子宮內膜癌的治療新趨勢與展望

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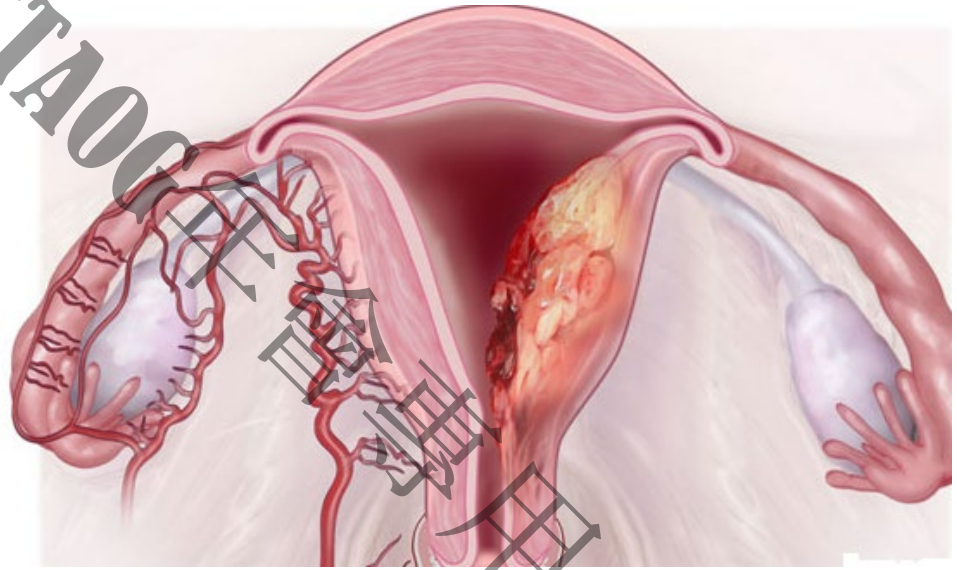
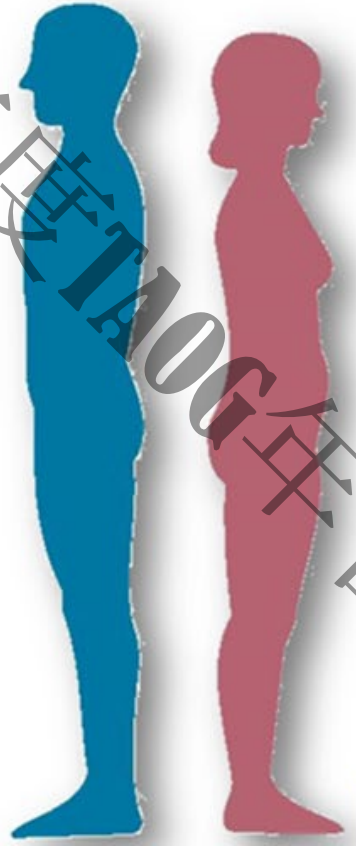


Outline

- Incidence during Covid-19
- Minimally invasive surgery
- Adjuvant therapy for advanced stage disease
- 2nd line treatment for recurrent disease
- Targeting Her2/neu
- Molecular classification of FIGO staging 2023

110 年台灣男女性 10 大癌症標準化發生率

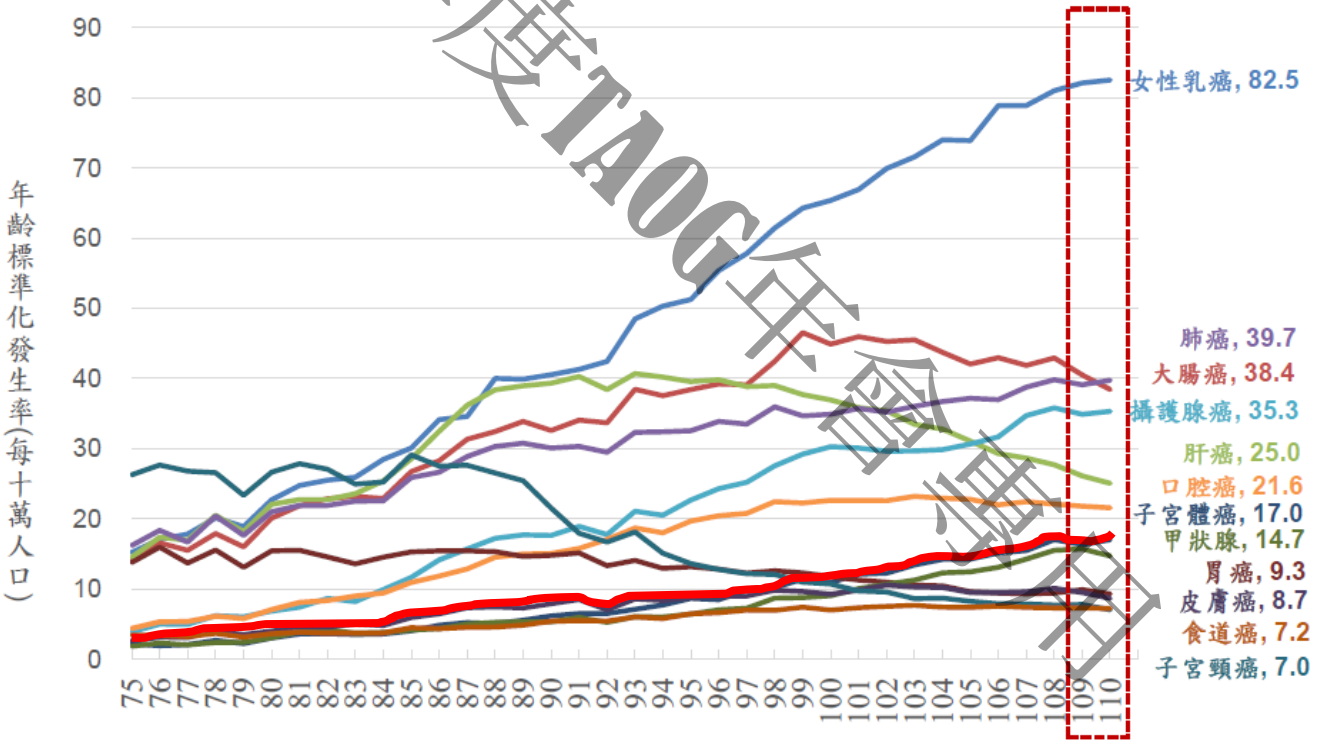
男性		女性	
(9,297人)大腸	47.1/10^5	82.5/10^5	乳房(15,448人)
(8,961人)肺、支氣管及氣管	44.5/10^5	36.0/10^5	肺、支氣管及氣管(7,919人)
(7,387人)口腔	40.4/10^5	30.7/10^5	大腸(6,941人)
(7,448人)肝及肝內膽管	37.6/10^5	22.1/10^5	甲狀腺(3,497人)
(7,481人)攝護腺	35.3/10^5	17.0/10^5	子宮體(3,181人)
(2,614人)食道	13.7/10^5	13.6/10^5	肝及肝內膽管(3,327人)
(2,413人)胃	11.8/10^5	10.2/10^5	卵巢、輸卵管及寬韌帶(1,793人)
(2,127人)皮膚	10.3/10^5	7.3/10^5	皮膚(1,827人)
(1,588人)白血症	10.0/10^5	7.2/10^5	胃(1,647人)
(1,727人)非何杰金氏淋巴瘤	9.4/10^5	7.1/10^5	非何杰金氏淋巴瘤(1,438人)
(12,680人)其他癌症			其他癌症(11,021人)
(63,723人) 總計	330.8/10^5	288.4/10^5 總計	(58,039人)



各癌症標準化發生率趨勢

110年與109年比較：

- **大腸癌、肝癌、口腔癌、胃癌、甲狀腺癌、皮膚癌、子宮頸癌及食道癌發生率下降**
- **乳癌、肺癌、攝護腺癌及子宮體癌發生率上升**

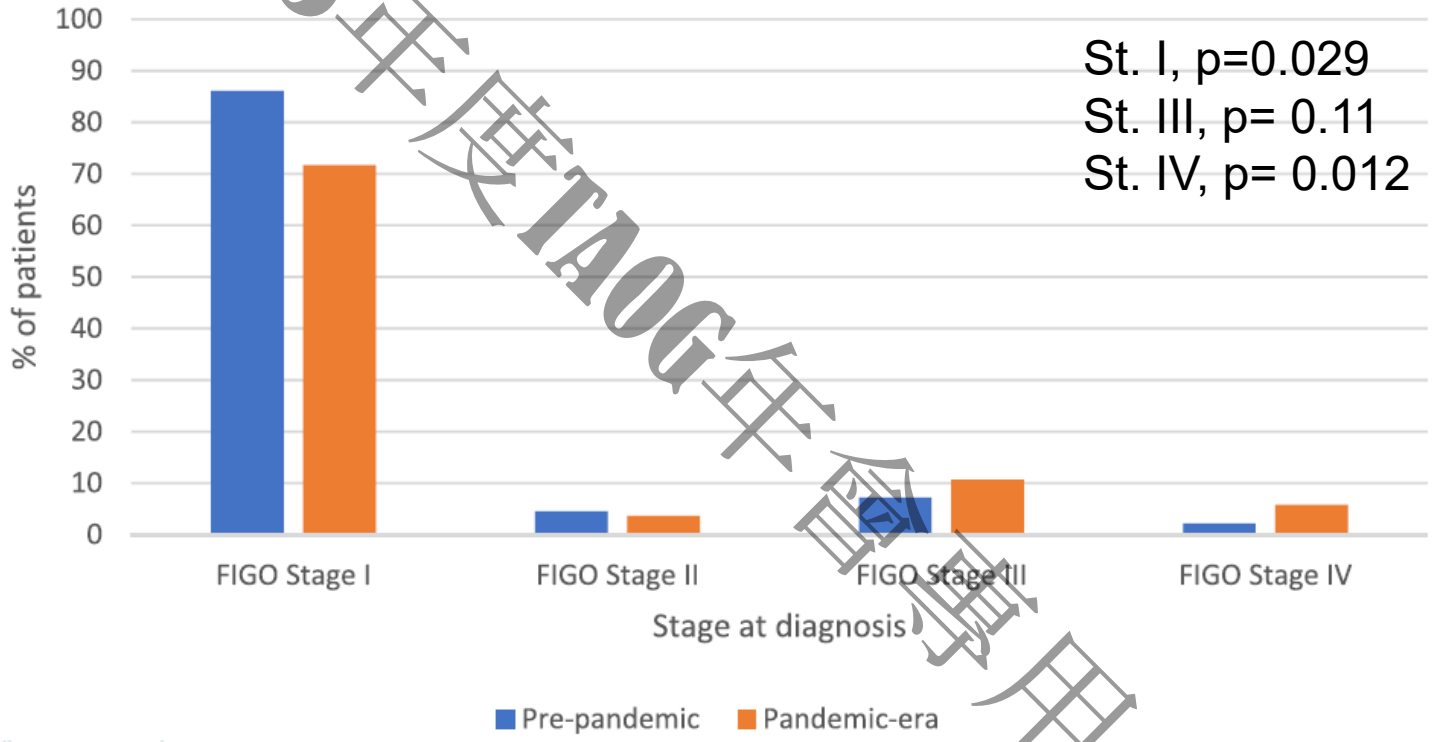


The impact of the Covid-19 pandemic on the stage of endometrial cancer at diagnosis

- Willamette Valley Cancer Center billing records (serves a population of at least 1 million people). Covering the greater part of Southern Oregon and the edge of Northern California.
- Between January 1, 2018, and April 30, 2022
- Pandemic cut-off: March 1, 2020.

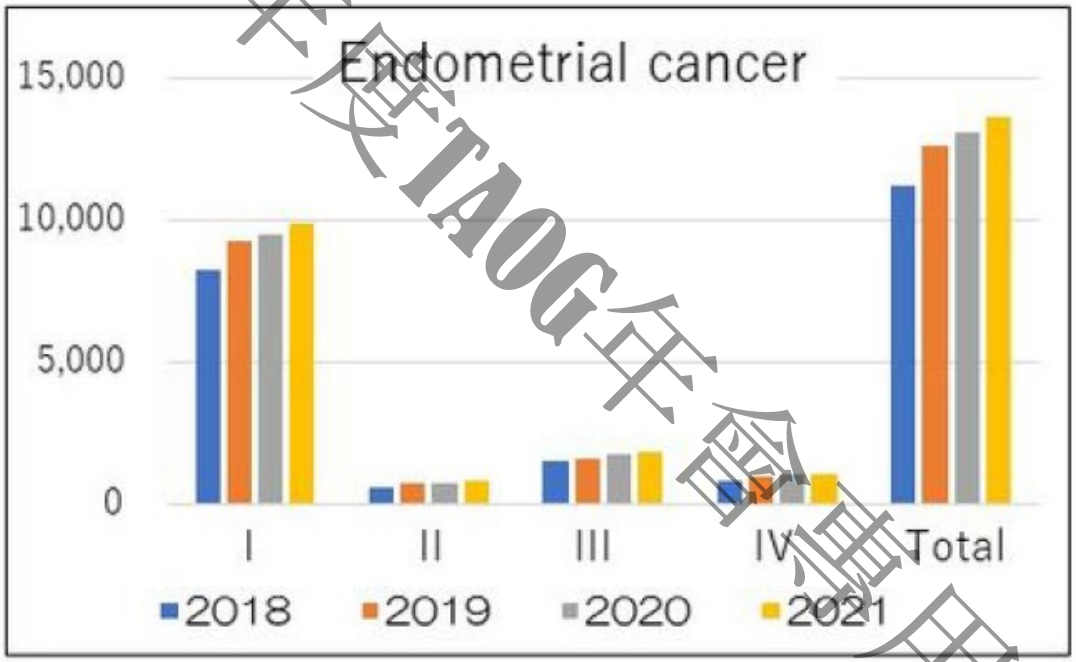
Gynecologic Oncology Reports 47 (2023) 101191

The impact of the Covid-19 pandemic on the stage of endometrial cancer at diagnosis



Gynecologic Oncology Reports 47 (2023) 101191

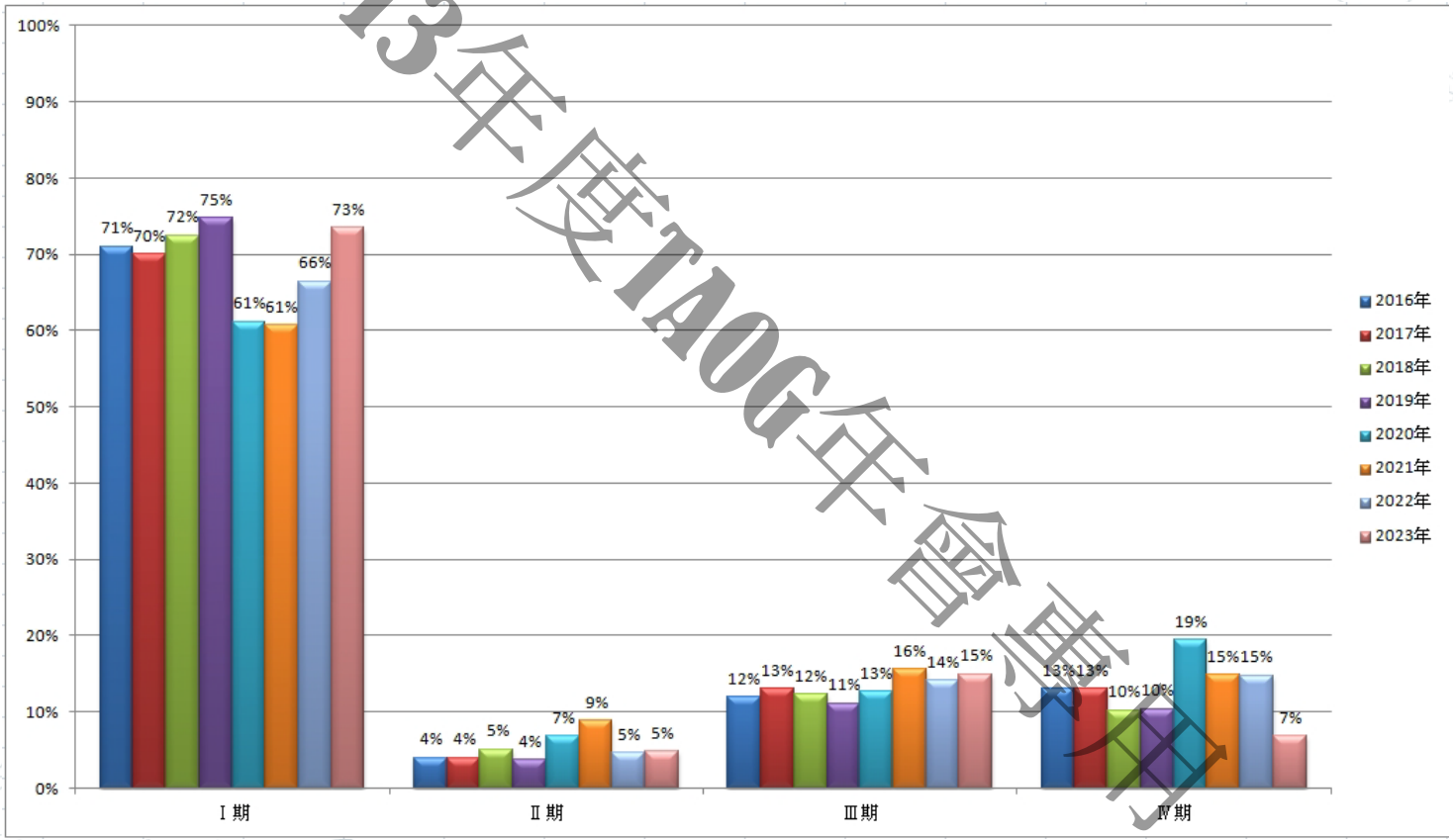
Impact of COVID-19 on Gynecological Cancer Incidence: A Large Cohort Study in Japan



#Japanese Society of Obstetricians and Gynecologic Oncology registry database

Int J Clin Oncol. 2024 Jan;29(1):72-77

Stage distribution before and after Covid-19 in TCVGH



Minimally invasive surgery

- Prevalence
- Robotic vs.LSC and laparotomy
- MIS in high-risk histology
- Uterine manipulator
- Sentinel lymph node in high-risk histology
- Stage II

Laparoscopy versus laparotomy for the management of early stage endometrial cancer – meta-analysis for OS

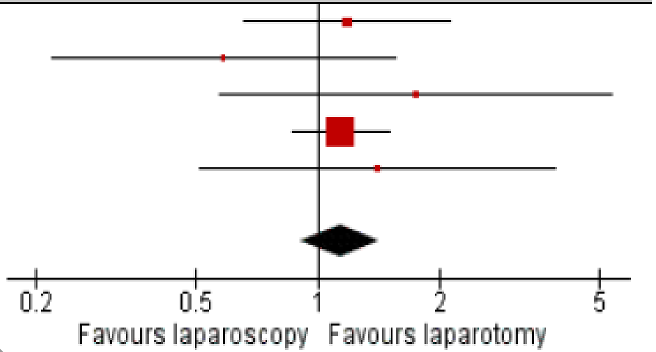
- 9 RCTs, N= 4389
- FIGO stage (1988): 70% of I-IIA
- Hysterectomy +/- PLND
- Laparoscopy: less blood loss, earlier discharge, increase QoL

Cochrane Database Syst Rev. 2018 Oct 31

Laparoscopy versus laparotomy for the management of early stage endometrial cancer – meta-analysis for PFS

Study or Subgroup	log[Hazard Ratio]	SE	Laparoscopy Total	Laparotomy Total	Weight	Hazard Ratio IV, Random, 95% CI
Janda 2017	0.17	0.3	407	353	15.2%	1.19 [0.66, 2.13]
Malzoni 2009	-0.54	0.5	81	78	5.5%	0.58 [0.22, 1.55]
Tozzi 2005	0.56	0.57	63	59	4.2%	1.75 [0.57, 5.35]
Walker 2012	0.13	0.14	1682	909	70.0%	1.14 [0.87, 1.50]
Zullo 2009	0.34	0.52	40	38	5.1%	1.40 [0.51, 3.89]
Total (95% CI)			**2273**	**1437**	**100.0%**	**1.14 [0.90, 1.43]**

Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.09 (P = 0.27)



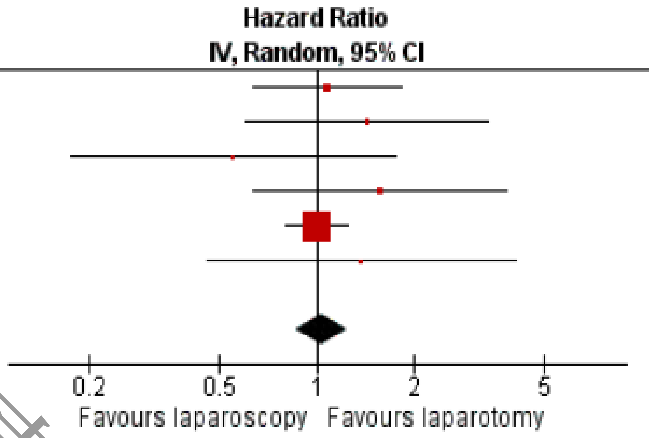
Cochrane Database Syst Rev. 2018 Oct 31

Laparoscopy versus laparotomy for the management of early stage endometrial cancer – meta-analysis for OS

Study or Subgroup	log[Hazard Ratio]	SE	Laparoscopy Total	Laparotomy Total	Weight	Hazard Ratio IV, Random, 95% CI
Janda 2017	0.08	0.27	407	353	12.2%	1.08 [0.64, 1.84]
Lu 2013	0.36	0.44	151	121	4.6%	1.43 [0.61, 3.40]
Malzoni 2009	-0.59	0.59	81	78	2.6%	0.55 [0.17, 1.76]
Tozzi 2005	0.45	0.46	63	59	4.2%	1.57 [0.64, 3.86]
Walker 2012	0	0.11	920	1682	73.6%	1.00 [0.81, 1.24]
Zullo 2009	0.32	0.56	40	38	2.8%	1.38 [0.46, 4.13]
Total (95% CI)			**1662**	**2331**	**100.0%**	**1.04 [0.86, 1.25]**

Heterogeneity: Tau² = 0.00; Chi² = 2.87, df = 5 (P = 0.72); I² = 0%

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



Cochrane Database Syst Rev. 2018 Oct 31

Long-term outcome of minimally invasive staging surgery for clinical stage I endometrial cancer: A single institute experience in Taiwan

- Clinical stage 1 endometrial cancer from 2009 to 2020 in TCVGH
- 665 cases: 412 MIS, 253 laparotomy
- Favor MIS: operation time, blood loss, hospital stay
- Median F/U: 82.6 months

Long-term outcome of minimally invasive staging surgery for clinical stage I endometrial cancer: A single institute experience in Taiwan

Pathological parameters

	MIS (n = 412)	Laparotomy (n = 253)	*p*
Uterus size, g, median (IQR)	125 (90.0-200.0)	150 (100.0-250.0)	<0.001
Pelvic lymphadenectomy cases, n (%)	390 (94.7)	236 (93.3)	0.462
Para-aortic lymphadenectomy cases, n (%)	136 (33)	191 (75.5)	<0.00001
Pelvic LN retrieved (n), median (IQR)	18.0 (12.3-24.0)	17.0 (13.0-25.8)	0.612
PA LN retrieved (n), median (IQR)	10.0 (6-14.0)	6 (4.0-10.0)	0.852
Pathology stagea			
1A, n (%)	344 (83.5)	170 (67.2)	<0.001
1B, n (%)	50 (12.1)	60 (23.7)	0.004
2, n (%)	4 (1.0)	7 (2.8)	0.114
3, n (%)	13 (3.2)	11 (4.4)	0.28
4, n (%)	1 (0.2)	5 (2)	0.052
Histology			0.002
Endometrioid, n (%)	400 (97.1)	206 (81.4)	<0.001
Grade			
1, n (%)	184 (46.0)	62 (30.1)	<0.001
2, n (%)	197 (49.2)	101 (49.0)	0.948
3, n (%)	19 (4.8)	43 (20.9)	<0.001
Type II carcinoma, n (%)	12 (2.9)	47 (18.6)	<0.001
Serous carcinoma, n (%)	11 (2.6)	41 (16.2)	0.002
Clear cell carcinoma, n (%)	1 (0.2)	6 (2.4)	0.014
MMR			0.923
Preserved, n (%)	126 (75.9)	42 (77.8)	
Loss, n (%)	40 (24.1)	12 (22.2)	
LVSI			0.091
Negative, n (%)	332 (80.6)	189 (74.7)	
Positive, n (%)	80 (19.4)	64 (25.3)	

J Chin Med Assoc. 2024 Jan 1;87(1):79-87

Long-term outcome of minimally invasive staging surgery for clinical stage I endometrial cancer: A single institute experience in Taiwan

Comparison of related literature in Taiwan

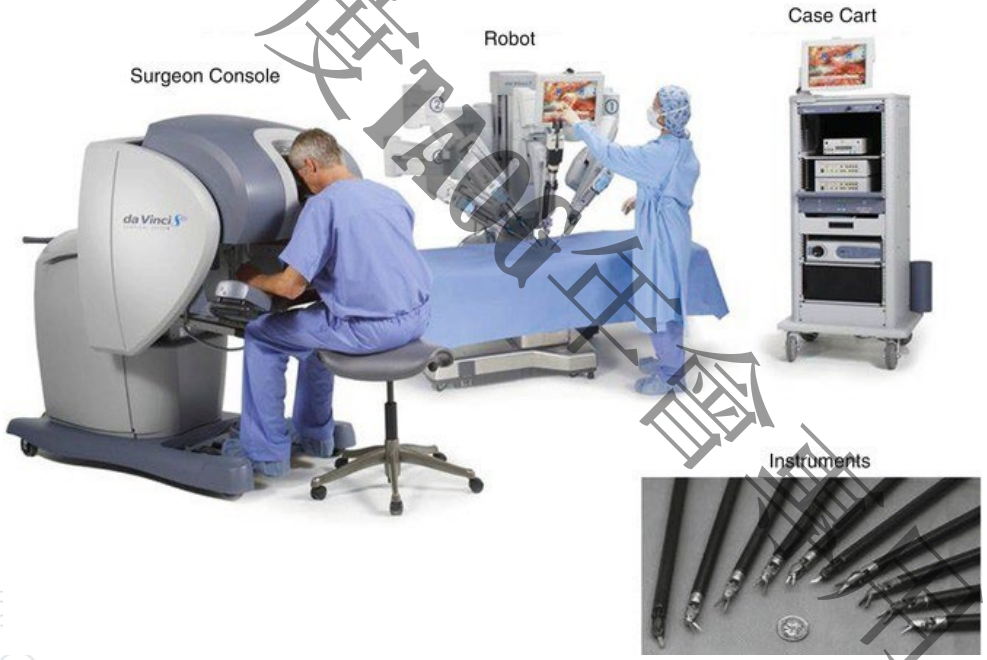
Author and title	Lee C-L, long-term survival outcome of laparoscopic staging surgery for endometrial cancer in Taiwanese experience[4]	Chiou HY, comparing robotic surgery with laparoscopy and laparotomy for endometrial cancer management: a cohort study[18]	Chu LH, comparison of the laparoscopic versus conventional open method for surgical staging of endometrial carcinoma[19]	Lu TF, long-term outcome of MIS surgery for clinical stage I endometrial cancer: a single institute experience in Taiwan
Study design	Retrospective cohort. Single arm. Clinical stage I.	Retrospective cohort. Double arm. Clinical stage IA to IIIC.	Retrospective cohort. Double arm. Clinical stage I and tumor mass of ≤2 cm.	Retrospective cohort. Double arm. Clinical stage I.
Patient number	105 patients.	365 patients.	151 patients.	665 patients.
MIS	Laparoscopic: 105 patients.	Laparoscopic: 150 patients. Robotic: 86 patients.	Laparoscopic: 70 patients.	Laparoscopic: 395 patients. Robotic: 17 patients.
5-y PFS rate	MIS: 93.39%	Robotic: 98.8% Laparoscopic: 91.3% Laparotomy: 88.4%	MIS: 97.1% Laparotomy: 96.3%	MIS: 95.9% Laparotomy: 88.6%
5-y OS rate	MIS: 98.05%	Robotic: 98.8% Laparoscopic: 98% Laparotomy: 94.6%	MIS: 98.6% Laparotomy: 97.5%	MIS: 99.4% Laparotomy: 94.9%

J Chin Med Assoc. 2024 Jan 1;87(1):79-87

2012-2021 子宮體癌一期手術微創比例

中榮vs.台灣

Robotic-assisted laparoscopy



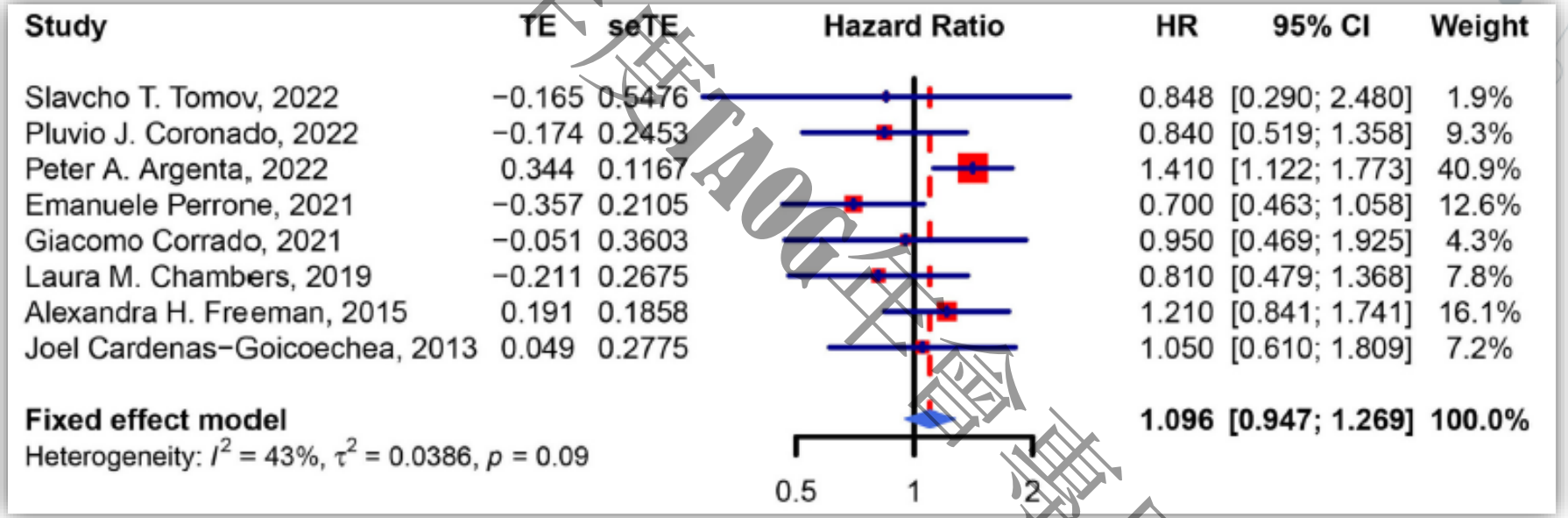
Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

- 21 trials, all retrospective cohort studies
- N= 164,999, 77662 in robotic, 32826 in laparoscopy, 54511 in laparotomy
- Stage I-IV

Gynecol Oncol. 2023 Jul;174:55-67

Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

PFS: Robotic vs. LSC



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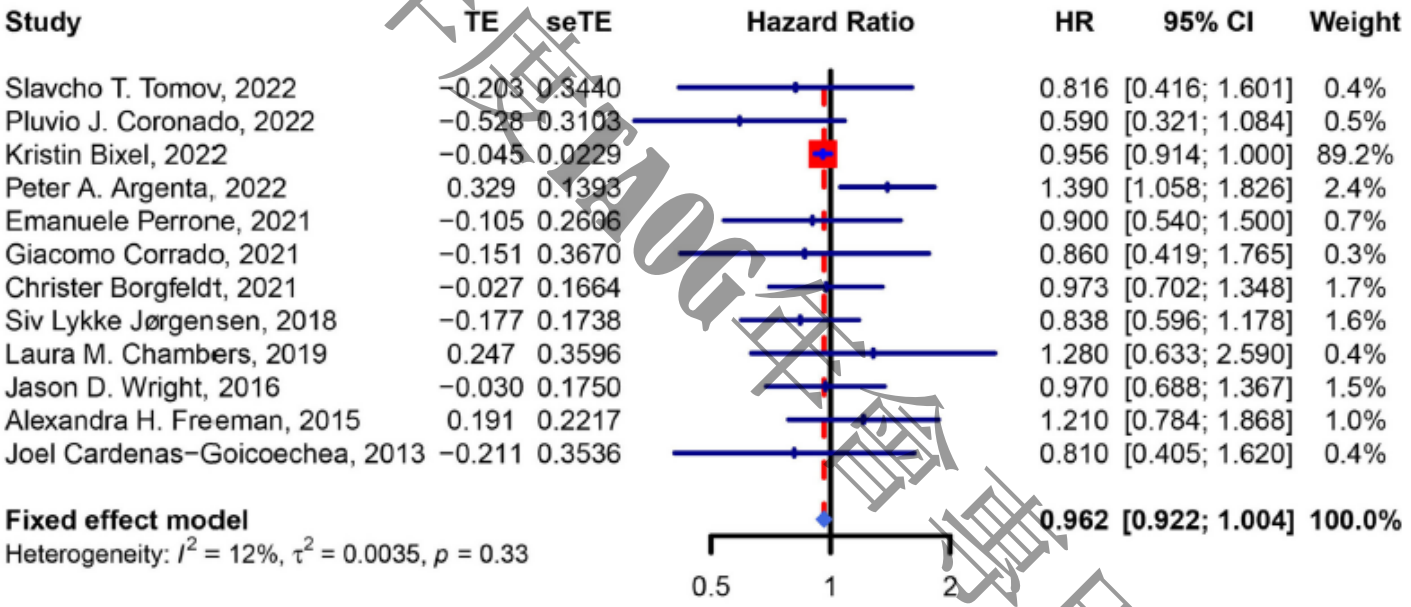
Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

OS Robotic vs. LSC



Gynecol Oncol. 2023 Jul;174:55-67

Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

Comparison	Indicator	*k*	HR (95% CI)	I^2	Egger's test	
					t	*P*
RALS vs CLS	OS	12	0.962 (0.922–1.004)	12%	0.13	0.90
	RFS	8	1.096 (0.947–1.296)	43%	−2.24	0.06
	DSS	4	1.489 (0.713–3.107)	84%	–	–
RALS vs LT	OS	13	0.682 (0.576–0.807)	63%	−1.79	0.10
	RFS	10	0.793 (0.653–0.964)	20%	1.03	0.33
	DSS	2	0.441 (0.298–0.652)	0%	–	–

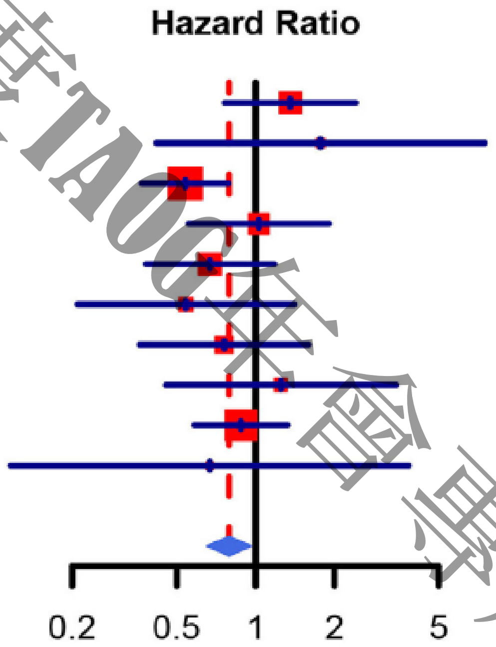
Gynecol Oncol. 2023 Jul;174:55-67

Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

PFS: Robotic vs. Laparotomy

Study	TE	seTE	HR	95% CI	Weight
Slavcho T. Tomov, 2022	0.305	0.2931	1.357	[0.764; 2.410]	11.5%
Massoud Shoraka, 2022	0.570	0.7358	1.768	[0.418; 7.478]	1.8%
Pluvio J. Coronado, 2022	−0.616	0.1935	0.540	[0.370; 0.789]	26.3%
Kyung Jin Eoh, 2021	0.030	0.3130	1.030	[0.558; 1.902]	10.0%
Anna Lindfors, 2020	−0.400	0.2869	0.670	[0.382; 1.176]	12.0%
Nidhi Nayyar, 2019	−0.612	0.4840	0.542	[0.210; 1.399]	4.2%
Tilley Jenkins Vogel, 2014	−0.274	0.3773	0.760	[0.363; 1.592]	6.9%
Andres A. Roma MD, 2015	0.223	0.5148	1.250	[0.456; 3.428]	3.7%
Hyo K. Park, 2015	−0.128	0.2098	0.880	[0.583; 1.328]	22.4%
Pluvio J. Coronado, 2012	−0.400	0.8920	0.670	[0.117; 3.849]	1.2%
Fixed effect model			**0.793**	**[0.653; 0.964]**	**100.0%**

Heterogeneity: $I^2 = 20\%$, $\tau^2 = 0.0263$, $p = 0.26$



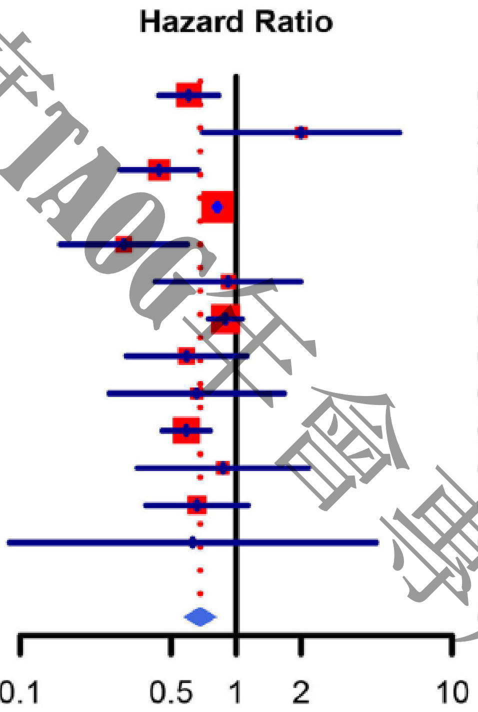
Gynecol Oncol. 2023 Jul;174:55-67

Survival outcomes of robotic-assisted laparoscopy versus conventional laparoscopy and laparotomy for endometrial cancer: A systematic review and meta-analysis

OS Robotic vs. laparotomy

Study	TE	seTE	HR	95% CI	Weight
Slavcho T. Tomov, 2022	−0.506	0.1628	0.603	[0.438; 0.830]	11.7%
Massoud Shoraka, 2022	0.693	0.5350	2.000	[0.701; 5.707]	2.3%
Pluvio J. Coronado, 2022	−0.821	0.2098	0.440	[0.292; 0.664]	9.1%
Kristin Bixel, 2022	−0.200	0.0146	0.819	[0.796; 0.843]	20.1%
Kyung Jin Eoh, 2021	−1.197	0.3448	0.302	[0.154; 0.594]	4.7%
Kyung Jin Eoh, 2021	−0.083	0.3943	0.920	[0.425; 1.992]	3.8%
Christer Borgfeldt, 2021	−0.113	0.0906	0.893	[0.748; 1.066]	16.5%
Anna Lindfors, 2020	−0.528	0.3277	0.590	[0.310; 1.121]	5.1%
Nidhi Nayyar, 2019	−0.420	0.4754	0.657	[0.259; 1.668]	2.8%
Siv Lykke Jørgensen, 2018	−0.531	0.1308	0.588	[0.455; 0.760]	13.7%
Tilley Jenkins Vogel, 2014	−0.139	0.4654	0.870	[0.349; 2.166]	2.9%
Hyo K. Park, 2015	−0.416	0.2780	0.660	[0.383; 1.138]	6.5%
Pluvio J. Coronado, 2012	−0.462	0.9974	0.630	[0.089; 4.450]	0.7%
Random effects model			**0.682**	**[0.576; 0.807]**	**100.0%**

Heterogeneity: $I^2 = 63\%$, $\tau^2 = 0.0363$, $p < 0.01$



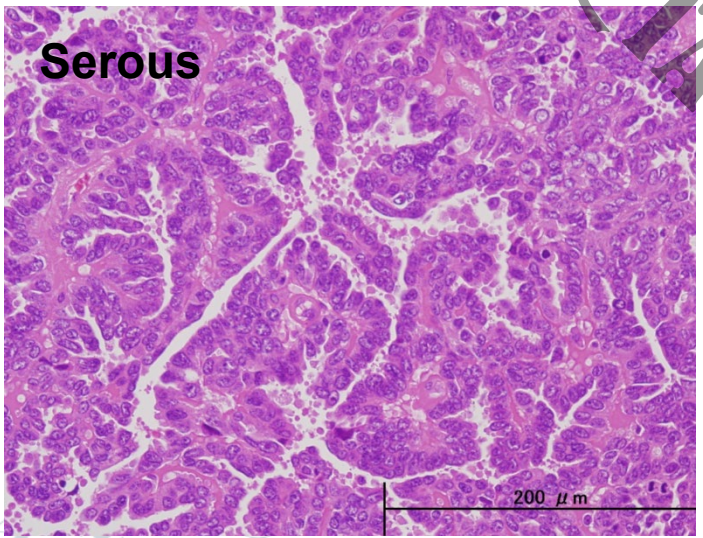
Gynecol Oncol. 2023 Jul;174:55-67

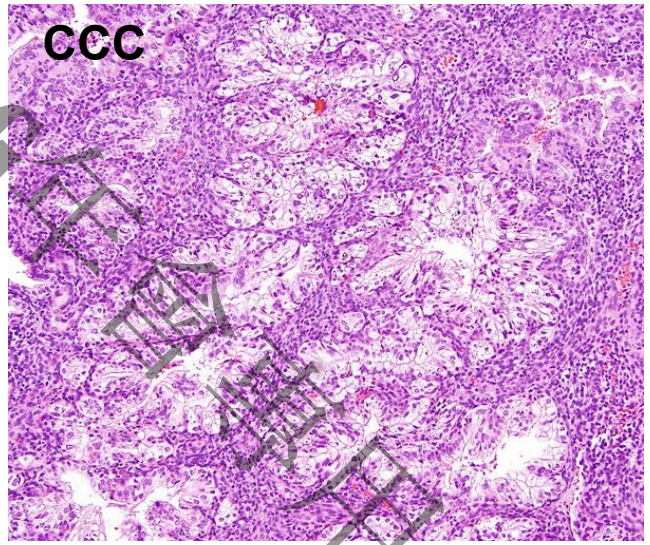
Comparative Effectiveness of Robotic Versus Laparoscopic Hysterectomy for Endometrial Cancer

- Population-based analysis, 2,464 women
- 41.7%LSC, 58.3% robotic
- all complication rate: 9.8% vs. 8.1% (NS)
- intraop complications: OR, 0.68 (NS)
- surgical site complications: OR, 1.49 (NS)
- prolonged hospitalization: OR 0.85 (NS)
- medical complications: OR 0.64 (NS)
- Mean cost: $8,996 vs. $10,618

J Clin Oncol. 2012 Mar 10;30(8):783-91

MIS in high-risk histology





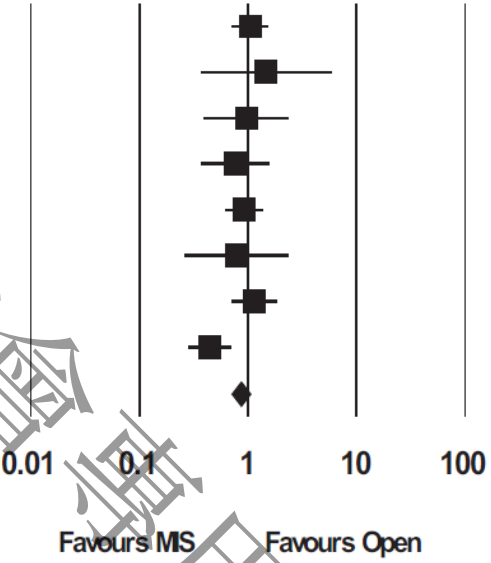
Minimally invasive surgery versus open surgery in high-risk histologic endometrial cancer patients: A meta-analysis

- Nine studies: 8 retrospective, one prospective). No RCT
- MIS N= 8877, open N=5751
- High risk: grade 3 endometrioid, serous, CCC, carcinosarcoma
- Stage I-IV

Gynecol Oncol. 2022 Aug;166(2):236-244

PFS

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Fader AN, et al. 2012	1.045	0.710	1.537	0.223	0.823
Feuer GA, et al. 2014	1.471	0.367	5.904	0.544	0.586
Pant A, et al. 2014	0.966	0.387	2.407	-0.075	0.940
Vogel TJ, et al. 2015	0.760	0.363	1.592	-0.727	0.467
Fader AN, et al. 2016	0.929	0.619	1.393	-0.357	0.721
Favero G, et al. 2016	0.792	0.262	2.397	-0.412	0.680
Koskas M, et al. 2016	1.139	0.698	1.859	0.520	0.603
Monterossi G, et al. 2017	0.443	0.278	0.705	-3.435	0.001
	0.860	0.707	1.046	-1.508	0.132



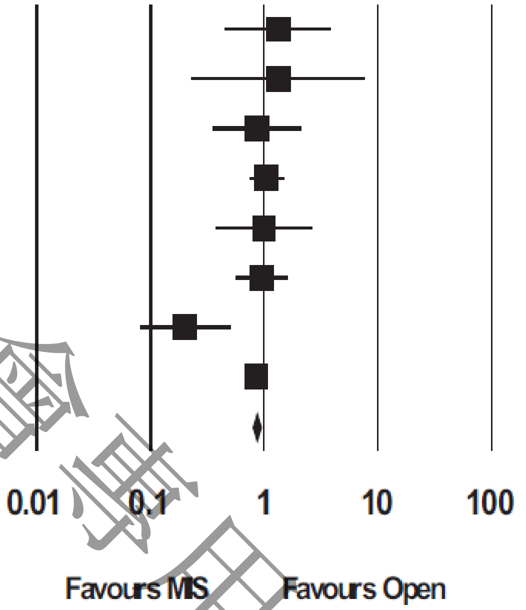
Gynecol Oncol. 2022 Aug;166(2):236-244

OS

Study name	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value
Fader AN, et al. 2012	1.323	0.450	3.888	0.509	0.611
Feuer GA, et al. 2014	1.323	0.229	7.661	0.313	0.755
Vogel TJ, et al. 2015	0.870	0.350	2.165	-0.299	0.765
Fader AN, et al. 2016	1.051	0.736	1.502	0.275	0.784
Favero G, et al. 2016	1.000	0.375	2.664	0.000	1.000
Koskas M, et al. 2016	0.951	0.560	1.615	-0.185	0.853
Monterossi G, et al. 2017	0.201	0.080	0.507	-3.401	0.001
Nasioudis D, et al. 2020	0.850	0.778	0.928	-3.622	0.000
	0.856	0.788	0.930	-3.660	0.000

Statistics for each study

Hazard ratio and 95% CI



Gynecol Oncol. 2022 Aug;166(2):236-244

Subgroup

PFS

Subgroup analyses comparing recurrence between minimally invasive surgery and open surgery.

	Number of studies	MIS patients (n)	OPS patients (n)	HR (95% CI) for recurrence	*P* value	Study heterogeneity	
						I^2	*P* value, Cochran Q
Stage							
Clinically early stage	5	706	532	0.79 (0.55–1.15)	0.22	54%	0.07
All stage	3	180	358	1.04 (0.70–1.54)	0.85	0%	0.59
Histology							
PS, CC	4	260	422	0.58 (0.41–0.83)	0.003	22%	0.28
Type of MIS							
RS	3	113	277	0.91 (0.53–1.54)	0.72	0%	0.70
LS	2	327	165	0.91 (0.62–1.33)	0.63	0%	0.79

OS

Subgroup analyses comparing mortality between minimally invasive surgery and open surgery.

	Number of studies	MIS patients (n)	OPS patients (n)	HR (95% CI) for mortality	*P* value	Study heterogeneity	
						I^2	*P* value, Cochran Q
Stage							
Clinically early stage	5	8650	5360	0.81 (0.55–1.18)	0.27	65%	0.02
All stage	3	180	358	0.95 (0.61–1.48)	0.83	0%	0.92
Histology							
PS, CC	4	260	422	0.64 (0.27–1.52)	0.31	62%	0.05
Type of MIS							
RS	2	66	244	0.95 (0.42–2.14)	0.90	0%	0.68
LS	2	327	165	1.05 (0.75–1.46)	0.80	0%	0.93

Gynecol Oncol. 2022 Aug;166(2):236-244

Minimally Invasive Compared With Open Surgery in High-Risk Endometrial Cancer

A Systematic Review and Meta-analysis

- 14 studies, all retrospective, N= 2,332+542 from Mayo
- Gr. 3 endometrioid, serous, CCC, mixed, carcinosarcoma
- Early and late stage

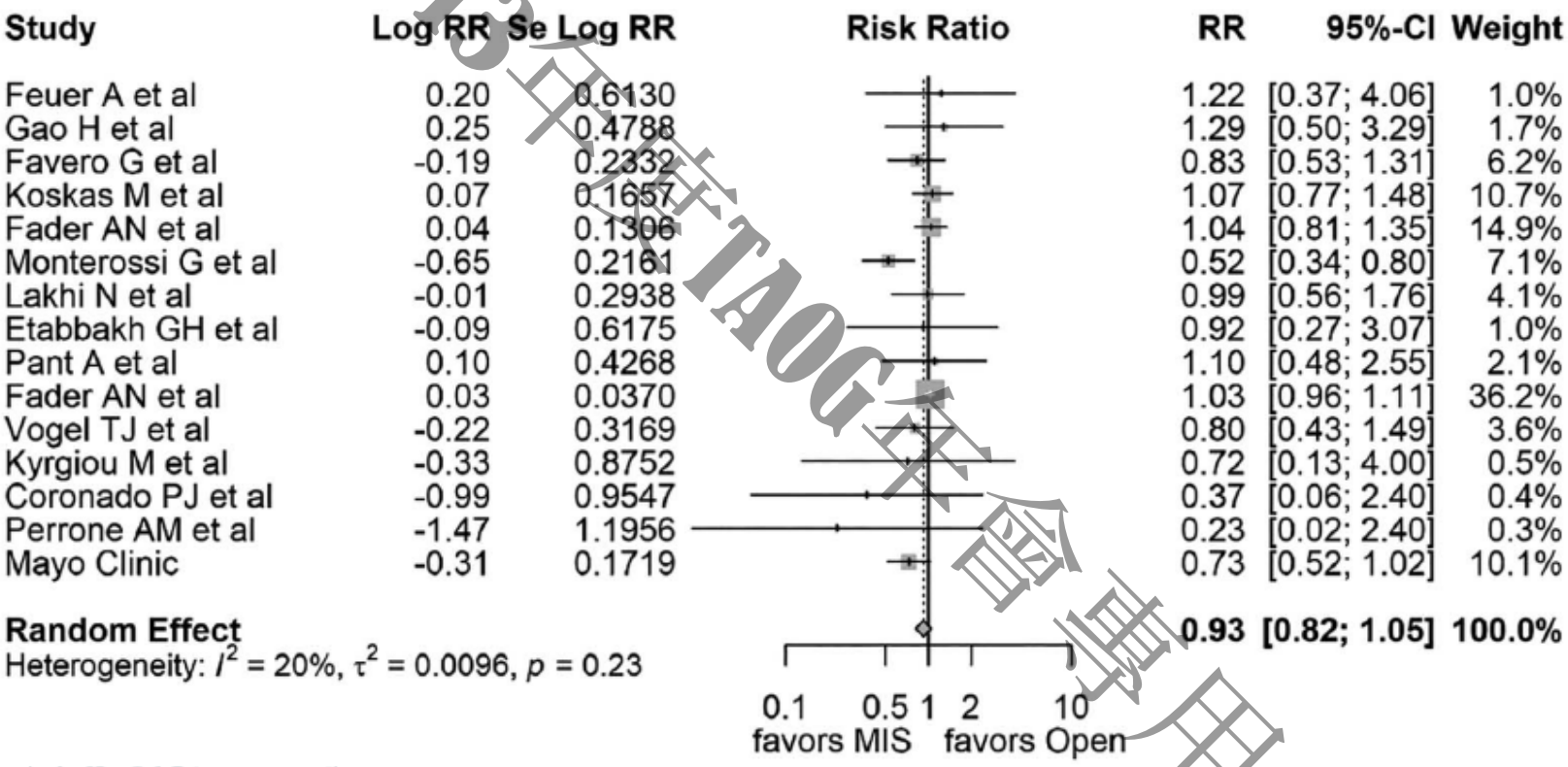
Obstet Gynecol. 2023 Jan 1;141(1):59-68

Characteristics of Studies

Study	Type of Surgery	Sample Size (n)	Age (y)			BMI (kg/m²)			NOS Score	Follow-up (mo)		Conversion Rate (%)
			Mean±SD	Median	*P*	Mean±SD	Median	*P*		Mean	Median	
Fader et al[11]	LPT	191	66.9±10.1		.22	31.9±8.5		.54	9	44		9.9
	MIS	192	65.4±11.4			30.1±7.1						
Feuer et al[28]	LPT	15	66.4±8.0		.76	32.8±7.0		.27	9	19.9		0
	MIS	17	67.3±8.9			29.9±7.1				27.1		
Vogel et al[15]	LPT	229	NA			NR			7	31		NR
	MIS	49										
Gao and Zhang[29]	LPT	81	58.26±0.99		.11	27.53±0.42		<.01	9	45		0
	MIS	81	56.05±0.96			25.82±0.38						
Favero et al[27]	LPT	36	71.1±9.8		.06	30.3±5.7			8	47		0
	MIS	53	65.9±6.9			30.6±6.2				38		
Koskas et al[30]	LPT	114	66.0			NA			7	69		5.3
	MIS	114	66.8							51		
Fader et al[12]	LPT	129		69.4			27.4		9	60		34.3
	MIS	274										
Monterossi et al[32]	LPT	142		69	.73		27	.83	8	60		2.1
	MIS	141		67			27					
Lakhi et al[31]	LPT	37		68	.80		30.7	.78	8	36		0
	MIS	22		71			28.4					
Eltabbakh[26]	LPT	11	61.1±13.3		.77	33.6±10.0		<.001	8		27	6
	MIS	9	62.0±12.9			28.8±7.1					48	
Pant et al[33]	LPT	33	65.9		.41	30.9		.89	9	36		3.03
	MIS	47	63.7			30.6						

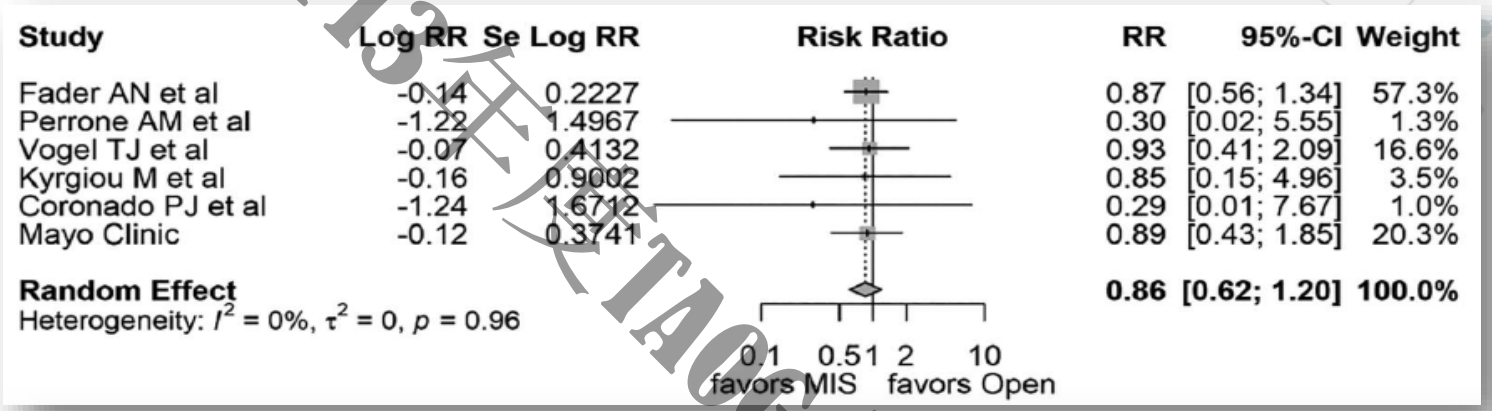
Obstet Gynecol. 2023 Jan 1;141(1):59-68

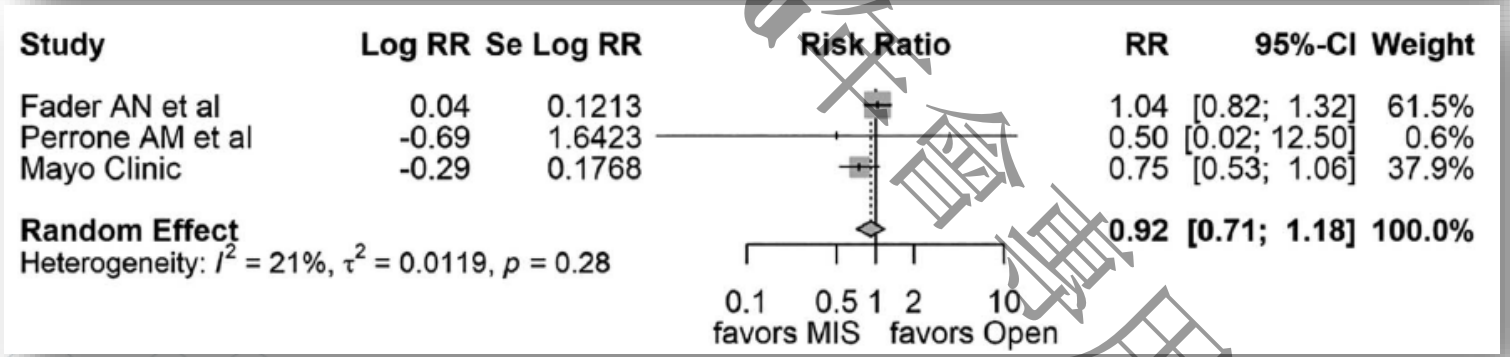
PFS



Obstet Gynecol. 2023 Jan 1;141(1):59-68

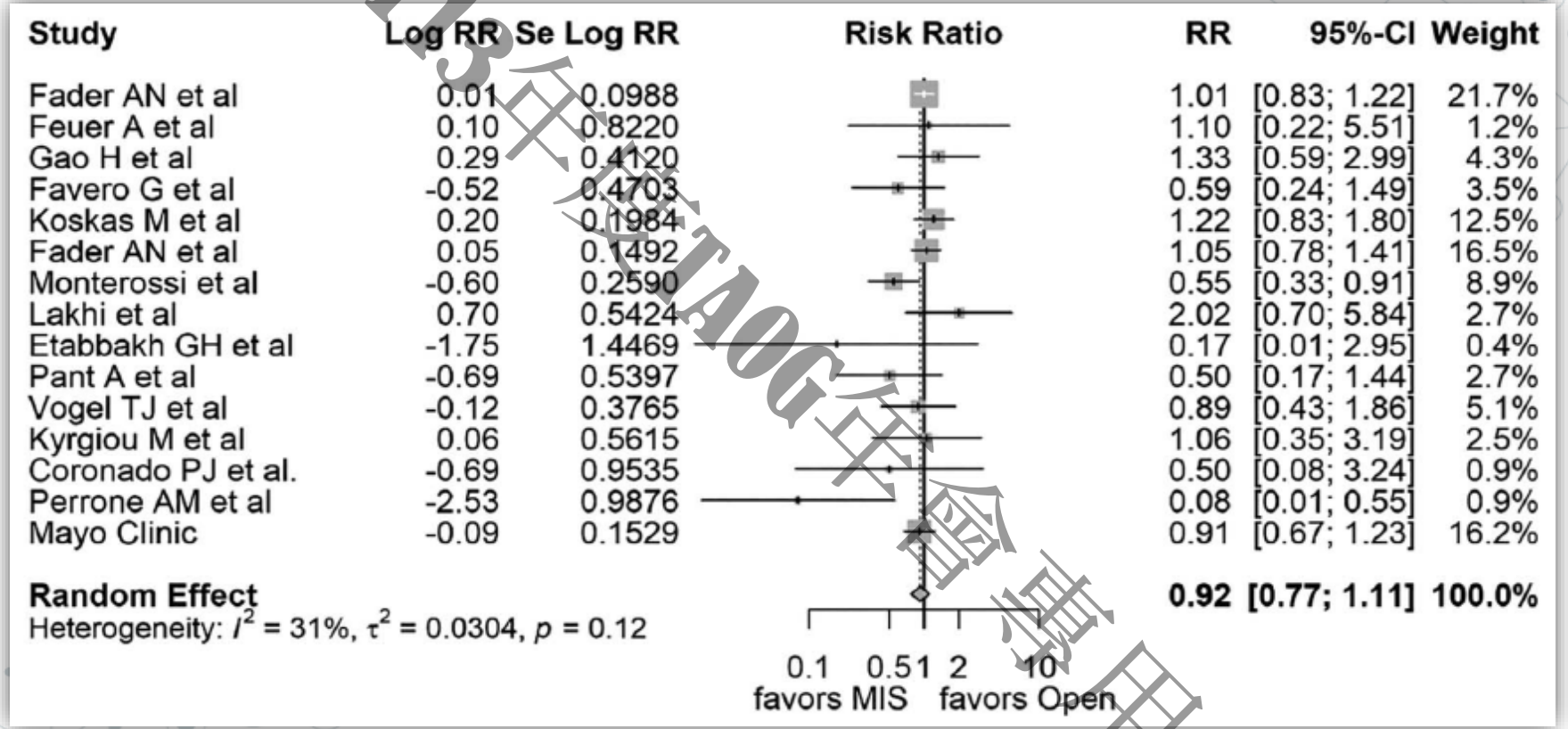
PFS in early and late stage





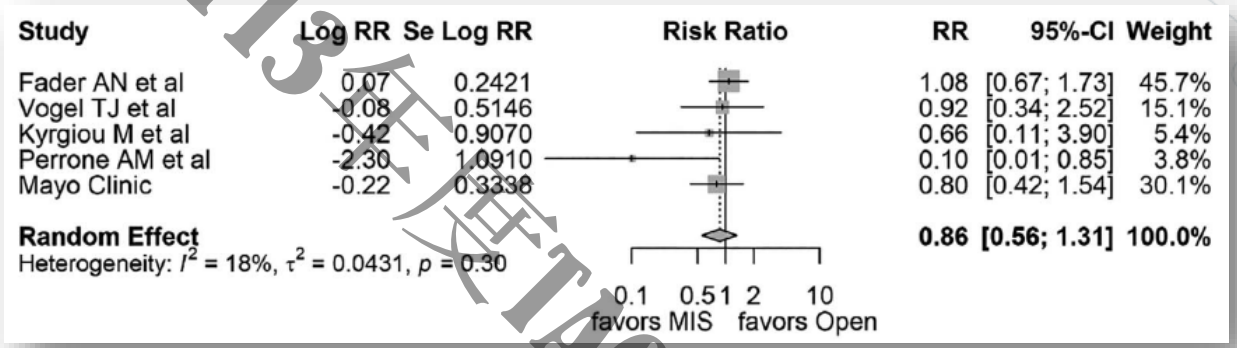
Obstet Gynecol. 2023 Jan 1;141(1):59-68

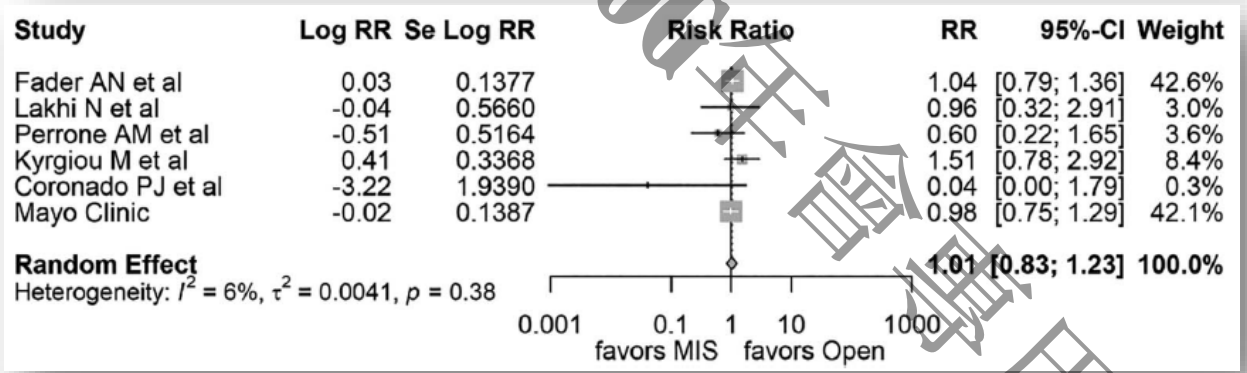
OS



Obstet Gynecol. 2023 Jan 1;141(1):59-68

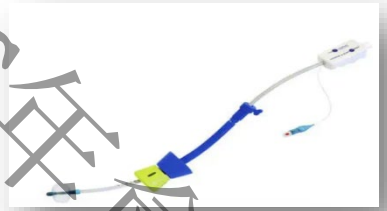
OS in early and late stage

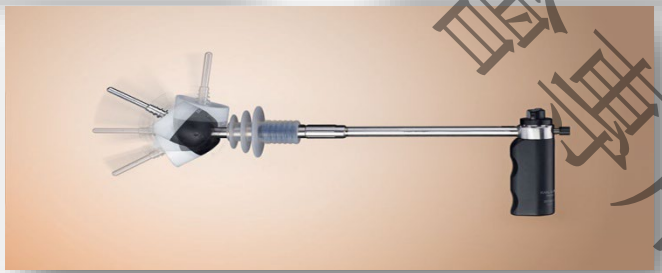




Obstet Gynecol. 2023 Jan 1;141(1):59-68

Uterine manipulator





Intrauterine manipulator during hysterectomy for endometrial cancer: a systematic review and meta-analysis of oncologic outcomes

◎14studies: 2 RCT, 12 retrospective, N= 5,019

◎Underwent total laparoscopic or robotic hysterectomy for endometrial cancer

◎85% stage IA/IB, endometrioid 85-97%

Am J Obstet Gynecol. 2024 Feb;230(2):185-198

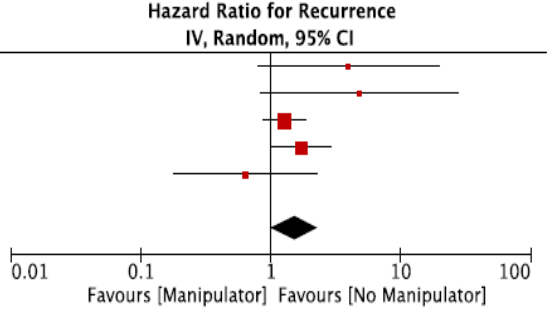
Forest plot for recurrence-free survival

A: 14 trials. B: RCTs

A

Study or Subgroup	log[Hazard Ratio for Recurrence]	SE	Manipulator Total	Without Manipulator Total	Weight	Hazard Ratio for Recurrence IV, Random, 95% CI	Year
Lee et al.	1.37	0.82	55	55	6.4%	3.94 [0.79, 19.63]	2013
Tinelli et al.	1.57	0.89	55	55	5.5%	4.81 [0.84, 27.51]	2016
Uccella et al.	0.24	0.19	579	372	45.2%	1.27 [0.88, 1.84]	2017
Padilla-Iserte et al.	0.54	0.27	1730	892	33.4%	1.72 [1.01, 2.91]	2021
Gueli Alletti et al.	-0.45	0.65	78	76	9.6%	0.64 [0.18, 2.28]	2021
Total (95% CI)			**2497**	**1450**	**100.0%**	**1.52 [0.99, 2.33]**	

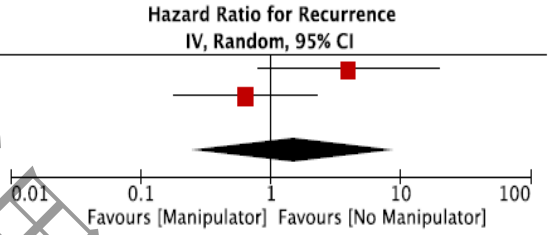
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 5.76$, df = 4 (P = 0.22); $I^2 = 31\%$
Test for overall effect: Z = 1.93 (P = 0.05)



B

Study or Subgroup	log[Hazard Ratio for Recurrence]	SE	Manipulator Total	Without Manipulator Total	Weight	Hazard Ratio for Recurrence IV, Random, 95% CI	Year
Lee et al.	1.37	0.82	55	55	46.2%	3.94 [0.79, 19.63]	2013
Gueli Alletti et al.	-0.45	0.65	78	76	53.8%	0.64 [0.18, 2.28]	2021
Total (95% CI)			**133**	**131**	**100.0%**	**1.48 [0.25, 8.76]**	

Heterogeneity: $Tau^2 = 1.11$; $Chi^2 = 3.03$, df = 1 (P = 0.08); $I^2 = 67\%$
Test for overall effect: Z = 0.43 (P = 0.67)



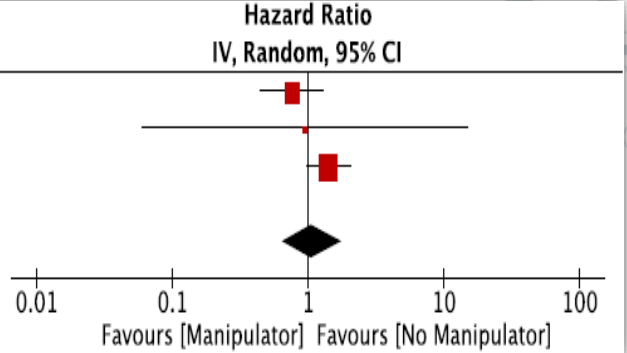
Am J Obstet Gynecol. 2024 Feb;230(2):185-198

Forest plot for overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Manipulator Total	Without Manipulator Total	Weight	Hazard Ratio IV, Random, 95% CI	Year
Uccella et al.	-0.28	0.27	579	372	41.9%	0.76 [0.45, 1.28]	2017
Gueli Alletti et al.	-0.06	1.41	78	76	3.1%	0.94 [0.06, 14.93]	2021
Padilla-Iserte et al.	0.34	0.19	1731	895	55.0%	1.40 [0.97, 2.04]	2021
Total (95% CI)			2388	1343	100.0%	1.07 [0.65, 1.76]	

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 3.55$, df = 2 (P = 0.17); $I^2 = 44\%$

Test for overall effect: Z = 0.27 (P = 0.79)



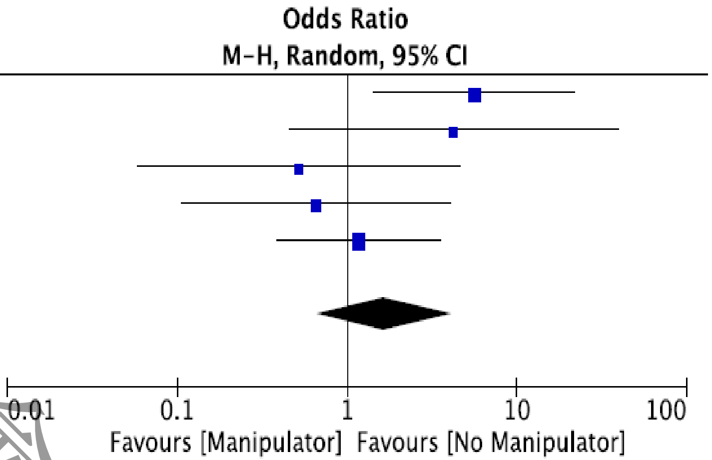
Am J Obstet Gynecol. 2024 Feb;230(2):185-198

Forest plot for peritoneal cytology status with *vs.* without IUM

Study or Subgroup	Manipulator Events	Manipulator Total	Without Manipulator Events	Without Manipulator Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Krizova et al.	5	40	4	161	25.2%	5.61 [1.43, 21.95]	2011
Lee et al.	4	55	1	55	13.1%	4.24 [0.46, 39.17]	2013
Raji et al.	1	18	6	59	13.4%	0.52 [0.06, 4.63]	2014
Tinelli et al.	2	55	3	55	17.4%	0.65 [0.10, 4.08]	2016
Seifi et al.	9	59	6	45	30.9%	1.17 [0.38, 3.57]	2019
Total (95% CI)		**227**		**375**	**100.0%**	**1.66 [0.67, 4.16]**	
Total events	21		20				

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 6.22$, df = 4 (P = 0.18); $I^2 = 36\%$

Test for overall effect: Z = 1.09 (P = 0.28)



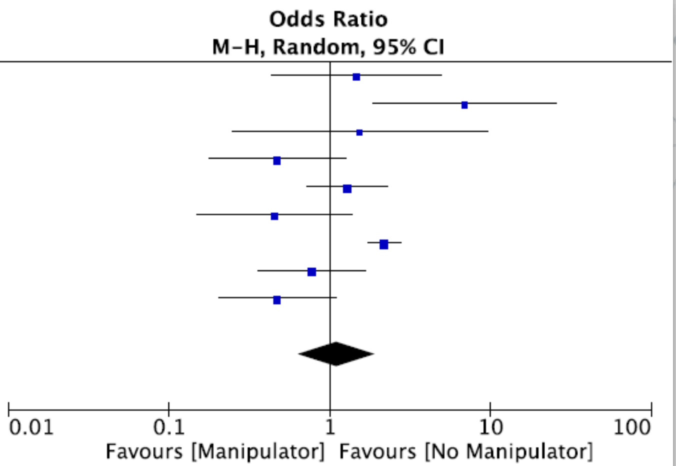
Am J Obstet Gynecol. 2024 Feb;230(2):185-198

Forest plot lymphovascular space invasion

A

Study or Subgroup	Manipulator Events	Manipulator Total	Without Manipulator Events	Without Manipulator Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Lee et al.	7	55	5	55	9.2%	1.46 [0.43, 4.91]	2013
Raji et al.	7	18	5	59	8.5%	6.87 [1.84, 25.68]	2014
Tinelli et al.	3	55	2	55	5.8%	1.53 [0.25, 9.53]	2016
Mitideri et al.	8	24	33	64	11.0%	0.47 [0.18, 1.25]	2017
Uccella et al.	35	270	21	202	14.3%	1.28 [0.72, 2.28]	2017
Seifi et al.	6	59	9	45	9.9%	0.45 [0.15, 1.38]	2019
Padilla–Iserte et al.	379	1756	102	905	16.5%	2.17 [1.71, 2.74]	2021
Gueli Alletti et al.	15	78	18	76	12.7%	0.77 [0.35, 1.66]	2021
Hudec et al.	10	87	18	83	12.1%	0.47 [0.20, 1.09]	2022
Total (95% CI)		**2402**		**1544**	**100.0%**	**1.11 [0.64, 1.90]**	
Total events	470		213				

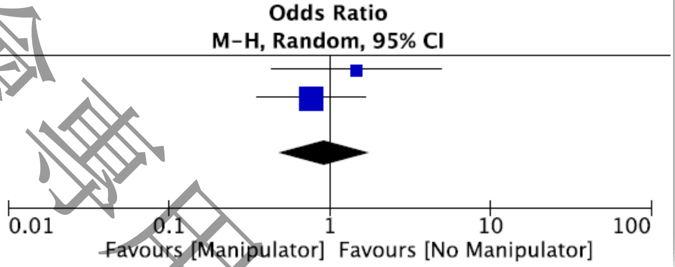
Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 34.24$, df = 8 ($P < 0.0001$); $I^2 = 77\%$
Test for overall effect: Z = 0.36 (P = 0.72)



B

Study or Subgroup	Manipulator Events	Manipulator Total	Without Manipulator Events	Without Manipulator Total	Weight	Odds Ratio M–H, Random, 95% CI	Year
Lee et al.	7	55	5	55	28.8%	1.46 [0.43, 4.91]	2013
Gueli Alletti et al.	15	78	18	76	71.2%	0.77 [0.35, 1.66]	2021
Total (95% CI)		**133**		**131**	**100.0%**	**0.92 [0.48, 1.77]**	
Total events	22		23				

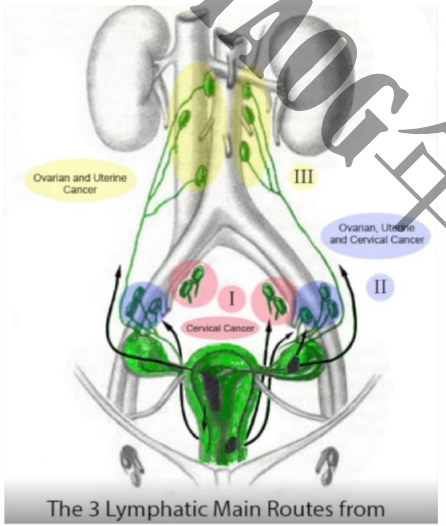
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.77$, df = 1 (P = 0.38); $I^2 = 0\%$
Test for overall effect: Z = 0.24 (P = 0.81)



Am J Obstet Gynecol. 2024 Feb;230(2):185-198

Sentinel LN biopsy in high-risk histology

Modified from Reiffenstuhl and Höckel

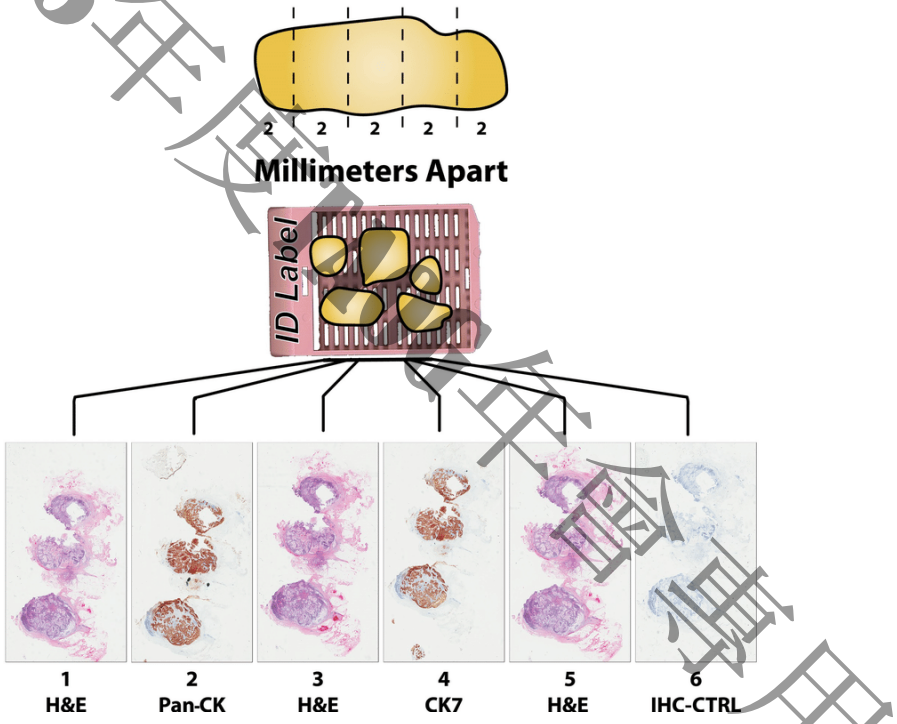


The 3 Lymphatic Main Routes from

Sentinel lymph node

- SLN algorithm, Ultrastaging during frozen section
- Systemic LN dissection if (+) or failed (may reinjection)
- Cervical injection with ICG: highest detection rate
- SLN mapping: decreased op and post-op morbidity, op time, lymphedema
- Isolated PA node mets: 0.8%–5%.

Ultrastaging lymph node processing



Sentinel lymph node biopsy in high-grade endometrial cancer: a systematic review and meta-analysis of performance characteristics

- Clinical stage I
- Gr. 3 endometrioid, serous, clear cell, carcinosarcoma, mixed, undifferentiated, dedifferentiated, and high-grade not otherwise specified
- Cervical injection of ICG
- At least BPLND as standard

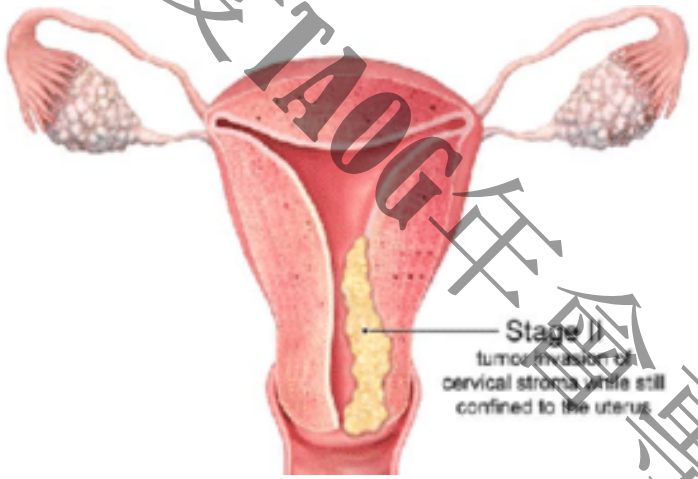
Am J Obstet Gynecol. 2021 Oct;225(4):367

Sentinel lymph node biopsy in high-grade endometrial cancer: a systematic review and meta-analysis of performance characteristics

- 16 prospective studies, N= 429
- Detection rates: 91%, 64% bilaterally
- Node positivity rate: 26%
- Sensitivity: 92%, FN: 8%, NPV: 97%
- Conclusion: SLN accurately detect lymph node metastases! Me??

Am J Obstet Gynecol. 2021 Oct;225(4):367

Radical hysterectomy for stage II?

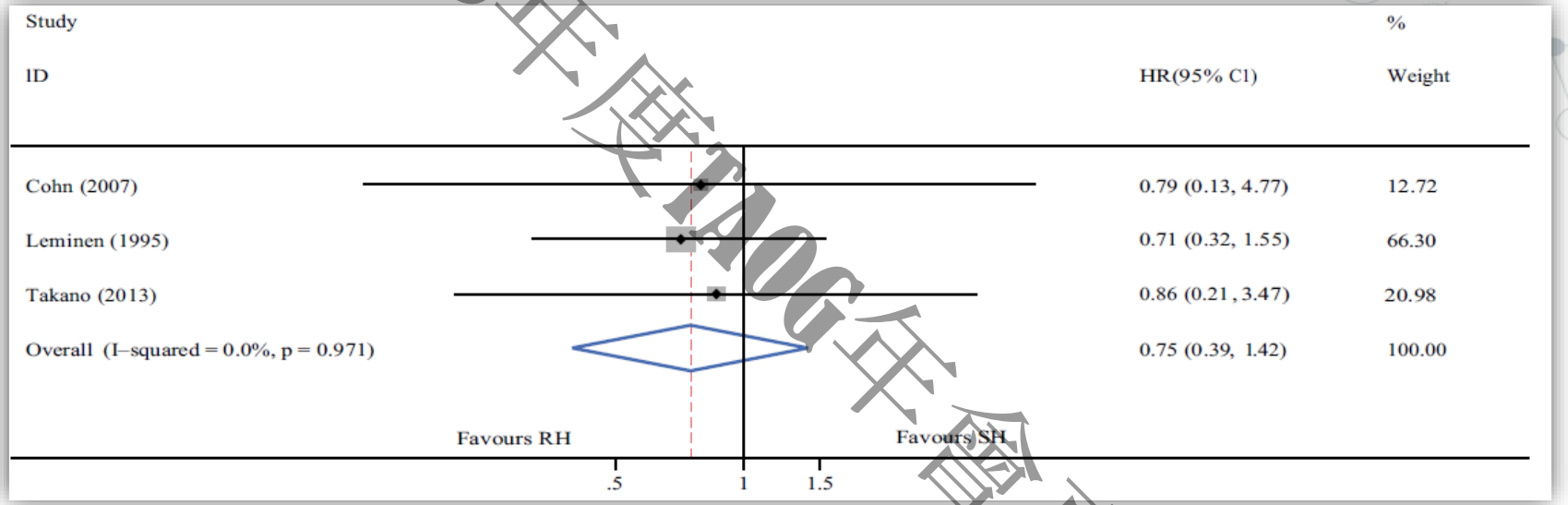


Impact of Radical Hysterectomy Versus Simple Hysterectomy on Survival of Patients with Stage 2 Endometrial Cancer: A Meta-analysis

- 10 retrospective cohort studies, N= 2866
- No RCT

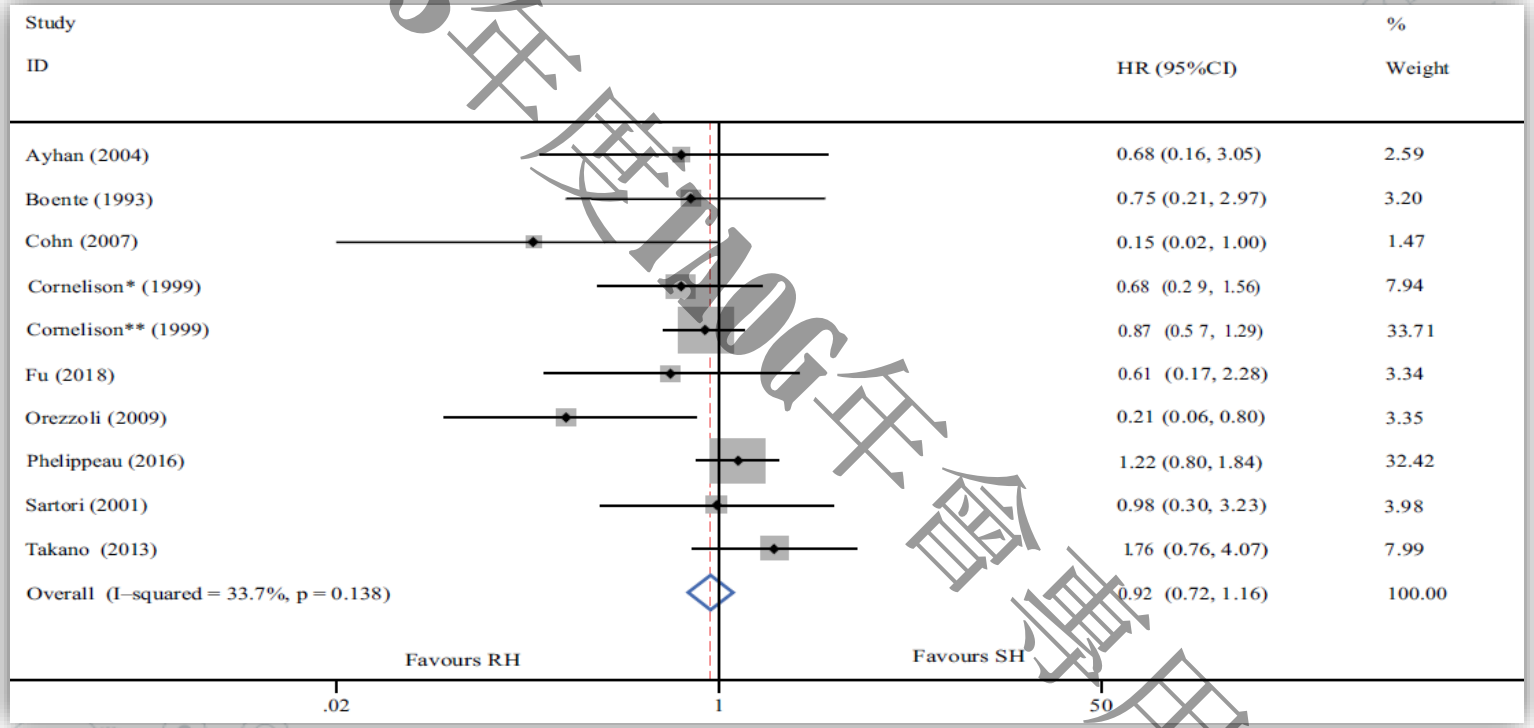
Ann Surg Oncol. 2019 Sep;26(9):2933-2942

Progression-free survival



Ann Surg Oncol. 2019 Sep;26(9):2933-2942

Overall survival



Ann Surg Oncol. 2019 Sep;26(9):2933-2942

Role of RH in stage II

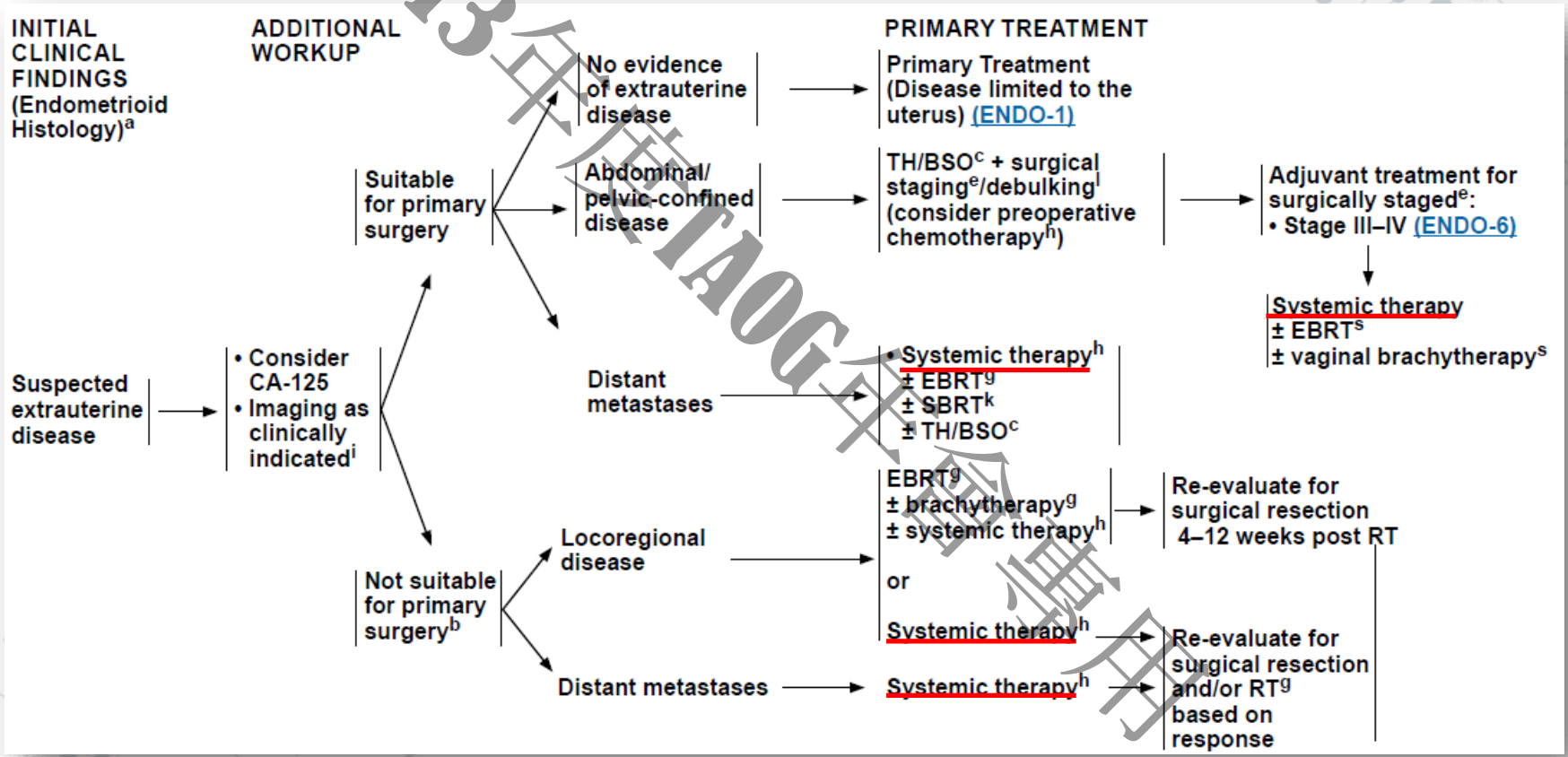
- To obtain negative margins
- Primary cervical cancer or stage II EM cancer cannot be determined

Strategies on surgeries

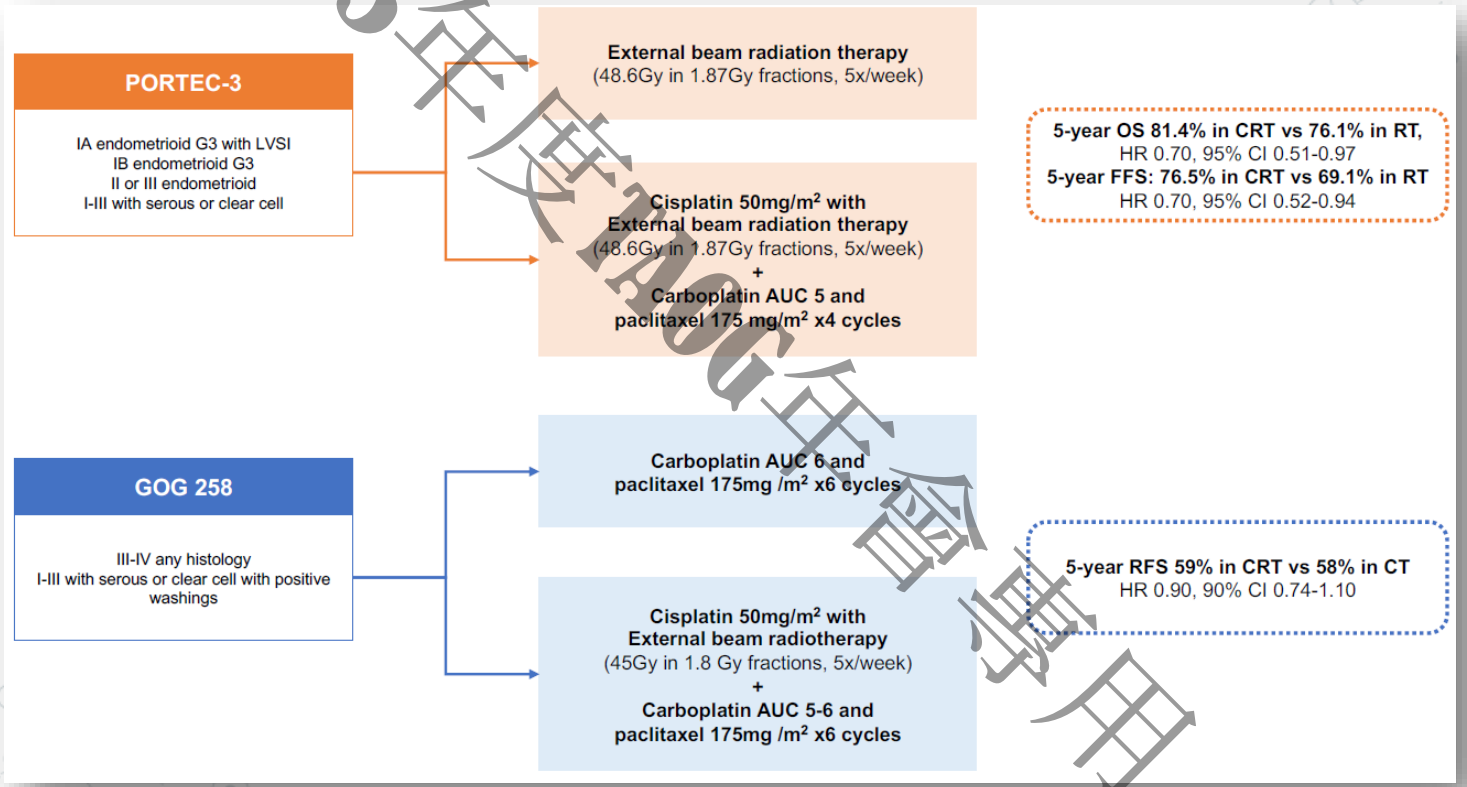
- MIS equal oncology outcomes in low- and high-risk histology, stages
- Robotic: similar PFS, OS, complications compare to LSC
- Manipulator safe, tubal occlusion before insertion
- Accurate sentinel LN biopsy in clinical stage I, even high-risk histology?

Adjuvant therapy for advanced stage disease

NCCN Guidelines Version 1.2024
Endometrial Carcinoma



PORTEC 3 and GOG 258 study Schema



Int J Gynecol Cancer. 2023 Sep 4;33(9):1408-1418

The ASCO Post

GOG 258 Final Results: No Improvement in Survival by Adding Radiotherapy to Chemotherapy in Advanced Endometrial Cancer

By Caroline Helwick

May 25, 2023

1. 813 patients, 75% stage IIIC1 or IIIC2
2. F/U 112 months, OS (HR=1.05; 95% CI, 0.82-1.34)

Sequential Chemotherapy and Radiotherapy in the Sandwich Method for Advanced Endometrial Cancer

A Meta-Analysis

Study	Study Type	No. of Patients	Stage of Disease	Pathological Type	Treatment Regimens	3-Year PFS	3-Year OS	NOS Star
Lan et al (2013)[13]	Retrospective	25	III–IV	UPSC + other types	''Sandwich'' protocol with unclear detail	62.4%	81.8%	5/9
Einstein et al (2012)[14]	Prospective	14	III–IV	UPSC	3 cycles of paclitaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy	NA	50%	6/9
Geller et al (2011)[15]	Retrospective	39	III–IV	UPSC + other types	3 cycles of docetaxel and carboplatin + radiotherapy + 3 cycles of chemotherapy	71%	NA	5/9
Secord et al. (2009)[16]	Retrospective	45	III–IV	UPSC + other types	''Sandwich'' protocol with unclear detail	69%	88%	6/9
Lupe et al. (2009)[17]	Prospective	43	III–IV	UPSC + other types	4 cycles of paclitaxel and carboplatin + radiotherapy + 2 cycles of chemotherapy	NA	68%	6/9

3-year PFS= 68%, OS= 75%

Medicine (Baltimore). 2015 Apr;94(16):e672

Comparing the survival rates of patients with stage IIIC endometrial cancer undergoing sandwich therapy to those undergoing sequential chemotherapy and radiotherapy: a meta-analysis

- 5 retrospective trials, N= 800
- Sandwich: superior 5-year OS
- Sandwich: superior 3-year OS for non-endometrioid histology, not statistical significant
- Toxicities: similar.

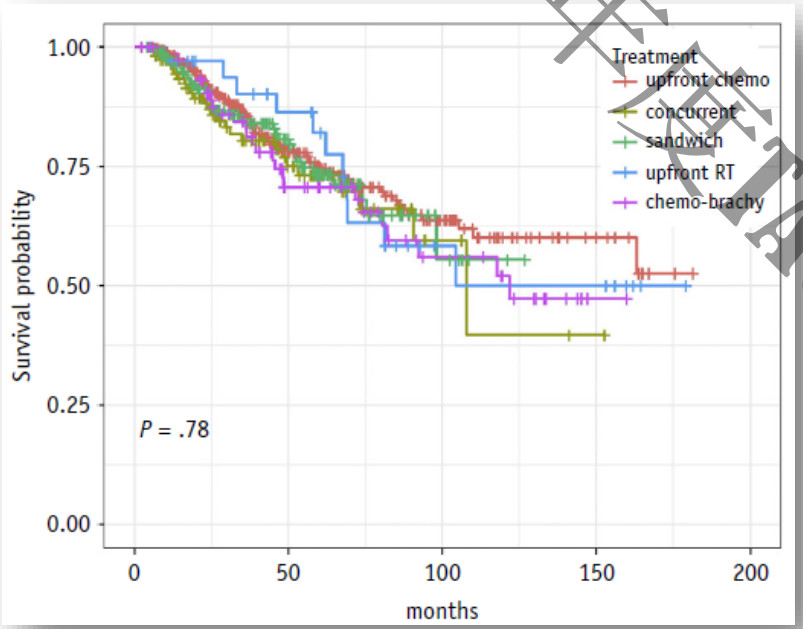
Clin Transl Oncol. 2023 Dec 11.

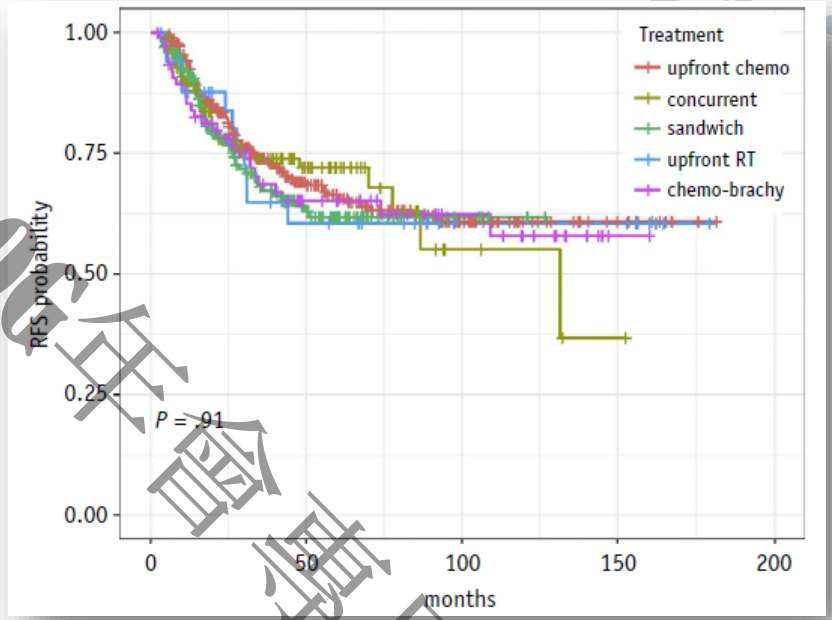
A Multi-Institutional Analysis of Adjuvant Chemotherapy and Radiation Sequence in Women With Stage IIIC Endometrial Cancer

	Entire cohort n = 686	Upfront chemo n = 292	Concurrent n = 113	Sandwich n = 170	Upfront RT n = 34	Chemo-brachy n = 77	*P* value
Histology							
Endometrioid	451 (66%)	187 (64%)	88 (78%)	104 (61%)	25 (73.5%)	47 (61%)	.025
Nonendometrioid	235 (34%)	105 (36%)	25 (22%)	66 (39%)	9 (26.5%)	30 (39%)	
Clear cell Ca	23 (3.4%)						
Serous Ca	130 (19.3%)						
Mixed Ca	70 (10.3%)						
Mucin Ca	5 (0.7%)						
Squamous cell Ca	1 (0.15)						
FIGO stage							
IIIC1	439 (64%)	191 (65%)	76 (67%)	108 (63.5%)	22 (65%)	42 (54.5%)	.4
IIIC2	247 (36%)	101 (35%)	37 (34%)	62 (36.5%)	12 (35%)	35 (45.5%)	
Radiation treatment							
EBRT	191 (28%)	45 (15%)	43 (38%)	90 (53%)	13 (38%)	0	<.0001
BT	94 (14%)	14 (5%)	0	1 (0.6%)	2 (6%)	77 (100%)	
Both	401 (58%)	233 (79%)	70 (62%)	79 (46.4%)	19 (56%)	0	
Median no. of chemotherapy cycles (IQR)	6 (5-6)	6 (5-6)	4 (4-6)	6 (6-6)	6 (4-6)	6 (6-6)	NS

Int J Radiat Oncol Biol Phys. 2021 Aug 1;110(5):1423-1431

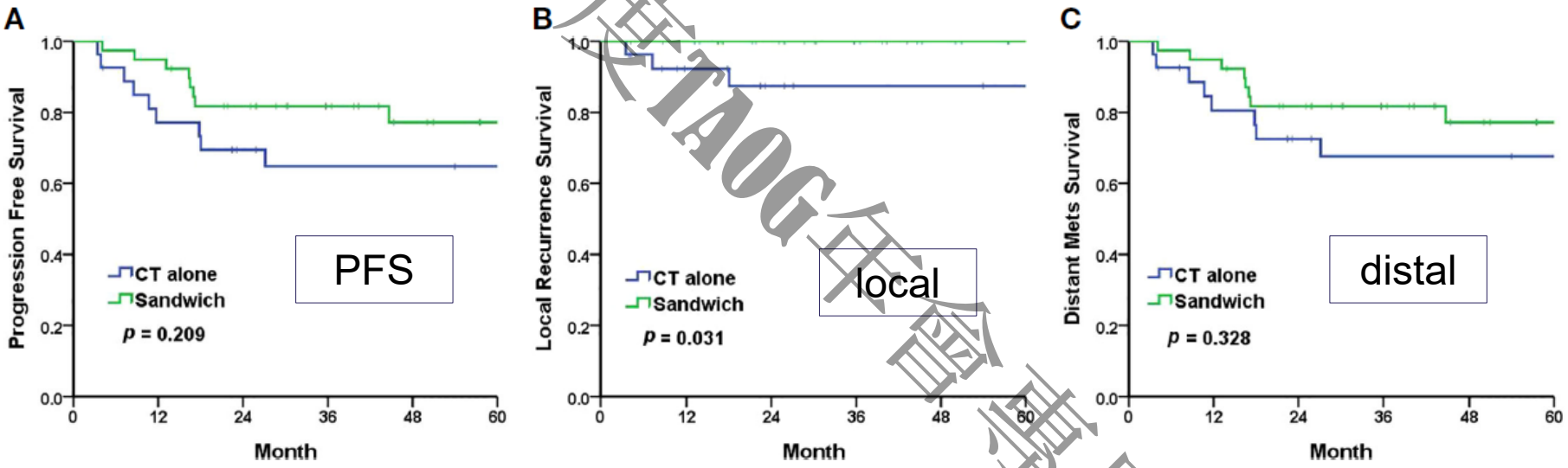
A Multi-Institutional Analysis of Adjuvant Chemotherapy and Radiation Sequence in Women With Stage IIIC Endometrial Cancer





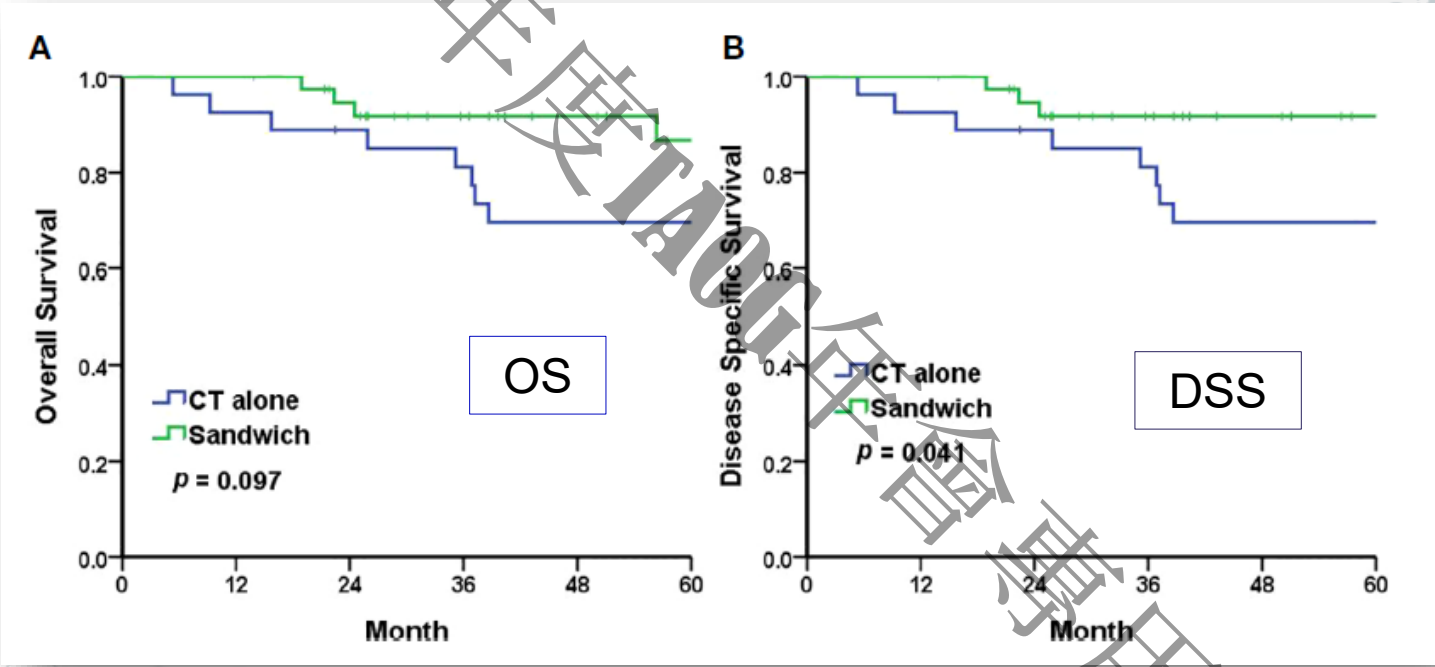
Int J Radiat Oncol Biol Phys. 2021 Aug 1;110(5):1423-1431

Outcomes of "sandwich" chemoradiotherapy compared with C/T alone for the adjuvant treatment of FIGO stage III endometrial cancer



Front Oncol. 2022 Sep 23:12:946113

Outcomes of “sandwich” chemoradiotherapy compared with C/T alone for the adjuvant treatment of FIGO stage III endometrial cancer



Front Oncol. 2022 Sep 23:12:946113

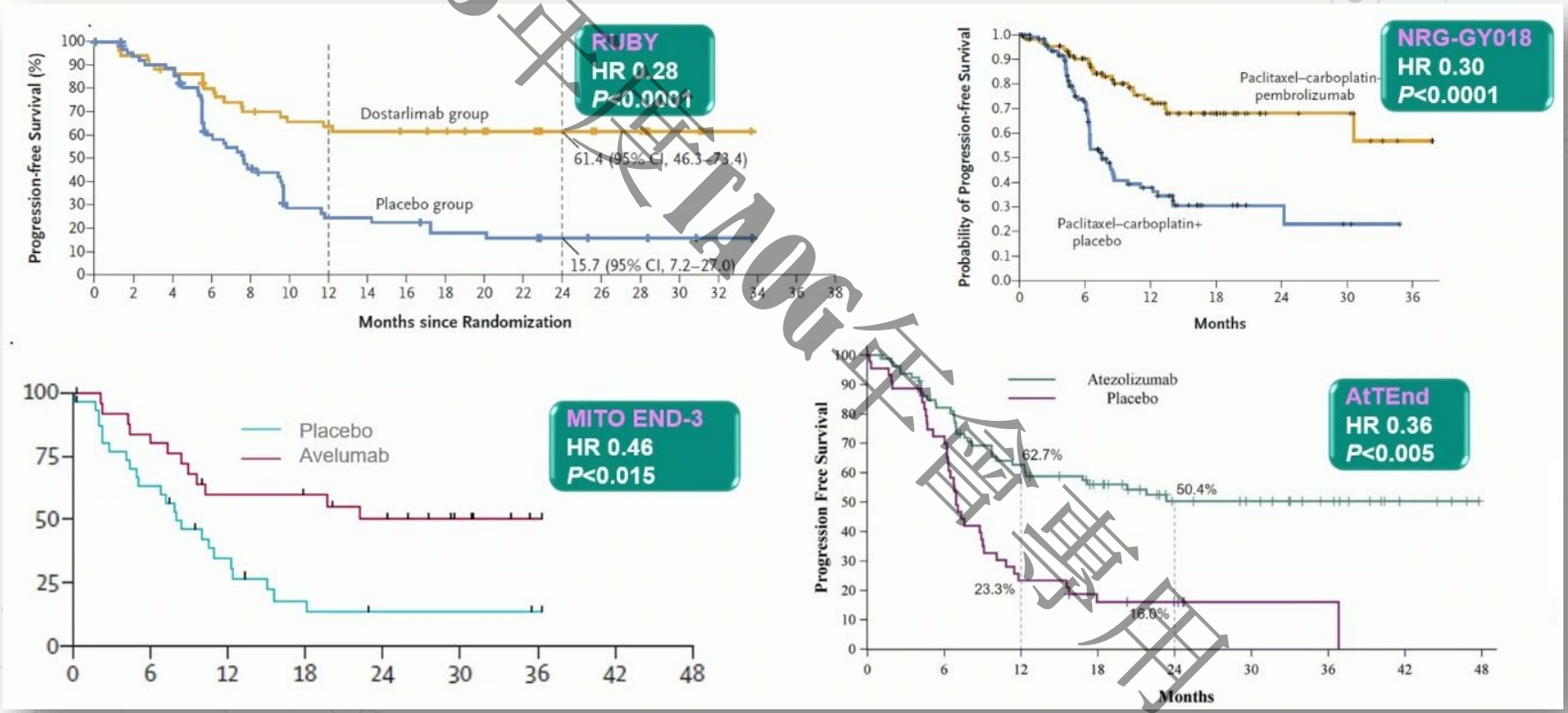
Immunotherapy in frontline adjuvant

SYSTEMIC THERAPY FOR ENDOMETRIAL CARCINOMA

Primary or Adjuvant Therapy (Stage I–IV)	
Chemoradiation Therapy	**Systemic Therapy**
Preferred Regimens • Cisplatin plus RT followed by carboplatin/paclitaxel[1,2] Other Recommended Regimens[a] (if cisplatin and carboplatin are unavailable) • Capecitabine/mitomycin[3] • Gemcitabine[4] • Paclitaxel[5,6]	Preferred Regimens • Carboplatin/paclitaxel[7] • Carboplatin/paclitaxel/pembrolizumab (for stage III–IV tumors, except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (for stage III–IV tumors) (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive uterine serous carcinoma)[d,f,g,10] • Carboplatin/paclitaxel/trastuzumab (for stage III/IV HER2-positive carcinosarcoma)[d,f,g,10]

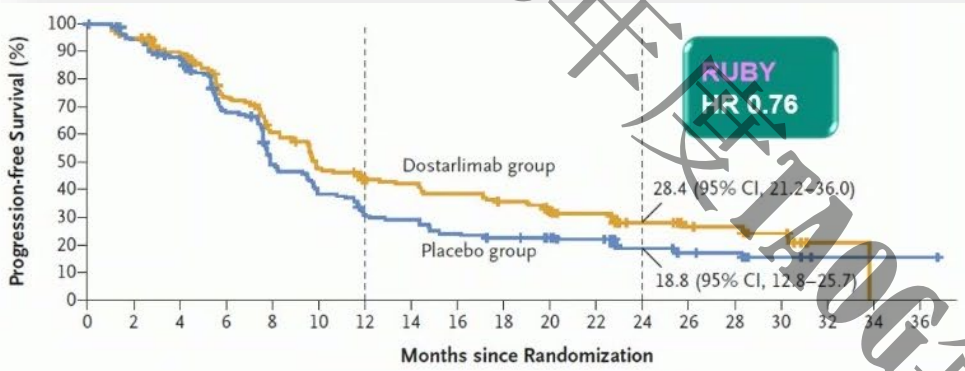
Immunotherapy + C/T in first line advanced/recurrence

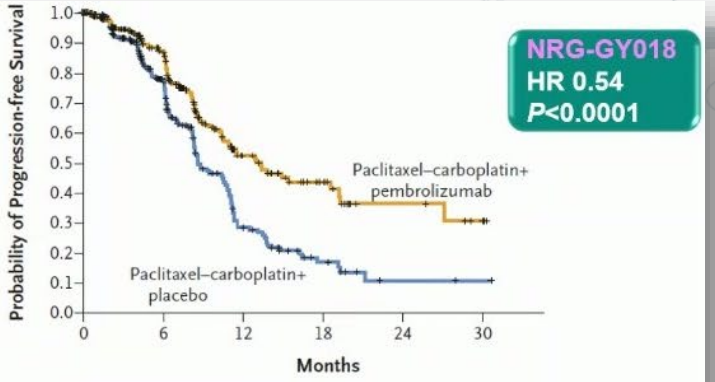
dMMR

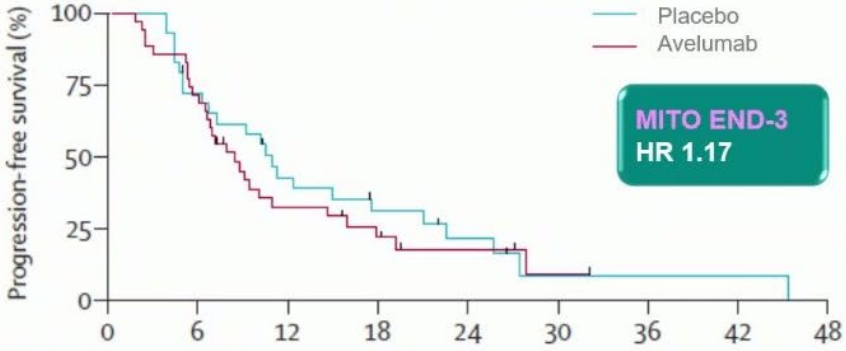


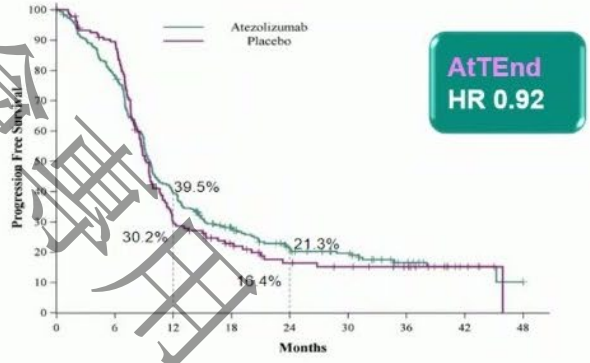
Immunotherapy + C/T in first line advanced/recurrence

pMMR

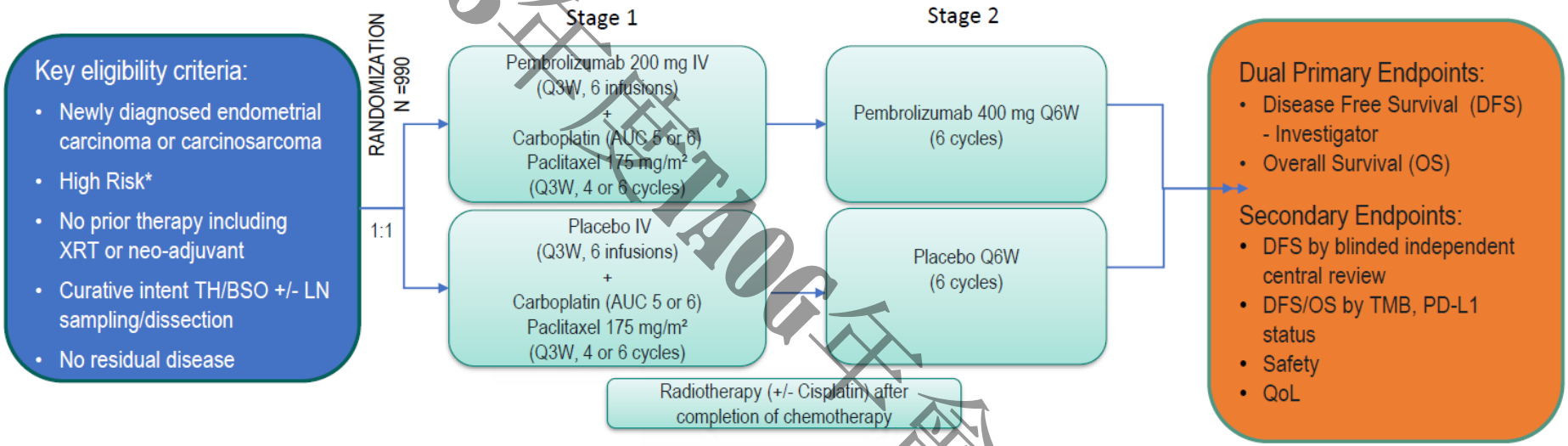








GOG-3053/KEYNOTE B21



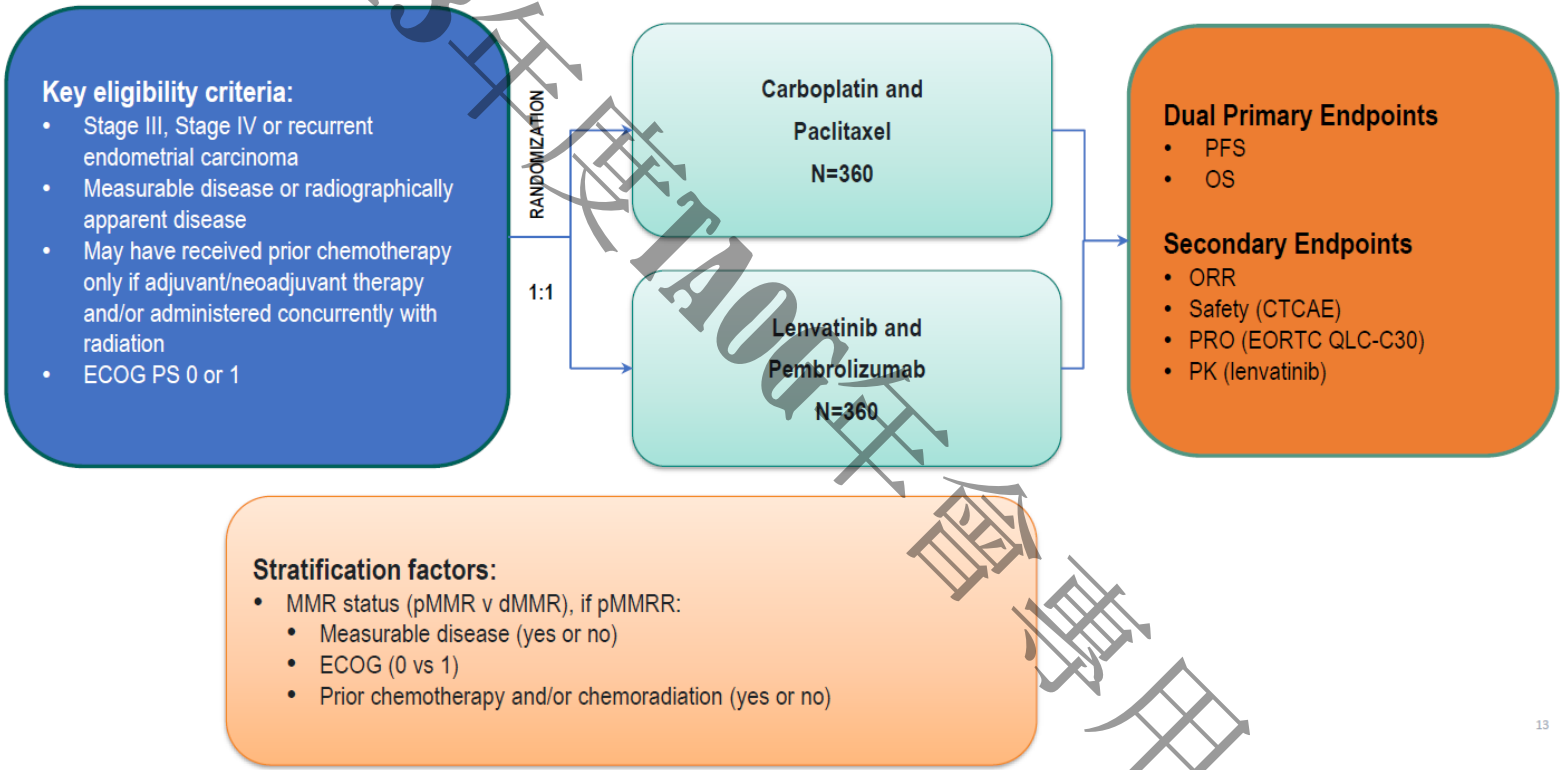
* High Risk:

- FIGO (2009) Surgical Stage I or II with myometrial invasion
  - or of non-endometrioid histology
  - or of any histology with known aberrant p53 expression or p53 mutation
- FIGO (2009) Surgical Stage III or IVA of any histology

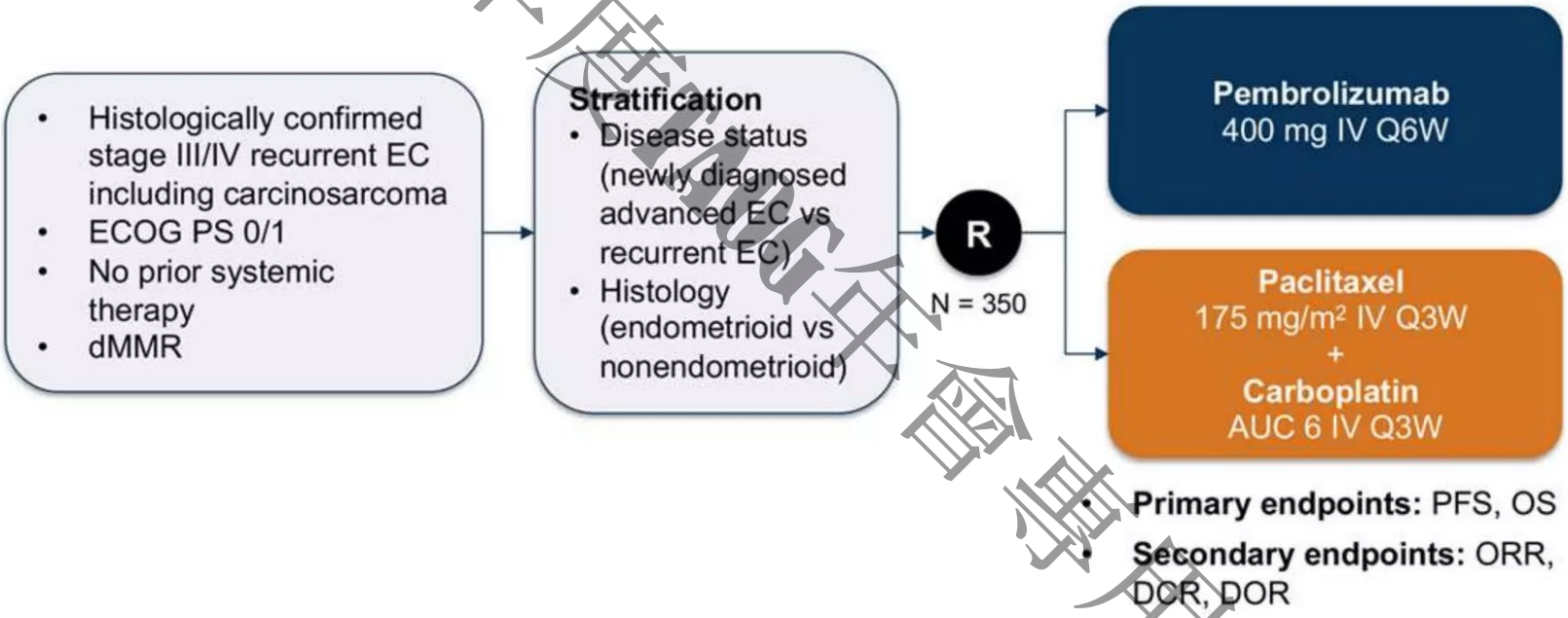
Stratification factors:

- MMR status (if pMMR then further stratification by:
  - Stage (I/II vs III/IVA)
  - Planned radiation (EBRT vs Chemo-EBRT vs no EBRT)
  - Histology (non-endometrioid vs endometrioid)

LEAP-001: 1L phase 3 in endometrial cancer



Phase 3 KEYNOTE C93: First-Line Pembrolizumab vs Chemotherapy in dMMR[1]

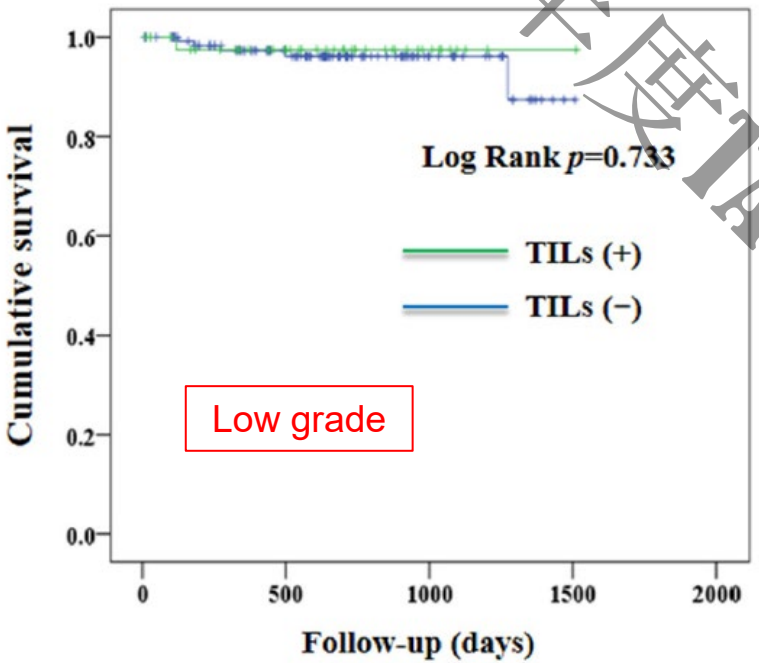


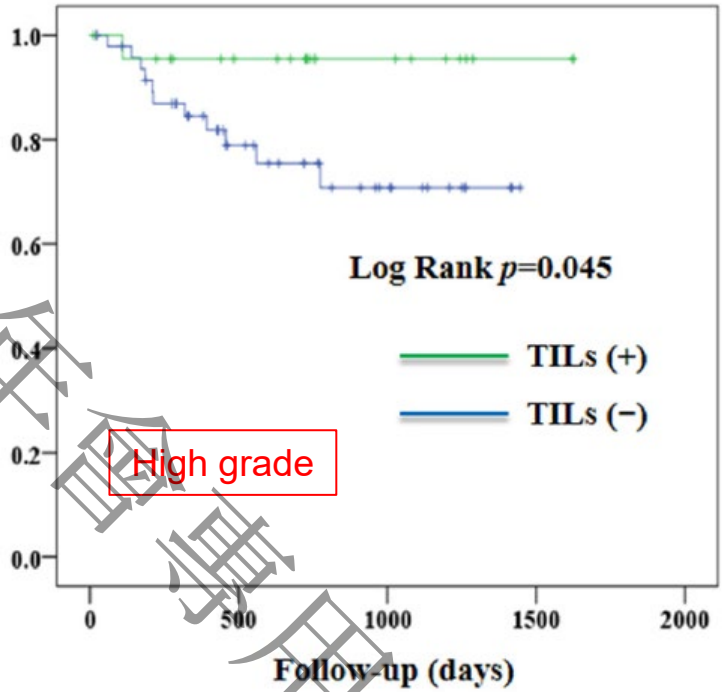
Improved Progression-Free Survival Associated with Tumor-Infiltrating Lymphocytes in High-Grade Endometrial Cancer

- TCVGH 2017-2022
- Pathology review for TILS, N= 237
- dMMR= 23%
- HG: Gr. 3 endometrioid, serous, CCC
- TILs may be a potential prognostic marker

J Clin Med. 2023 Jan 11;12(2):603

Improved Progression-Free Survival Associated with Tumor-Infiltrating Lymphocytes in High-Grade Endometrial Cancer

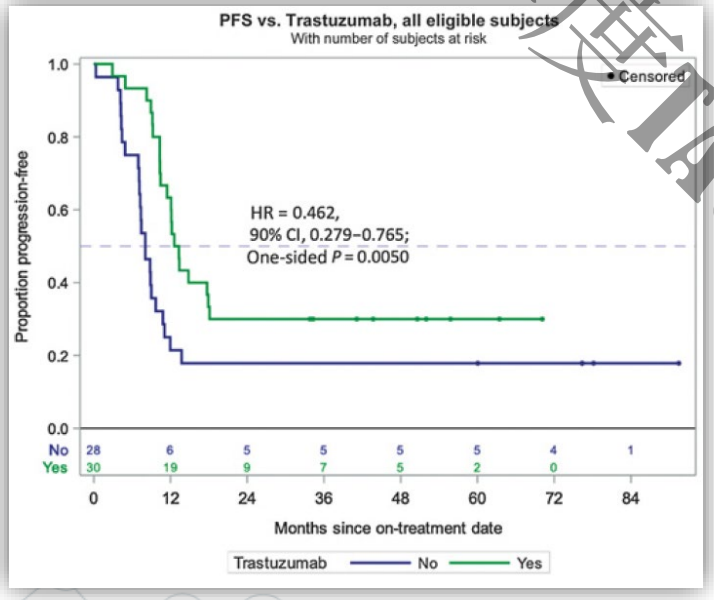


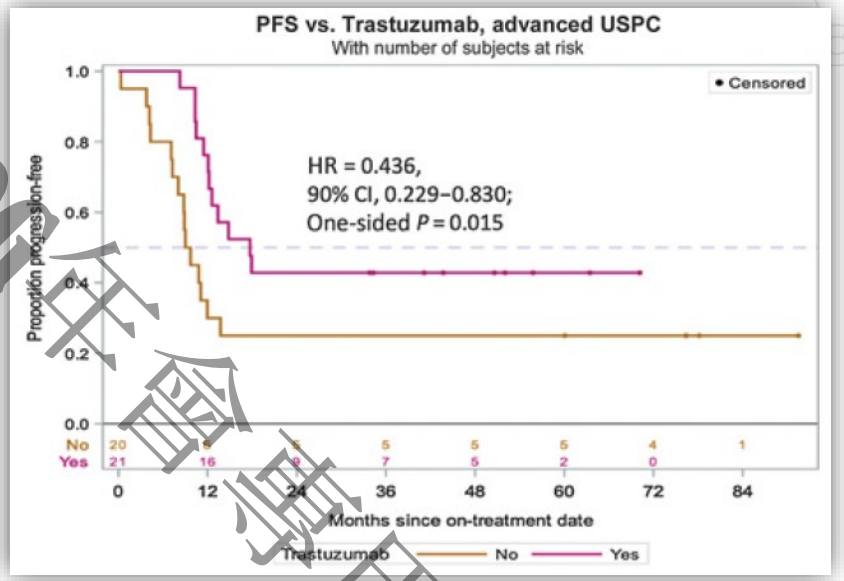


J Clin Med. 2023 Jan 11;12(2):603

Her2/neu Targeting

Randomized Phase II Trial of Carboplatin–Paclitaxel Compared with Carboplatin–Paclitaxel–Trastuzumab in Advanced (Stage III–IV) or Recurrent Uterine Serous Carcinomas that Overexpress Her2/Neu (NCT01367002): Updated Overall Survival Analysis (N=41+20)





J Clin Oncol. 2018 Jul 10;36(20):2044-2051
Clin Cancer Res. 2020 Aug 1;26(15):3928-3935

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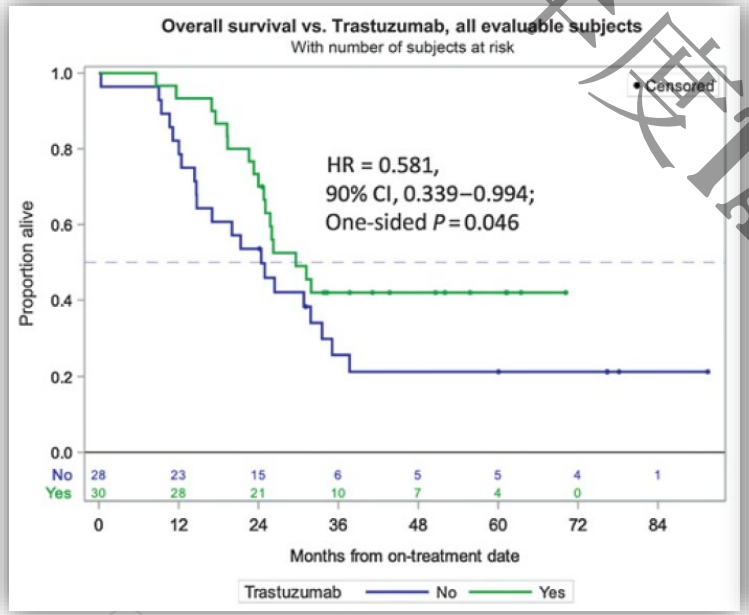

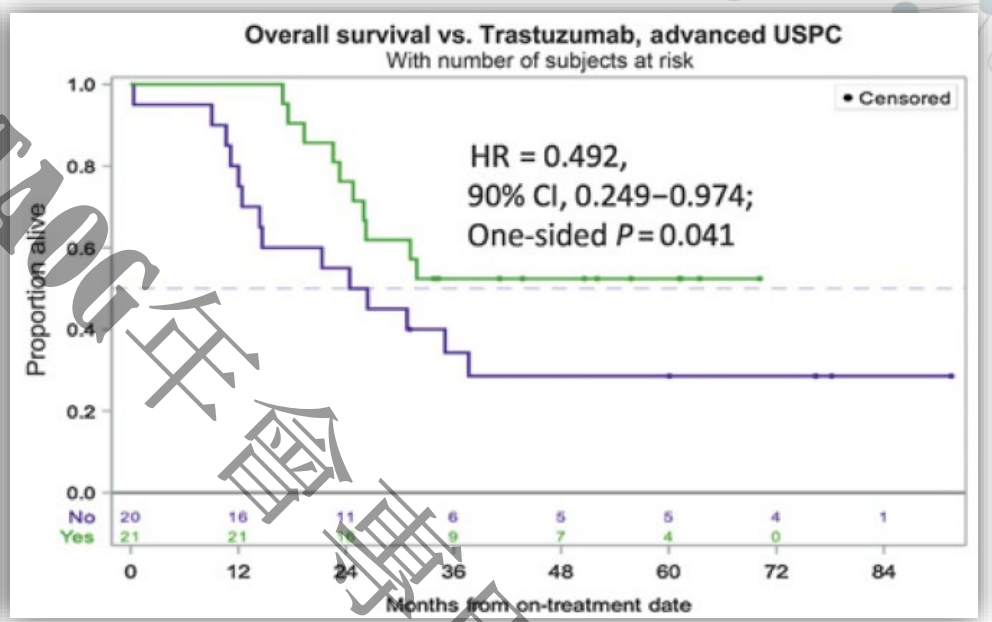

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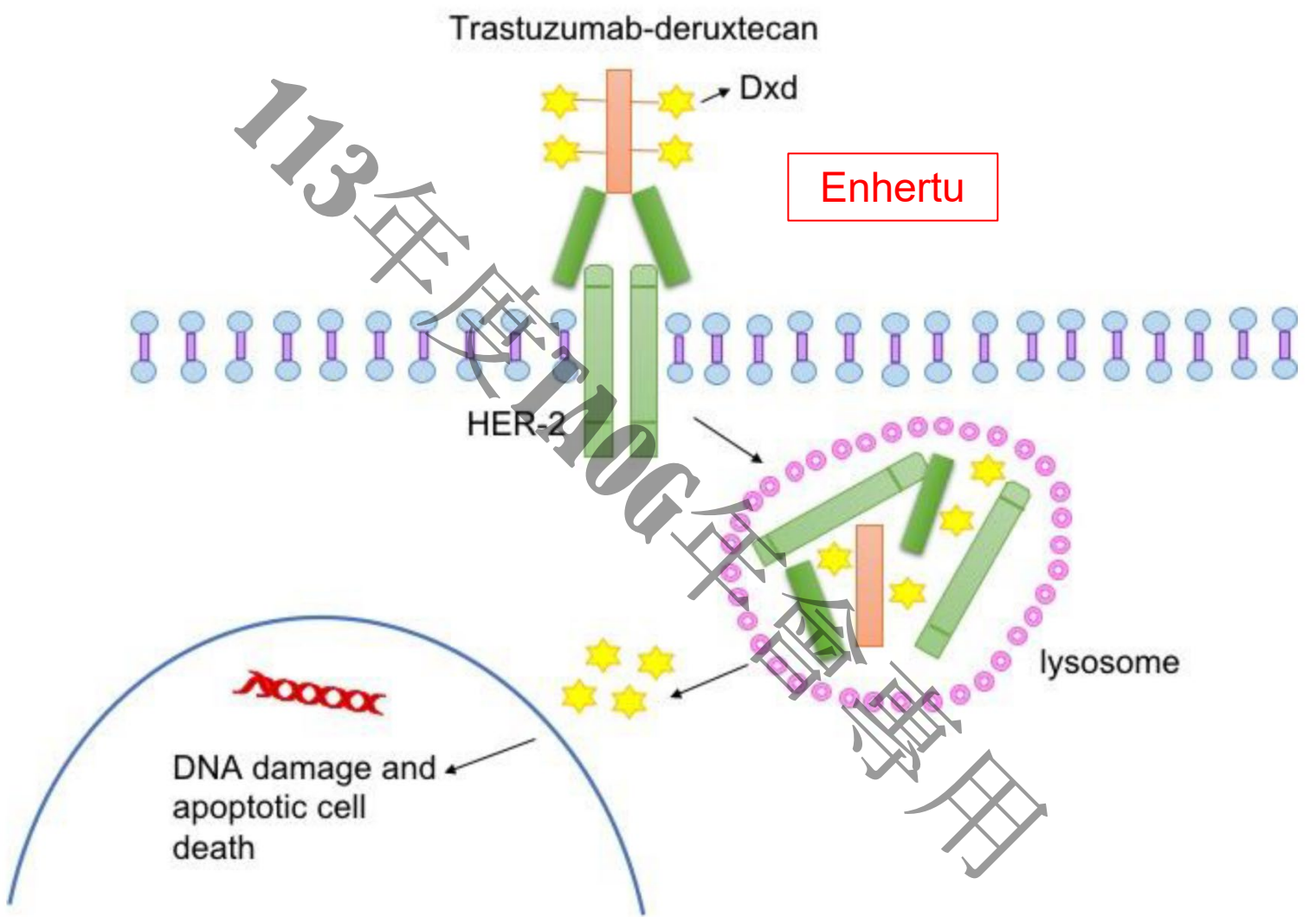
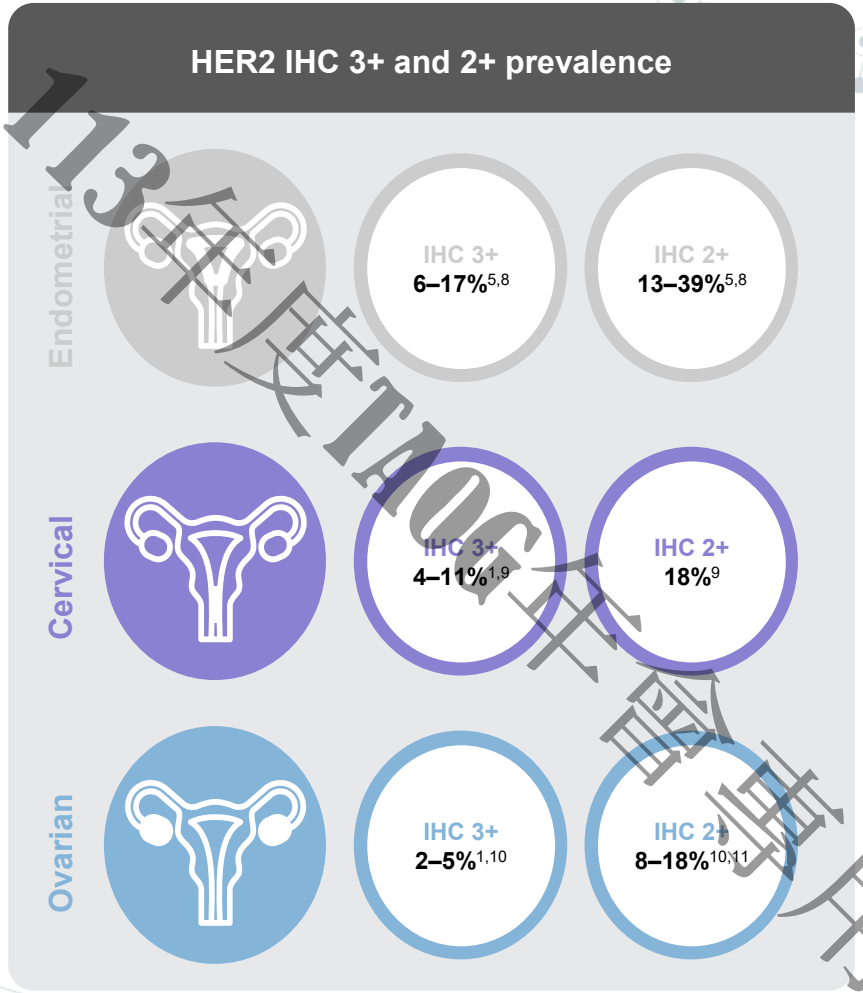
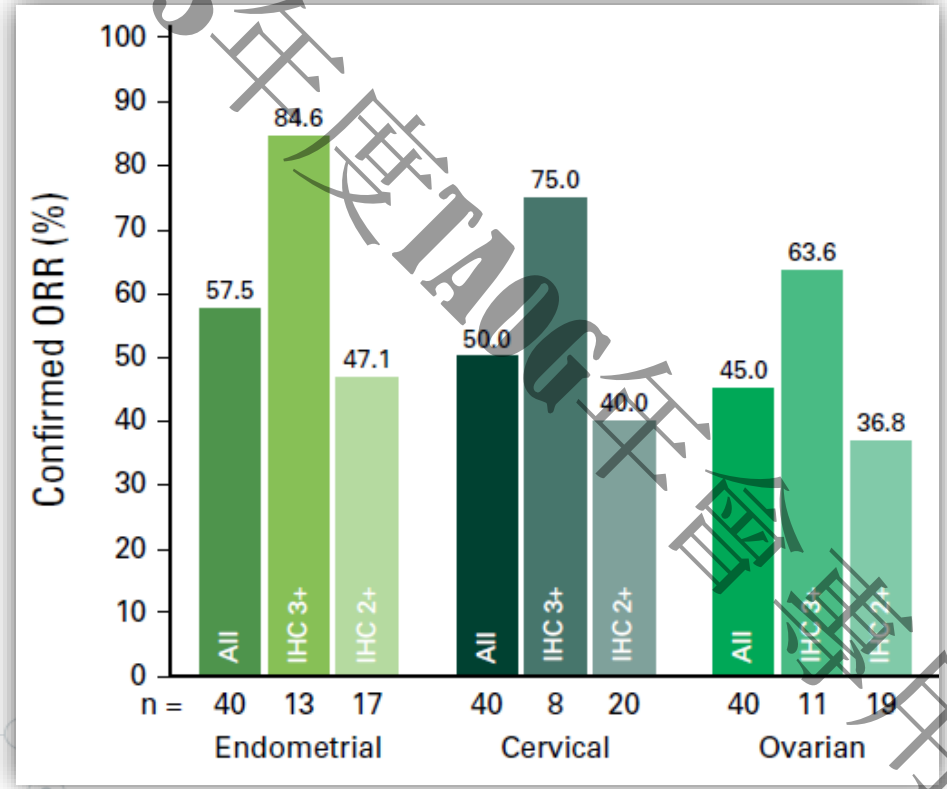
ADC: antibody drug conjugate





Efficacy and Safety of Trastuzumab Deruxtecan in Patients With HER2-Expressing Solid Tumors: Primary Results From the DESTINY-PanTumor02 Phase II Trial



J Clin Oncol. 2024 Jan 1;42(1):47-58

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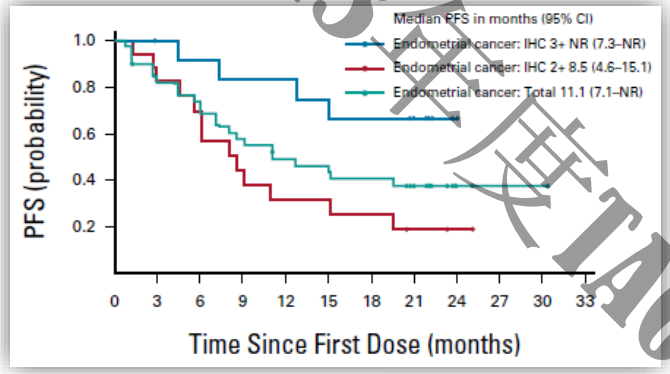

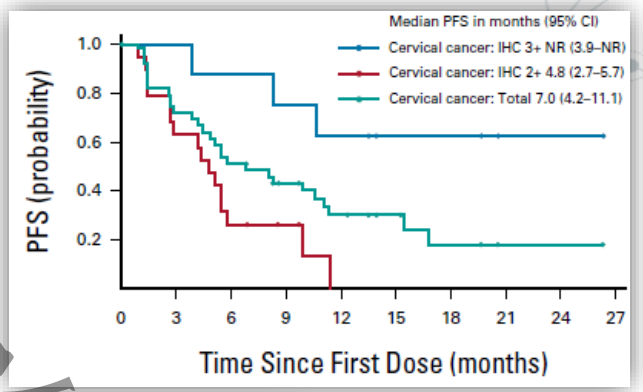

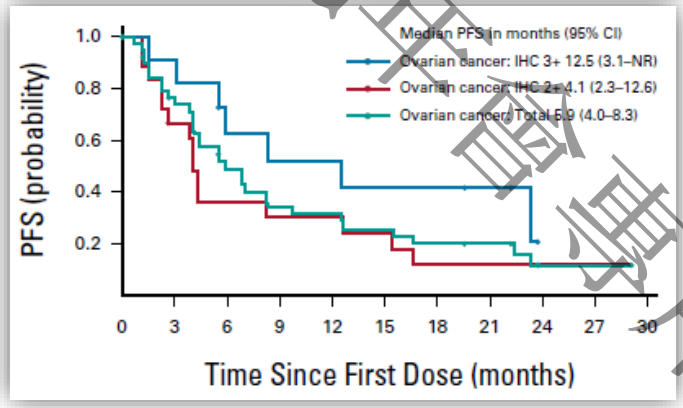

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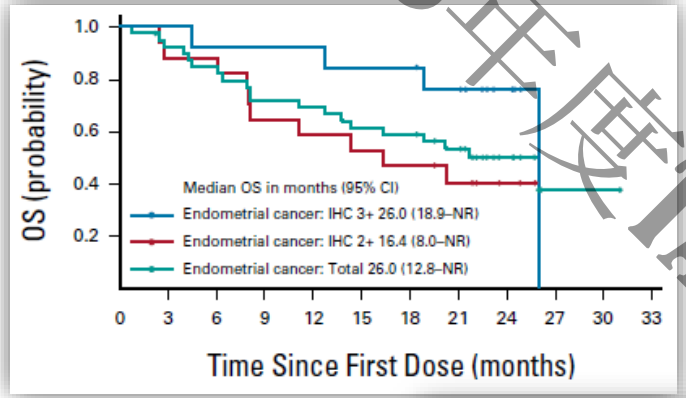
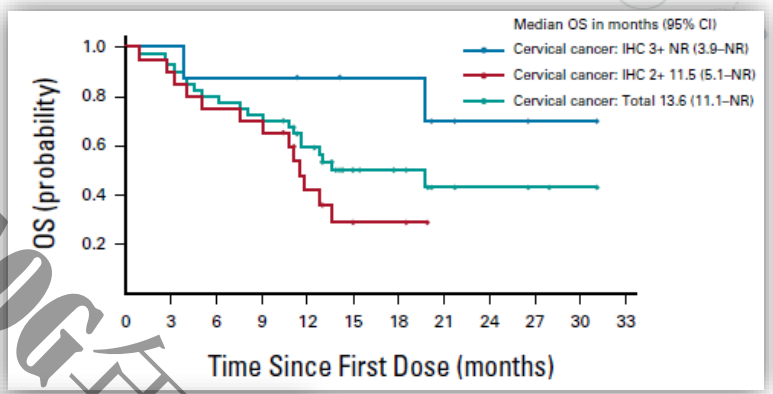
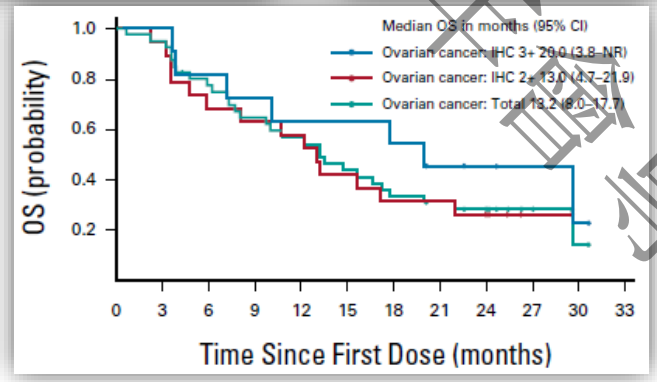






J Clin Oncol. 2024 Jan 1;42(1):47-58

2nd line treatment for recurrent disease

Study Design

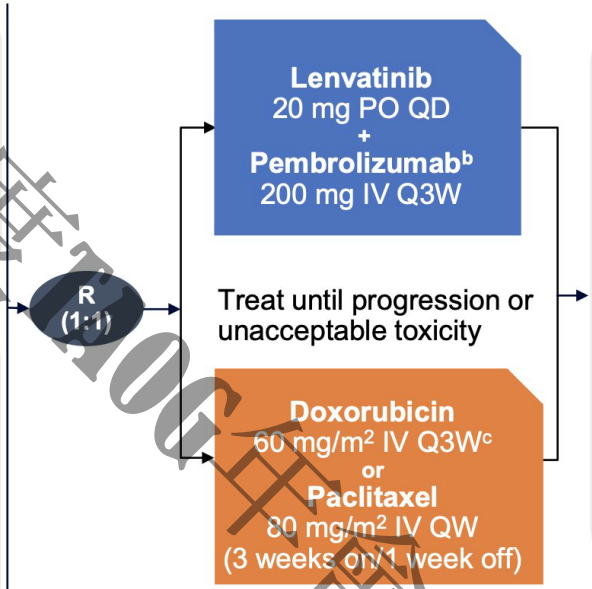
Key eligibility criteria

- Advanced, metastatic, or recurrent endometrial cancer
- Measurable disease by BICR
- 1 Prior platinum-based CT[a]
- ECOG PS 0-1
- Tissue available for MMR testing

Stratification factors

MMR status (pMMR vs dMMR) and further stratification within pMMR by:

- Region (R1: Europe, USA, Canada, Australia, New Zealand, and Israel, vs R2: rest of the world)
- ECOG PS (0 vs 1)
- Prior history of pelvic radiation (Y vs N)



Primary endpoints

- PFS by BICR
- Overall survival

Secondary endpoints

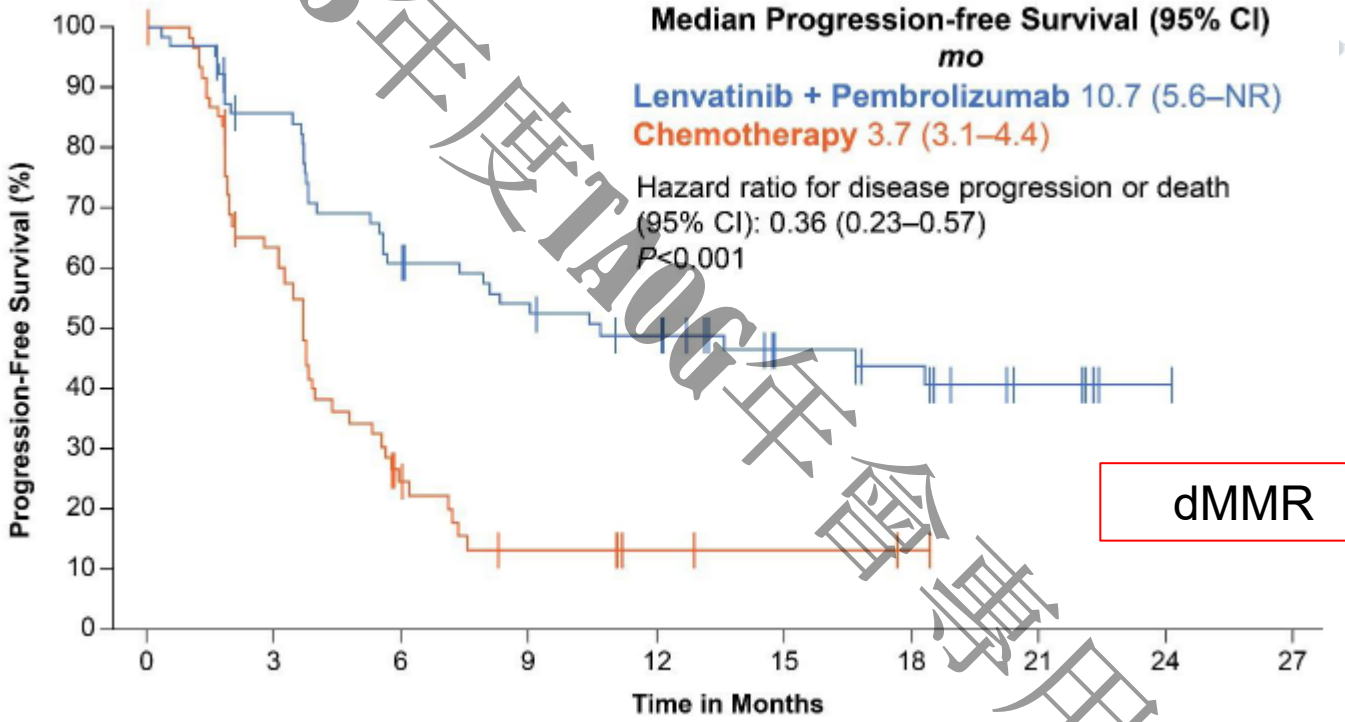
- ORR
- HRQoL
- Pharmacokinetics
- Safety

Key exploratory endpoint

- Duration of response

[a]Patients may have received up to 2 prior platinum-based CT regimens if 1 is given in the neoadjuvant or adjuvant treatment setting. [b]Maximum of 35 doses. [c]Maximum cumulative dose of 500 mg/m².
BICR, blinded independent central review; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQoL, health-related quality of life; IV, intravenous; PFS, progression-free survival; pMMR, mismatch repair-proficient; ORR, objective response rate; PO, per os (by mouth); QD, once daily; Q3W, every 3 weeks; QW, once weekly.

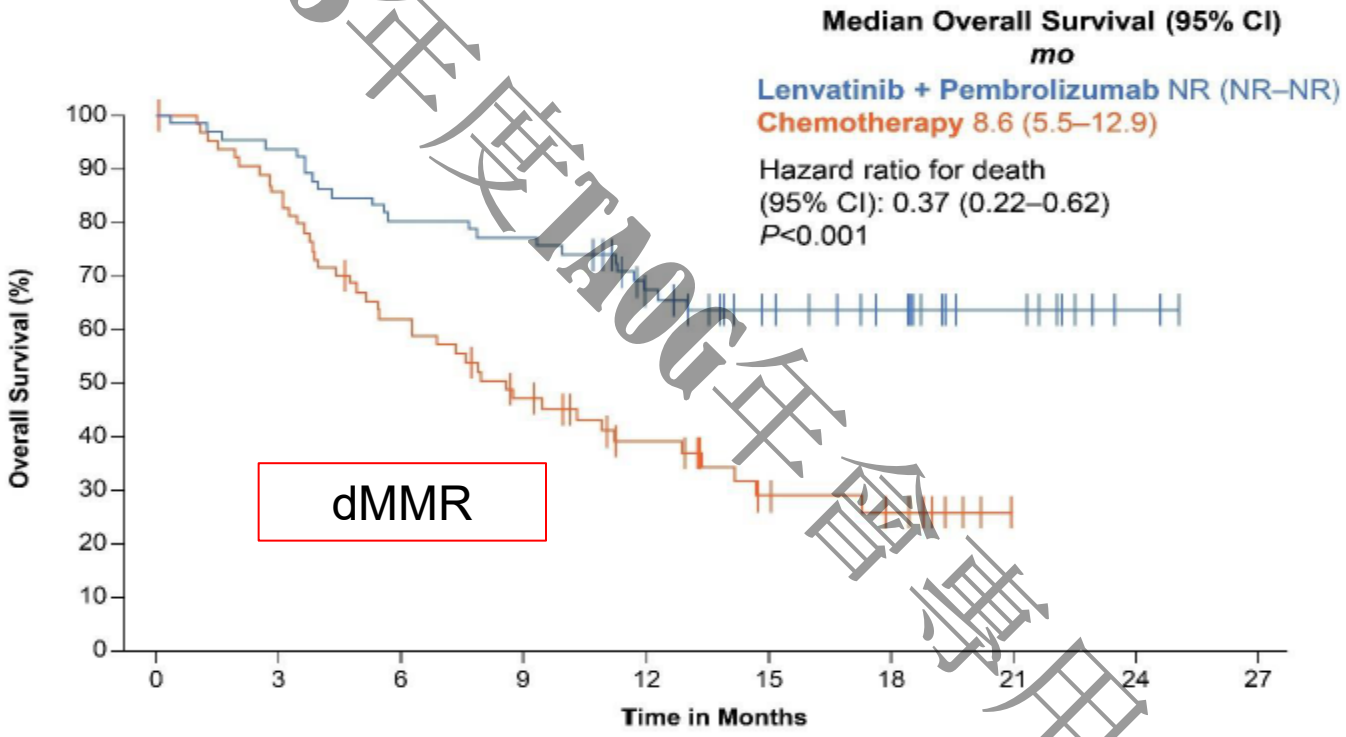
Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer



dMMR

N Engl J Med. 2022 Feb 3;386(5):437-448

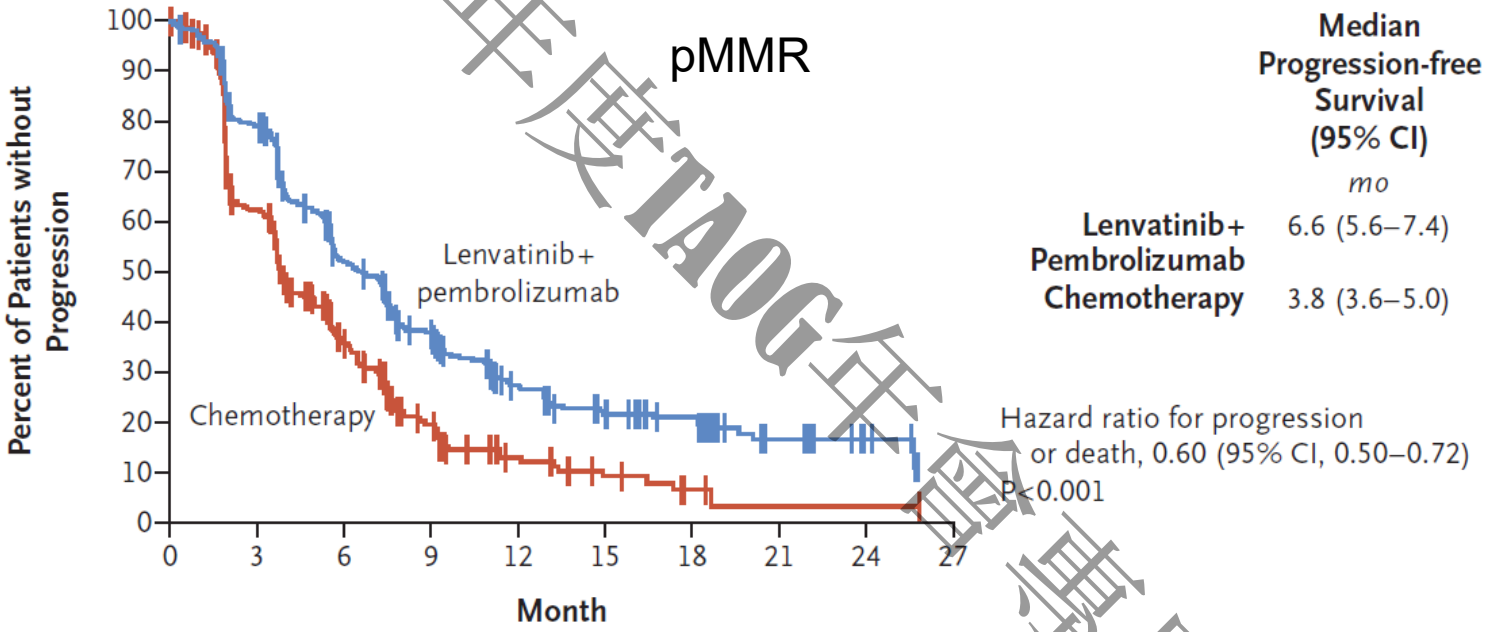
Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer



N Engl J Med. 2022 Feb 3;386(5):437-448

Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer

pMMR



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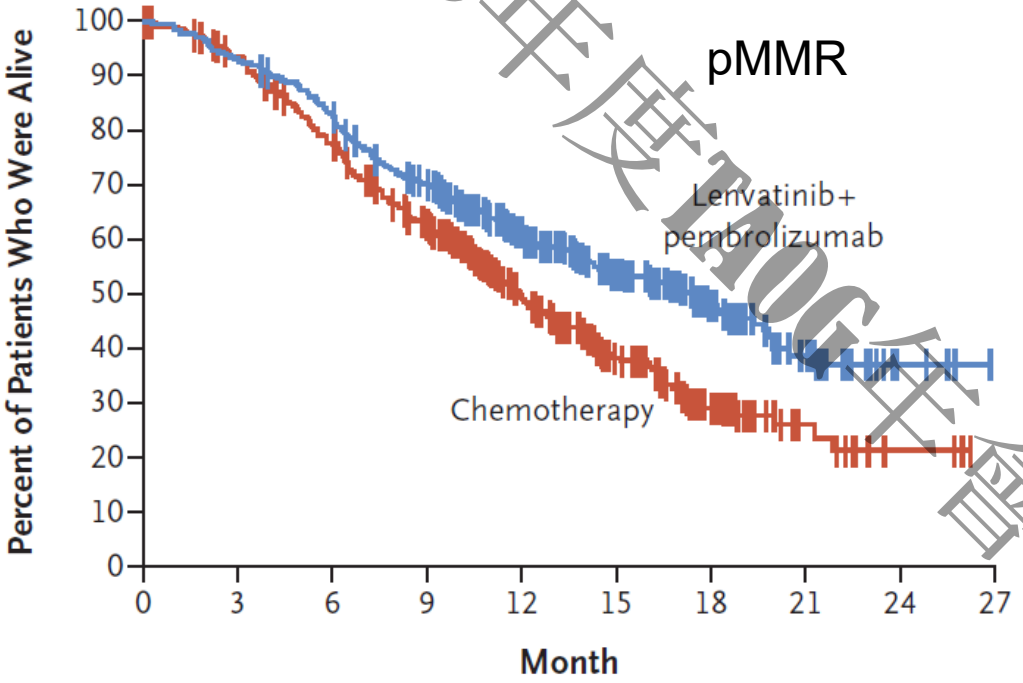

	Median Overall Survival (95% CI)
	mo
Lenvatinib+ Pembrolizumab	17.4 (14.2–19.9)
Chemotherapy	12.0 (10.8–13.3)

Hazard ratio for death, 0.68 (95% CI, 0.56–0.84)
P<0.001

N Engl J Med. 2022 Feb 3;386(5):437-448

SYSTEMIC THERAPY FOR RECURRENCE

RECURRENT DISEASE[h,i]	
First-Line Therapy for Recurrent Disease[j]	Second-Line or Subsequent Therapy
<u>Preferred</u> • Carboplatin/paclitaxel (category 1 for carcinosarcoma)[k,7] • Carboplatin/paclitaxel/pembrolizumab (except for carcinosarcoma) (category 1)[b,c,d,8] • Carboplatin/paclitaxel/dostarlimab-gxly (category 1)[c,d,e,9] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive uterine serous carcinoma)[d,10] • Carboplatin/paclitaxel/trastuzumab[d,g] (for HER2-positive carcinosarcoma)[f,10] <u>Other Recommended Regimens</u> • Carboplatin/docetaxel[l] • Carboplatin/paclitaxel/bevacizumab[d,m,11,12] <u>Useful in Certain Circumstances (Biomarker-directed therapy: after prior platinum-based therapy including neoadjuvant and adjuvant)</u> • MMR-proficient (pMMR) tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n] ▸ Pembrolizumab[c,14] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16]	<u>Other Recommended Regimens</u> • Cisplatin/doxorubicin[17] • Cisplatin/doxorubicin/paclitaxel[p,14] • Cisplatin • Carboplatin • Doxorubicin • Liposomal doxorubicin • Paclitaxel[14] • Albumin-bound paclitaxel[q] • Topotecan • Bevacizumab[m,r,19] • Temsirolimus[20] • Cabozantinib • Docetaxel (category 2B) • Ifosfamide (for carcinosarcoma) • Ifosfamide/paclitaxel (for carcinosarcoma)[21] • Cisplatin/ifosfamide (for carcinosarcoma) <u>Useful in Certain Circumstances (Biomarker-directed therapy)</u> • pMMR tumors ▸ Lenvatinib/pembrolizumab (category 1)[c,13] • TMB-H tumors[n,12] ▸ Pembrolizumab[c] • MSI-H/dMMR tumors[o] ▸ Pembrolizumab[c,15] ▸ Dostarlimab-gxly[c,16] ▸ Avelumab[c] ▸ Nivolumab[c,22] • HER2-positive tumors (IHC 3+ or 2+) ▸ Fam-trastuzumab deruxtecan-nxki[23] • *NTRK* gene fusion-positive tumors ▸ Larotrectinib ▸ Entrectinib

NCCN Guidelines version 1.2024

Applicability of the concept of "platinum sensitivity" to recurrent endometrial cancer: The SGSG-012/GOTIC-004/Intergroup study

Response	Platinum free interval (months)			
	PFI < 6	6 ≤ PFI < 12	12 ≤ PFI < 24	24 ≤ PFI
Complete response	7	8	17	24
Partial response	9	17	24	19
Stable disease	11	18	8	8
Progression disease	35	19	14	10
Not evaluable	2	3	4	5
Total	64	65	67	66
Overall response (%)	25	38	61	65

Gynecol Oncol. 2013 Dec;131(3):567-73

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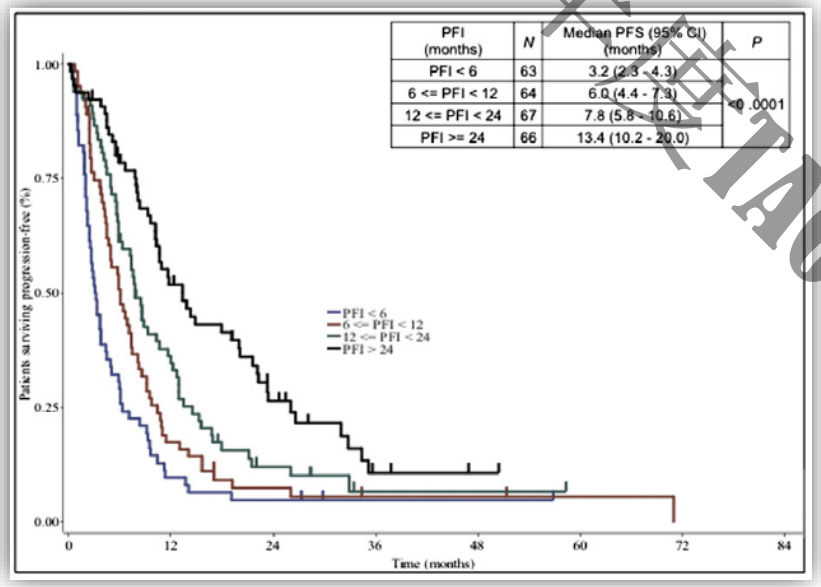
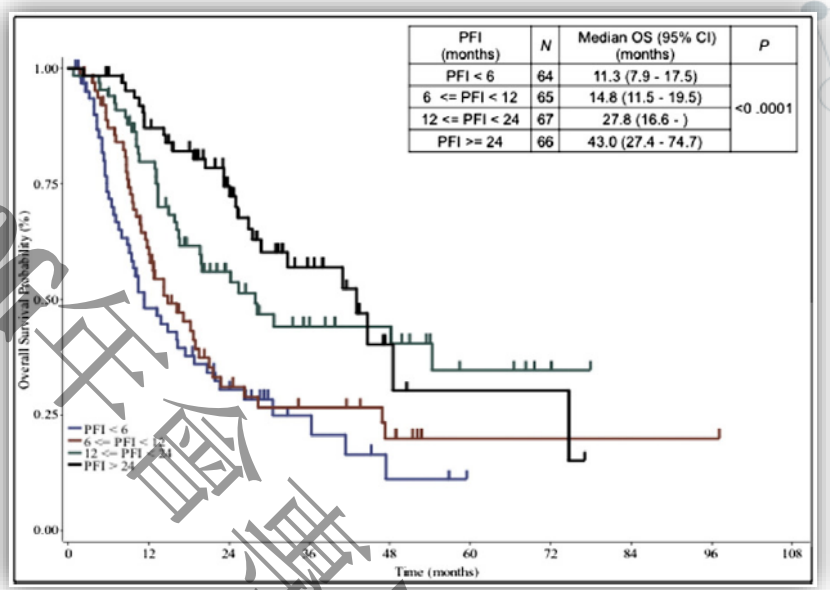




Gynecol Oncol. 2013 Dec;131(3):567-73

FIGO staging 2023

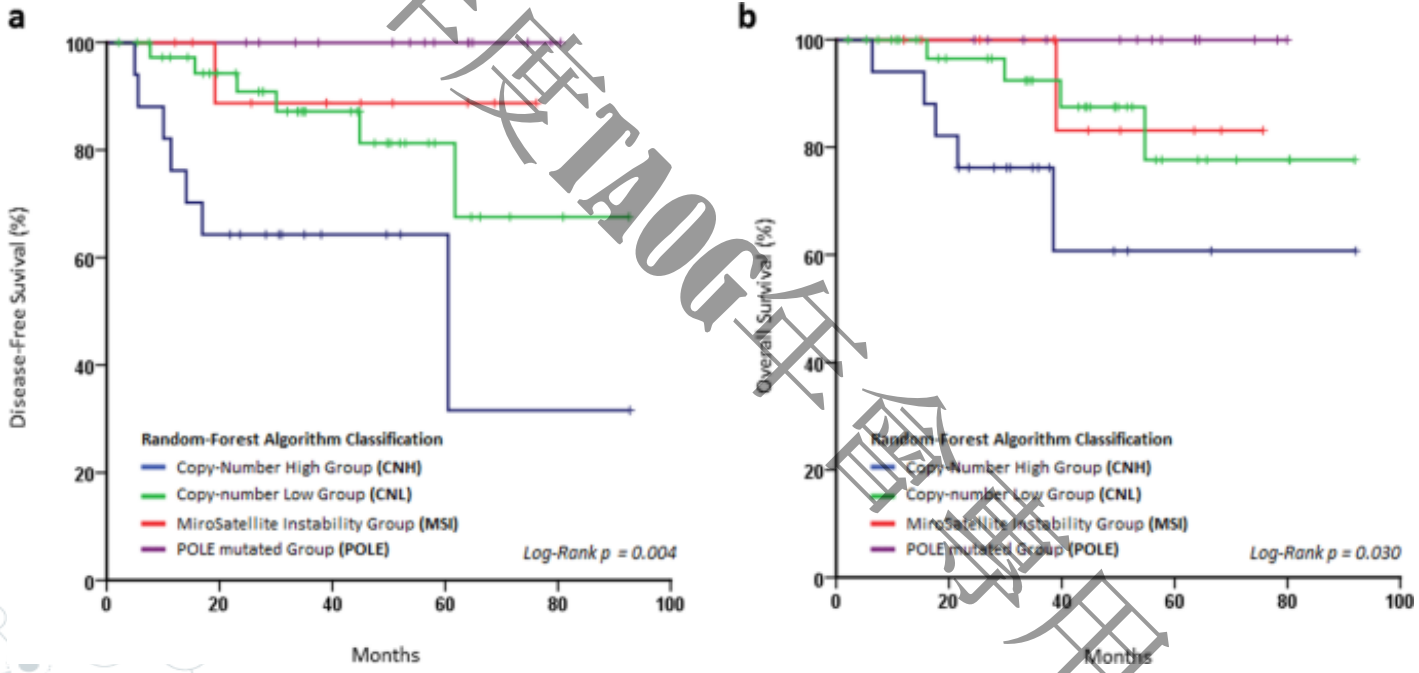
2023 Figo Stage	Defining Criteria
IA1	non-aggressive histological type limited to the endometrium or an endometrial polyp
IA2	non-aggressive histological type involving <50% myometrium, with no/focal LVSI
IA3	low-grade EEC limited to the uterus and ovary
$IA1m_{POLEmut}$	*POLEmut EC, confined to the uterine corpus or with cervical extension, regardless of LVSI or histological type*
IB	non-aggressive histological type involving ≥50% myometrium, and with no/focal LVSI
IC	aggressive histological type limited to the endometrium or an endometrial polyp
IIA	non-aggressive histological type with invasion of the cervical stroma
IIB	non-aggressive histological type with substantial LVSI
IIC	aggressive histological type with any myometrial infiltration
$IICm_{p53abn}$	*p53abn EC, confined to the uterine corpus with any myometrial infiltration, with or without cervical invasion, and regardless of LVSI or histological type*
IIIA1	spread to ovary or fallopian tube (except if it meets the Stage IA3 criteria)
IIIA2	involvement of uterine subserosa/serosa
IIIB1	metastasis or direct spread to the vagina and/or the parametria
IIIB2	metastasis to the pelvic peritoneum
IIIC1	metastasis to the pelvic lymph nodes (micrometastasis = IIIC1i/macrometastasis = IIIC1ii)
IIIC2	metastasis to para-aortic lymph nodes up to the renal vessels, with or without metastasis to the pelvic lymph nodes (micrometastasis = IIIC2i/macrometastasis = IIIC2ii)
IVA	invasion of the bladder mucosa and/or the intestinal 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

P53abn for each histotype (N=3769)

Histotype	Total	p53abn (n (%))
Endometrioid endometrial carcinoma grades 1–2	2515	130 (5.2)
Endometrioid endometrial carcinoma grade 3	900	199 (22.1)
Serous endometrial carcinoma	122	113 (92.6)
Clear cell carcinoma	61	23 (37.7)
Carcinosarcoma	171	146 (85.4)
Total	**3769**	**611 (16.2)**

Int J Gynecol Cancer. 2021 Jun;31(6):907-913

P53abn



Nature 497, 67–73 (2013)

P53abn

- Most aggressive molecular type
- PORTEC 3(stage I/II 55%): p53abn in serous vs. other histology, 5-yr OS: 57.7 vs. 50.7%
- PORTEC-3: PFS CCRT+C/T vs. R/T= 59 vs. 36%
- Effect of I/O: modest
- 5-15% BRCAmut
- GOG-86P: improve PFS, OS when add Bevacizumab

Take home messages

- A perfect surgery make first successful step.
- PTx6 and CCRT+PTx4 equal efficacy, less toxicity.

  Role of sandwich still not fade away
- Adding I/O to frontline C/T increase PFS, (OS?) in advanced stage
- Add Herceptin to PT improve OS in MMMT and serous
- PT re-treat same efficacy with pembro/lenva in PFI > 6M


謝謝聆聽 敬請指教