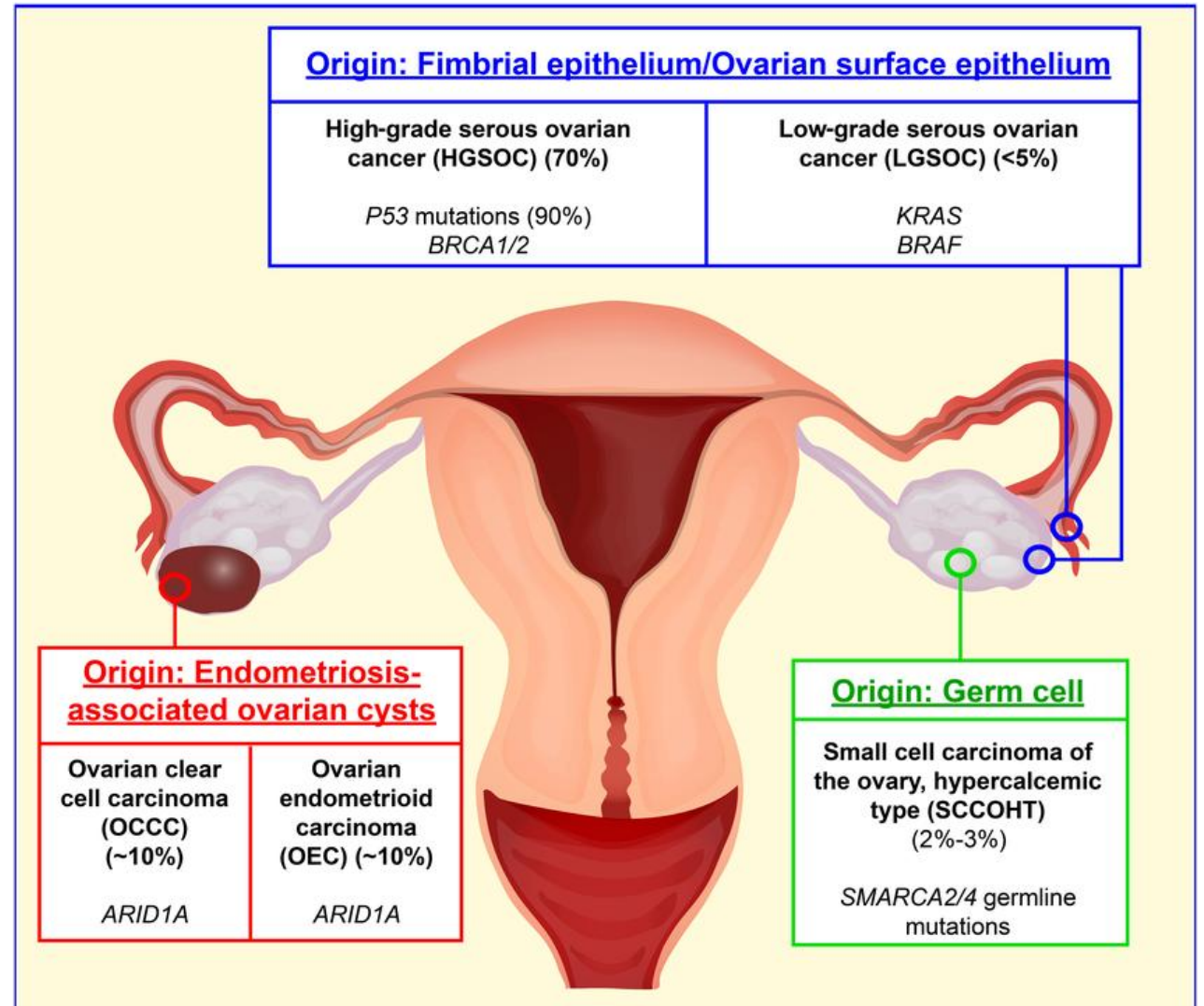
→ Geen verschil in incidentie OC

→ Geen verschil in aantal patiënten wat overlijdt aan OC

Preventie?



TUBA-WISP II
study



Laag stadium ovariumcarcinoom stageren

Doel stageren:

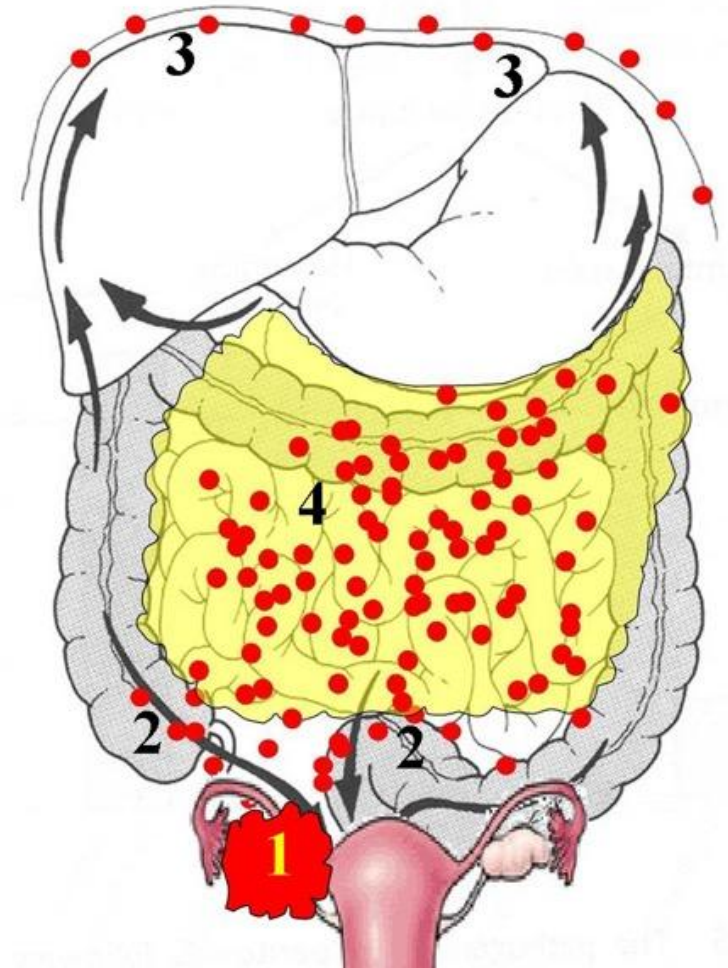
- Detectie van occult hoger stadium
- Daarmee indicatie voor chemotherapie
- Kans upstaging stadium = 12-19 %
- Kans positieve klieren = 4-8%

Methode stageren:

- Laparoscopisch of laparotomie

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



Ovariumcarcinoom stadiëring bij klinisch laag stadium

Spoelvocht of ascites

Uterus + adnexextirpatie

Biopten peritoneum

Omentectomie

Darminspectie (meckelen)

Para-aortaal en pelviene lymfeklieren sampling



Maar, heel vaak hoog stadium ovariumcarcinoom...

Omental cake

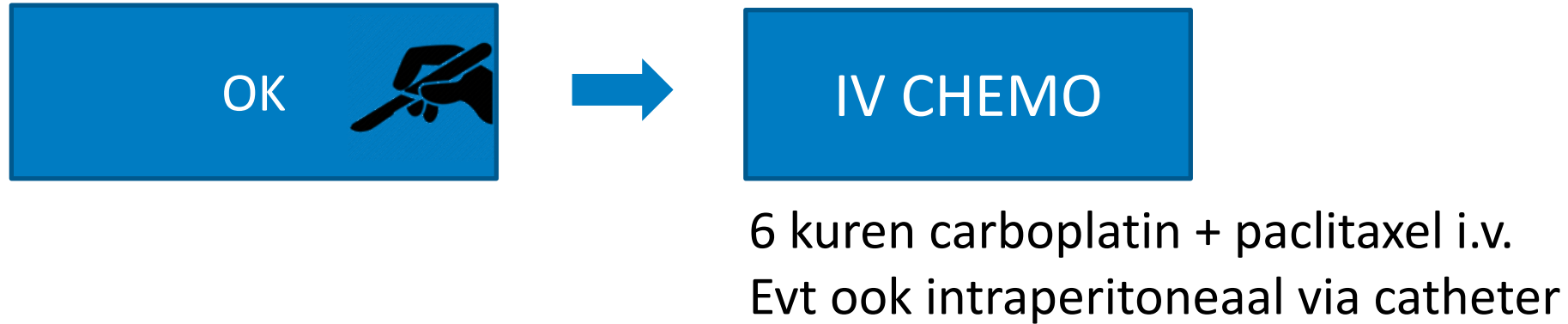
Hoog stadium ovariumcarcinoom

Omental cake

Mesenterium met
tumordeposities

Hoog stadium ovariumcarcinoom; behandelstrategie

Primaire debulking

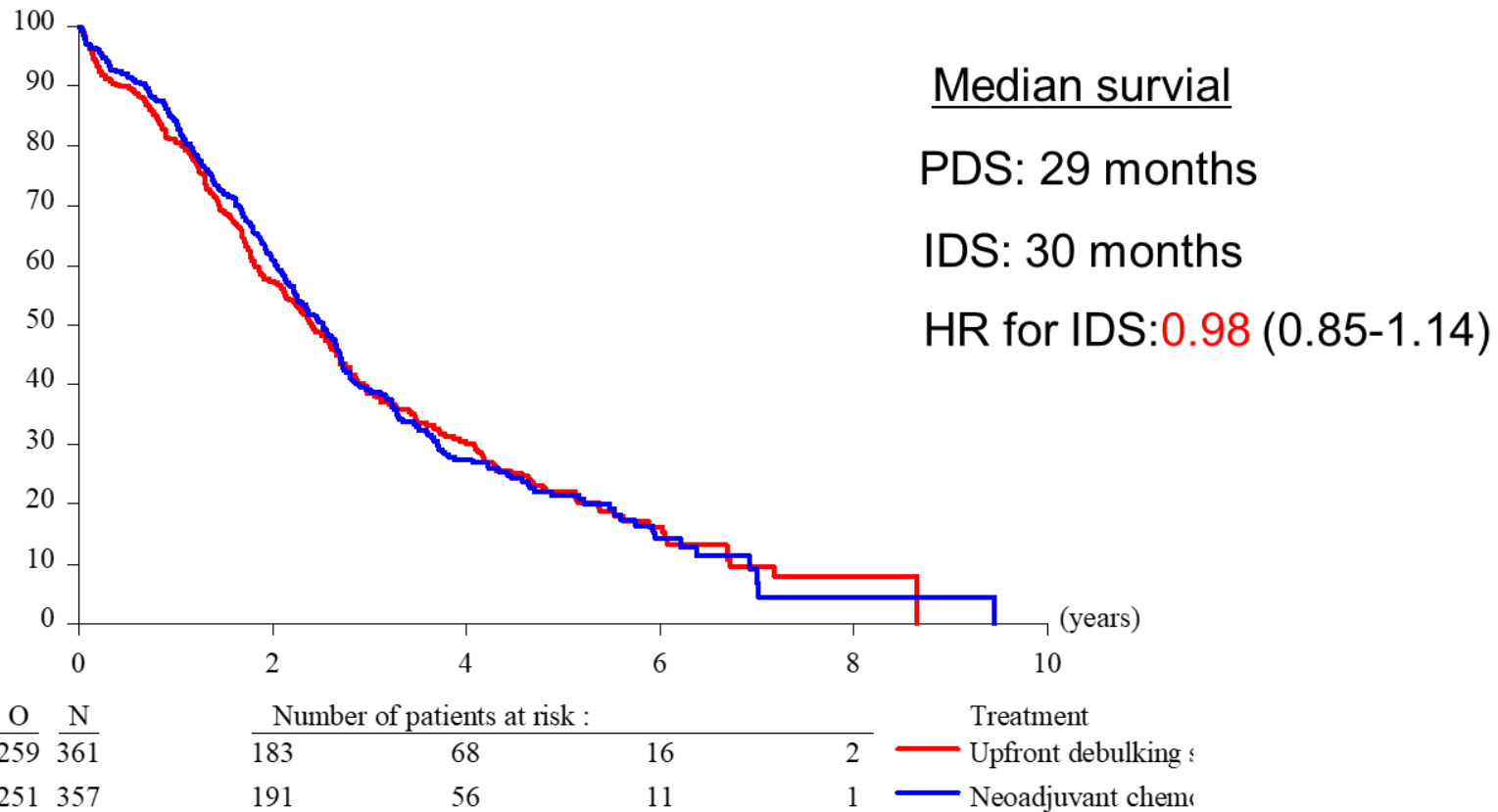


NACT gevolgd door intervaldebulking



Primaire debulking of interval debulking?

Overall survival



Vergote, NEJM 2010;363:943-53

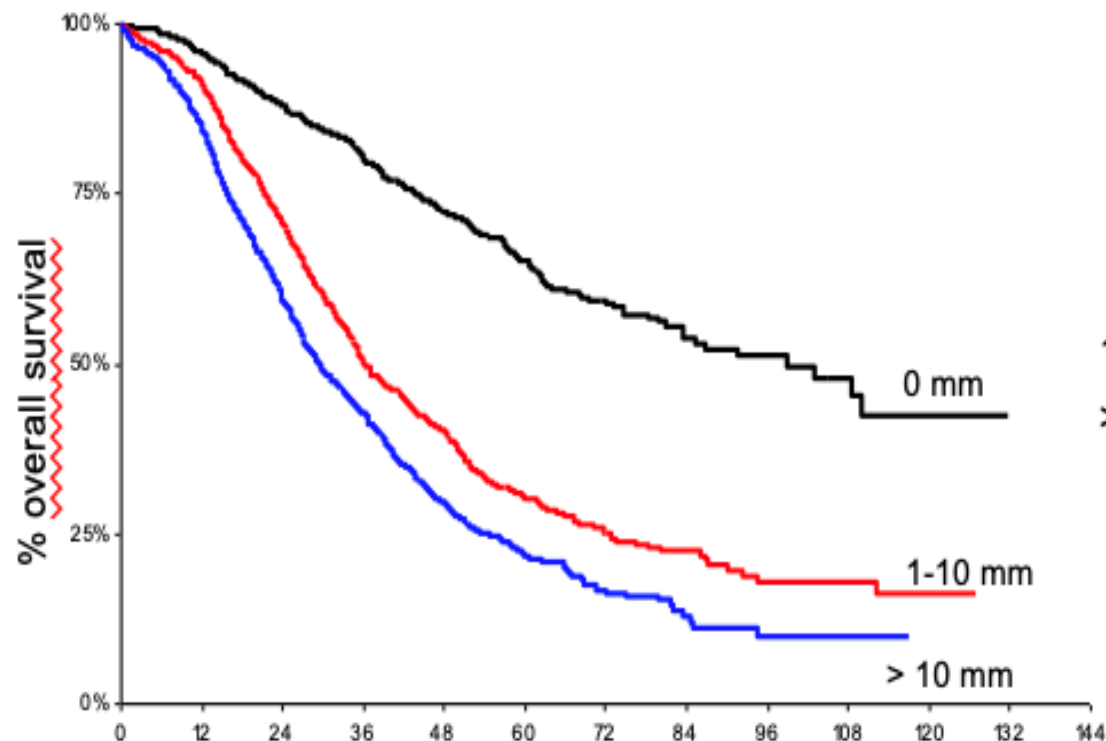
Doel: complete debulking (geen zichtbare tumorrest)
(optimaal <1cm, incompleet >1cm)

Uterus- en adnexextirpatie,
omentum, metastasen

Indien nodig voor complete resectie:
darmresectie met anastomose/stoma
Evt miltextirpatie
Evt peritoneum, strippen diafragma

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)

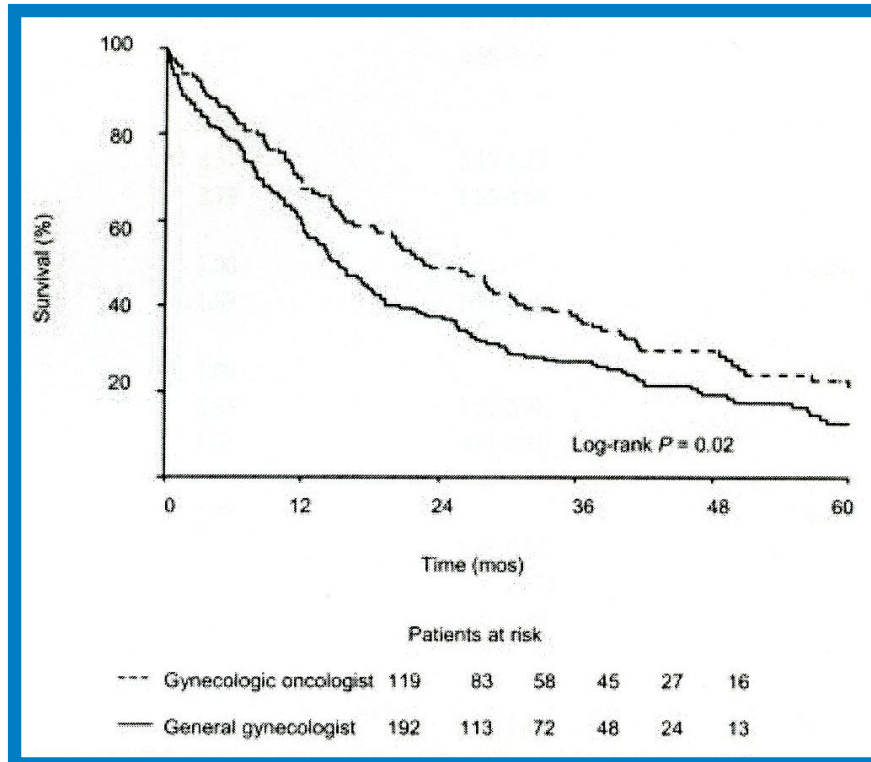
1-10 mm vs. 0 mm: 2.70 (2.37; 3.07)

>10 mm vs. 1-10 mm: 1.34 (1.21; 1.49)

log-rank: $p < 0.0001$

Stadium IIB en hoger

De operateur is belangrijk!



GO verwijderen vaker alle macroscopische tumor (24% vs. 12%; $P = 0.02$)

GG lieten vaker tumor achter < 2 cm (62% vs 45%, $P = 0.05$)

In de GO groep was 5-jaars overleving 32% versus 11% ($P < 0.001$)

Engelen MJA. Cancer 2006;106:589-98

Het grote dilemma: 'NACT of PDS'

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)	<i>P</i>
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)		

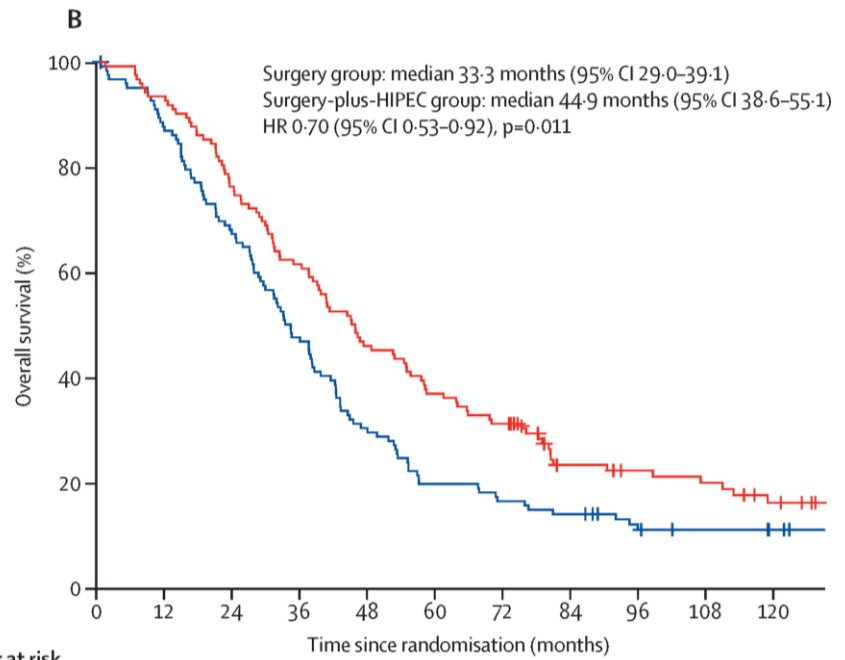
Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; RR, relative risk.

* > 1 cm of residual disease after primary cytoreductive surgery.

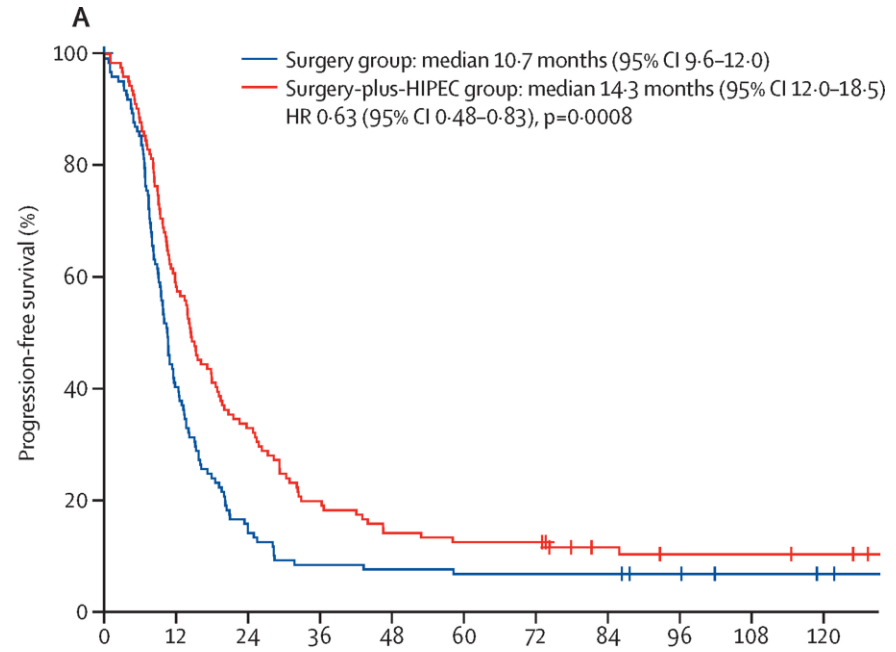
† > 0 cm of residual disease after primary cytoreductive surgery.

Steeds vaker NACT en IDB....





	0	12	24	36	48	60	72	84	96	108	120
Number at risk											
(number censored)											
Surgery group	123	106	83	57	36	24	20	17	10	9	7
	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(5)	(6)	(8)
Surgery-plus-HIPEC group	122	113	91	74	56	45	38	22	19	17	11
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(8)	(10)	(10)	(13)



	0	12	24	36	48	60	72	84	96	108	120
Number at risk											
(number censored)											
Surgery group	123	49	17	10	9	8	8	8	5	4	3
	(0)	(1)	(1)	(1)	(1)	(1)	(1)	(1)	(4)	(5)	(6)
Surgery-plus-HIPEC group	122	70	40	24	17	15	15	9	7	7	6
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(5)	(6)	(6)	(7)

→ 3.5 vs 12.0 mnd voordeel van HIPEC PFS vs OS
 → Vergelijkbare toxiciteit

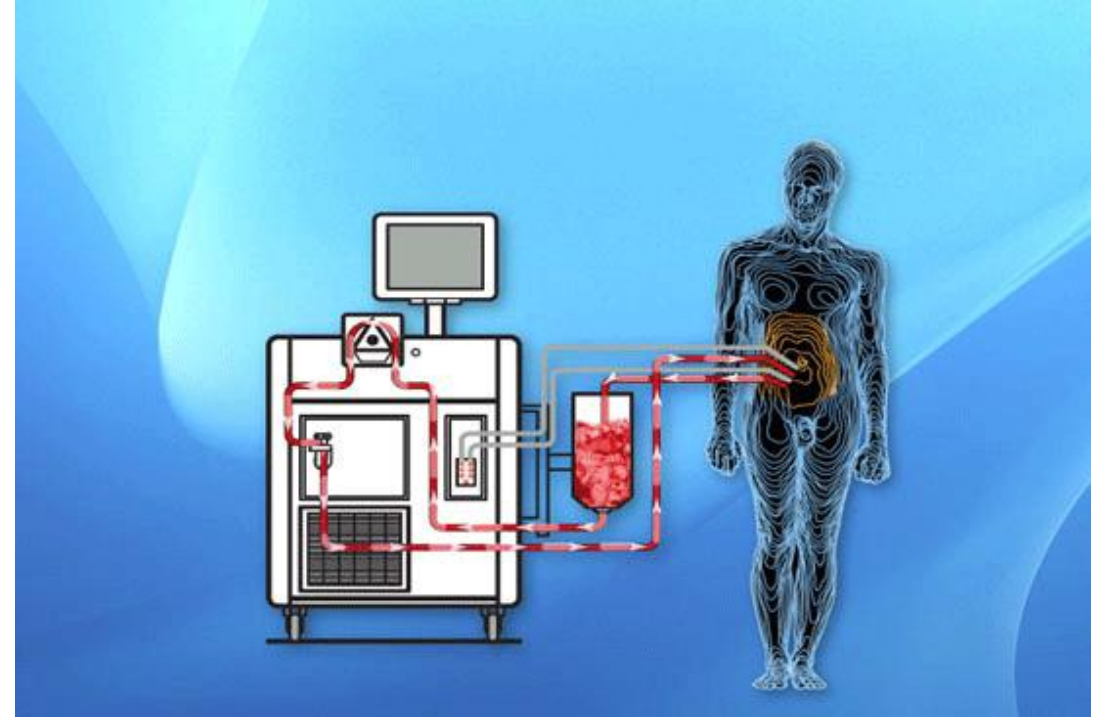
Hypertherme IntraPeritoneale Chemotherapie -HIPEC

Tijdens intervaldebulking

Continue circulatie Cisplatinum 100 mg/m²

40 - 41° C

90 minuten perfusie



Maar...

Randomisatie voor operatie

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

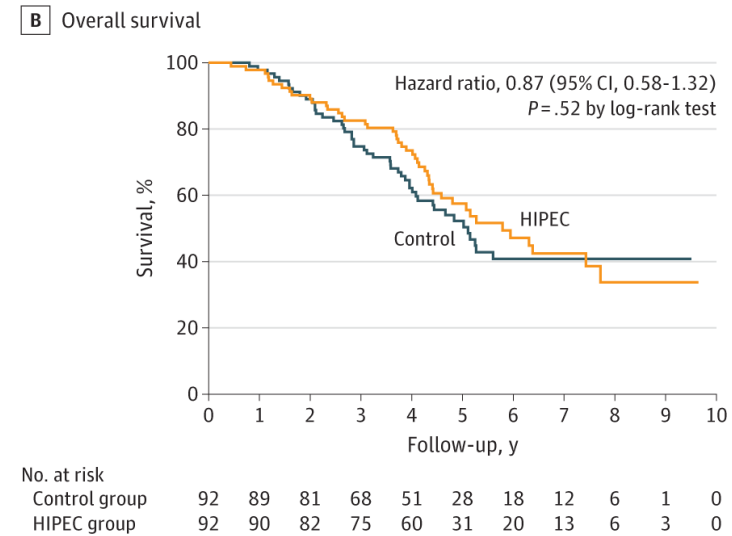
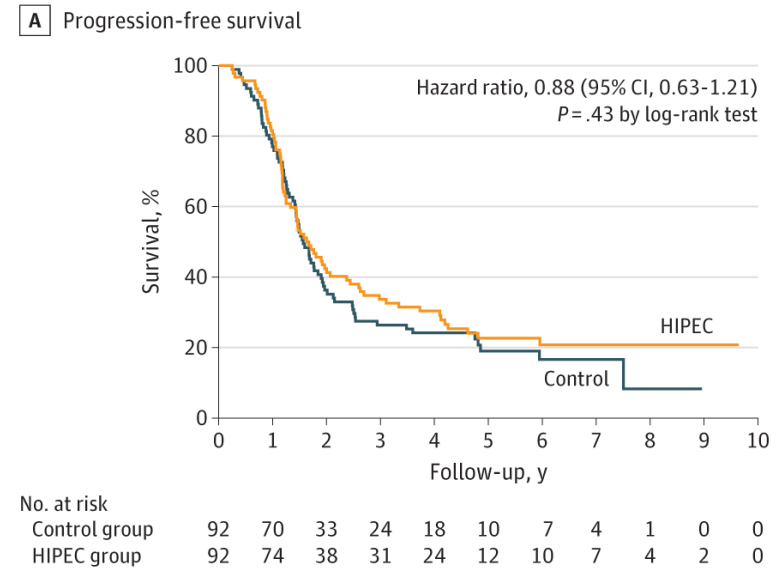
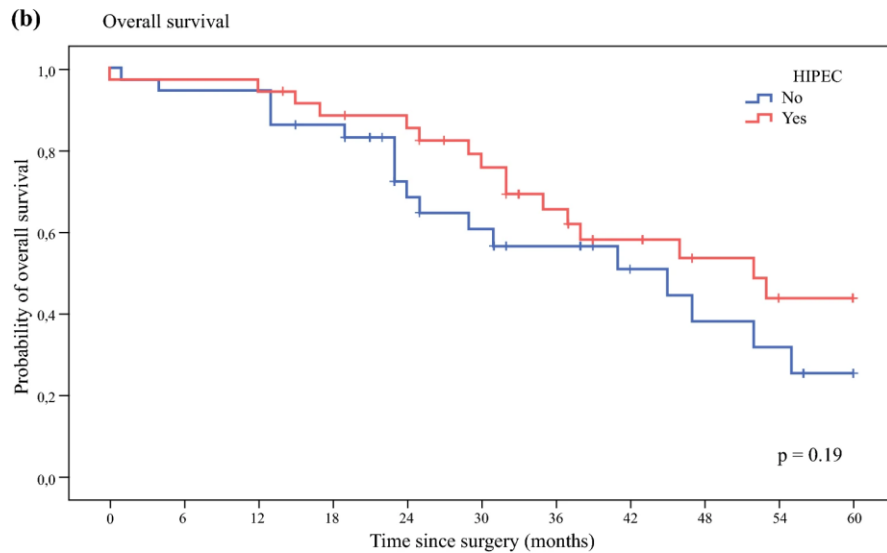
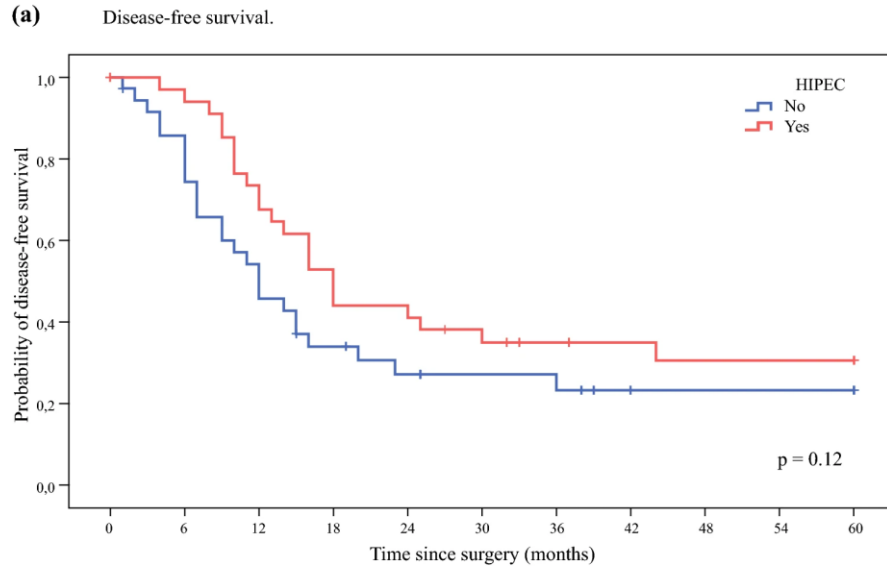
'maar' 80% R0 na operatie, snijtijd verdubbeld in HIPEC groep

3.5 vs 12.0 mnd voordeel van HIPEC PFS vs OS

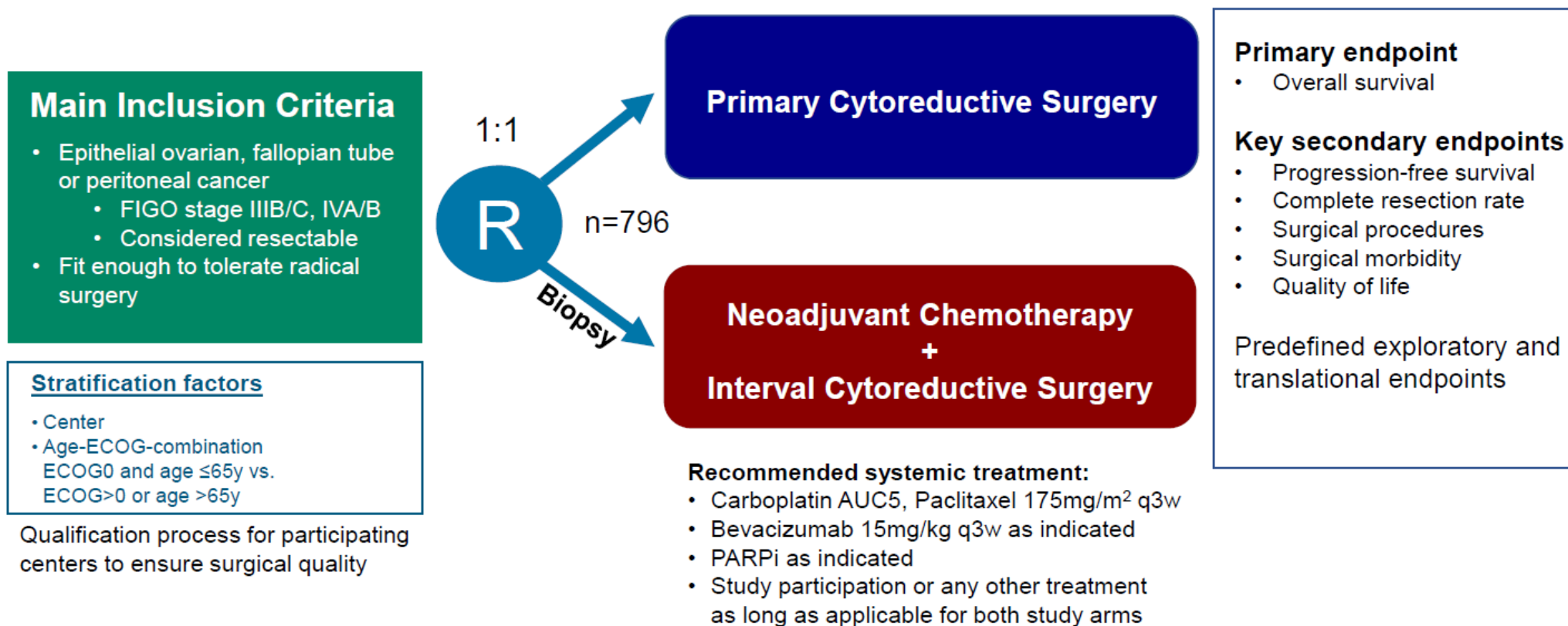
Vergelijkbare toxiciteit

Heel veel studies zonder voordeel van HIPEC

Maar...



TRUST Study Design



TRUST Results: Surgical Outcome

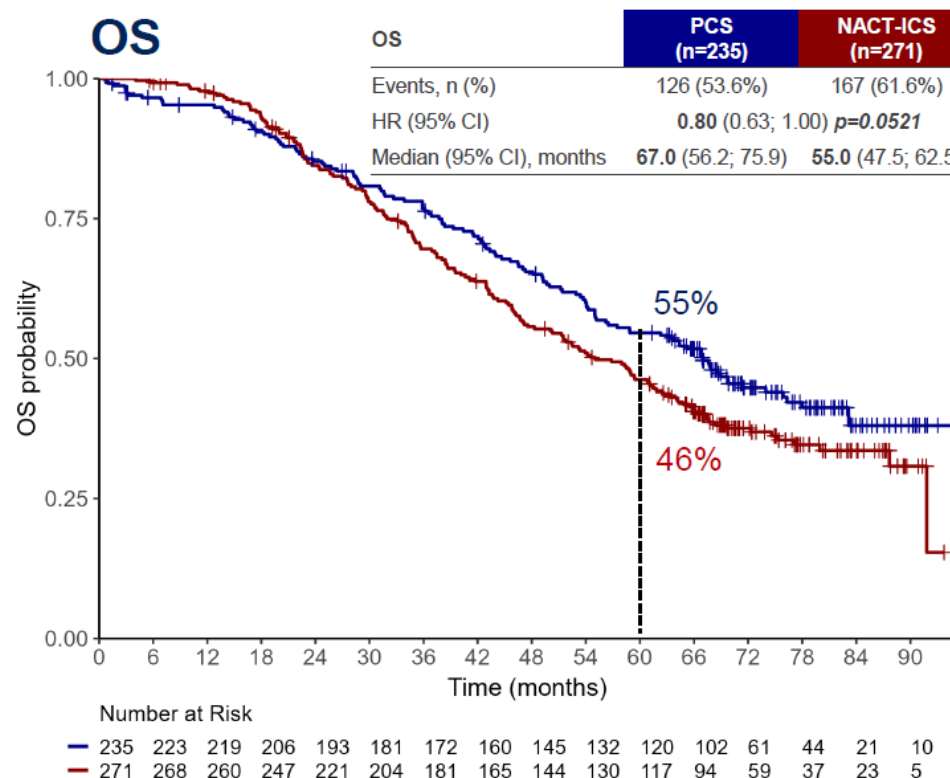
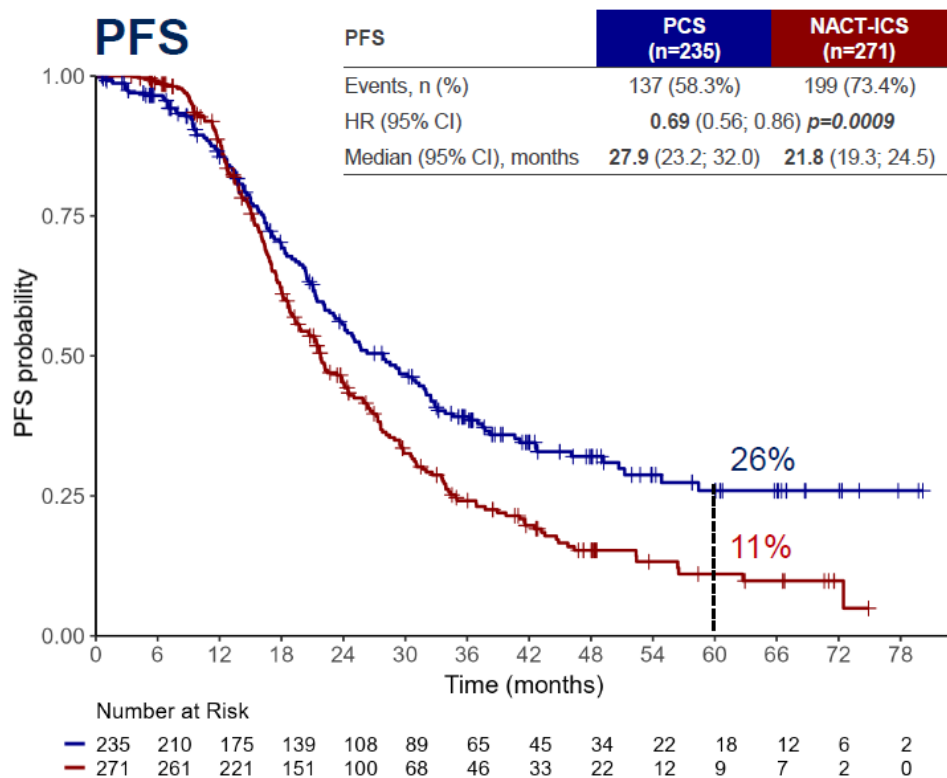


	PCS (n=345)	NACT-ICS (n=343)	Total (n=688)
Residual disease, n (%)			
complete gross resection	235 (68%)	271 (79%)	506 (74%)
macroscopic residual disease	99 (29%)	49 (14%)	148 (22%)
0.1-0.5 cm	39 (11%)	29 (8.5%)	68 (9.9%)
0.6-1 cm	25 (7.3%)	7 (2.0%)	32 (4.7%)
> 1 cm	35 (10%)	13 (3.8%)	48 (7.0%)
not operated / not reported	11 (3.2%)	23 (6.7%)	34 (4.9%)

**Documented complete resections
in operated patients, n (%)**

235/334 (70%)	271/320 (85%)	506/654 (77%)
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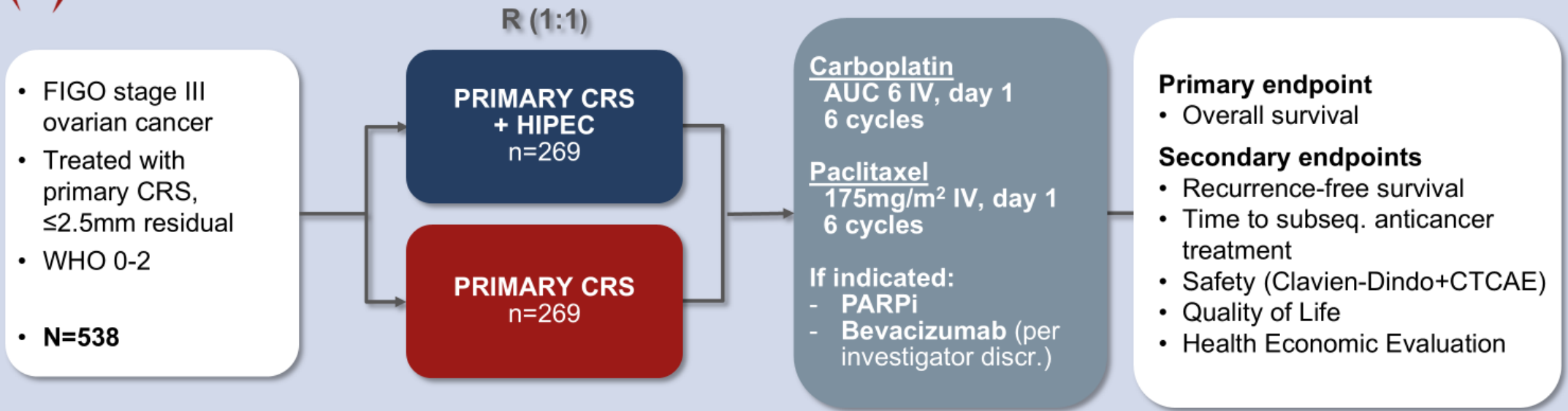
TRUST Results: Prespecified Exploratory Subgroup Analysis **Complete Gross Resection in All FIGO Stages**





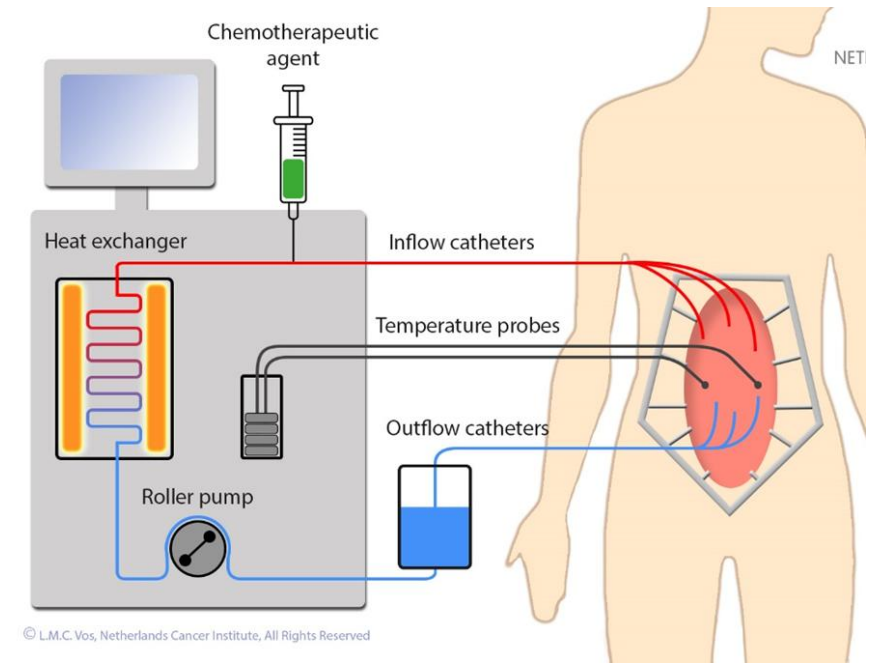
OVHIPEC-2

OVHIPEC-2 is registered at ClinicalTrials.gov (NCT03772028)
Willemien van Driel (w.v.driel@nki.nl)



- Randomization during surgery, **after** CRS
- 5 years follow-up

Accrual complete



Take home messages ovariumcarcinoom

- Erfelijkheid, sBRCA vs gBRCA, screening, preventie
- 75% diagnose hoog stadium
- Silent lady killer

- **Laag stadium:** staging (detectie occulte tumor)

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

