Surgery in Recurrent Ovarian Cancer - an emerging area of evidence -

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A long and winding road to define the role of surgery in relapsed OC called *AGO-DESKTOP Alley*

DESKTOP I: **Retrospective multicentre series**

1. **Identify an appropriate endpoint / goal of surgery**
2. **Create a hypothetic model for a predictive score to select patients who could achieve the endpoint (allowing patient selection for further studies)**

DESKTOP II: **Prospective international non-interventional study**

1. **Validation of the DESKTOP I model (AGO score)**
2. **Descriptive analysis of the selection bias for offering surgery to patients with ROC**
3. **Description of ROC surgery associated morbidity**

DESKTOP III: **Prospectively randomised controlled phase III trial**

1. **Evaluation of the impact of ROC surgery on OS**
2. **acute and delayed morbidity**

AGO DESKTOP-OVAR I

Predictive score for successful surgery (= complete resection), multivariate analysis

Pre-surgery variable	OR (95%CI)	p-value
Performance status (ECOG 0 vs >0)	2.65 (1.56–4.52)	<0.001
Residual disease after 1st surgery (0 vs >0)	2.46 (1.45–4.20)	<0.001
Ascites less than 500mL*	5.08 (1.97–13.16)	<0.001

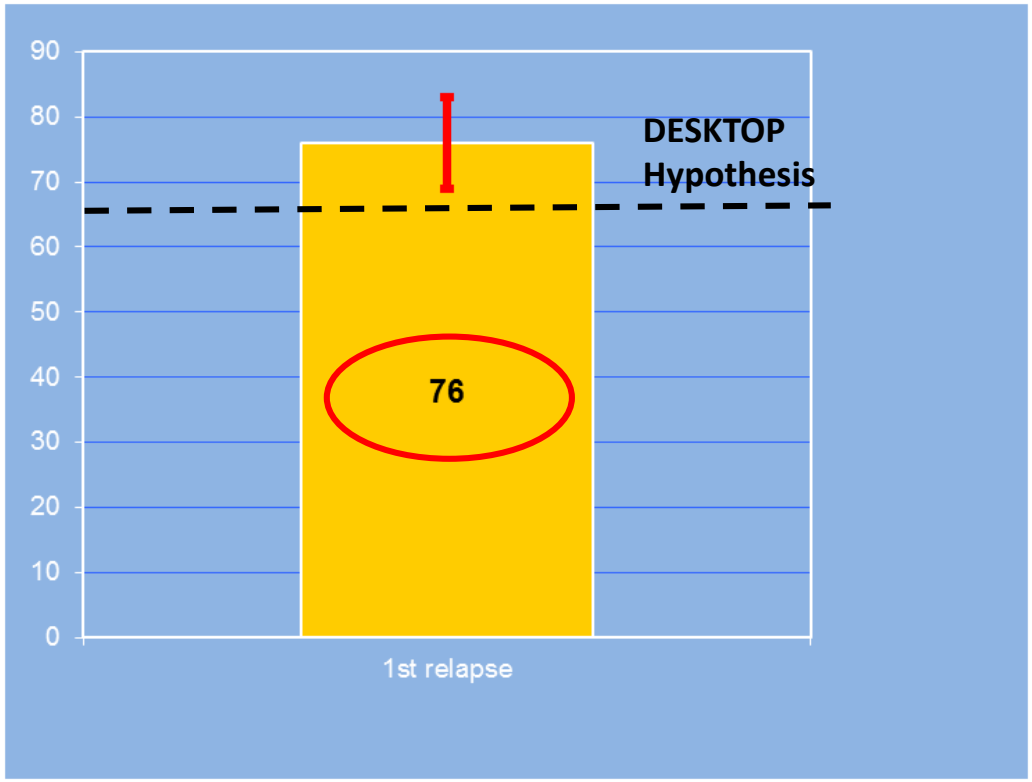
*Exclusively CA-125 CA 125 excluded from analysis due to strong correlation with ascites

Not significant for complete resection in multivariate model
(multivariate model with all significant pre-surgery variables)

- Localisation of recurrent disease (pelvic vs other)
- Therapy-free interval

AGO DESKTOP OVAR II

Frequency of complete resection by applying the AGO score within a prospective validation trial in 524 patients



complete resection in 76% of the study cohort

=

AGO score could predict with 95% probability A complete resection in at least 2 out of 3 patients

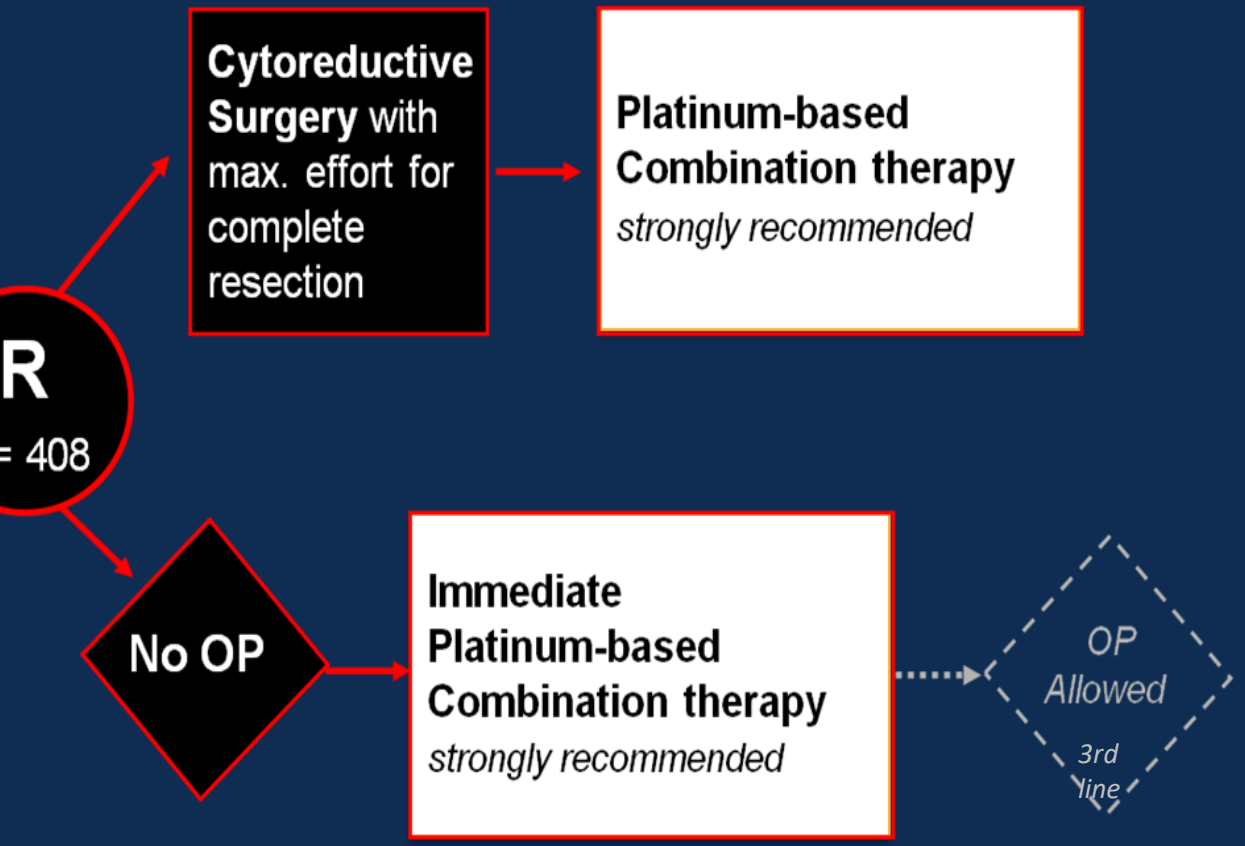
-> first prospective trial with succesfull validation of a predictive score

Harter P,…du Bois A. Int J Gynecol Cancer 2011

Design: AGO DESKTOP III

(ENGOT-ov20; NCT01166737)

Sponsor: AGO
ENGOT Model A



- 1st pt in 9/2010
- Recruitment completed 3/2015
- 407 of 409 pts evaluated
  (2 screening failures)

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AGO DESKTOP III: Patients' Characteristics

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	P-value
Pts. (n)	203	204	
Age (median, yrs)	**62.2**	**60.7**	**0.24**
No prior chemo	2 (1.0%)	2 (1.0%)	**0.57**
Prior platinum w/o taxan	16 (7.9%)	10 (4.9%)	
Prior platinum + taxan	**182 (89.7%)**	**191 (93.6%)**	
Pt-free-Int. > 12 months	**152 (74.9%)**	**155 (76.0%)**	**0.80**
CA 125 at study entry:			
• > 70 U/ml	**183 (45%)**		
• < 70 U/ml	**197 (48%)**		
• missing	**27 (7%)**		

CA 125: Additional data added after ASCO presentation

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AGO DESKTOP III: Therapy

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No 2nd surgery	2nd Surgery	P-value
Non compliant with random arm	**8 (3.9%) with OP**	**12 (5.9%) w/o OP**	0.36
Post-random chemotherapy:			
Platinum containing therapy	**185 (91.1%)**	**181 (88.7%)**	0.51
Non-platinum	6 (3.0%)	5 (2.5%)	
None / missing data	12 (5.9%)	18 (8.8%)	
Bevacizumab	45 (22.2%)	38 (18.6%)	0.32
PARP Inhibitors	1 (0.5%)	0 (0%)	0.25
Post-event surgery after 2nd relapse (within 3 mos after 2nd relapse)	**20 (11%)**	**9 (5.4%)**	0.09

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AGO DESKTOP III: Surgery

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	median	Quartiles 25-75%
Duration of surgery (minutes)	222	150 – 300
Bowel resection	33.3%	
Stoma diversion temporary / permanent	3.5% / 3.5%	
Blood loss (ml)	250	50 - 500
RBC transfusion	20.3%	
Fever > 38° C	4.8%	
Antibiotic treatment	19.0%	
Peri-OP thrombosis / embolism	1.1% / 0	
Re-laparotomy	3.2%	
Macroscopic complete resection rate	**72.5%**	

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AGO DESKTOP III: Outcome 1 (Mortality / OS)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	No surgery	Surgery	
30-days mortality (%)	-	-	Peri-OP 1
60-days mortality (%)	1 pt (0.49%)	-	Peri-OP 2
90-days mortality (%)	1 pt (0.49%)	1 pt (0.49%)	Peri-OP $_{MAYO}$
6 months mortality (%)	5 pts (2.46%)	1 pt (0.49%)	End of 2nd line thx

- The observed pooled 2-YSR was 83% and much higher than the assumed 2-YSR in the overall trial population.
- According to the trial protocol a planned interim analysis took place after observation of 122 OS events. The local significance level was set to alpha=0.0052 for a two-sided test – which was not met (O'Brien-Fleming group sequential plan).

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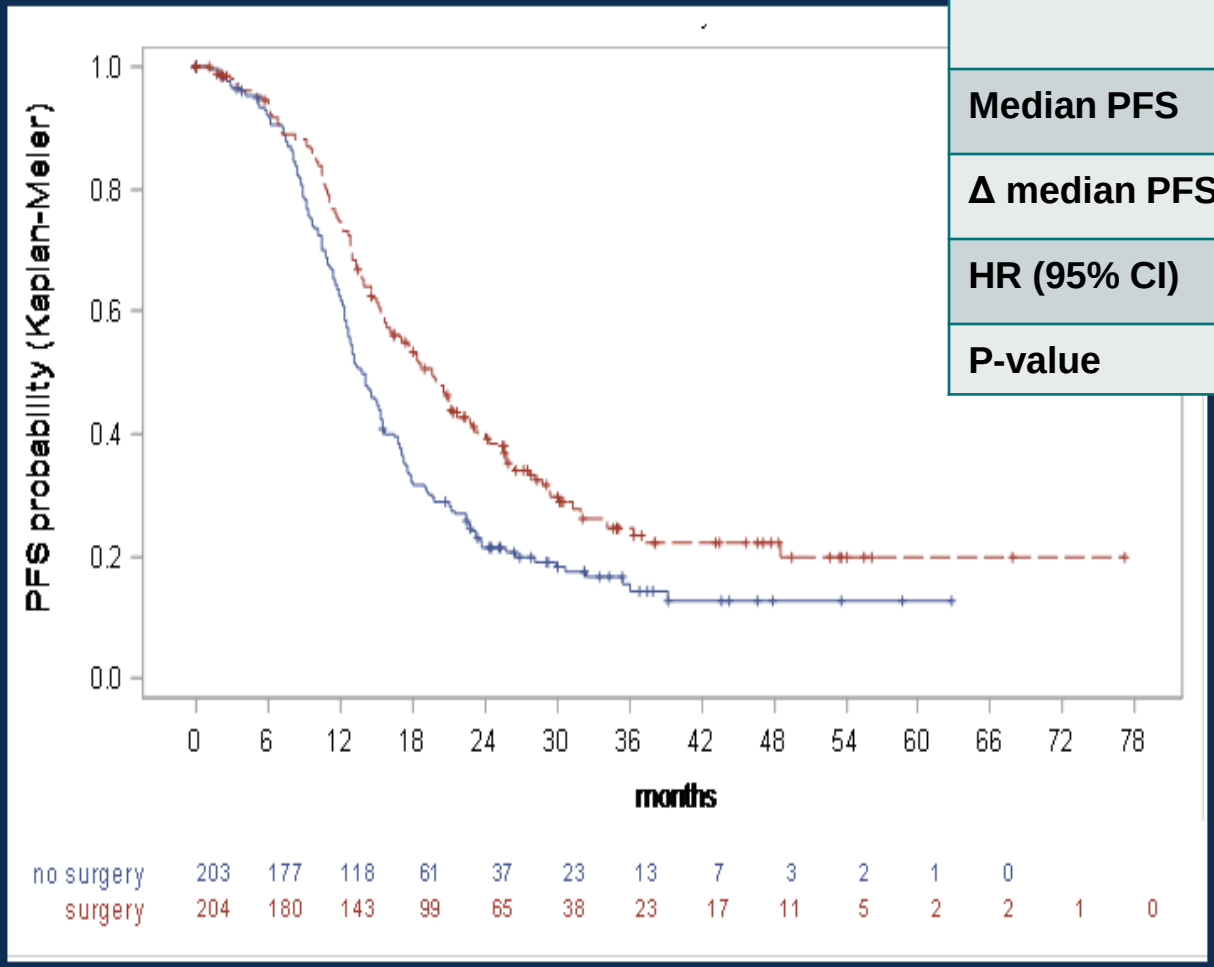
AGO DESKTOP III: Outcome 2 (PFS)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median PFS	19.6 mos	14.0 mos
Δ median PFS	5.6 mos	
HR (95% CI)	0.66 (0.52 – 0.83)	
P-value	< 0.001	

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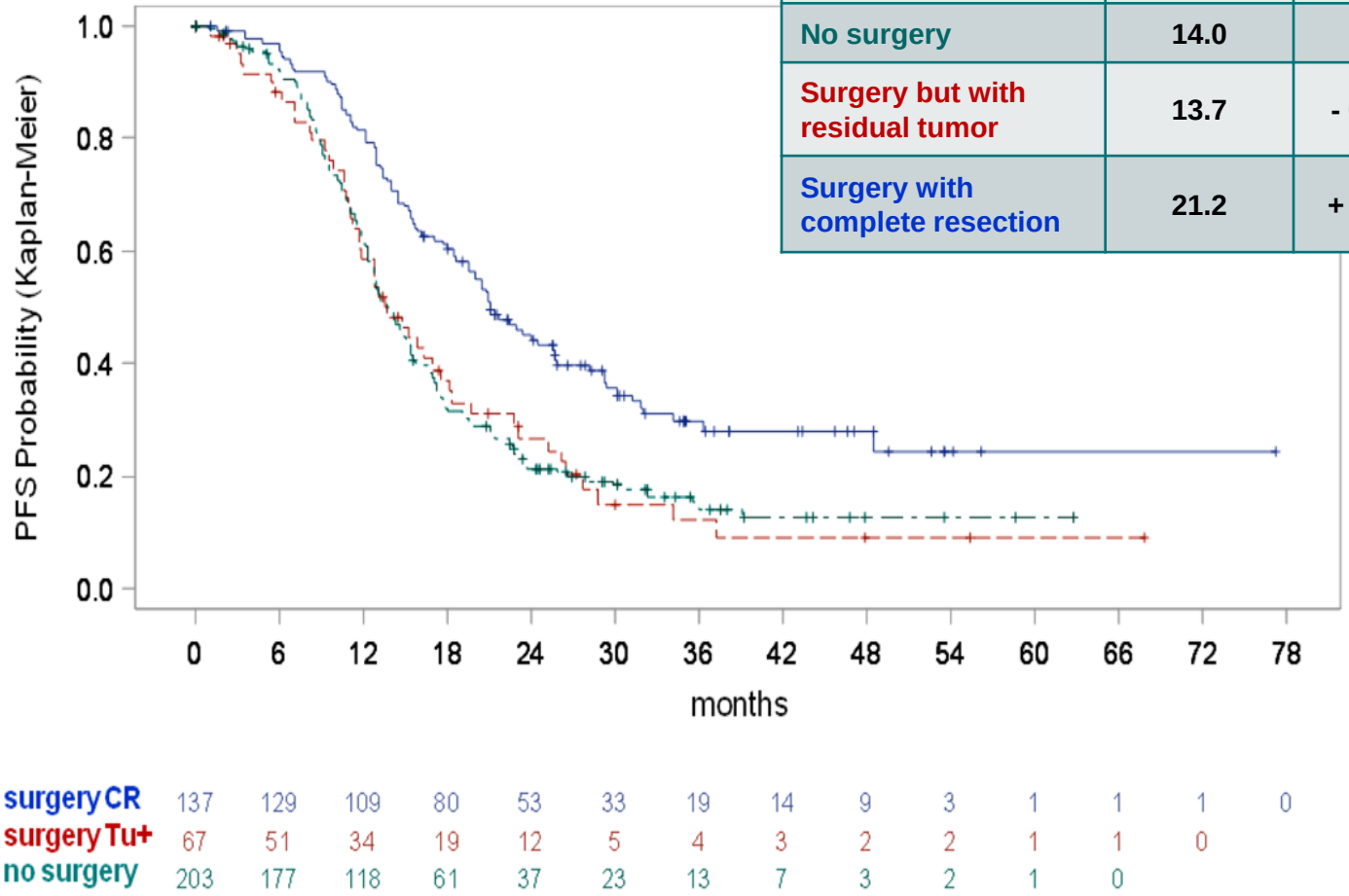
Positive Phase III 2nd line Therapy Trials in PSROC

Trials	Treatment	med. PFS (mos)	PFS gain (mos)	HR / p-value	OS (mos)	HR / p
ICON 4 (n = 802) Lancet 2003	Platinum	9	3	0.76 < 0.001	24 29	0.82 P = 0.02
	Platinum + Paclitaxel	12				
AGO OVAR 2.5 (n = 366) JCO 2006	Carboplatin	5.8	2.8	0.72 p = 0.003	17.3 18	0.96 P = 0.73
	Gem/Carboplatin	8.6				
CALYPSO (n = 976) JCO 2010	Carboplatin + Paclitaxel	9.4	1.9	0.82 p = 0.005	33.0 30.7	0.99 P = 0.94
	Carboplatin + PLD	11.3				
OCEANS (n =484) JCO 2012, Gyn Onc 2015	Gem/Carboplatin	8.4	4.0	0.48 p < 0.0001	33.6 32.9	0.96 P = 0.65
	Gem/Carbo + Bevacizumab	12.4				
ICON6 (n = 456) Lancet 2016	Platinum + Paclitaxel	8.7	2.4	0.56 p < 0.0001	21 26.3	0.77 P = 0.11
	Chemo + cediranib + maintenance cediranib	11.1				
GOG 213 (n = 674) Lancet Onc in press 2017	Carboplatin – Paclitaxel	10.4	3.4	0.63 p < 0.0001	37.3 42.2	0.829 (0.823)* P=0.056 (P=0.044)* *sensitivity analysis with corrected PFI data
	Carbo-Paclitaxel + Bev	13.8				
DESKTOP III ASCO 2017	**Platin-based +/- surgery**	14.0 19.6	5.6	0.66 p < 0.001	n.a. n.a.	n.a.

AGO DESKTOP III: Outcome 3 (PFS by surgical outcome)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

	Median PFS [mos]	Δ PFS [mos]	HR (95% CI)	P-value Wald-test
No surgery	14.0	-	1	-
Surgery but with residual tumor	13.7	- 0.3	0.98 (0.71 – 1.35)	0.8952
Surgery with complete resection	21.2	+ 7.2	0.56 (0.43 – 0.72)	< 0.0001



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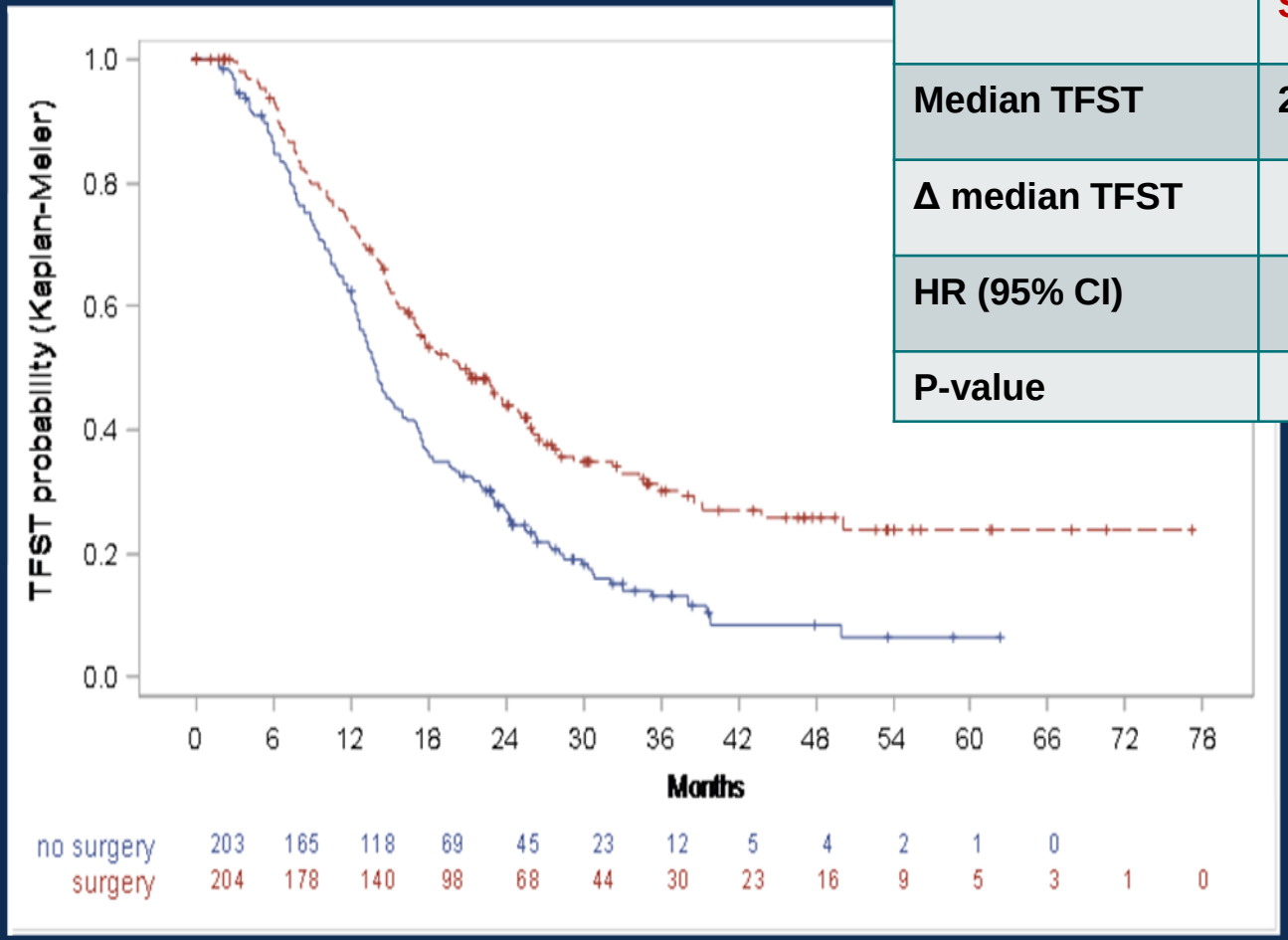
AGO DESKTOP III: Outcome 4 (TFST = time to 3rd line)

(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)



	Surgery	No surgery
Median TFST	21.0 mos	13.9 mos
Δ median TFST	7.1 mos	
HR (95% CI)	0.61 (0.48 – 0.77)	
P-value	< 0.001	

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AGO DESKTOP III: Conclusions 1
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

- 1st randomized controlled trial on 2nd cytoreductive surgery in ROC
- OS in this patients cohort treated in selected centres is better than expected.
- 2nd surgery in pts with AGO Score positive PSROC resulted in:
  - a meaningful PFS and TFST advantage of 5.6 and 7.1 months
  - a PFS gain at least comparable with all published positive phase III trials in 2nd line therapy for PSROC so far.
  - no increase in short-term mortality (30-180 d) and morbidity (60 d)
- 2nd surgery should be discussed with all AGO Score +ve PSROC pts.

AGO DESKTOP III: Conclusions 2
(AGO–OVAR OP.4; ENGOT-ov20; NCT01166737)

- **a benefit of surgery was exclusively seen in pts. with complete resection (CR) indicating the importance of selecting both:**

  - **the right centre with capability to achieve a CR in the majority of pts.**
  - **and the right pts** (eg. AGO Score selects app 50% of PSROC pts)

- so far, our data do not support more aggressive follow-up. The role of CA125 and time of relapse diagnosis is subject of further analysis.
- hopefully,
  further follow-up will show that this PFS benefit translates into OS

A question which became even more important after DESKTOP III:

How to identify the “right” clinic for surgery in recurrent ovarian cancer

Procedures in ROC surgery		HSK/KEM series* N = 217 pts (%)	Mayo series** N= 192 pts (%)
Bowel resection	any	**41.0**	**29.2**
	large bowel	37.3	
	small bowel	12.9	
Diverting stoma		8.3	1.6
Splenectomy		**13.4**	**17.2**
Pancreatic tail resection		3.2	
Liver partial resection		**15.7**	**11.5**
Lymphadenectomy	any	**56.7**	
	groins	1.8	
	pelvic	38.2	16.7
	para-aortic	38.2	24.5
	Upper abdomen LNE	8.2	5.7
	above diaphragm	1.4	
Diaphragmatic peritoneum	Partial	24.0	19.8
	Complete	**19.8**	
	full thickness	**6.5**	
Abdominal wall		10.0	
urinary bladder / ureter resection		5.1	6.3
Nephrectomy		2.3	

**Harter P, …, du Bois A. Gynecol Oncol 2014, ** Janco J, …., Cliby W, Gynecol Oncol 2016*

Quality Assurance in Advanced (FIGO III-IV) Ovarian Cancer Surgery

European Society of Gynaecologic Oncology Quality Indicators for Advanced Ovarian Cancer Surgery

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10 quality indicators

certification process

TRUST-Quality Manual

STUDY OF
PRIMARY RADICAL CYTOREDUCTIVE SURGERY FOR ADVANCED EPITHELIAL OVARIAN CANCER

TRUST

Protocol ID:
AGO-OVAR OP.7

A prospectively randomised open multi-centre study
A project of the AGO study group

TRUST Quality Control Manual

Version: V01MASTER international
Date: 02.03.2016

Authors: S. Mahner, A. du Bois

The right patient

- performance status / age / co-morbidity
- motivation

The right disease presentation

- initially resectable (if max. effort was tried)
- ascites < 500 ml
- no irresectable lesions (eg.imaging/laparoscopy)

The right centre

- resources (intensive care unit, transfusion unit)
- interdisciplinar and interprofessional peri-op management

The right surgical team

- skills & experience
- training (numbers)
- motivation