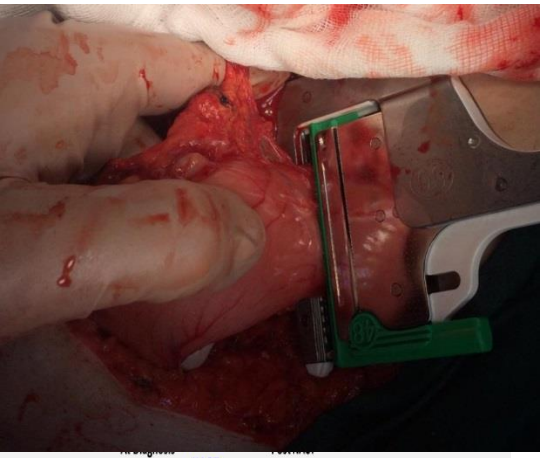
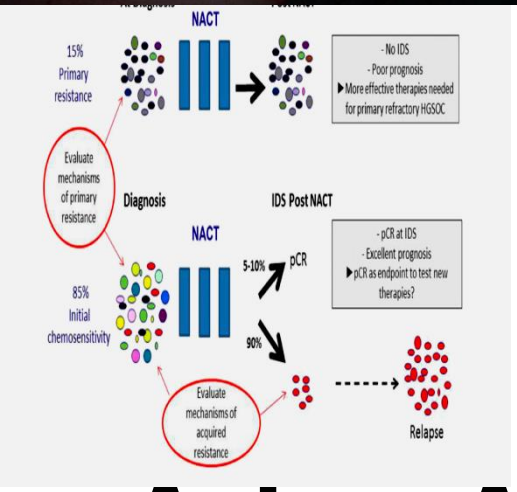
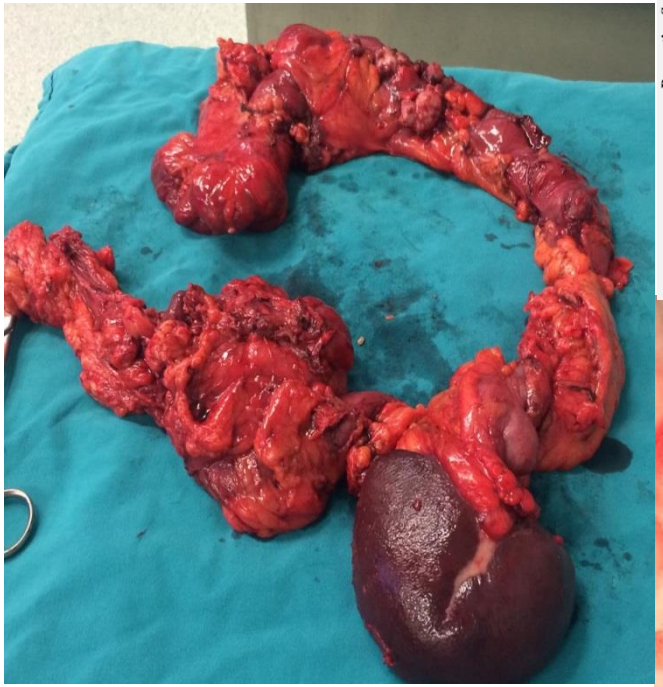
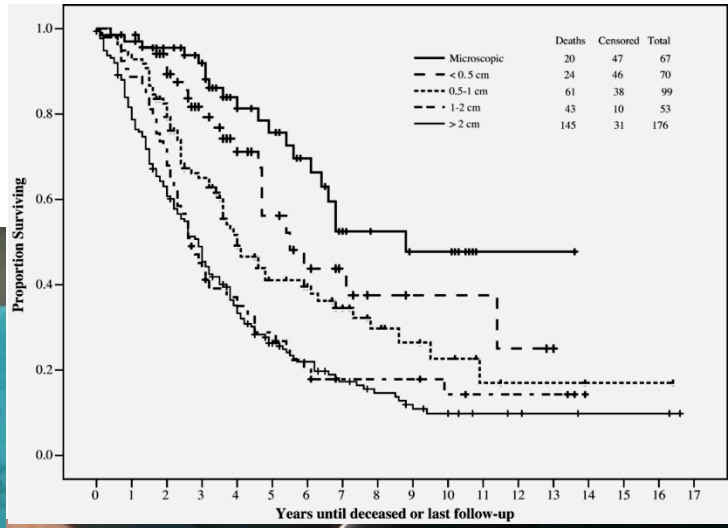
Role of Agressive surgery in Advanced Stage EOC

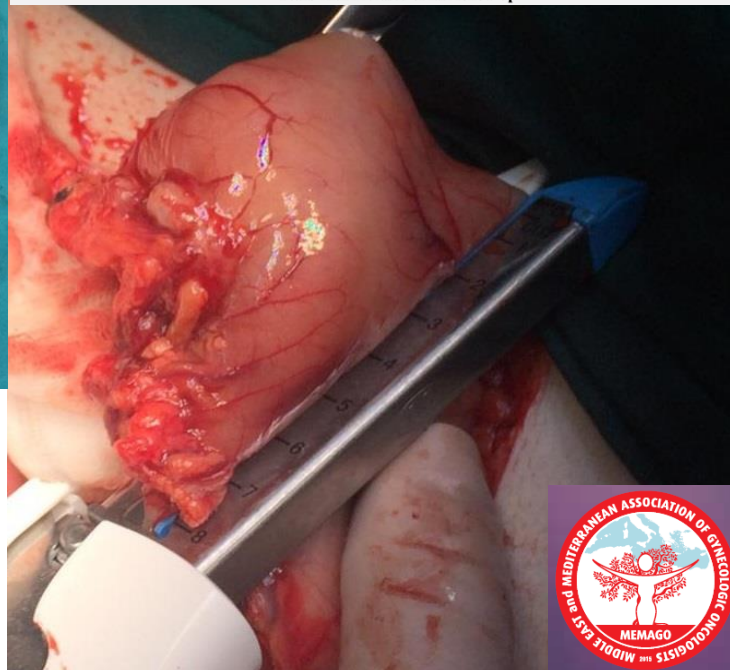


ESGO
European Society of Gynaecological Oncology









Ayhan Ali, MD

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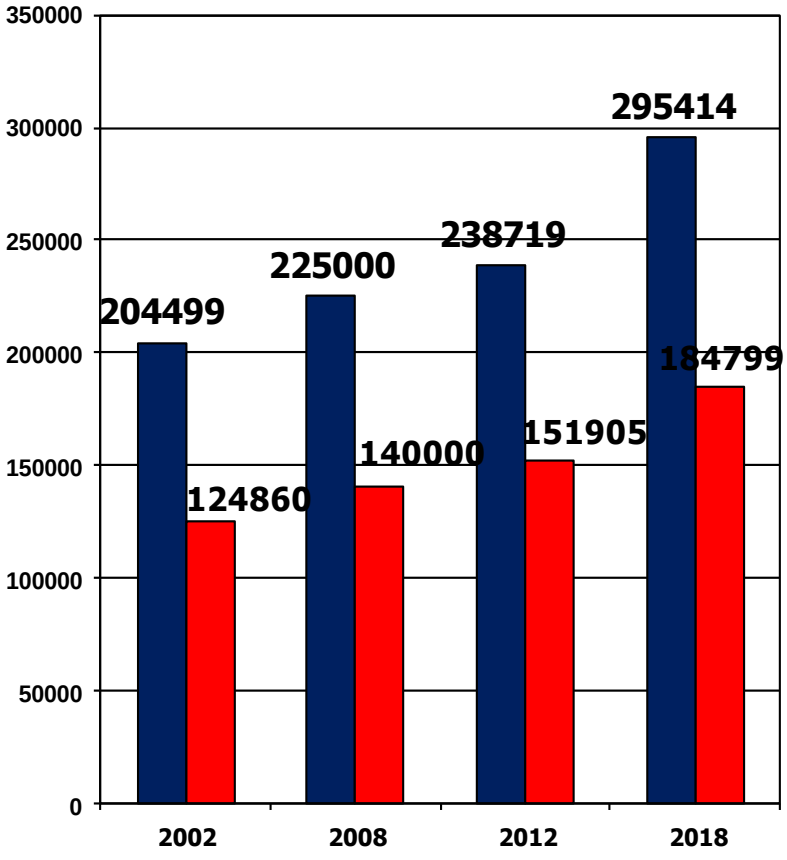
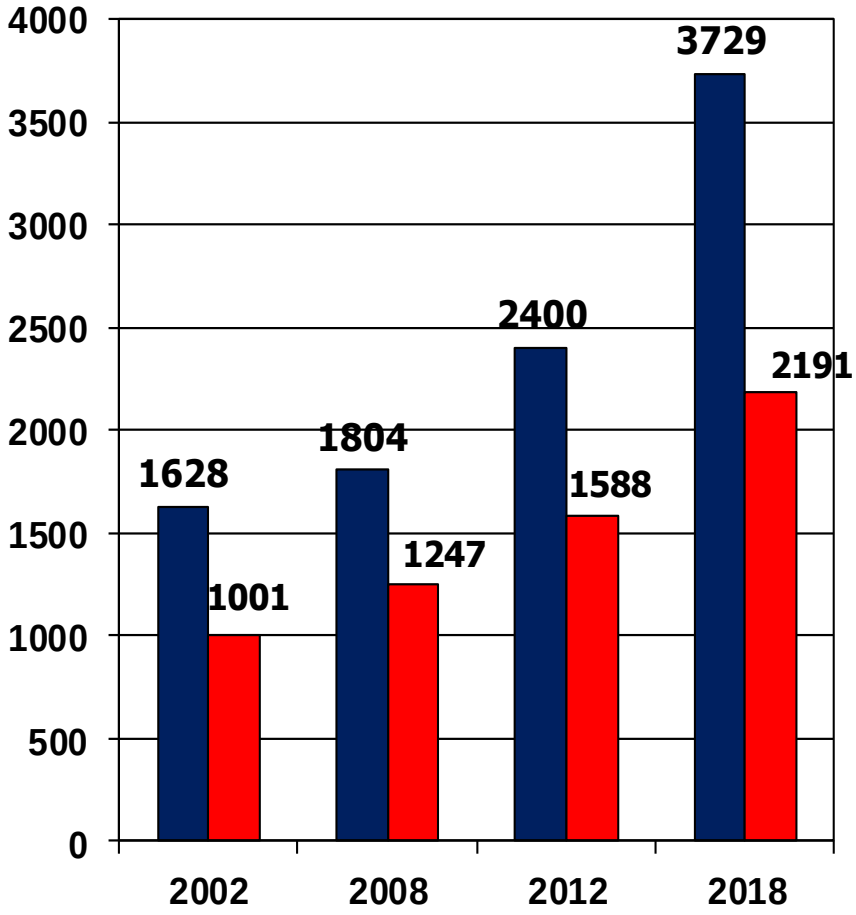
Division of Gynecologic Oncology

OVARIAN CANCER

World



Turkey

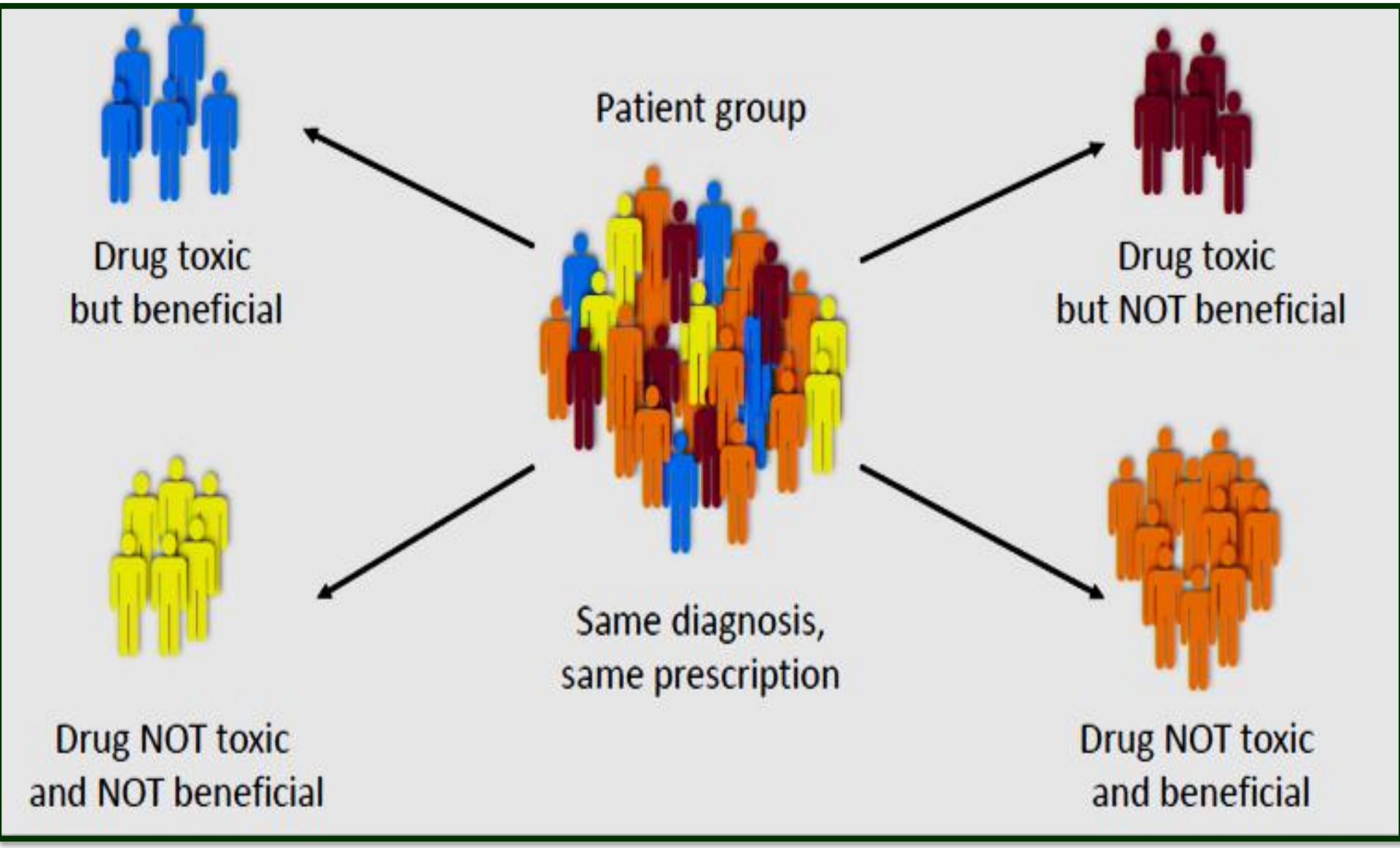


GLOBOCAN

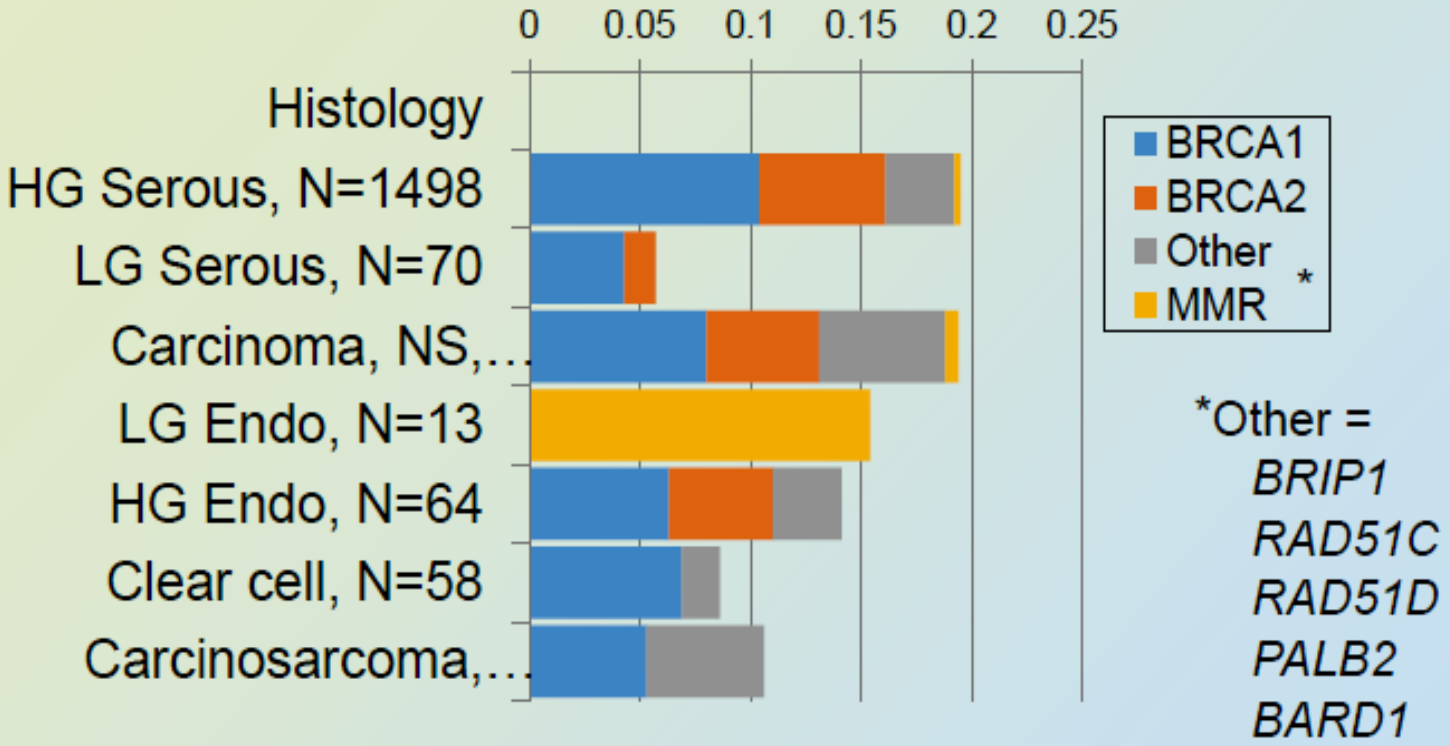
Ovarian Cancer

- No effective screening
- More than 60% stage III-IV
- Gene based risk reduction surgery (BRCA1/2)
- Agressive cytoreduction + chemotherapy(TC)
- Cure rate is 25-30%(5y)

Genomic Profiling, Defining Populations and Determining Clinical Activity of an Agent



OC Mutations by Histology



All women with invasive OC should be offered genetic testing

Norquist et al JAMA Oncol 2016

Therapy depends on:

Patients' factor

(Age, performance)

Tumor factors

(Histology, grade, molecular markers)

Genetic alterations

Surgeon factor

Clinical factors

(Accurate diagnosis, extend of tumor, experienced team, high-volume hospital)

Pre-operative work-up

History-Examination

Lab studies

(cyto, chemical marker… etc)

Imaging (evaluation of paranchimal lesions)

L/S (triage)

(Primary or metastatic

possibility of total resection– Fagotti's, Bristow's,

Leuven-Essen criterias)

M. Petrillo et al. Gyn Oncol 139 (2015) 5-9
Vergote et al. J Clin Ocol Vol 34 No 32 (Nov 10), 2016 Leisewortz et al.Int J Gynecol Cancer 2017

Currently Standard Upfront Therapy in Advanced stage EOC

Debulking surgery (PRM-INT)
Aiming to remove all visible tumor tissue (R0) followed by

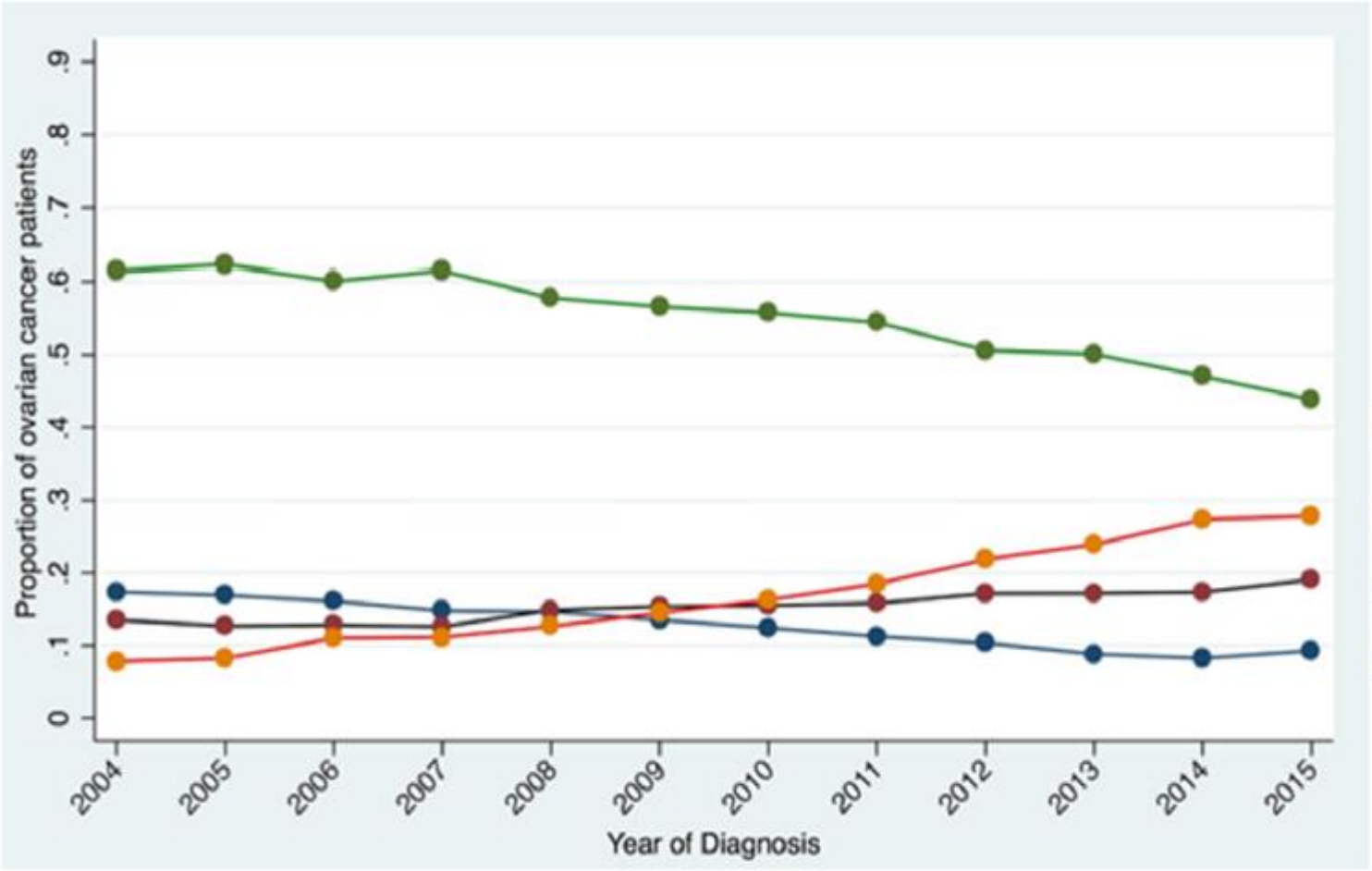
Adjuvant CT with Platinum/Taxane±Bevacizumab

Surgical Paradigm Shift&GCIG

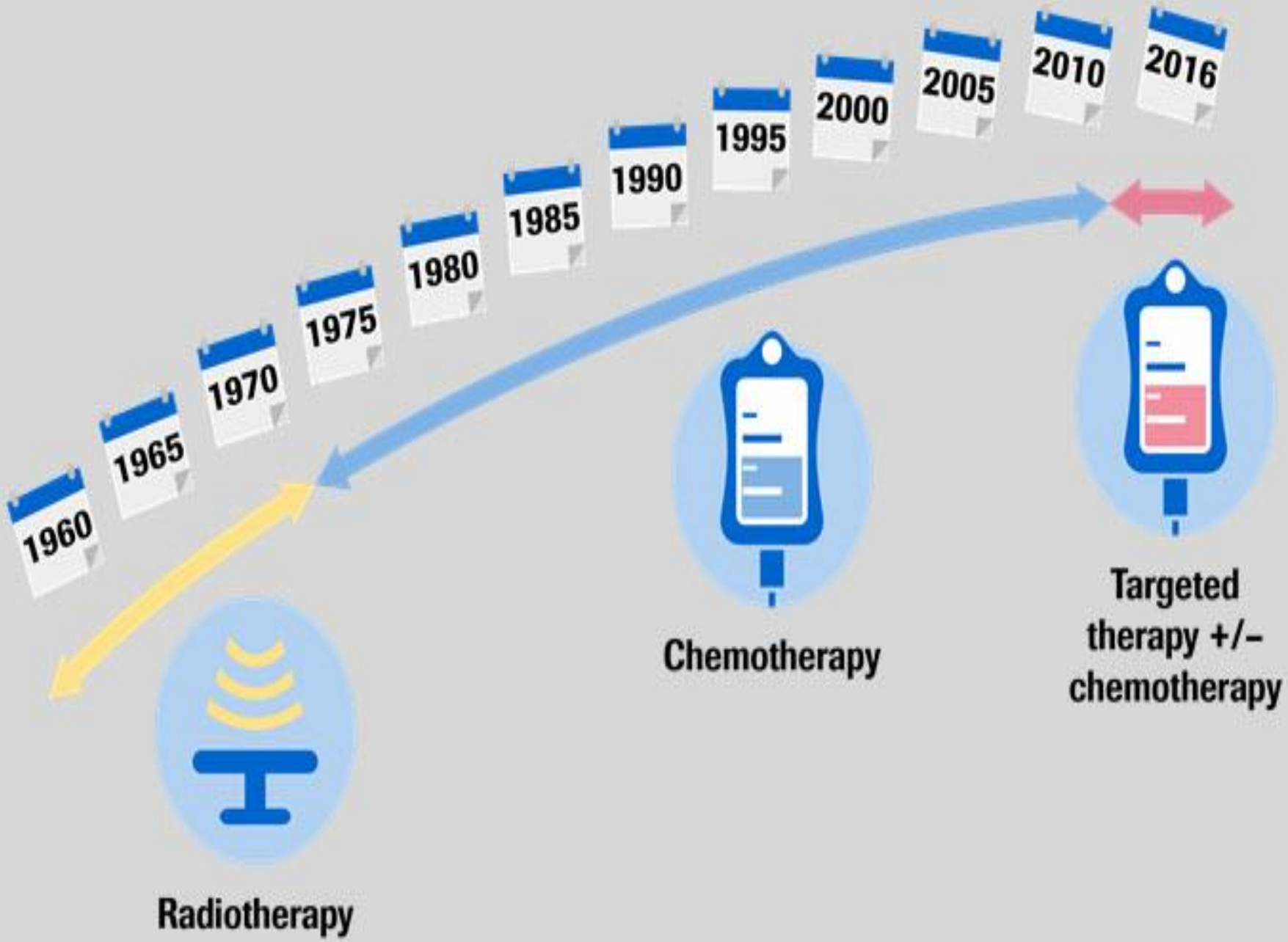
1980 -1990	1990 - 2000	2000 - 2010	2010 - 2017
Low abd. and Pelvic Debulking	Low-Mid. Abdominal Debulking	Upper Abdominal Debulking	Extra-Abdominal Debulking
	• En bloc resections • Colectomy • İleal resections • Mesenteric debulking • Peritenectomy	• Liver resection • Splenectomy • Pancreatectomy • Diaphragma stripping and resection • Celiac and Portal disease	• VATS • Thoracic debulking • CPLND

SUBOPTIMAL	MINIMAL RESIDUAL=LESS THAN 1cm optimal	OPTIMAL and finally COMPLET

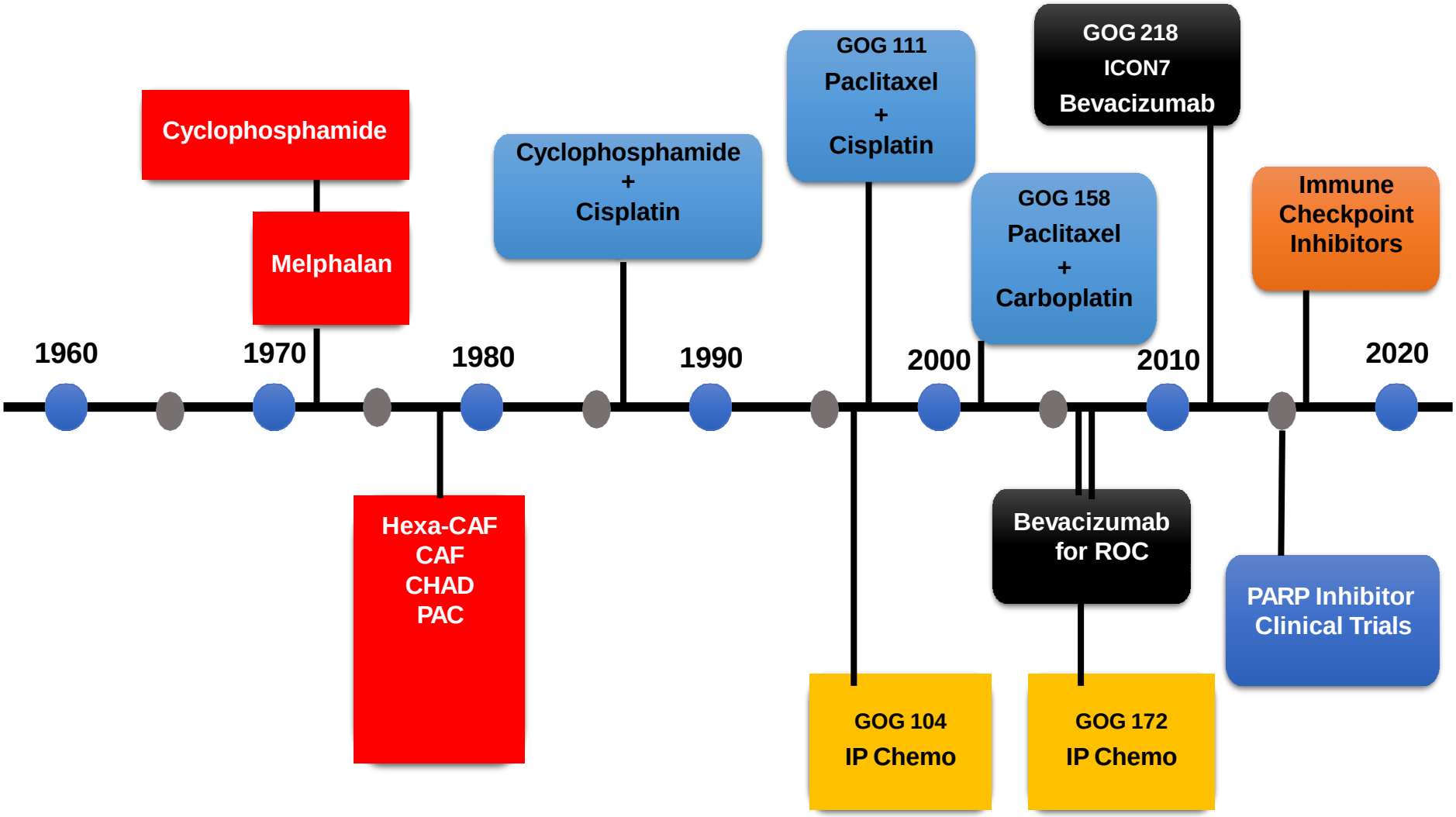
Trends in treatment modalities 2004-2015



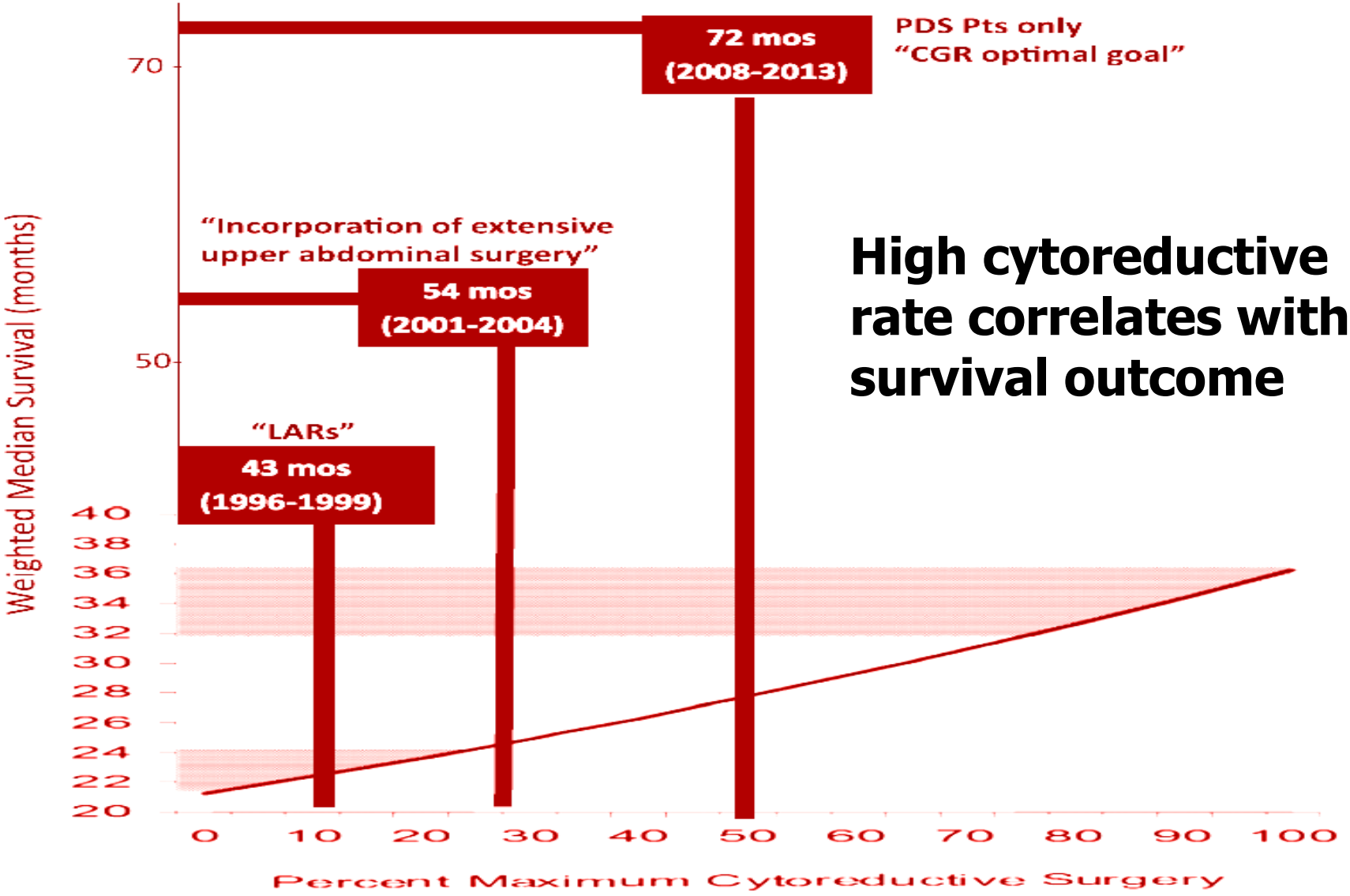
W. Horner et al. / Gynecologic Oncology 154 (2019) 283–289


1960
1965
1970
1975
1980
1985
1990
1995
2000
2005
2010
2016
Radiotherapy
Chemotherapy
Targeted therapy +/– chemotherapy

50 Years of Progress in Epithelial Ovarian Cancer Therapy



MSKCC Primary Cytoreduction OS and CGR Rates



High cytoreductive rate correlates with survival outcome

Leary et al. ESGO Educational Book 2016

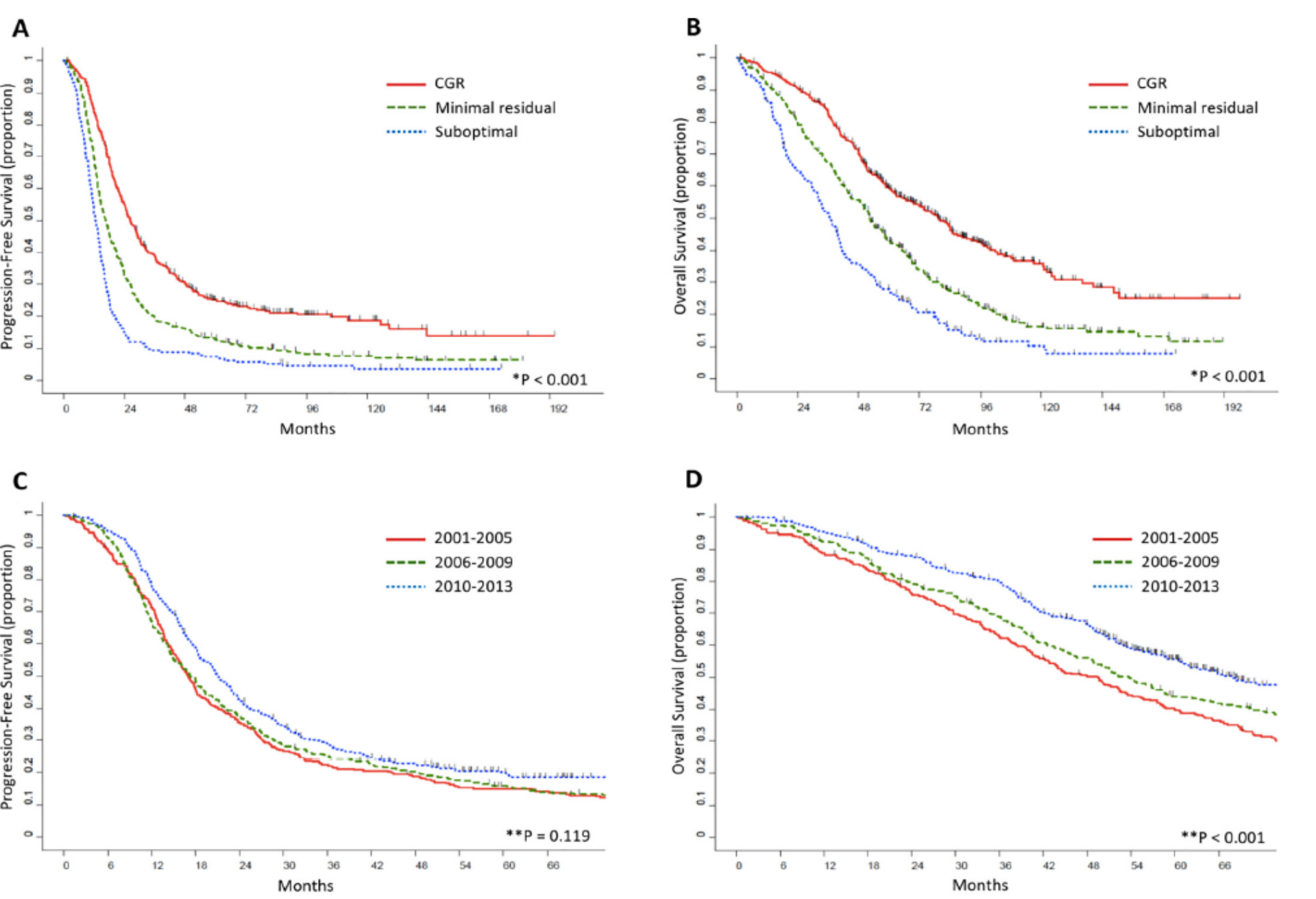
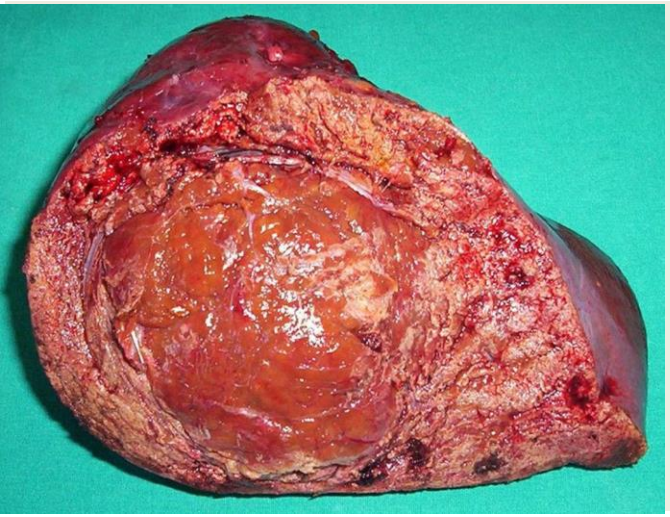
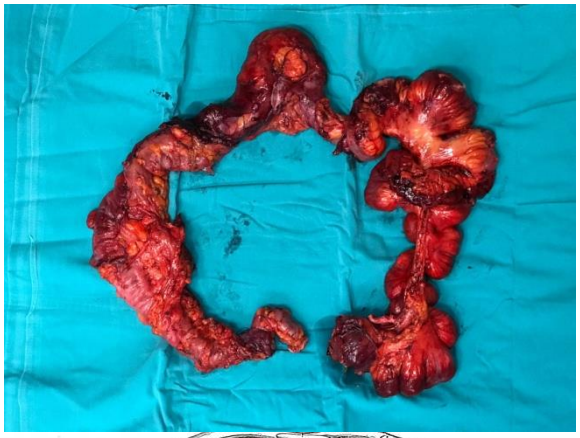
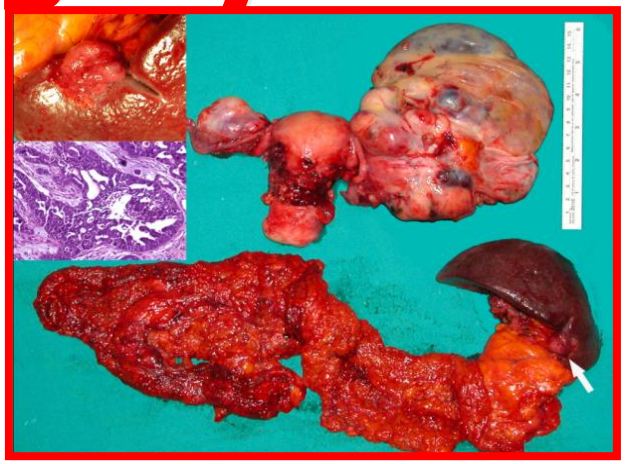


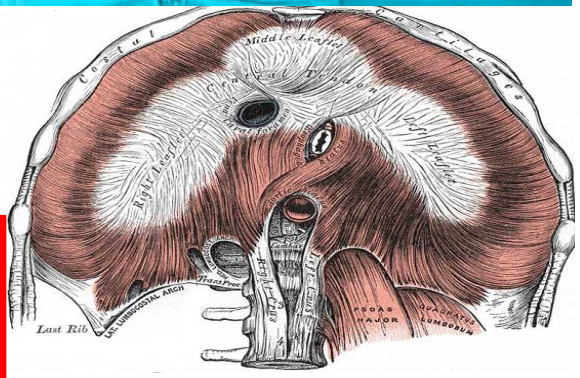
Fig. 1. (A) Progression-free survival and (B) overall survival stratified by residual disease. (C) Progression-free survival and (D) overall survival stratified by PDS-Year group. CGR, residual disease 0 mm; Minimal residual, residual disease 1–10 mm; suboptimal, residual disease >10 mm *Log-rank p value **Chi-square p value at 5-year time point PDS, primary debulking surgery; CGR, complete gross resection.

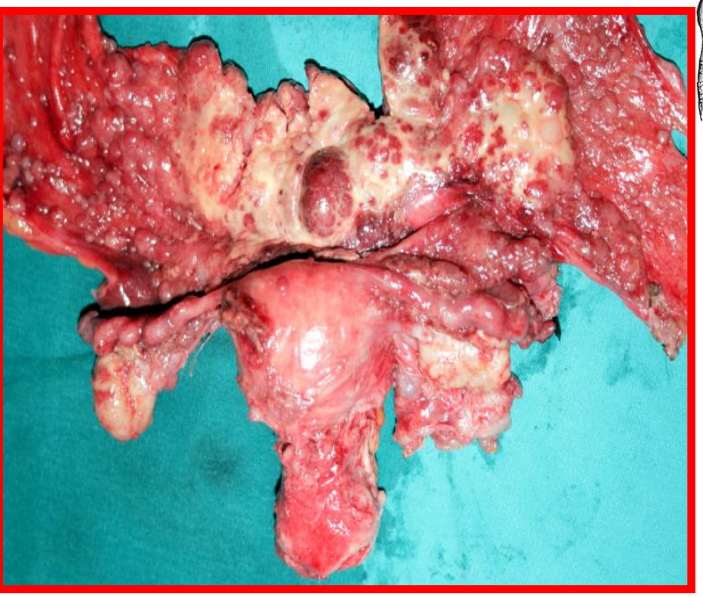
Extended Surgery

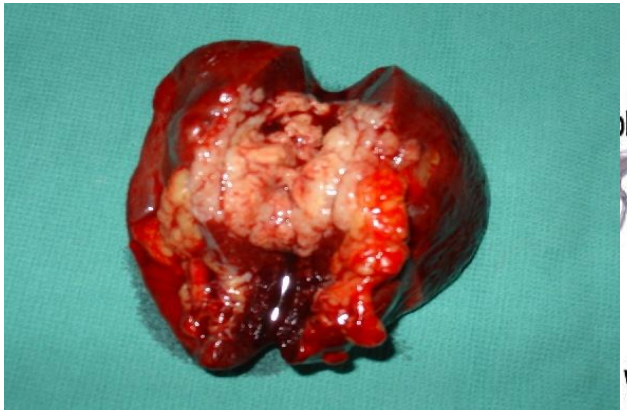


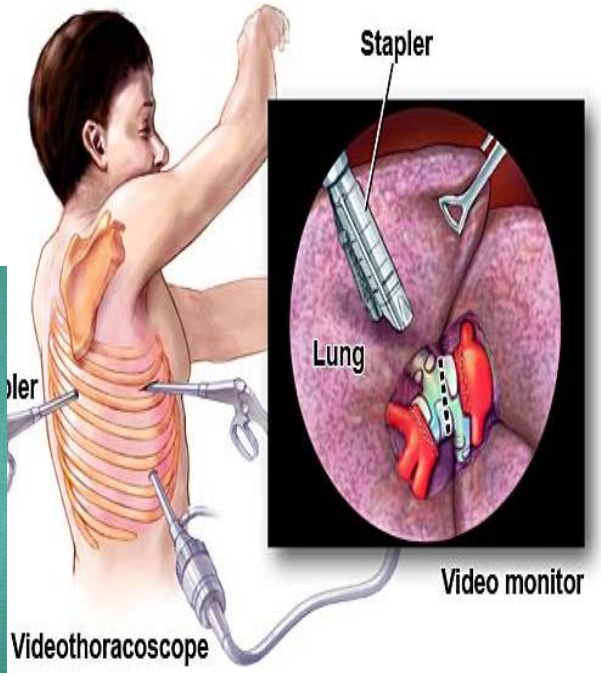


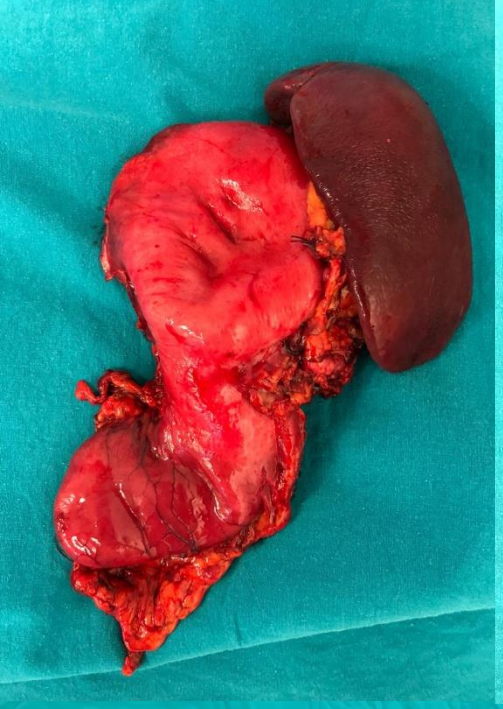
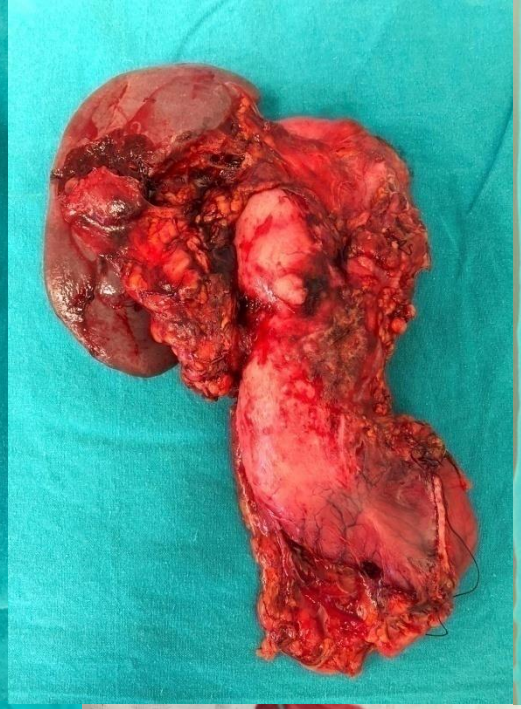
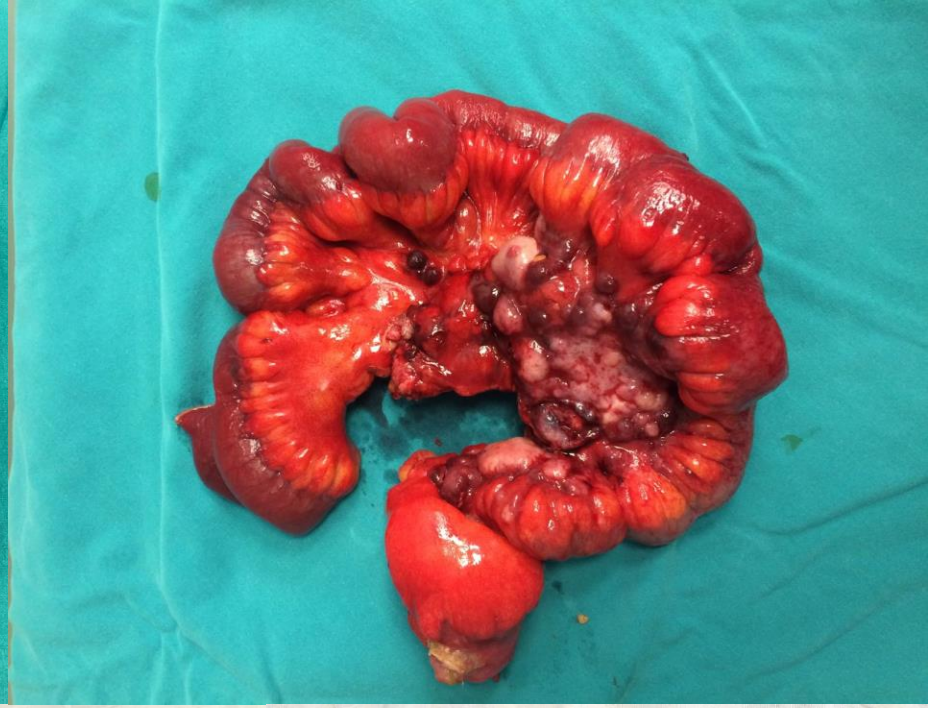
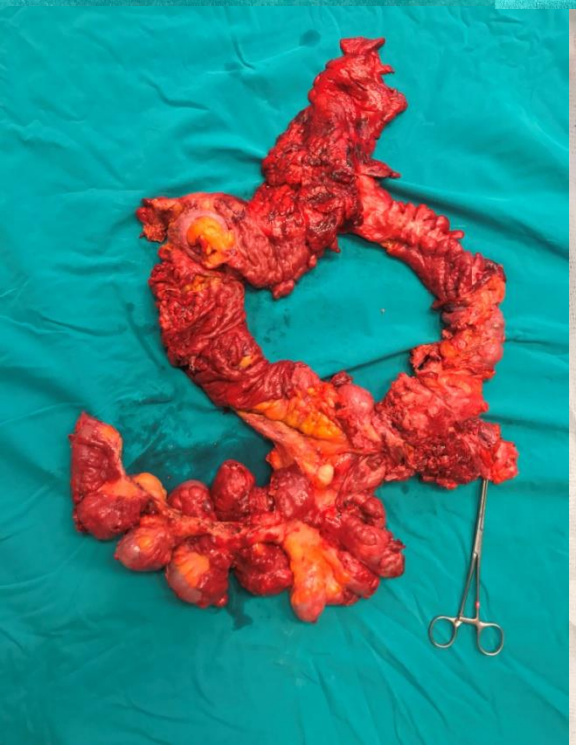
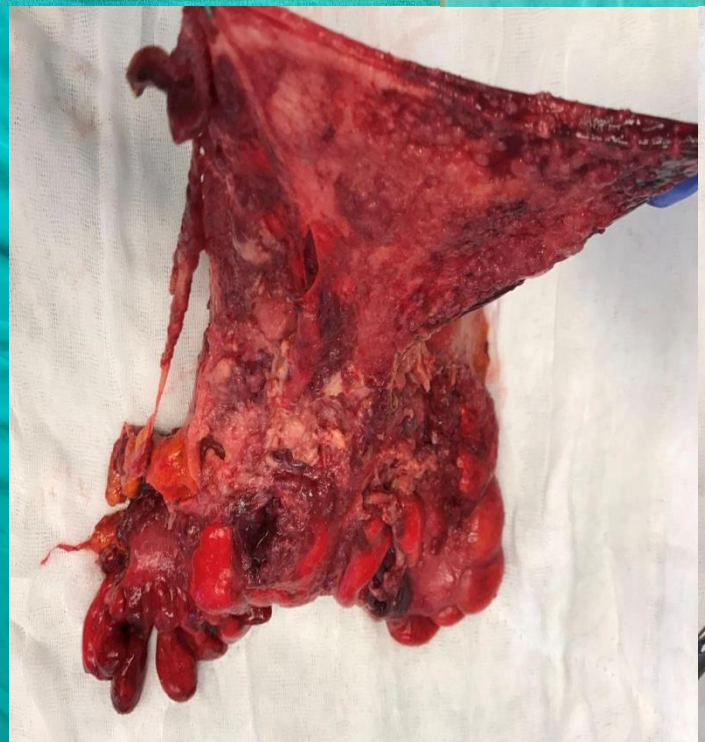
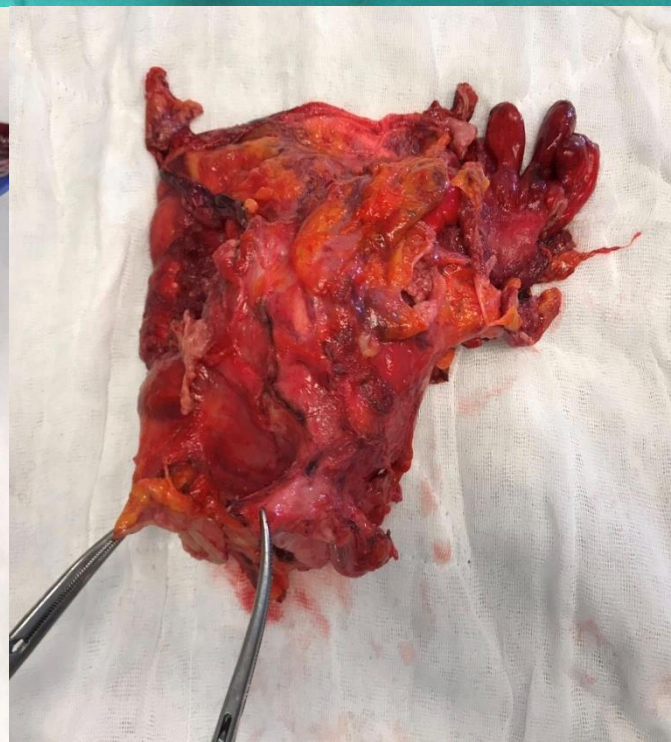


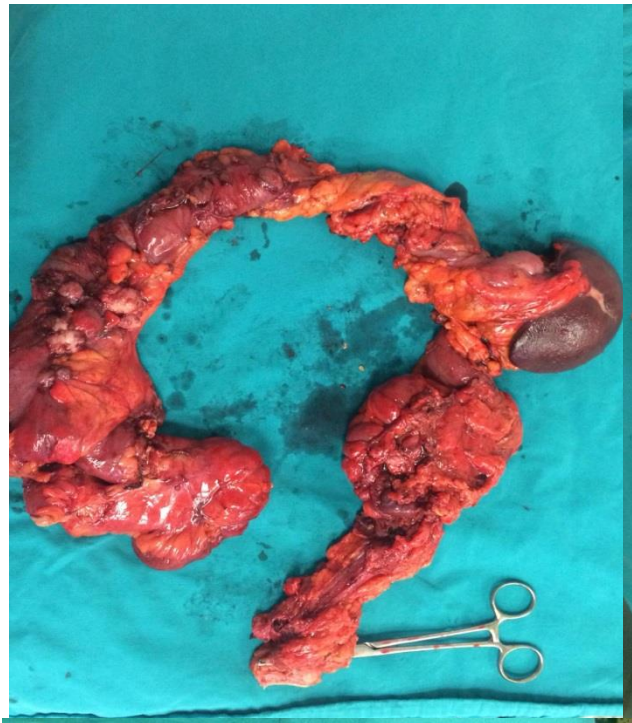
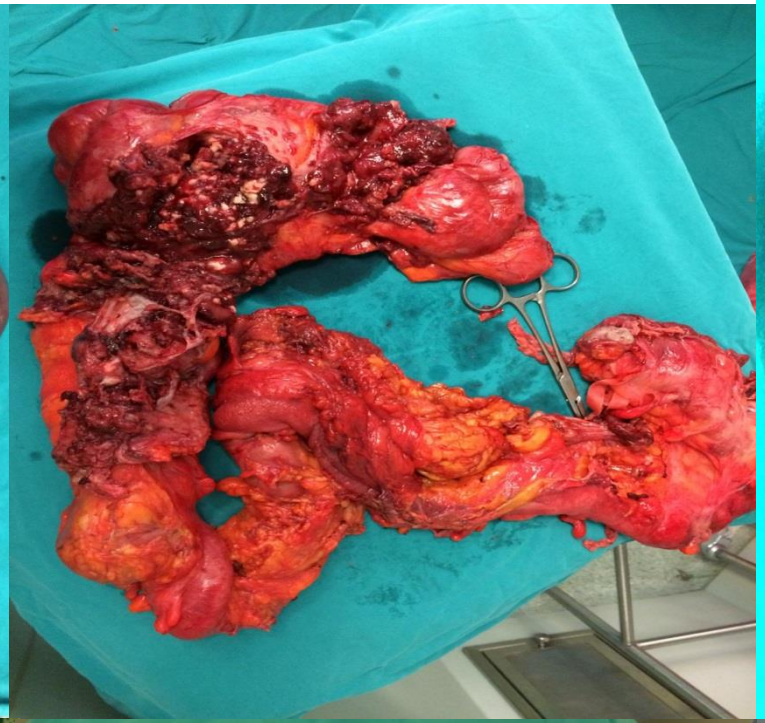
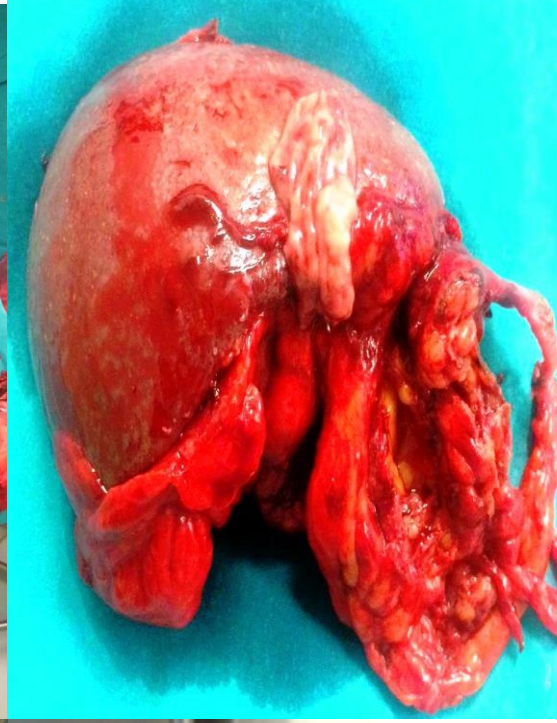
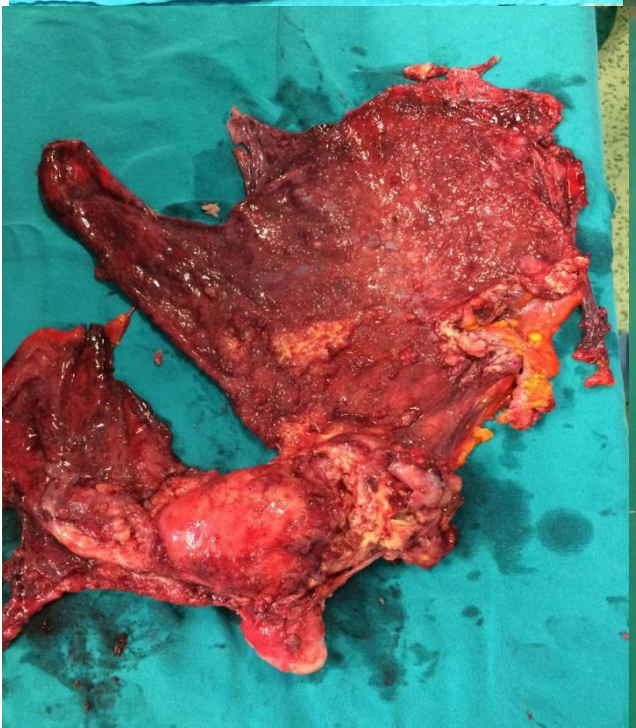
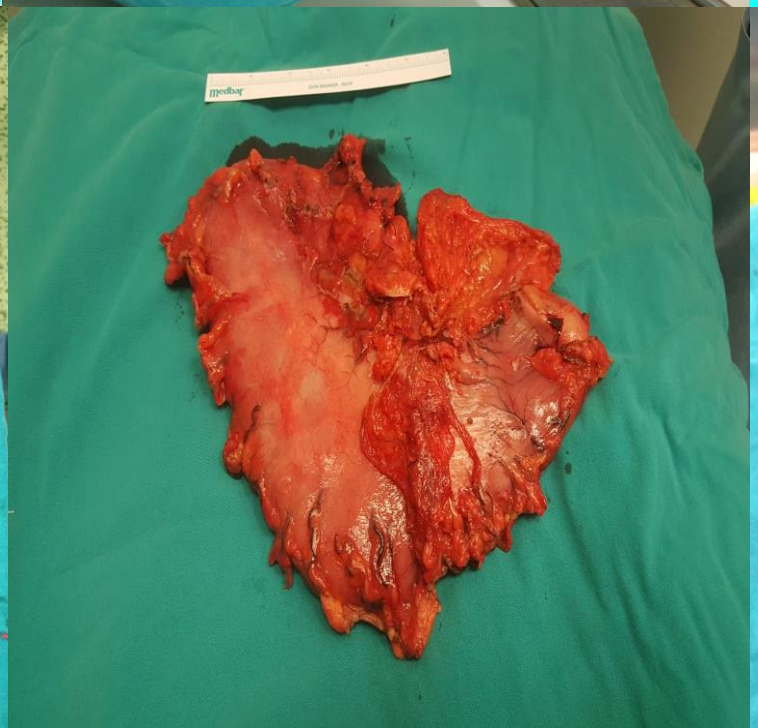
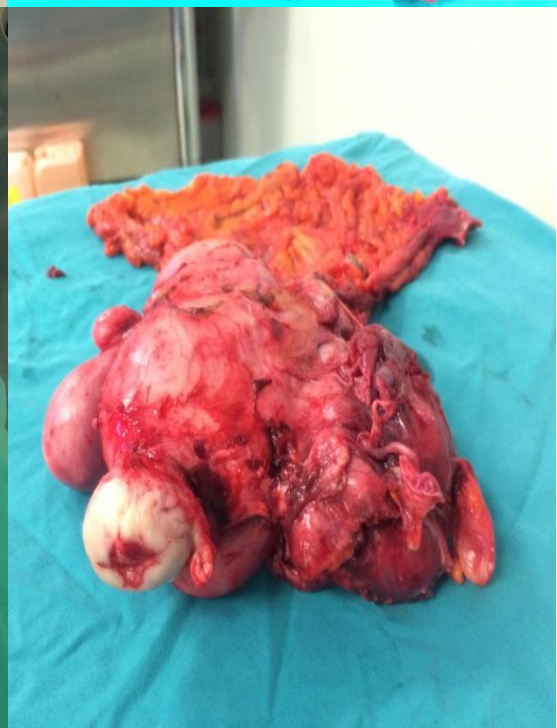




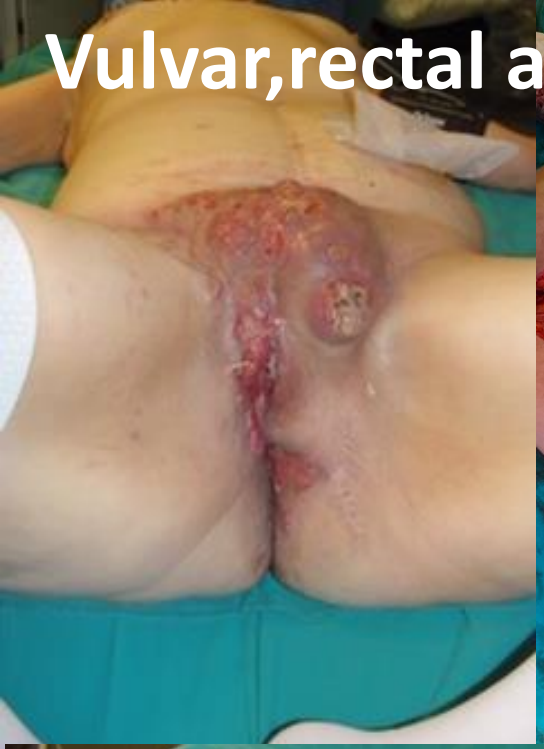


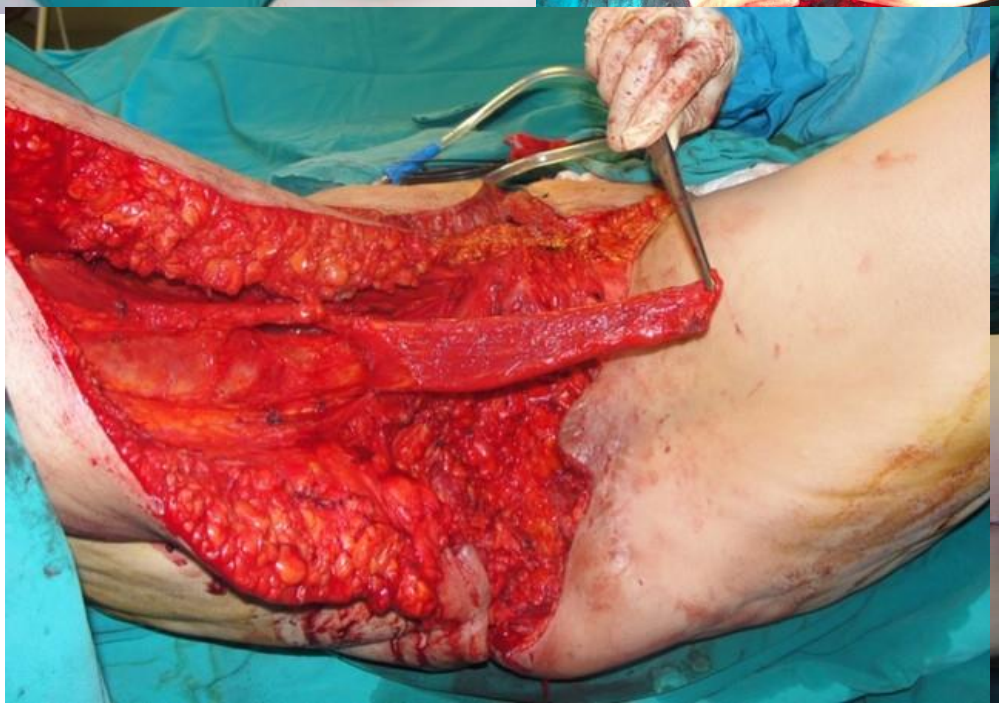


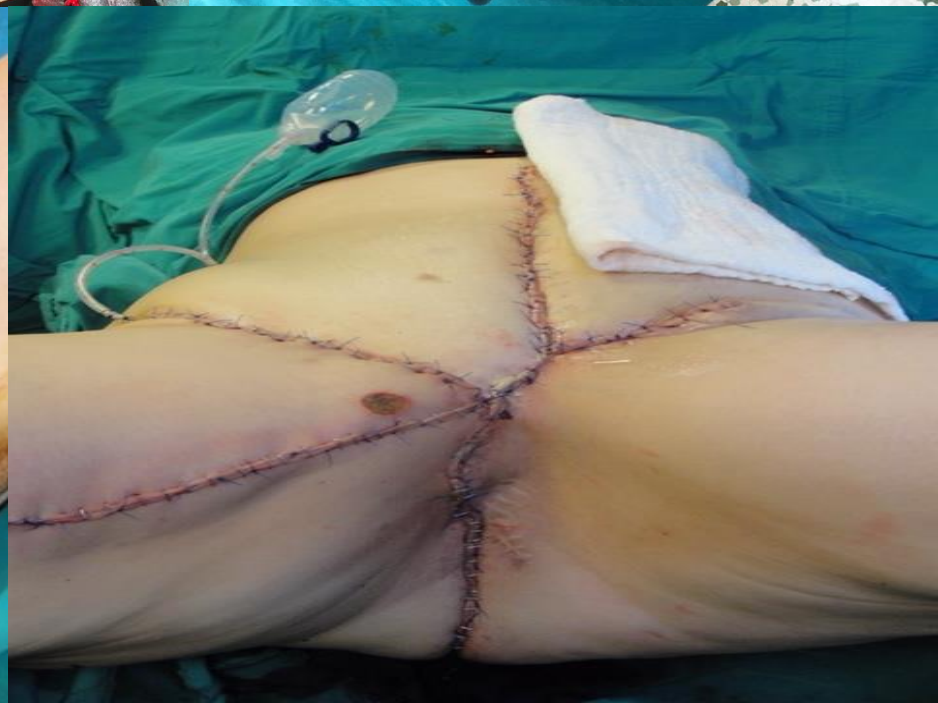







Vulvar,rectal and cystic metastases of ovarian cancer

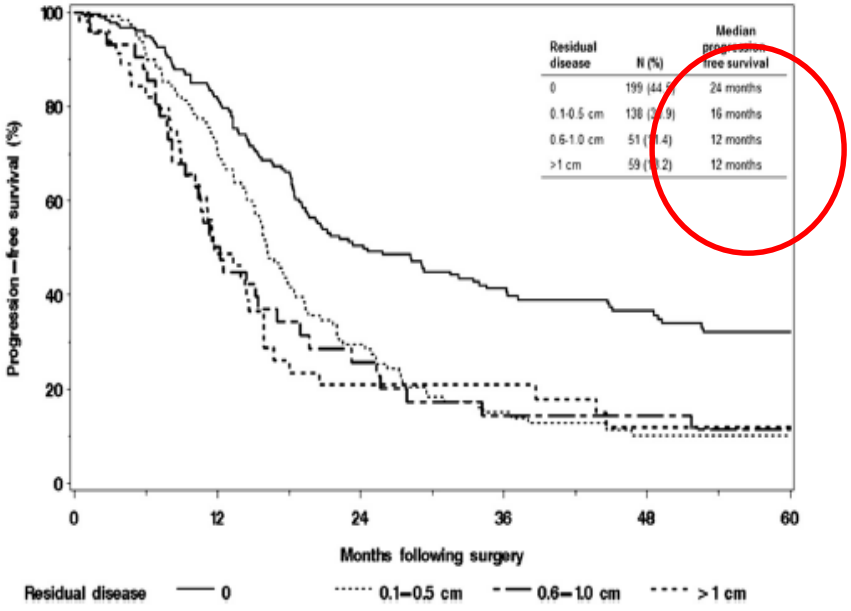


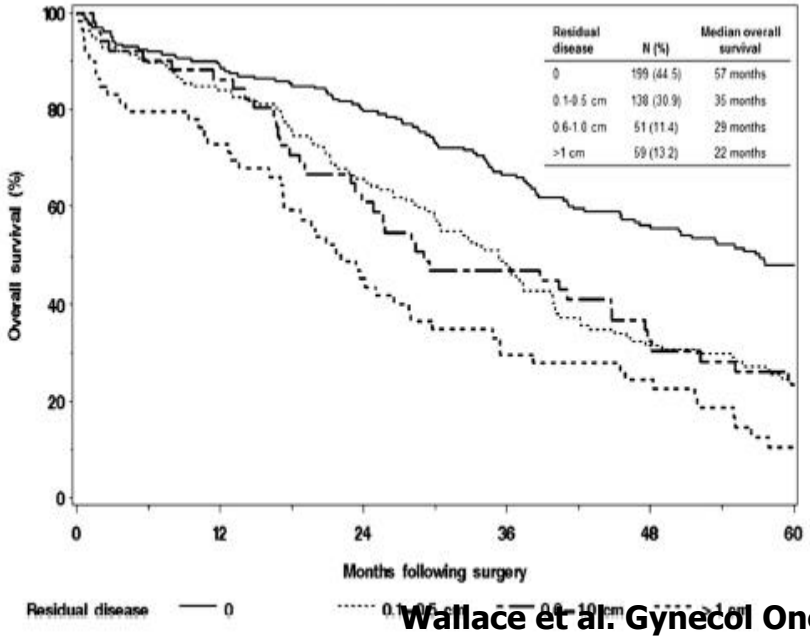




Survival Impact of Optimal Debulking (R0 vs Others)

447 patients	n:	PFS	OAS
RD 0 cm	199	24	57
RD 0.1-0.5 cm	138	16	35
RD 0.5-1 cm	51	12	29
RD > 1 cm	59	12	22





Wallace et al. Gynecol Oncol 2017

Moving beyond "complete surgical resection" and "optimal": is low-volume residual disease another option?

Beryl Manning-Geist MD[a,c], Katherine Hicks-Courant MD[d], Allison Gockley MD[a,b], Rachel Clark MD[c], Marcela del Carmen MD[c], Whitfield Growdon MD[c], Neil Horowitz MD[a,b], Ross Berkowitz MD[a,b], Michael Muto MD[a,b], Michael Worley Jr. MD[a,b]

a Division of Gynecologic Oncology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
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c Division of Gynecologic Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA.
d Department of Obstetrics and Gynecology, Tufts Medical Center, Tufts Medical School, Boston, MA.

PDS: 240

NACT: 270

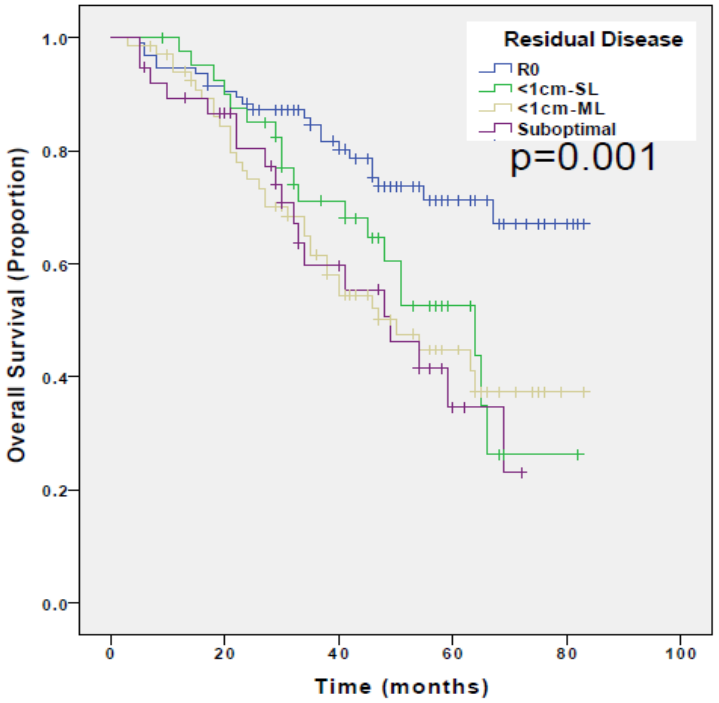
Groups

1. **R0**
2. **≤1cm single location (≤1cm-SL)**
3. **≤1cm multiple location (≤1cm-ML)**
4. **Suboptimal residual (>1cm)**

95 total deaths (39.6%)

- **Median OS**
- **-R0: Not yet reached**
- **-≤1cm-SL: 64 months**
- **-≤1cm-ML: 50 months**
- **-Suboptimal: 49 months**

- **Multiple site metastasis has similar outcome with suboptimal surgery**



Gynecologic Oncology Volum 150, Issue 2, August 2018, Pages 233-238

GOG 182

2655pts with optimal CR(<1cm)

482(18,1%) pts - 590UAP performed

351 (13,1%) diaphragmatic surgery
112 (4,2%) liver surgery
108 (4%) splenectomy
12 (0,5%) pancreatectomy
7 (0,2%) porta hepatis surgery

UAS vs non UAS

PFS : 18,2 vs 14,8 mts (p<0,01)
OAS : 49,8 vs 43,7 mts (p: 0,01)

No RT (n:141) vs Minimal (<1cm) RT (n:341)

OAS : 54,6 vs 40,4 mts (p: 0,0005)

UAS should be performed when no residual tm is attainable

N. Rodriguez et al /Gynecologic Oncology 130(2013) 487-492

Ann Surg Oncol (2019) 26:2943–2951
https://doi.org/10.1245/s10434-019-07516-3

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GYNECOLOGIC ONCOLOGY

Maximal-Effort Cytoreductive Surgery for Ovarian Cancer Patients with a High Tumor Burden: Variations in Practice and Impact on Outcome

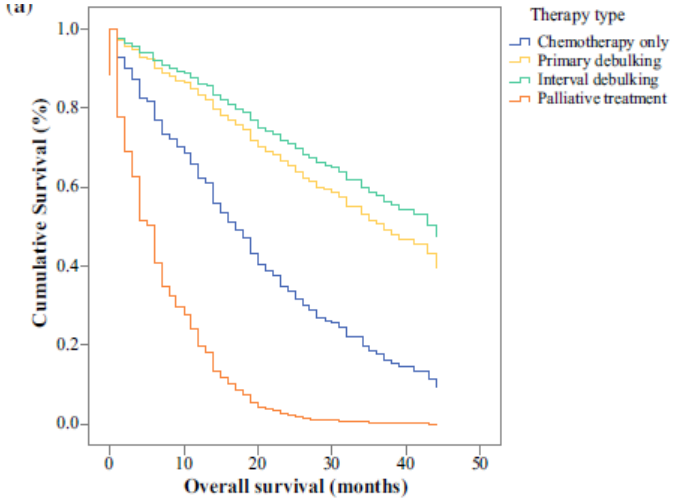
Marcia Hall, MD, PhD[1], Konstantinos Savvatis, MD, PhD[2,3], Katherine Nixon, MD[4], Maria Kyrgiou, MD, PhD[4], Kuhan Hariharan, MD[1], Malcolm Padwick, MD[5], Owen Owens, MD[5], Paula Cunnea, MD, PhD[4], Jeremy Campbell, MD[6], Alan Farthing, MD[4], Richard Stumpfle, MD[6], Ignacio Vazquez, MD[1], Neale Watson, MD[7], Jonathan Krell, MD, PhD[4], Hani Gabra, MD, PhD[4,8], Gordon Rustin, MD, PhD[1], and Christina Fotopoulou, MD, PhD[4,6]

[1]Mount Vernon Cancer Centre, Northwood, Middlesex, UK; [2]Inherited Cardiovascular Diseases Unit, Barts Heart Centre, London, UK; [3]William Harvey Research Institute, Queen Mary University, London, UK; [4]Department of Surgery and Cancer, Imperial College London and West London Gynecological Cancer Centre, Imperial College NHS Trust, London, UK; [5]West Hertfordshire Gynaecological Cancer Centre, WHH NHS Trust, Watford, UK; [6]Department of Anaesthetics, Centre for Perioperative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, Ham House, Hammersmith Hospital, London, UK; [7]Department of Gynaecology, Hillingdon Hospital, Uxbridge, UK; [8]Early Clinical Development, IMED Biotech Unit, AstraZeneca, Cambridge, UK

- Retrospective ,stage 3 –IV EOC
- 249 pts high burden of tm,diseminated
- 2 centers

Variable	HR	95 % CI	p
Histology (serous vs non-serous)	1,6	1,04-2,61	0,031
ECOG-status (3/4-1/2)	1,9	1,15-3,13	0,012
Primary surgery vs Chemothepahy alone	0,39*	0,22-0,67	0,001
İDS vs Chemo alone	0,315*	0,188-0,52	<0,001
Palliative alone vs chemo alone	3,43	1,51-7,81	0,003

*Protective



- CRS requies more complex procedures
- More resources
- Longer hospital stay
  BUT
- Better OS

Liver resection

- **İn selected patients**

  Sytemic tumor burden low
- **Generally superficial metastases**
- **Limited size of tm**
- **More than 1 cm in depth**

multisegmenter metastases[×]

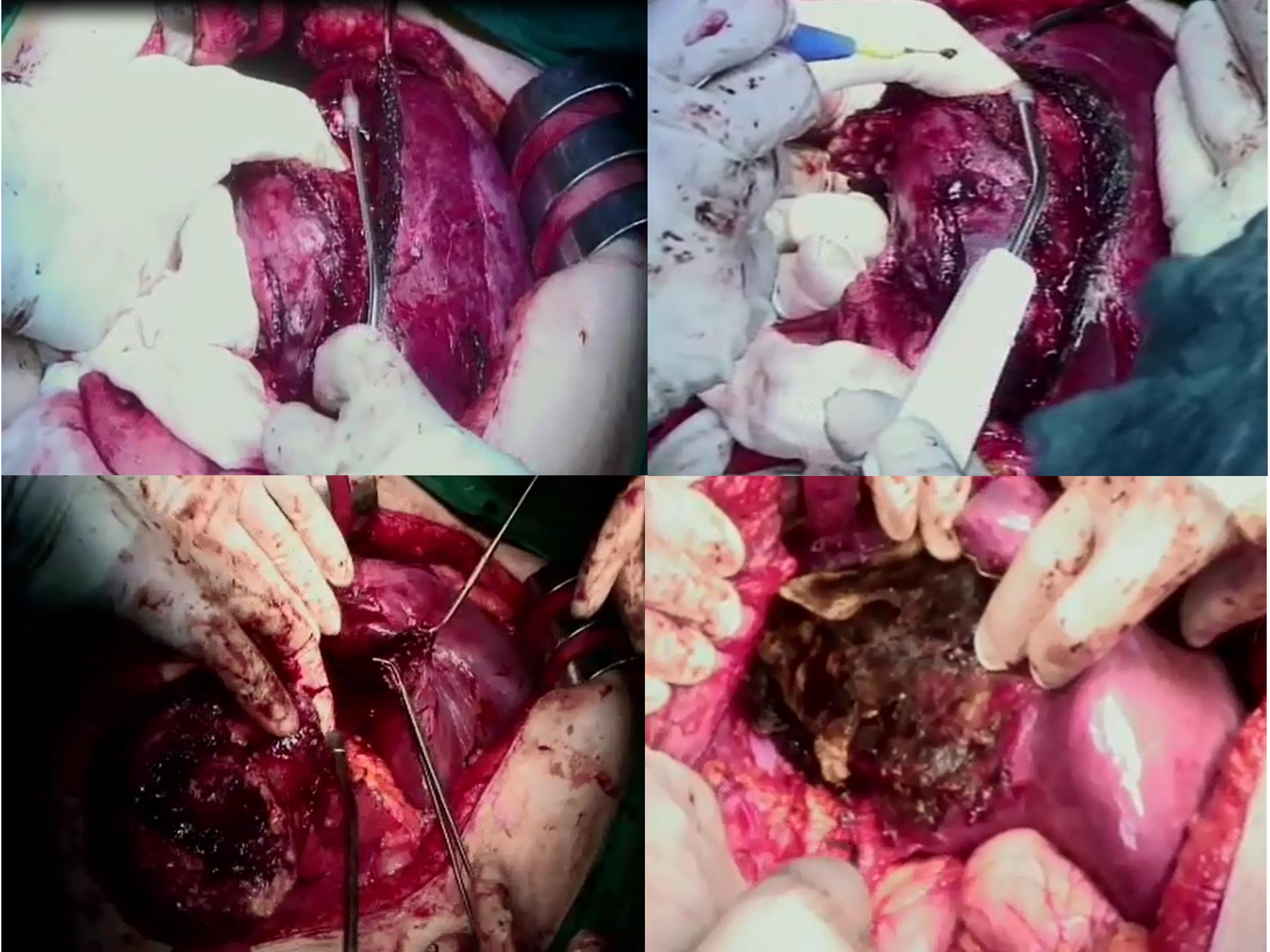
[×]İf needed call hepatobilier surgeon

Liver resection vs Overall Survival

Liver resection ×	OS months
RO LR	50,1 m
Non-RO	20,0 m
Unresectable	10 m

×must be tumor free border

Hepatobilier surgery 2019 8 (2) 129-137



Survival Impact of Liver Resection in EOC

Study	Ptx N	Optimal CRS (%)	Negative Resection Margin (%)	OS (m)
Meredith et al (2003)	26	80,8	NA	26,3 Optimal 27,3 Suboptimal 8,6
Yoon et al (2003	24	66,7	54,1	62
Loizzi et al (2005)	29	NA	NA	25
Abood et al (2008)	10	100	50	33
Pekmezci et al (2010)	8	NA	100	24
Roh et al (2010)	18	66,7	66,7	38 (3-78)
Niu et al (2012)	60	NA	90	39 (5-79)
Neumann et al (2012)	70	NA	NA	Optimal 42 Suboptimal 4,6
Kolev et al (2014)	27	92,6%	88,9	56 (12-249)

Gasparri et al., J Cancer Research Clin Oncol Dec 2015
Hacker et al Best Practice & Research Clinical Obstetrics & Gynaecology Volume 41, May 2017, Pages 71-87

The influence of splenic metastases on survival in FIGO stage IIIC epithelial ovarian cancer.

Ayhan A[1], Al RA, Baykal C, Demirtas E, Ayhan A, Yüce K. Int J Gynecol Cancer. 2004 Jan-Feb;14(1):51-6.

N:34 (IIIC EOC) Splenic Metastasis	N	Overall median survival
Present	18	28.9
Absent	16	41.3

Survival Impact of Splenectomy

N:131	N	OAS%	DFS%
Splenectomy	33	66,6	30,3
No splenectomy	99	59,6	33,3

Splenic met prevelance : 2,3-7,1%
Incidence up to 20% in autopsies

Zapardel et al; Intenational Journal of Gynecological Cancer, vol 22,2012

Survival Impact of Diaphragmatic Surgery

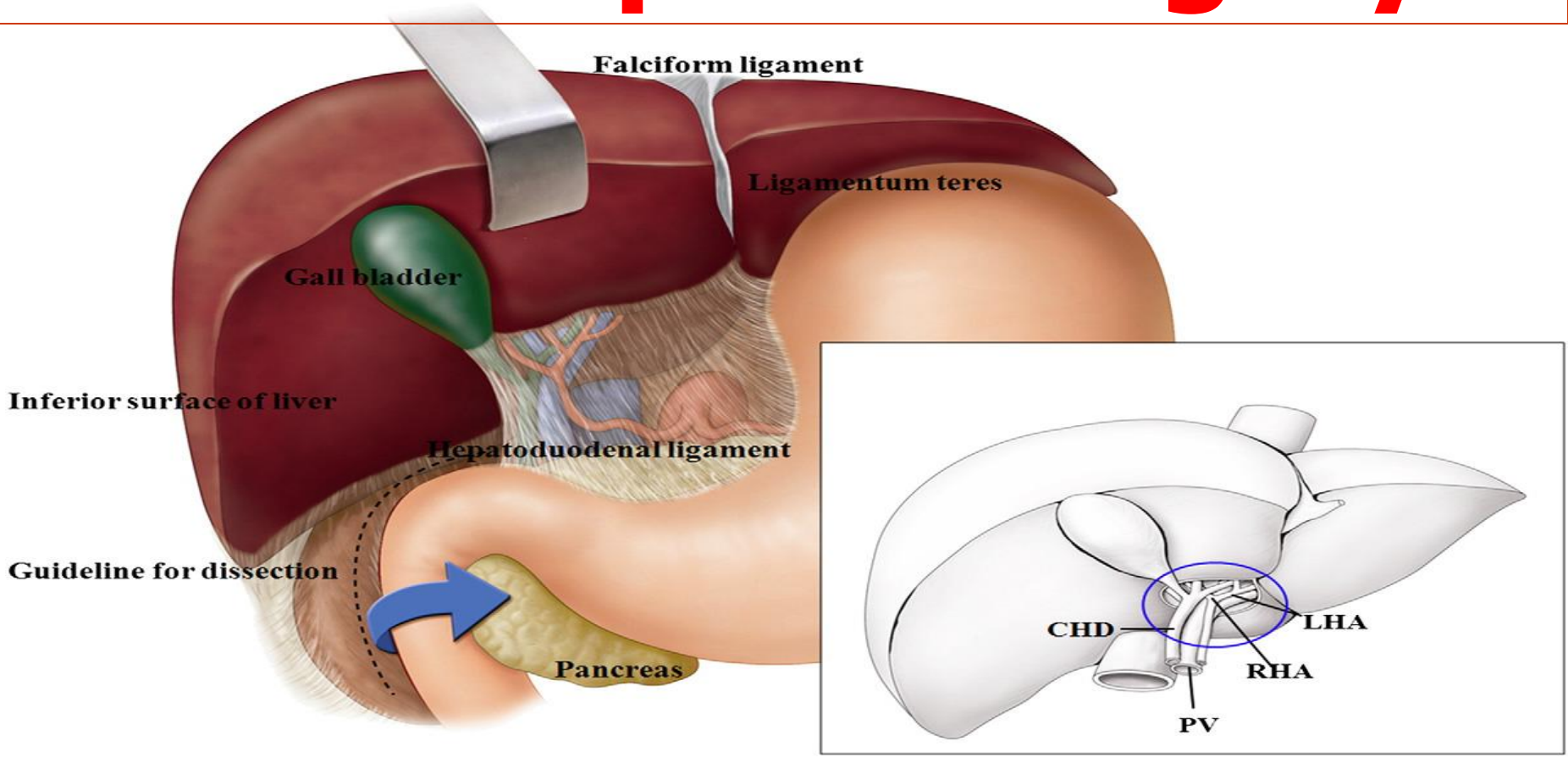
	Surgery OS	Non surgery OS
Aletti et al 2006	% 55	% 28
Muallem et al 2016	28 m	29 m

Diafragmatic resection has better DFS than stripping but no OS advantage

.

Zapardiel et al İnt Journal of Gyn Cancer. 21(9):1698–1703, DEC 2011
Muallem et al ANTICANCER RESEARCH 36: 4707-4714 (2016)
Aletti et al Gynecol Oncol. 2006 Feb;100(2):283-7. Epub 2005 Sep 22
Pounds et al j.ejogrb 2018.05.24

Porta Hepatis Surgery



11 patients, heterogenous history of disease

Multidisciplinary approach for prevention of morbidity

Limited number direct survival effect is unclear

Indirectly YES

Y.J. Song et al. / Gynecologic Oncology 121 (2011) 253–257

What is Survival impact of Optimal Debulking Surgery in Stage IV Ovarian

Study	Optimal debulking n (%)	Criteria (cm)	Optimal Median OS* (m)	Suboptimal Median OS* (m)
Curtin et al 1997	41 (45)	≤2	40	19
Liu et al 1997	14 (30)	≤2	37	17
Munkarah et al 1997	31 (31)	≤2	25	15
Bristow et al 1999	25 (30)	≤1	38	10
Akahira et al 2001	70 (31)	≤2	32	16
Aletti et al 2008	50 (46)	≤1	37	16
Winters et al 2008	78 (22)	0.1-1	29	20

* All SS

Curr Treat Options in Oncol 2016; 17:1

What is the Limitation of PDS according to Metastatic Sites and Dissemination

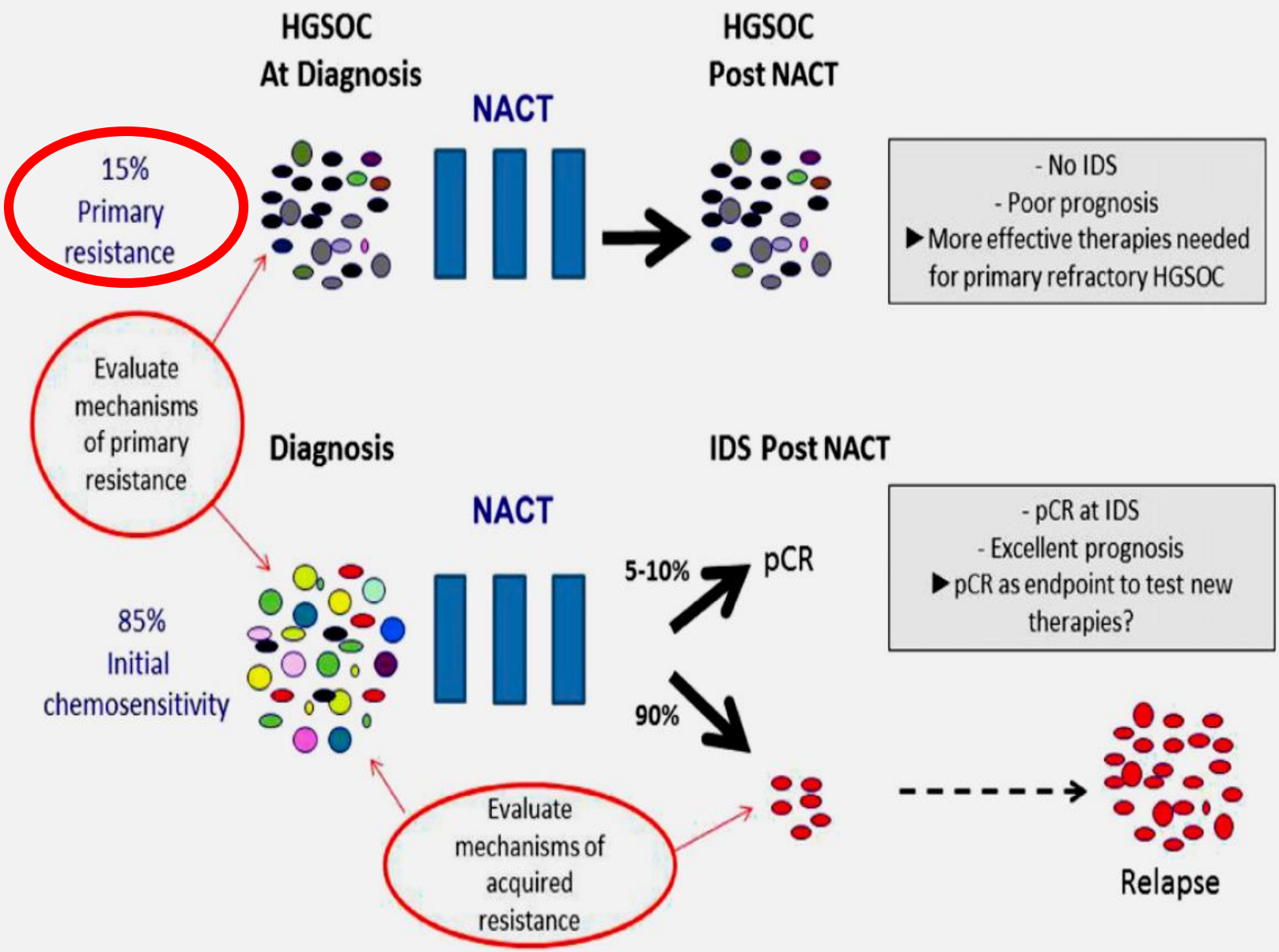
658 patients
578 upfront surgery
191 had residual disease
p: 0.001

Residue	OAS (months)
R0	56
0-10 mm	32
>10 mm	17

Location of Residuel Tm	ALL N:191	TR 1-10 mm N:144 (75,4%)	TR>10 mm N:47 24,6%	p
Small intestine	150(79,8%)	124(87,9%)	26(55,3%)	<0.001
Portahepatis Lig.hepatoduodenale	19(10,1%)	7(5%)	12(25,5%)	<0.001
Multisegmental Parenchymal Liver met.	8(4,3%)	1(0,7%)	7(14,9%)	<0.001
Supradiaphragmatic	25(14,9)	21(14,9%)	7(14,9%)	1.000
Pancreas	15(8%)	4(2,8%)	11(23,4%)	<0.001
Stomach	6(3,2%)	2(1,4%)	4(8,5%)	0.035
T.coeliacus	5(2,7%)	2(1,4%)	3(6,4%)	0.101

Heitz et al Gynecol Oncol 2016 May;141(2):264-70

NACT Setting: A Translational Research Oppurtinity



Leary et al. ESGO Educational Book 2016

PDS vs IDS in Stage III or IV

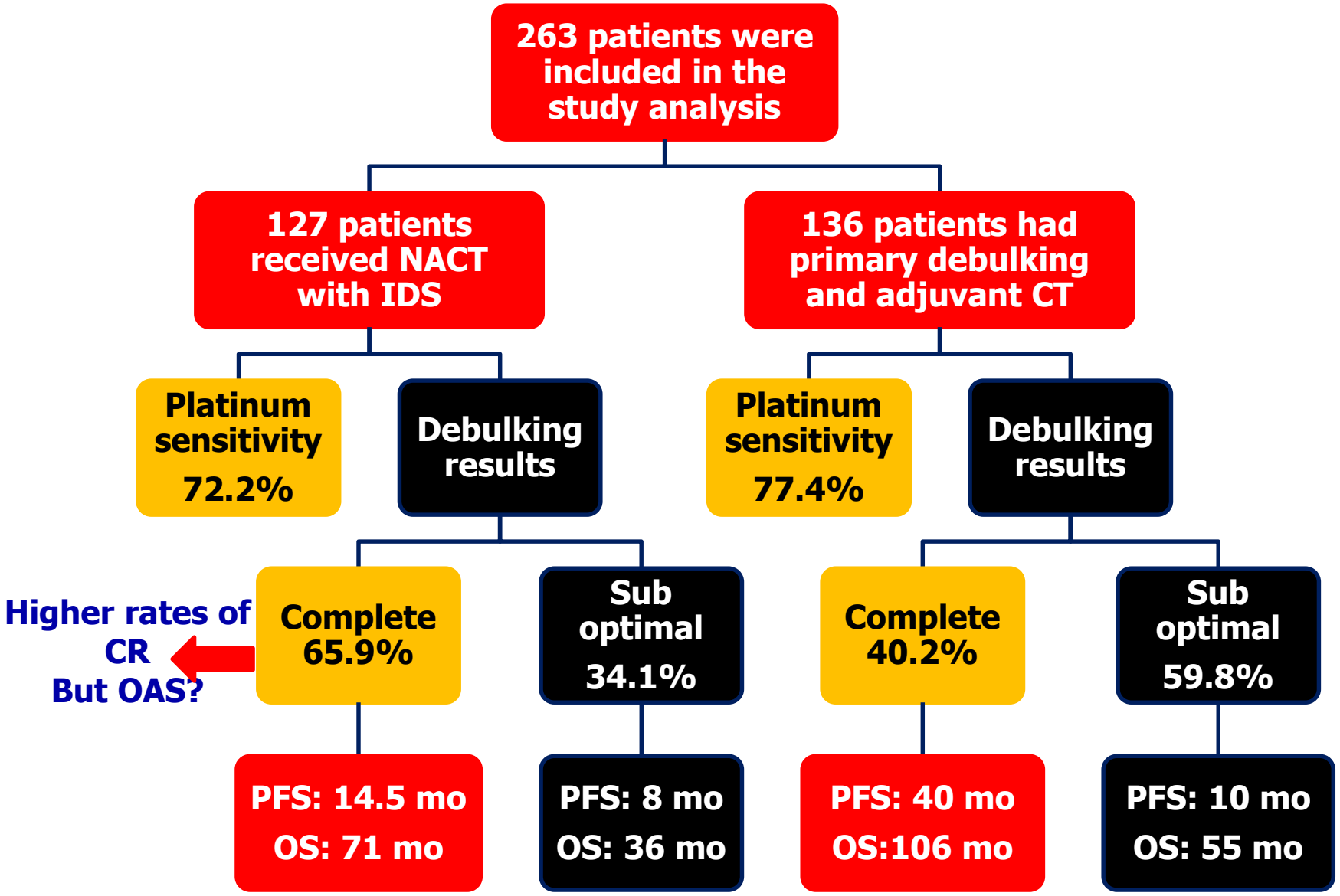
Year Study	Primary Endpoint	Study Arm	n	Stg IV (%)	No Residual (%)	PFS (Months)	OAS (months)
2016 Scorpion (Fagotti's)	OS	NACT	87	7	58	15	NR
		PCS	84	15	46	14	41
2015 CHORUS	OS	NACT	274	25	39	12.0	24.1
		PCS	276	25	17	10.7	22.6
2014 JCOG 0602	OS	NACT	152	30	63	16.4	44.3
		PCS	149	32	30	15.1	49
2010 EORTC 5591	OS	NACT	334	24	51	12	30
		PCS	336	23	19	12	29

Wright et al. Gynecol Oncol 143 (2016) 3-15

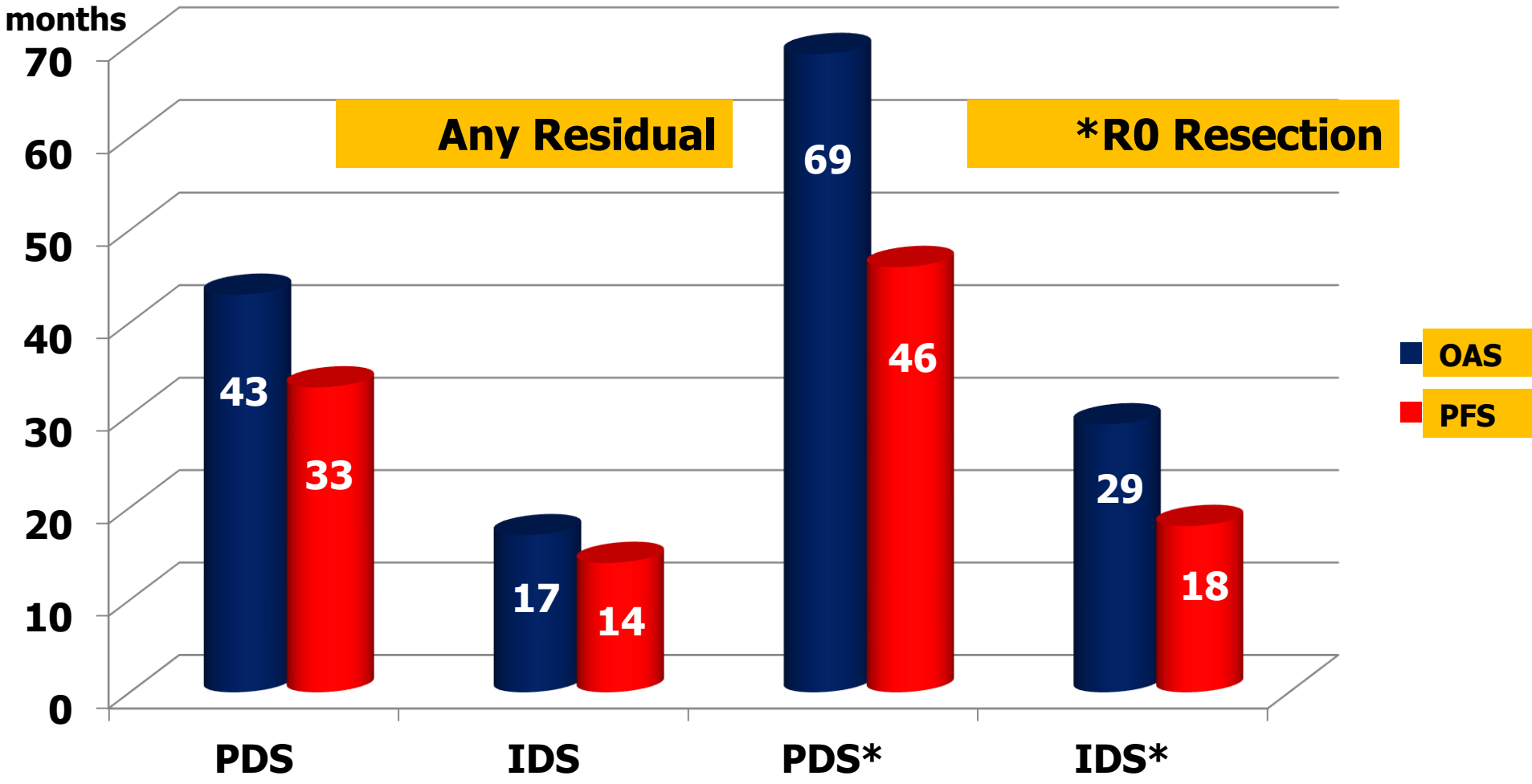
Clinical outcome of neoadjuvant chemotherapy for advanced ovarian cancer☆

Roy Kessous, Ido Laskov, Jeremie Abitbol, Joanna Bitharas, Amber Yasmeen, Shannon Salvador, Susie Lau, Walter H. Gotlieb *

Gynecologic Oncology 144 (2017) 474–479



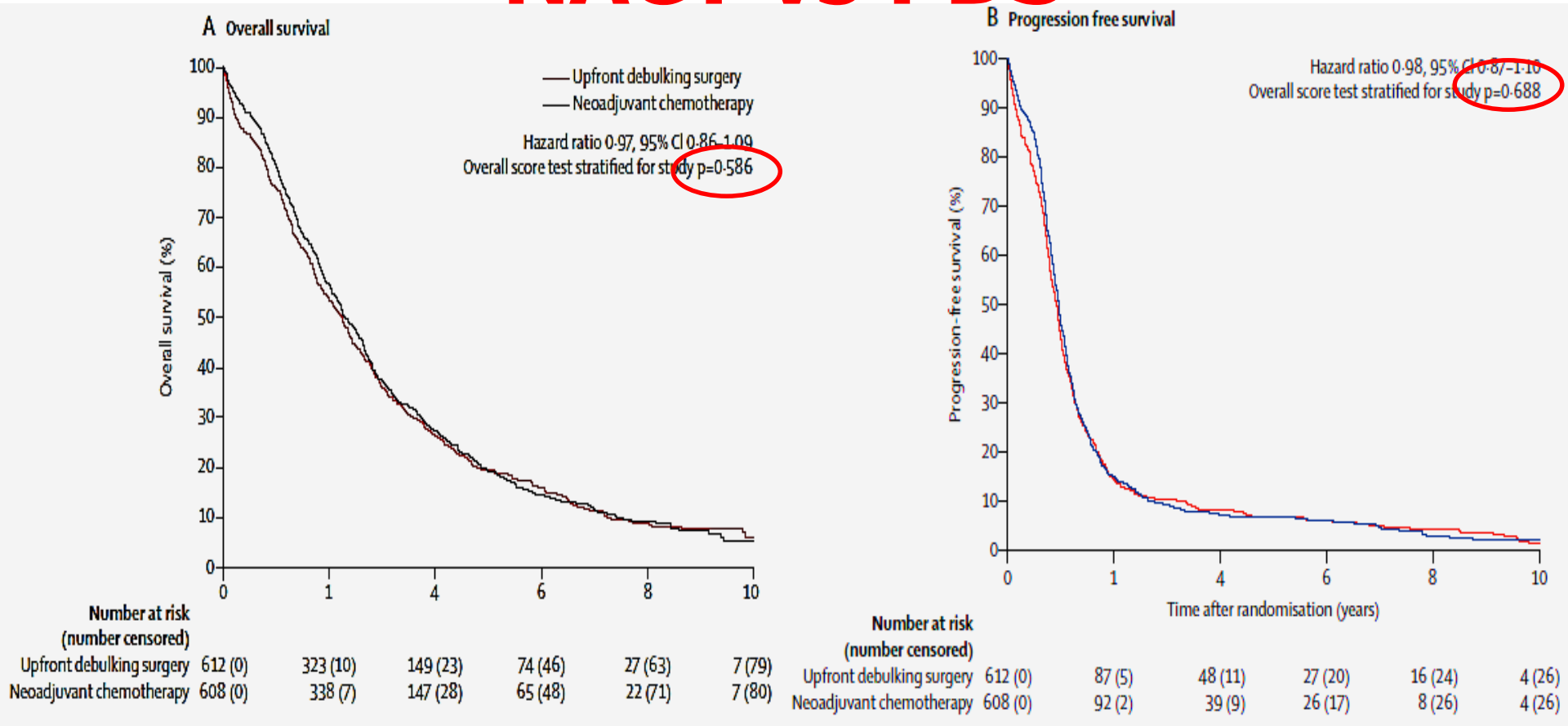
Long Term Survival of PDS vs IDS



n:14182 (PDS; 11871 + IDS; 2311) median follow-up 43 m

Ann Surg Oncol. 2016 May;23(5):1666-73

Long Term Survival
NACT vs PDS



NACT is non-inferior OS and PFS as compared with upfront debulking surgery
NACT has better OS at stage IV disease

Lancet Oncol 2018; 19: 1680-87

Disadvantages of NACT

- 15% primary resistance
- Development of Chemo-resistant colones
- LGSC, CC, Mucinous tm
- Limited response to classical paclitaxel – carboplatin regimen

NACT+IDS Short Term Advantages (n:1607, AOC Patients)

High optimal cytoreduction
Low perioperative morbidity and mortality
Quality of life*

Better QOL than PDS*
Fatigue
Role of function
Emotional function
Cognitive function

Yang et al journal.pone 01186725 2017

What About Survival Impact of HIPEC After NACT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

W.J. van Driel, S.N. Koole, K. Sikorska, J.H. Schagen van Leeuwen,

245 EOC pts

3 cycles of NACT (at least stable disease ,NO progressive or refractory)

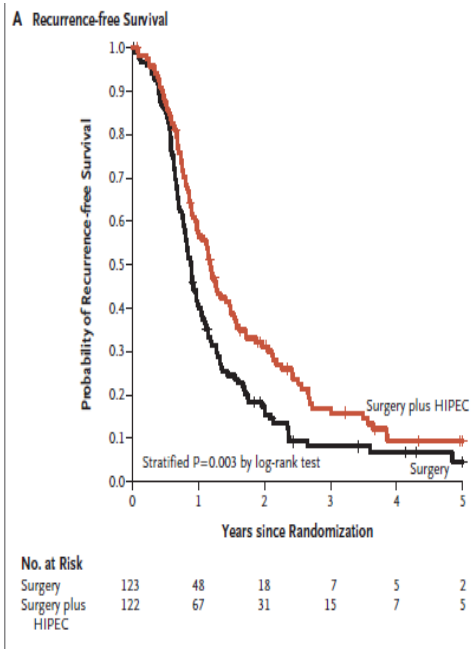
+

Surgery (complete resection or maxımum 10 mm residual tm)

± HİPEC (100 mg per sq Cisplatin)

HİPEC :122 pts

Without HİPEC:123 pts



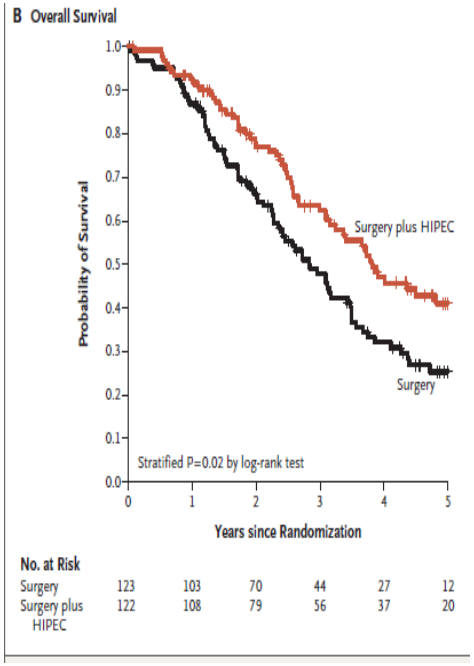
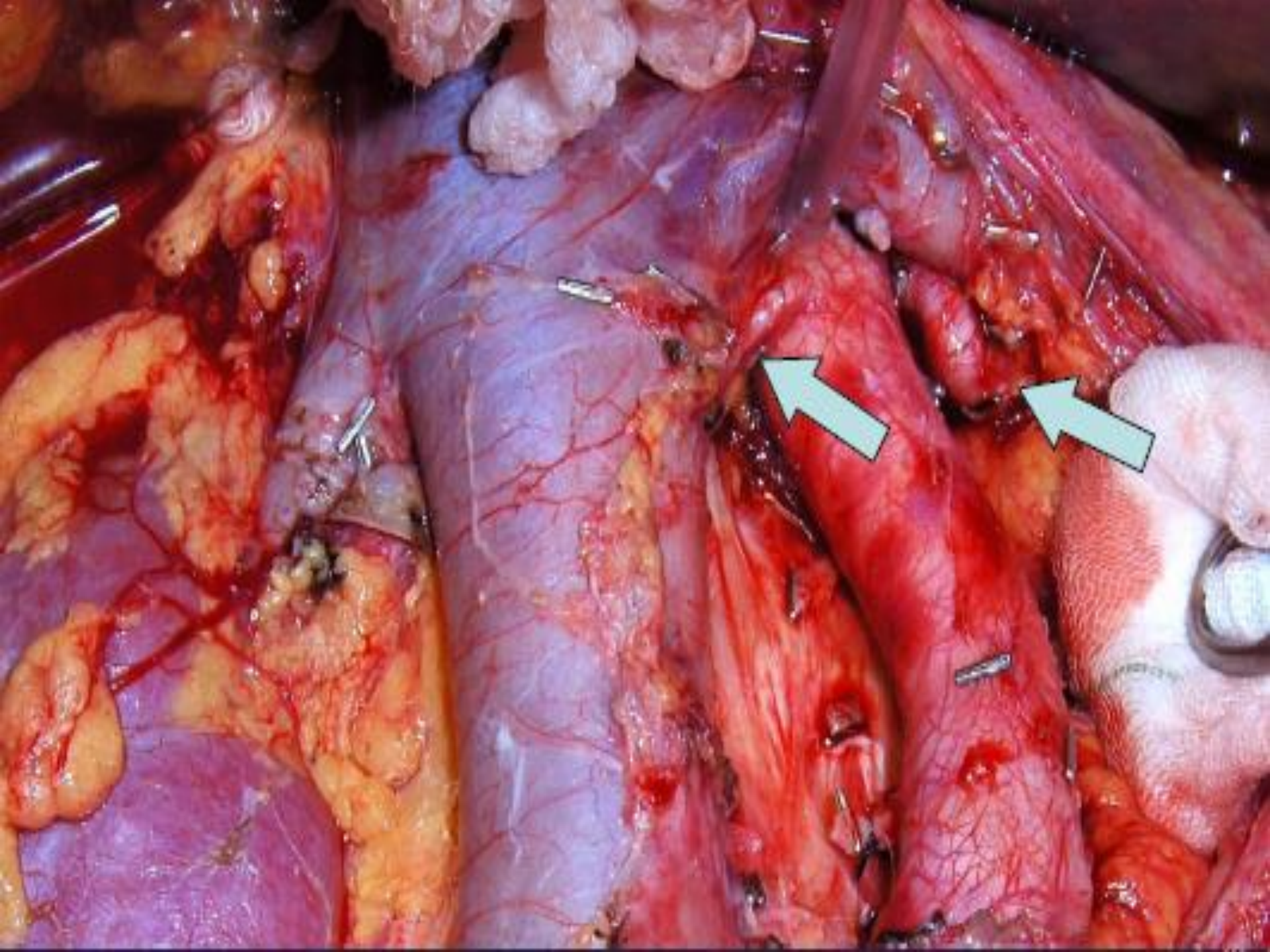


Table 3. Mortality risk factors, univariate analysis.

Variable	Modality	Population	Hazard ratio (95% CI)	*p* value
Age (years) at the time of first HIPEC	≥50	54 (69.2%)	1.00	.004
	<50	24 (30.8%)	4.2 (1.6–11.1)	
Time between diagnosis and HIPEC			0.99 (0.98–1.01)	.26
Number of HIPEC	1	64 (82.1%)	1.00	.08
	2	10 (12.8%)	0 (0-.)	
	3	4 (5.1%)	5.1 (1.2–21.1)	
Experience of the centre (years)[a]	[0–7]	15 (19.2%)	1.00	.83
	]7–11]	33 (42.3%)	1.27 (0.07–22.80)	
	>11	30 (38.5%)	0.97 (0.03–27.73)	
Peritoneal Cancer Index		Missing data: 13		.049
	[0–8]	38 (58.5%)	1.00	
	>8	27 (41.5%)	2.8 (1.0–7.7)	
Adjuvant chemotherapy (first HIPEC)		Missing data: 28		.78
	No	36 (72.0%)	1.00	
	Yes	14 (28.0%)	1.2 (0.3–4.2)	
CA125 at the time of first HIPEC		Missing data: 44		.02
	<30	7 (20.6%)	1.00	
	[30–100[	9 (26.5%)	1.1 (0.1–13.3)	
	≥100	18 (52.9%)	74.2 (2.5–2216.8)	
CC-score at the time of first HIPEC	CC-0	60 (76.9%)	1.00	.057
	CC-1 + CC-2	18 (23.1%)	2.8 (1.0–7.8)	
ASA		Missing data: 10		.44
	1	17 (25.0%)	1.00	
	2	51 (75.0%)	0.6 (0.2–2.3)	
Performance Status (PS) at the time of the first HIPEC[a]		Missing data: 17		1.00
	0	23 (37.1%)	1.00	
	1	38 (61.3%)	44.3 (1.2–1703.3)	
	2	1 (1.6%)	36.2 (0.3–4611.0)	
Gilly's groups[1]		Missing data: 51		.40
	0-1-2	12 (44.4%)	1.00	
	3–4	15 (55.6%)	2.0 (0.4–10.3)	
Indication	Advanced EOC	7 (9.0%)	1.00	.20
	Recurrent EOC	71 (91.0%)	0.3 (0.1–1.8)	
Platinum-sensitivity		Missing data: 2		.38
	Platinum-resistant	37 (48.7%)	1.00	
	Platinum-sensitive	32 (42.1%)	1.4 (0.5–3.4)	
	Advanced frontline	7 (9.2%)	3.5 (0.6–21.2)	
Histology and grade	HGSOC	39 (50.0%)	1.00	.45
	Other	39 (50.0%)	1.8 (0.4–8.5)	
Number of chemotherapeutic agents (HIPEC)	1	39 (50.0%)	1.00	.58
	2	39 (50.0%)	1.5 (0.3–6.8)	
Initial residual disease		Missing data: 14		.64
	No	21 (32.8%)	1.00	
	Yes	43 (67.2%)	1.4 (0.4–5.2)	
Resection of metastases		Missing data: 4		.48
	No	71 (95.9%)	1.00	
	Yes	3 (4.1%)	1.8 (0.3–10.0)	

[a]with Firth correction [42].

O. Le Saux et al. Int J Hyperthermia DOI 10.1080/02656736.2018.1518544



Survival Impact Of Lymphadenectomy in Advanced Stage Ovarian Cancer

- **The Incidence of (+) LN in Advanced Ovarian Cancer = 66%**
- **49% positive LN > 1 cm diameter**
- **17% had positive LN > 1cm not identified by palpation or inspection**

Eisenkop SM et al, Gynecol Oncol 2001

Survival Impact of Lymphadenectomy in Advanced EOC (bulky nodes excluded)

		Lymphadenectomy	No Lymphadenectomy	
Benedetti Panici et al., 2005 **Prospective** J Natl Cancer Inst. 2005 Apr 20;97(8):560-6.	PFS	31.2 %	21.6 %	p=0.02
	OS	48.5 %	47 %	
LION **ESGO 2017** **Prospective** Journal of Clinical Oncology *35, no. 15_suppl (May 20 2017) 5500-5500.*	PFS	25,5 m	25,5 m	
	OS	65,5 m	69,2 m	
Du Bois et al., 2010 **Retrospective** J Clin Oncol. 2010 Apr 1;28(10):1733-9. doi: 10.1200/JCO.2009.25.3617. Epub 2010 Mar 1.	OS	67,4 %	59,2 %	
GOG 182 **Retrospective** Cancer. 2017 May 15;123(6):985-993. doi: 10.1002/cncr.30414. Epub 2016 Nov 16.	PFS	18,5 m	16 m	p<0,01
	OS	53,3 m	42,8 m	p<0,01

MIS in EOC

Staging & Treatment

(peritoneal cytology-biopsy + Pelvic paraaortic LND + Hysterectomy + BSO + Ommentectomy)

Re-Staging

-Nezhat et al. n:36 follow-up 55,9 mts , OS %100

-Chi et al. n:50 ls :20 lt : 30 all results same, lower morbidity in LS group

-Restaging GOG 9302-9402

Triage for resectability

(Vergote n:285, Fagotti n:64...)

Cyto-reductive surgery* for primary or recurrent EOC in selected cases

(Amara et al, Nezhat et al .....)

*HALS (Hand assisted Laparoscopic Surgery)

L/S vs L/T in the Treatment of Early Stage EOC

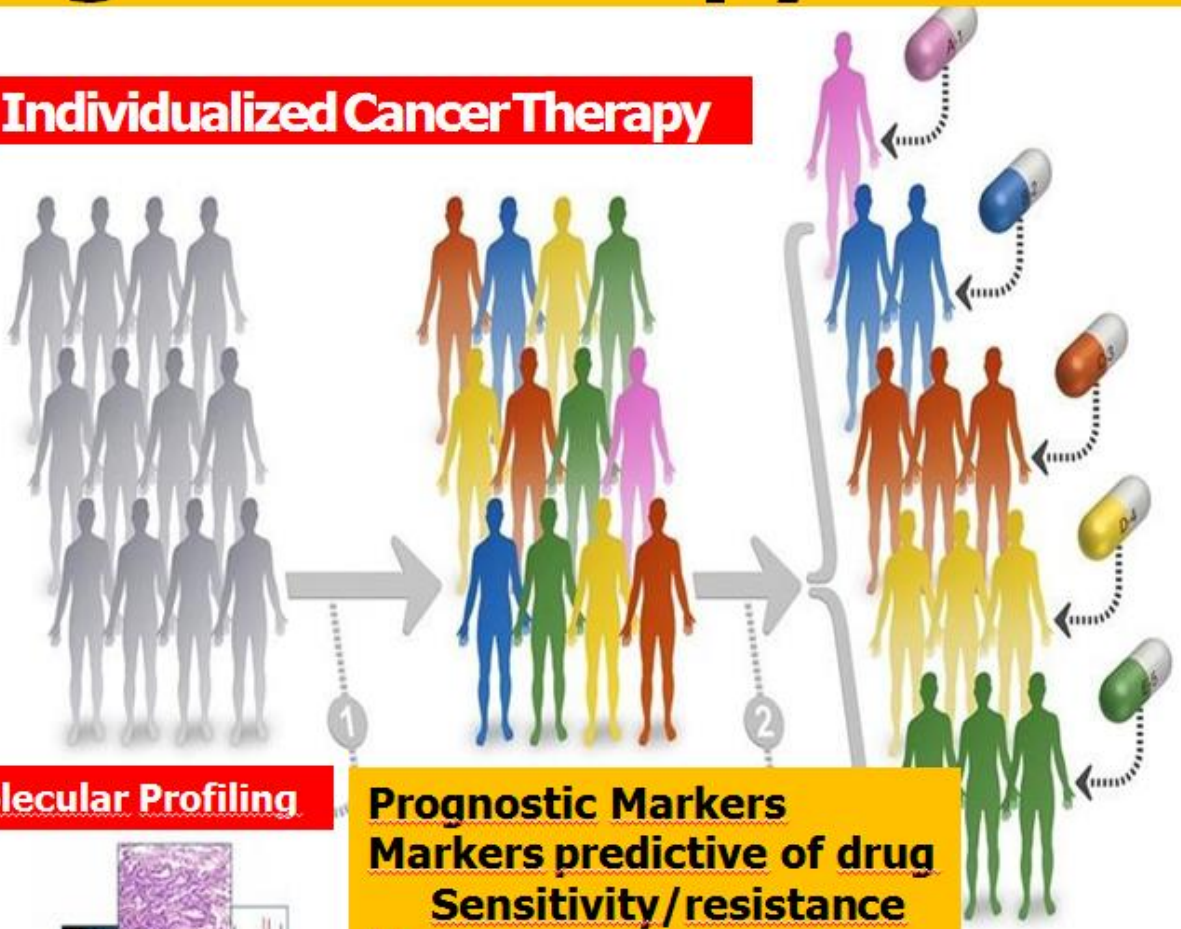
	L/S (n:66)	L/T (n:120)
Adjuvant CT (70%)	Similar	
Recurrence	5 (8,3%)	16 (13,3%)
PFS (4y)	89%	81%
OAS	92%	91%

NOT SIGNIFICANT

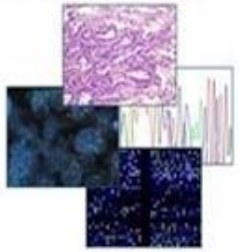
J Min Inv Gynecol (2016); 03 006

Implementing a Targeted Therapy Strategy

Individualized Cancer Therapy



Molecular Profiling



Prognostic Markers
Markers predictive of drug Sensitivity/resistance
Markers predictive of Adverse events

BIOMARKERS

New Approaches in the Management of EOC

Gene based chemotherapy

Novel biologic agents

(VEGF. PARP. m-TOR. inhibitors etc…)

IP chemotherapy (Regular and HIPEC)

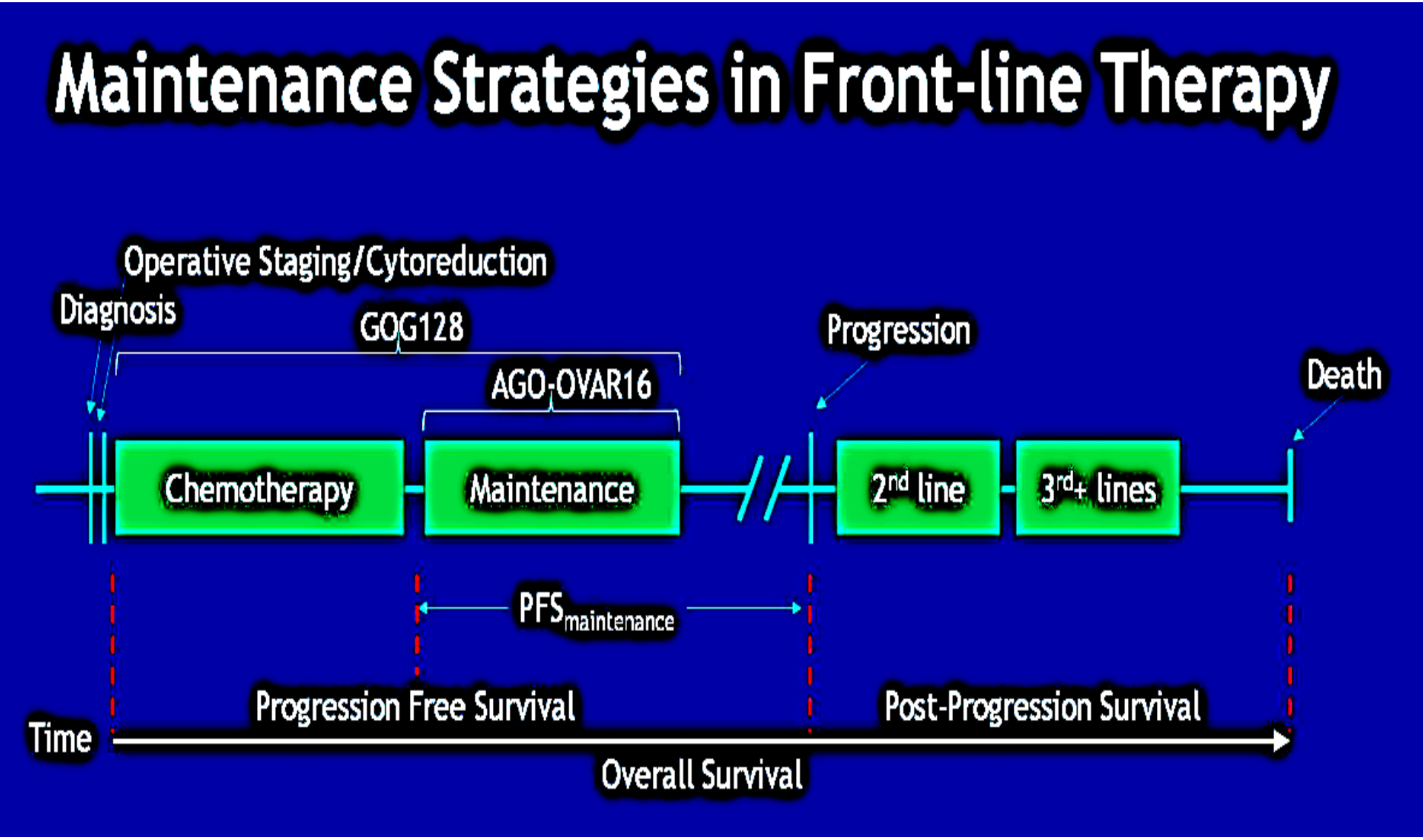
NACT

Check-point inhibitors

(Vaccination & Immunotherapy)

DO NOT FORGET THE BIOLOGICAL BEHAVIOR OF THE TUMOR!!!!

Maintenance Strategies in Front-line Therapy



Presented By Stephanie Gaillard at 2018 ASCO Annual Meeting

Conclusion

OC remains as the most lethal GYN neoplasm

No effective screening programme

but risk reduction surgery (BRCA 1,2)

More than 60% is advanced stage

Currently PDS with no residual tm + Adjuvant CT is the standard of care

NACT + IDS is not standard yet, just in selected cases

Early diagnose or close follow up

ESGO
European Society of Gynaecological Oncology

Thank you for your attention

MEMAGO
MIDDLE EAST and MEDITERRANEAN ASSOCIATION OF GYNECOLOGIC ONCOLOGISTS

TÜRK
JİNEKOLOJİK ONKOLOJİ DERNEĞİ