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NETHERLANDS CANCER INSTITUTE
ANTONI VAN LEEUWENHOEK

Uterine and ovarian carcinosarcoma

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Declaration of interests

MiMark scientific advisory board

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Take home message

- **Monoclonal theory CS: metaplasia in epithelial cancer**
- **Surgical staging/debulking similar to high grade endometrial or ovarian cancer**
- **Paclitaxel-Carboplatin best efficacy/toxicity**

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Agenda

- Tumour biology carcinosarcoma
- Uterine carcinosarcoma
- Ovarian carcinosarcoma

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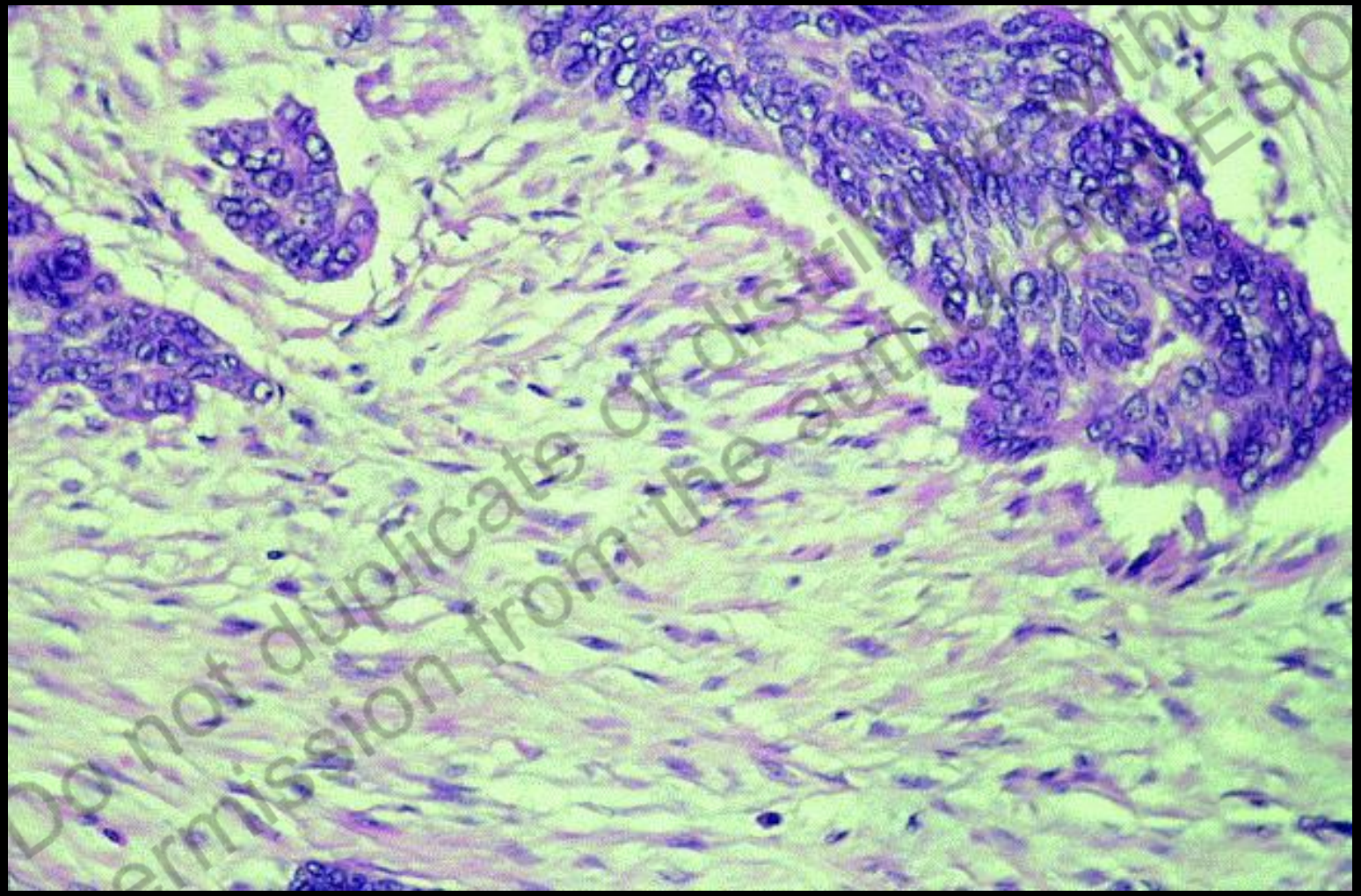
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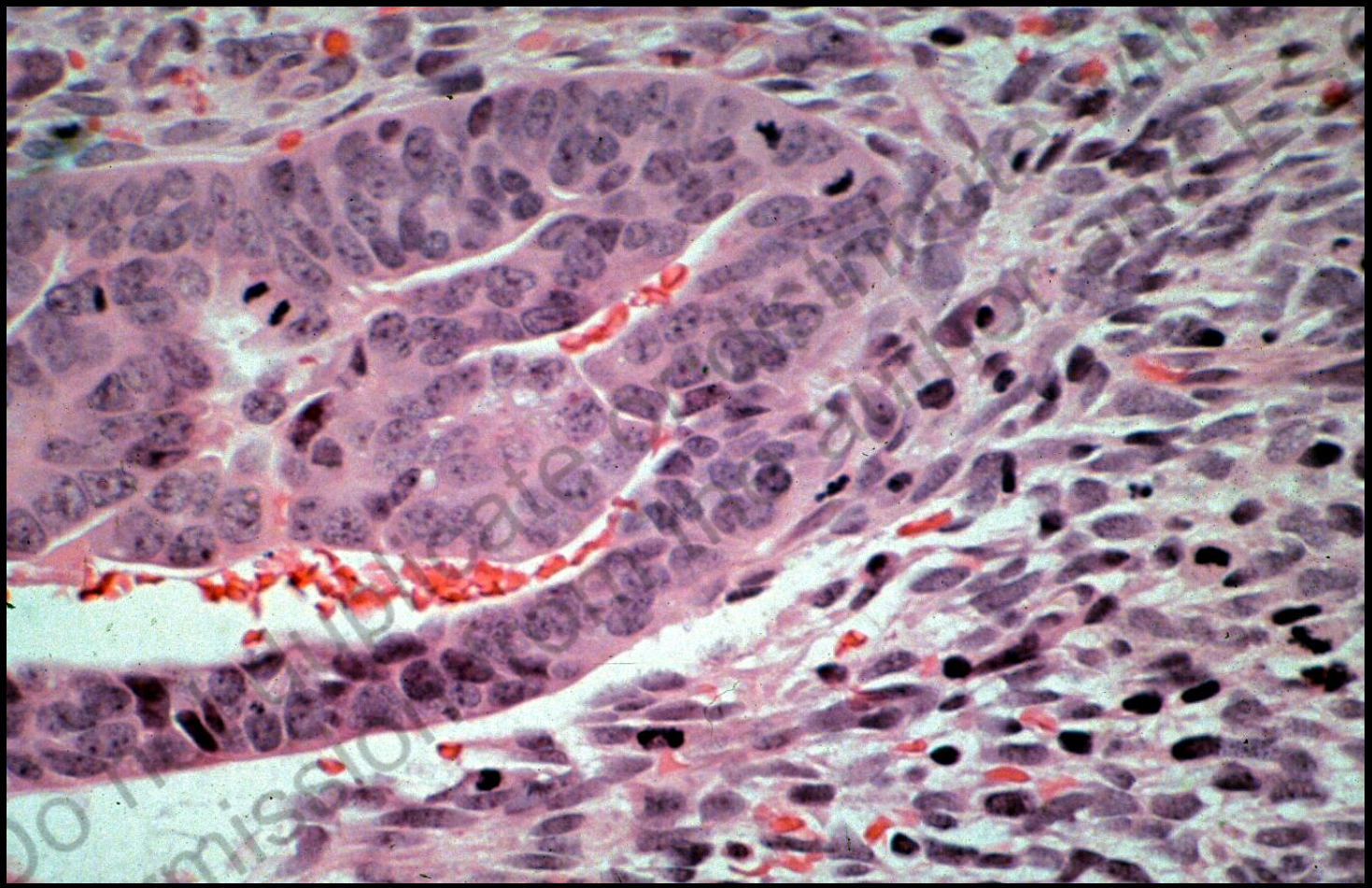

Morphologic features: biphasic tumor

Epithelial component

- High grade
  - Endometrioid
  - Serous
  - Clear cell
  - Undifferentiated

Mesenchymal component

- Homologous
  - Round cell or spindle cell sarcomatous proliferation
- Heterologous
  - Cartilago
  - Osteosarcoma
  - Rhabdomyosarcoma
  - Melanoma
  - Liposarcoma
  - (Neural)
  - (Angiomatoid differentiation)

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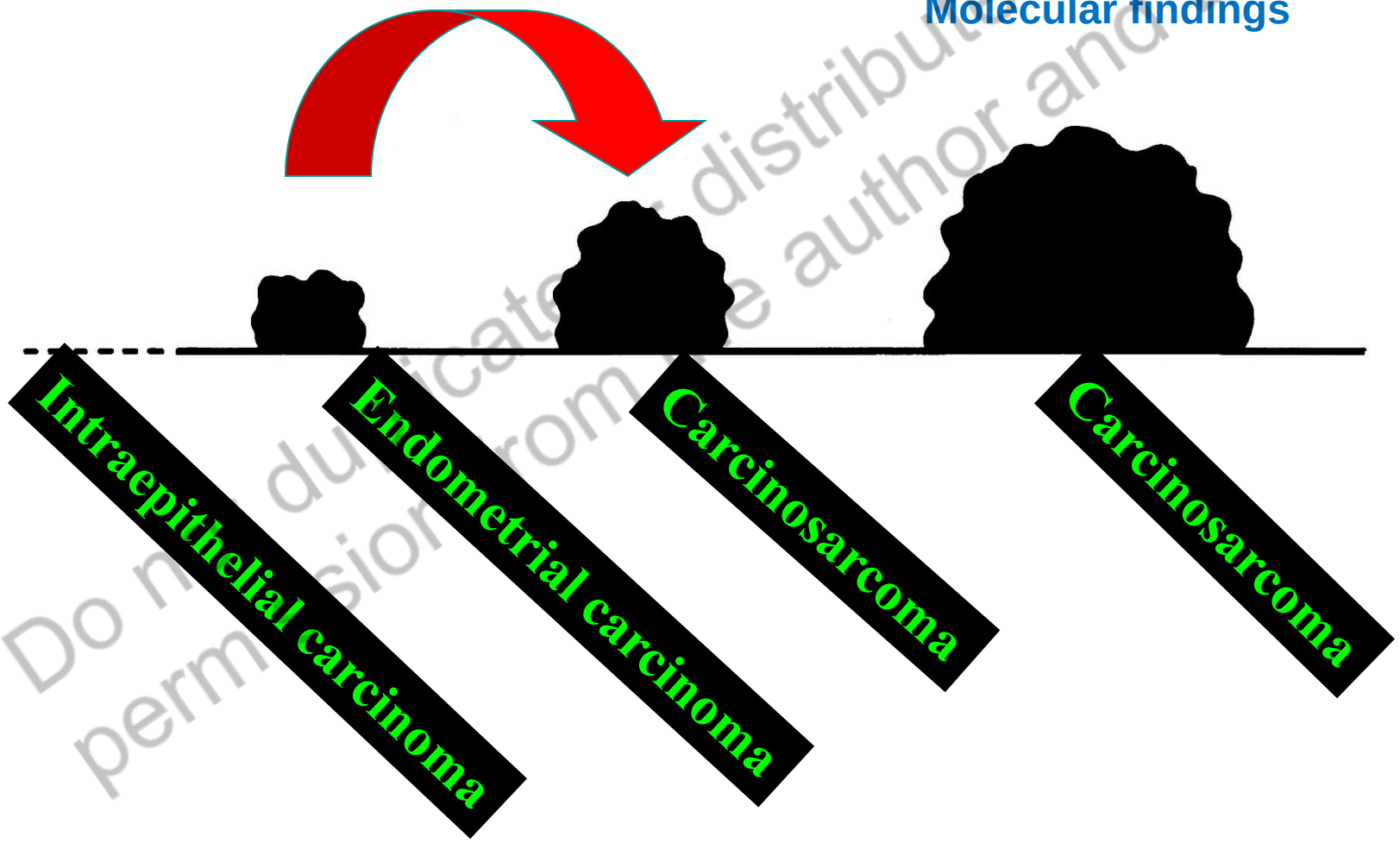
Histogenesis

Monoclonal theory

Immunohistochemistry
Clinicopathologic findings
In vitro and in vivo studies
Molecular findings



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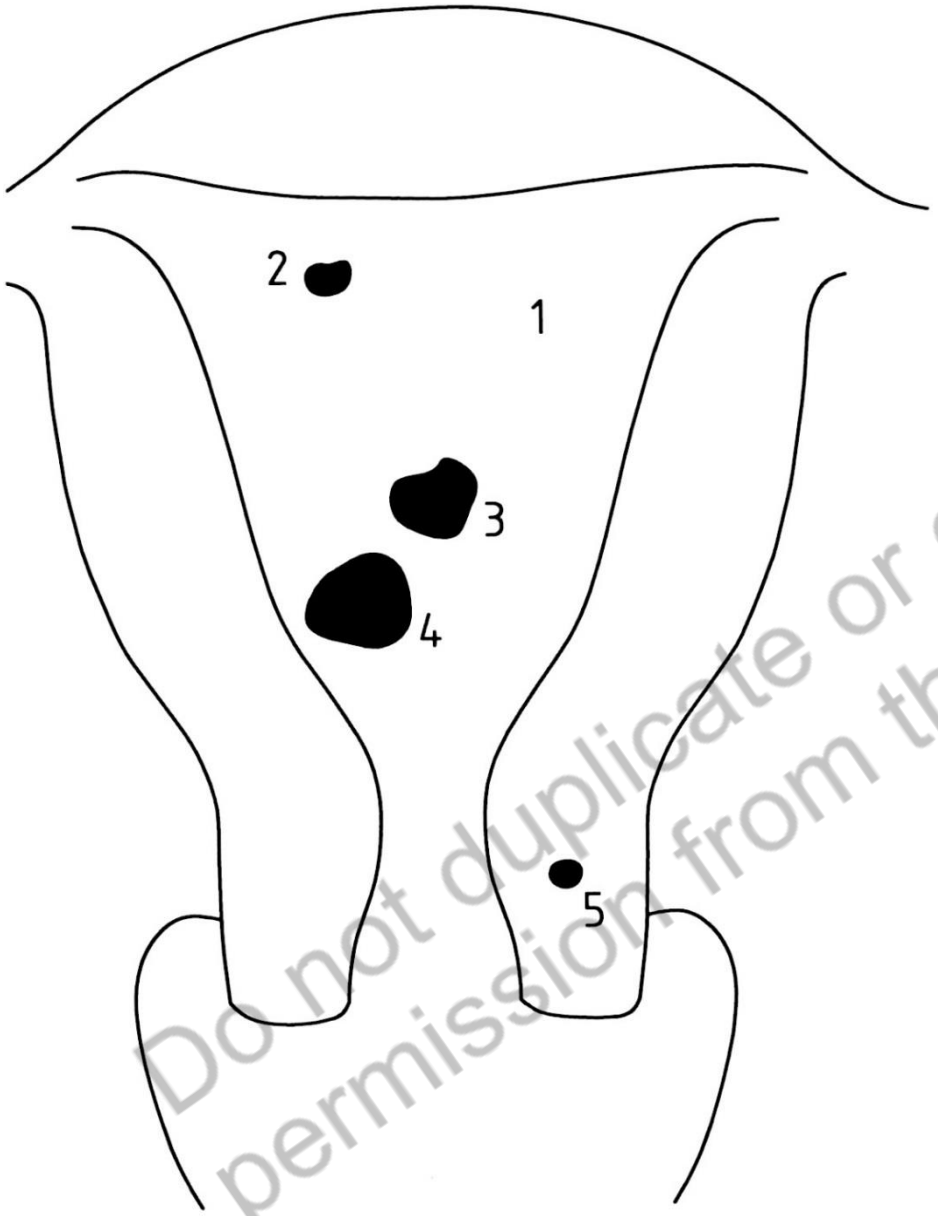

1. *Intramucosal papillary serous adenosarcoma*
2. *Papillary serous adenosarcoma*
3. *Carcinosarcoma*
4. *Carcinosarcoma with melanocytic differentiation*
5. *Carcinoma*

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Amant et al., Int J Gynecol Pathol 2001;20:186-190

Clinicopathologic findings

- 203 uterine carcinosarcomas
- Metastases were studied in 40 cases

- None with pure sarcoma
- Majority pure carcinoma (n=30)
- Predominant (34/40) pelvic and para-aortic lymph nodes

Silverberg et al., Int J Gynecol Pathol 1990;9:1-19
(Bitterman et al., Am J Surg Pathol 1990;14:317-328)
(Sreenan et al., Am J Surg Pathol 1995;19:666-7)

Epithelial component is the driving force

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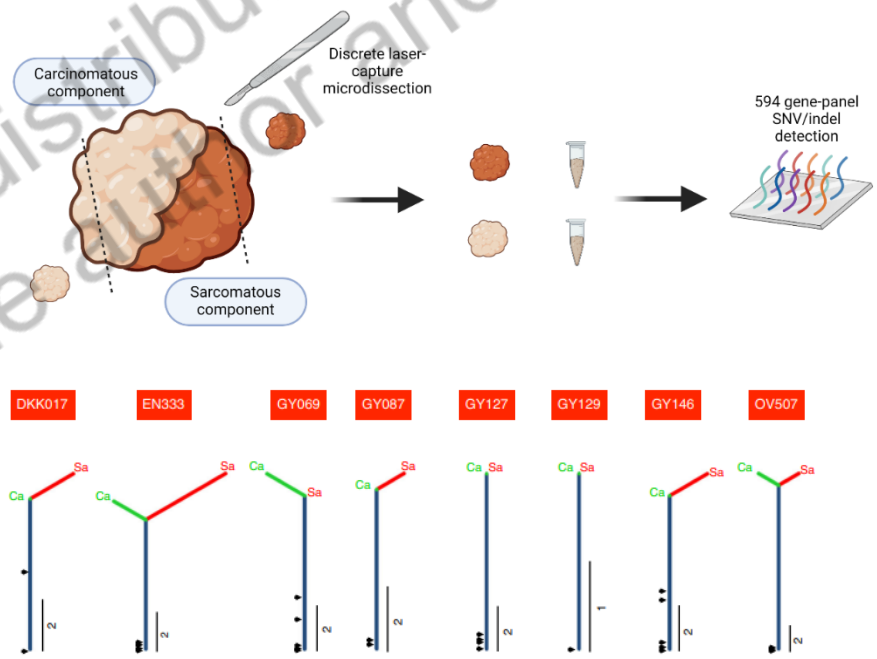
Mutational landscape of uterine and ovarian carcinosarcomas

Zhao et al., PNAS 2016

- **Sarcoma and carcinoma components shared most of the SNV/indels of the 596-gene panel**
- **Driver events exclusively occurred on the trunk**
- **Driver events on the trunk were clonal**
- **No recurrent mutations in SNVs/indels or CNVs were differentially detected between the carcinoma and sarcoma components**
- **Supports the clonal origin of CS cells and conversion theory**



Gotoh et al., nat. comm., 2019
Zhao et al., Proc Natl Acad Sci USA, 2016

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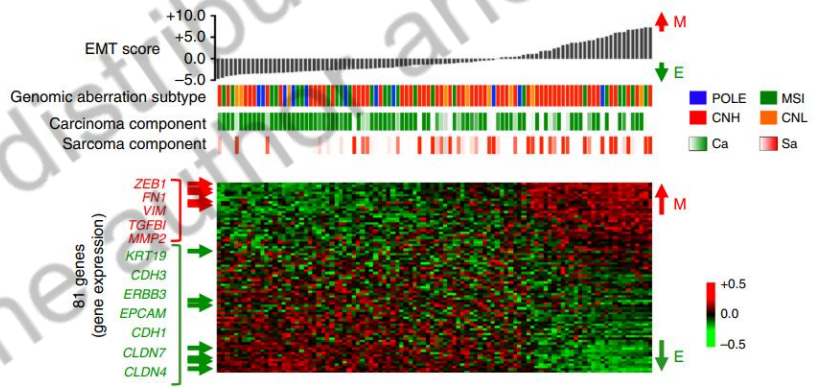
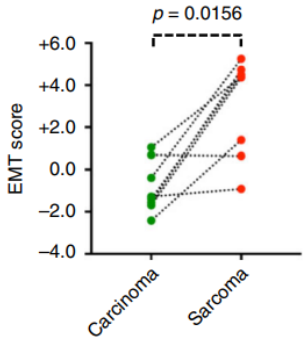
Epithelial-mesenchymal transition in CS

Zhao et al, Proc Natl Acad Sci USA, 2016, Gotoh et al, Nat Comm 2019

- EMT score calculated for CS samples based on RNA-seq profile
- EMT score highly concordant with content of carcinoma and sarcoma elements in primary tumor
- Carcinoma cells convert into sarcoma cells within CS tumors through EMT
- EMT score did not correlate with any other clinicopathological parameter





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Transition of epithelial toward mesenchymal differentiation during ovarian carcinosarcoma tumorigenesis.

Amant et al., Gynecol Oncol 2003

Composition of metastatic ovarian carcinosarcoma as reported in literature

Author (year)	Cases	Time	Composition (%)				
			100% C	>50% C	CS	>50% S	100% S
Plaxe et al. (1990) [19]	15	P		60		40	
Barakat et al. (1992) [20]	26	P	39		61		
Muntz et al. (1995) [21]	27	P				++	
Ariyoshi et al. (2000) [12]	21	P	33		57		9
Present series	18	P	66	20		12	2
Plaxe et al. (1990) [19]	8	R				100	
Present series	4	R	0	13		50	37
Czernobilsky et al. (1967) [16]	5	A			60		40
Dehner et al. (1970) [17]	12	A	17			83	
Dinh et al. (1988) [18]	14	P+R+A	28			71	

Note. C, consisting of carcinoma cells only; CS, a combination of carcinoma and sarcoma cells; S, consisting of sarcoma cells only; A, autopsy; P, primary; R, recurrence; ++, probably the authors mean “many” or “most”

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Implications of histogenesis on treatment

- Carcinoma directed cytotoxic treatment in primary setting

- Sarcoma directed cytotoxic treatment in recurrent setting

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Agenda

- Tumour biology carcinosarcoma
- Uterine carcinosarcoma
  - 5% of uterine cancers
  - OS: 8-26 mts
  - Stage I: 50 % OS
- Ovarian carcinosarcoma

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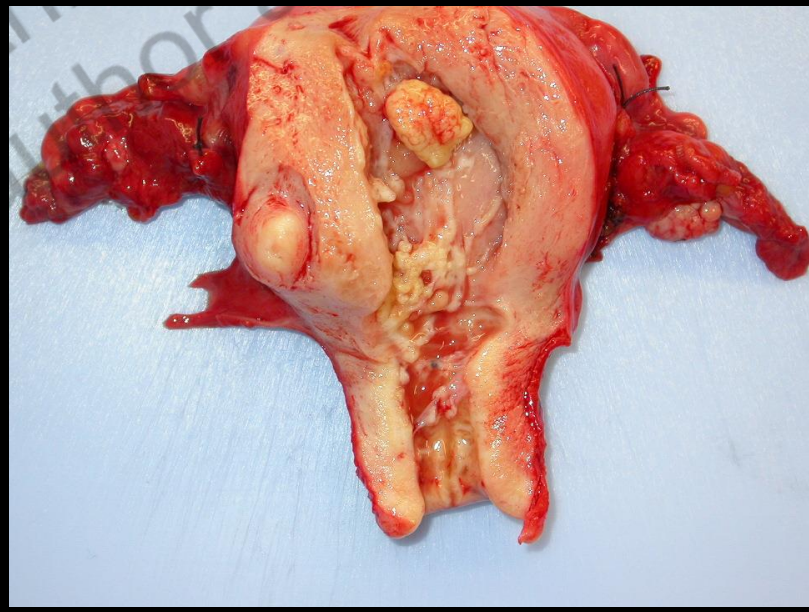
Endometrial carcinosarcoma

(mixed Müllerian malignant tumors, MMT)



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Overview on spread pattern in different subtypes of endometrial cancer as reported in literature

Amant et al., Gynecol Oncol 2005;98:274-80

N (%)	Peritoneal cytology	Adnexal	Omental	Pelvic LN
Grade 3 E	86/668 (13)	41/721 (6)	3/25 (12)	78/734 (11)
Carcinosarcoma	72/373 (19)	75/512 (15)	15/96 (16)	80/423 (19)
Serous	17/57 (13)	27/125 (22)	47/202 (23)	72/244 (30)
Clear cell	7/20 (35)	3/32 (9)	3/6 (50)	9/20 (45)

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Surgical staging for apparent early CS: ~ high grade endometrial or ovarian cancer

Surgical staging through midline incision performing hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection, omentectomy, biopsy of any abnormal peritoneal lesion

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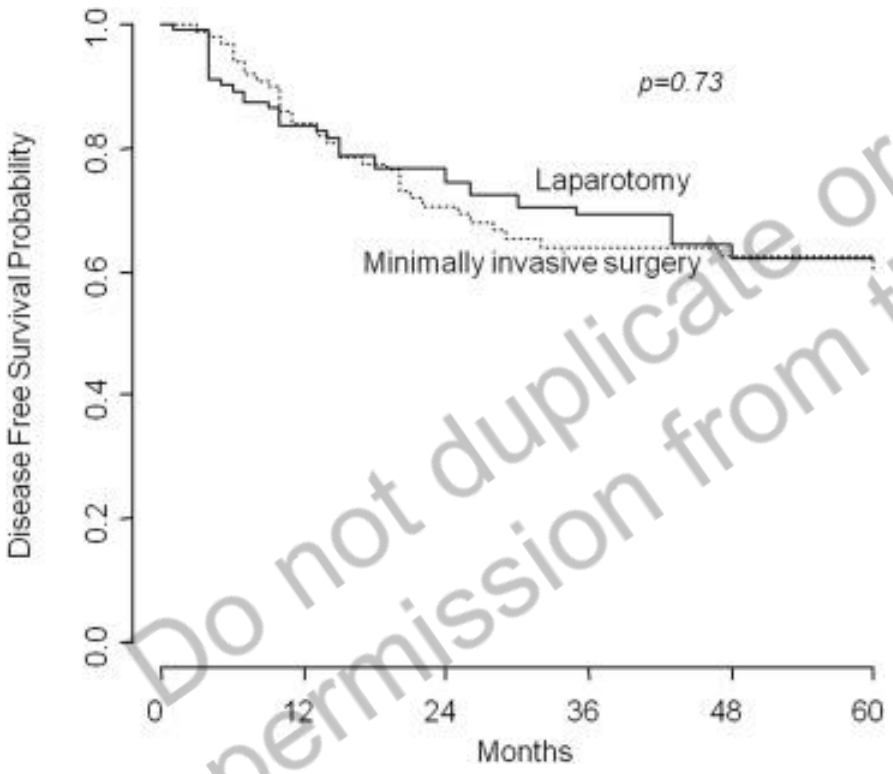
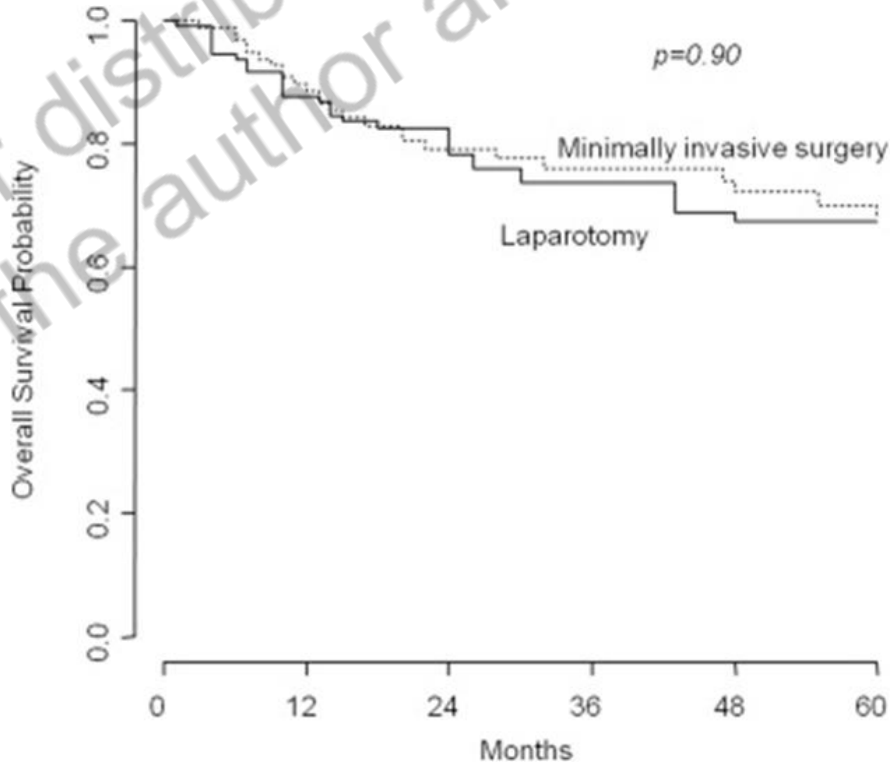
Long-term oncological safety of minimally invasive surgery in high-risk endometrial cancer

Koskas et al., Eur J Ca 2016





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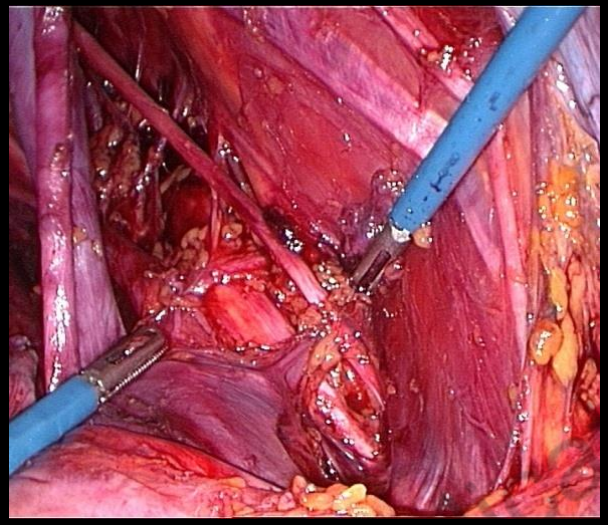
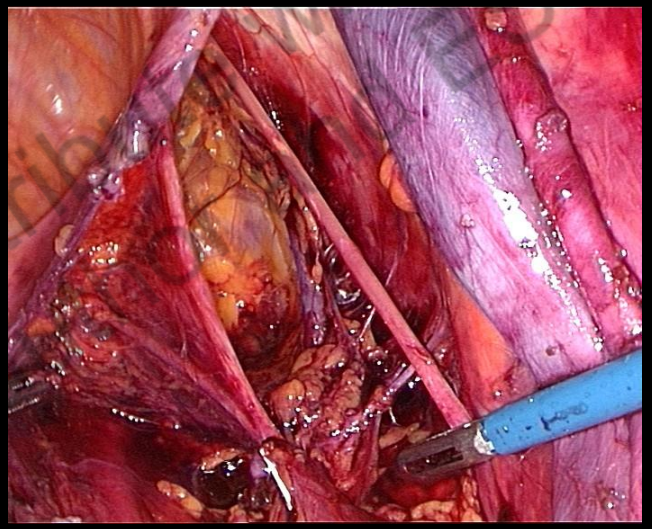
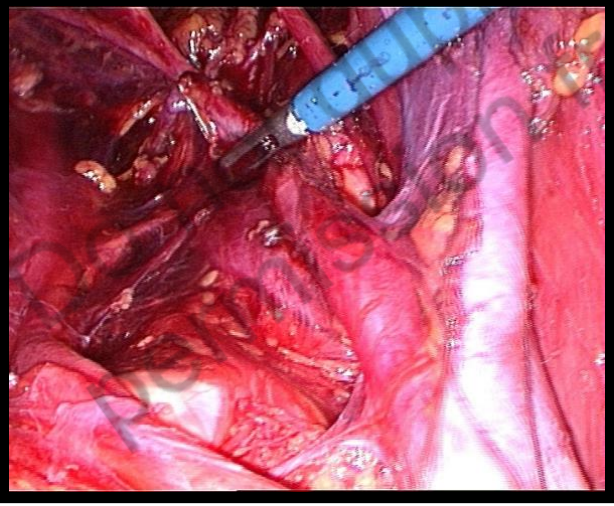
Surgical staging is possible through laparoscopy

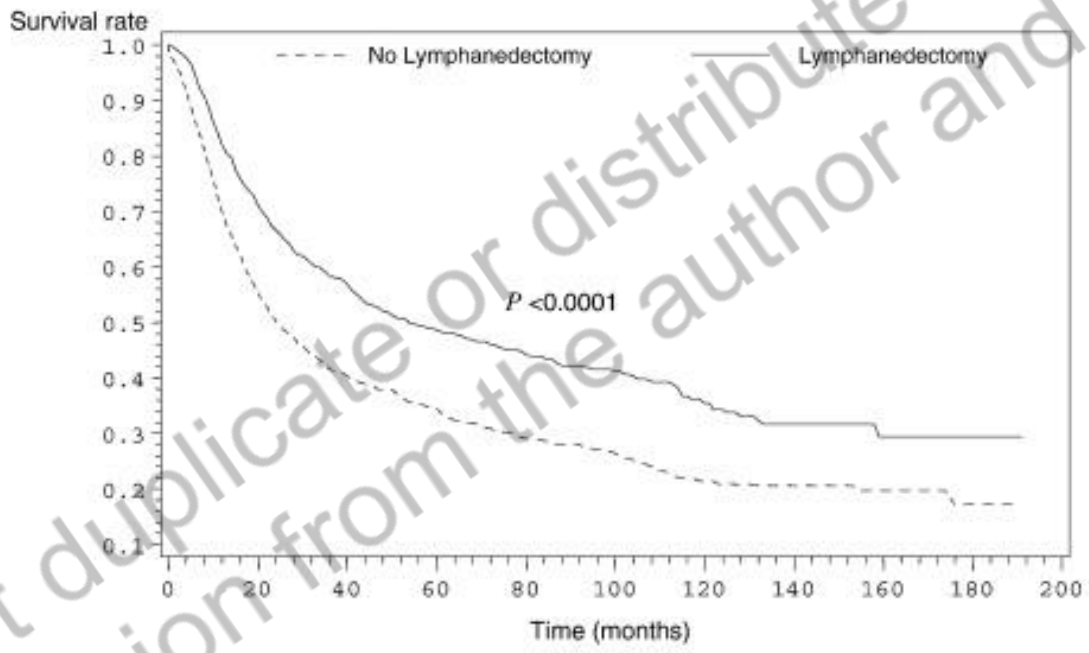






Improved survival in CS with lymphadenectomy, but no benefit of radiotherapy: a SEER analysis

Nemani, Gynecol Oncol 2008;111:82-8



	LND (with or without RT)	No LND (with or without RT)
5-year OS	49%	34%
8-year OS	42%	27%
Median survival (months)	54 (95% CI : 44-72)	25 (95% CI: 22-29)

N=1855

Retrospective bias: fewer comorbid illnesses, better PS, experience surgeon

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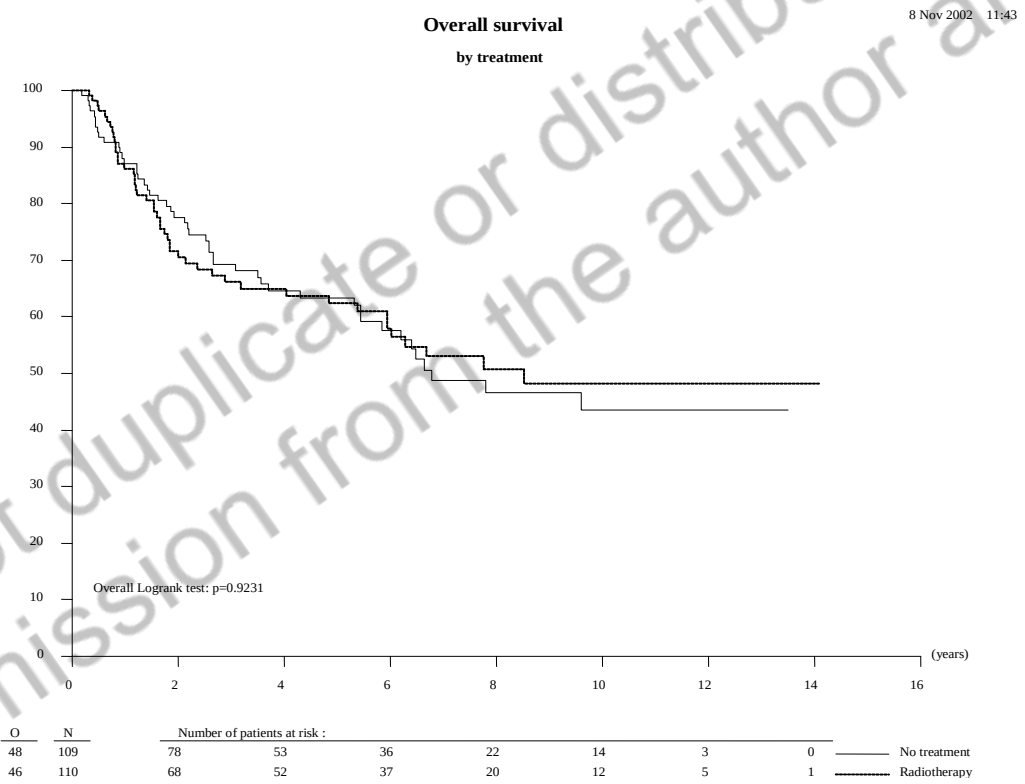
Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I & II: EORTC 55874 (RT vs observation)

Reed et al. Eur J Cancer 2008;44:808-18



No survival benefit in retrospective series

(Hornback, 1986;Chi, 1997; Knocke, 1998; Gerszten, 1998, Gonzales Bosquet, 2010)

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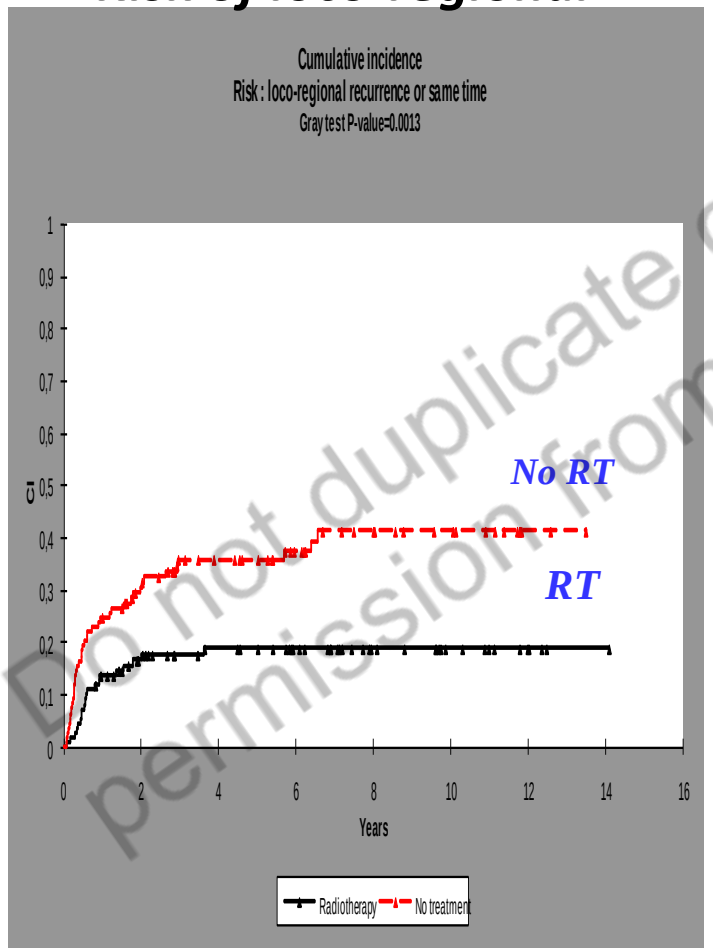
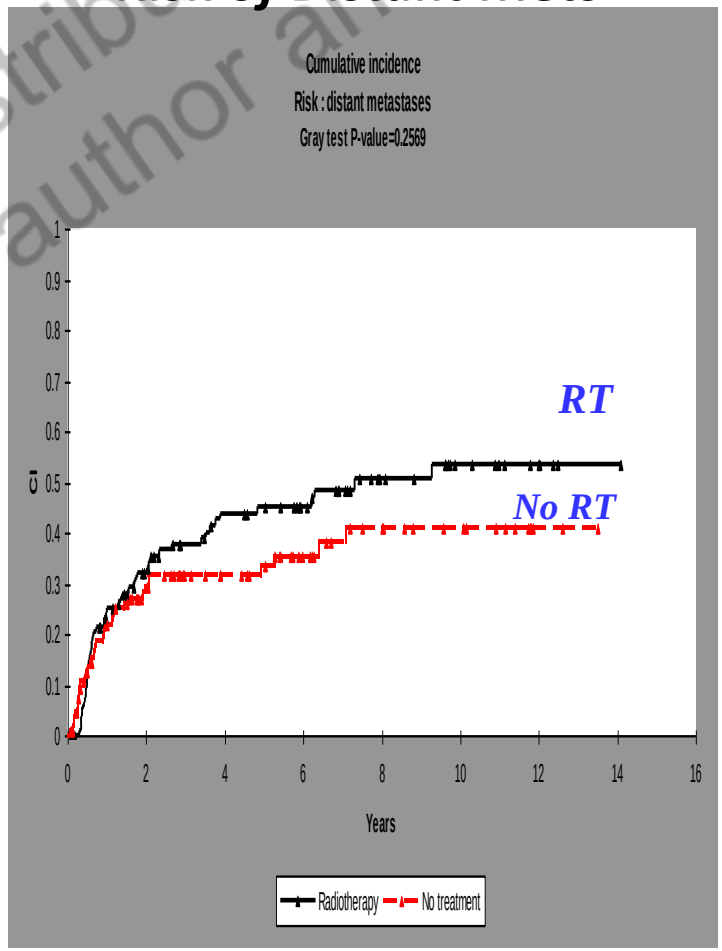
Phase III randomised study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I & II: EORTC 55874 (RT vs observation)

Reed et al. Eur J Cancer 2008;44:808-18

Cumulative Incidence Risk of loco-regional



Cumulative Incidence Risk of Distant Mets



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Adjuvant chemotherapy, randomised trial

Omura et al., J Clin Oncol 1985;3:1240-5

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- 156 uterine sarcomas (93 CS + 48 LMS)
- Stage I-II disease
- Pelvic irradiation was optional
- Doxorubicin 60mg/m², 3 weekly, x8
- No survical benefit
- Different pattern of recurrence relates to different tumor biology: pulmonary (LMS) vs extrapulmonary (CS)

The role of adjuvant chemotherapy in surgical stages I-II serous and clear cell carcinomas and carcinosarcoma of the endometrium: a collaborative study.

Vandenput I et al. Int J Gynecol Cancer. 2011 Feb;21(2):332-6.

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TABLE 2. Recurrence according to histological subtype and survival data for group A (adjuvant chemotherapy) and group B (no adjuvant chemotherapy)

	Group A		Group B	
No. patients	34		35	
Recurrence, n (%)	11 (32)		12 (34)	
RFS, median (range), mo	22 (13–51)		10 (1–59)	
DOD at time of analysis, n (%)	5 (15)		9 (26)	
DSS, median (range), mo	29 (20–59)		17 (4–64)	
	Type II	**CS**	**Type II**	**CS**
No. patients	23	11	28	7
Time of follow-up, median (range), mo	48 (20–159)	44 (13–64)	32 (4–179)	17 (1–64)
Recurrence According to Type, n (%)	8 (35)	3 (27)	8 (29)	4 (57)
Pelvic	1 (4)	0	1 (4)	1 (14)
Systemic	7 (30)	3 (27)	7 (25)	3 (43)
RFS, median (range), mo	23 (17–51)	14 (13–47)	13 (3–44)	7 (1–59)
DOD at time of analysis, n (%)	3 (13)	2 (18)	5 (18)	4 (57)
DSS, median (range), mo	29 (25–49)	30	29 (4–56)	16 (8–64)

Type II refers to serous and clear cell endometrial cancer.

CS, carcinosarcoma; median time of follow-up, from diagnosis till death or last follow-up; DOD, died of disease; DSS, disease-specific survival; RFS, recurrence-free survival.

Combination chemotherapy in carcinosarcoma

	N	Cytotoxic	Dosage	CR	PR	RR
Currie, 1996	32	Hydroxyurea Dacarbazine Etoposide	2g 100mg/m² 2x100mg/m²	2/32	3/32	16%
Van Rijswijk, 2003	41	Cisplatin Ifosfamide Doxorubicin	50 mg/m² 5 g/m² 45 mg/m²	11	7	56%
Ramondetta, 2003	16	Cisplatin Ifosfamide	75mg/m² 1,2mg/m² Too toxic	0	2/6	33%
Toyoshima, 2004	6	Paclitaxel Carboplatin	175mg/m² AUC 6	4/5	0	80%
Pectasides, 2008	29	Paclitaxel Carboplatin Peg Lip Doxo	175mg/m² AUC 5 25mg/m²	10	8	62%
Powell, 2010	46	Paclitaxel Carboplatin	175mg/m² AUC 6	6 (13%)	19 (41%)	54%

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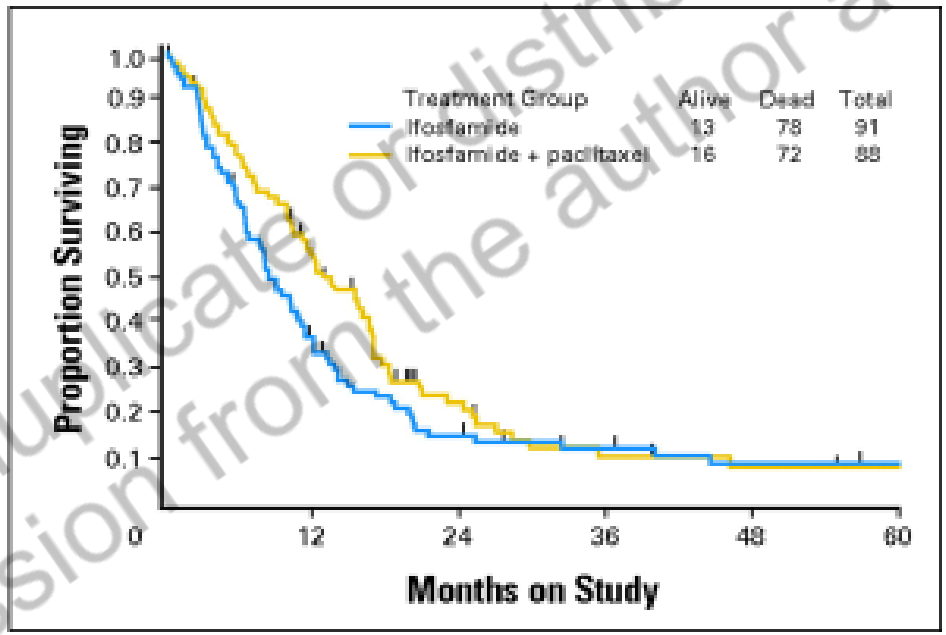
Phase III trial of ifosfamide with or without paclitaxel in advanced uterine carcinosarcoma: a Gynecologic Oncology Group Study

Homesley et al., J Clin Oncol 2007;25:526-31



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A phase III trial of ifosfamide with or without cisplatin in carcinosarcoma of the uterus

Sutton et al, Gynecol Oncol 2000

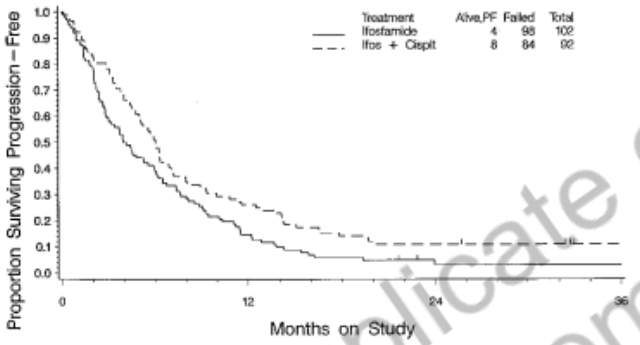

FIG. 1. Progression-free survival by treatment.

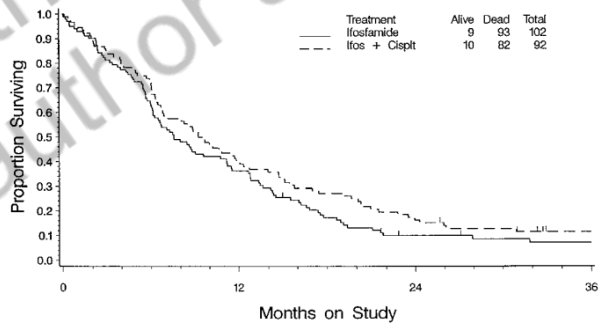

FIG. 2. Survival by treatment.

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the combination offers a slight prolongation of PFS but no significant survival benefit

- Ifosfamide plus paclitaxel appears to be more effective and better tolerated compared with ifosfamide and cisplatin

- Decisions about optimal therapy have been driven by unacceptable rates of chemotherapy toxicity

- Ifosfamide related toxicity

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Carboplatin plus paclitaxel for advanced or recurrent uterine malignant mixed mullerian tumors

Hoskins et al., Gynecol Oncol 2008

- *Response rates were 60% and 55% with median PFS of 16 and 12 months.*
- *Toxicity: Dose reduction occurred in 5%, treatment delay in 10%.*

Carboplatin–paclitaxel is effective against uterine MMMT, with similar efficacy to ifosfamide combinations. It is more convenient, less costly and easy to deliver.

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Trastuzumab in endometrial carcinosarcoma?

- **Amant et al., Gynecol Oncol 2004;95:583-7**
  - **7/22 CS ERBB-2 ++ or +++; 3/7 FISH+, 3/22 (14%)**
  - **Sarcoma component negative**

- **Raspollini et al., Int J Gynecol Ca 2006;16:416-22**
  - **9/22 (32%) CS ERBB-2 +; all four ++/+++ FISH+**

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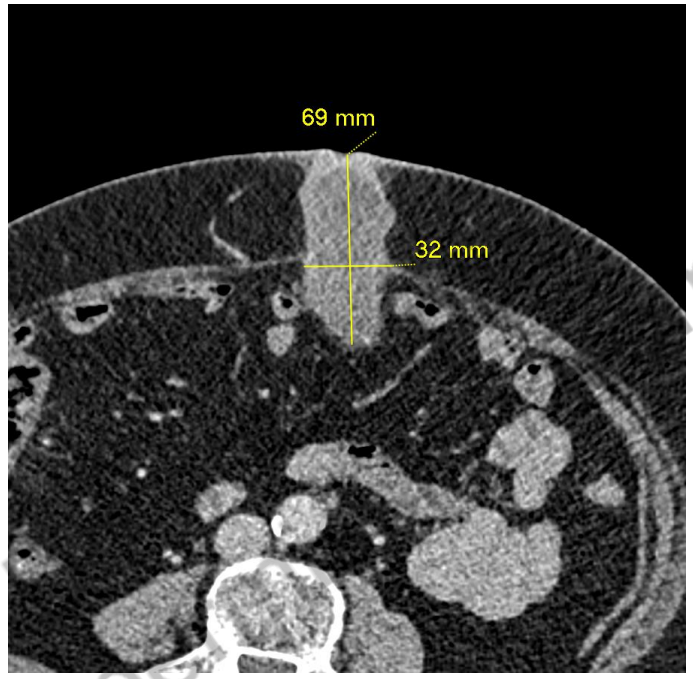
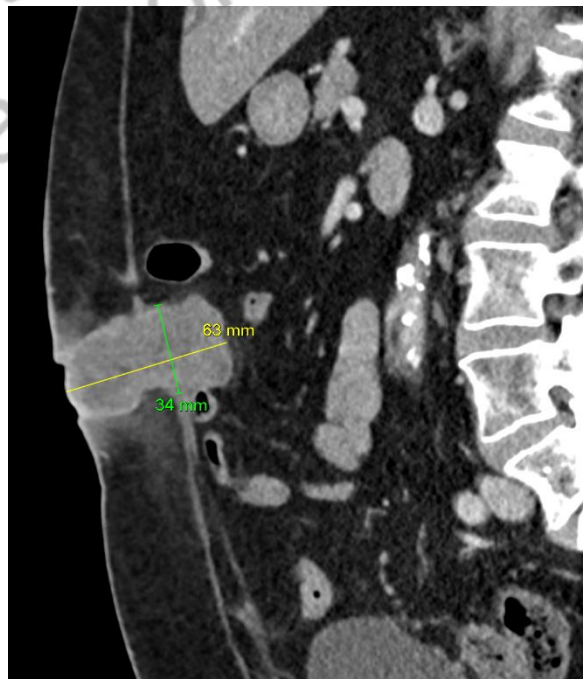
Atypical biologic behaviour of uterine CS

Netherlands Cancer Institute

Juni 2016: robot staging, stage Ia, no adjuvant treatment
September 2021: unifocal umbilical port site recurrence





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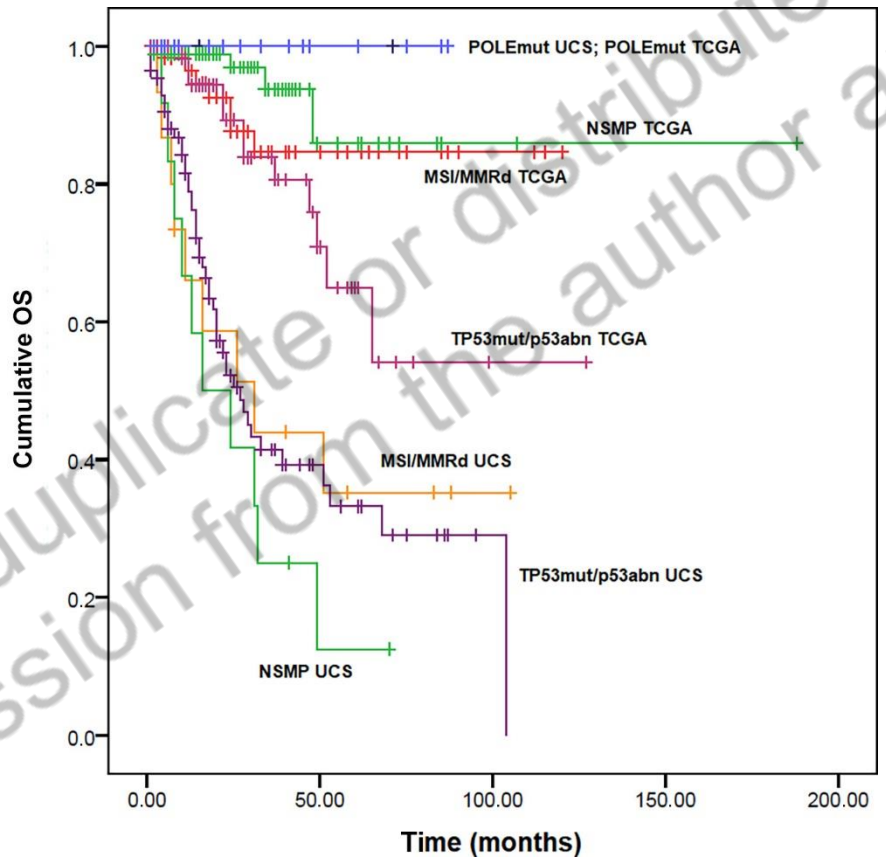
Prognostic value of the TCGA molecular classification in uterine carcinosarcoma

Travaglino et al., IJOG 2021



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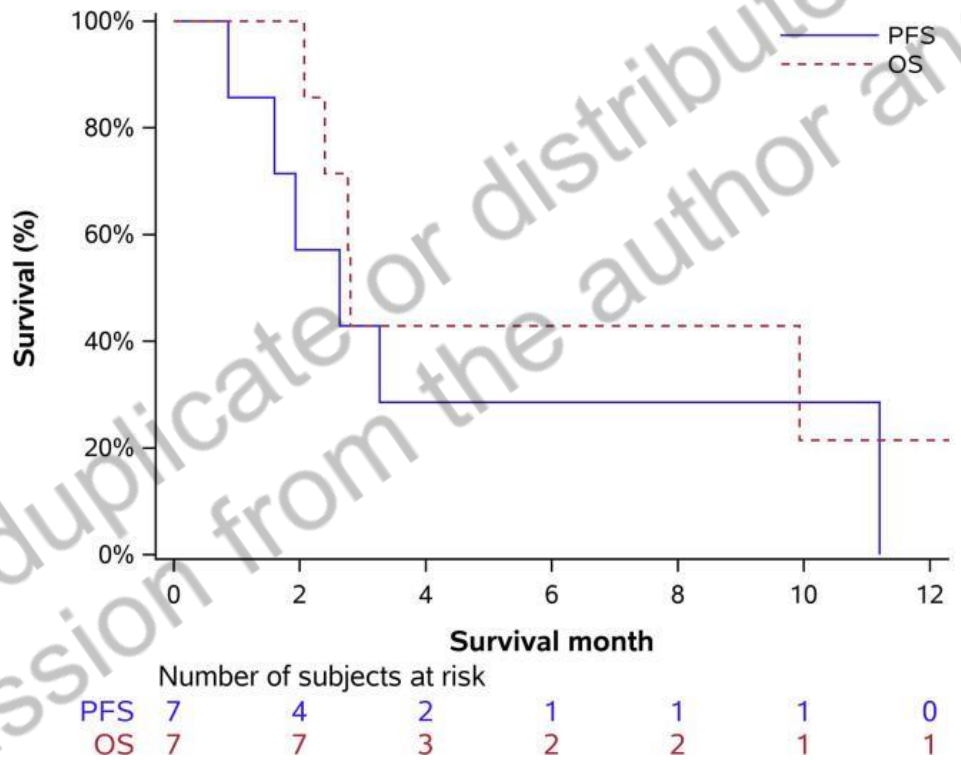
Lenvatinib plus pembrolizumab in patients with advanced or recurrent uterine carcinosarcoma

Hunt J et al., Gynecol Oncol Rep 2021



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no complete or partial responses, and a 28.6% rate of stable disease

Uterine carcinosarcoma: conclusion

- **Complete surgical staging followed by systemic chemotherapy, both in early and advanced stage disease**
- **Carboplatin-paclitaxel is most commonly used**

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Agenda

- Tumour biology carcinosarcoma
- Uterine carcinosarcoma
- Ovarian carcinosarcoma

  - 1-3% of ovarian cancers
  - 10% early stage
  - OS: 7-27 mts

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Comprehensive surgical staging for early stage ovarian cancer

- Completed family:
  - Vertical midline incision
  - Cytology
  - Complete abdominal inspection and palpation
  - Resection of ovaries, fallopian tubes and uterus
  - Omentectomy
  - Random peritoneal biopsies
  - Retroperitoneal lymph node resection
- Children and young women aiming to preserve fertility, USO and staging procedure, not recommended for carcinosarcoma

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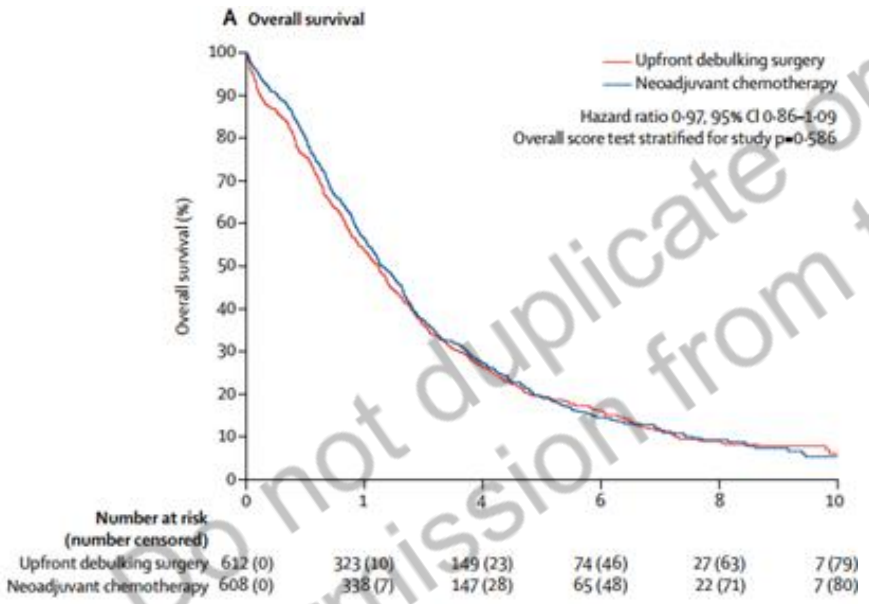
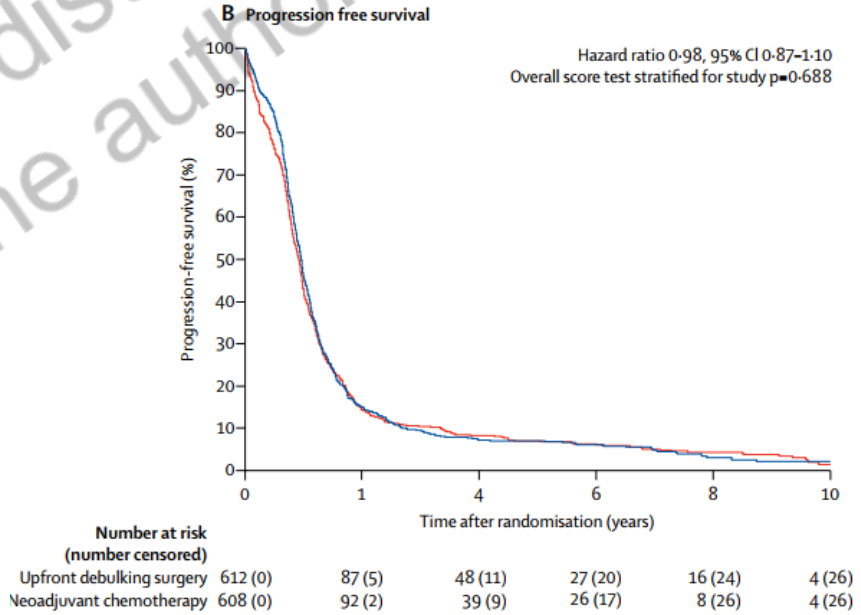
Neoadjuvant chemotherapy versus debulking surgery in advanced tubo-ovarian cancers: pooled analysis of individual patient data from the EORTC 55971 and CHORUS trials

Vergote-Kehoe, Lancet Oncol 2018





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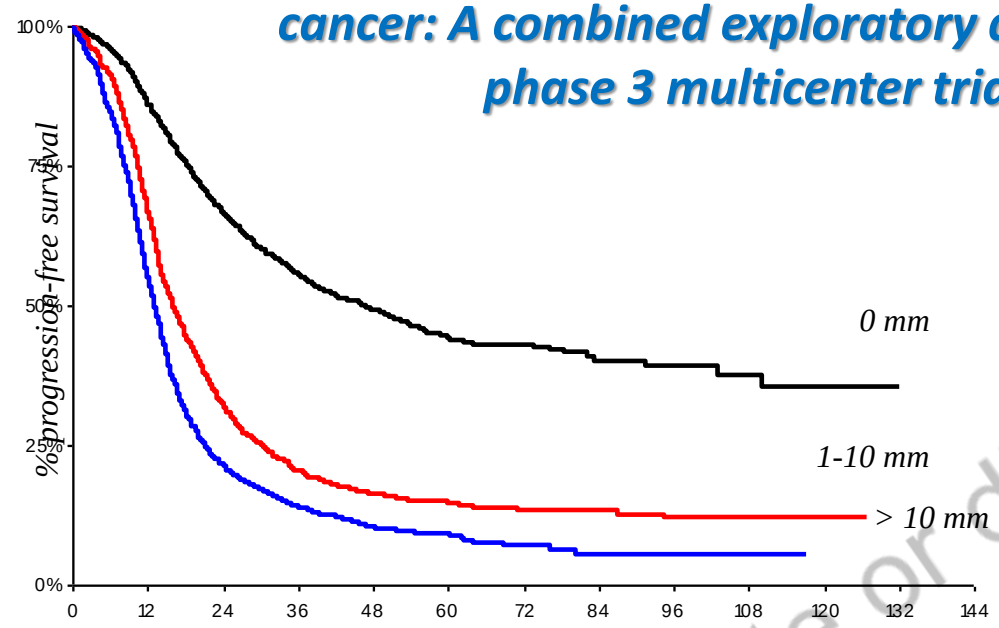
Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials (n=3126) (Du Bois et al., Cancer, 2009)

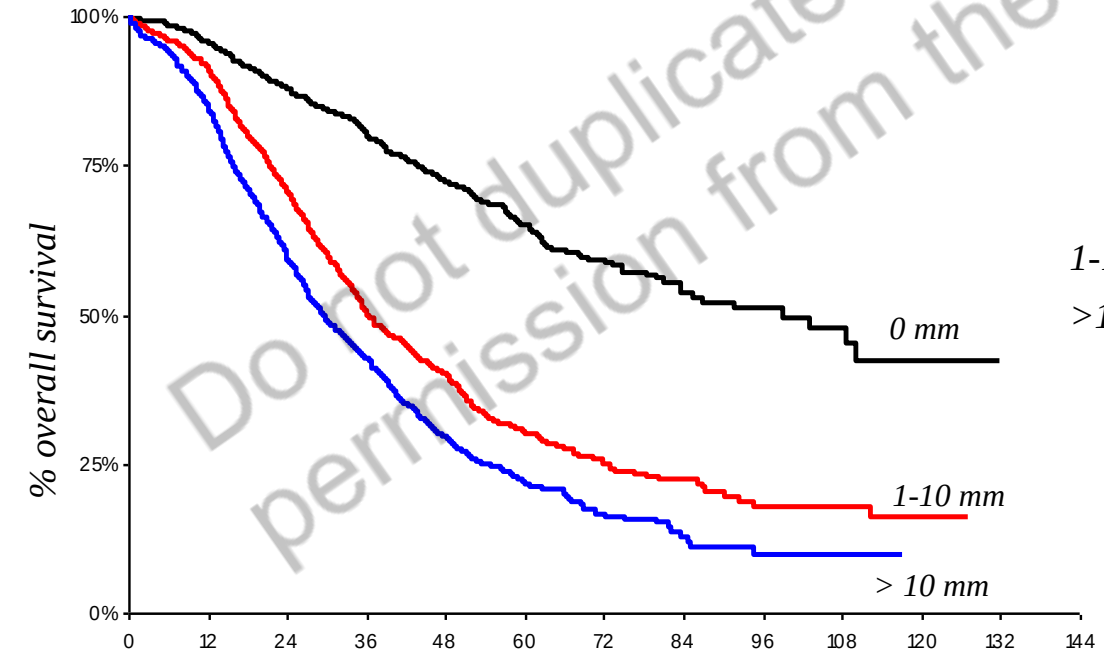


HR (95%CI)

1-10 mm vs. 0 mm: 2.52 (2.26;2.81)

>10 mm vs. 1-10 mm:1.36 (1.24;1.50)

log-rank: $p < 0.0001$



HR (95%CI)

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

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

log-rank: $p < 0.0001$

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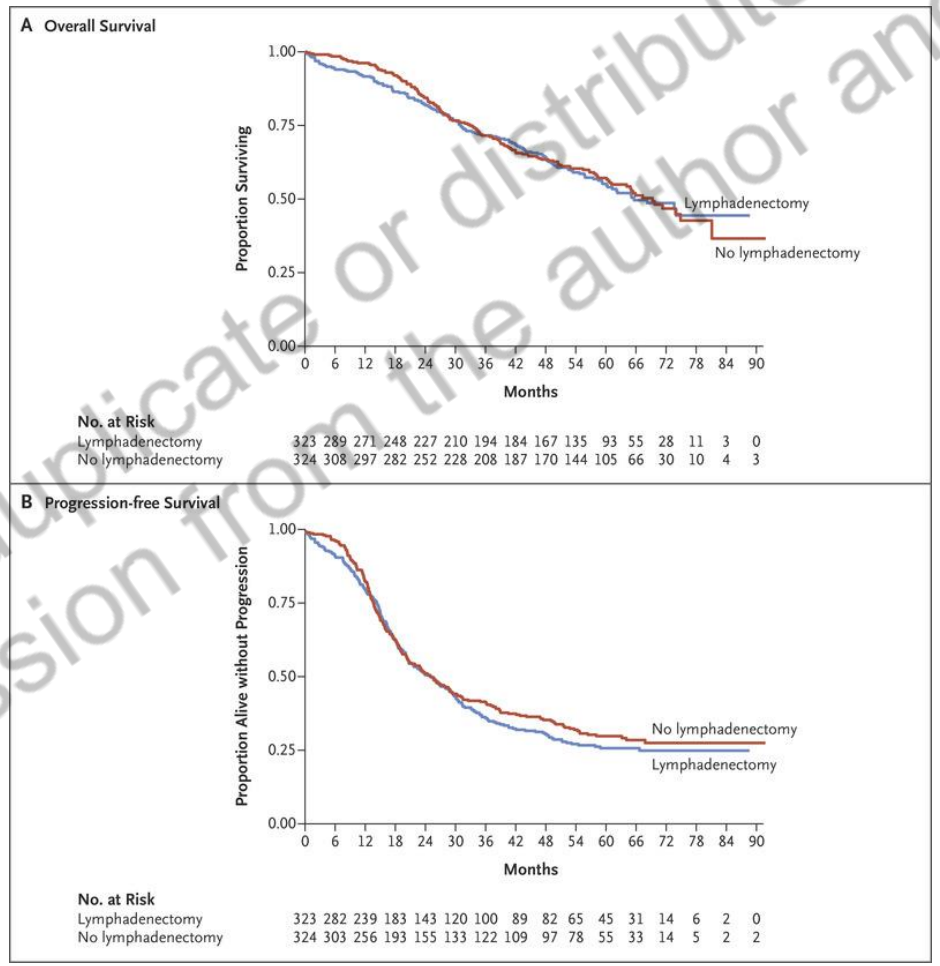
A Randomized Trial of Lymphadenectomy in Patients with Advanced Ovarian Neoplasms (LION-trial)

Harter et al., NEJM 2019



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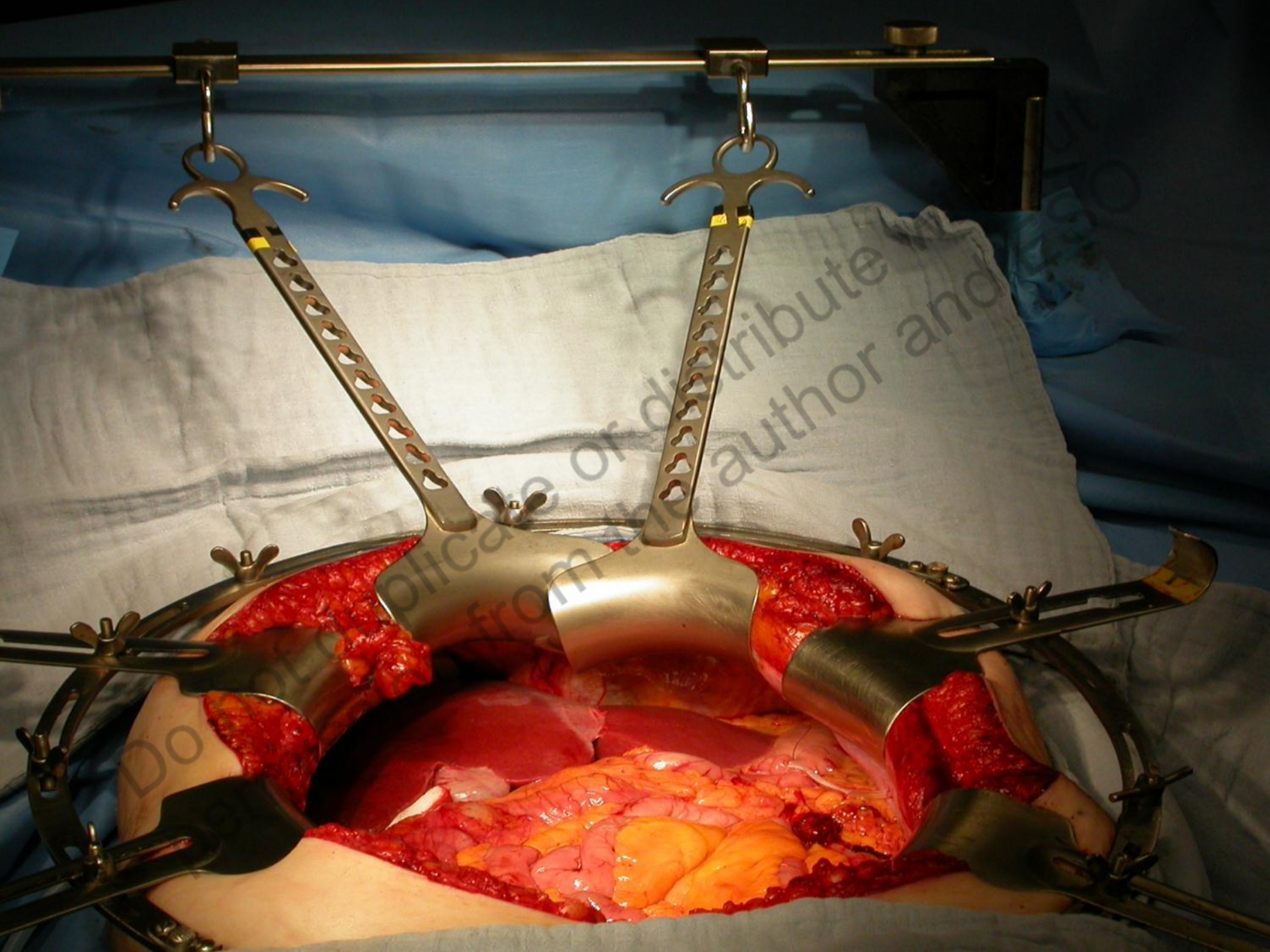
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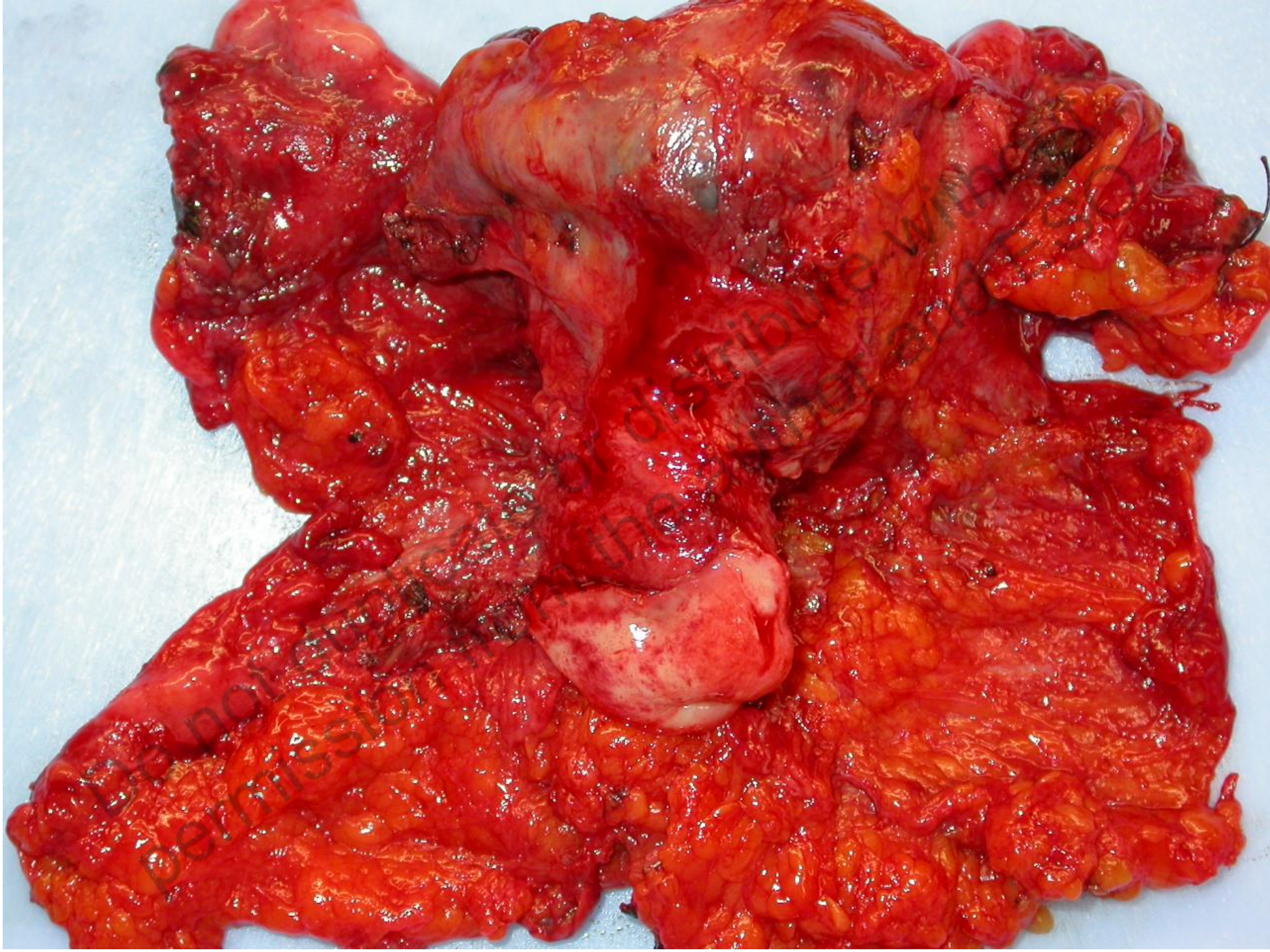
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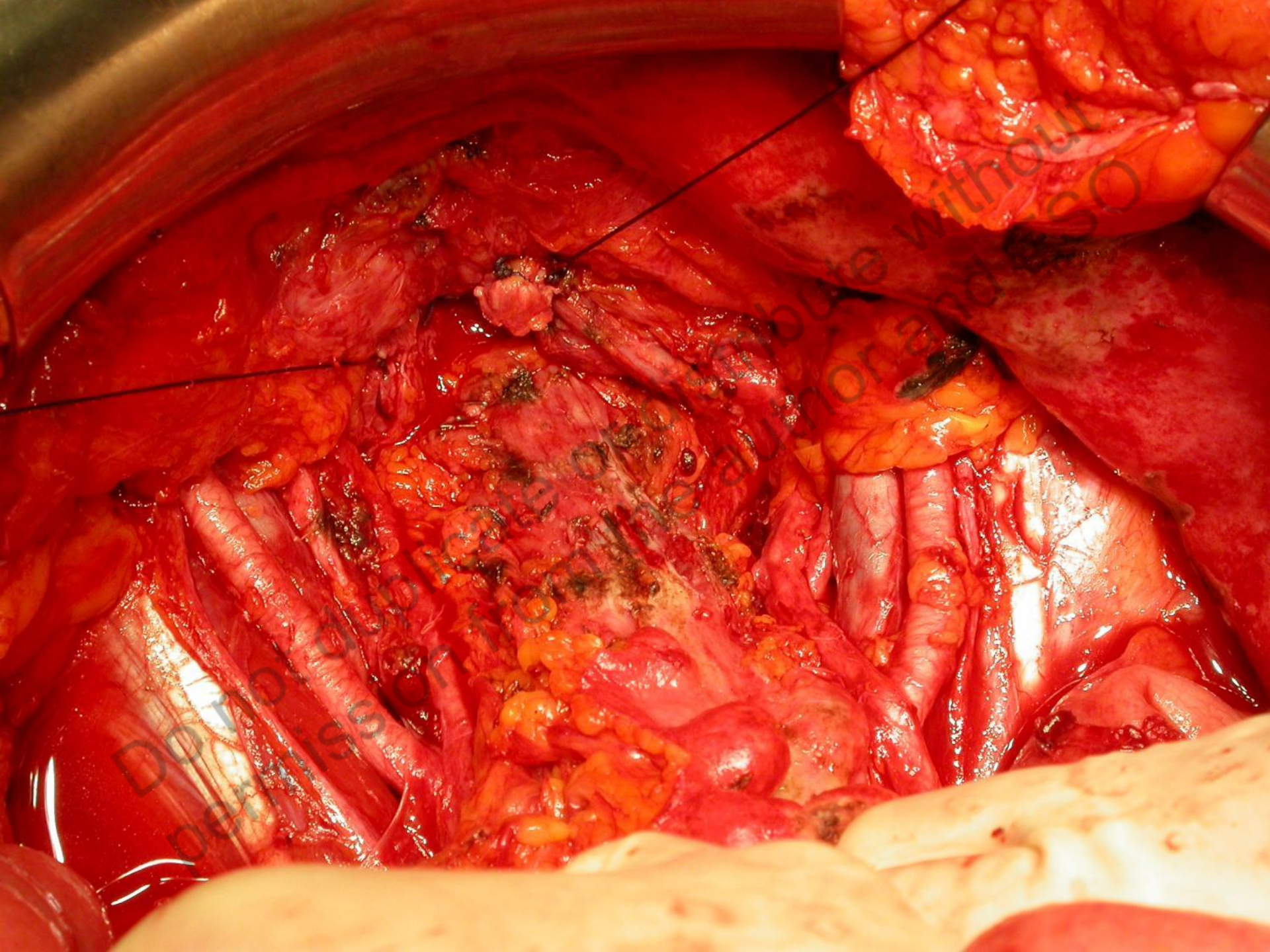
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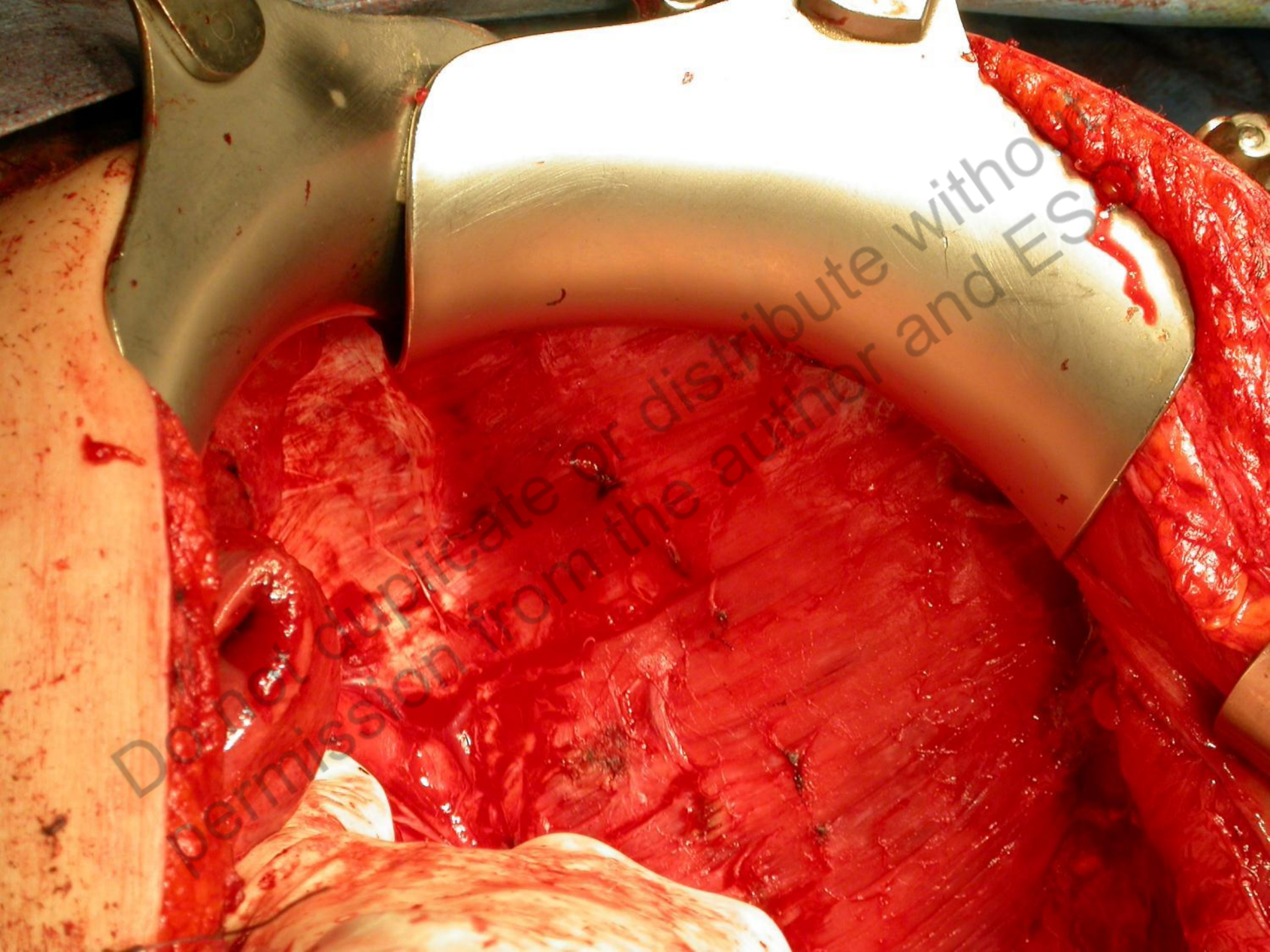
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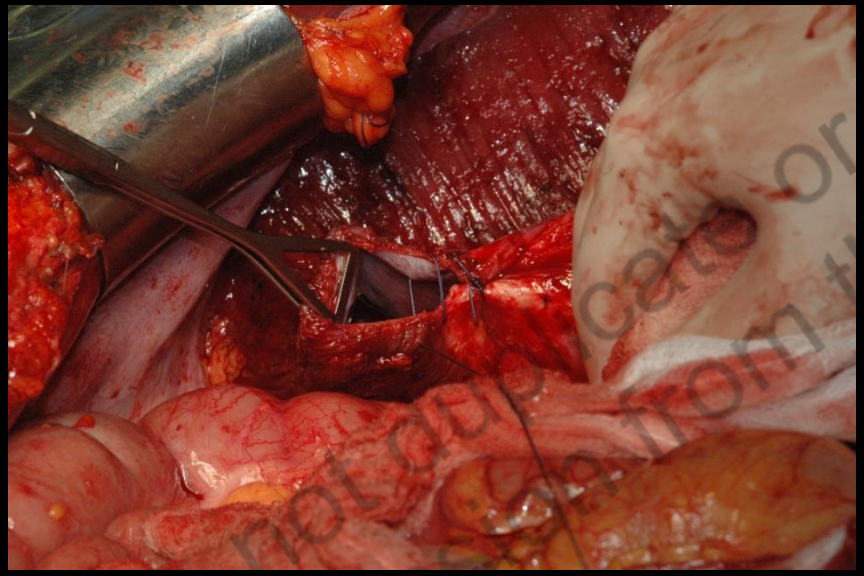
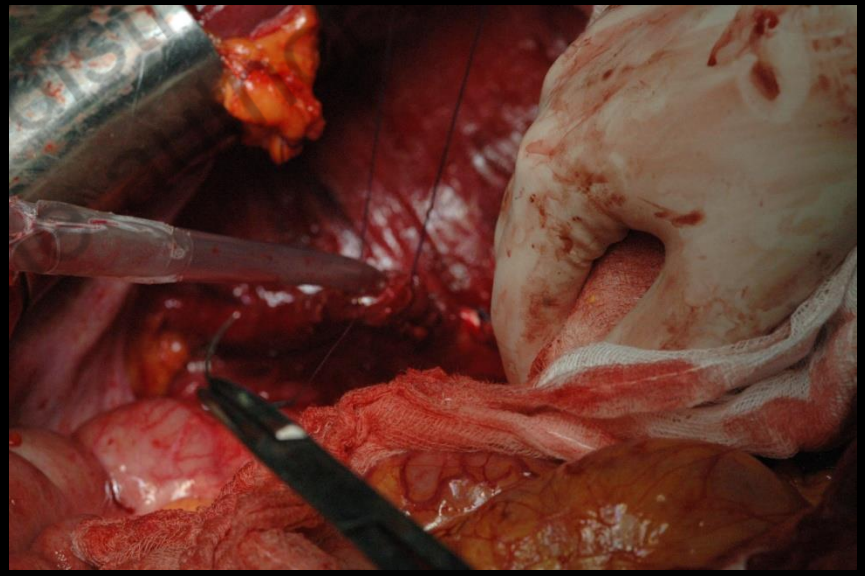
Prevention of thoracal drain after pleurotomy





Ovarian Cancer, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology

Armstrong D, et al. J Nat Compr Ca Netw, *2021*

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Table 2. NCCN Recommended Management Options Following Up-Front Primary Surgery for Stage–IIIV[a]

Cancer Type	Recommended Options (Category 2A Unless Otherwise Noted)	
	Standard IV Platinum-Based Chemotherapy ± Bevacizumab[b]	Other
High-grade serous	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Grade 2/3 endometrioid	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Carcinosarcoma	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only) Carboplatin/ifosfamide Cisplatin/ifosfamide Paclitaxel/ifosfamide (category 2B)
Clear cell carcinoma	Yes	IP/IV paclitaxel/cisplatin (optimally debulked stage III only)
Mucinous carcinoma	Yes	5-FU/leucovorin/oxaliplatin ± bevacizumab (category 2B for bevacizumab) Capecitabine/oxaliplatin ± bevacizumab (category 2B for bevacizumab)
Low-grade serous	Yes	Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)
Grade 1 endometrioid	Yes	Hormone therapy (aromatase inhibitors [anastrozole, letrozole, exemestane], leuprolide acetate, tamoxifen) (category 2B)

Phase II Study Evaluating PegLiposomal Doxorubicin and Carboplatin Combination Chemotherapy in Gynecologic Sarcomas and Mixed Epithelial-Mesenchymal Tumors A Phase II Protocol of the Arbeitsgemeinschaft Gynaekologische Onkologie Study Group (AGO-GYN 7)

Harter P, IJGC 2016

TABLE 3. Response rates in patients with measurable disease

Tumor Evaluation by RECIST	Leiomyosarcoma n (%)	Endometrial Stromal Sarcoma n (%)	Carcinosarcoma n (%)	Total n (%)
Complete response	0 (0.0)	0 (0.0)	3 (23.1)	3 (11.1)
Partial response	3 (30.0)	1 (25.0)	2 (15.4)	6 (22.2)
Stable disease	4 (40.0)	2 (50.0)	4 (30.8)	10 (37.0)
Progressive disease	3 (30.0)	1 (25.0)	4 (30.8)	8 (29.6)
Total	10	4	13	27

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. 2020;98(10):699-705.

doi: 10.1159/000507333. Epub 2020 Jun 11.

Treatment Outcome of Second-Line Chemotherapy for Gynecologic Carcinosarcoma

- Ebata t et al
- Paper niet beschikbaar

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Ovarian carcinosarcoma: conclusion

- **Complete staging or cytoreduction till to residual tumor**
- **Carboplatin-paclitaxel in adjuvant setting**

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Take home message

- **Monoclonal theory CS: metaplasia in epithelial cancer**
- **Surgical staging/debulking similar to high grade endometrial or ovarian cancer**
- **Paclitaxel-Carboplatin best efficacy/toxicity**

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