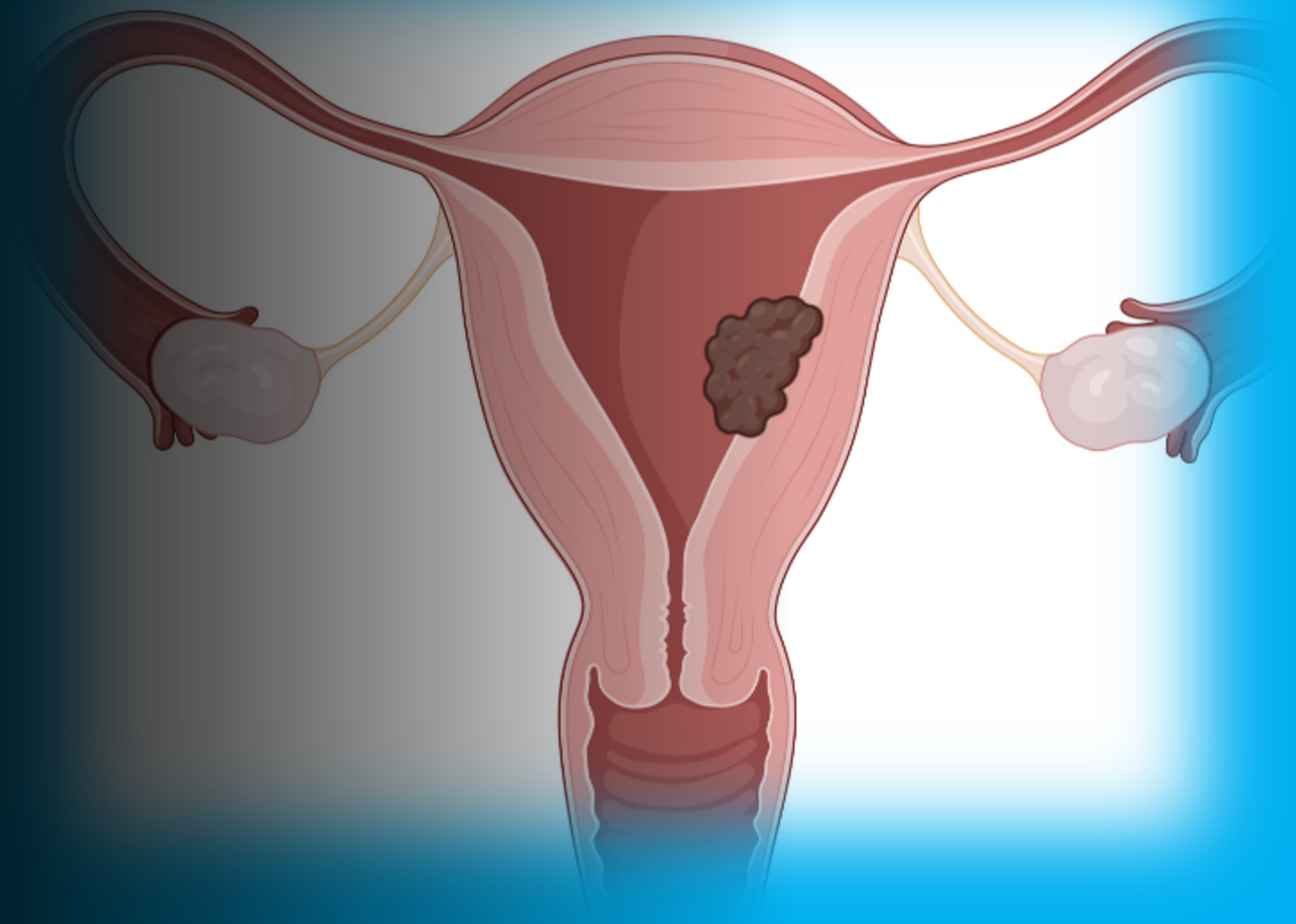
Câncer de corpo de útero



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Cronograma

1. Introdução
   - 1.1 Epidemiologia
   - 1.2 Fatores de risco
   - 1.3 História natural

2. Apresentação clínica
   - 2.1 Sintomas
   - 2.2 Estadiamento
   - 2.3 Classificação

3. Tratamento
   - 3.1 Cirurgia
   - 3.2 Adjuvância

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Epidemiologia

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Carcinoma de Endométrio = 95% dos casos

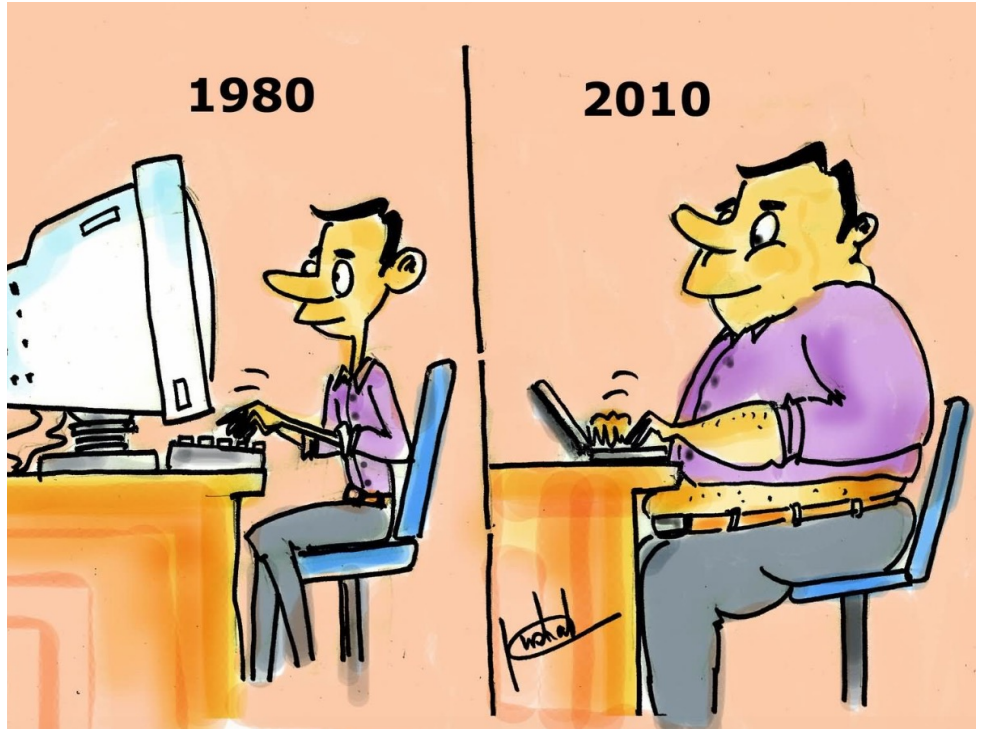
Neoplasia maligna em ginecologia mais comum nos países desenvolvidos.

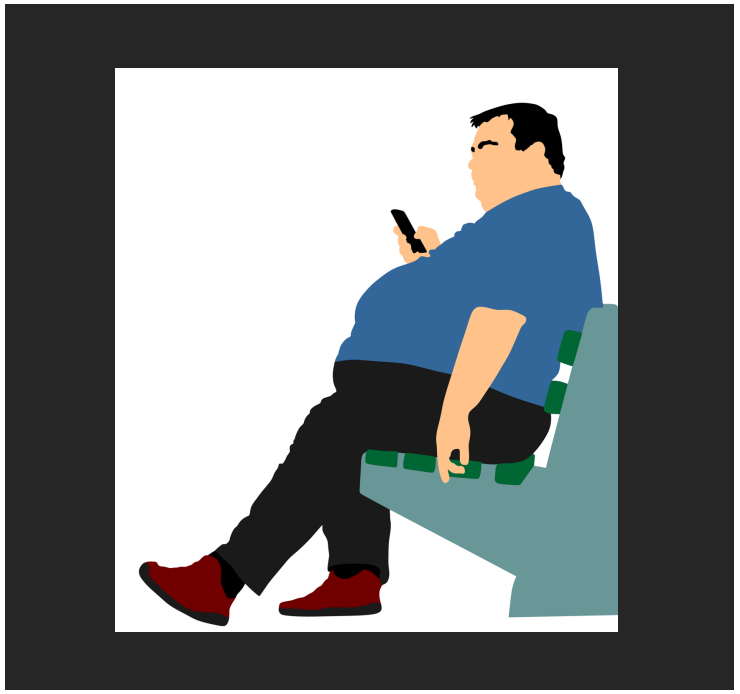
Câncer mais comum relacionado à obesidade

	Localização Primária	Casos	%
Mulheres	Mama feminina	73.610	30,1%
	Cólon e reto	23.660	9,7%
	Colo do útero	17.010	7,0%
	Traqueia, brônquio e pulmão	14.540	6,0%
	Glândula tireoide	14.160	5,8%
	Estômago	8.140	3,3%
	Corpo do útero	7.840	3,2%
	Ovário	7.310	3,0%
	Pâncreas	5.690	2,3%
	Linfoma não Hodgkin	5.620	2,3%

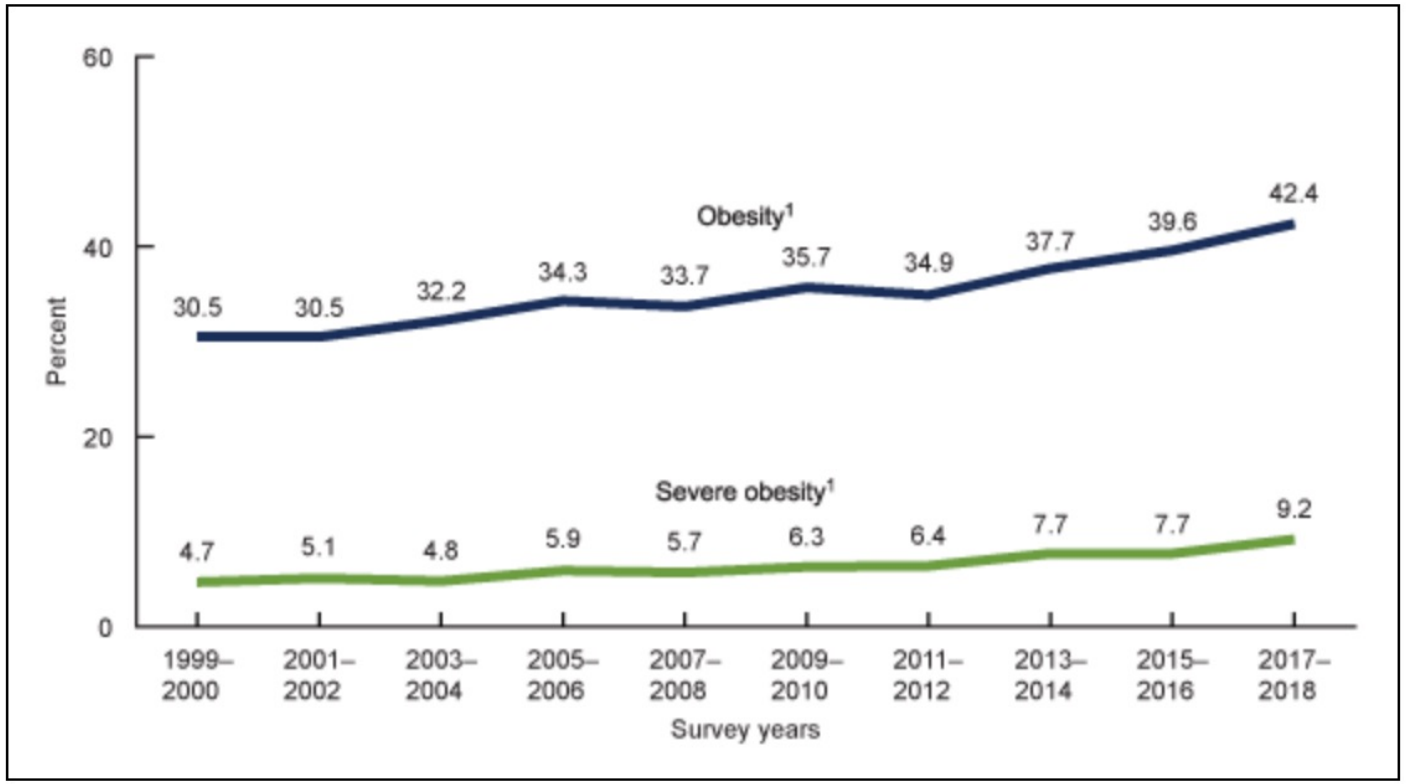
Distribuição proporcional dos dez tipos de câncer mais incidentes estimados para 2023 por sexo, exceto pele não melanoma – INCA estimativa 2023

Epidemiologia





Epidemiologia



CDC in https://www.cdc.gov/nchs/products/databriefs/db360.htm

Fatores de Risco

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Estrogênio não contrabalanceado

Obesidade

Diabetes

Idade = 60 anos (20% antes da menopausa)

Predisposição genética (5% associado a Sd Lynch)

Tamoxifeno (RR2.3)

Hiperplasia endometrial atípica

Protetores

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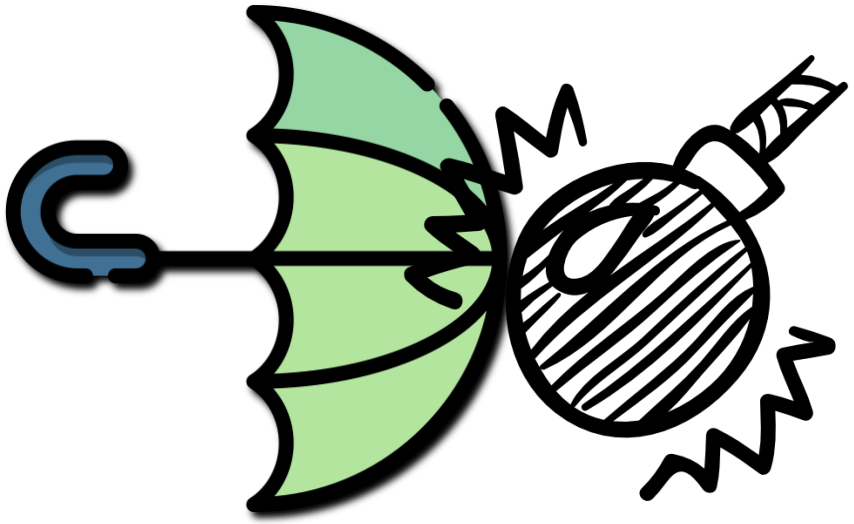
ACO: 12 meses

Tabagismo



História Natural

Hiperplasia sem atipia:

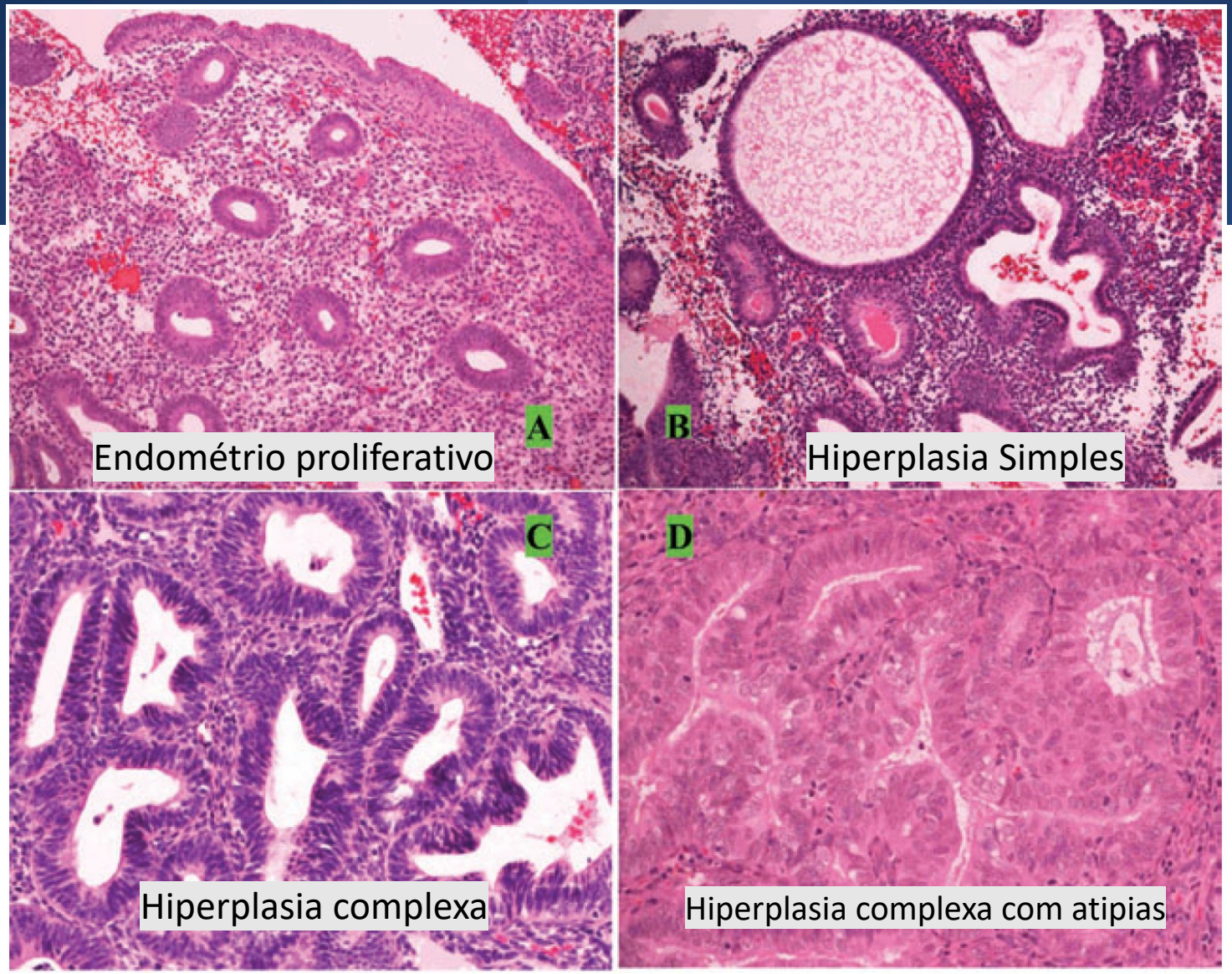
Simples: 1%

Complexa: 3%

Hiperplasia com atipia:

Simples: 8%

Complexa: 29%



Review Endometrial hyperplasia The Obstetrician & Gynaecologist Palmer et al 2008

Sintomas (90% são sintomáticas)

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- Sangramento Uterino Anormal
- Dor em BV
- Sangramento de odor fétido
- Sangramento após menopausa

Morice et al Endometrial Cancer Lancet 2015

Causas de Sangramento após menopausa

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- Atrofia do endométrio (30%)
- Terapêutica hormonal (30%)
- Câncer de endométrio (15%)
- Pólipos endometriais (10%)
- Hiperplasia endometrial (5%)

Berek & Hackers Gynecologic Oncology - Wolters Kluwer 6th ed 2015

Estadiamento

FIGO 2023

TABLE 1 2023 FIGO staging of cancer of the endometrium.[a,b]

Stage	Description
Stage I	Confined to the uterine corpus and ovary[c]
IA	Disease limited to the endometrium OR non-aggressive histological type, i.e. low-grade endometroid, with invasion of less than half of myometrium with no or focal lymphovascular space involvement (LVSI) OR good prognosis disease
	IA1 Non-aggressive histological type limited to an endometrial polyp OR confined to the endometrium
	IA2 Non-aggressive histological types involving less than half of the myometrium with no or focal LVSI
	IA3 Low-grade endometrioid carcinomas limited to the uterus and ovary[c]
IB	Non-aggressive histological types with invasion of half or more of the myometrium, and with no or focal LVSI[d]
IC	Aggressive histological types[e] limited to a polyp or confined to the endometrium
Stage II	Invasion of cervical stroma with extrauterine extension OR with substantial LVSI OR aggressive histological types with myometrial invasion
IIA	Invasion of the cervical stroma of non-aggressive histological types
IIB	Substantial LVSI[d] of non-aggressive histological types
IIC	Aggressive histological types[e] with any myometrial involvement
Stage III	Local and/or regional spread of the tumor of any histological subtype
IIIA	Invasion of uterine serosa, adnexa, or both by direct extension or metastasis
	IIIA1 Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)[c] IIIA2 Involvement of uterine subserosa or spread through the uterine serosa
IIIB	Metastasis or direct spread to the vagina and/or to the parametria or pelvic peritoneum
	IIIB1 Metastasis or direct spread to the vagina and/or the parametria IIIB2 Metastasis to the pelvic peritoneum
IIIC	Metastasis to the pelvic or para-aortic lymph nodes or both[f]
	IIIC1 Metastasis to the pelvic lymph nodes IIIC1i Micrometastasis IIICii Macrometastasis IIIC2 Metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes IIIC2i Micrometastasis IIIC2ii Macrometastasis
Stage IV	Spread to the bladder mucosa and/or intestinal mucosa and/or distance metastasis
IVA	Invasion of the bladder mucosa and/or the intestinal/bowel mucosa
IVB	Abdominal peritoneal metastasis beyond the pelvis
IVC	Distant metastasis, including metastasis to any extra- or intra-abdominal lymph nodes above the renal vessels, lungs, liver, brain, or bone

Grau histológico

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Arquitetural

G1: < 5% partes sólidas

G2: 6-50% partes sólidas

G3: > 50% partes sólidas

Atipia nuclear intensa: somar 1 ponto

Classificação Clínico patológica (Bokhman's)

Tipo I = endometrióide

- Mais comum (80%)
- Perimenopausa
- Estrogênio isolado
- Carcinoma pouco ou mod. Diferenciado
- Melhor prognóstico
- Mutação PTEN e Kras

Tipo II = seroso p. e cels claras

- Atrofia endometrial
- Mulheres mais velhas
- (magras e pós menopausa)
- Pior prognóstico
- Invasão miometrial profunda e disseminação peritoneal
- Mutação p53 e instabilidade cromossômica

Classificação molecular

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Alto nº de cópias 10%

Equivale ao tipo II
Mutação P53
(PIK3 e PTEN)
Pior prognóstico

Hipermutado 30%

Instabilidade microssatélite
Defic Mismach repair
Graus Variados
Mutação MLH1, PIK3 e PTEN

Baixo número de cópias 50%

Baixo grau
Mutação PTEN, KRAS, SOX17
Sem perfil molecular específico

Ultra-mutado (POLE) 10%

Ótimo prognóstico
Mutação PTEN, PIK3
Estímulo estrogêncio isolado
Aparência mais agressiva no AP

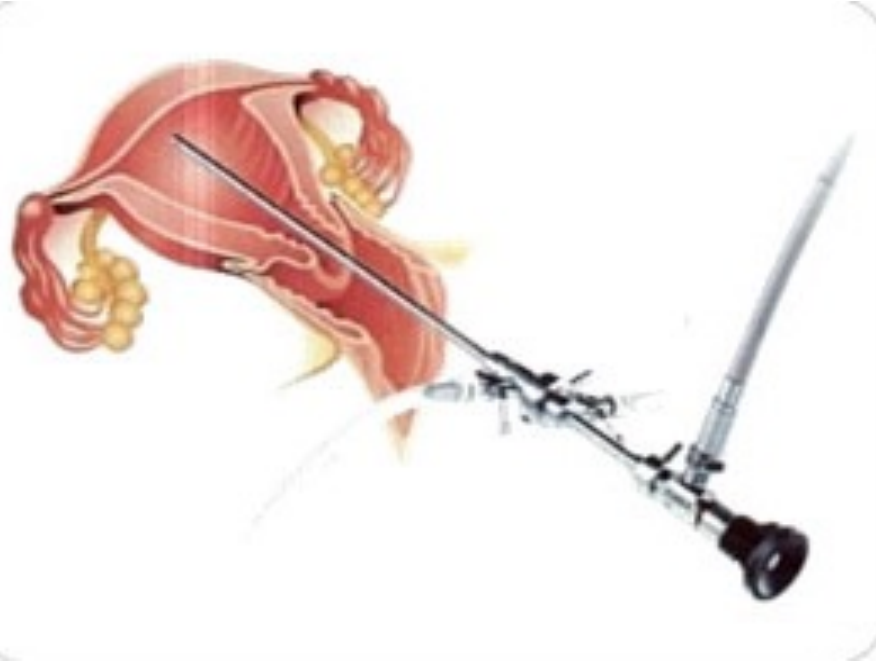
Rafone et al;TCGA molecular groups of endometrial cancer; Gynecol Oncol 2019

Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	▶ Stage IA endometrioid + low-grade‡ + LVSI negative or focal	▶ Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ▶ Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	▶ Stage IB endometrioid + low-grade‡ + LVSI negative or focal ▶ Stage IA endometrioid + high-grade‡ + LVSI negative or focal ▶ Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	▶ Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ▶ Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ▶ Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	▶ Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB endometrioid high-grade‡ regardless of LVSI status ▶ Stage II	▶ Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ▶ Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ▶ Stage II **MMRd/NSMP** endometrioid carcinoma
High	▶ Stage III–IVA with no residual disease ▶ Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	▶ Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ▶ Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ▶ Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	▶ Stage III–IVA with residual disease ▶ Stage IVB	▶ Stage III–IVA with residual disease of any molecular type ▶ Stage IVB of any molecular type

ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma 2020

Diagnóstico



Histeroscopia com Bx

Cirurgia

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Cirurgia

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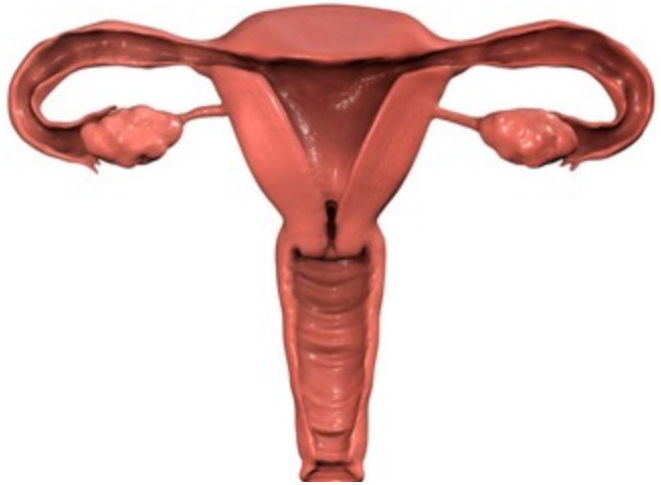
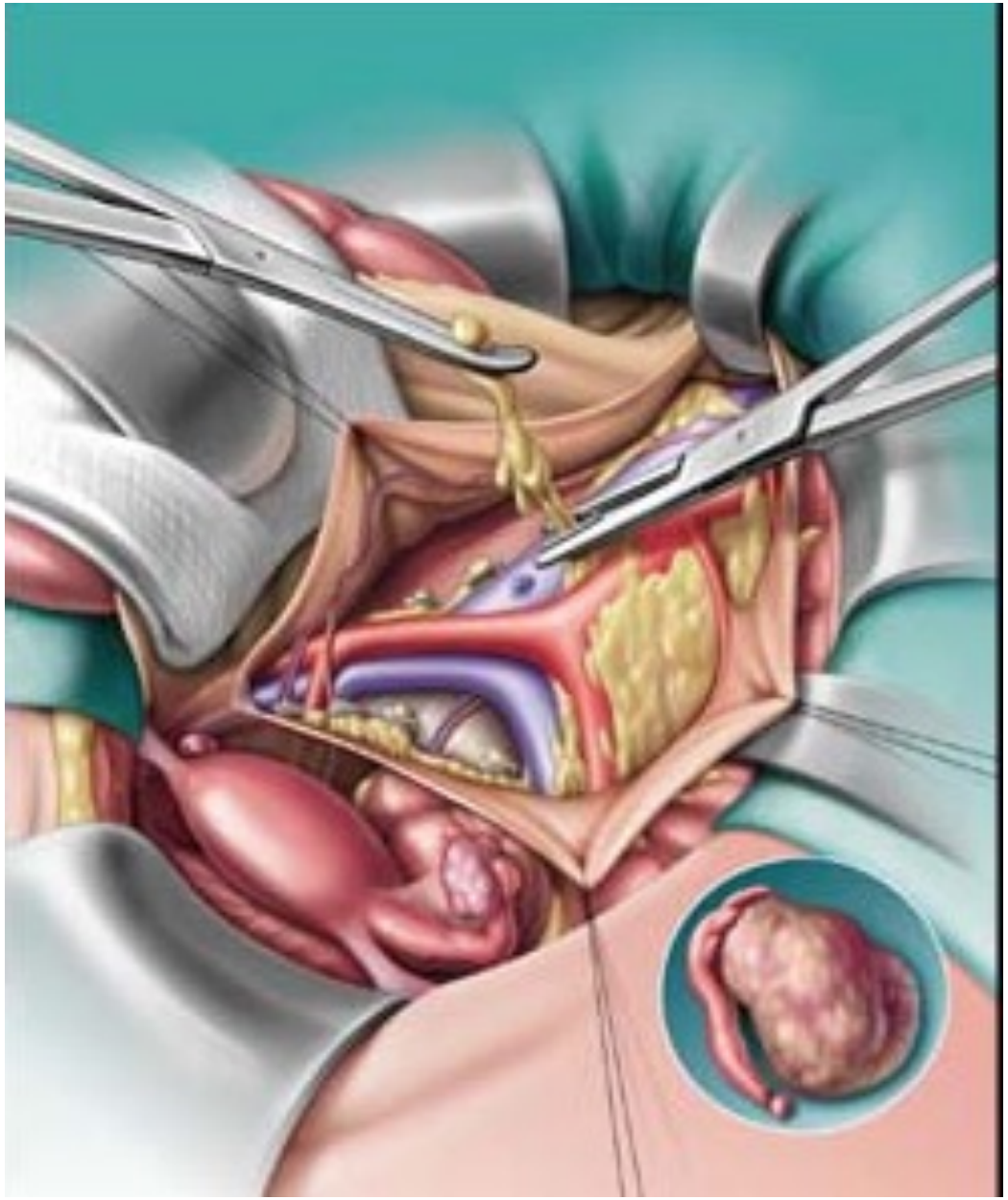
Histerectomia aberta

+ Salpingo-oforectomia bilateral
+ ~~Linfonodectomia pélvica e para-aórtica~~



Incisão xifo-púbica



Linfonodectomia para-aórtica

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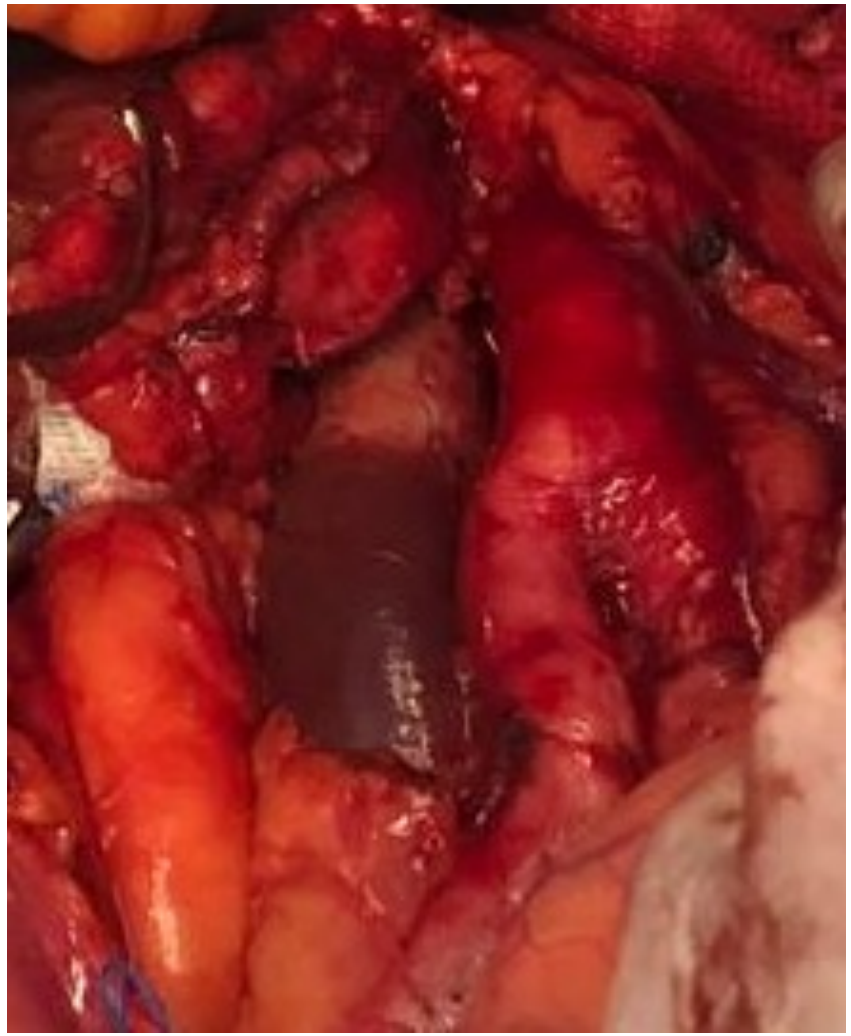

Cochrane Library 2018

Laparoscopia

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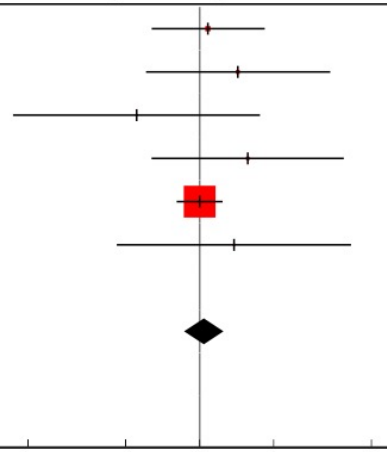
Laparoscopy versus laparotomy for the management of early stage endometrial cancer (Review)

Analysis 1.1. Comparison 1 Primary outcomes, Outcome 1 Overall survival.

Study or subgroup	Laparoscopy N	Laparotomy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Janda 2017	407	353	0.1 (0.27)		12.21%	1.08[0.64,1.84]
Lu 2013	151	121	0.4 (0.44)		4.6%	1.43[0.61,3.4]
Malzoni 2009	81	78	-0.6 (0.59)		2.56%	0.55[0.17,1.76]
Tozzi 2005	63	59	0.5 (0.46)		4.21%	1.57[0.64,3.86]
Walker 2012	920	1682	0 (0.11)		73.58%	1[0.81,1.24]
Zullo 2009	40	38	0.3 (0.56)		2.84%	1.38[0.46,4.13]
Total (95% CI)					**100%**	**1.04[0.86,1.25]**

Heterogeneity: $Tau^2=0$; $Chi^2=2.87$, df=5(P=0.72); $I^2=0\%$

Test for overall effect: Z=0.42(P=0.68)



Favours laparoscopy — Favours laparotomy

Cochrane Library 2018

Laparoscopia

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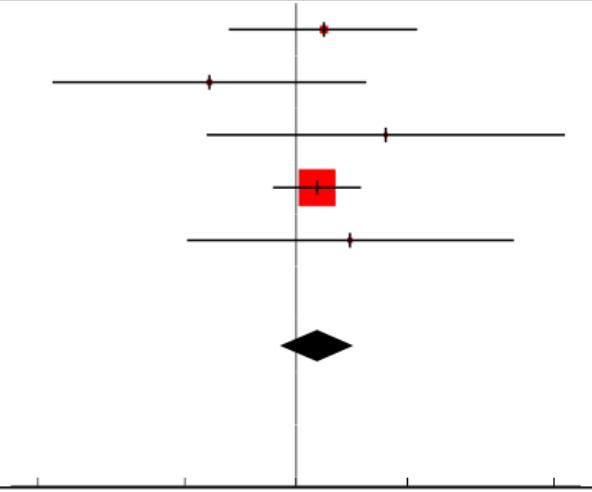
Laparoscopy versus laparotomy for the management of early stage endometrial cancer (Review)

Analysis 1.2. Comparison 1 Primary outcomes, Outcome 2 Recurrence free survival.

Study or subgroup	La-paroscopy N	Laparo-tomy N	log[Hazard Ratio] (SE)	Hazard Ratio IV, Random, 95% CI	Weight	Hazard Ratio IV, Random, 95% CI
Janda 2017	407	353	0.2 (0.3)		15.24%	1.19[0.66,2.13]
Malzoni 2009	81	78	-0.5 (0.5)		5.49%	0.58[0.22,1.55]
Tozzi 2005	63	59	0.6 (0.57)		4.22%	1.75[0.57,5.35]
Walker 2012	1682	909	0.1 (0.14)		69.98%	1.14[0.87,1.5]
Zullo 2009	40	38	0.3 (0.52)		5.07%	1.4[0.51,3.89]
Total (95% CI)					**100%**	**1.14[0.9,1.43]**

Heterogeneity: Tau^2=0; Chi^2=2.55, df=4(P=0.64); I^2=0%

Test for overall effect: Z=1.09(P=0.27)



Favours laparoscopy — Favours laparotomy

JOURNAL OF CLINICAL ONCOLOGY
2009

Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: GOG study LAP2

Walker et al

Table 2. Pathology Findings

Pathology	Laparotomy No. of Patients	Laparotomy %	Laparoscopy No. of Patients	Laparoscopy %	*P*
Surgical stage					.841*
IA	310	35	609	37	
IB	266	30	451	28	
IC	104	12	193	12	
IIA	20	2	37	2	
IIB	32	4	61	4	
IIIA	42	5	96	6	
IIIC	84	9	143	9	
IVB	28	3	39	2	
Unstaged†	0	0	1	< 1	

JOURNAL OF CLINICAL ONCOLOGY

Laparoscopy compared with laparotomy for comprehensive surgical staging of uterine cancer: GOG study LAP2

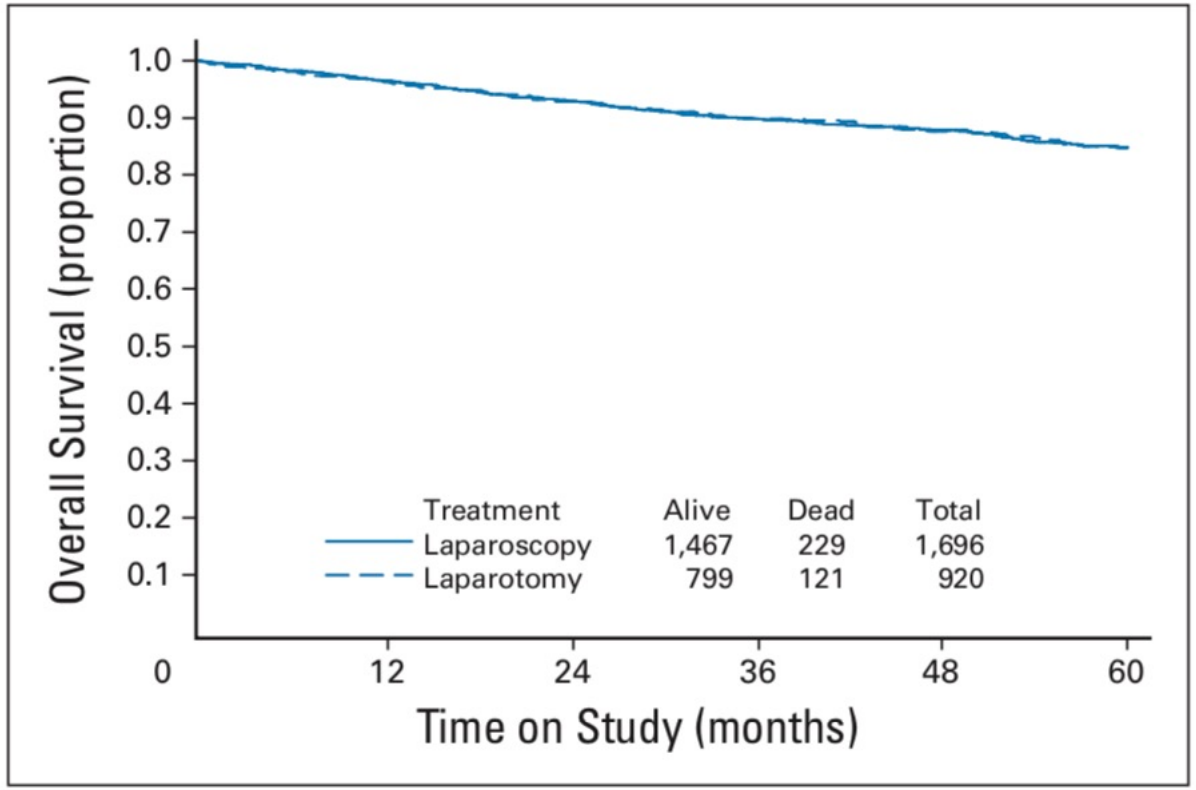
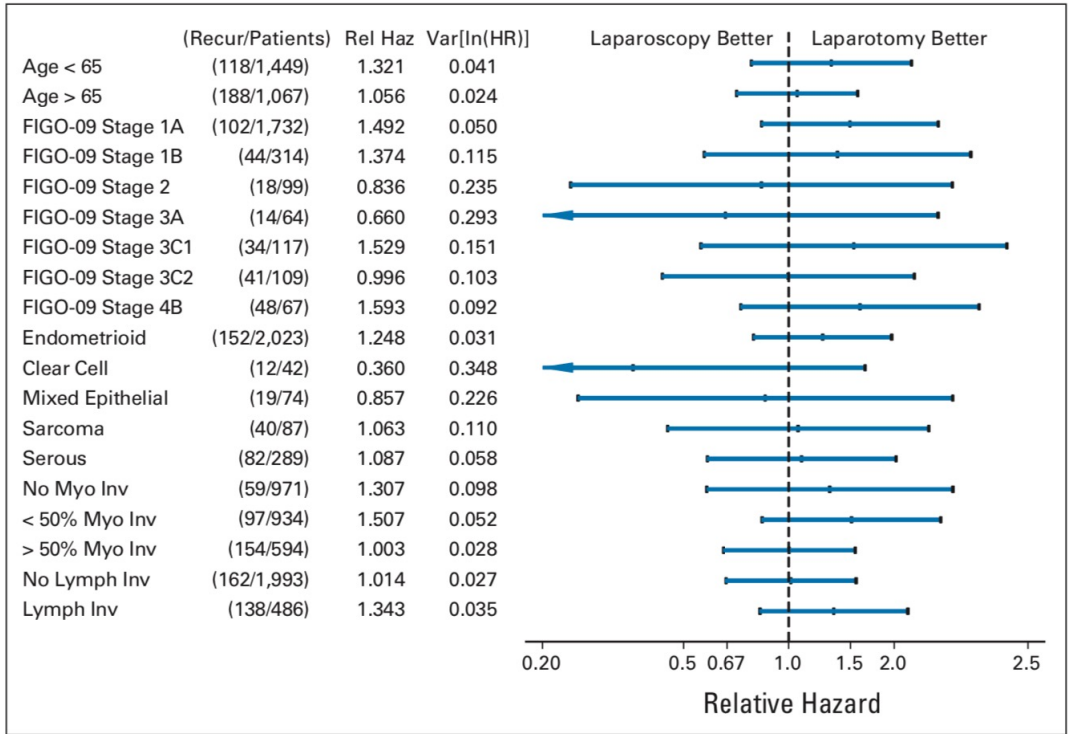


Fig 3. Overall survival by randomly assigned treatment group.



Cirurgia

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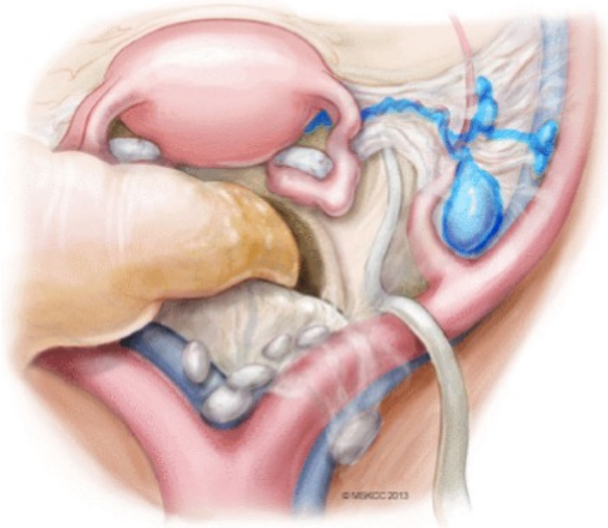
Histerectomia laparoscópica

+ Salpingo-oforectomia bilateral
+ Pesquisa de linfonodo sentinela



Pesquisa de linfonodo sentinela

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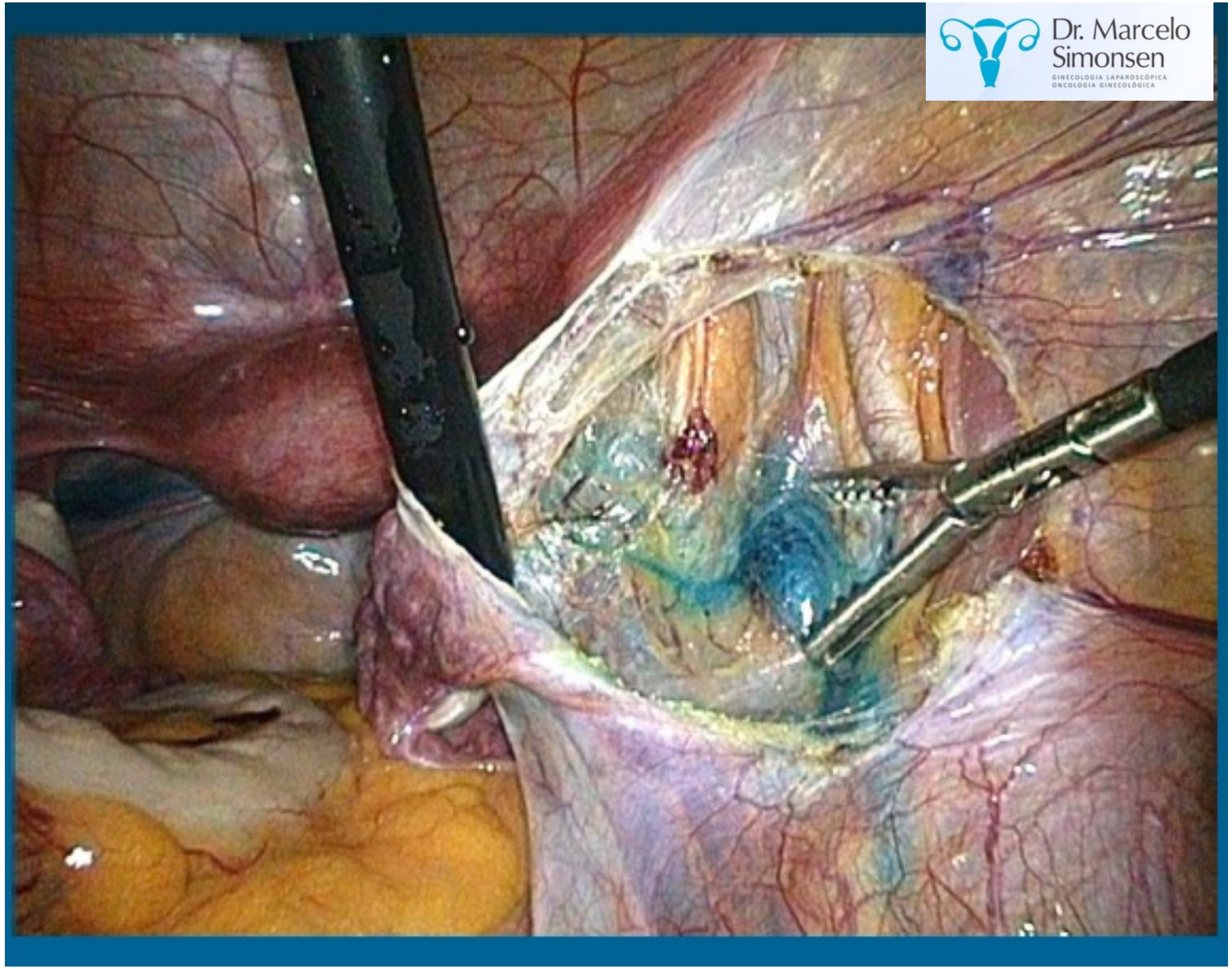
Linfonodo sentinela



Marcadores
(detecção bilateral)

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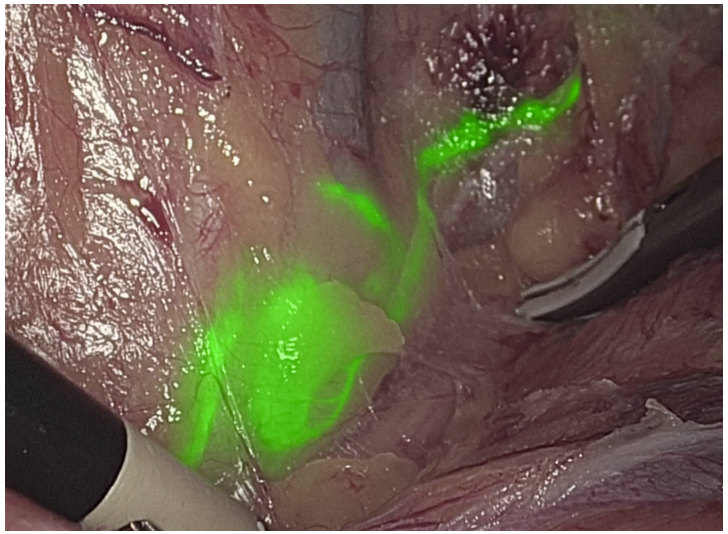
Azul patente (31%)

Tecnécio (71%)

Indocianina verde (81%)



Até que estadio presumido fazer sentinela?

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Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging

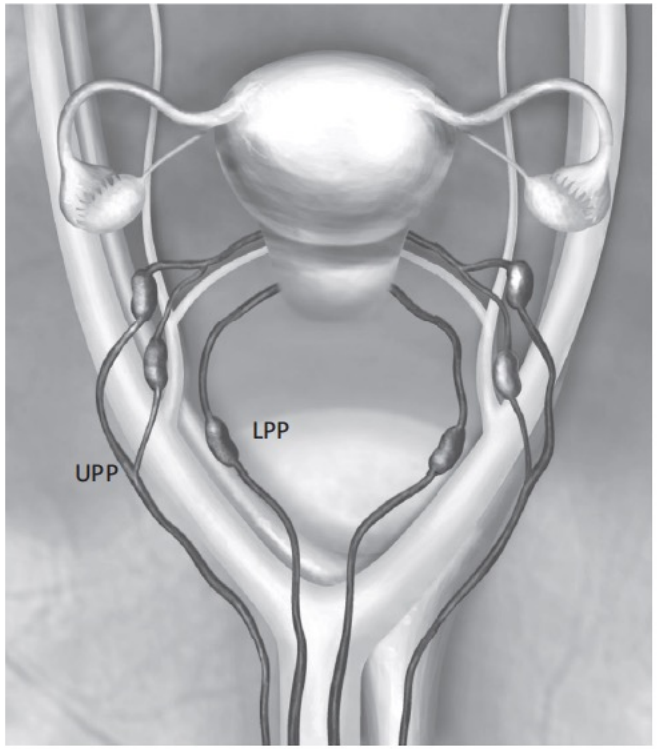
Persson et al Europ J of Cancer 2019

Left obturator area:
SLN-ICG[1]: 63%
Metastatic SLNs[2]: 25%
Any metastatic LN[2]: 34%

Left external iliac area:
SLN-ICG[1]: 82%
Metastatic SLNs[2]: 41%
Any metastatic LN[2]: 45%

Left presacral area:
SLN-ICG[1]: 52%
Metastatic SLNs[2]: 5%
Any metastatic LN[2]: 13%

Left common iliac area:
SLN-ICG[1]: 13%
Metastatic SLNs[2]: 2%
Any metastatic LN[2]: 7%

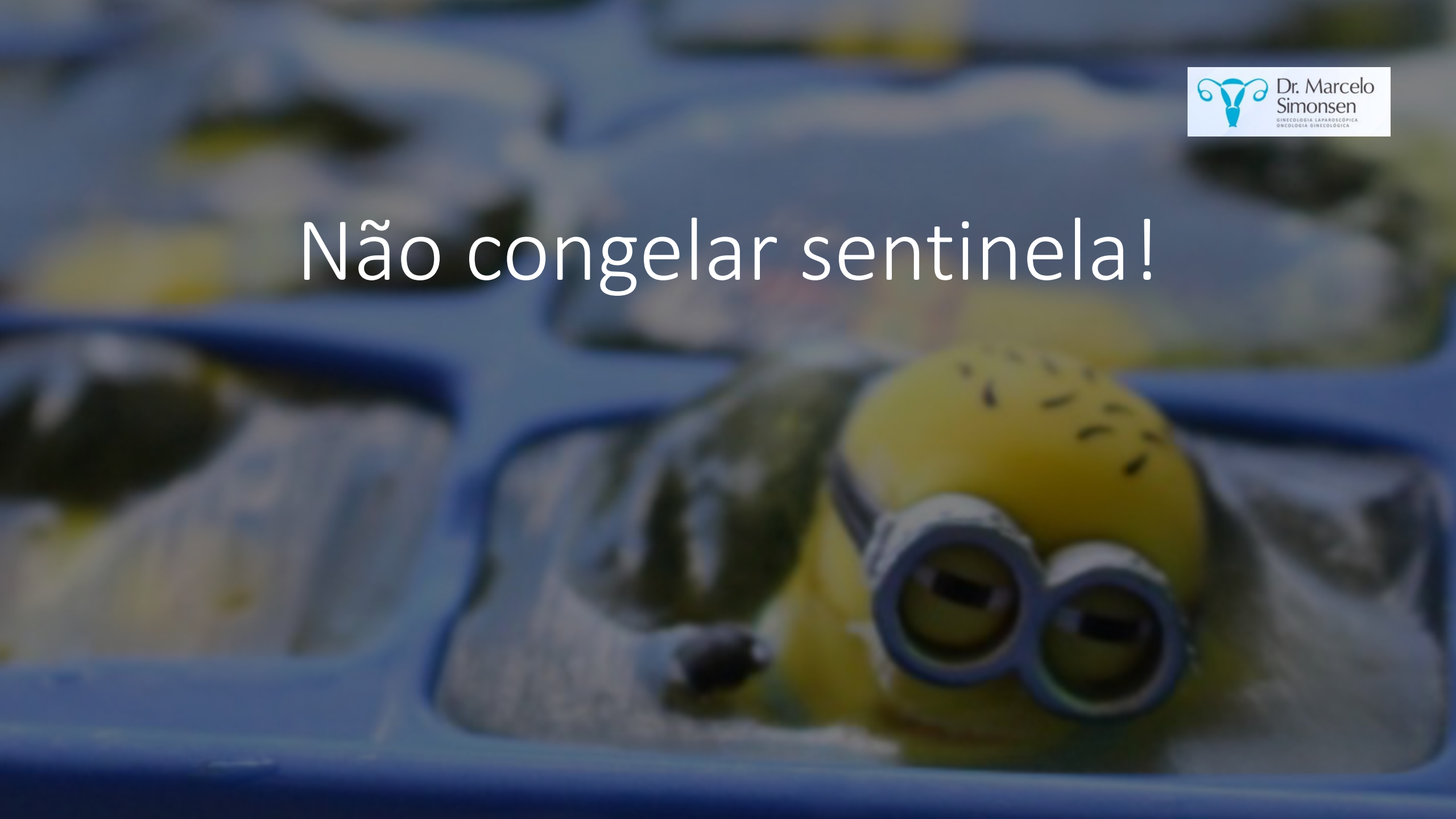


Right Obturator area:
SLN-ICG[1]: 62%
Metastatic SLNs[2]: 36%
Any metastatic LN[2]: 43%

Right external iliac area:
SLN-ICG[1]: 80%
Metastatic SLNs[2]: 25%
Any metastatic LN[2]: 29%

Right presacral area:
SLN-ICG[1]: 59%
Metastatic SLNs[2]: 9%
Any metastatic LN[2]: 13%

Right common iliac area:
SLN-ICG[1]: 13%
Metastatic SLNs[2]: 4%
Any metastatic LN[2]: 16%



Não congelar sentinela!

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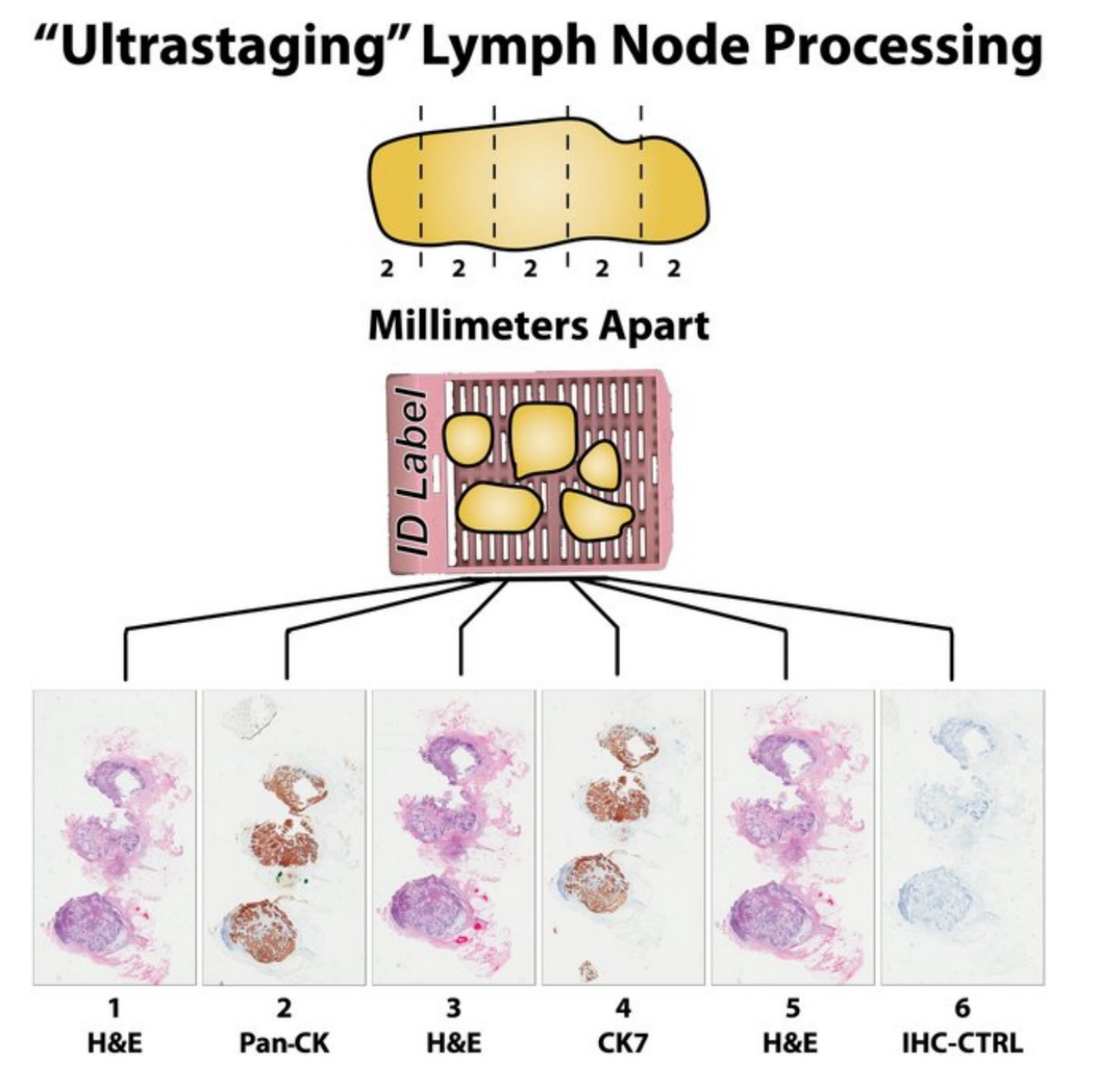
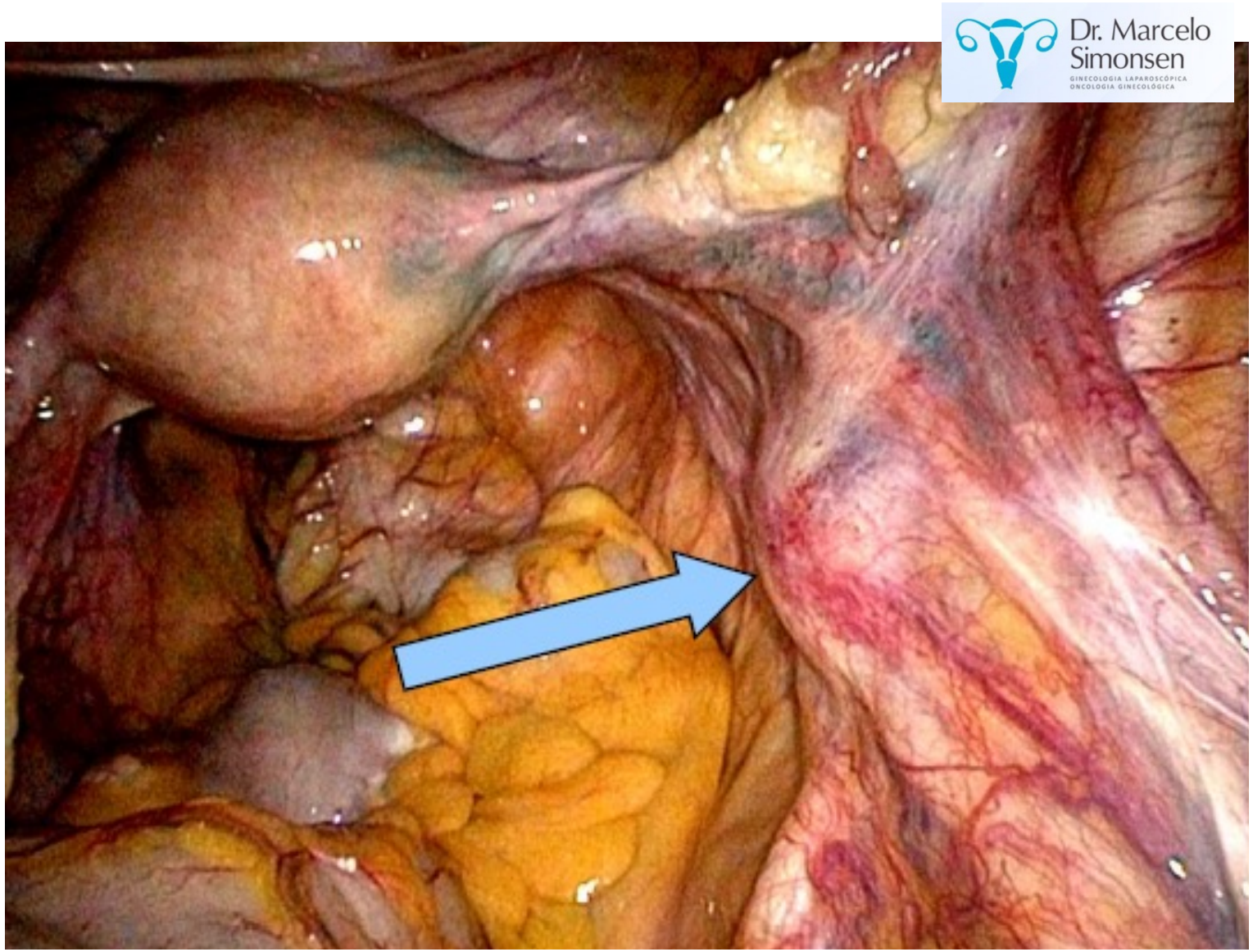


Kang et al Plos One 2020

Debulking linfonodal



Linfonodos comprometidos
Presunção vs realidade

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IaG1: 5%

IaG3: 9%

IbG2 e 3: 10% pélvicos e 4% para-aórticos

Apenas 1% comprometimento PA quando pélvicos livres

SGO Clinical Practice Endometrial Cancer Working Group 2014

Manipulador Uterino?

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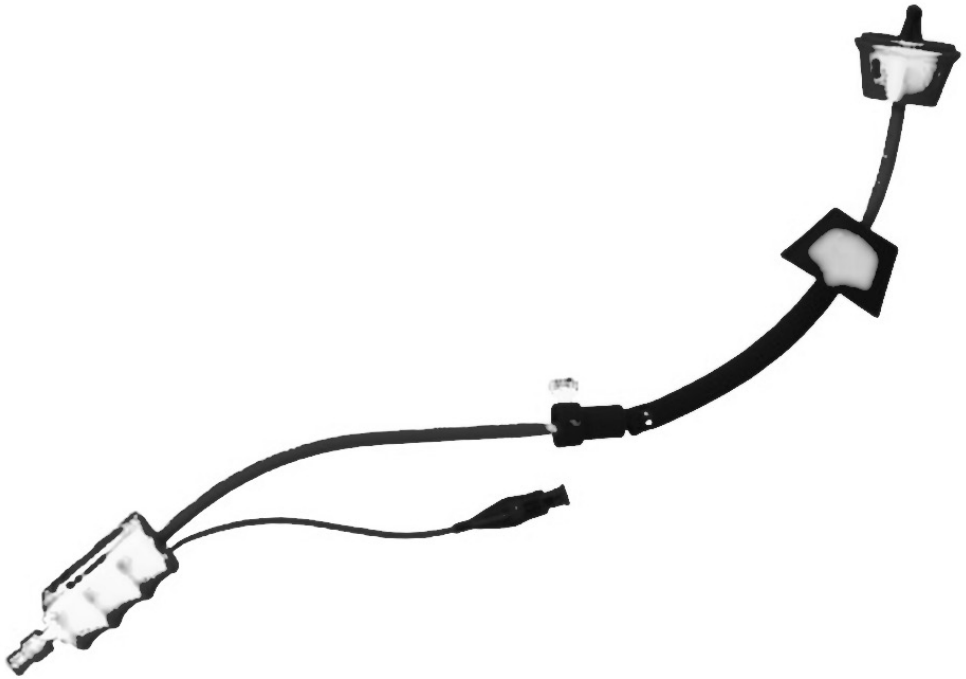

Manipulador Uterino?

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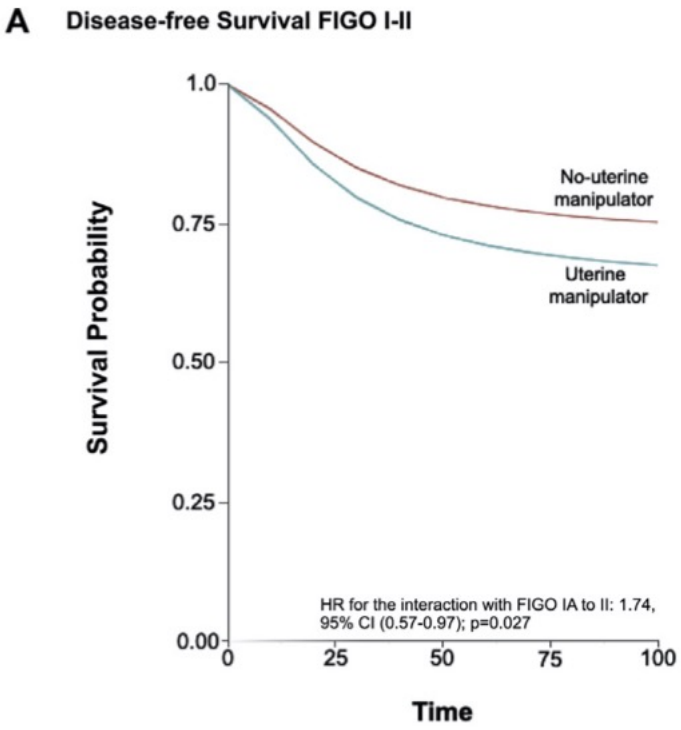
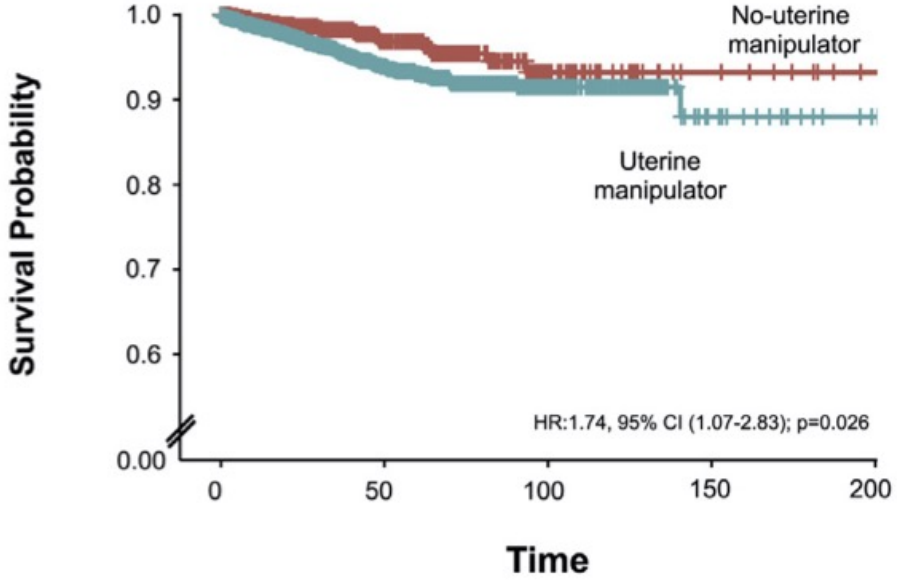
Impact of uterine manipulator on oncological outcome in endometrial cancer surgery

Padilla Iserte 2020





Influence of uterine manipulator on oncological outcome in minimally invasive surgery of endometrial cancer: A systematic review and meta-analysis

Scutiero et all Europ J Surg Oncol 2022

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Study or Subgroup	With UM Events	With UM Total	Without UM Events	Without UM Total	Weight	Risk Ratio M-H, Random, 95% CI
Lee 2013	5	55	1	55	4.0%	5.00 [0.60, 41.42]
Tinelli 2016	3	55	2	55	5.5%	1.50 [0.26, 8.63]
Gueli Alletti 2021	4	78	6	76	9.9%	0.65 [0.19, 2.21]
Marcos-Sanmartìn 2016	6	77	14	70	15.0%	0.39 [0.16, 0.96]
Uccella 2017	78	579	43	372	31.4%	1.17 [0.82, 1.65]
Padilla 2021	205	1756	67	905	34.2%	1.58 [1.21, 2.05]
Total (95% CI)		**2600**		**1533**	**100.0%**	**1.11 [0.71, 1.74]**
Total events	301		133			

Heterogeneity: Tau² = 0.13; Chi² = 12.13, df = 5 (P = 0.03); I² = 59%
Test for overall effect: Z = 0.47 (P = 0.64)

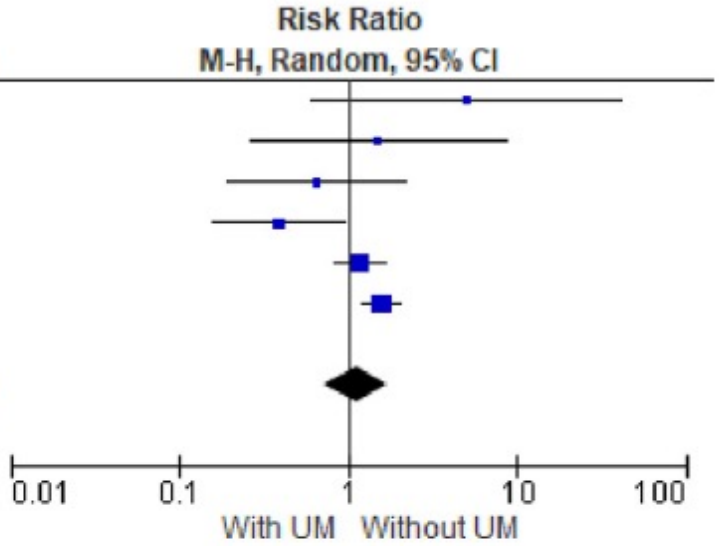
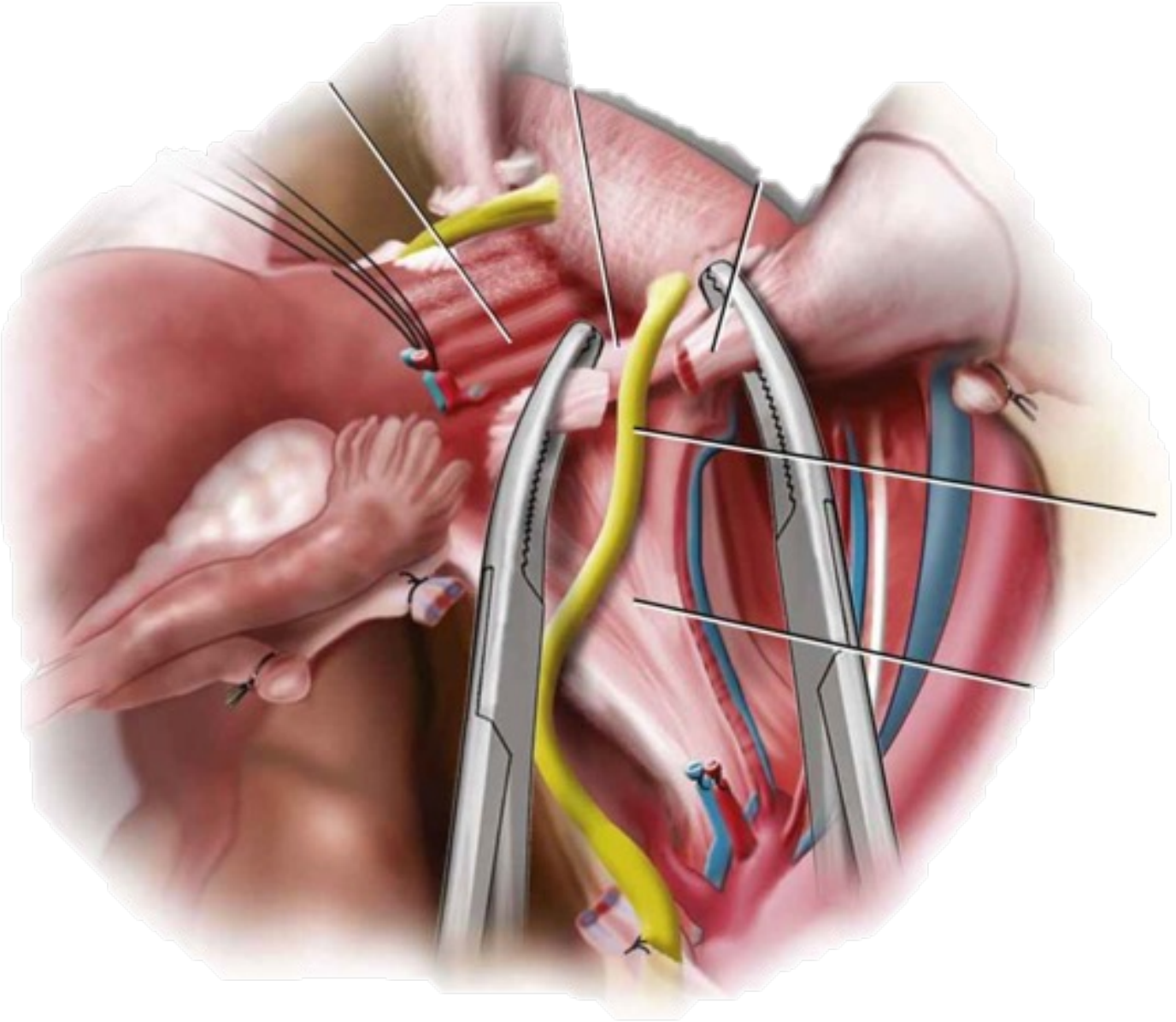


Fig. 5. Forest plot of comparison: Risk ratio (RR) and Forest Plot for the incidence of recurrence with or without uterine manipulator, outcome: recurrence. In the graph. Left graph label: with UM (LH). Right graph label: without UM (LH).

Histe[illegible]nia [illegible]ical



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Histerectomia Radical

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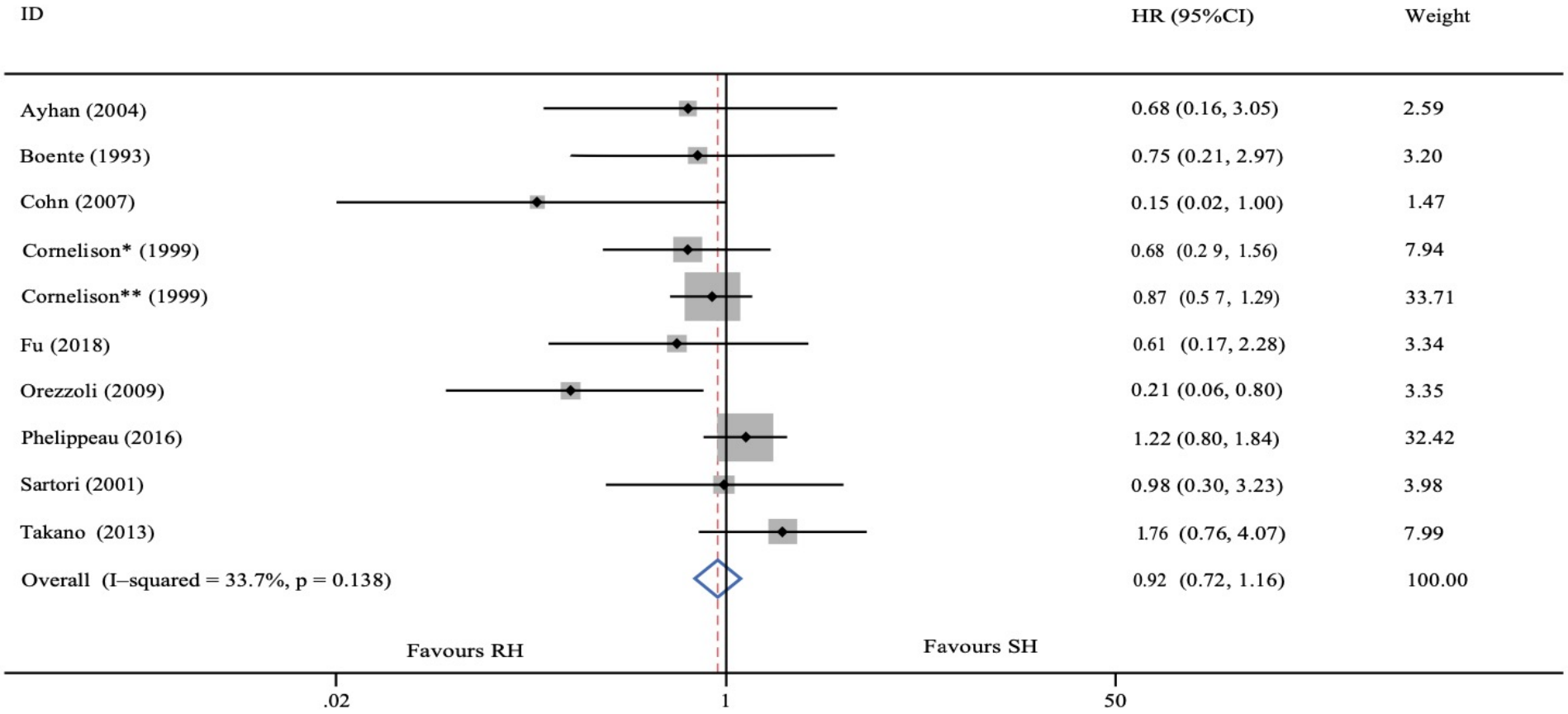
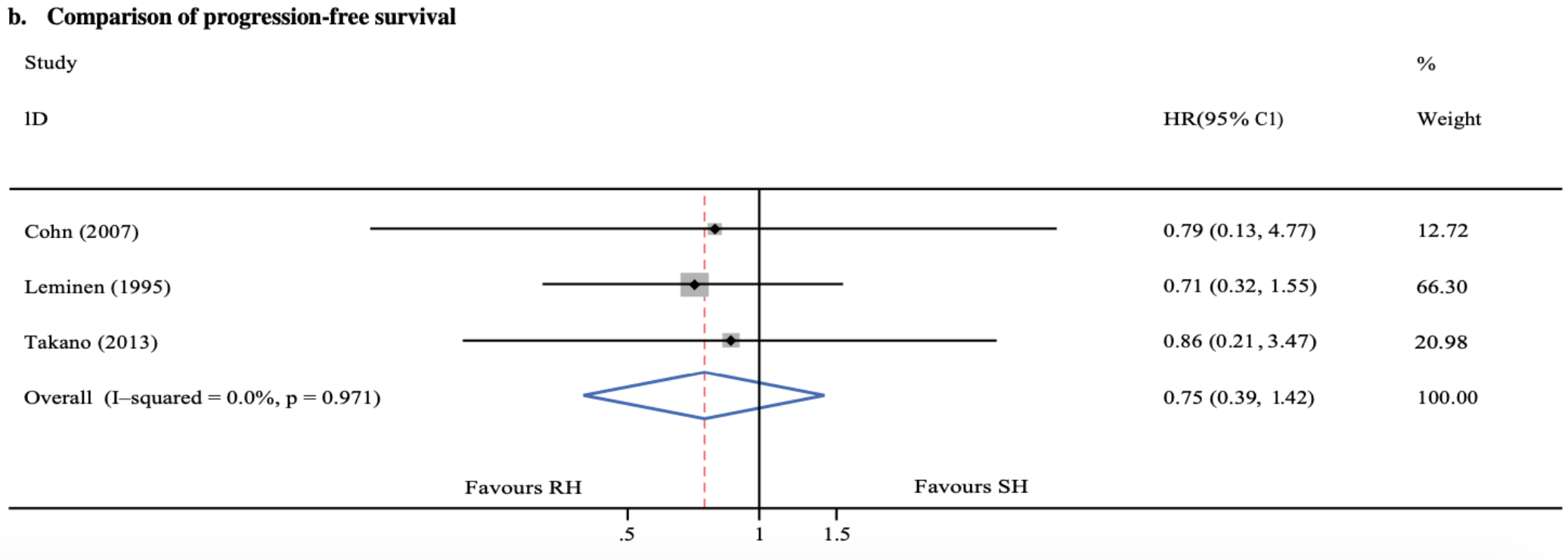
Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis

Liu et al 2019

a. Comparison of overall survival



Histerectomia Radical



Linfonodectomia para aórtica?

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Fig. 2 5-year overall survival forest plot

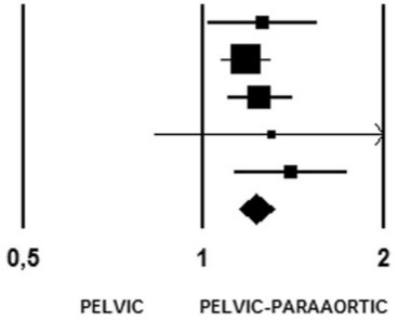
5-YEAR OVERALL SURVIVAL

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Eggemann 2016	1,050	0,977	1,127	1,325	0,185
Yoon 2016	1,116	0,978	1,275	1,625	0,104
Todo 2010	1,152	1,035	1,281	2,600	0,009
Mariani 2000	1,354	1,121	1,637	3,141	0,002
	1,134	1,038	1,239	2,773	0,006

Fig. 3 5-year disease-free survival forest plot

5-YEAR DISEASE-FREE SURVIVAL

Study name	Statistics for each study				
	Risk ratio	Lower limit	Upper limit	Z-Value	p-Value
Yoon 2016	1,253	1,015	1,547	2,098	0,036
May 2013	1,178	1,071	1,295	3,379	0,001
Todo 2010	1,243	1,100	1,405	3,487	0,000
Fujimoto 2007	1,305	0,828	2,056	1,147	0,251
Mariani 2000	1,399	1,126	1,738	3,034	0,002
	1,227	1,148	1,311	6,019	0,000



Combined pelvic and para-aortic is superior to only pelvic lymphadenectomy in intermediate and high-risk endometrial cancer: a systematic review and meta-analysis

Dr. Marcelo Simonsen
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Fig. 2 5-year overall survival forest plot

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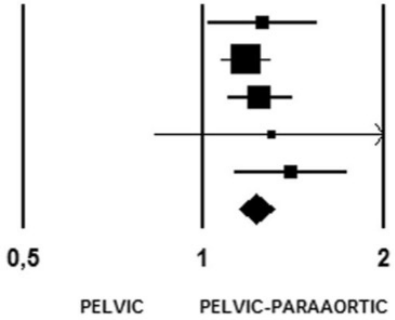

Petousis et all Arch Gynecol Obstet 2020

Adjuvância em Estadio inicial

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FRs:

- Invasão profunda,
- G3,
- > 60anos,
- IAL

2 indicam Braquiterapia!!!

Adjuvância NCCN 2023

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CLINICAL FINDINGS (Endometrioid Histology)[a]

HISTOLOGIC GRADE/ADJUVANT TREATMENT[g,h,m]

Surgically staged: Stage I[e] →

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Consider vaginal brachytherapy if lymphovascular space invasion (LVSI) and/or age ≥60 y[n]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion or Consider EBRT if either age ≥70 y or LVSI (category 2B)
IB	G1	Vaginal brachytherapy preferred or Consider observation if age <60 y and no LVSI
	G2	Vaginal brachytherapy preferred or Consider EBRT if ≥60 y and/or LVSI or Consider observation if age <60 y and no LVSI
	G3	RT (EBRT and/or vaginal brachytherapy) ± systemic therapy (category 2B for systemic therapy)

Mensagens finais

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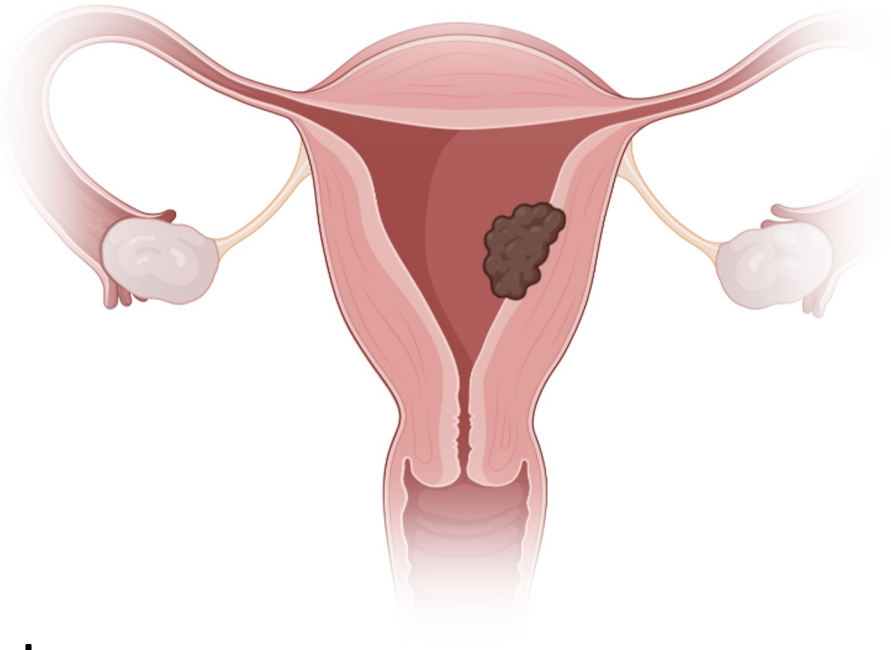
- Melhor via minimamente invasiva
- Cuidado com manipulador uterino
- PLS estadios iniciais
- Não congelar linfonodo sentinela
- Linfonodectomia PA alto risco
- Histerectomia radical raramente indicada



Obrigado!