VIII CONGRESSO INTERNACIONAL DE

GINECOLOGIA ONCOLÓGICA

3 E 4 DE AGOSTO | 2018

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Tratamento sistêmico pós-operatório do câncer precoce de ovário - Favoreço de rotina

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Declaração de conflito de interesse

Resolução CFM nº 1595/2000, 18/05/2000
RDC ANVISA nº 102, 30/11/2000

Sem conflitos de interesse

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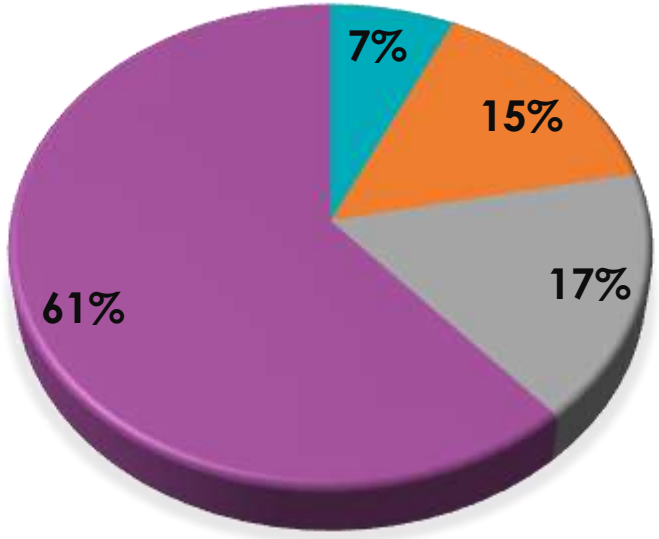
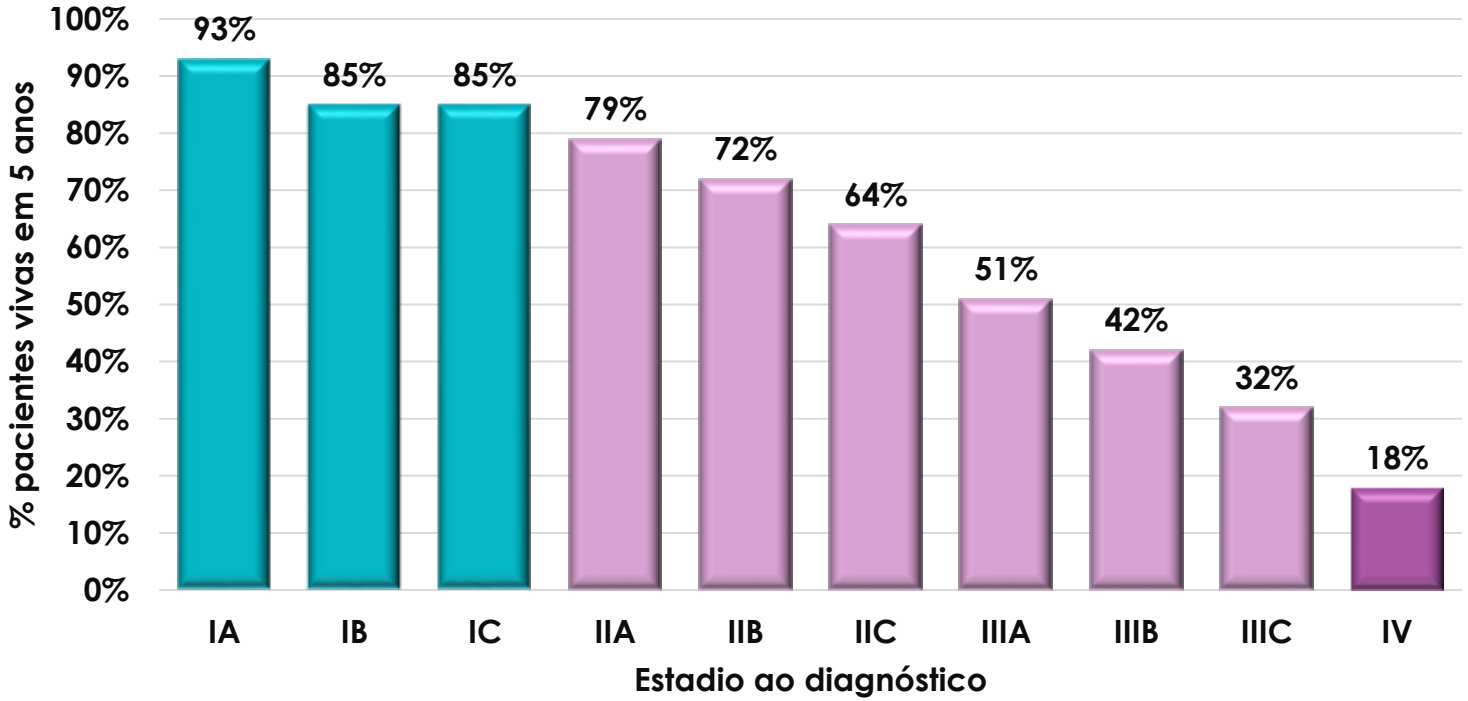
Estadio e prognóstico

Estadio ao diagnostico (% pacientes)



Sobrevida em 5 anos carcinoma ovário & estadio



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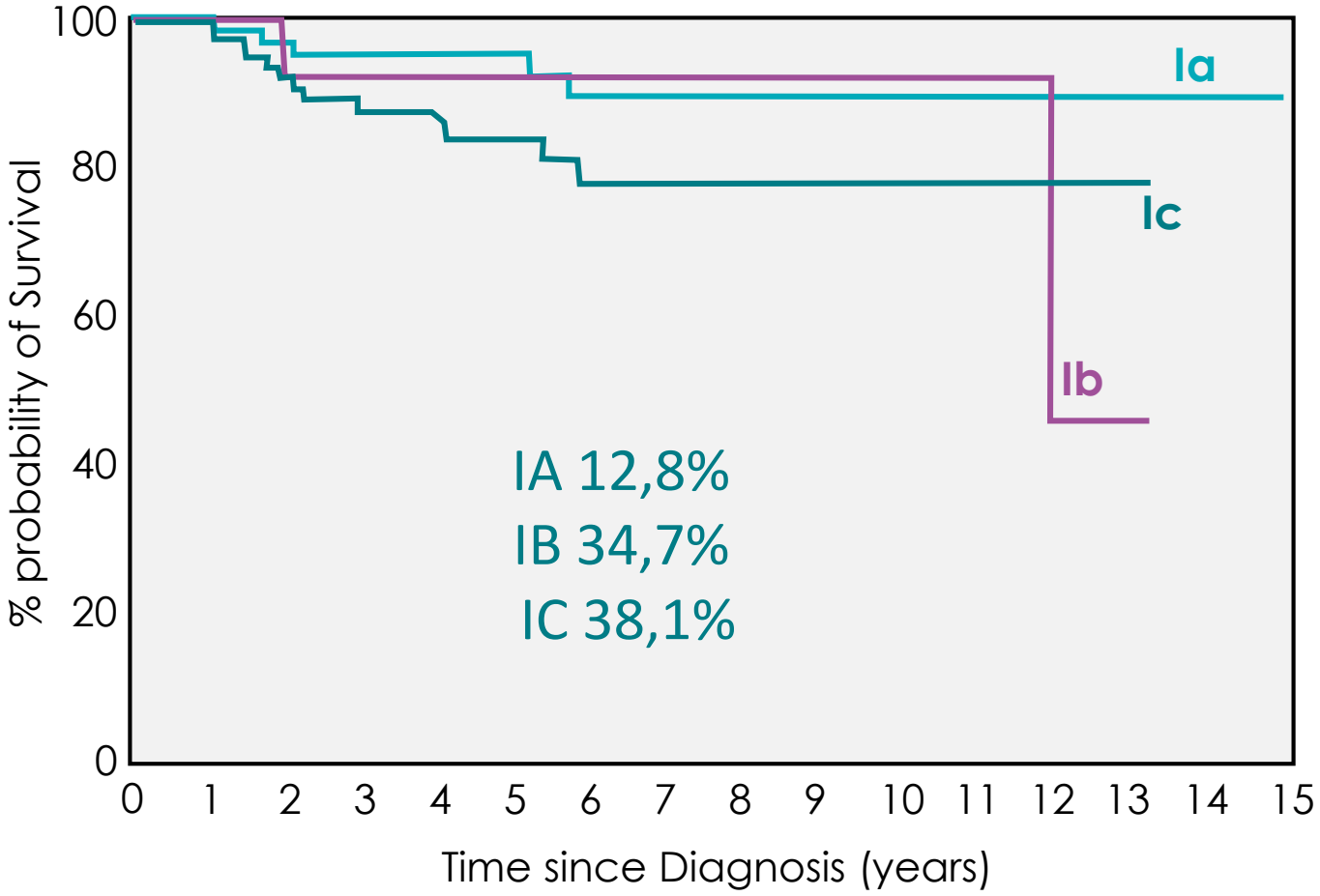

O risco de recaída não é insignificante

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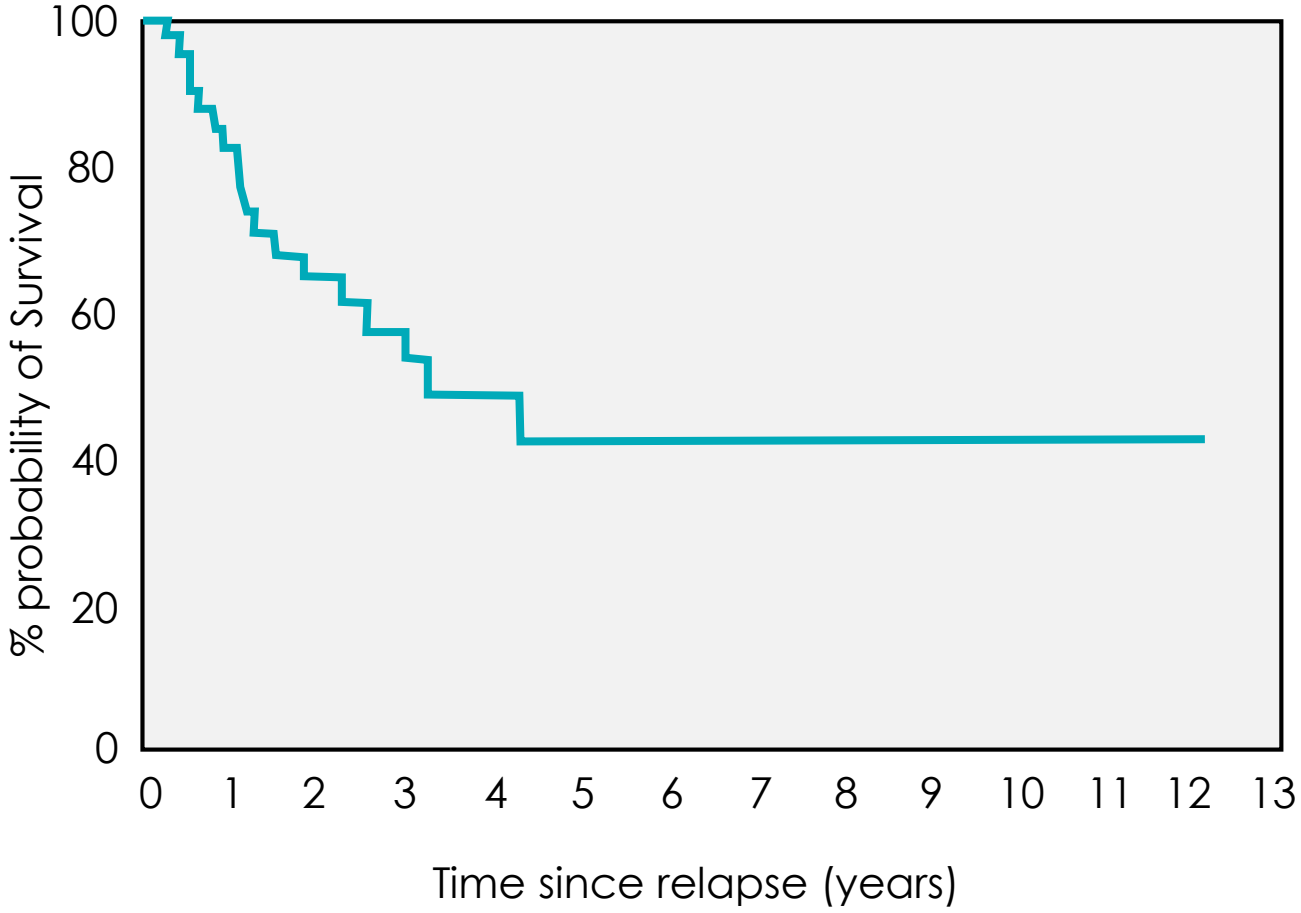
Ahmed FY, J Clin Oncol. 1996;14(11):2968.

Sobrevida após recaída



Ahmed FY, J Clin Oncol. 1996;14(11):2968.

Quimioterapia adjuvante

Quimioterapia adjuvante

↓

Erradicação precoce de micrometástase

Uma doença, várias questões...

- Quem tratar?

Uma doença, várias questões...

- Quem tratar?
- Qual esquema de quimioterapia?

Uma doença, várias questões...

- Quem tratar?
- Qual esquema de quimioterapia?
- Quantos ciclos?

Uma doença, várias questões...

- Quem tratar?
- Qual esquema de quimioterapia?
- Quantos ciclos?
- Seroso de alto grau x outras histologias – abordado em outra aula

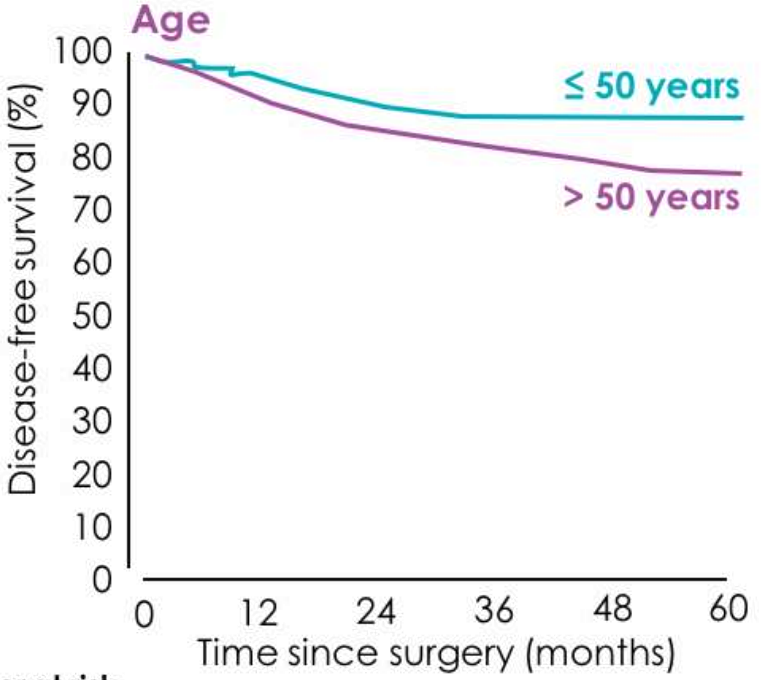
Uma doença, várias questões...

- **Quem tratar ?**
- Qual esquema de quimioterapia?
- Quantos ciclos?

Fatores prognósticos na doença inicial

Fatores prognósticos independentes:

- Idade > 50 ou 60 anos



Number at risk

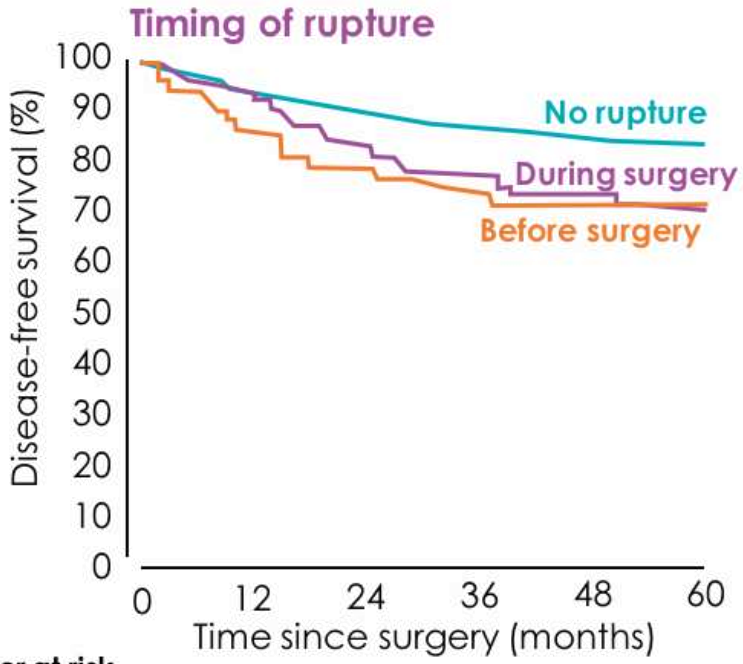
≤ 50 years	470	374	347	322	287	247
> 50 years	1070	789	702	618	513	408

Chan JK Cancer. 2008 May 15;112(10):2202-10

Fatores prognósticos na doença inicial

Fatores prognósticos independentes:

- Idade > 50 ou 60 anos
- Ruptura de capsula espontânea ou cirúrgica



Number at risk

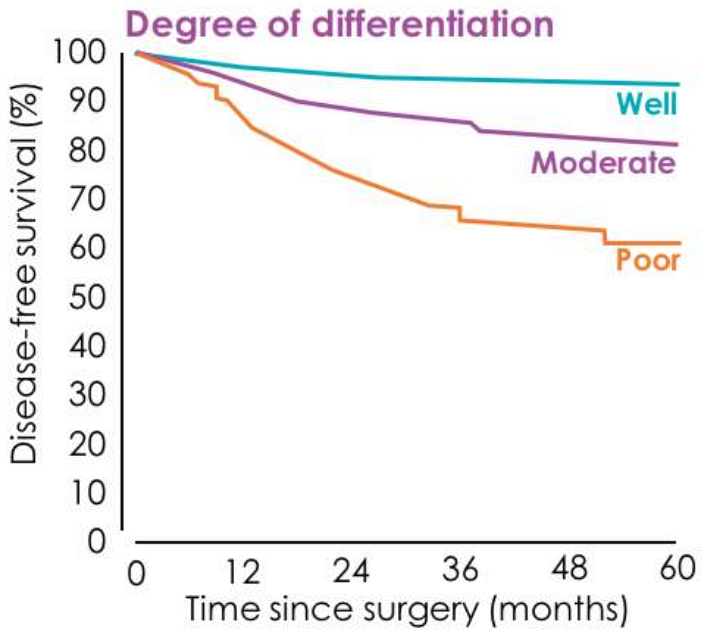
No rupture	859	758	692	618	517	417
During surgery	122	109	89	66	54	35
Before surgery	89	76	69	63	56	51

Chan JK Cancer. 2008 May 15;112(10):2202-10

Fatores prognósticos na doença inicial

Fatores prognósticos independentes:

- Idade > 50 ou 60 anos
- Ruptura de capsula espontânea ou cirúrgica
- Grau histológico



Number at risk						
Well differentiated	529	491	469	427	362	302
Moderately differentiated	473	415	364	319	273	216
Poorly differentiated	347	274	223	189	153	122

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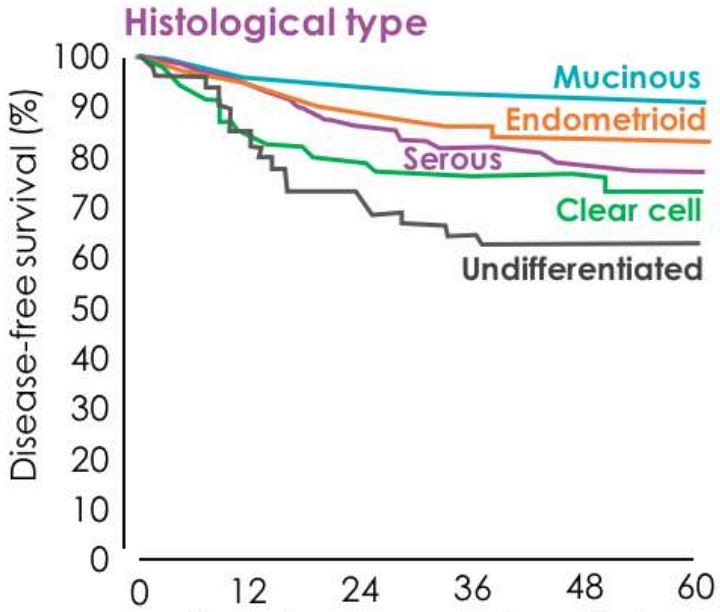
Chan JK Cancer. 2008 May 15;112(10):2202-10

Fatores prognósticos na doença inicial

Fatores prognósticos independentes:

- Idade > 50 ou 60 anos
- Ruptura de capsula espontânea ou cirúrgica
- Grau histológico
- Histologia células claras



Number at risk						
Mucinous	410	366	341	314	273	233
Endometrioid	354	314	286	250	220	185
Serous	430	377	331	295	250	195
Clear-cell	185	150	135	119	98	75
Undifferentiated	49	39	30	27	18	14

Chan JK Cancer. 2008 May 15;112(10):2202-10

Fatores prognósticos na doença inicial

Fatores prognósticos independentes:

- Idade > 50 ou 60 anos
- Ruptura de capsula espontânea ou cirúrgica
- Grau histológico
- Histologia células claras
- Estadiamento cirúrgico completo ou não

Chan JK Cancer. 2008 May 15;112(10):2202-10

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Estudos randomizados antes do ACTION/ICON1

- 16 estudos
- ≈ 2500 pacientes
- Grande variação de
  - Critérios de inclusão
  - Tratamento
  - Tipo de quimioterapia

Study ID	Recruitment period	Staging	Comparison	Randomisation	Intention to treat	5-year follow-up
Smith 1975	1969 to 1974	No	CT vs RT	Unspecified	No	Incomplete
Dembo 1979	1971 to 1975	No	RT vs RT+CT	Stratified	No	median 52 months
Hreshchyshyn 1980	1971 to 1978	No	Ct vs RT vs NA	Unspecified	No	No
Sigurdsson 1982	1975 to 1978	No	NT vs Ct, Rt vs CT or (RT + CT)	Stratified, quasi-randomised	No	Yes
Sevelda 1987	1980 to 1985	Yes complete in 60.5%	NA vs Rt vs (RT + CT)	Unspecified	No	Median 42 months
Grõnroos 1984	1976 to 1978	No	NA vs Rt and NA vs CT	Randomised by birth month (quasi-randomisation)	No	3-year follow-up
Klaassen 1988	1975 to 1984	No	CT vs RT vs IPR	Central telefone	Yes	Median 8 years
Sell 1990	1981 to 1987	Complete	RT vs (RT + CT)	Block randomisation	Yes	4 years
Young 1990	1976	Complete	Ct vs NA or IPR	Central, computer stratified	Yes	> 6 years
Young 2000 Bell 2006		Complete	3xCT vs 6xCT	Central, computerised	Yes	> 6 years
Young 2003		Complete	Ct vs IPR	central computerised	Yes	
Vergote 1992	1982 to 1988	Complete	CT vs IPR	Central, computer stratified	Yes	Median 62 months
Chiara 1994	1985 to 1989	Complete 87%	CT vs RT	Central, computerised	Yes	
Bolis 1995	1983 to 1990	Complete	CT vs NA or IPR	Central, random generated numbers	Yes	Yes
Tropé 2000	1992 to 1997	Complete	CT vs NA	Central, computerised		Median 46 months
Kojs 2001	1990 to 1996	Complete	CT vs RT	Method not explicit		Yes

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Cochrane Database Syst Rev. 2015

Estudos randomizados Fase 3

- Critérios de inclusão:
  - ACTION:
    - Estadio Ia e Ib GII ou III, Ic, IIa e carcinomas de células claras.
    - Tratamento: (4 x) regime à base de platina (ciclofosfamida + cisplatina 47%; carboplatina isolada 32%)

Estudos randomizados Fase 3

- Critérios de inclusão:
  - ACTION:
    - Estadio Ia e Ib GII ou III, Ic, IIa e carcinomas de células claras.
    - Tratamento: (4 x) regime à base de platina (ciclofosfamida + cisplatina 47%; carboplatina isolada 32%)
  - ICON 1:
    - Pacientes com indicação de QT pelo medico assistente
    - Tratamento : (6 x) CAP ou carboplatina isolada (82%)

Endpoint Primário → Sobrevida Global

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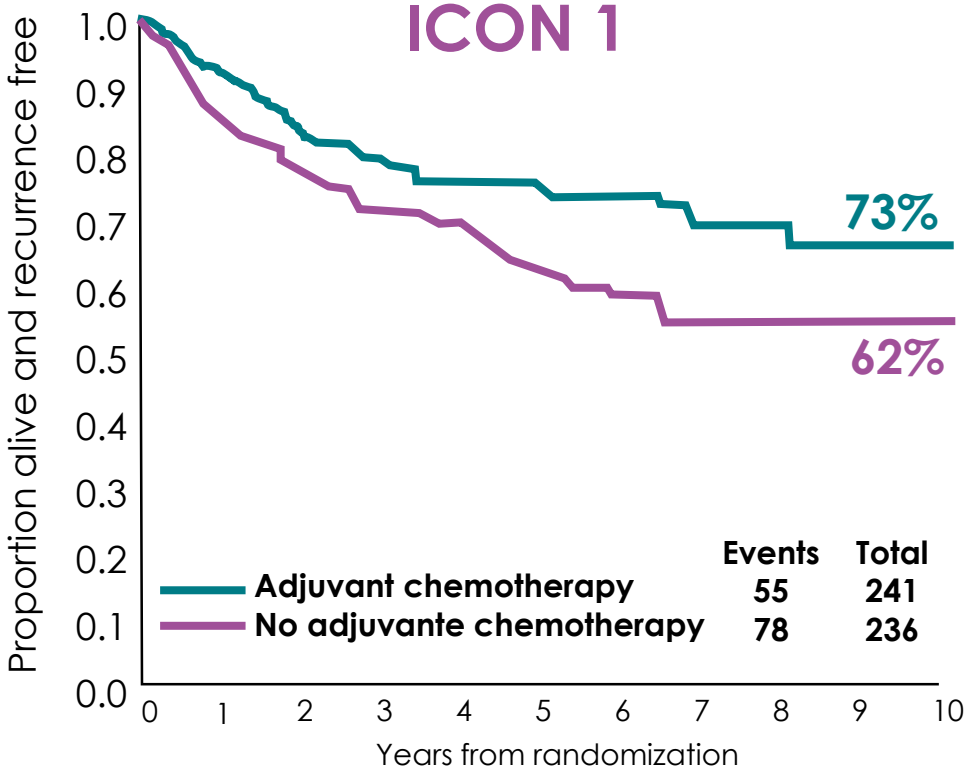
Sobrevida livre de recorrência

ICON 1

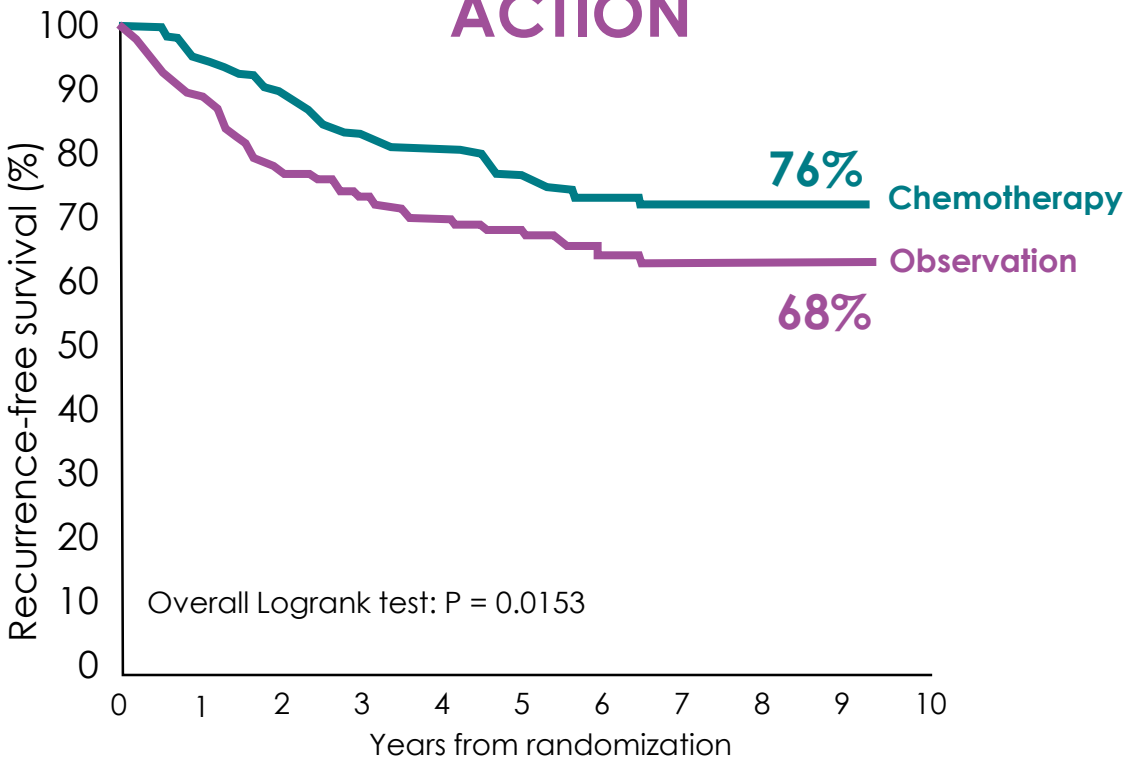


Patients at risk

Adjuvant chemotherapy	241	202	162	126	98	79	61	41	22	10	7
No adjuvante chemotherapy	236	179	153	120	94	68	51	31	18	8	3

HR 0.65, *P* .01

ACTION



O	N	No. of patients at risk:								
46	224	202	167	141	119	88	69	49	28	6
66	224	189	143	124	102	79	58	40	18	3

HR 1.59, P .02

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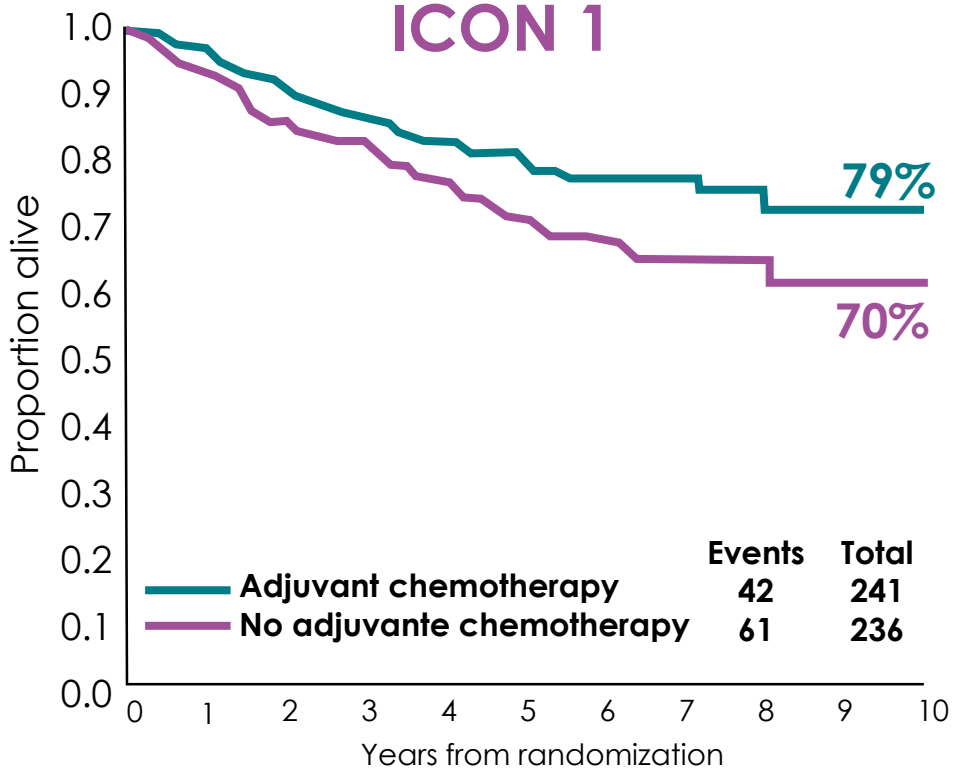
Sobrevida global

ICON 1

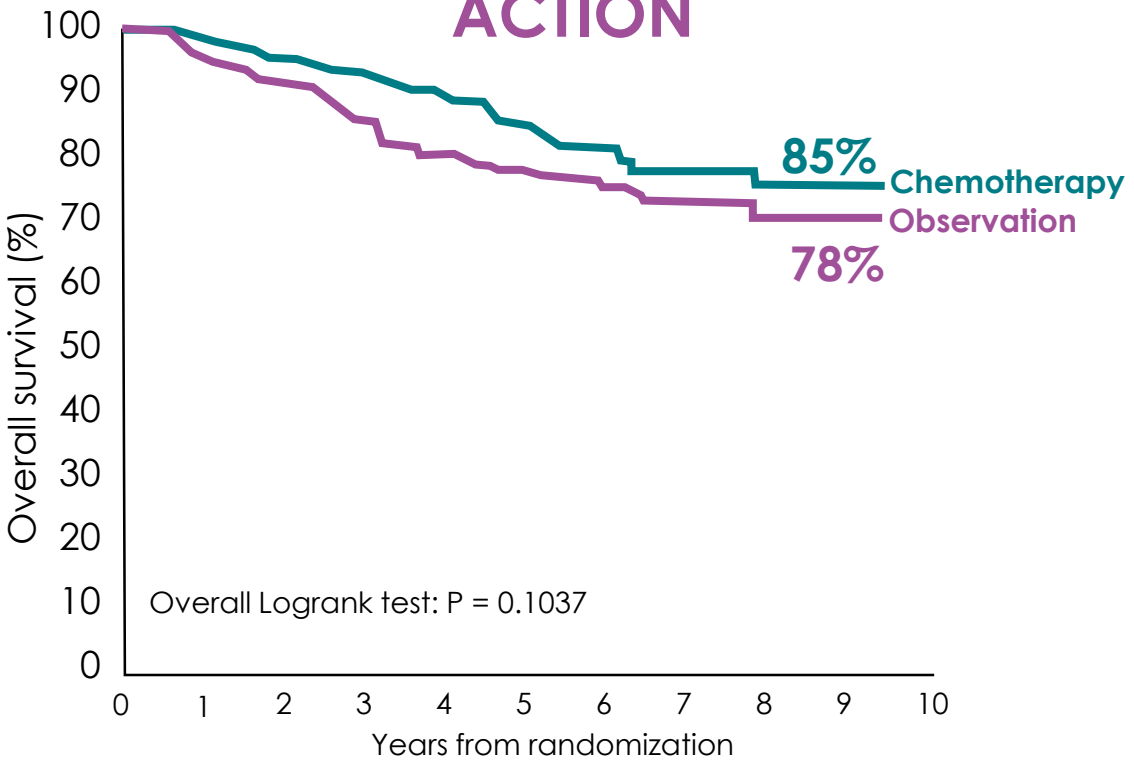


Patients at risk

Adjuvant chemotherapy	241	222	185	142	109	85	65	45	23	10	7
No adjuvante chemotherapy	236	205	175	142	108	81	59	37	20	9	3

HR 0.66, P = .03

ACTION



O	N	No. of patients at risk:								
33	224	210	177	159	135	102	80	56	29	6
45	224	202	172	148	122	94	69	46	21	3

HR 1.45, P .10

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ACTION + ICON1

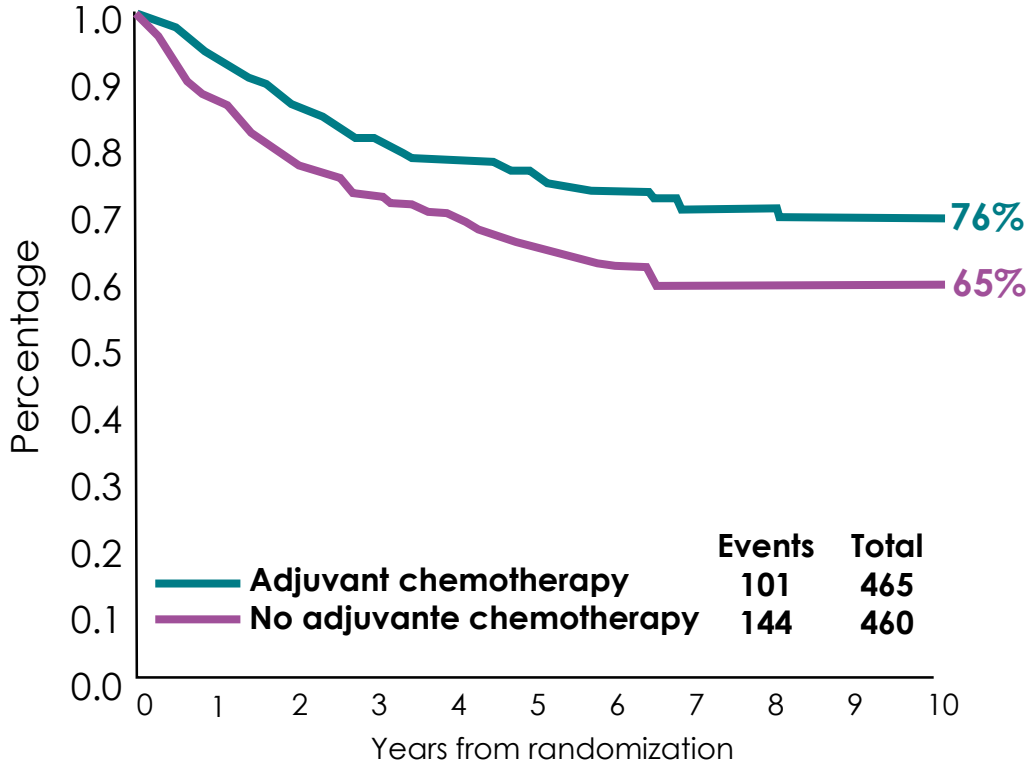
Population: 925 patients

ICON1 (n = 477 pts) + ACTION (n = 448 pts)

Chemotherapy	Risk	Absolute Difference	% @ 5 years	P
PFS	0.64	11%	76%	0.001
OS	0.67	8%	82%	0.01

Trimbos JB, J Natl Cancer Inst. 2003 Jan 15;95(2):105-12.

ACTION + ICON1 – Sobrevida livre de recorrência



Patients at risk

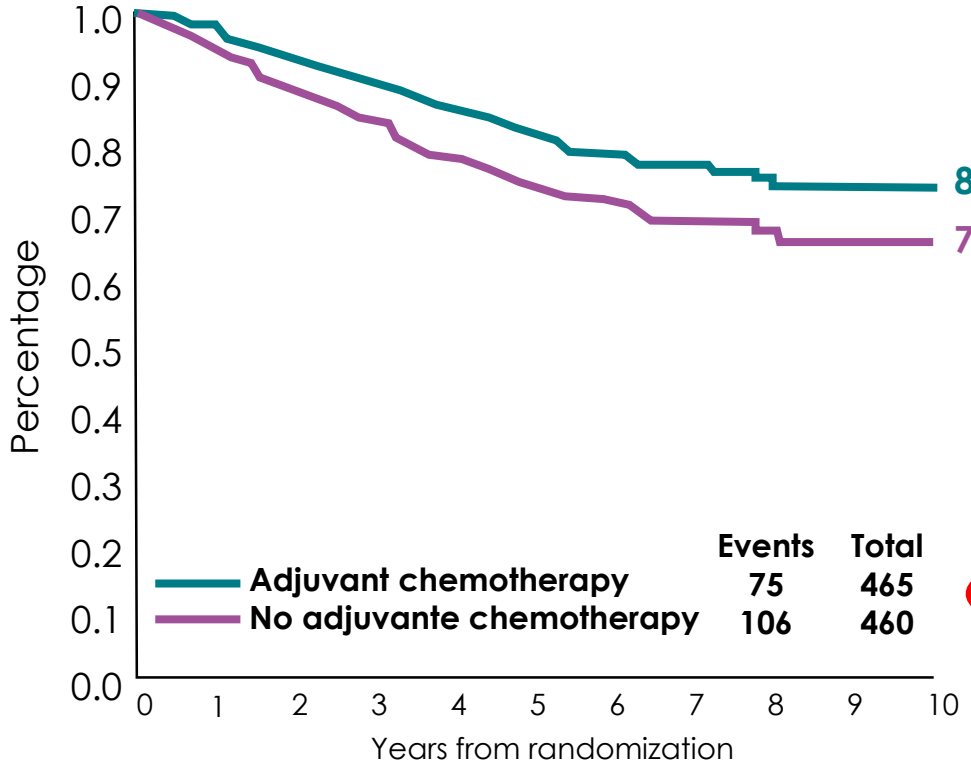
Adjuvant chemotherapy	465	404	329	267	217	167	130	90	50	16	7
No adjuvante chemotherapy	460	368	296	244	196	147	109	71	36	11	3

HR 0,64 p=0.001

Diferença absoluta de 11%

Trimbos JB, J Natl Cancer Inst. 2003 Jan 15;95(2):105-12.

ACTION + ICON1 – Sobrevida global



Patients at risk

Adjuvant chemotherapy	465	432	362	301	244	187	145	101	52	16	7
No adjuvante chemotherapy	460	407	347	290	230	175	128	83	41	12	3

HR 0,67 p=0.008

Diferença absoluta em 5 anos de 8%

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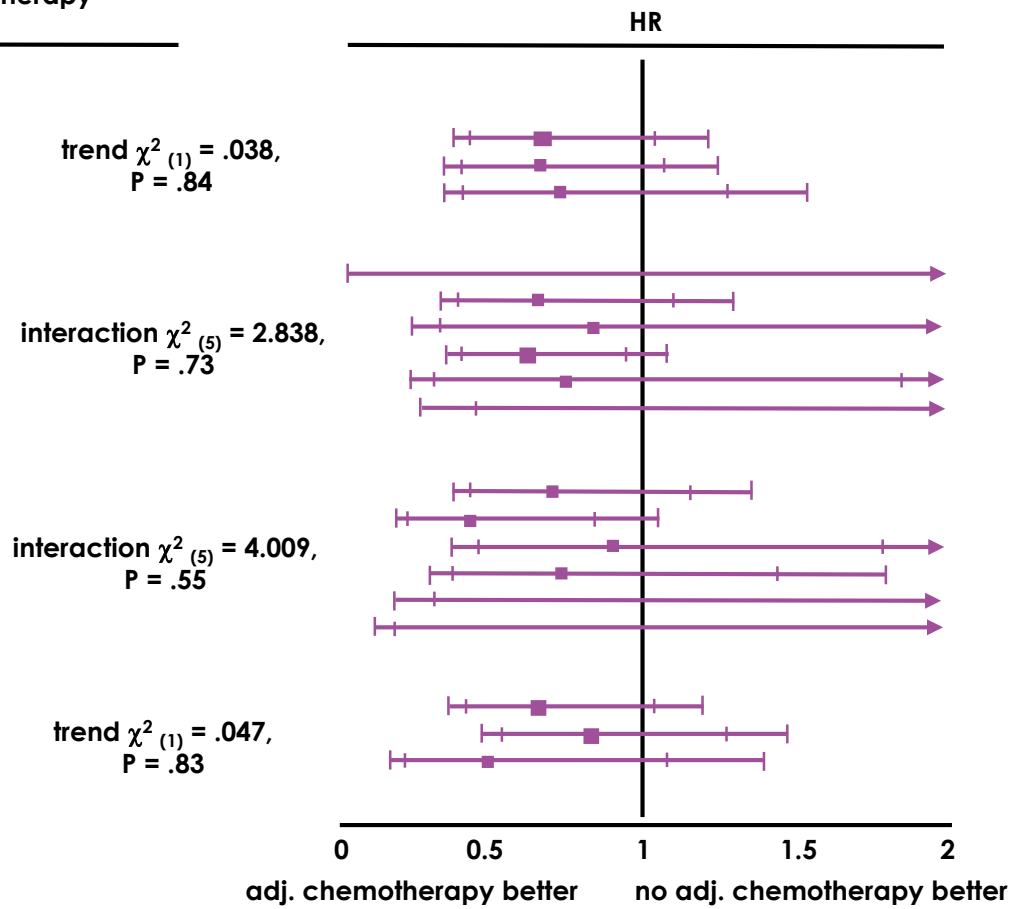
Trimbos JB, J Natl Cancer Inst. 2003 Jan 15;95(2):105-12.

ACTION + ICON1 – Análise de subgrupo

	Adj. chemotherapy	No Adj. chemotherapy
	(No. of events/No. of patients)	
Age		
< 55	30/233	
55-65	22/126	
> 65	23/105	
Tumor stage		
I	1/9	
Ia	22/168	
Ib	8/46	
Ic	32/208	
II	8/30	
III	3/3	
Histological cell type		
Serous	27/161	
Mucinous	10/90	
Endometrioid	13/94	
Clear	16/68	
Undifferentiated	3/9	
Other	3/23	
Cell differentiation		
Poor	29/139	
Intermediate	37/210	
Well	7/97	



A análise de subgrupo não revelou diferenças entre os vários subgrupos em relação ao efeito benéfico do tratamento de quimioterapia adjuvante.

Trimbos JB, J Natl Cancer Inst. 2003 Jan 15;95(2):105-12.

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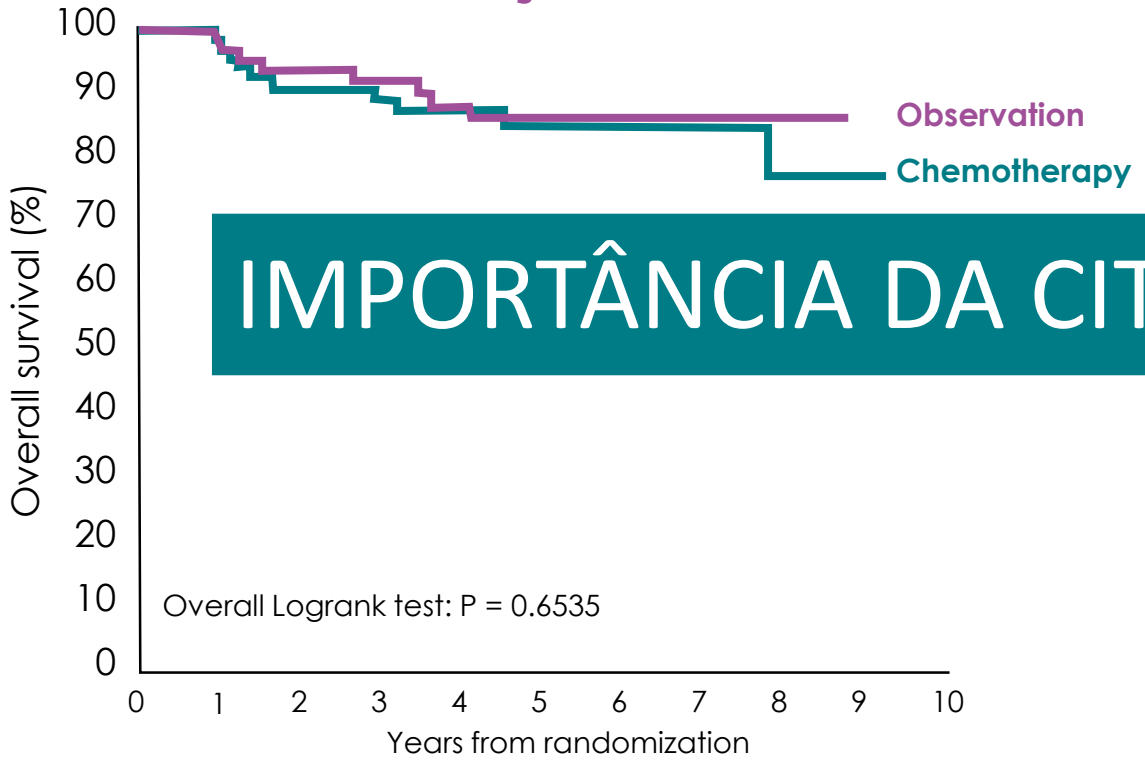
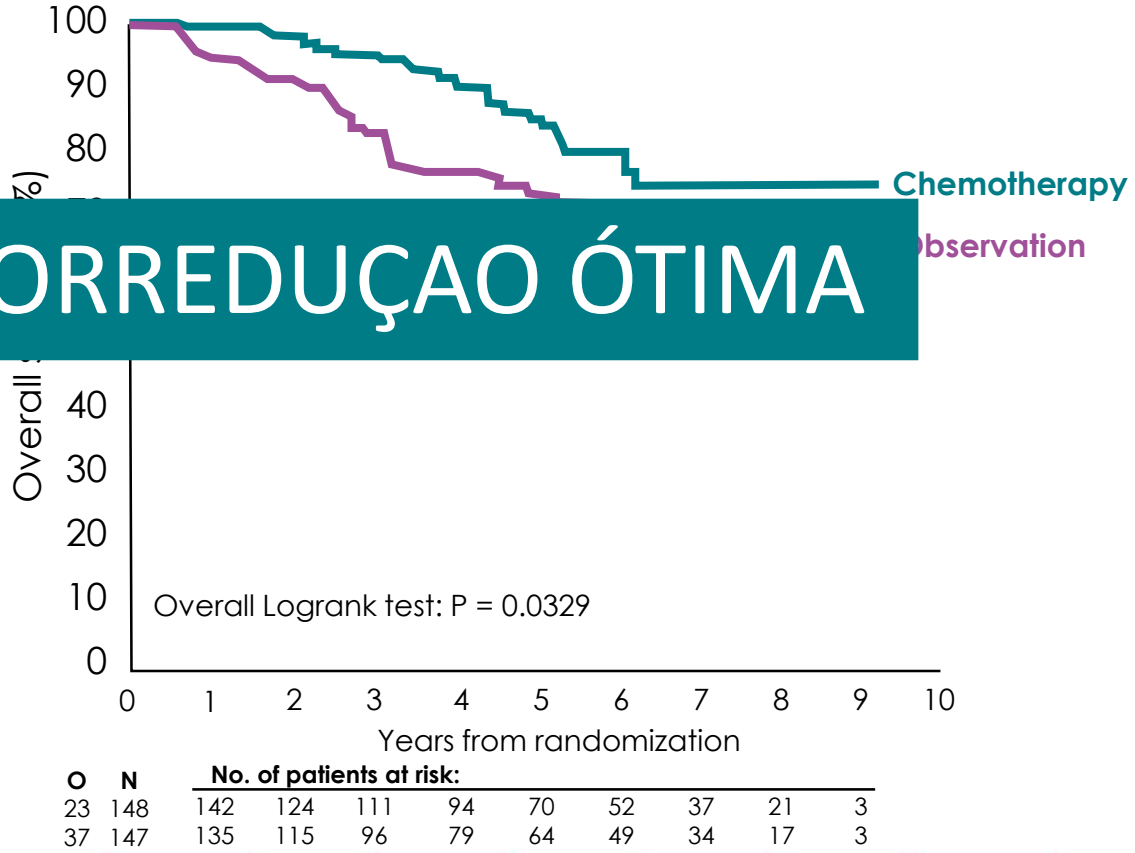
Impacto da cirurgia no tratamento adjuvante ACTION

Citorredução Ótima



Citorredução não Ótima



IMPORTÂNCIA DA CITORREDUÇAO ÓTIMA

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Cochrane Database of Systematic Reviews

Sobrevida Global

Analysis 1.1. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 1 Overall survival (5 yr).

Review: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

Comparison: 1 Adjuvant chemotherapy versus observation

Outcome: 1 Overall survival (5 yr)

Study or subgroup	Chemotherapy N	Observation N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
ACTION 2003	224	224	-0.3711 (0.2291)		38.6 %	0.69 [0.44, 1.08]
Bolis 1995	41	42	0.1823 (0.4867)		8.6 %	1.20 [0.46, 3.11]
ICON1 2003	241	236	-0.4155 (0.1959)		52.8 %	0.66 [0.45, 0.97]
Total (95% CI)	**506**	**502**			**100.0 %**	**0.71 [0.53, 0.93]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.32$, df = 2 (P = 0.52); $I^2 = 0.0\%$

Test for overall effect: Z = 2.44 (P = 0.015)

Test for subgroup differences: Not applicable

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Cochrane Database Syst Rev. 2015

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Cochrane Library
Cochrane Database of Systematic Reviews

Sobrevida Livre de Progressão

Analysis 1.5. Comparison 1 Adjuvant chemotherapy versus observation, Outcome 5 Progression-free survival (5 yr).

Review: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer

Comparison: 1 Adjuvant chemotherapy versus observation

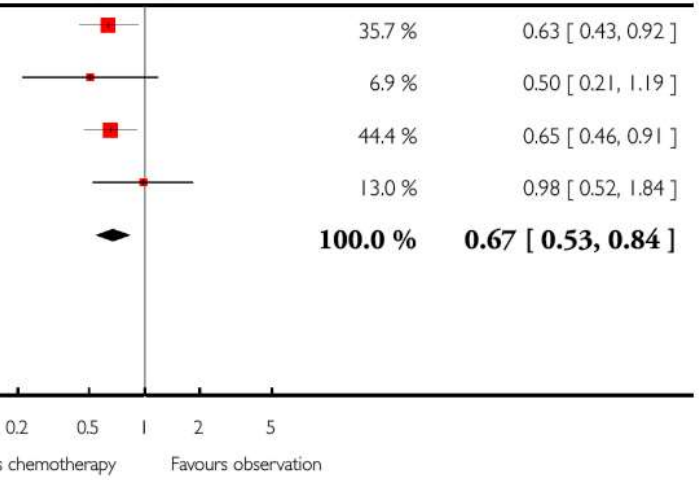
Outcome: 5 Progression-free survival (5 yr)

Study or subgroup	Chemotherapy N	Observation N	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Weight	Hazard Ratio IV,Random,95% CI
ACTION 2003	224	224	-0.462 (0.194)		35.7 %	0.63 [0.43, 0.92]
Bolis 1995	41	42	-0.6931 (0.4425)		6.9 %	0.50 [0.21, 1.19]
ICON1 2003	241	236	-0.4308 (0.174)		44.4 %	0.65 [0.46, 0.91]
Trop 2000	81	81	-0.0202 (0.321)		13.0 %	0.98 [0.52, 1.84]
Total (95% CI)	**587**	**583**			**100.0 %**	**0.67 [0.53, 0.84]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.97$, df = 3 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 3.51 (P = 0.00046)

Test for subgroup differences: Not applicable



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Cochrane Database Syst Rev. 2015

Uma doença, várias questões...

- Quem tratar?

- **Qual esquema de quimioterapia?**

- Quantos ciclos?

Qual esquema de quimioterapia?

Study ID	Participants	Intervention	5-year survival/ statistics	5-year survival/ statistics	10-year survival rates	Adverse effects	Comments
ICON1 2003	447 FIGO I-III 93% FIGO stage I	Immediate adjuvante **platinum- based chemotherapy** vs treatment on progression	OS 79% (adjuvante arm) vs 70% (no treatment)	HRs OS: HR 0.66; 95% CI to 0.97; P = 0.03	OS 73% (adjuvante arm) vs 64% (no treatment)	Not reported	Survival improvement with adjuvante therapy
ACTION 2003	448 FIGO Ia-Ib grade II-III FIGO Ic-IIa FIGO I-IIa clear cell	Imemdiate adjuvante platinum- based chemotherapy vs progression **Cisplatin dose - 75 mg/m^2** **Carboplatin dose - 350 mg/m^2**	OS 85% (adjuvante arm) vs 78% (no treatment)	HRs OS: HR 0.69; 95% CI 0.44 to 1.08; P = 0.10 RFS: HR 0.63; 95% CI 0.43 to 0.92; P = 0.02	OS 77% (adjuvante arm) vs 70% (no treatment)	Not reported	Sub-group analysis showed that non-optimally staged patients in observation arm had significantly worse survival
Tropé 2000	162 high risk stage I 36% patients had low- volume residual disease	**Carboplatin 6 cycles Q28/7 AUC - 7 vs chemo at progression**	No difference between arms DFS 70% vs 71%, OS 86% vs 85%	Log rank test DFS P = 0.41 OS P = 0.43	NR	HRs DFS: HR 0.98; 95% CI 0.52 to 1.83 DSS: HR 0.94; 95% CI 0.37 to 2.36	Not reported
Young 1990	48 treatment 44 observation	**Melphalan vs no further treat**	DFS 91% vs 98% OS 94% vs 98%	Log rank test DFS P = 0.41 OS P = 0.43	NR	Melphalan: 16% had severe myelosuppression. 26% had gastrointestinal side effects. One death: myeloproliferative disorder aplastic anaemia 6 years after completing treatment	rial under powered to show any real differences
Bolis 1995	85 FIGO (1976) IA-IB Grade 2 and 3	**Cisplatin 50 mg/m2 x 6 cycles Q28/7 vs no further treatment**	DFS 83% vs 64% OS 88% vs 82%	HRs DFS: HR 0.50; 95% CI 0.21 to 1.19; P = 0.17 OS: HR 1.20	NR	Nausea and vomiting in more than two-thirds of patients in cisplatin arm. Severe in less	There were patients with residual disease in both arms

Qual esquema de quimioterapia ?

- Com base nos resultados observados na doença avançada, a doublet baseado em platina é adotada para doença inicial

Qual esquema de quimioterapia ?

- Com base nos resultados observados na doença avançada, a doublet baseado em platina é adotada para doença inicial.
- Não há evidências de que a combinação de carboplatina + paclitaxel seja superior à carboplatina isolada.

Qual esquema de quimioterapia ?

- Com base nos resultados observados na doença avançada, a doublet baseado em platina é adotada para doença inicial.
- Não há evidências de que a combinação de carboplatina + paclitaxel seja superior à carboplatina isolada.
- A carboplatina isolada pode ser uma alternativa aceitável em estadio I.

Uma doença, várias questões...

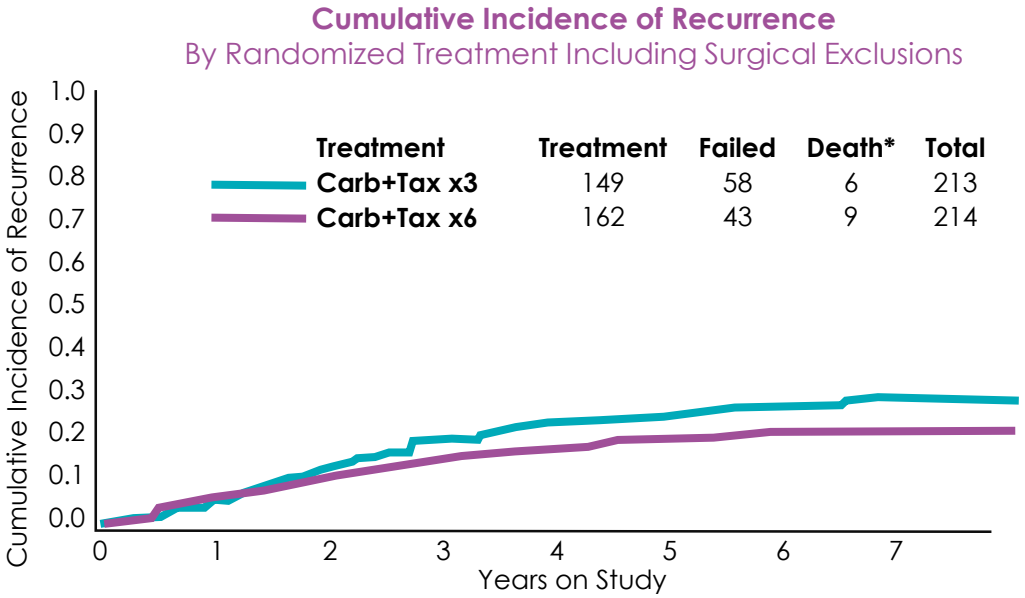
- Câncer de ovário em estágio inicial: tratar ou não tratar?
- Qual esquema de quimioterapia?
- **Quantos ciclos ?**

Quantos ciclos ? 3 vs 6 ciclos

N = 427

IA G 3, IB G 3, células claras, IC, e II

citorredução ótima.



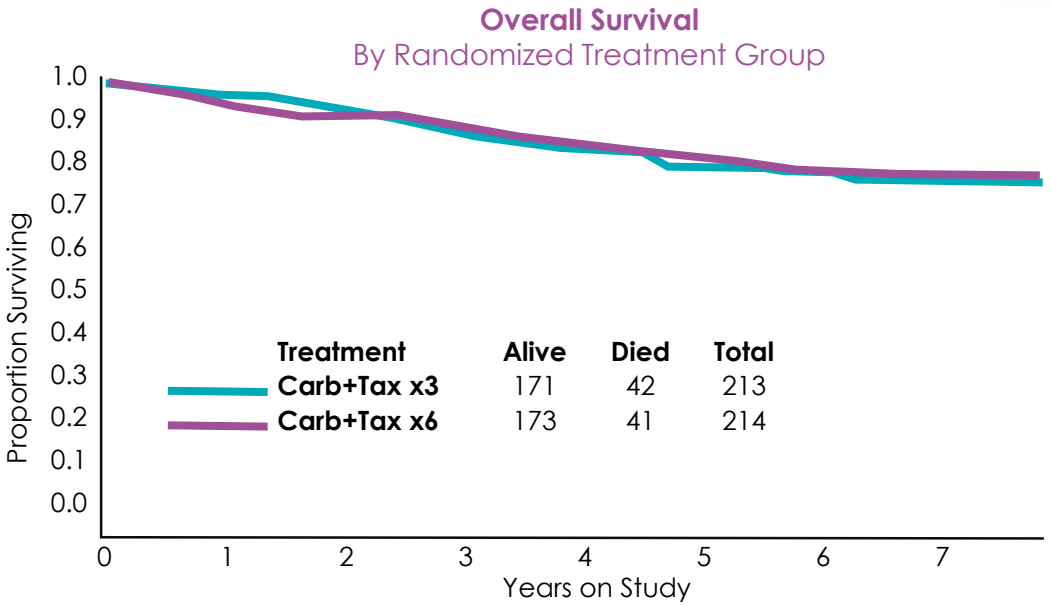
Bell J, Gynecol Oncol. 2006 Sep;102(3):432-9

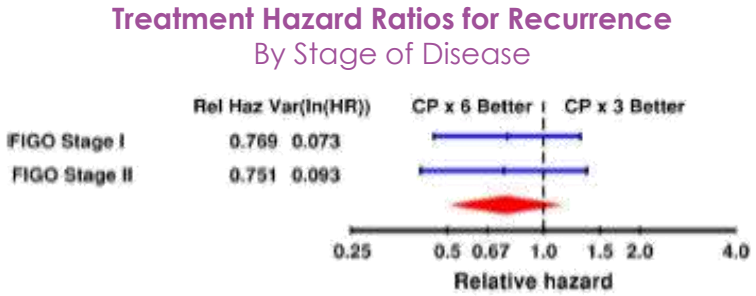
Quantos ciclos ? 3 vs 6 ciclos

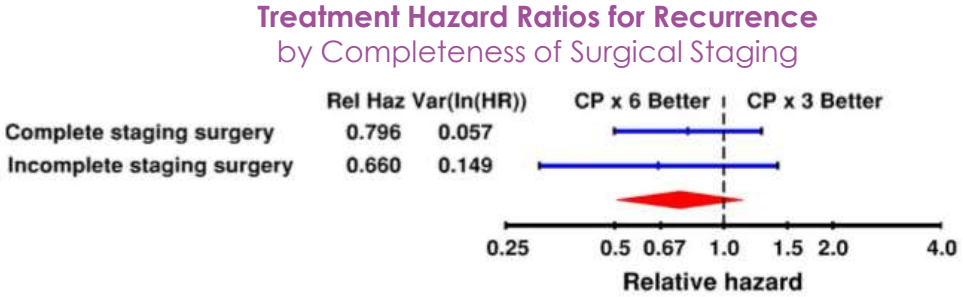
N = 427

IA G 3, IB G 3, células claras, IC, e II

citorredução ótima.







Bell J, Gynecol Oncol. 2006 Sep;102(3):432-9

VIII CONGRESSO INTERNACIONAL DE GINECOLOGIA ONCOLÓGICA
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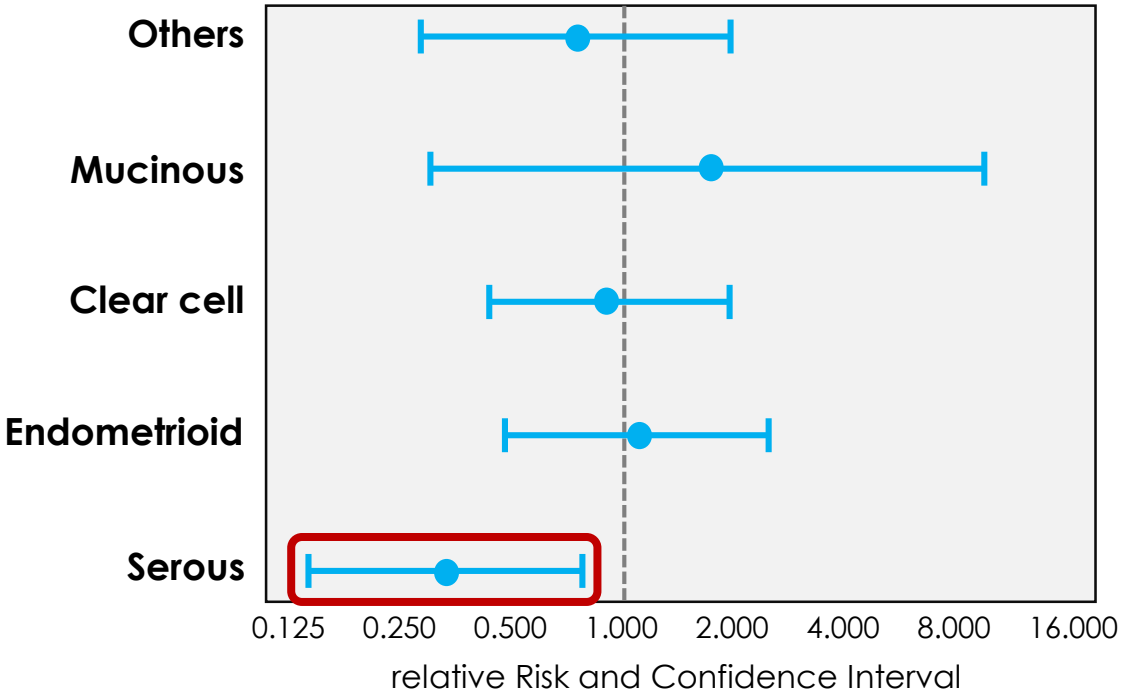
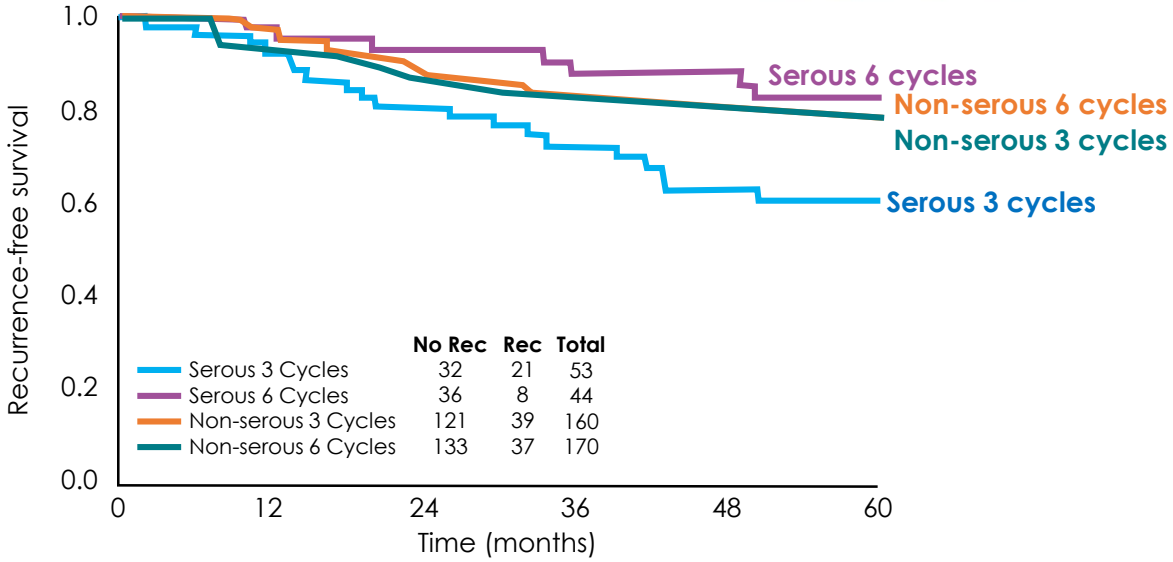
Quantos ciclos? 3 vs 6 ciclos – histologia





	Recurrence-free survival			Overall survival		
	6 cycles	3 cycles	p[a]	6 cycles	3 cycles	p[a]
Serous 2 years (%) 5 years (%)	93.0 82.7	60.8 60.4	0.007	95.5 85.6	90.6 73.2	0.191
Non-serous 2 years (%) 5 years (%)	87.5 78.7	88.7 78.6	0.806	92.3 83.0	95.0 84.1	0.791

[a]Long-rank test to compare the RFS or OS distributions between 6-cycle and 3-cycle arms.

Chan JK. Gynecologic Oncology 116 (2010) 301–306

HOSPITAL SANTA LÚCIA

Tratamento sistêmico pós-operatório do câncer precoce de ovário – Favoreço rotina para:

- Estadios IA grau 3, IB grau 2 ou 3, IC de qualquer grau e em todos os estadios com carcinomas de células claras.

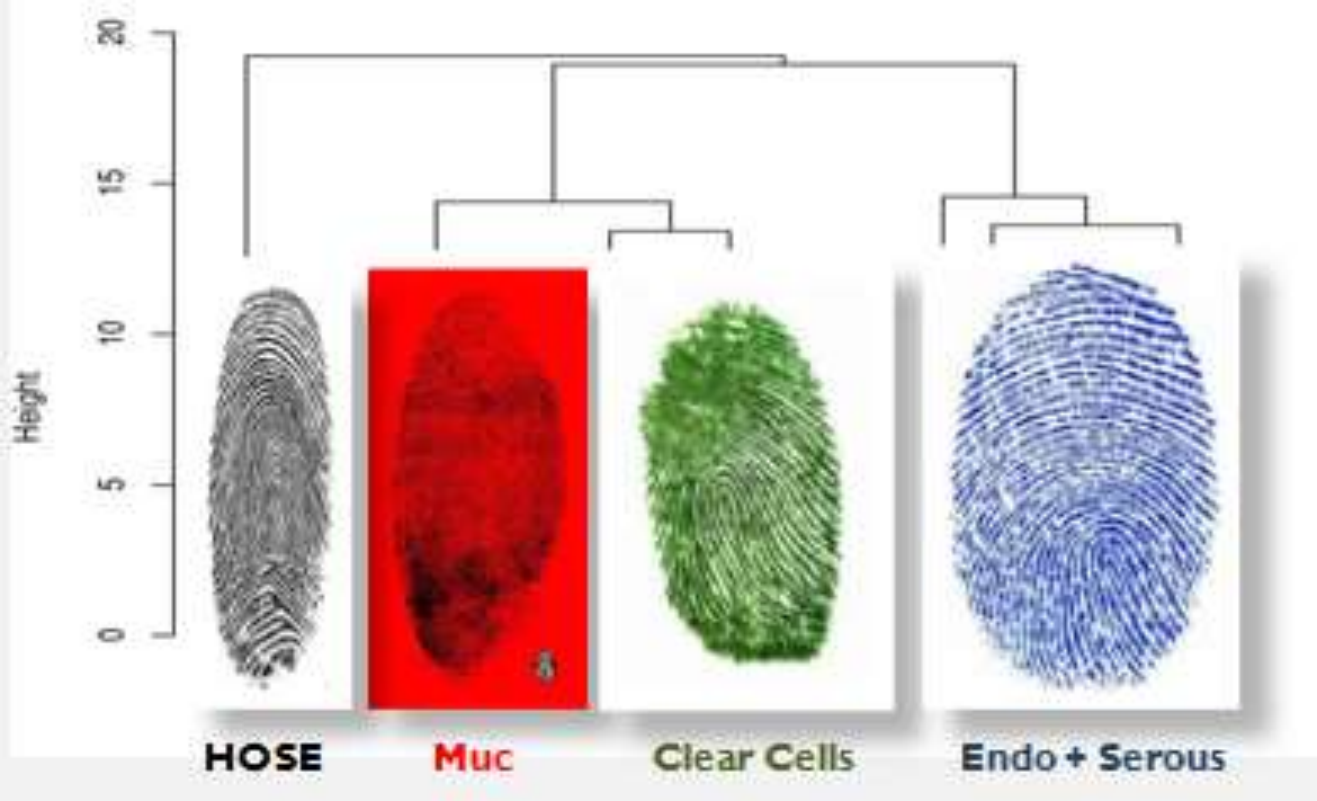
Tratamento sistêmico pós-operatório do câncer precoce de ovário – Favoreço rotina para:

- Estadios IA grau 3, IB grau 2 ou 3, IC de qualquer grau e em todos os estadios com carcinomas de células claras.
- Estadio IA grau 2 e IB grau 1 – discussão multidisciplinar

Tratamento sistêmico pós-operatório do câncer precoce de ovário – Favoreço rotina para:

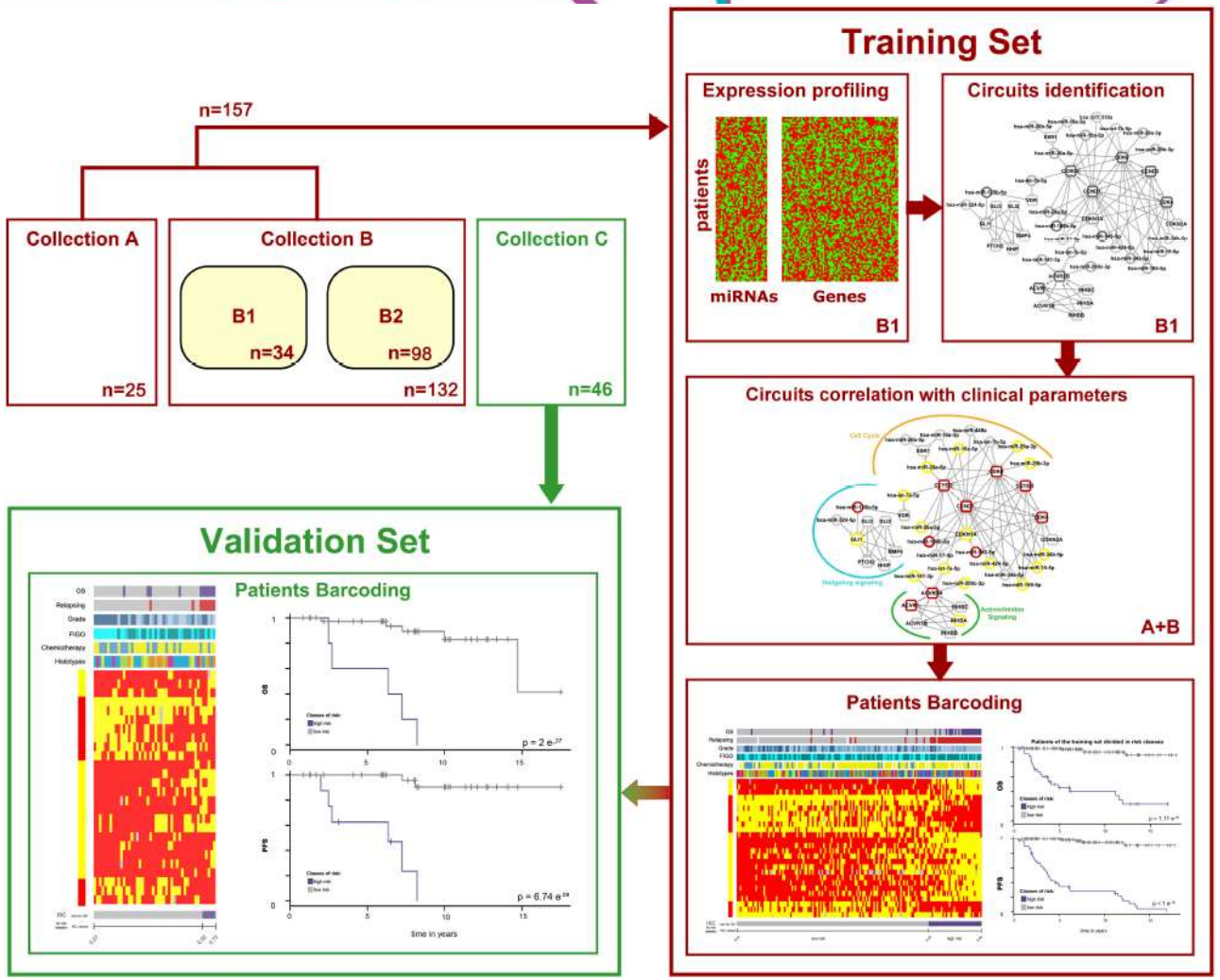
- Estadios IA grau 3, IB grau 2 ou 3, IC de qualquer grau e carcinomas de células claras qualquer estadio.
- Estadio IA grau 2 e IB grau 1 – discussão multidisciplinar
- Preferencialmente esquema carboplatina e paclitaxel por pelo menos 3 ciclos
  - 6 ciclos para seroso de alto grau

O futuro……



Calura E. Ann Oncol. 2016 Aug;27(8):1511-9.

- N= 203
- 26 dos 44 elementos (10 genes e 16 miRNAs) foram associados com o prognóstico da paciente em OS e PFS.
- Geração de um "código de barra" de pior prognóstico



Calura E. Ann Oncol. 2016 Aug;27(8):1511-9.

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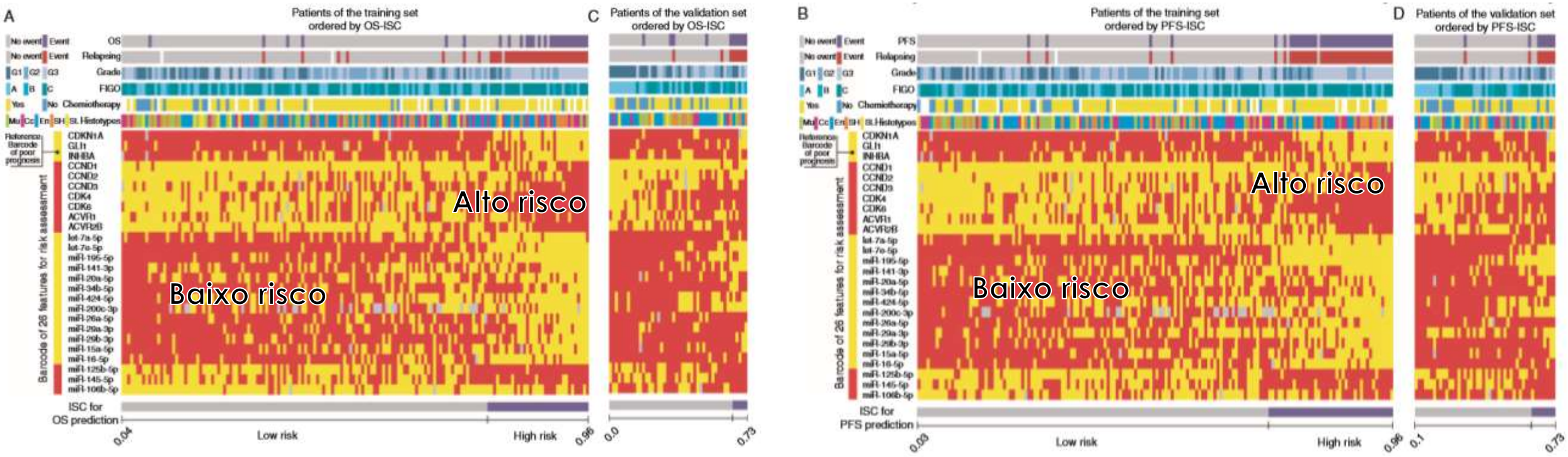
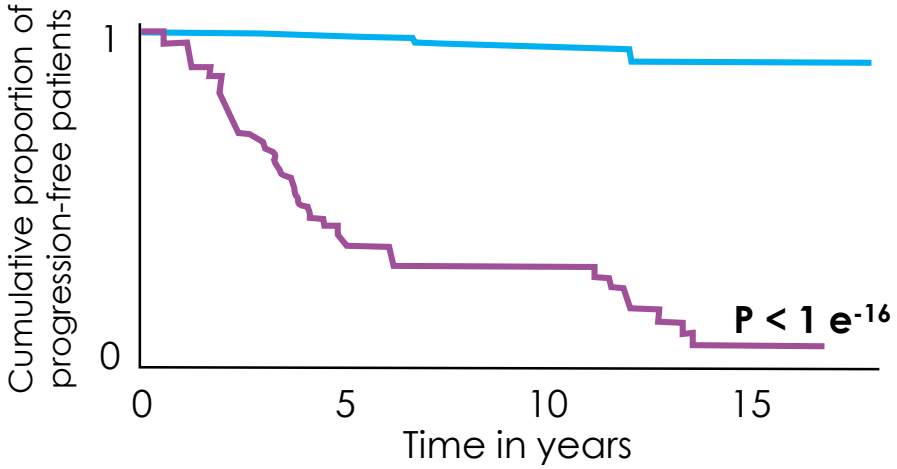


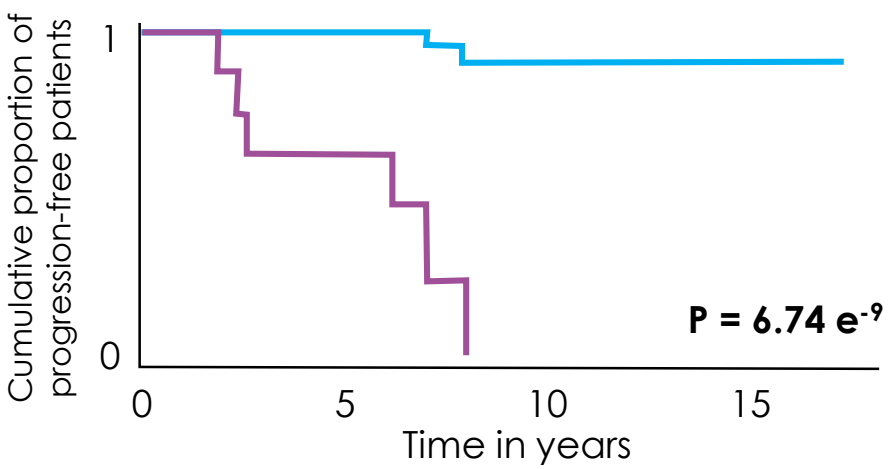
HOSPITAL SANTA LÚCIA

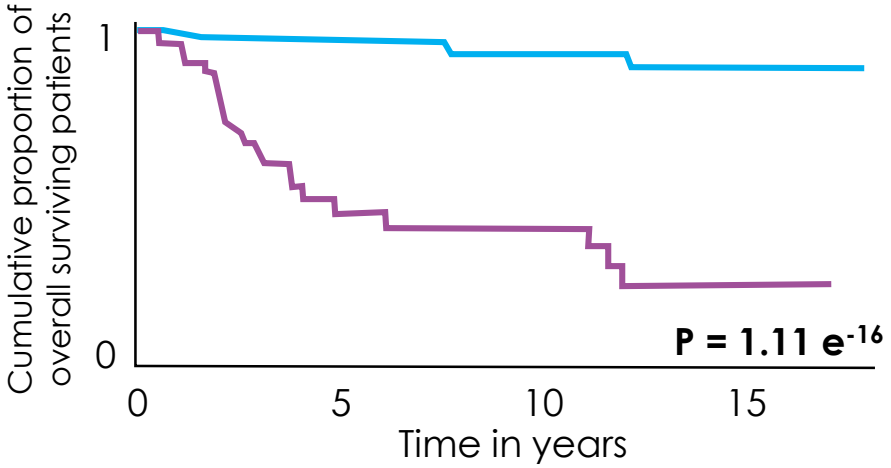
Calura E. Ann Oncol. 2016 Aug;27(8):1511-9.

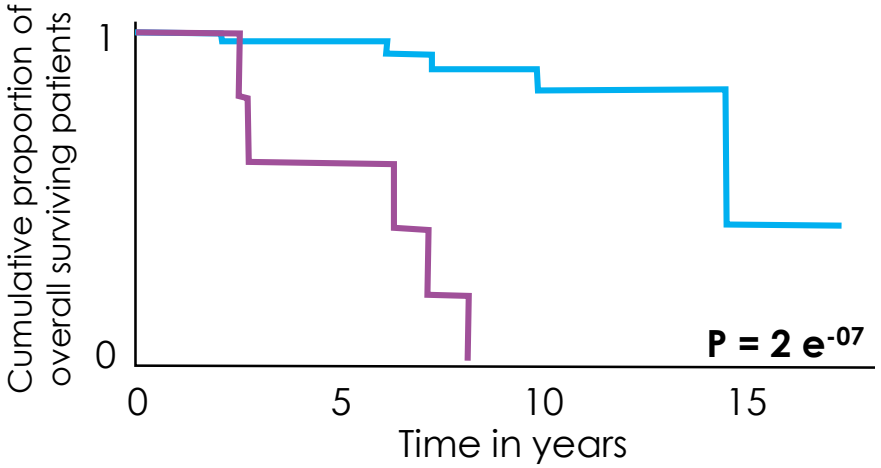
Patients of the training set divided in risks classes



Patients of the validation set divided in risks classes







ISC risk classes: High risk High risk

accdemoura@gmail.com