Indication for CRS & HIPEC: Ovarian Cancer

Masterclass – Management of Peritoneal Surface Malignancy
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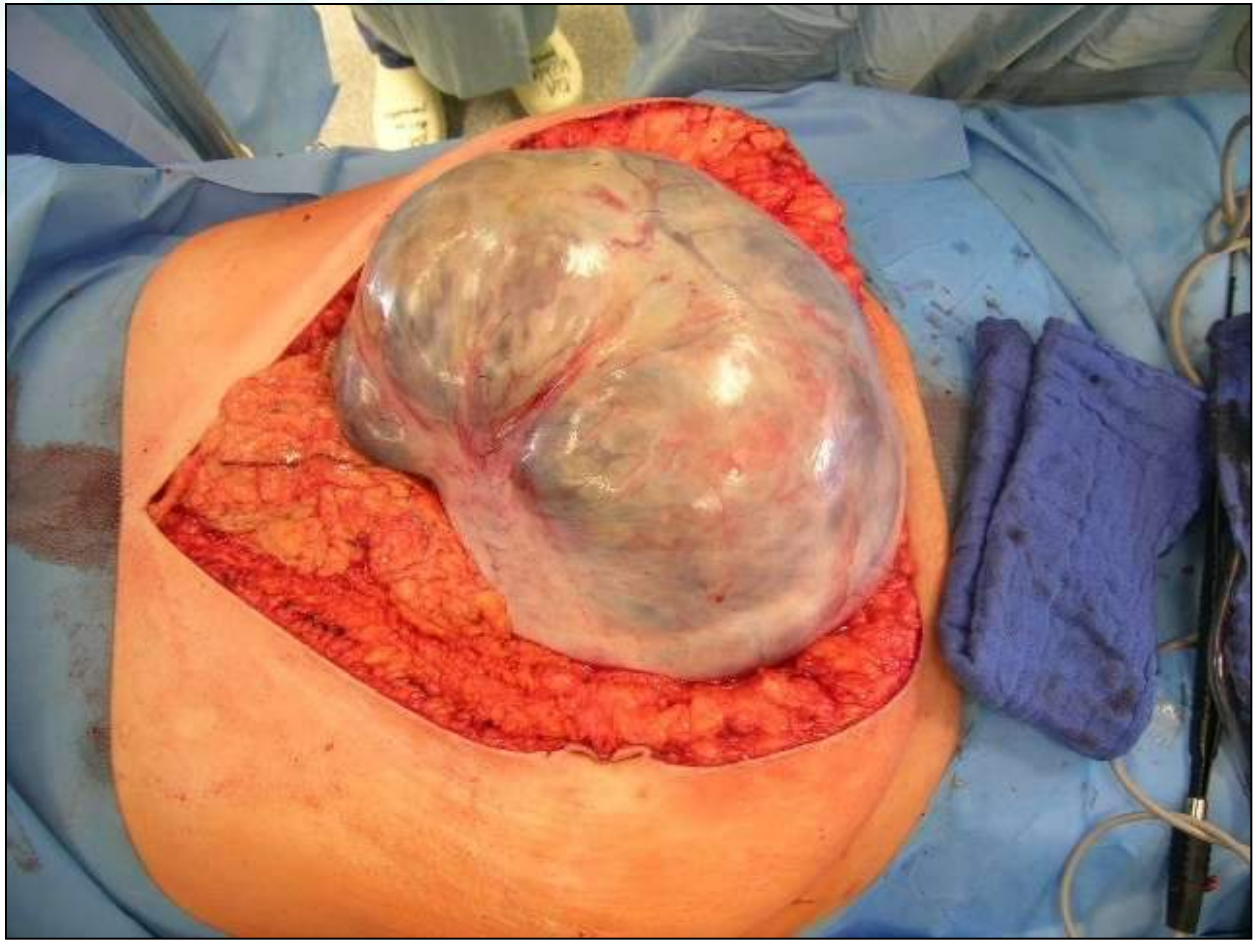
SOCIETY OF SURGICAL ONCOLOGY

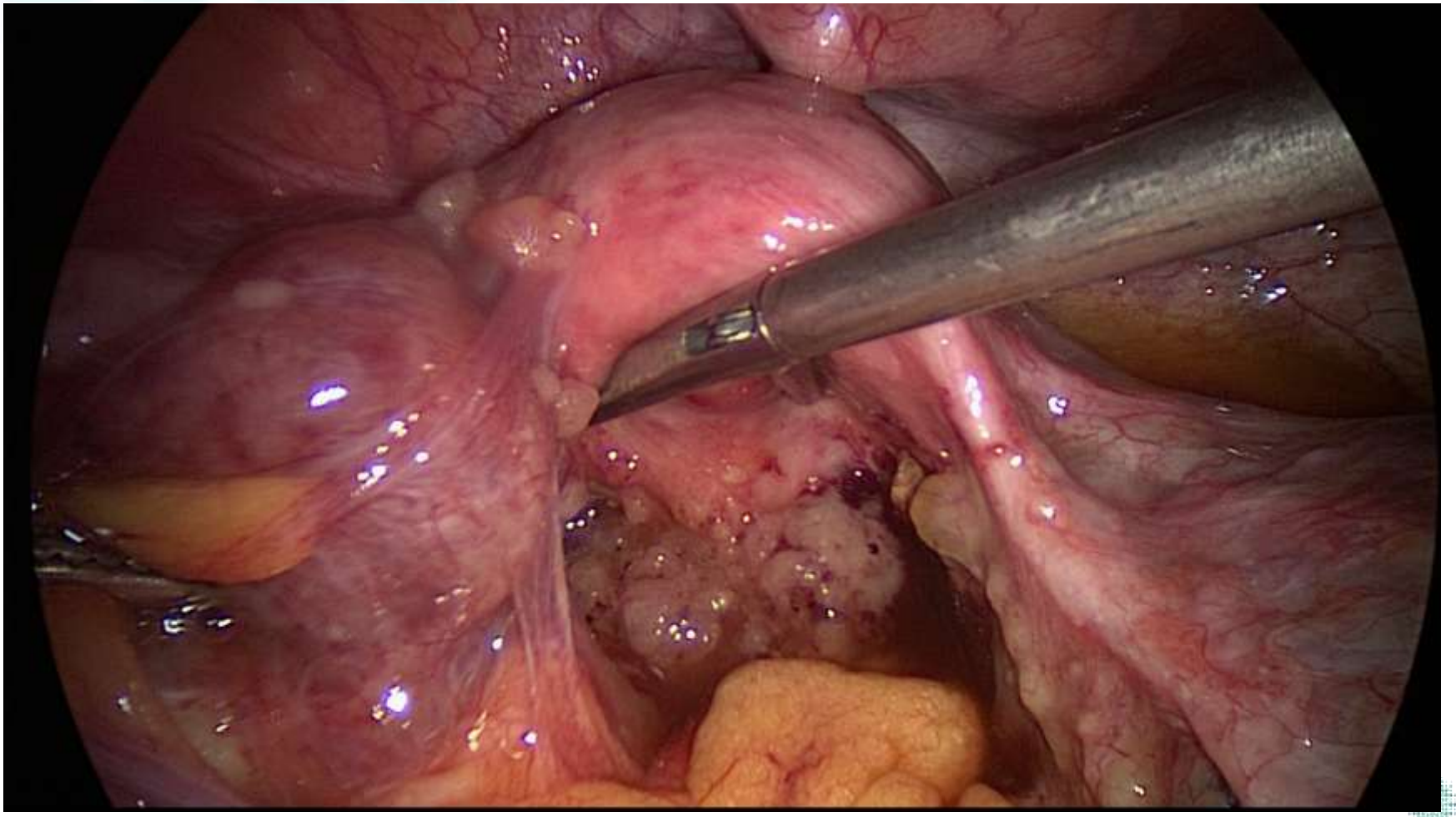
No conflicts of interest

Preliminary remarks

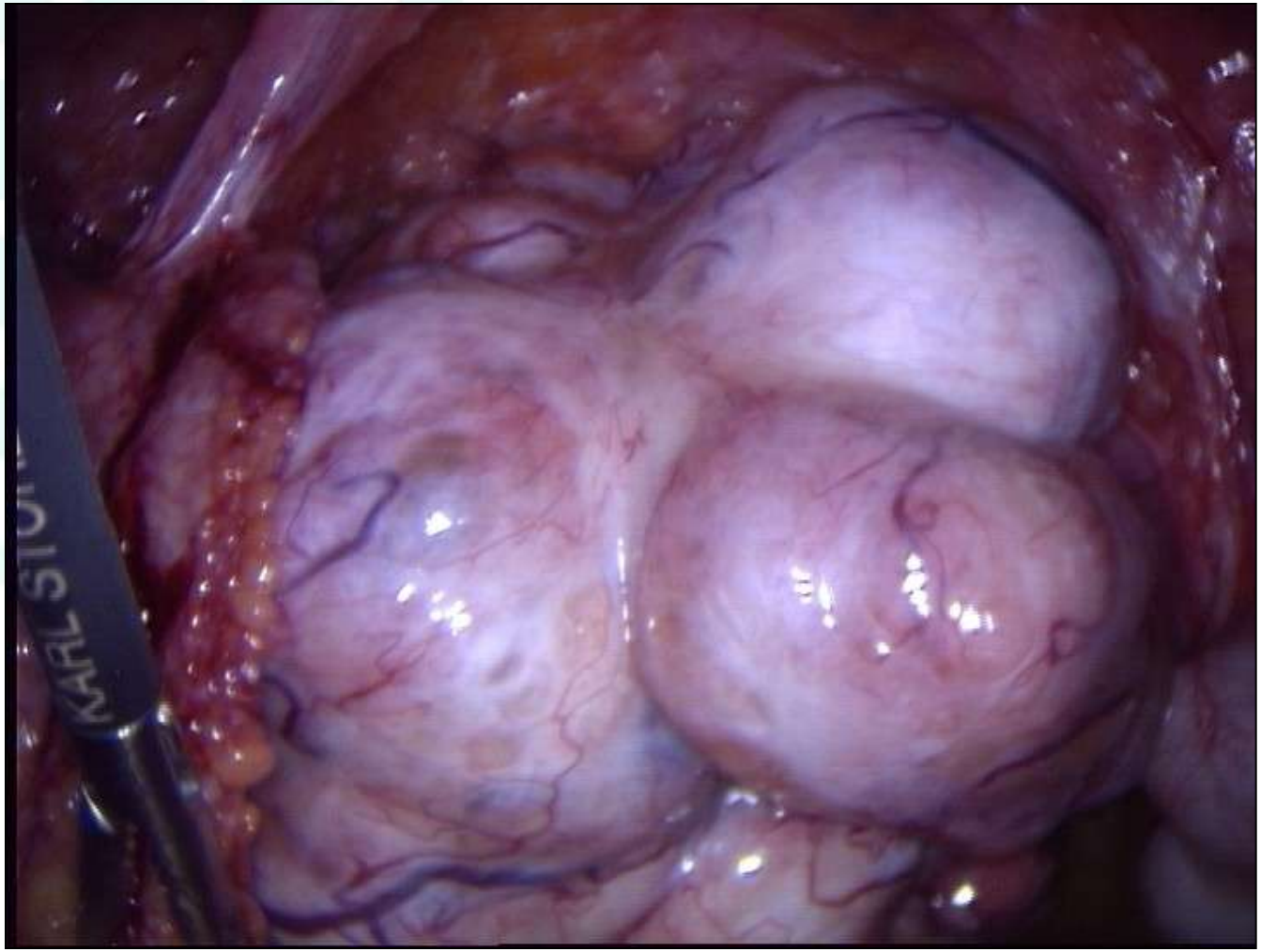
Huge ovarian tumor – dignity?



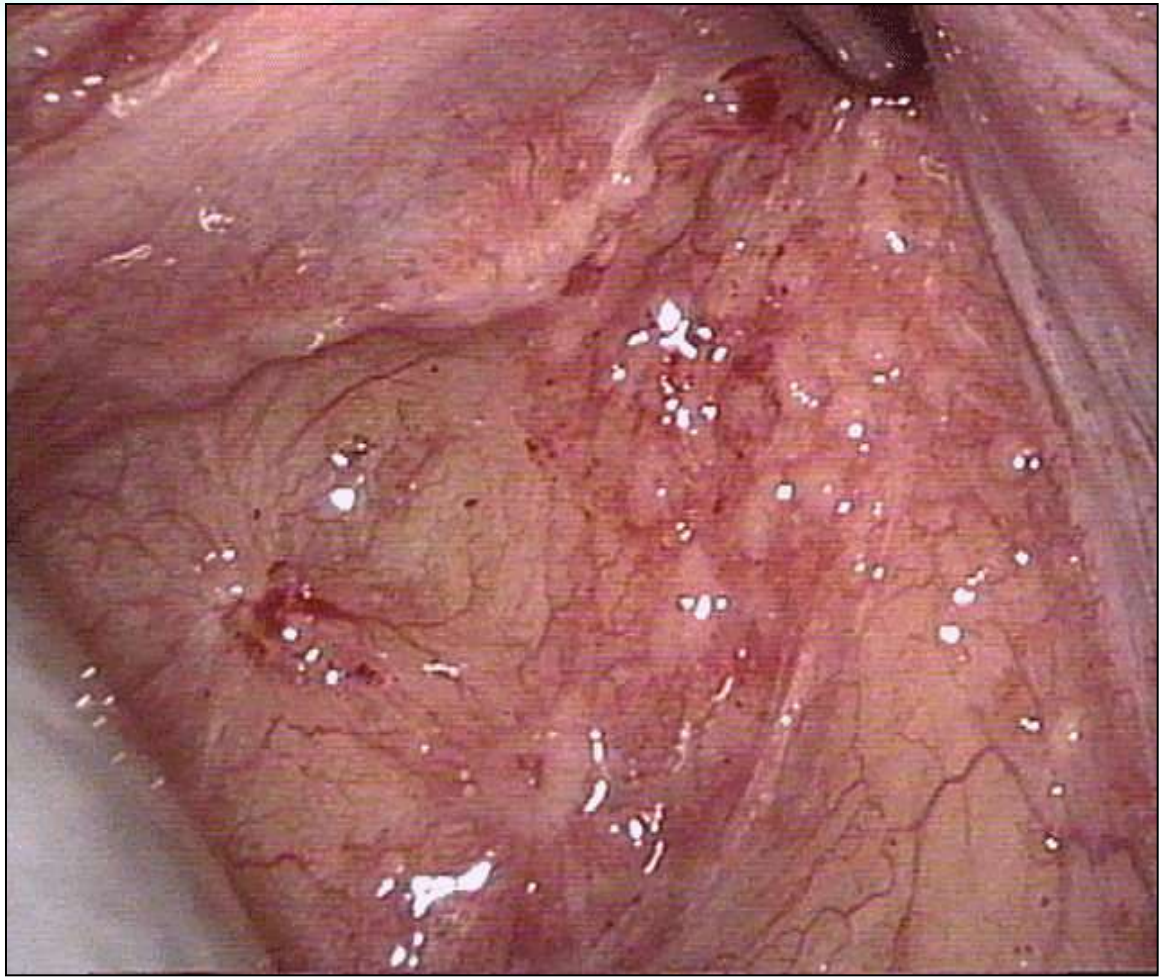
Advanced ovarian cancer – pelvic situs



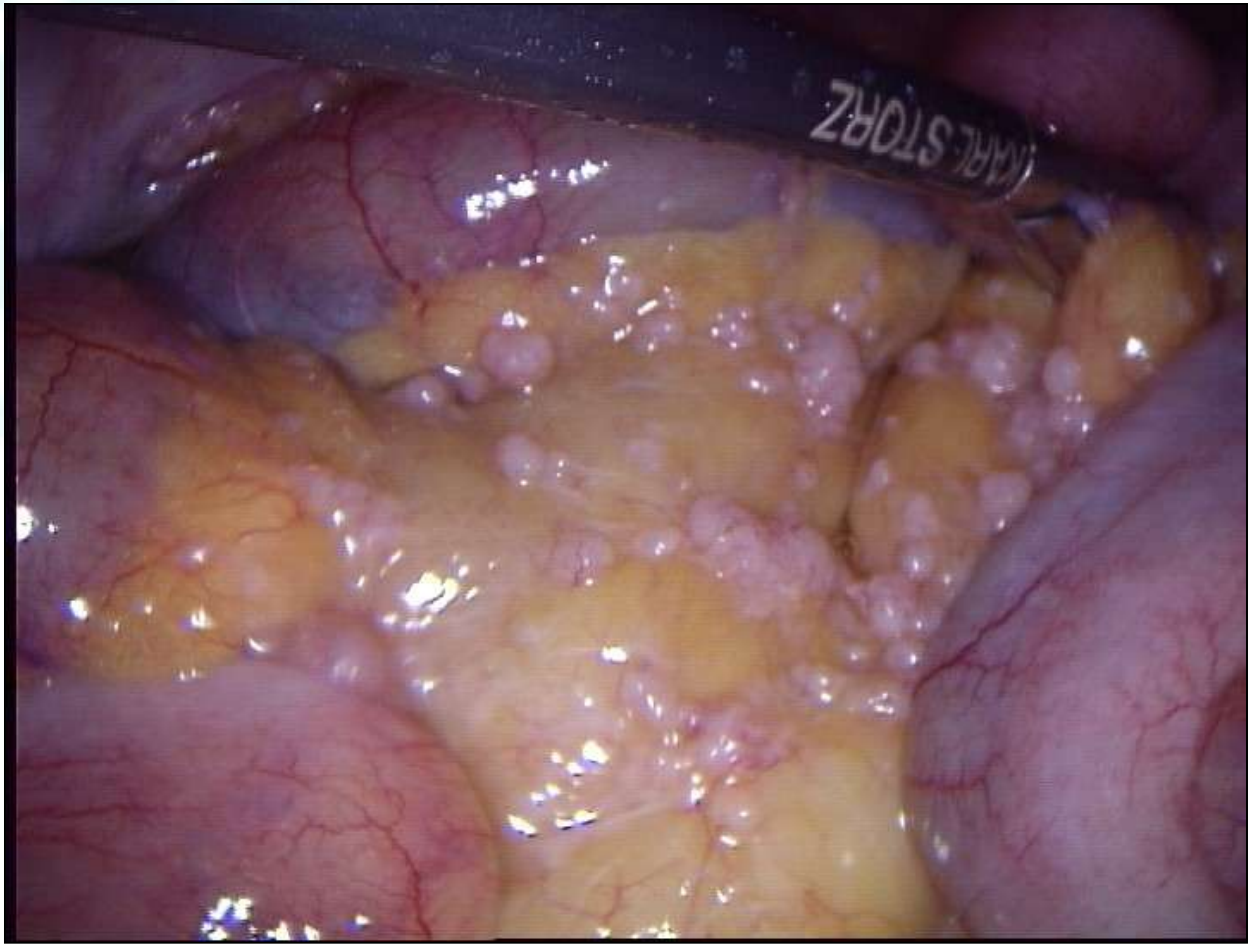
Advanced ovarian cancer – pelvic situs



Ovarian cancer – spread to cul-de-sac



Ovarian cancer – spread to small bowel mesenterium



Tumor spread in patients with OC (FIGO III/IV)

- Peritoneum 76%
- Lymph nodes 68% (but LIONS TRIAL ASCO 2017)
- Colon 52%
- Diaphragm 44%
- Mesenterium 36%
- Ascites >500cc 30%
- Small bowel 27%
- Bursa omentalis 12%

Sehouli et al., Journal of Surgical Oncology 2009

Ovarian Cancer in Germany

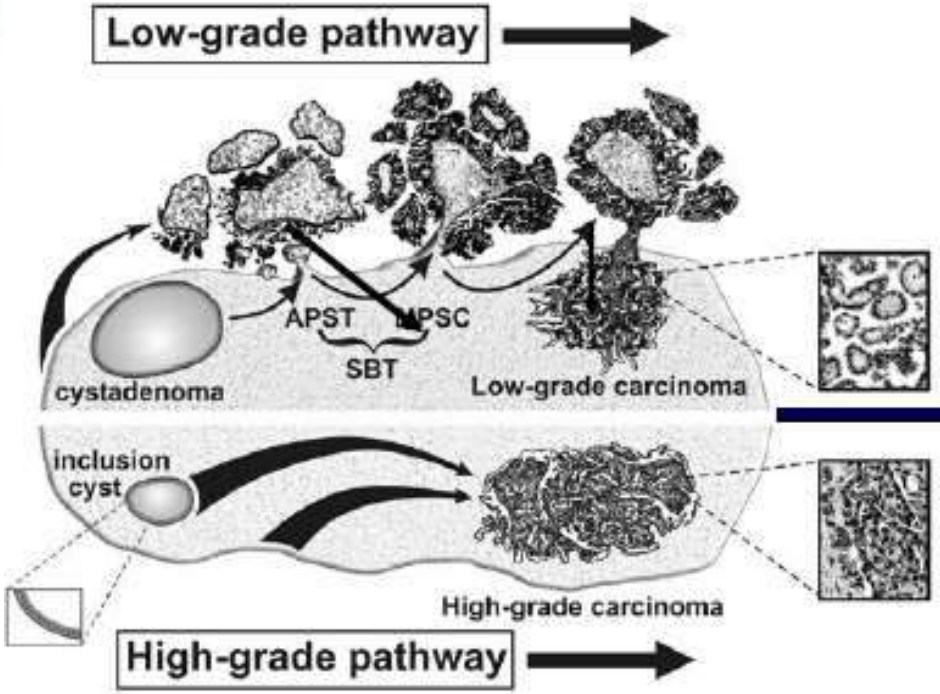
	2009	2010	2011	2012	prognosis 2016
New diseases	7910	7790	7750	7380	7200
Death by Cancer	5623 (71%)	5599 (72%)	5837 (75%)	5646 (76%)	

5-year survival: **32%**

Krebs in Deutschland 2011/2012. Robert-Koch-Institut (Hrsg.) 2015, Berlin

New theories of pathogenesis

Serous ovarian cancer – progression model

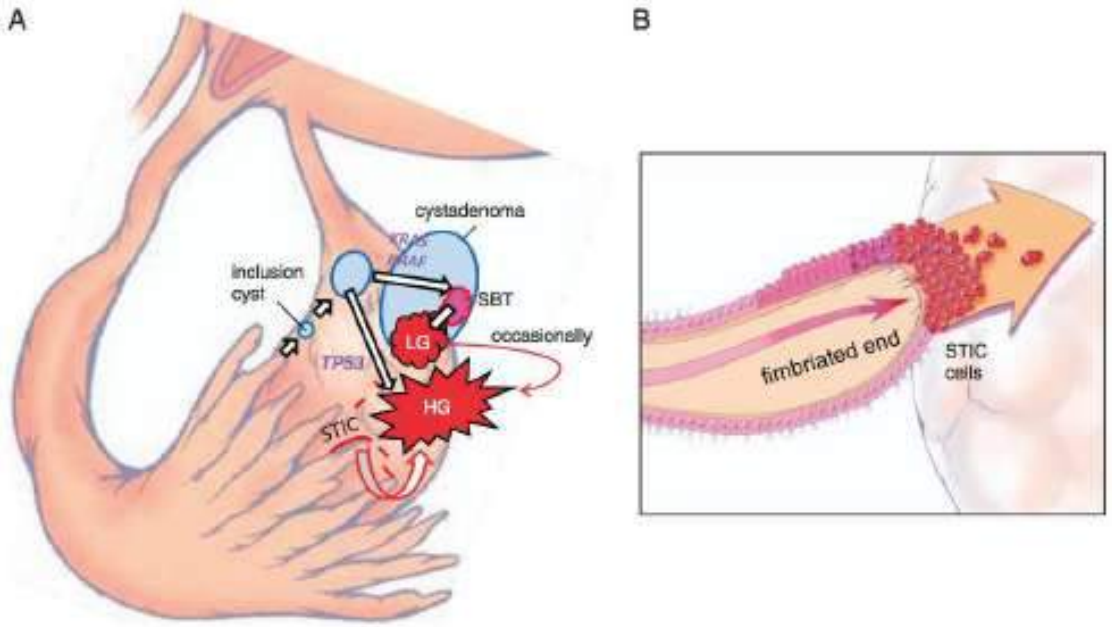


Type I tumors
Genetically stable
KRAS/BRAF, β-Catenin,
PTEN, ErbB2 mutations
LOH Ch1p+Ch19q
Unique gene expression

Type II tumors
De novo
Aggressive
Genetically unstable
TP53 mutations
Unique gene expression

Shih and Kurman, 2005:
Ovarian Tumorigenesis – A Proposed Model Based on Morphological and Molecular Genetic Analysis
American Journal of Pathology 164 (5), 1511-18

Fallopian tube (STIC) – origin of high grade serous ovarian cancer?



Kurman and Shih, 2010:
The Origin and Pathogenesis of Epithelial Ovarian Cancer – A Proposed Unifying Theory
American Journal of Surgical Pathology 34 (3), 433-443

Histologic types of ovarian cancer

- High grade serous — new theory
- Endometroid — new theory
- Clear cell — new theory
- Mucinous
- Low grade serous
- Other or cannot be classified
- Germ cell
- Sex-cord stromal cell tumors

Same Surgery!

BRCA 1 and 2 play important role for prognosis and therapy!

Rationale for surgery

What size of residual tumor does significantely improve prognosis?

Initial FIGO stage	No macroscopic residual tumor		Any residual tumor		HR (95% CI)	No residual tumor	Any residual tumor	HR (95% CI)	
	Pts. (n)	PFS (mos)	Pts (n)	PFS (mos)		Median survival (months)			
FIGO IIB-IIIB	497	91.7	317	19.1	**0.37 (0.31; 0.45)**	108.6	48.3	**0.37 (**	+ 60,3 mon.
FIGO IIIC	486	35.0	1293	14.5	**0.39 (0.35; 0.45)**	81.1	34.2	**0.36 (**	+ 46,9 mon.
FIGO IV	63	19.2	467	12.1	**0.53 (0.39; 0.72)**	54.6	24.6	**0.49 (**	+ 30,0 mon.

HR = Hazard Ratio, reference class for HR is “Any residual tumor”

Initial FIGO stage	residual tumor 1-10 mm		residual tumor > 10 mm		HR (95% CI)	residuals 1-10 mm	residuals > 10 mm	HR (95% CI)	
FIGO IIB-IIIB	205	22.2	112	16.7	**0.73 (0.56; 0.95)**	52.3	41.0	0.75 (	+ 11,3 mon.
FIGO IIIC	613	15.9	680	13.7	**0.78 (0.70; 0.88)**	35.6	30.7	**0.80 (**	+ 4,9 mon.
FIGO IV	156	13.5	311	11.5	0.84 (0.69; 1.03)	26.2	23.9	0.86 (	+ 2,3 mon.

HR = Hazard Ratio, reference class for HR is “residual tumor > 10 mm”

Quality of operation in FIGO IIB-IV OC

In specialised centres residual tumor (RT) 0: 70%, RT 1-10mm 20%, RT >1cm: 10%

no residual tumor 1-10 mm > 1 cm residual tumor

Who should perform ovarian cancer surgery?

Best operativ result can be reached by interdisciplinary cooperation between gynecologic oncologist and GI-surgeon!

cancer: A systematic review 2009 Gynecol Oncol

Mercado C et al. Quality of care in advanced ovarian cancer: The importance of provider specialty. Gynecol Oncol 2010

Bristow RE et al. Impact of surgeon and hospital ovarian cancer surgical case volume on in-hospital mortality and related short-term outcomes. Gynecol Oncol 2009

Kumpulainen S et al.The effect of hospital operative volume, residual tumor and first-line chemotherapy on survival of ovarian cancer – a prospective nation-wide study in Finland. Gynecol Oncol 2009

Bristow RE et al. Analysis of contemporary trends in access to high-volume ovarian cancer surgical care. Ann Surg Oncol 2009

„Price“ of primary surgery

- ✓ Perioperative mortality: 3.7% (2.5-4.8)

  in operations with bowel resection 0-5.9%

  Causes: 25% embolism, 29% surgical complications including sepsis, 13% cardiac reasons (Gerestein et al. Gynecol Oncol 2009;114:523-527)

- ✓ In older patients (>70 years) mortality 6%,

  38% postoperative complications, 10% re-laparotomies (Fotopoulou et al., Int J Gynecol Cancer 2010;20:34-40)

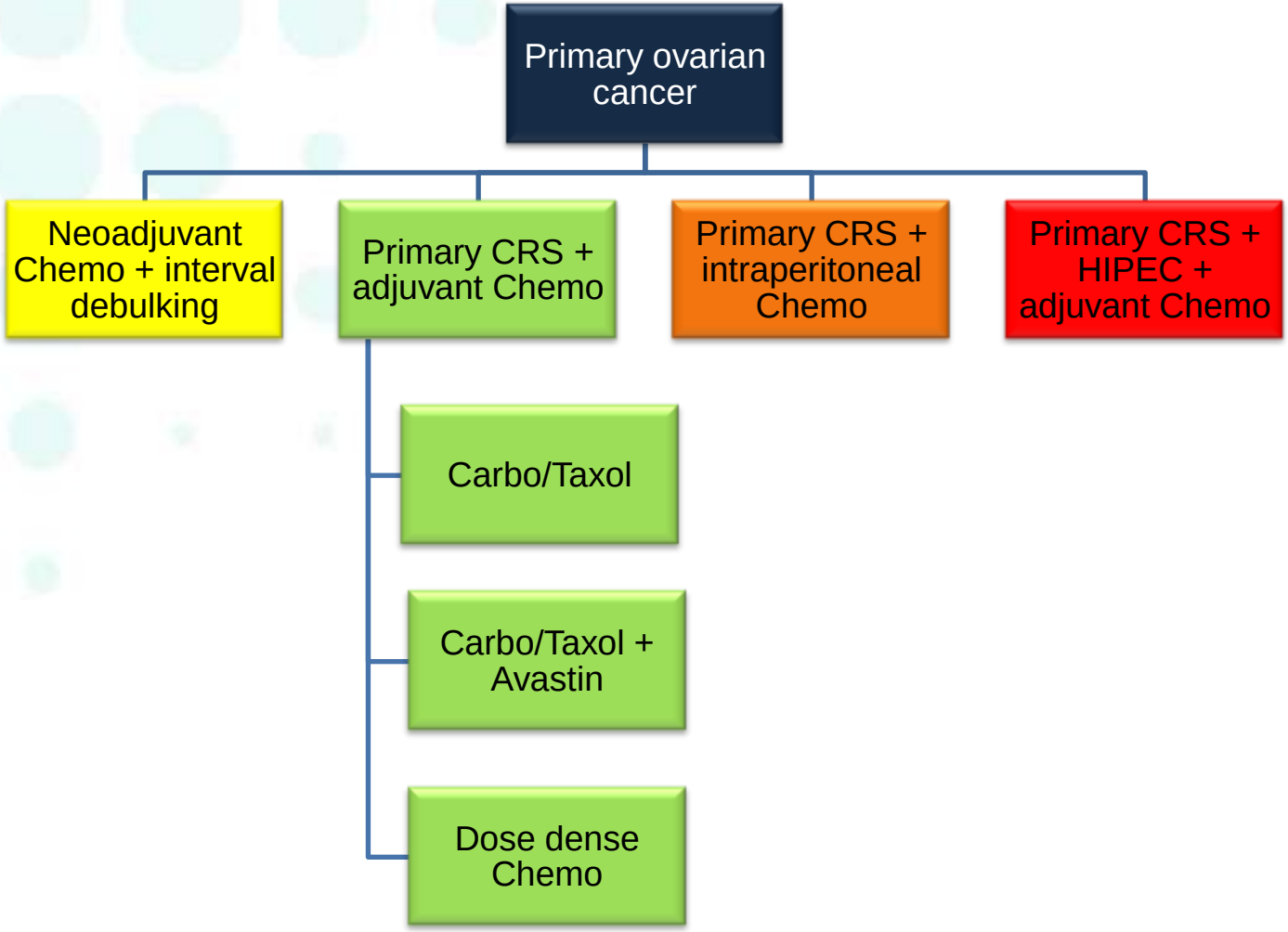
ASCO 2017 3 new randomised trials

Harter et al., Abstract 5500: LION: Lymphadenectomy in ovarian neoplasms—A prospective randomized AGO study group Trial.

- Incl.-criteri: advanced epithelial OC Stages IIB-IV
  Good performance status (ECOG 0-1)
  Clinival/radiaologic negative nodes
- 1895 registered day before surgery **– excluded 1245**!!!!!!
- Complete resection in 99.4 %
- 180 patients had lymh node mts (56%)
- But not differences in OS!!
- OS in both groups : 67 months – 5-year OS 55%
- But: only 80% in both groups underwent Platinum and Taxan????

Treatment options in ovarian cancer

Advanced primary ovarian cancer



Recurrent ovarian cancer

Platin refractary OC

Platin sensitive OC

Recurrence after multiple chemo (hopeless?)

- Secondary CRS + second line chemo?
- Second line Chemo±targeted therapy?
- Secondary CRS + HIPEC?

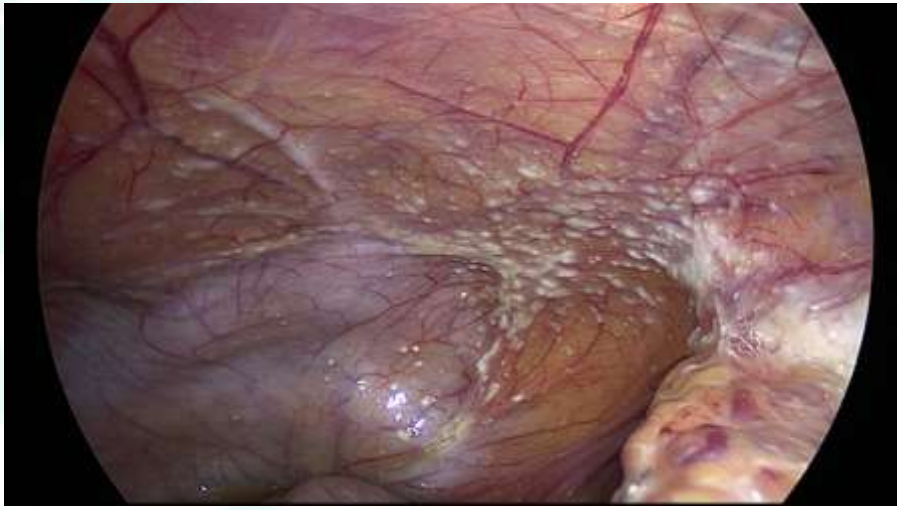
ASCO 2017 3 new randomised trials

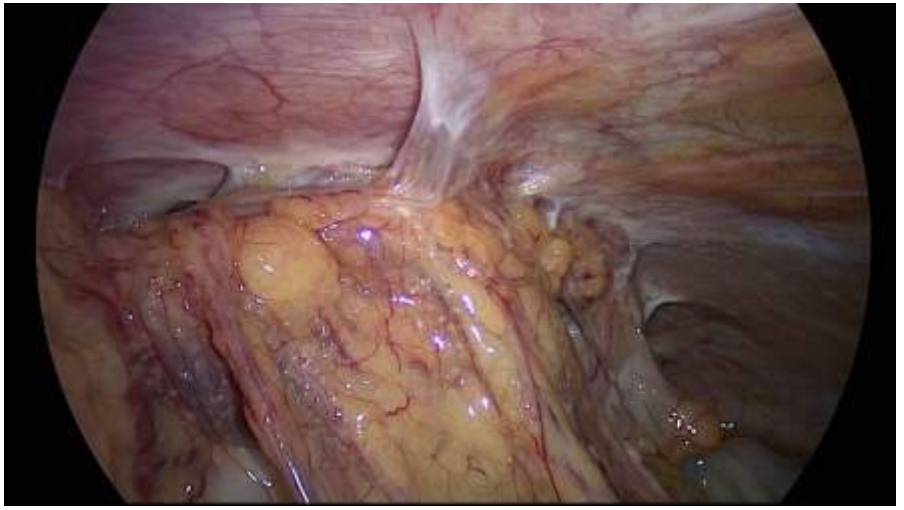
Du Bois et al., Abstract 5501: **Randomized controlled phase III study evaluating the impact of secondary cytoreductive surgery in recurrent ovarian cancer: AGO DESKTOP III/ENGOT ov20**

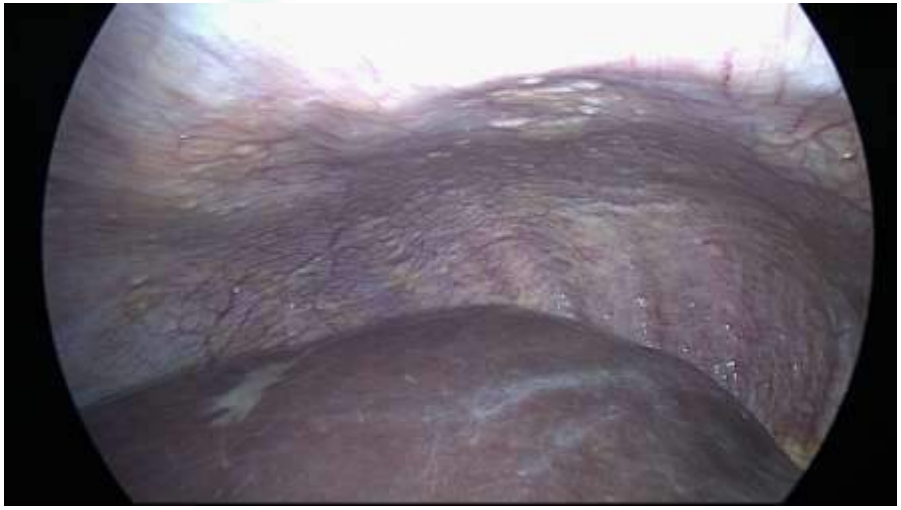
- **Prospective study in first platinum recurrent OC**
- **AGO score fullfiled**
- **Randomisation: 203 versus 204 patients: platinumbased chemo versus secondary CRS+ pltunim based chemo**
- **Macroscopic complete resection in 83%**
- **Median PFS after 2 years: 21 vs. 14 months** (data premature for OS), but only, if complete resection was achieved

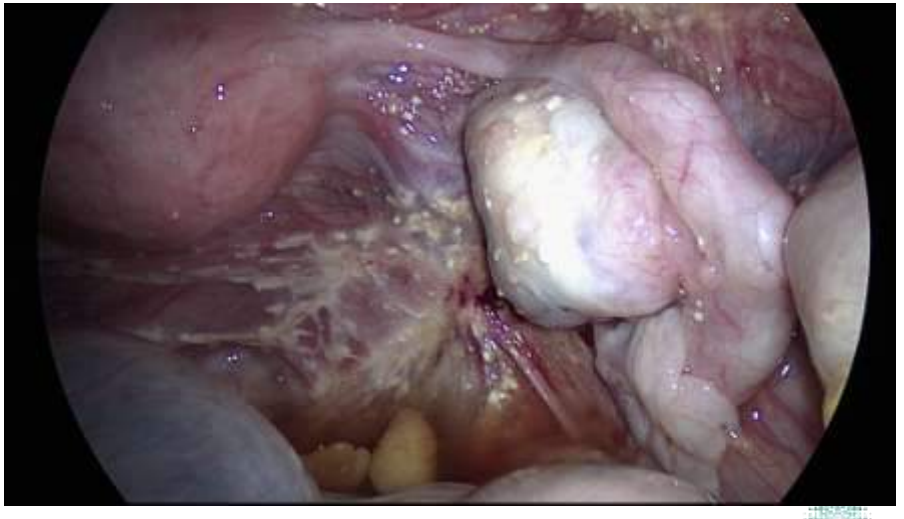
Current discussions in advanced ovarian cancer

Neoadjuvant chemotherapy ?!

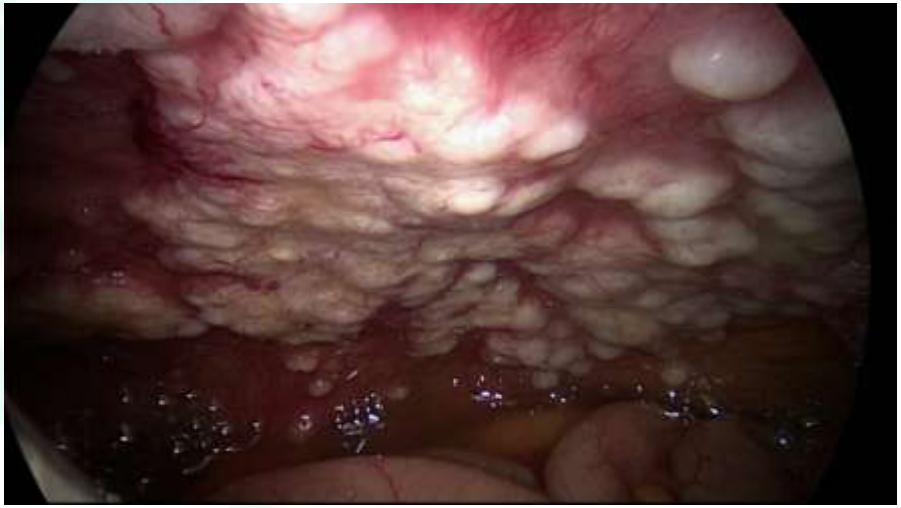


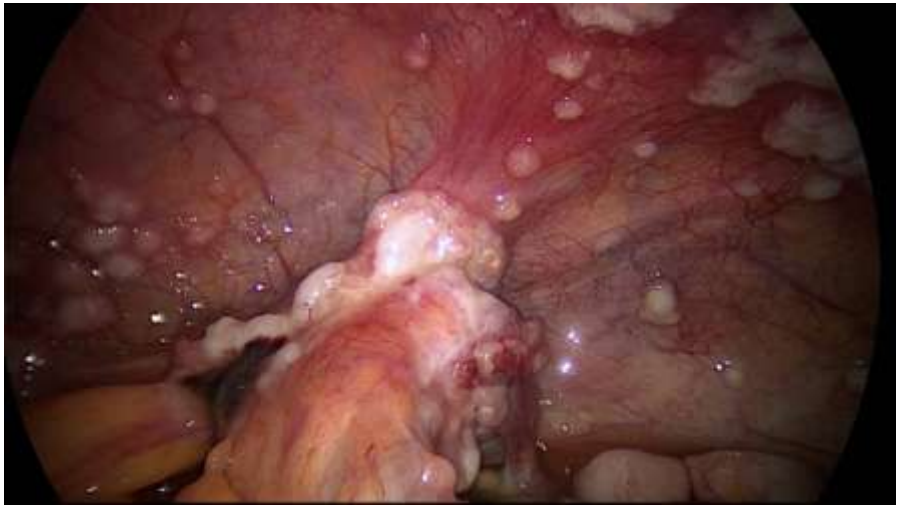


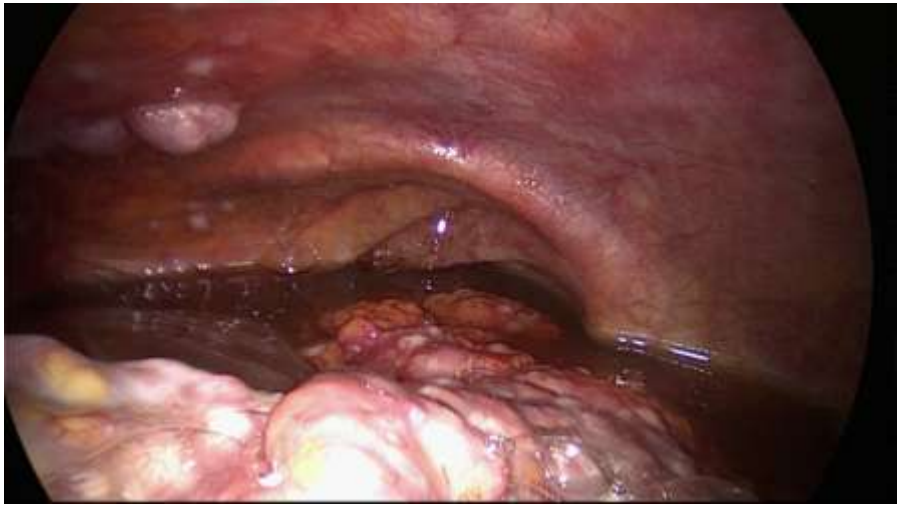


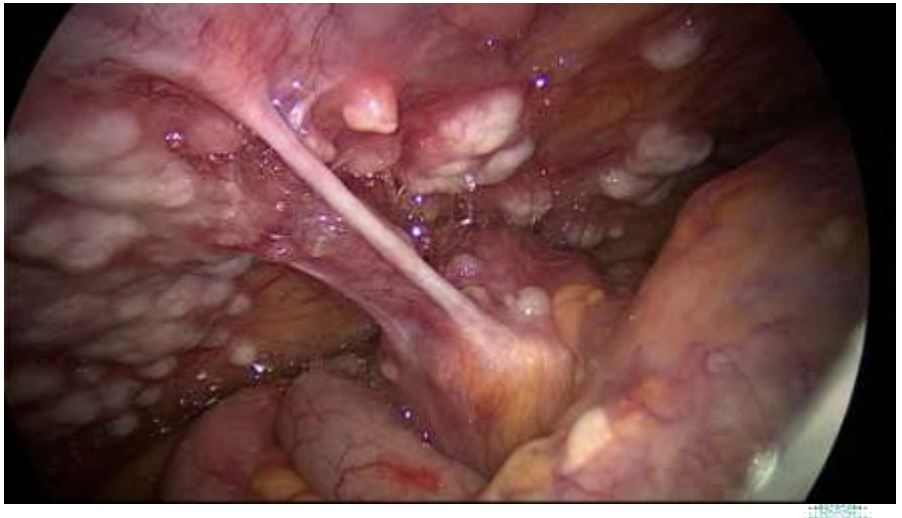


Neoadjuvant chemotherapy ?!

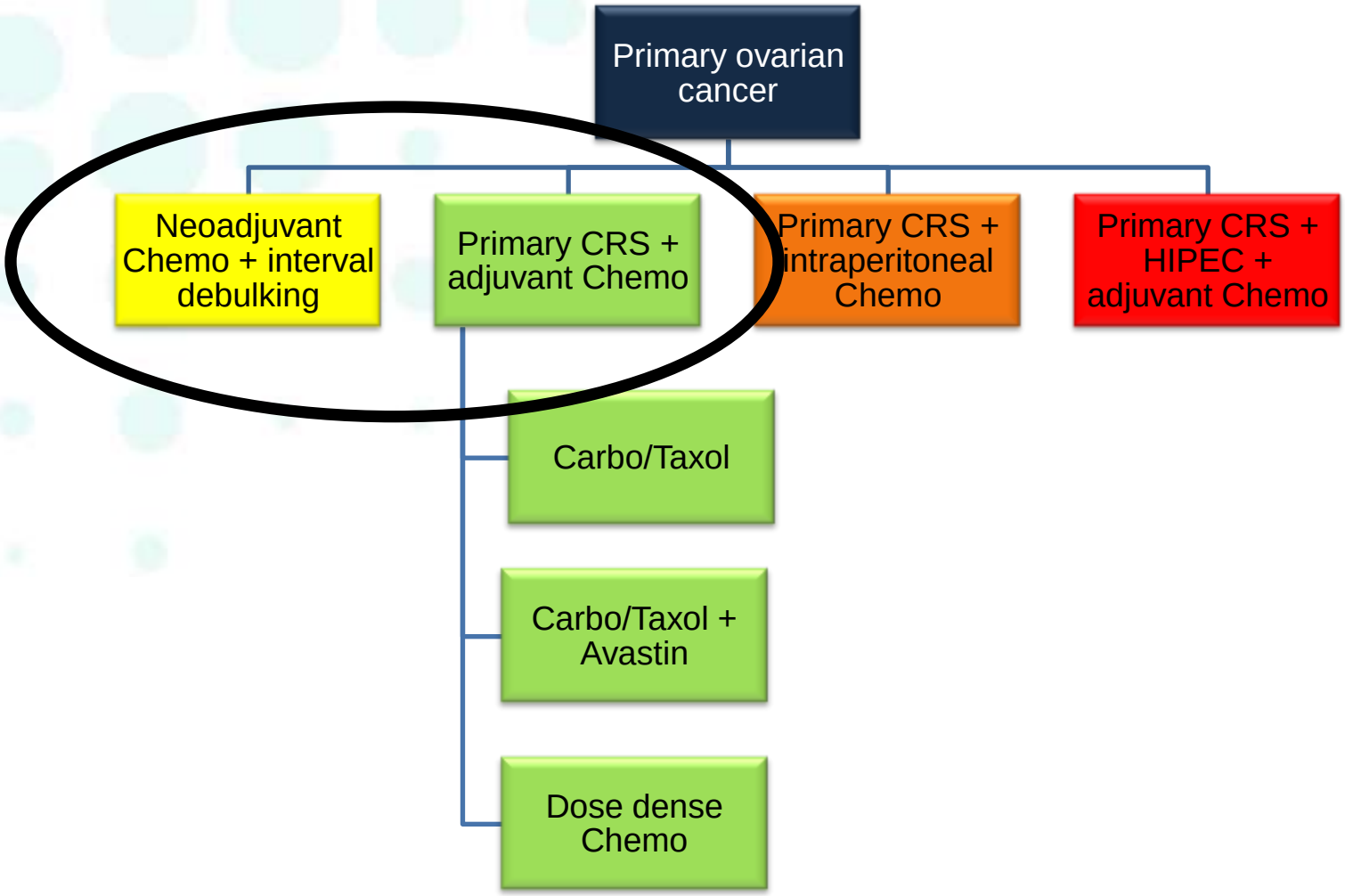








Advanced primary ovarian cancer



Pro and Cons regarding neoadjuvant chemo in OC

21 out of 23 panelists

Neoadjuvant Chemo followed by interval debulking

4th ovarian cancer consensus meeting 2011

2 out of 23 panelists

Primary CRS followed by adjuvant Chemo

"Delayed primary surgery after neoadjuvant chemotherapy is an option for selected patients with stage IIIC or IV ovarian cancer as included in the EORTC55971"

"Neoadjuvant chemotherapy cannot be regarded as adequate routine therapy of advanced ovarian cancer and should be limited to selected patients with very advanced FIGO stage IIIC or IV disease and contraindications against upfront debulking surgery or tumor dissemination, implying no chance for complete resection."

Vergote I et al., Neoadjuvant chemotherapy or primary Surgery in stage III and IV ovarian cancer. NEJM 2010;363:945-953

Du Bois A et al., Neoadjuvant Chemotherapy cannot be regarded as adequate routine therapy strategy of advanced ovarian cancer. Int J Gynecol Cancer 2012;22:182-185

Pro and Cons regarding neoadjuvant chemo in OC

2 prospective, randomised, multicentric trials could demonstrate non-inferiority of neoadj. chemo followed by IDS vs. primary (CS with lower morbidity).

Vergote et al, NEJM 2010;363:943-953
Kehoe et al., (CHORUS Trial) Lancet 215;386:249-257

Agreement for primary Surgery: 80-85%
No agreement for primary surgery -
pro neoadjuvant chemo: 15-20%

Vergote I et al., Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? Gynecol Oncol 2013;128:6-11

„German problem“

AGO-Ovar group does not believe in neoadjuvant chemo trials:

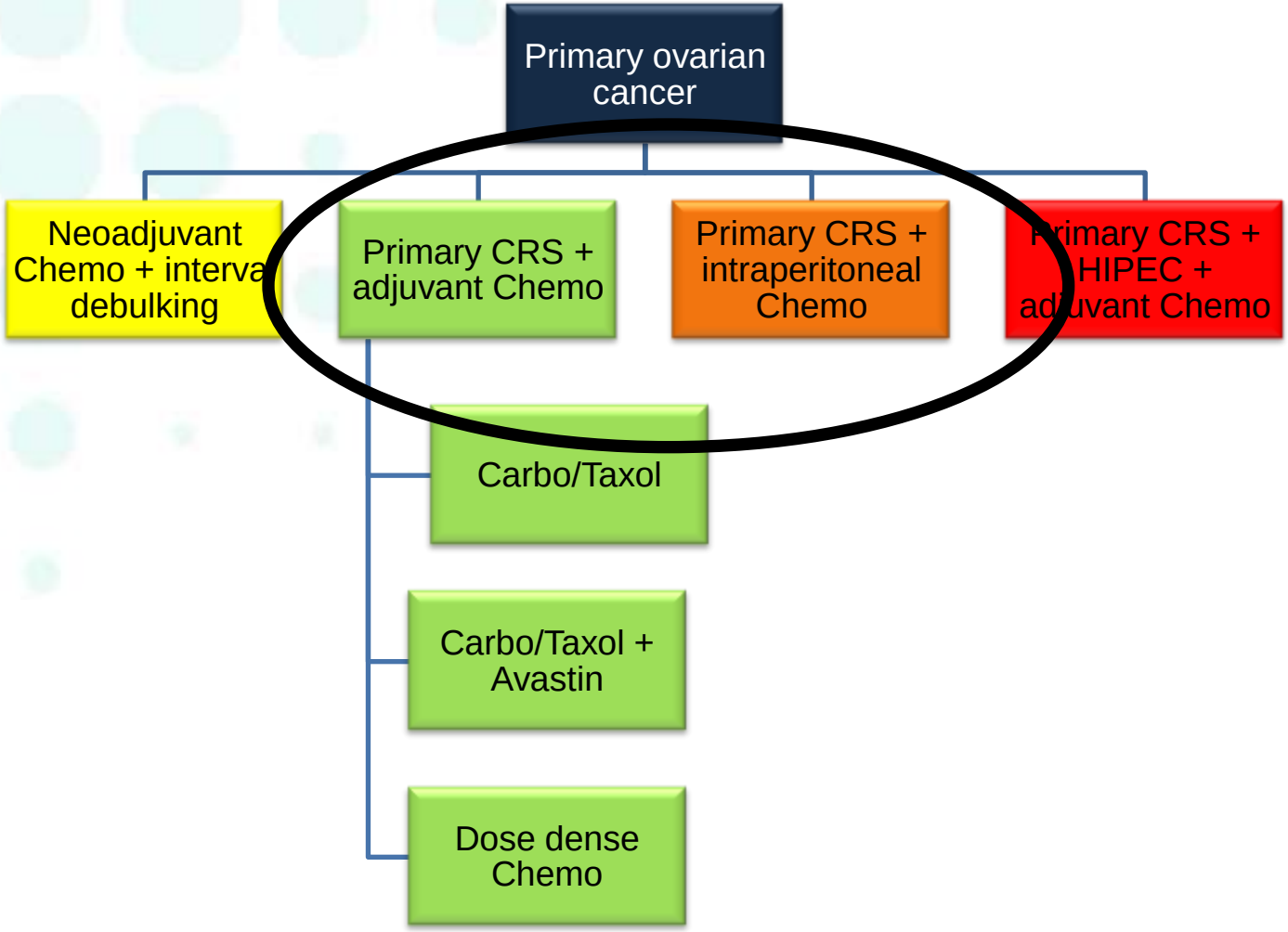
AGO-OVAR OP.7 TRUST/AGO-OVAR 19

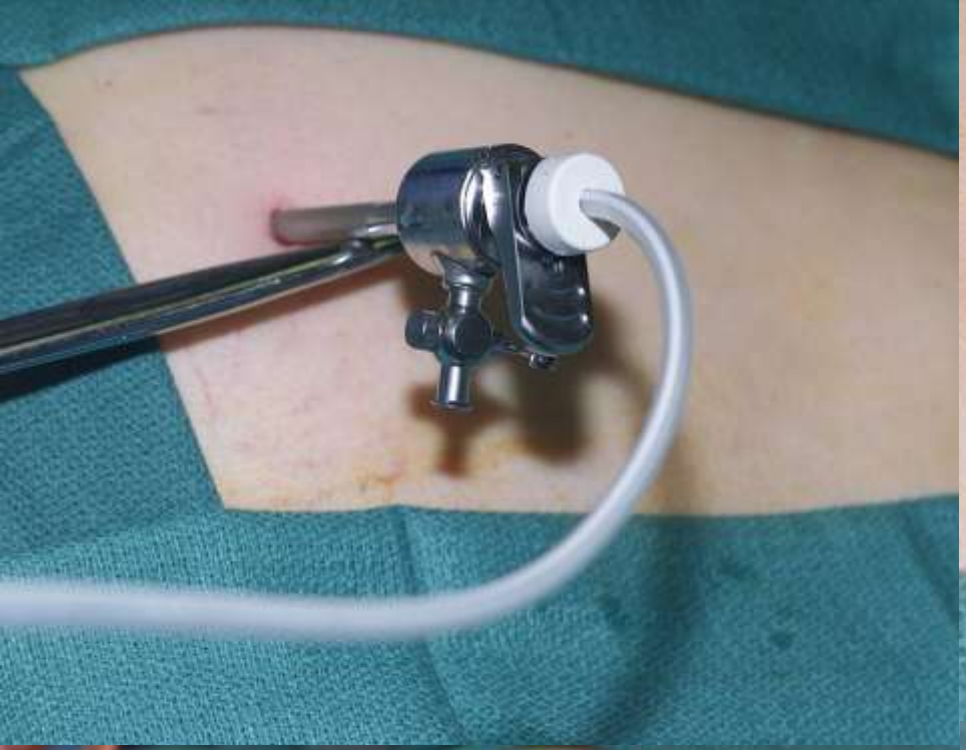
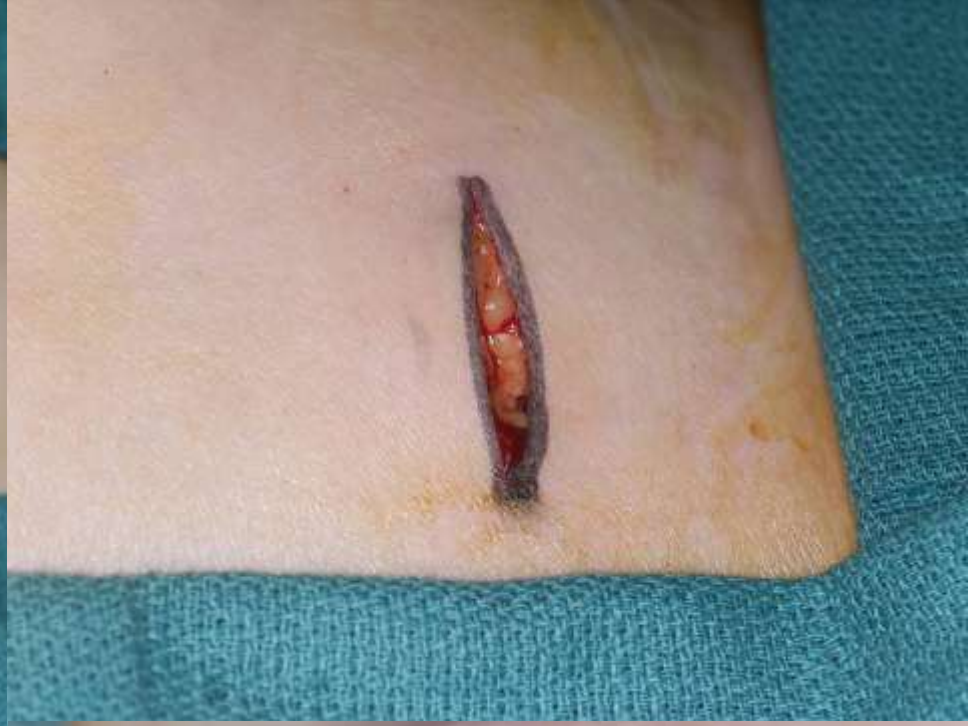
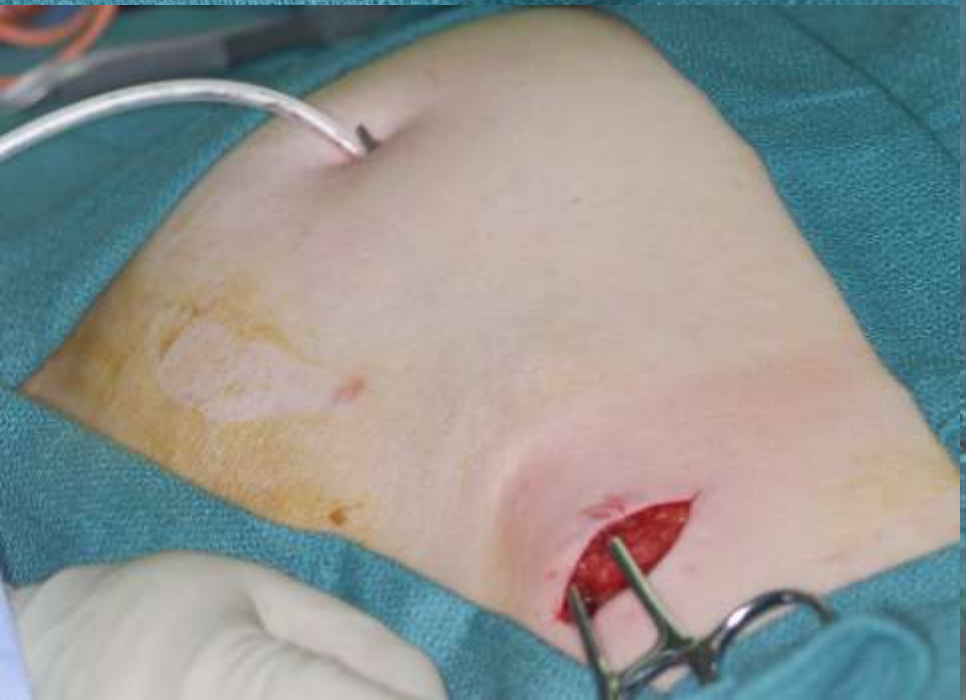
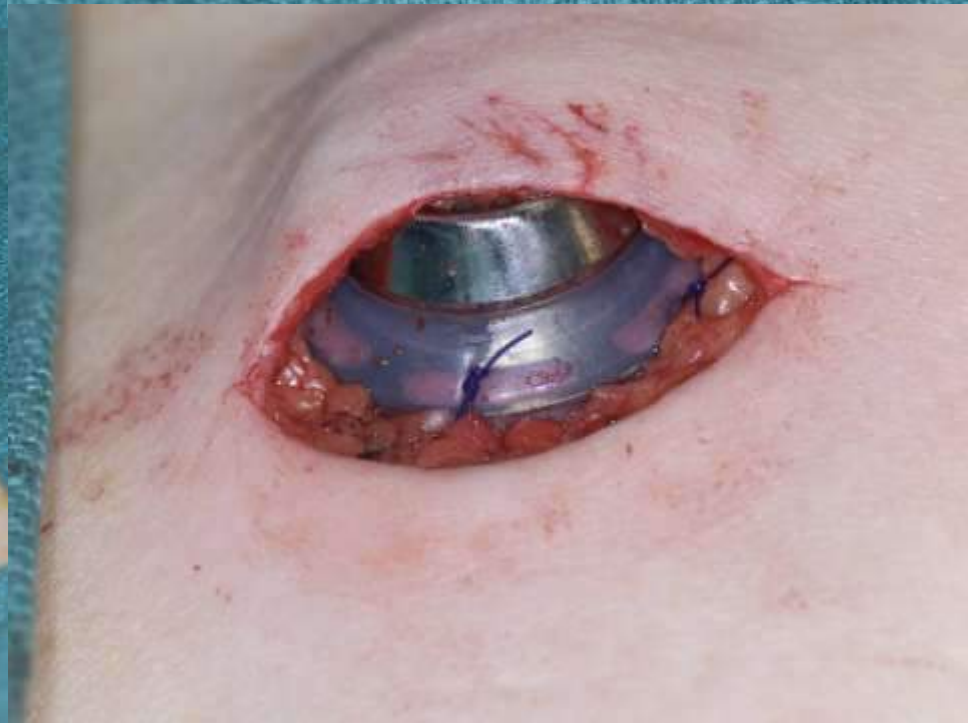
n=686

Arm I: PDS with the aim of complete tumor resection followed by 6 cycles taxan/platin-based i.v. chemotherapy

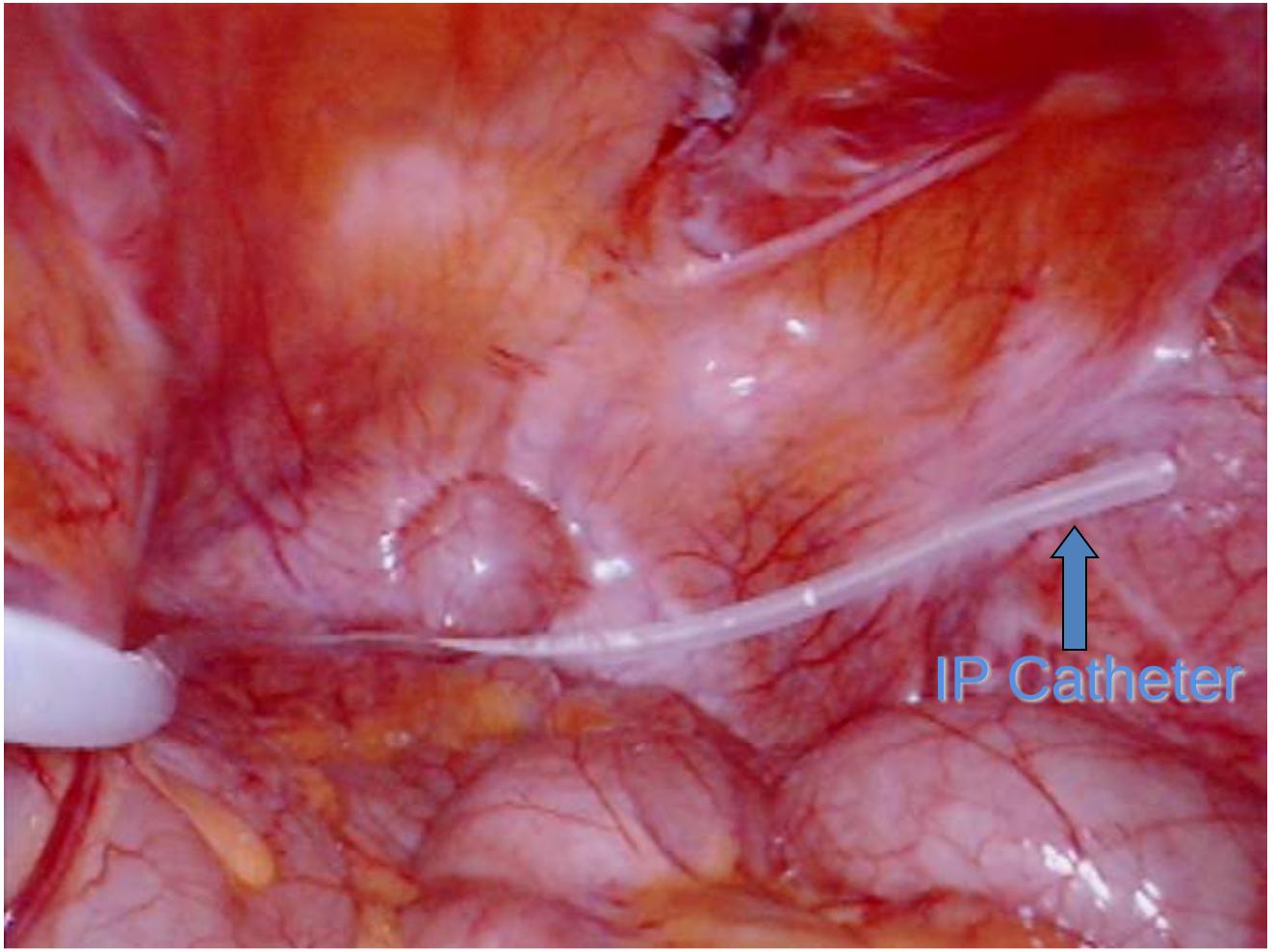
Arm II: 3 cycles taxan/platin-based i.v. neoadjuvant chemotherapy Zyklen Taxan/Platin-basierte followed by IDS with the aim of complete tumor resection followed by 3 additional cycles taxan/platin-based i.v. chemotherapy

Advanced primary ovarian cancer



Picture showing IP catheter placed in the pelvis



Major randomised trials i.p. chemo

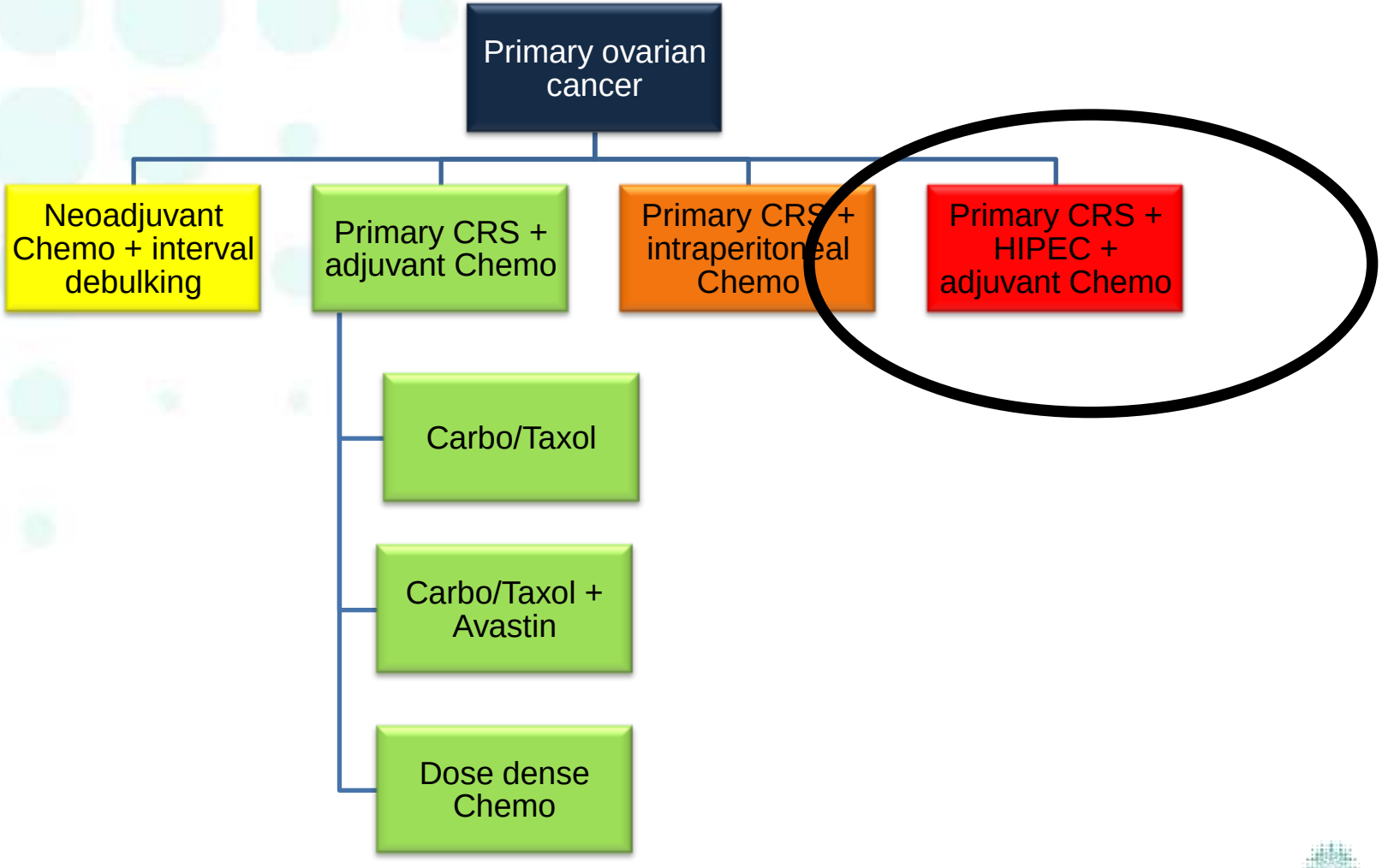
Study/ Author	Stage/ residual disease	Number of patients	Arms	Median OS (month)	p-value	HR
GOG-WO104/SG-8501 (Alberts)	Stage III, < or = 2 cm	546	**IP:** CDDP i.p. CTX i.v. **vs IV**: CDDP i.v. CTX i.v	**49 i.p. 41 i.v.**	0.02	0.76
GOG-114/SWOG-9227 (Markman)	Stage III, < or = 1cm	462	**IP**: Carbo AUC 9, Taxol i.v. CDDP i.p. **vs IV**: CDDP i.v. Taxol i.v.	**63 i.p. 52 i.v.**	0.05	0.81
GOG-172 (Armstrong)	Stage III, < or = 1 cm	417	**IP**: Taxol i.v CDDP i.p. Taxol i.p vs **IV:**CDDP i.v. and Taxol i.v.	**66 i.p. 50 i.v.**	0.03	0.75

IP-chemotherapy

- ✓ GOG 172: stage III OC, residual tumor <1cm
  i.v. chemo versus i.p. chemo – only 42% in i.p. group recieved 6 cycles (Armstrong et al., NEJM 2006;354:34-43)
- ✓ Best long term survival data OS: PFS – 24.9 months, OS 61.8 months (Landrum et al., Gynecol Oncol 2013;130:12-18)
- ✓ Today improved technique – 83% 6 cycles (Lesnock et al. Gynecol Oncol 2010;116:345-350)
- ✓ i.p. in 6 trials with better OS and DFS (HR 0.81 and 0.78)
  (Jaaback K et al, Cochrane Database Syst Rev 2011;CD005340)

HIPEC in OC

Advanced primary ovarian cancer



Treatment options for HIPEC in ovarian cancer patients

- Upfront CRS + HIPEC
- Interval CRS + HIPEC

- Secondary CRS + HIPEC after incomplete response (Benefit)
- Salvage CRS for recurrence (Benefit)

- Palliative HIPEC for chemotherapy resistent ascites (*Ba M et al., Int J Gynecol Cancer 2016;26:1571-1579)*

Mulier S et al., Survival Benefit of Adding Hyperthermic IntraPEritoneal Chemotherapy (HIPEC) at the Different Time-points of Treatment of Ovarian Cancer: Review of Evidence. Current Pharmaceutical Design 2013;18:3739-3803

Drugs used for HIPEC

- ✓ Cisplatin
- ✓ Mitomycin
- ✓ Carboplatin
- ✓ Oxaliplatin
- ✓ Cealyx
- ✓ Taxans
- ✓ Doxorubicine

Bakrin et al. Peritoneal carcinomatosis treated with cytoreductive surgery and HIPEC for advanced ovarian carcinoma: a French multicentre retrospective cohort study of 566 patients. Eur J Surg Oncol 2013;39:1435-1443

- Retrospective multi-institutional cohort study
- N=566, 474 recurrent cancers, 92 first-line treatment

- Complete cytoreduction in 75%
- Mortality: 0.8%, grade 3+4 morbidity 31%
- OS 35 months primary OC
- No sign. difference between chemosensitive and chemoresistant recurrences
- PCI Index most important prognostic factor.

Spiliotis et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol 2015:22:1570-1575

- First rand. trial for HIPEC in recurrent ovarian cancer
- N=120, Group A CRS+HIPEC+systemic chemo vs.
  Group B: CRS+systemic chemo

- Median survival A vs. B: 26.7 vs. 13.4 months
- No difference in HIPEC arm between platin-resistent and platinum-sensitive recurrence.
- PCI <15 appeared to have longer survival

(similar non randomized results – by Petrillo et al., Ann Surg Oncol 2016;23:1660-1665 and Sleightholm et al., J Surg Oncol 2016;114:779-784, Manzanedo et al., Minerva Ginecol 2017;69:119-127)

Di Giorgio et al. (Peritonectomy Procedures) combined with HIPEC in advanced ovarian cancer: retrospective Italian multicenter observational study of 511 cases
Ann Surg Oncol 2016, Nov 28

- Retrospective multi-institutional study
- N=511, primary and recurrent OC

- Complete cytoreduction in 72%
- Overall major morbidity: 17%
- OS 54 months, PFS 16.6 months
- Multivariate analysis: completeness of CRS, PCI and time of HIPEC are independent factors.

Morbidity and mortality HIPEC in ovarian cancer

	Year	Number	Mortality	Grade III/IV Morbidity
Frenel	2010	31	0%	29%
Roviello	2010	53	0%	23%
Pomel	2010	31	0%	29%
Pavlov	2009	56	1.8%	2%
Di Giorgio	2008	47	4.2%	21%
Rufian	2006	33	0%	6%
Raspargliesi	2006	40	0%	0
Bakrin	2013	566	0.8%	31%

Bakrin et al, Journal of Visceral Surgery 2014;151:347-353

Oncologic data HIPEC in ovarian cancer

- CRS+HIPEC in primary ovarian cancer
  - OS: 37 months
  - DFS: 14.4 months
  - 5-year survival rate: 40%
- CRS+HIPEC in recurrent ovarian cancer
  - OS: 36.5 months
  - DFS: 20.2 months

Chiva et al, Gynecol Oncol 2015;136:130-135

Our ovarian cancer patients deserve to know the relative benefits and risks of this interesting but unproven treatment modality!

Herzog, The Role of Heated Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer: Hope or Hoax? Ann Surg Oncol (2012) 19:3998–4000

Oncologic data HIPEC in ovarian cancer compared to other regimen

- CRS+HIPEC in primary ovarian cancer
  OS: 37 months DFS: 14.4 months
  5-year survival rate: 40% *(Chiva et al, Gynecol Oncol 2015;136:130-135)*
- CRS and i.v. chemo carbo+paclitaxel

Bookmann 2008:	OS 44 months	DSF 16 months
Du Bois 2009	OS 44 months	DFS 18 months
Chi 2012	OS 58 months	PFS 28 months

- CRS+chemo+anti angiogenic therapy

GOG 218	OS 41 months	PFS 14 months
ICON 7	OS 36 months	PFS 24 months
OVAR 12		PFS 18 months

- Dose-dense chemo

JGOG 3016	OS 110 months	PFS 28 months (Japan)
MITO 7 (Europe)		PFS 18 months (Failed)

Many open questions - HIPEC in OC

Interesting and feasible, but:

- ✓ Effect based on better surgery or HIPEC or both?
- ✓ Which drugs?
- ✓ Duration of application?
- ✓ Temperature?
- ✓ Best indication?
- ✓ Adjuvant therapy?
- ✓ Not supported by industry
- ✓ Data from only 1 randomised trials
- ✓ Considerable morbidity (0-40%) and mortality (0-10%)
  (Chua J Cancer Res Clin Oncol 2009;135:1637-1645, Chiva Gynecol Oncol 2015;136:130-135)

New concept – mix of all?

Gouy S et al., Gynecol Oncol 2016;142:237-242

„Results of a multicenter phase I dose-finding trial of hyperthermic intraperitoneal cisplatin after neoadjuvant chemotherapy and complete cytoreductive surgery and followed by maintenance bevacicumab in initially unresectable ovarian cancer.“

Few original data – many reviews

- Bhatt and Glehen, Indian J Surg Oncol 2016;7:188-197
- Cowan et al., Int J Hypertherm 2017; Epub
- Chiva, Gynecol Oncol 2015;136:130-135
- Polom et al, Int J Hypertherm 2016;32:298-310
- Hotouras et al., Int J Gynecol Cancer 2016;26:661-670
- Harter et al, Int J Gynecol Cancer 2017;27:246-247
- Spiliotis et al., Curr Oncol 2016;23:e266-e275
- Deraco, Gynecol Oncol Rep 2016;15:7-8

Same data – different interpretations!

Ongoing randomised trials

Study	Population	Accrual goal	Anticipated completion	Study ID Number
Interval Debulking ± HIPEC	Front-line stage III Intervall CR	280	ASCO 2017	NCT 00426257
Secondary Debulking ± HIPEC	Recurrence 1st	444	2020	NCT 01376752
Surgery ±HIPEC	Recurrent Platin-sensitive	158	2018	NCT 01539785
CRS+HIPEC vs. Surgery alone	Stage III unresectable OC	94	2018	NCT 01628380
CRS+HIPEC vs. CRS followed by Chemo	Recurrent OC	98	2018	NCT 01767675

ASCO 2017 3 new randomised trials

Van Driel et al - Abstract 5519: A phase 3 trial of hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer.

n=245, Stage III Ovarian cancer, all 3 cycles neoadjuvant Chemo Carbo/Tax

Randomisation: Intervall CRS **with or without** HIPEC, followed by 3 cycles i.v. Carbo/Tax.

Group with HIPEC RFS: 15 vs. 11 months

OS: **48** vs. 34 months

Number of grade 3/4 adverse events: n.s. (28% vs. 24%)

First randomised trail with survival benefit in OC-patients!!!

„Another German problem“

Statement AGO-Ovar group:

„HIOPEC should not used to treat ovarian, fallopian tube or primary peritoneal cancer outside ….trials, neither for primary therapy or to treat recurrence…..

After careful analysis of the most recent literature the authors conclude that HIPEC remains experimental. Its use is not recommended and should be rejected outside prospective controlled trials.“

AGO State of the Art meeting 2017 April Munich: Presentation:

„**Neue Argumente gegen IP, HIPEC und PIPAC beim Ovarialkarzinom.“** Jalid Sehouli

Harter et al., Geburtshilf Frauenheilk 2016;76:147-149

Conclusion

Conclusion

- Ovarian cancer is an ideal target for primary CRS and HIPEC due to pattern of spread.
- Most important for patients with ovarian cancer is optimal cytoreduction followed by optimal adjuvant therapy. Interdisciplinary multivisceral surgerys is often needed to reach operativ goal.
- Survival results for CRS and HIPEC in current availible studies are promising but under strong discussion!
- Results of ongoing randomised trials are urgently needed to define role of HIPEC in patient with primary and recurrent ovarian cancer.

Thank you for the invitation and your kind attention!