



IRE

ISTITUTO NAZIONALE TUMORI

REGINA ELENA

ISTITUTO DI RICOVERO E CURA A CARATTERE SCIENTIFICO

Meet the Professor: CARCINOMA OVARICO

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TUMORE OVARICO & OBESITÀ – DIETA – DIABETE

- L'obesità è un fattore di rischio per il cancro
- Evidenze epidemiologiche suggeriscono una correlazione tra obesità e carcinoma epiteliale dell'ovaio
- > dei fattori secreti dalle cellule adipose (leptina)
- > degli estrogeni ed androgeni circolanti, quindi > del rischio soprattutto di tumore endometriode dell'endometrio e secondario dell'ovaio
- Iperinsulinemia e > dell'IGF1 che contribuiscono ad aumentare la conversione ovarica di androgeni in estrogeni
- C'è una probabile correlazione tra dieta e carcinoma dell'ovaio, ma non esistono evidenze forti in letteratura

TUMORE OVARICO & DISTURBI MESTRUALI - COC

- C'è una correlazione tra la sindrome di Stein-Leventhal e il tumore endometrioidale dell'endometrio
- Una recente revisione sistematica della letteratura non ha evidenziato nessuna associazione significativa tra la sindrome di Stein-Leventhal e il tumore dell'ovaio¹
- I contraccettivi ormonali sembrano associati a una riduzione del rischio di carcinoma epiteliale ovarico e di carcinoma dell'endometrio²

1. [Harris HR, Terry KL. Polycystic ovary syndrome and risk of endometrial, ovarian, and breast cancer: a systematic review. Fertil Res Pract. 2016 Dec 5;2:14.](#)

2. [La Vecchia C. Oral contraceptives and ovarian cancer: an update, 1998–2004. Eur J Cancer Prev. 2006;15:117–124.](#)

TUMORE OVARICO & TERAPIA ORMONALE SOSTITUTIVA

- La terapia ormonale sostitutiva non sembra incrementare il rischio di carcinoma ovarico
- Le pazienti trattate per carcinoma ovarico in giovane età possono beneficiare di un trattamento ormonale sostitutivo senza un incremento significativo del rischio di recidiva, a fronte di notevoli benefici
- Il timore dei ginecologi nel prescrivere ormoni a queste donne rimane alto

TUMORE OVARICO & PATOLOGIE ENDOCRINE

- Fattori di rischio riconosciuti per il carcinoma dell'ovaio sono la nulliparità e le induzioni ripetute dell'ovulazione di pazienti infertili
- Al contrario, la contraccezione ormonale, le gravidanze e l'allattamento al seno sembrano avere un ruolo protettivo
- Non ci sono correlazioni significative tra patologie endocrine e carcinoma ovarico

***Ovarian
Carcinoma***
**5 Histological
Types (98%)**

- Sierosi di alto grado (70%)
- Sierosi di basso grado (< 5%)
- Endometrioidi (10%)
- Cellule chiare (10%)
- Mucinosi (3%)

Ovarian Carcinoma

5

Histological Types

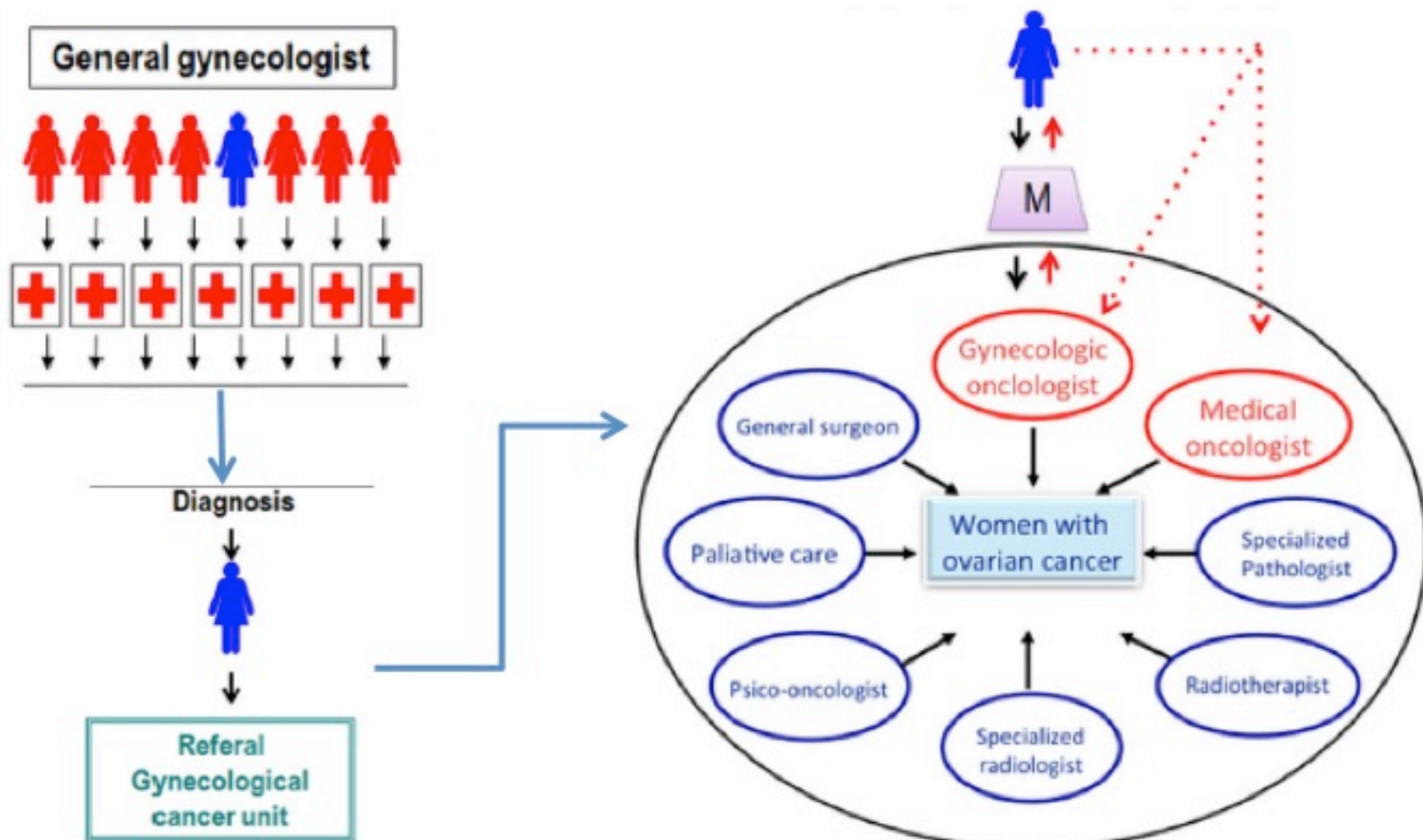
Differenze:

- *Fattori di rischio*
- *Caratteristiche genetiche*
- *Precursori (sierosi HG, clear cells ed endometrioid derivano dalla tuba e dall'endometrio)*
- *Diffusione*
- *Risposta alla terapia*
- *Prognosi*

OVARIAN CARCINOMA clinical & molecular features

	HGSC	LGSC	MC	EC	CCC
Risk factors	<i>BRCA1/2</i>	?	?	HNPCCa	?
Precursor lesions	Tubal intraepithelial carcinoma	Serous borderline tumor	Cystadenoma/ borderline tumor?	Atypical endometriosis	Atypical endometriosis
Pattern of spread	Very early transcoelomic spread	Transcoelomic spread	Usually confined to ovary	Usually confined to pelvis	Usually confined to pelvis
Molecular abnormalities	<i>BRCA, p53</i>	<i>BRAF, KRAS</i>	<i>KRAS, HER2</i>	<i>PTEN, ARID1A</i>	HNF1, <i>ARID1A</i>
Chemosensitivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma; CCC, clear-cell carcinoma. ^aHereditary nonpolyposis colorectal carcinoma.

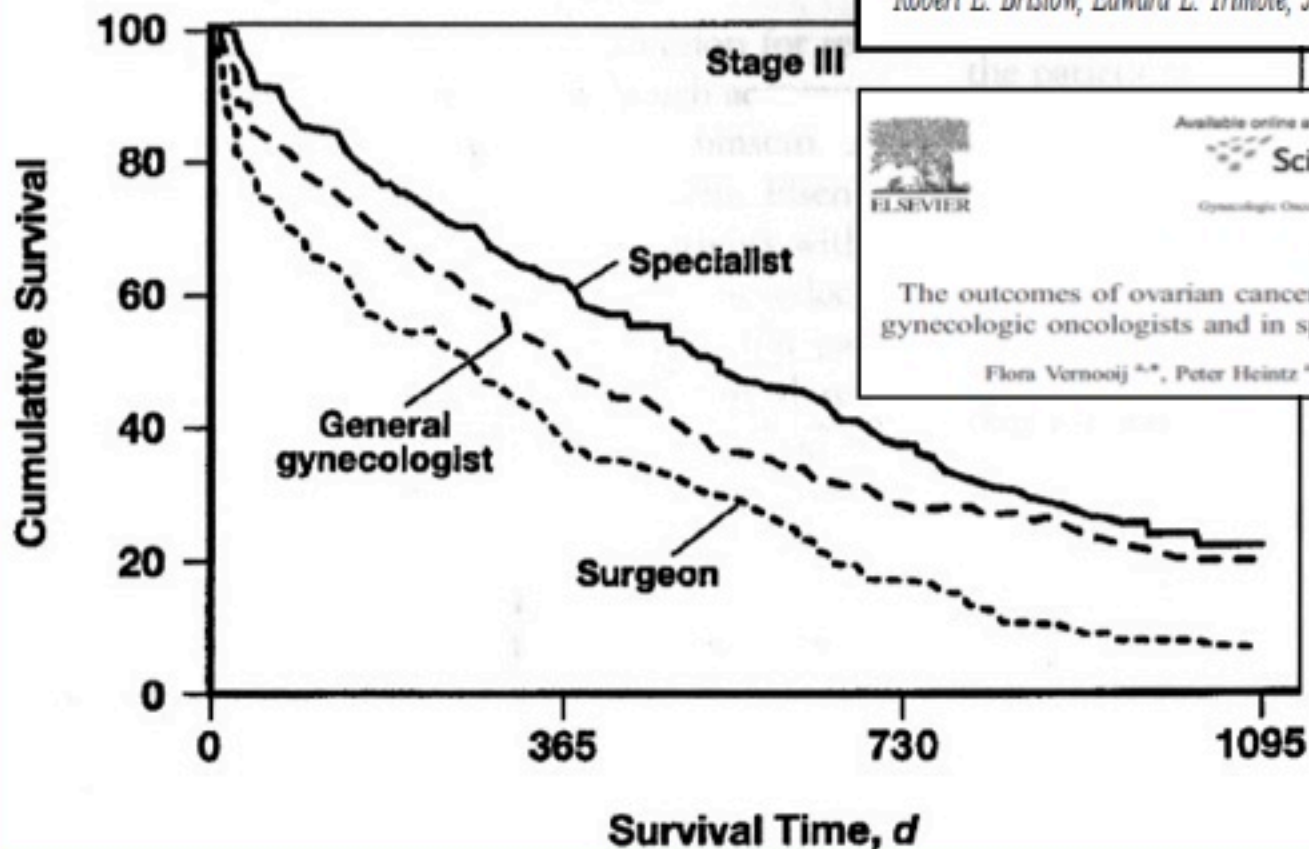


OS of stage III OC according to specialty of surgeon performing initial surgery

ARTICLES

Associations Between Hospital and Surgeon Procedure Volumes and Patient Outcomes After Ovarian Cancer Resection

Deborah Schrag, Craig Earle, Feng Xu, Katherine S. Panageas, K. Robin Yabroff, Robert E. Bristow, Edward L. Trimble, Joan L. Warren



Available online at www.sciencedirect.com

ScienceDirect

Gynecologic Oncology 105 (2007) 801–812

Gynecologic Oncology

www.elsevier.com/locate/ygyn

Review

The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: A systematic review

Flora Vernooij ^{a,}, Peter Heintz ^a, Els Witteveen ^b, Yolanda van der Graaf ^c*

KEY POINTS

- **CHIRURGIA**
- **CHEMIOTERAPIA**
- **CARATTERIZZAZIONE MOLECOLARE**



1st LPS Pelvic lymphadenectomy



1st LPS Aortic lymphadenectomy

1st LPS ovarian staging



300 cases of LPS ovarian staging



1991

1993

1994

1999

2014



Laparoscopic staging of apparent early stage ovarian cancer: Results of a large, retrospective, multi-institutional series

V. Gallotta^{a,*}, F. Ghezzi^b, E. Vizza^c, V. Chiantera^d, M. Ceccaroni^c, M. Franchi^e, A. Fagotti^f, A. Ercoli^h, F. Fanfani^a, C. Parrino^a, S. Uccella^b, G. Corrado^c, G. Scambia^a, G. Ferrandina^a

^a Gynecologic Oncology Unit, Catholic University of the Sacred Heart, Rome, Italy

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^d Gynecologic Oncology Unit, Fondazione "Giovanni Paolo II", Compianso, Italy

^e Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally-Invasive Pelvic Surgery, Sacred Heart Hospital, Niguarda, Verona, Italy

^f Department of Obstetrics and Gynecology, University of Verona, Verona, Italy

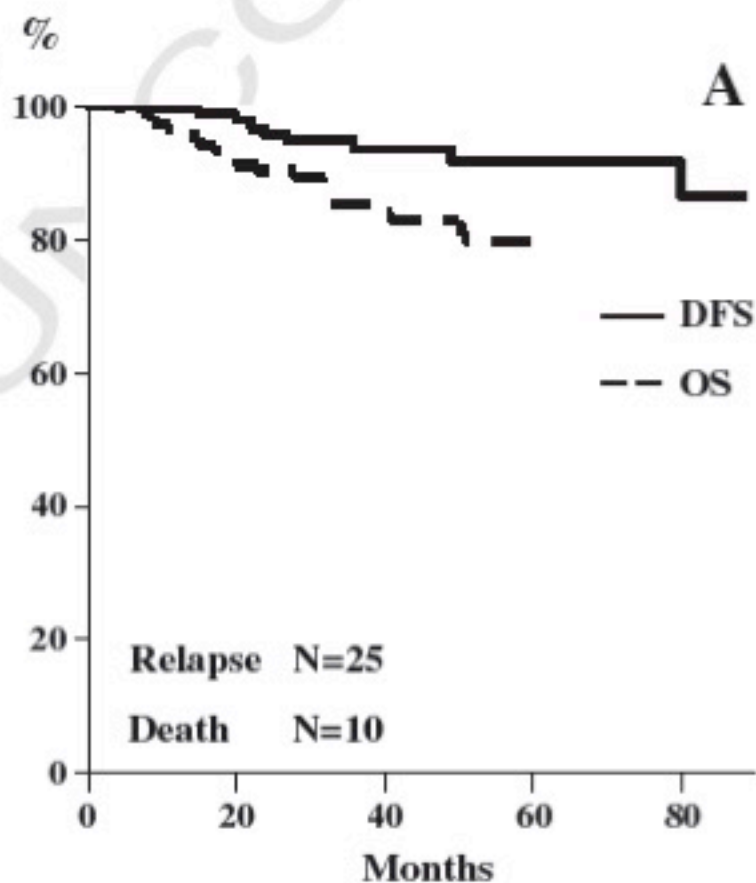
^g Division of Minimally Invasive Gynecologic Surgery, Department of Surgery, St. Maria Hospital—University of Perugia, Terni, Italy

^h Policlinic of Abano Terme, Padova, Italy



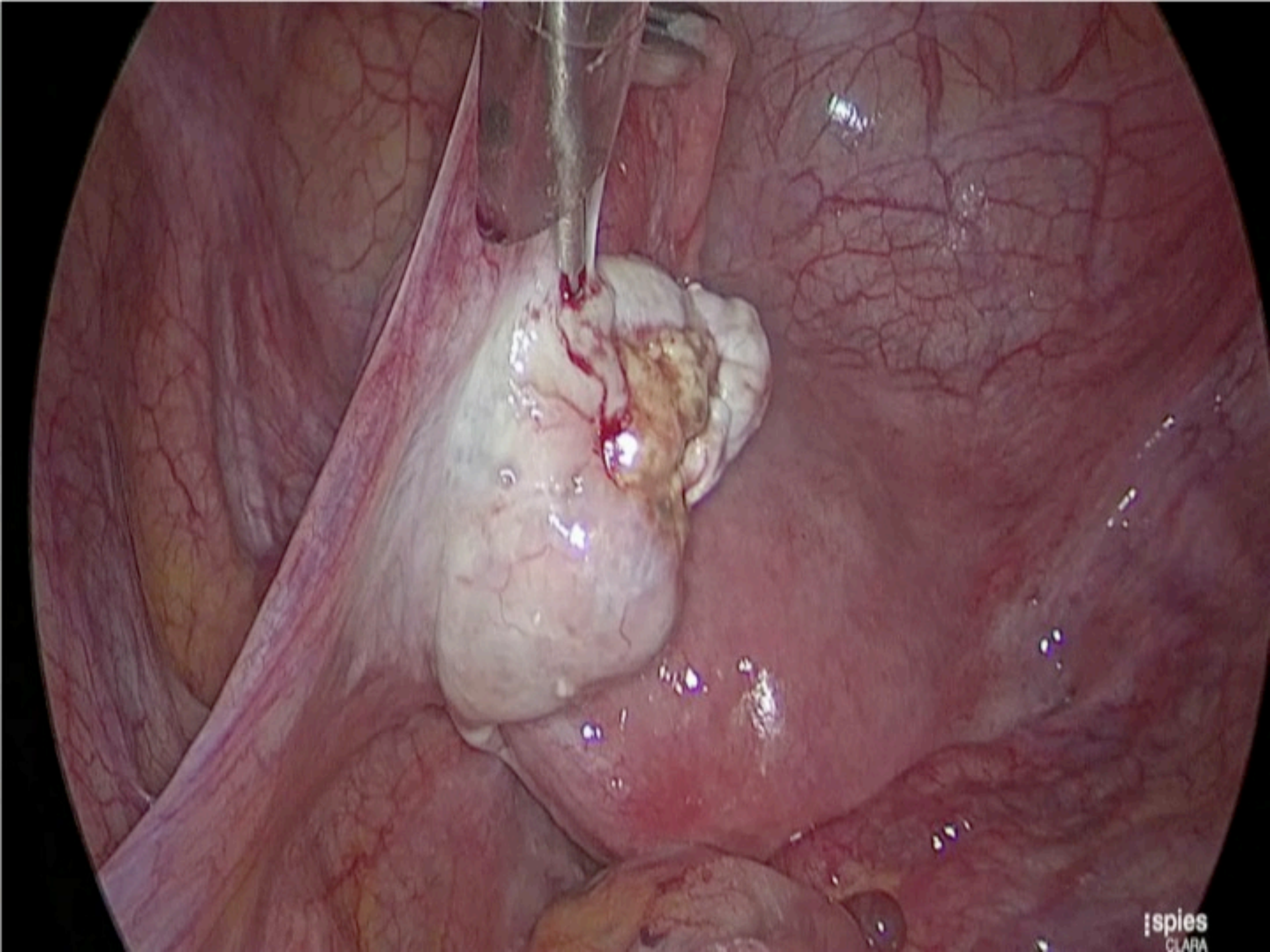
Variable	Whole series N. (%)	Group 1 Immediate staging N. (%)	Group 2 Delayed staging N. (%)	p value ^a
All cases	300	150	150	–
Age, years				
Median	49 (11–81)	53 (13–81)	45 (11–73)	0.0002
(range)				
BMI, kg/m ²				
Median	22.8 (16.6–	23.4 (17.0–39.0)	22.8 (17.0–	n.s.
(range)	49.9)		49.9)	
Menopause				
No	148	59 (39.9)	89 (60.1)	
Yes	148	87 (58.8)	61 (41.2)	
not specified.	4	4		0.0001
Previous abdominal surgery				
None	165	80 (48.5)	85 (51.5)	
1	100	50 (50.0)	50 (50.0)	
2	25	16 (64.0)	9 (36.0)	
3	5	2 (40.0)	3 (60.0)	
4	5	2 (40.0)	3 (60.0)	n.s.
History of endometriosis				
No	246	134 (54.5)	112 (45.5)	
Yes	54	16 (29.6)	38 (70.4)	0.0009

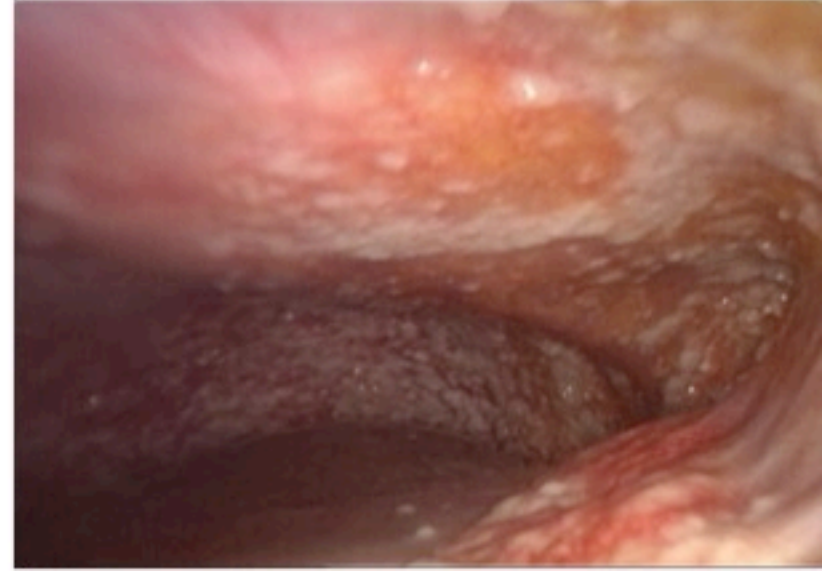
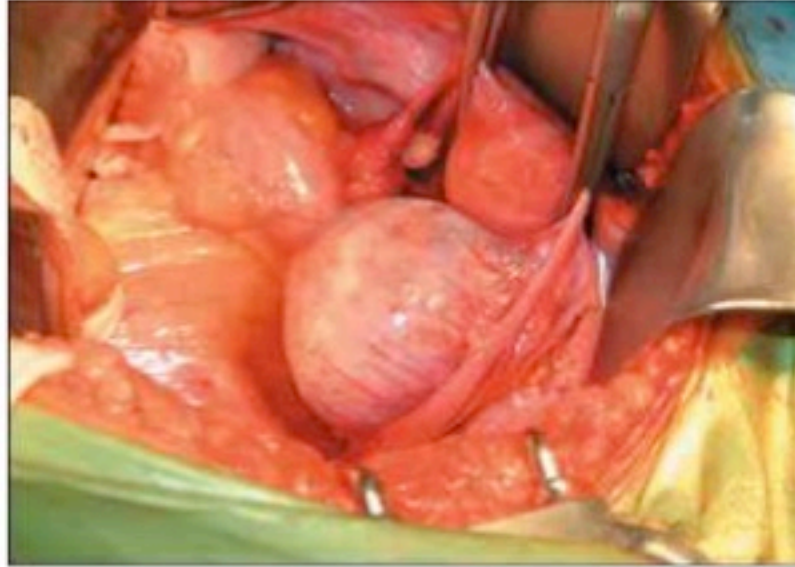
Variable	Group 1 (Immediate staging) N. (%)	Group 2 (Delayed staging) N. (%)	p value ^a
All cases	150	150	-
Time interval to laparoscopic staging (days)			
Median (range)	n.a.	51 (3-181) ^b	-
Fertility preserving surgery (FPS)			
No	142 (94.7)	110 (73.3)	
Yes	8 (5.3)	40 (26.7)	0.0001
Operative time, min			
Median (range)	250 (60-525)	195 (48-453)	0.0001
Estimated blood loss, ml			
Median (range)	200 (10-3000)	100 (20-800)	0.0008
Intraoperative transfusions			
No	146 (97.3)	150 (100)	
Yes	4 (2.6)	0	0.0032
Spillage/rupture of ovarian capsule			
No	132 (88.0)	147 (98.0)	
Yes	18 (12.0)	3 (2.0) ^c	0.0016
Laparotomic conversion			
No	126 (84.0)	147 (98.0)	
Yes	24 (16.0)	3 (2.0)	0.0001
Intraoperative complications			
No	144 (96.0)	147 (98.0)	
Yes	6 (4.0)	2 (1.3)	0.23
Type of intraoperative complications			
Postoperative complications			
No	112 (87.7)	116 (87.2)	
Yes	16 (12.3)	17 (12.8)	
Not specified	20	17	0.69



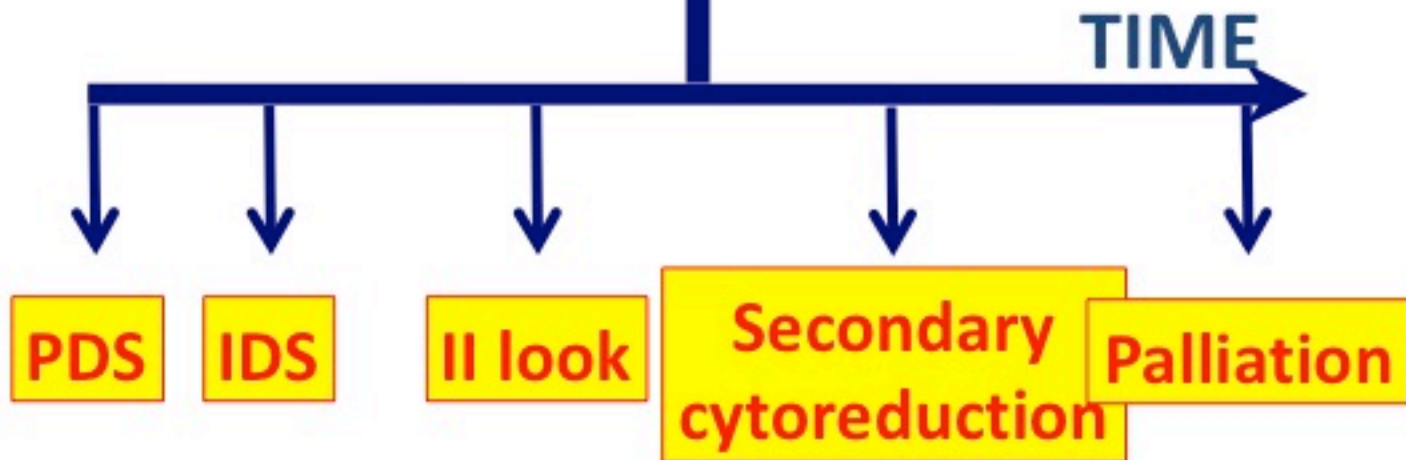
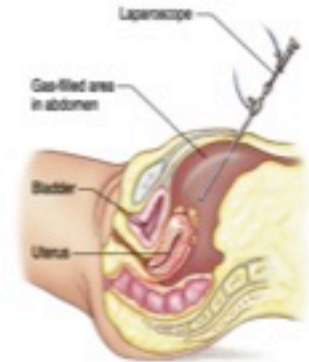
ROLE OF SENTINEL LYMPH NODE BIOPSY IN OVARIAN CANCER

- In apparent I stage ovarian carcinoma the incidence of retroperitoneal metastases has been reported to be relatively low (5-15%)
- Many gynecologic oncologists perform only selective ipsilateral retroperitoneal staging for clinical IA stage disease.
- Surgical morbidity related to systematic lymphadenectomy staging include lymphocistis, nerve and vessels injuries and increased operative time and blood-loss
- Growing interest in [SENTINEL LYMPH NODE TECHNIQUES](#)





SURGERY IN OVARIAN CANCER



Survival effect of maximal cytoreductive surgery for advanced OC during the platinum era

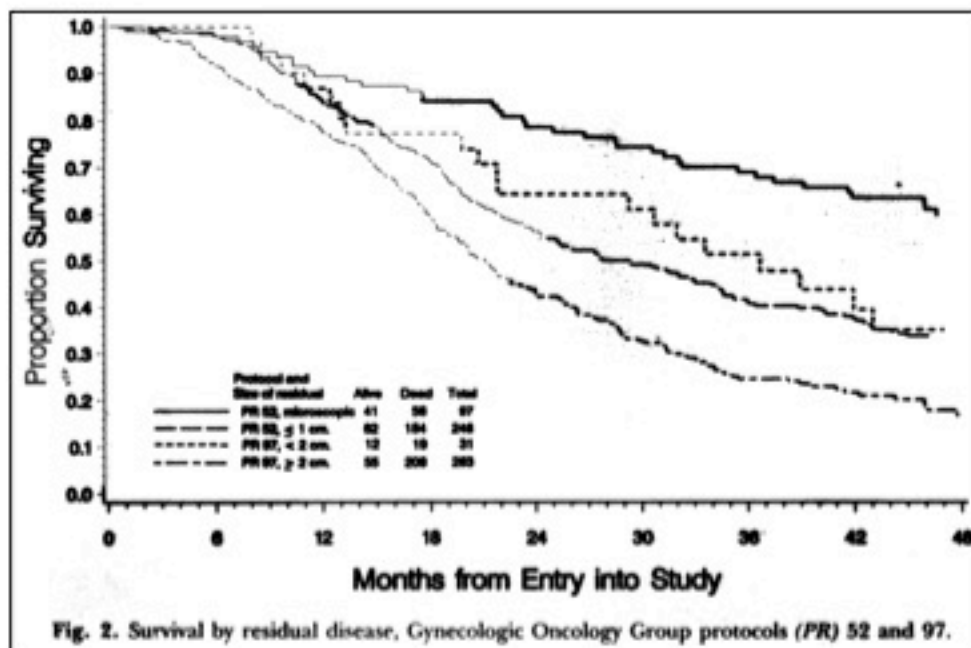
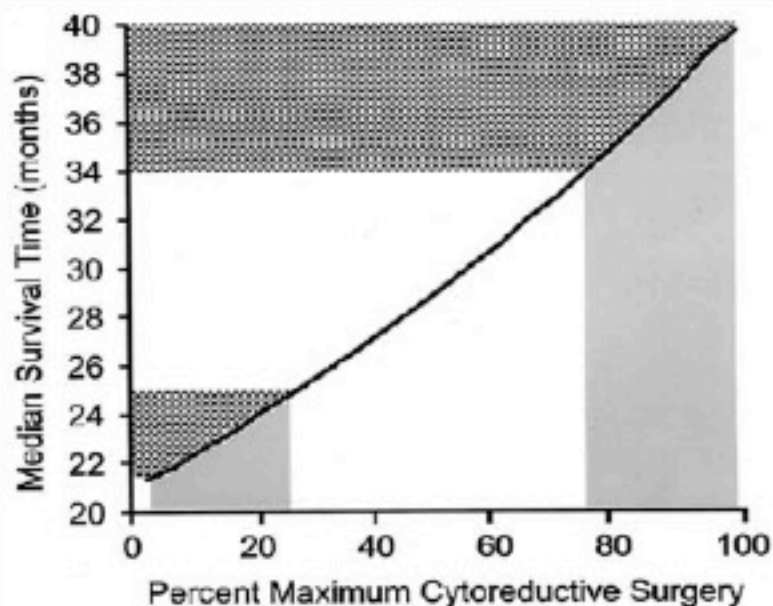


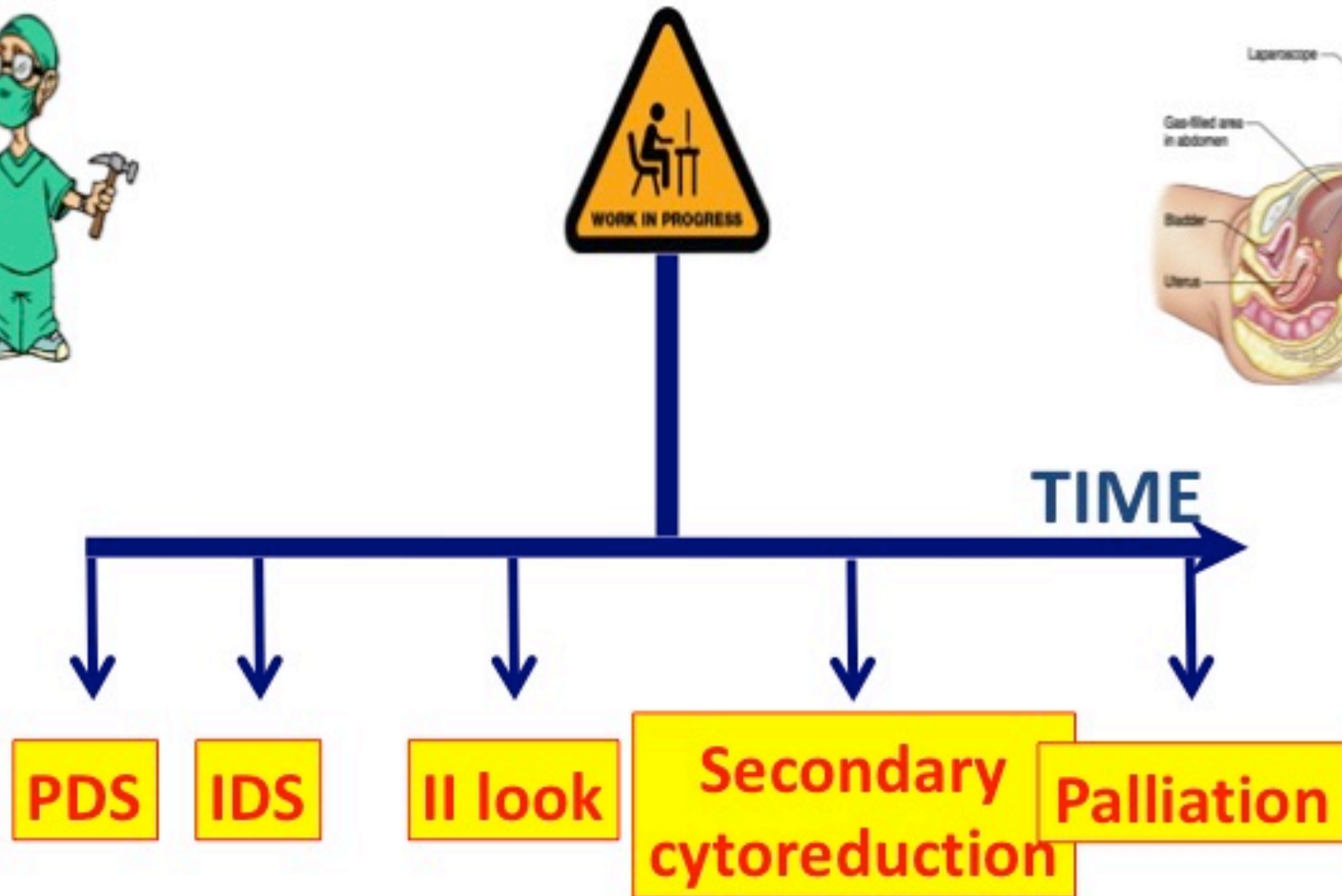
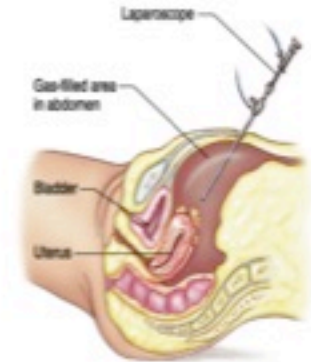
Fig. 2. Survival by residual disease, Gynecologic Oncology Group protocols (PR) 52 and 97.

Hoskins , 1994

Each 10% increase of optimal cytoreduction rate produces a 5.5% increase in median survival

Bristow , 2002

SURGERY IN OVARIAN CANCER



SURGERY

WHEN? WHERE? HOW? WHO?

■ Fagotti laparoscopic score (2008)

- ▶ Omental cake
- ▶ Peritoneal carcinomatosis
- ▶ Diaphragmatic carcinomatosis
- ▶ Mesenteric retraction
- ▶ Stomach infiltration
- ▶ Liver metastases

Each parameter was attributed a score of 0 to 2
Cytoreduction is incomplete in 100% of patients
with a score ≥ 8



PRINCIPLES OF SURGERY (1 of 2)¹

MIS approaches may be useful when evaluating whether maximum cytoreduction can be achieved in newly diagnosed and recurrent OC^{109,122,123,135,136}

***Level of evidence:
IIB***

122. Liu CS, Nagarsheth NP, Nezhat FR. Laparoscopy and ovarian cancer: a paradigm change in the management of ovarian cancer? J

Minim Invasive Gynecol 2009;16:250-262. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19321390>.

135. Fagotti A, Vizzielli G, De Iaco P, et al. A multicentric trial (Olympia-MITO 13) on the accuracy of laparoscopy to assess peritoneal spread in ovarian cancer. Am J Obstet Gynecol 2013;209:462 e461-462 e411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23891632>.

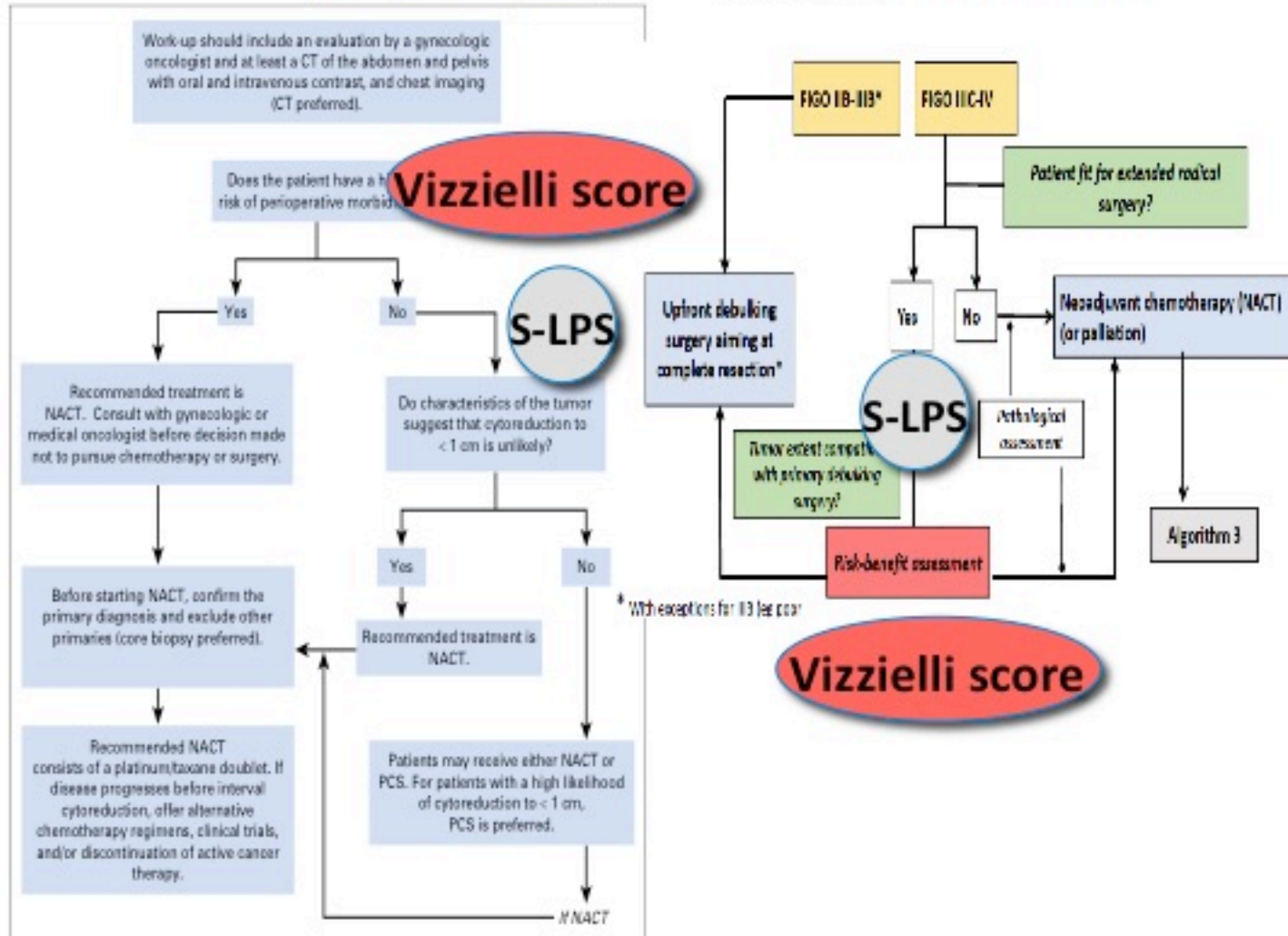
MANAGEMENT OF AOC

Neoadjuvant Chemotherapy for Newly Diagnosed, Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline

ASCO SPECIAL ARTICLE

ESGO
European Society of
Gynaecological Oncology

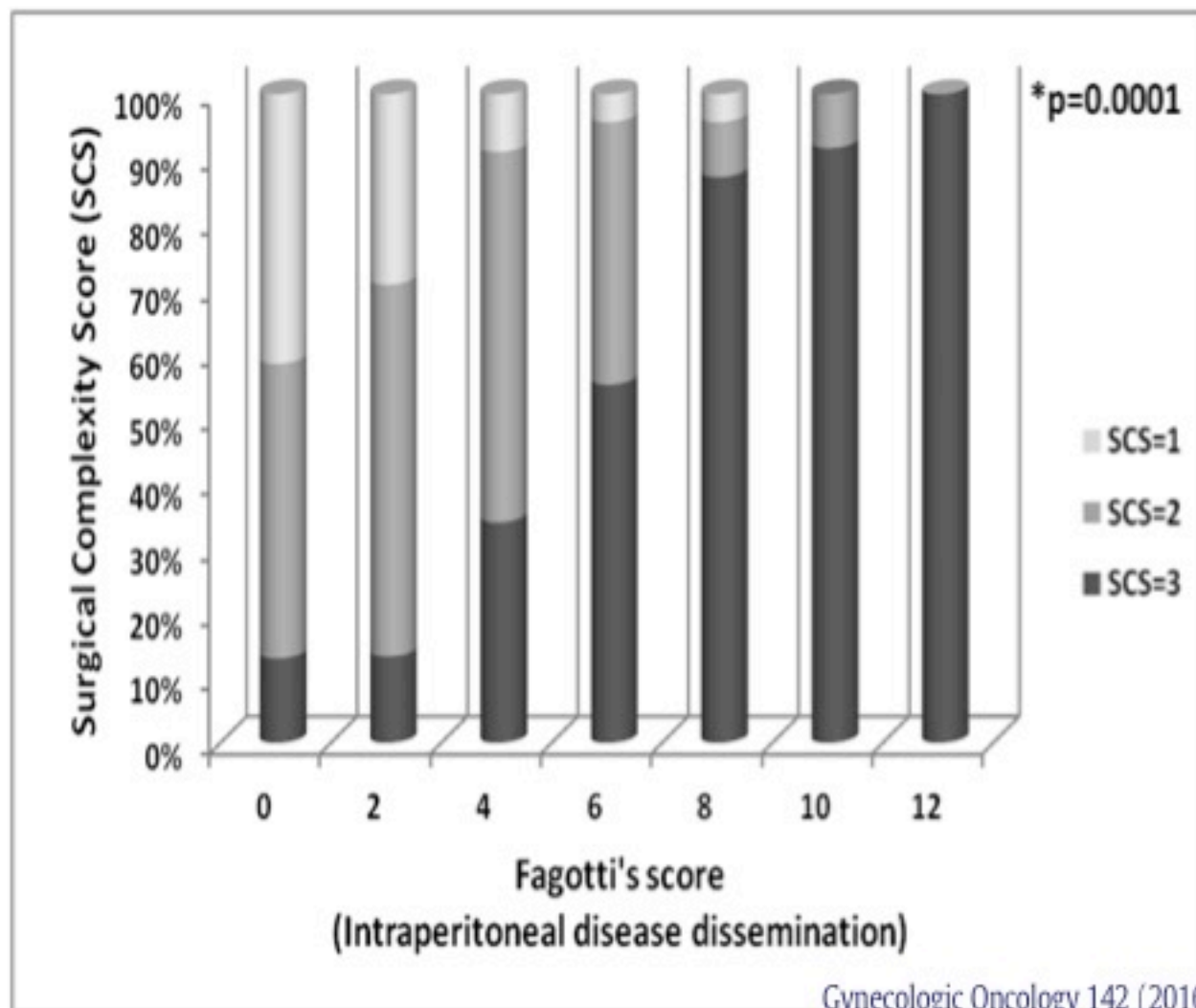
GUIDELINES



A laparoscopic risk-adjusted model to predict major complications after primary debulking surgery in ovarian cancer: A single-institution assessment



Vizzielli G.^{a,*}, Costantini B.^a, Tortorella L.^a, Pitruzzella I.^{a,b}, Gallotta V.^a, Fanfani F.^c, Gueli Alletti S.
Cosentino F.^a, Nero C.^a, Scambia G.^a, Fagotti A.^{a,d}



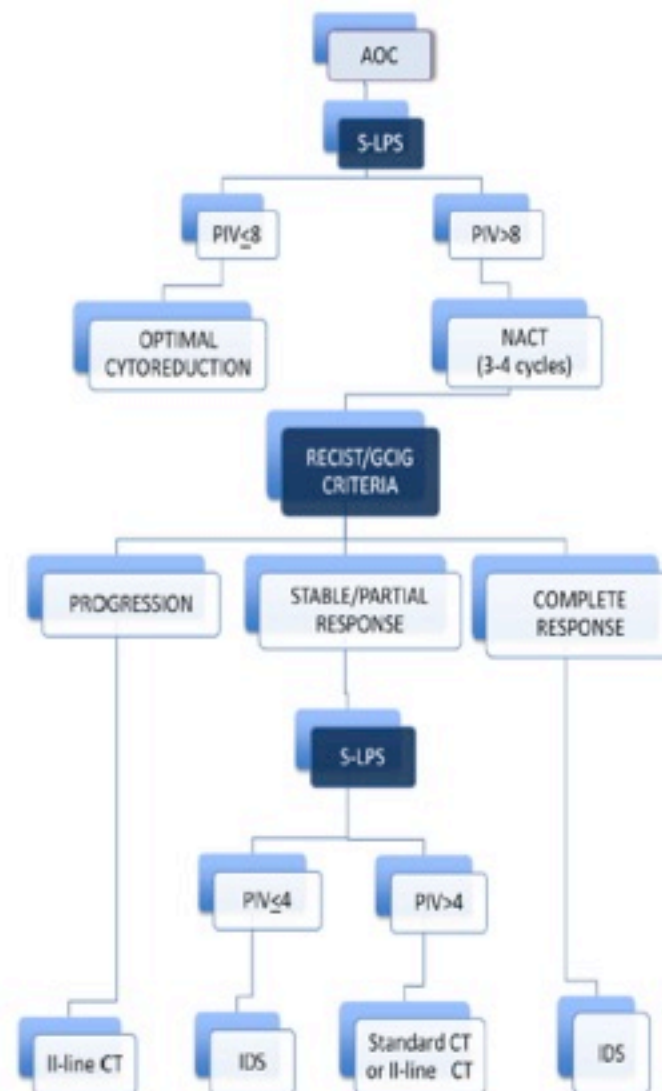
SURGERY

WHEN? WHERE? HOW? WHO?

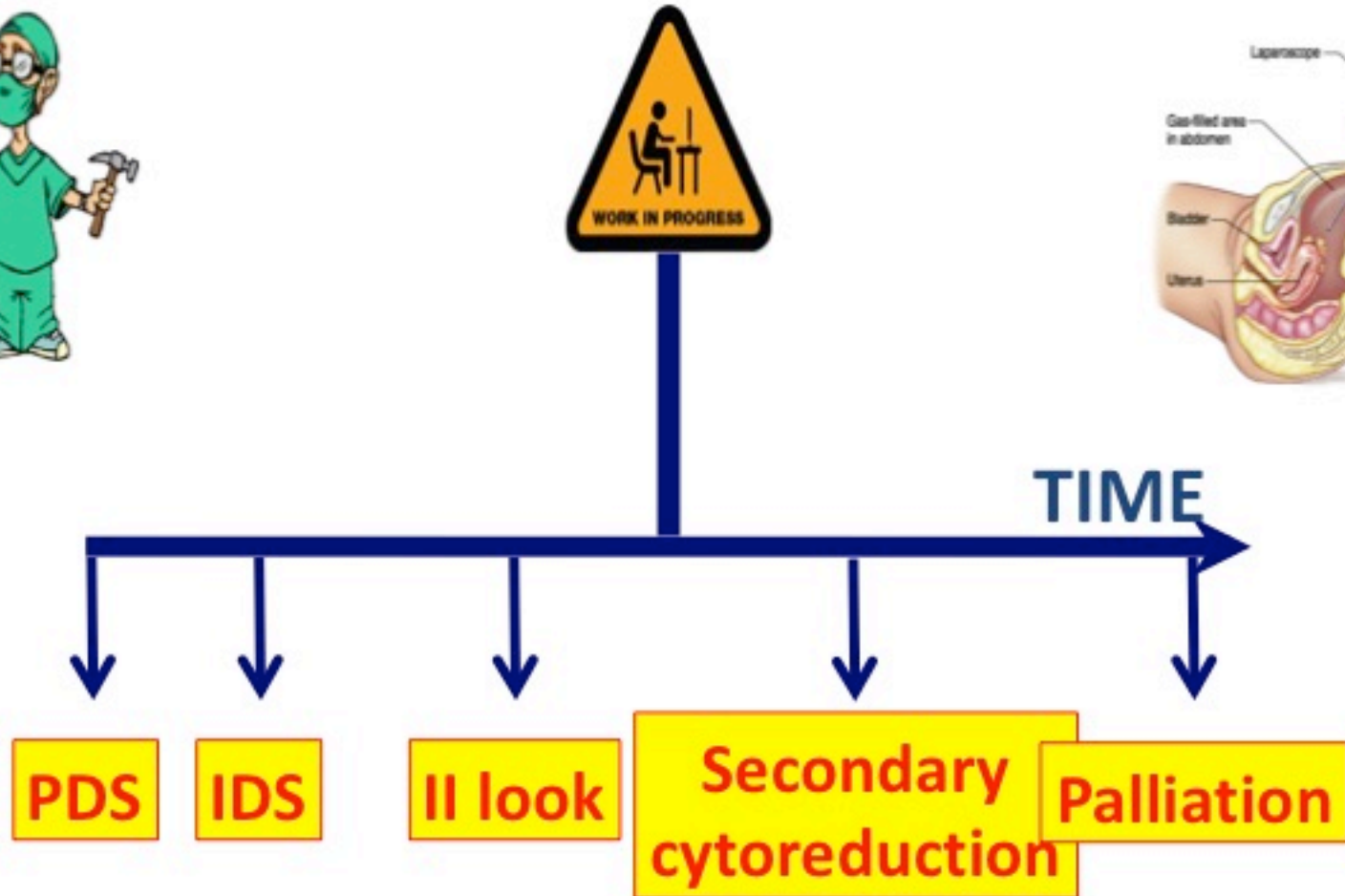
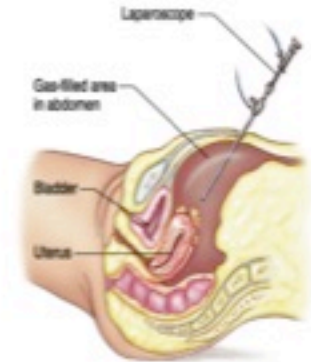
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SURGERY IN OVARIAN CANCER

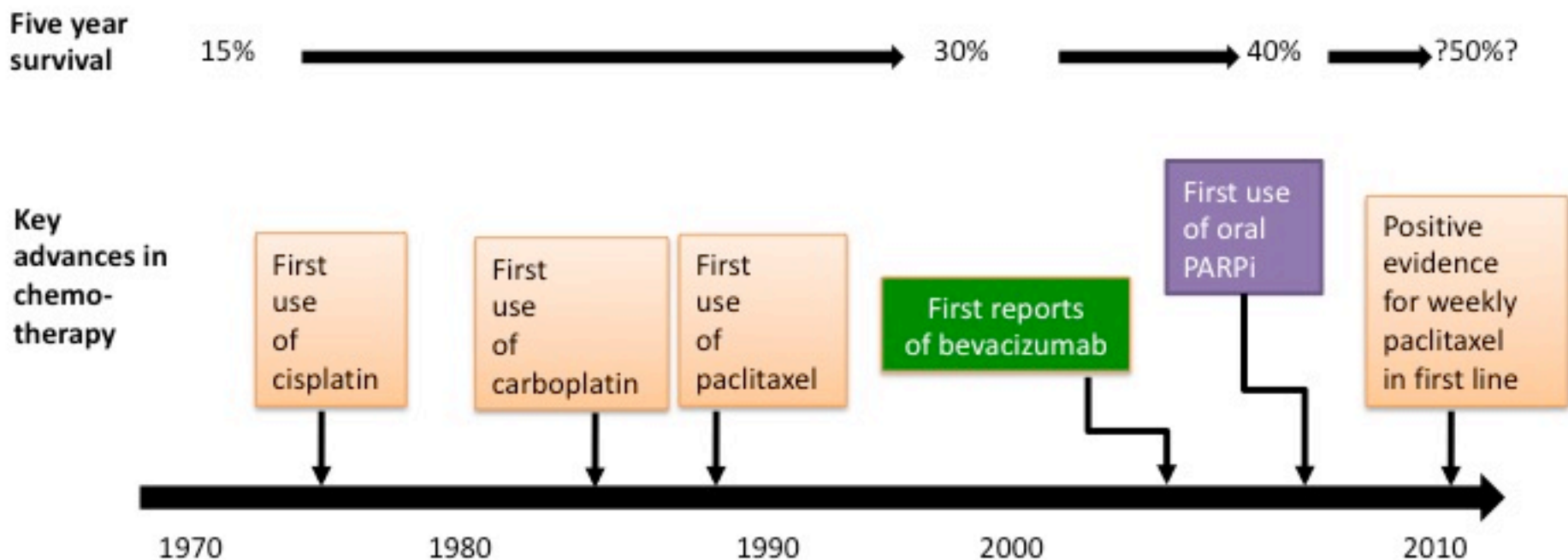


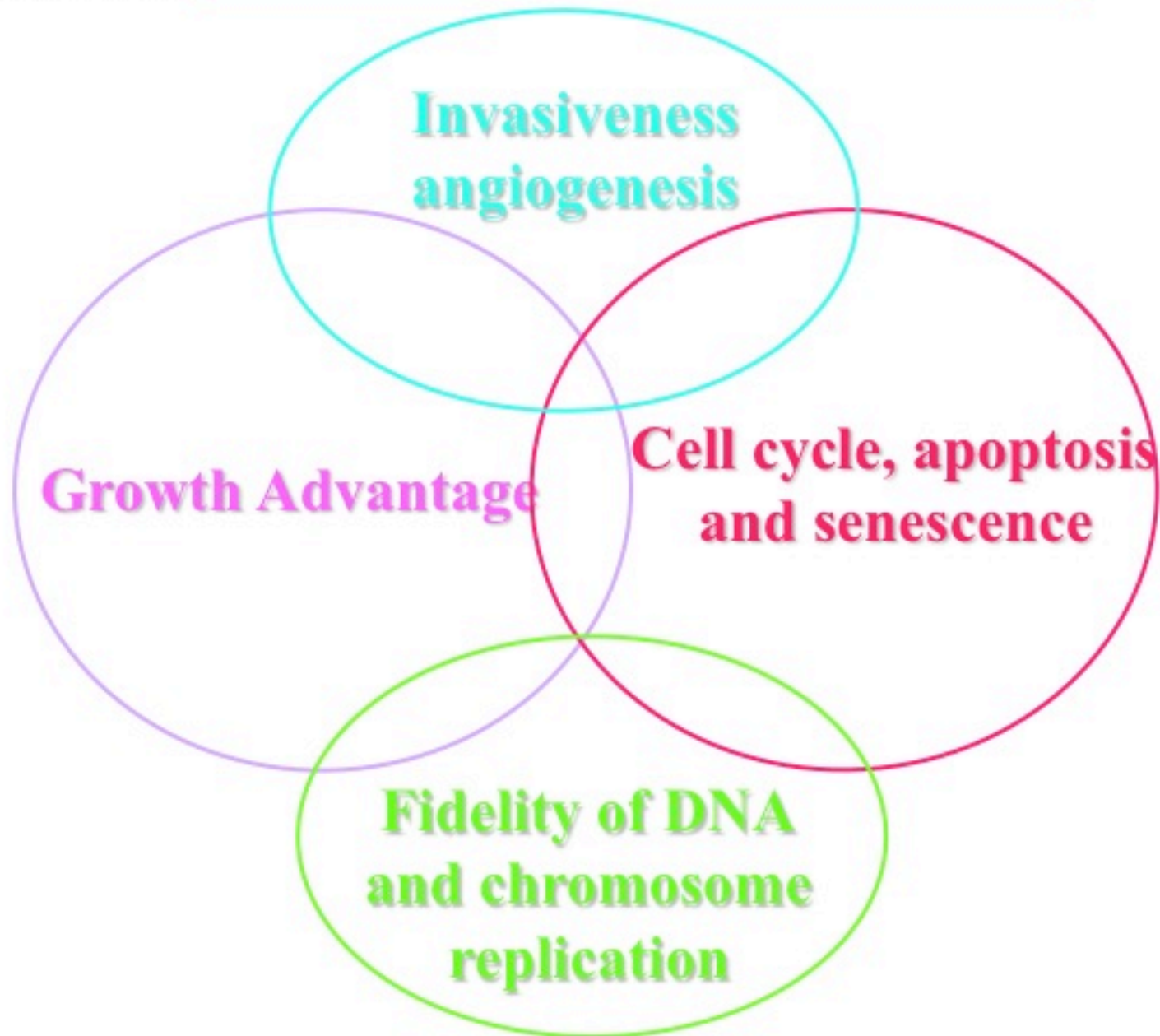
KEY POINTS

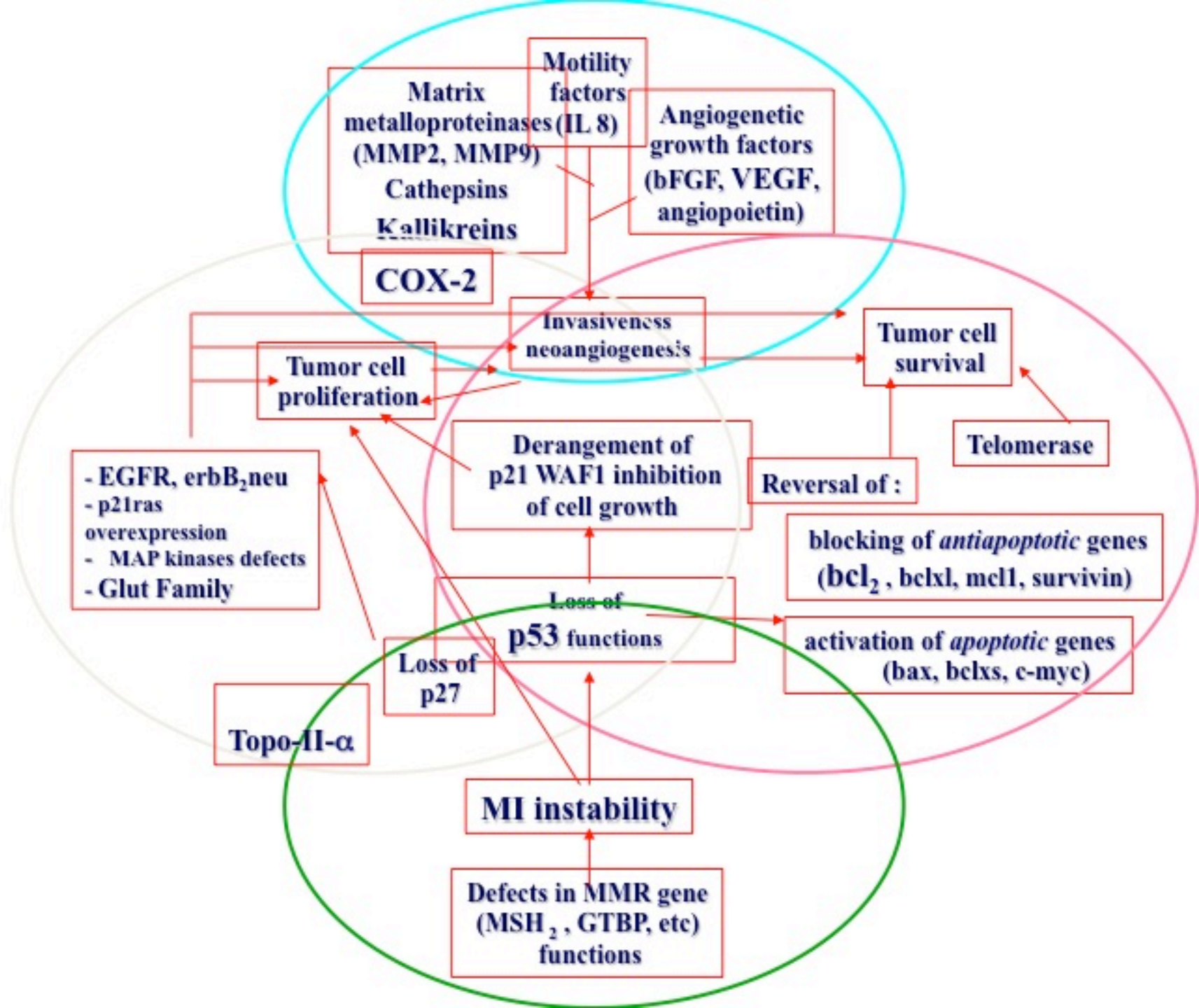
- **CHIRURGIA**
- **CHEMIOTERAPIA**
- **CARATTERIZZAZIONE MOLECOLARE**



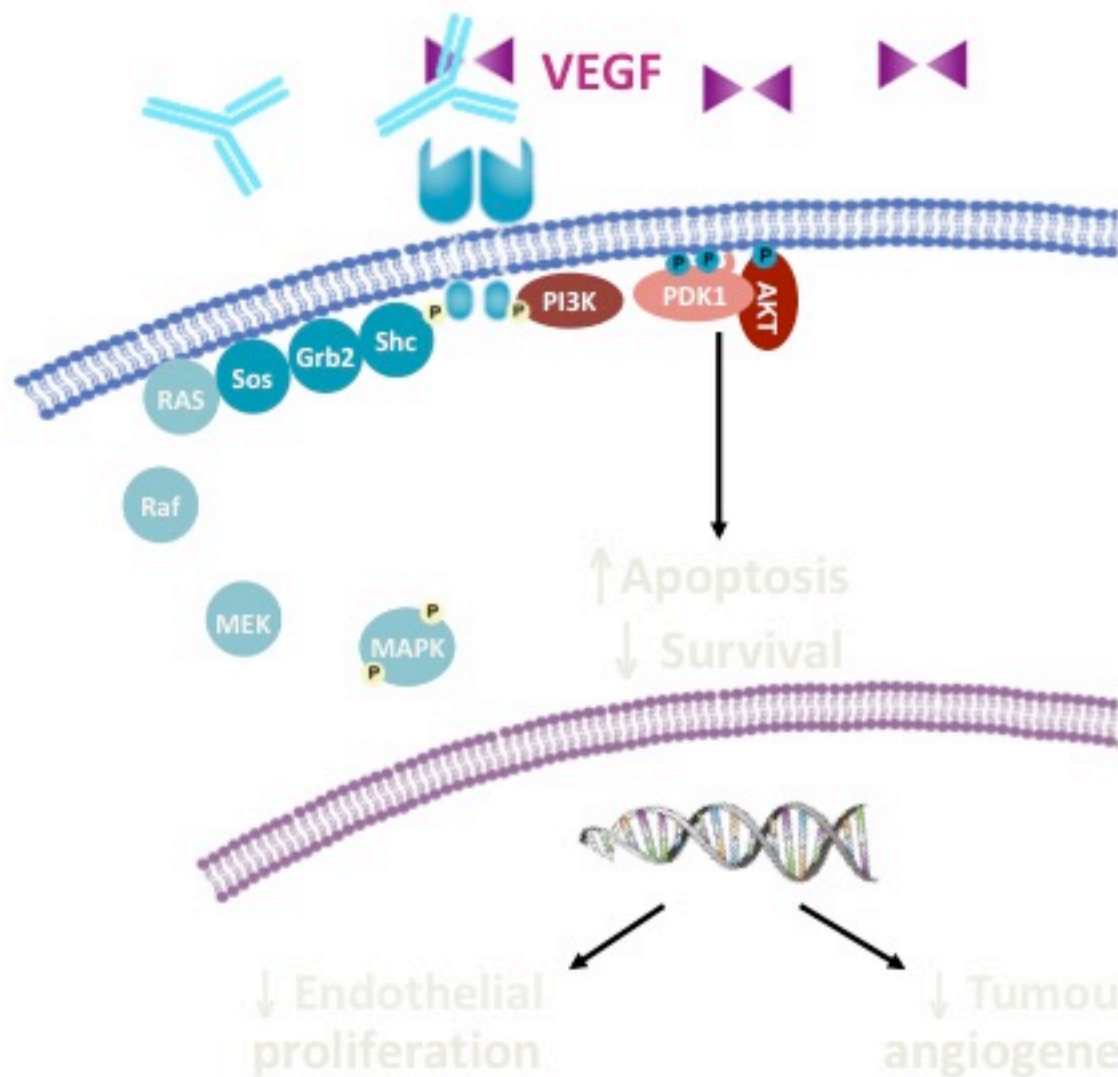
Progress In The Management Of Ovarian Cancer: Evolution Over 40 Years







Mechanism of action of bevacizumab

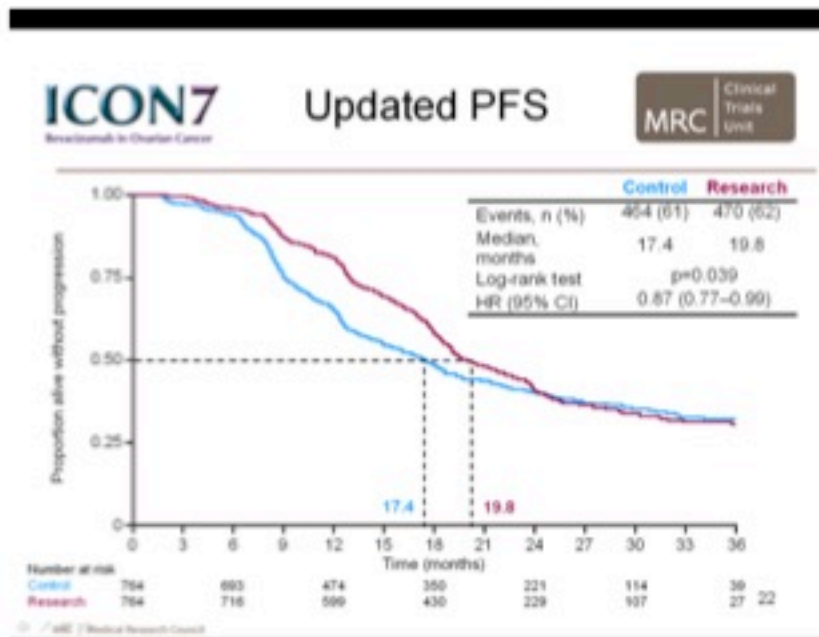
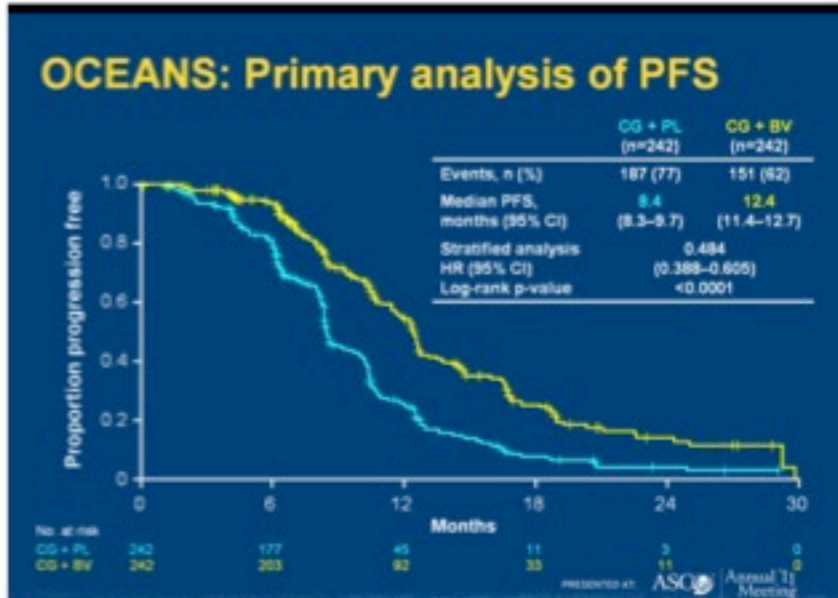
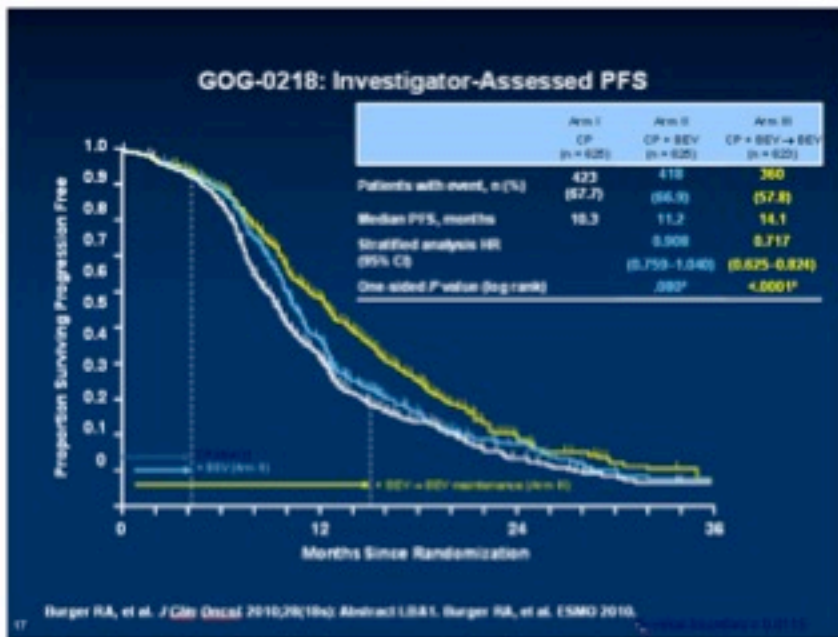


Bevacizumab binding to VEGF prevents binding to the VEGF receptor

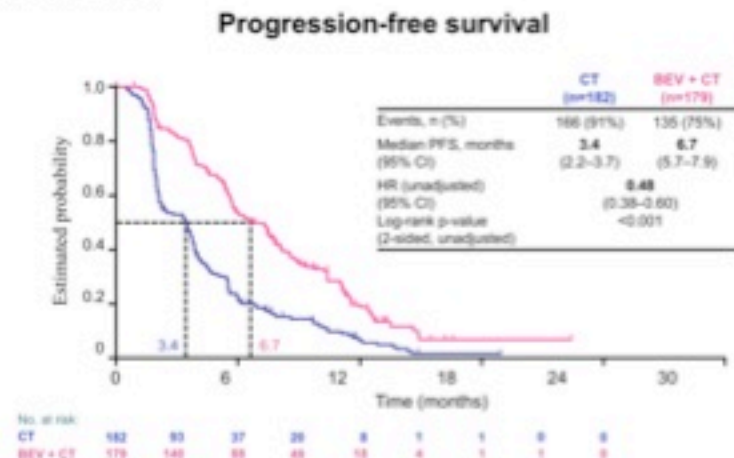
VEGF receptor signalling pathways are not stimulated

Apoptosis is increased and cell survival is decreased due to reversion of VEGF receptor signalling

Endothelial cell proliferation and tumour angiogenesis are thus decreased



AURELIA



Meccanismo d'azione dei PARP-Inibitori

DNA SSBs occur all the time in cells and PARP detects and repairs them

During the replication process unrepaired SSBs are converted into DSBs



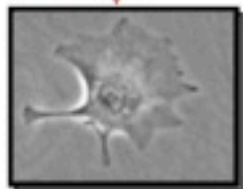
Replicating cells



Normal cell

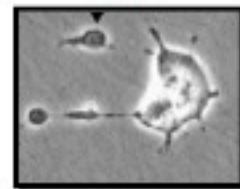
Cancer cell with HRD

Repair by Homologous Recombination
Survival



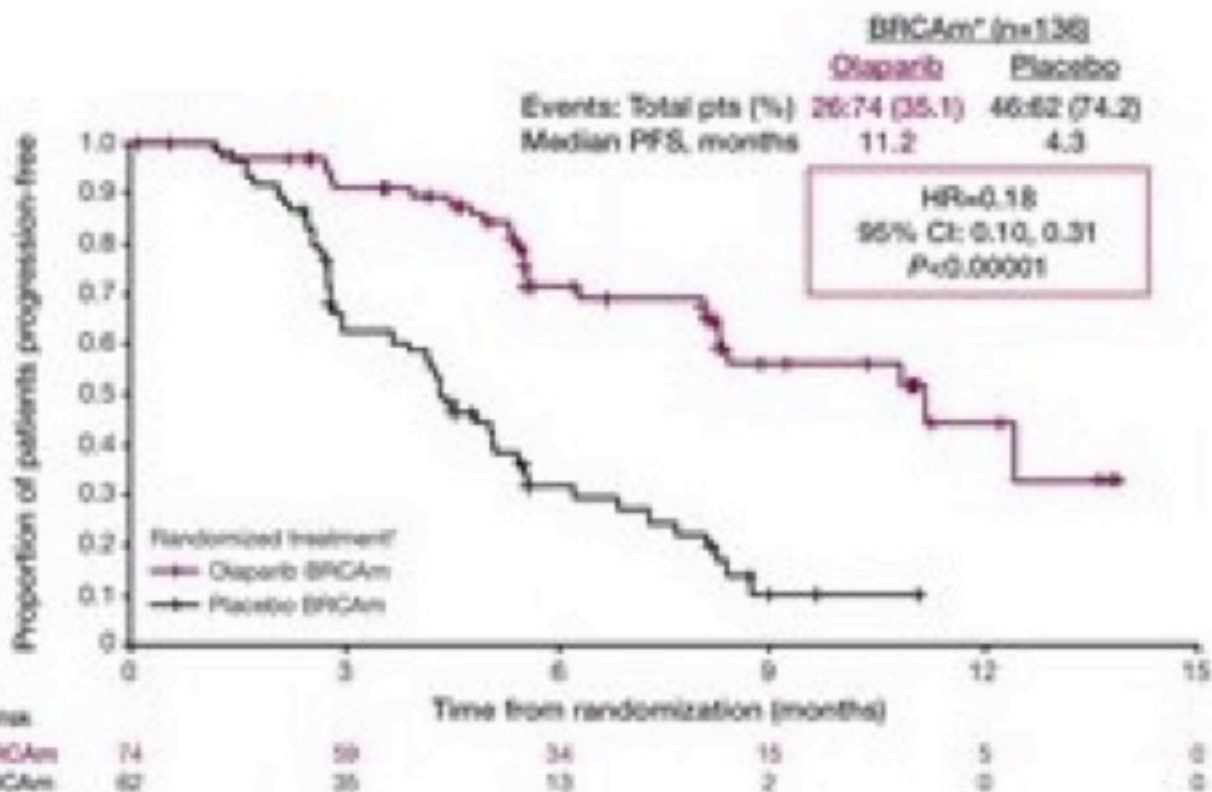
Tumor specific killing by Olaparib

No effective repair (No HR pathway)

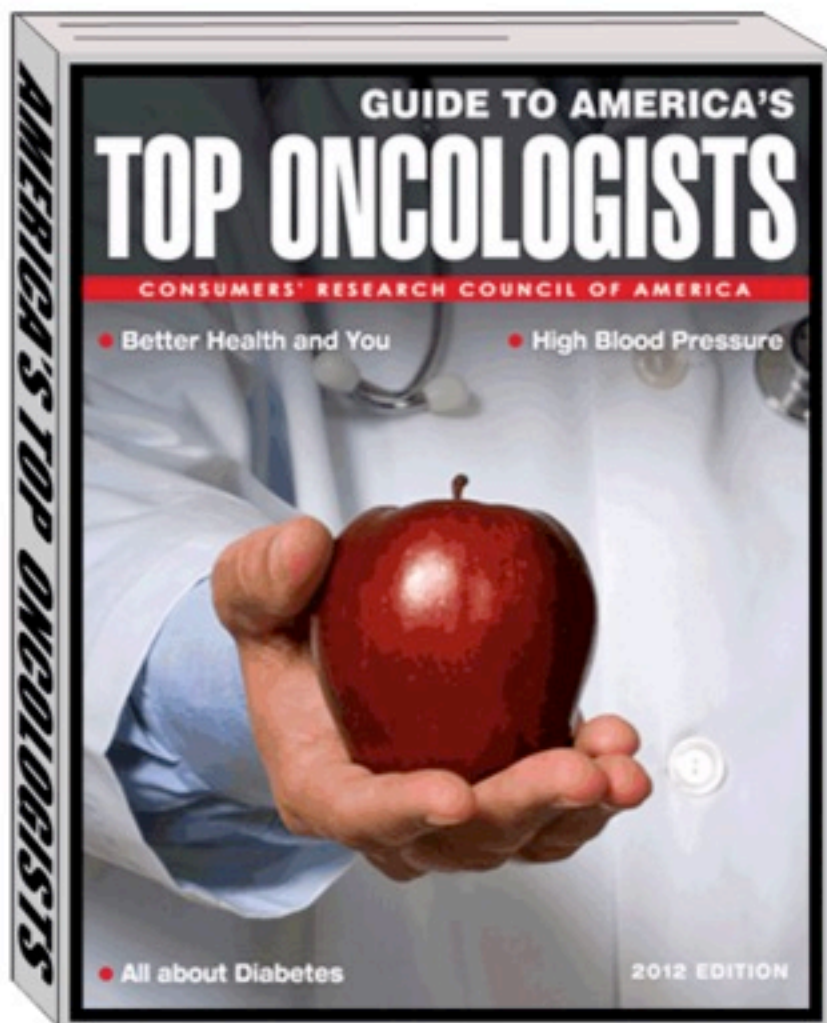


Cell death

Figure 1. PFS results from the subset of patients with a BRCAm



Includes patients with germline and/or somatic mutations.
 Statistical significance based on stratified log-rank test.



- Chemotherapy
- HIPEC
- Target therapy
- Onco-biology
- Onco-fertility

Ca125 DNA Index PCNA ER PR EGFR Her-2 p53 p21 p27 GST Glut-1 CatD nm23



Age Stage Histo Grade RT Ascite CT Response Status PFS

	G-E	38	IIIC	serous	G3	<2	yes	P+TX	yes	NED	102
	A-O	44	IIIC	serous	G3	<2	yes	P+TX	yes	Rec	23






- ✓ Molecular alteration guided biotherapy
- ✓ High risk profiling
- ✓ Molecular alteration guided chemotherapy

OVARIAN CARCINOMA clinical & molecular features

	HGSC	LGSC	MC	EC	CCC
Risk factors	<i>BRCA1/2</i>	?	?	HNPCCa	?
Precursor lesions	Tubal intraepithelial carcinoma	Serous borderline tumor	Cystadenoma/ borderline tumor?	Atypical endometriosis	Atypical endometriosis
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Chemosensitivity	High	Intermediate	Low	High	Low
Prognosis	Poor	Intermediate	Favorable	Favorable	Intermediate

HGSC, high-grade serous carcinoma; LGSC, low-grade serous carcinoma; MC, mucinous carcinoma; EC, endometrioid carcinoma; CCC, clear-cell carcinoma. ^aHereditary nonpolyposis colorectal carcinoma.

TARGET THERAPY (ongoing trials)

- Sierosi di alto grado 
 - Sierosi di basso grado 
 - Endometrioidi 
 - Cellule chiare 
 - Mucinosi 
- PARP inhibitors: bloccando gli enzimi PARP rendono difficile la riparazione del DNA nelle cellule con mutazione dei geni BRCA
 - MEK inhibitors (selumetinib) e inibitori della degradazione di p 53 (Nutlin-2): risultati promettenti
 - mTOR inhibitors (temsirolimus)
 - HER2 inhibitors (trastuzumab)

Cancer & Fertility



Fertility Preservation

2. *Biological Approach*

- **Cryopreservation
(Oocytes and Embryos and Ovarian Tissue)**



Clinical efficiency (cancer patients)

Case report

Healthy twins delivered after oocyte cryopreservation and bilateral ovariectomy for ovarian cancer



Eleonora Porcu has been Medical Doctor and Assistant Professor in Reproductive Medicine at the University of Bologna since 1977. She is the Director of the Infertility and Assisted Reproduction Center at the S. Orsola-Malpighi University Hospital in Bologna. Her fields of research include adolescent hyperandrogenism and polycystic ovary syndrome, endocrinology of infertility, reproductive cryostorage with special involvement in human oocyte cryopreservation. She received the International Federation of Fertility Societies 30th Anniversary Recognition Award for significant contributions in the field of infertility and reproductive medicine.

Slow Freezing

Live birth after the transfer of human embryos developed from cryopreserved oocytes harvested before cancer treatment

Dunsong Yang, M.D.,^a Samuel E. Brown, M.D.,^a Kevin Nguyen, M.T.,^a Vijay Reddy, M.D.,^b Cindy Brubaker, R.N.,^a and Kevin L. Winslow, M.D.^b

^aFlorida Institute for Reproductive Medicine, Jacksonville, Florida and ^bHematology/Oncology, University of Florida, Gainesville, Florida

Slow Freezing

ORIGINAL ARTICLE: FERTILITY PRESERVATION

Five years' experience using oocyte vitrification to preserve fertility for medical and nonmedical indication

Juan A. García-Velasco, M.D.,^{a,d} Javier Domingo, M.D.,^b Ana Cobo, Ph.D.,^c María Martínez, M.D.,^a Luis Carmona, M.D.,^b and Antonio Pellicer, M.D.^c

^aIVI-Madrid, Madrid; ^bIVI-Las Palmas, Las Palmas; ^cIVI-Valencia, Valencia; and ^dRey Juan Carlos University, Madrid, Spain

Vitrification

Reproductive Biomedicine Online (2014) 28, 663–668



ELSEVIER

www.sciencedirect.com
www.rbmonline.com



REVIEW

Live birth using vitrified–warmed oocytes in invasive ovarian cancer: case report and literature review



Manuel Alvarez ^{a,*}, Miquel Solé ^a, Marta Devesa ^a, Rafael Fábregas ^b, Montserrat Boada ^a, Rosa Tur ^a, Buenaventura Coroleu ^a, Anna Veiga ^{a,c}, Pedro N Barri ^a

Vitrification

J Assist Reprod Genet (2011) 28:1167–1170
 DOI 10.1007/s12015-011-9481-y

FERTILITY PRESERVATION

Live birth with vitrified–warmed oocytes of a chronic myeloid leukemia patient nine years after allogeneic bone marrow transplantation

Mi Kyoung Kim · Dong Ryul Lee · Ji Eun Han ·
 You Shin Kim · Woo Sik Lee · Hyung Jae Won ·
 Ji Won Kim · Tae Ki Yoon

View

Vitrification

Received: 10 October 2011 / Accepted: 9 November 2011 / Published online: 25 November 2011
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Fertility Preservation

3. *Surgical Approach*

- **Fertility Sparing Surgery**



Fertility-Sparing Surgery in BOT

TABLE 2

Oncologic and obstetric outcomes in patients with borderline ovarian tumors undergoing fertility preserving surgery

Author	Patients	Pregnancies	Live births	Recurrences	Deaths
Zanetta et al ⁴⁶	189	44	N/A	35	0
Lim-Tan et al ⁴⁷	35	8	6	6	0
Morice et al ⁴⁸	44	17	10	9	0
Boran et al ⁴⁹	62	13	10	4	0
Fauvet et al ⁵⁰	162	30	18	27	0
Donnez et al ⁵¹	16	12	12	3	0
Seracchiolo et al ⁵²	19	6	6	1	0
Camatte et al ⁵³	17	8	8	9	0
Morris et al ⁵⁵	43	25	16	14	1
Gotlieb et al ⁵⁴	39	22	21	3	0
Total	626	185 (30%)	107 (58%)	111 (18%)	1 (0.2%)

N/A, not available.

Eskander. Fertility preservation in patients with gynecologic malignancies. Am J Obstet Gynecol 2011.

Malignant Germ Cell Tumors

TABLE 3

Oncologic and obstetric outcomes in patients with malignant germ cell tumors treated conservatively

Author	Patients	Pregnancies	Live births	Recurrences	Deaths
Gershenson ⁵⁸	40	22	22	3	2
Kanazawa et al ⁵⁹	21	11	9	1	1
Low et al ⁶⁰	74	19	14	7	2
Gershenson et al ⁶³	71	37	30	10	4
Zanetta et al ⁶¹	138	41	28	16	3
Perrin et al ⁵⁷	45	8	7	4	2
Tangir et al ⁶²	64	47	38	5	3
Total	453	185 (41%)	148 (80%)	46 (10%)	17 (3.8%)

Eskander. Fertility preservation in patients with gynecologic malignancies. Am J Obstet Gynecol 2011.

Invasive Epithelial Ovarian Cancers

Years: 1997 - 2013

Oncological outcome

Author [reference]	Year of publication	Patients n	Median age (years)	FIGO stage n (%)	Grade n (%)	Histology n (%)	Relapses n (%)	5-Year survival
Total		793	28.6	474(60) IA 6(1) IB 308(38) IC 5(1) II-III	557(70) G1 138(17) G2 98(13) G3	420(53) muc 144(18) serous 77(10) clear cell 144(18) endo 8(1) mixed	91(11.5)	91.1%

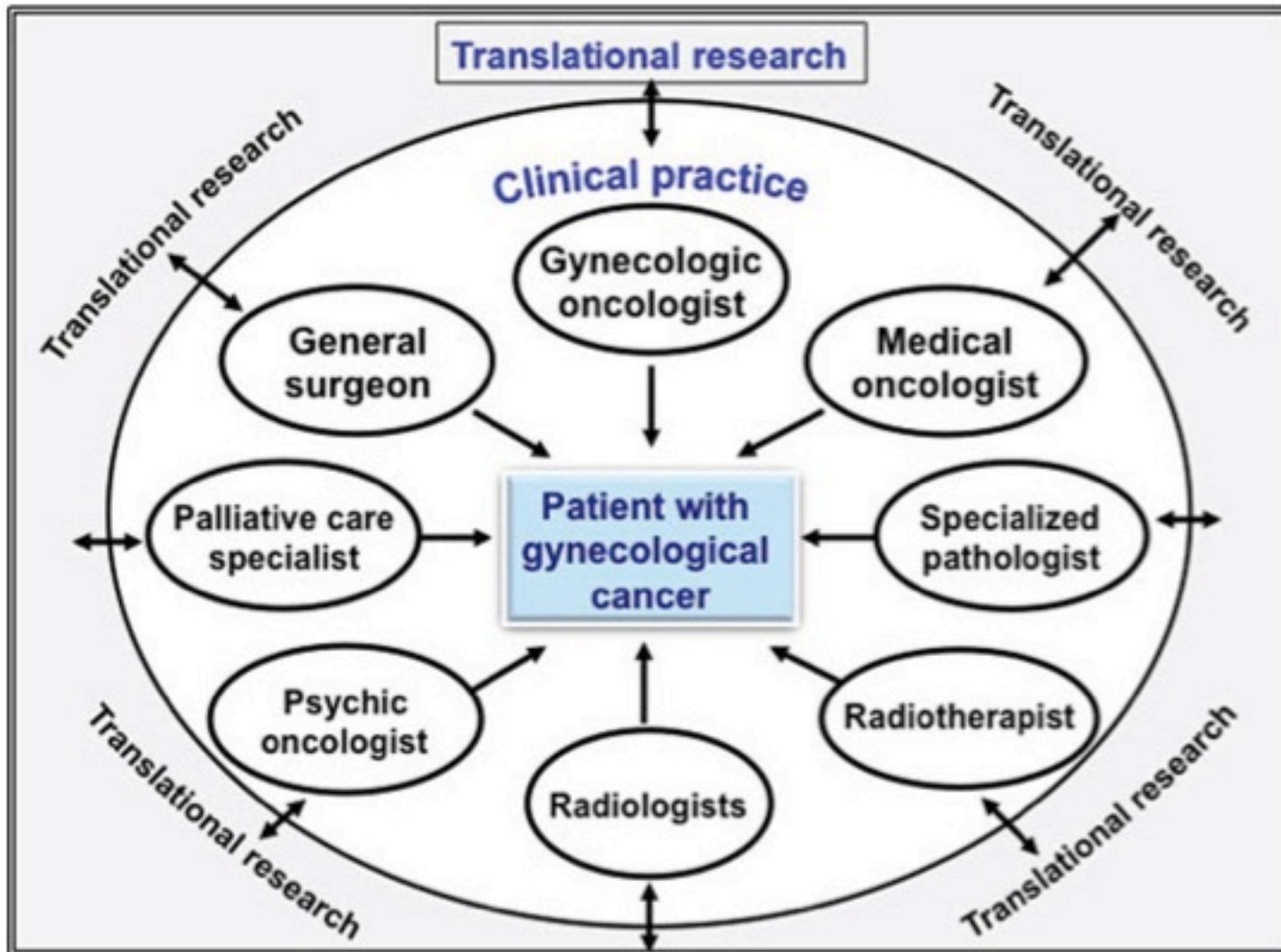
Controlateral ovarian recurrence: 4.4%

Fertility outcome

Author [reference]	Year of publication	Patients n	Mean age years	FIGO stage n (%)	Childbearing wish n (%)	Successful conception	Abortions n (%)	IVF n (%)
Total		697	29	419 (60) IA 6 (1) IB 252 (36) IC 20 (3) II-III	NRA	215 (74)	38 (18)	5

Why an ovarian
cancer unit?





**Thanks for your
attention!**

