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Ovarian Cancer

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Disclosures

I have no actual or potential conflict of interest in relation to this program/presentation.

Discussion of Non-FDA Approved uses: none

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Learning Objectives

1) Review primary systemic treatment options for epithelial ovarian cancer

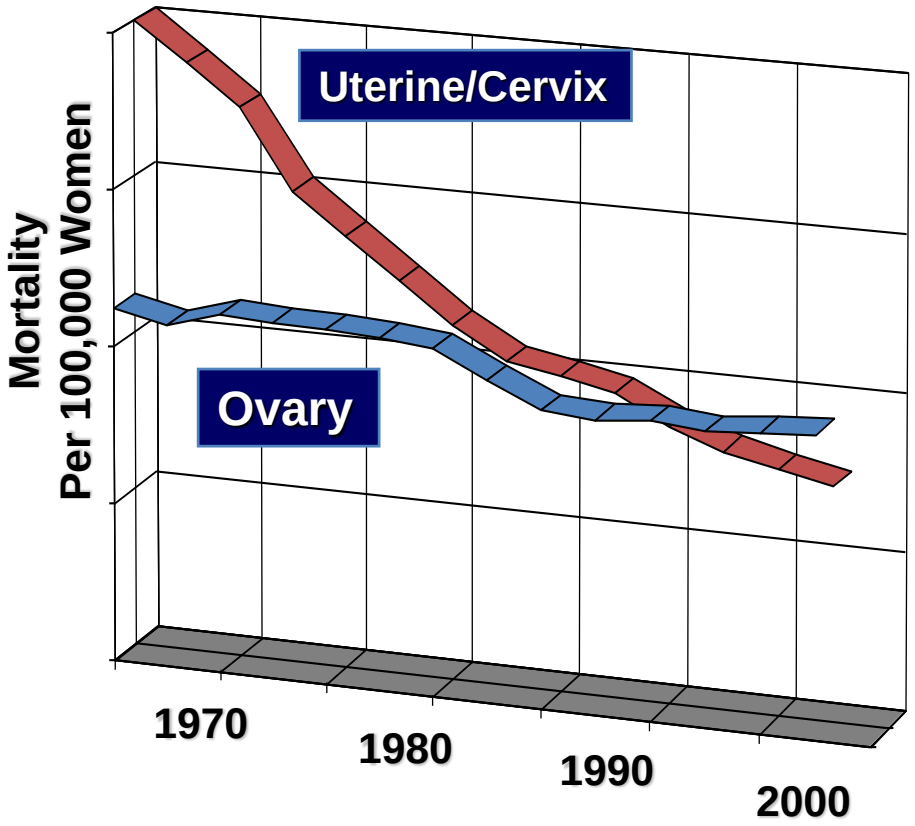
2) Review current indications for targeted therapy of ovarian cancer

Ovarian Cancer

- Germ Cell
- Stromal cell
- Epithelial

The Impact of Ovarian Cancer

- Estimated incidence and mortality in the United States (2006)[1]
  - 20,810 new cases
  - 15,310 deaths
- Approximately 6% of all cancer deaths in women
- 10-year survival: 8%–20%[2]



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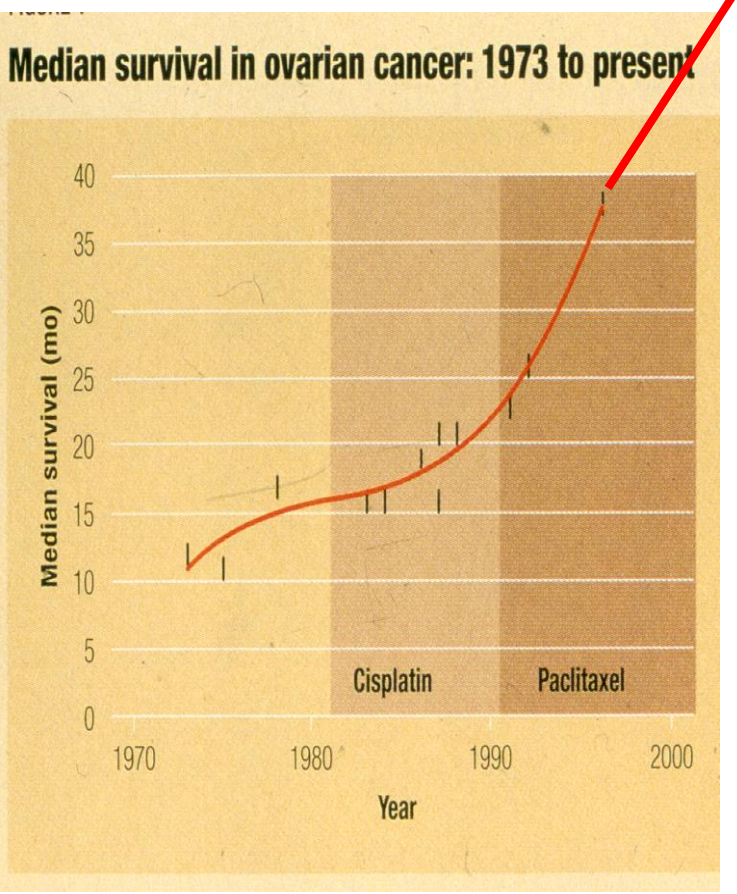
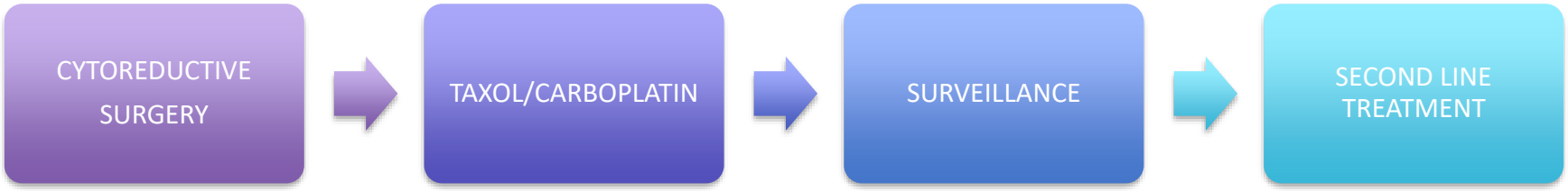
Advanced Ovarian Cancer



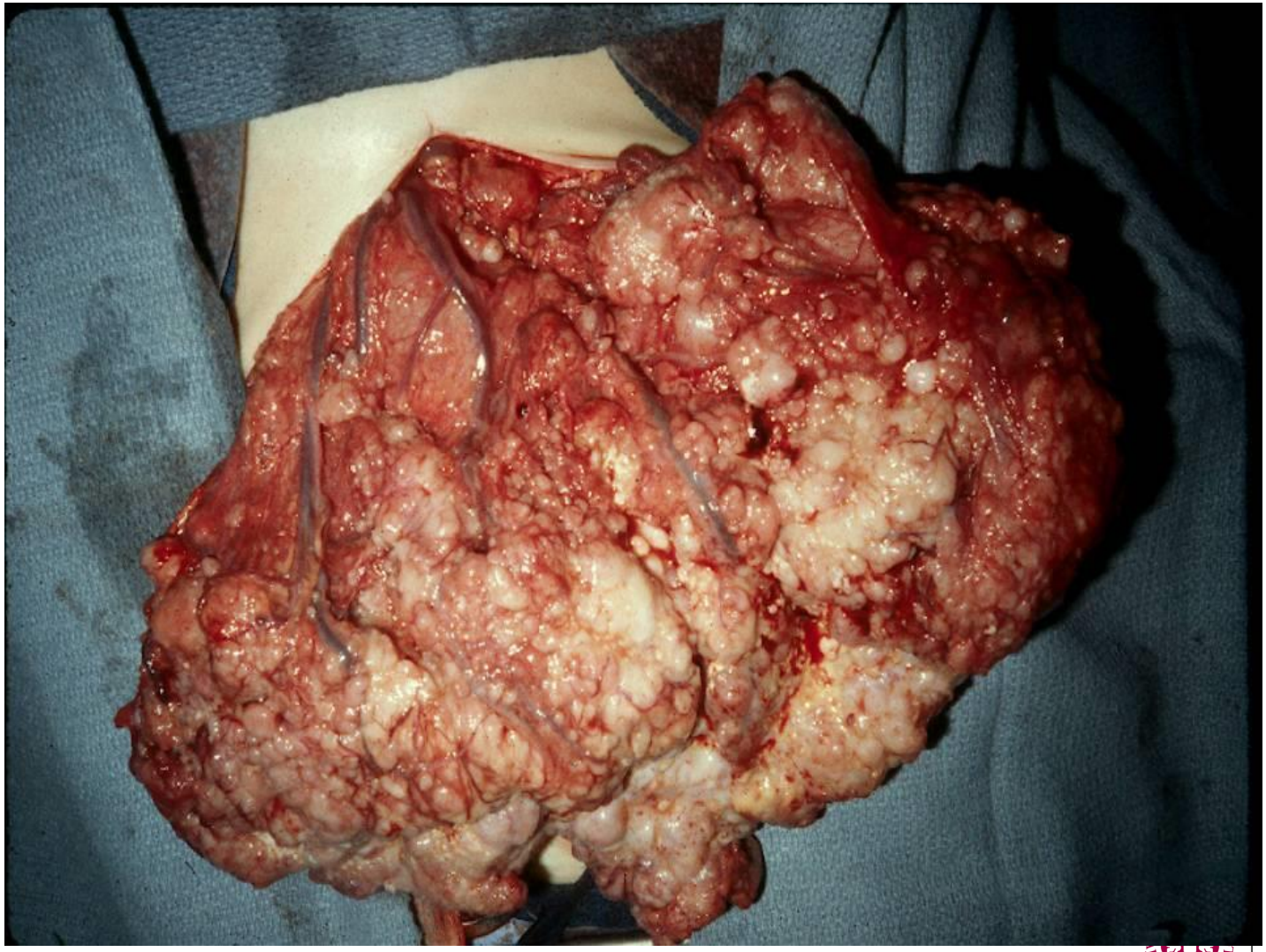
Study	Agent	Median Survival (Best Arm)
GOG 22 1983	Ctxn, Doxo	14.2 mo.
GOG 47 1986	Ctxn, Doxo, CDDP (CAP)	19.7 mo.
GOG 111 1996	Paclitaxel, CDDP	38 mo.
GOG 104 1996	IP CDDP	49 mo.
GOG 114 2001	IP CDDP, IP Paclitaxel	63 mo.
GOG 172 2006	IP CDDP, IP Paclitaxel	67 mo.

Natural History



Tumor Reductive Surgery

Defined not by the surgery performed or the amount of tumor removed but by how large the residual disease is.



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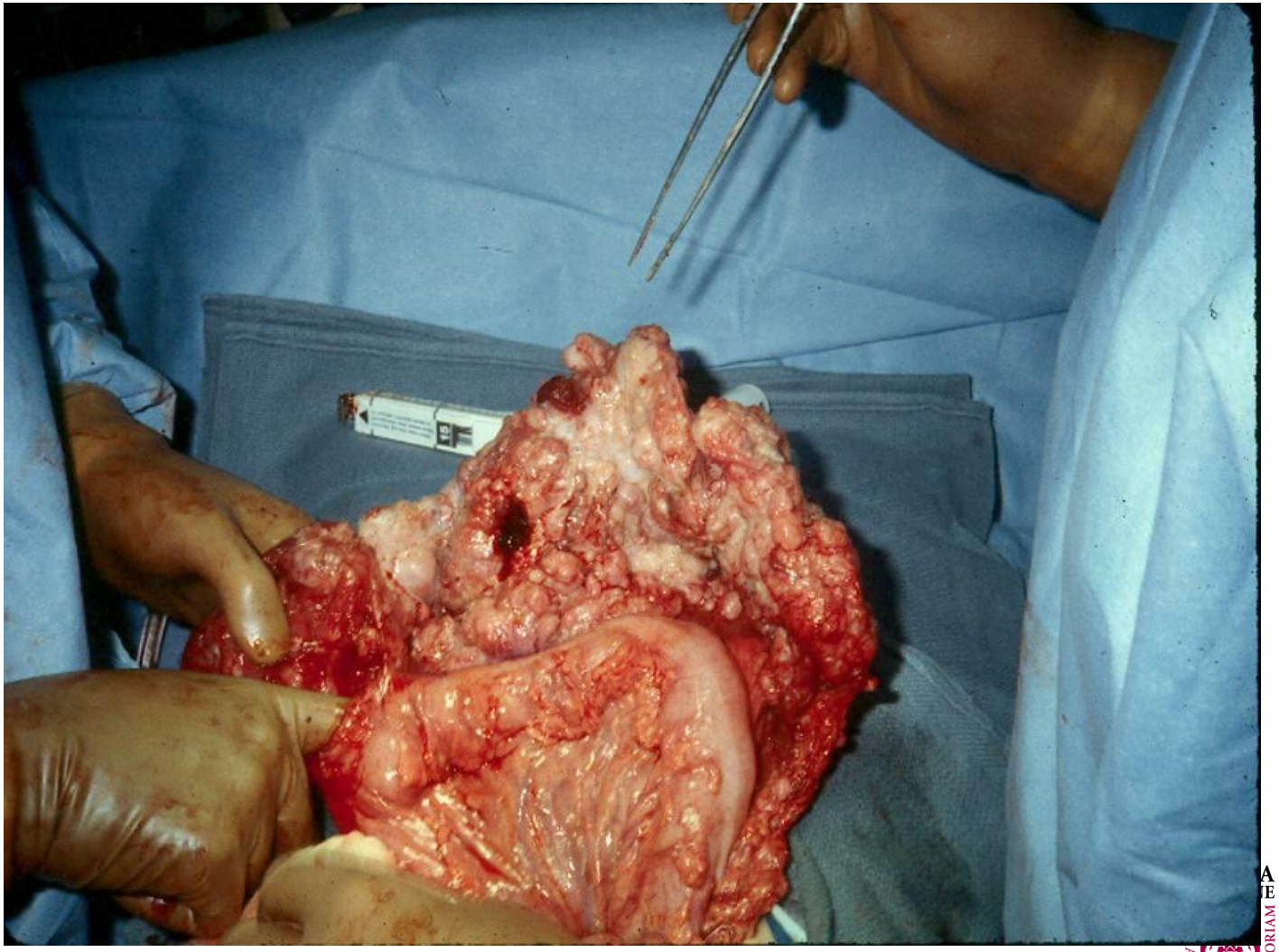

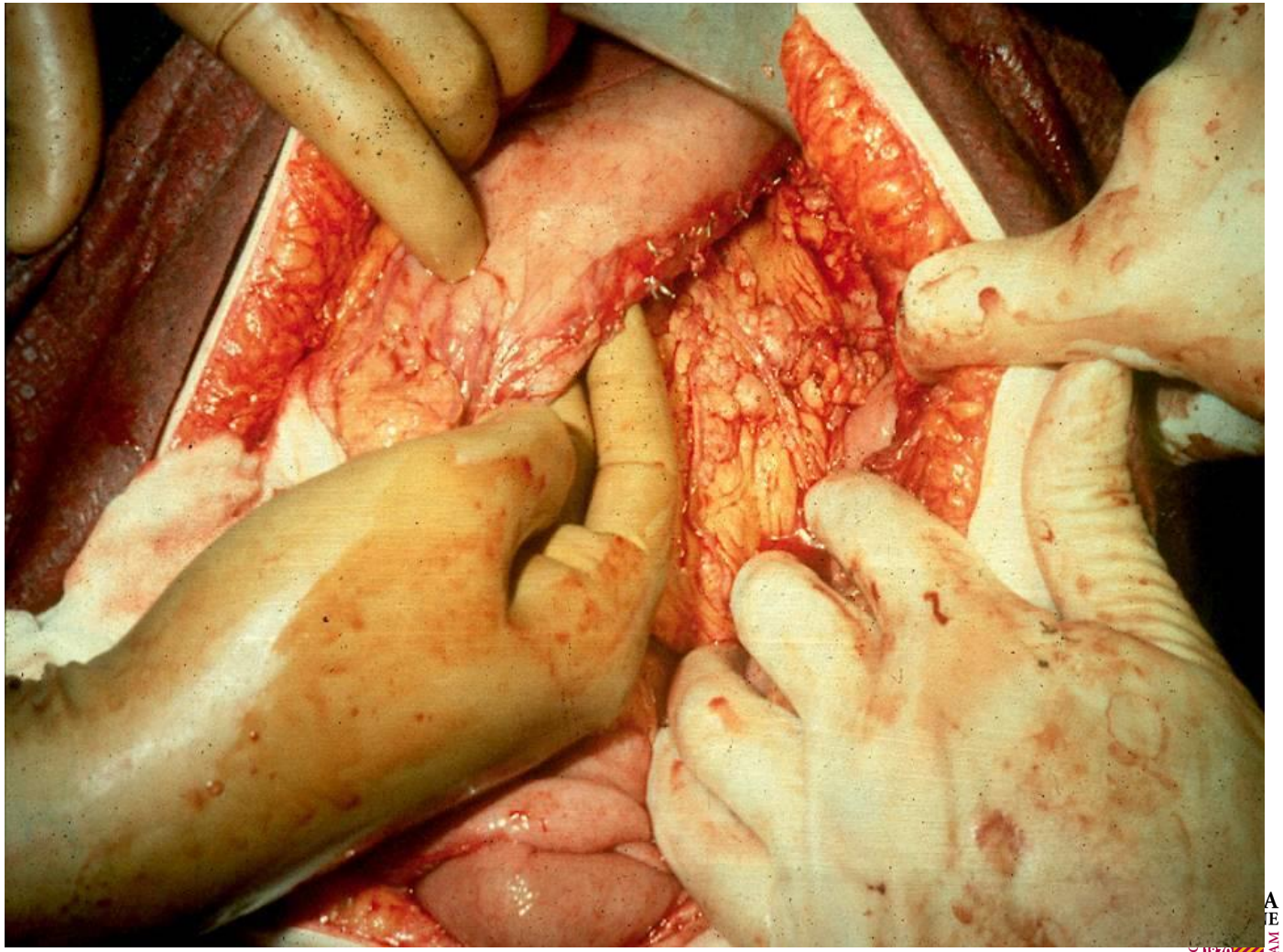

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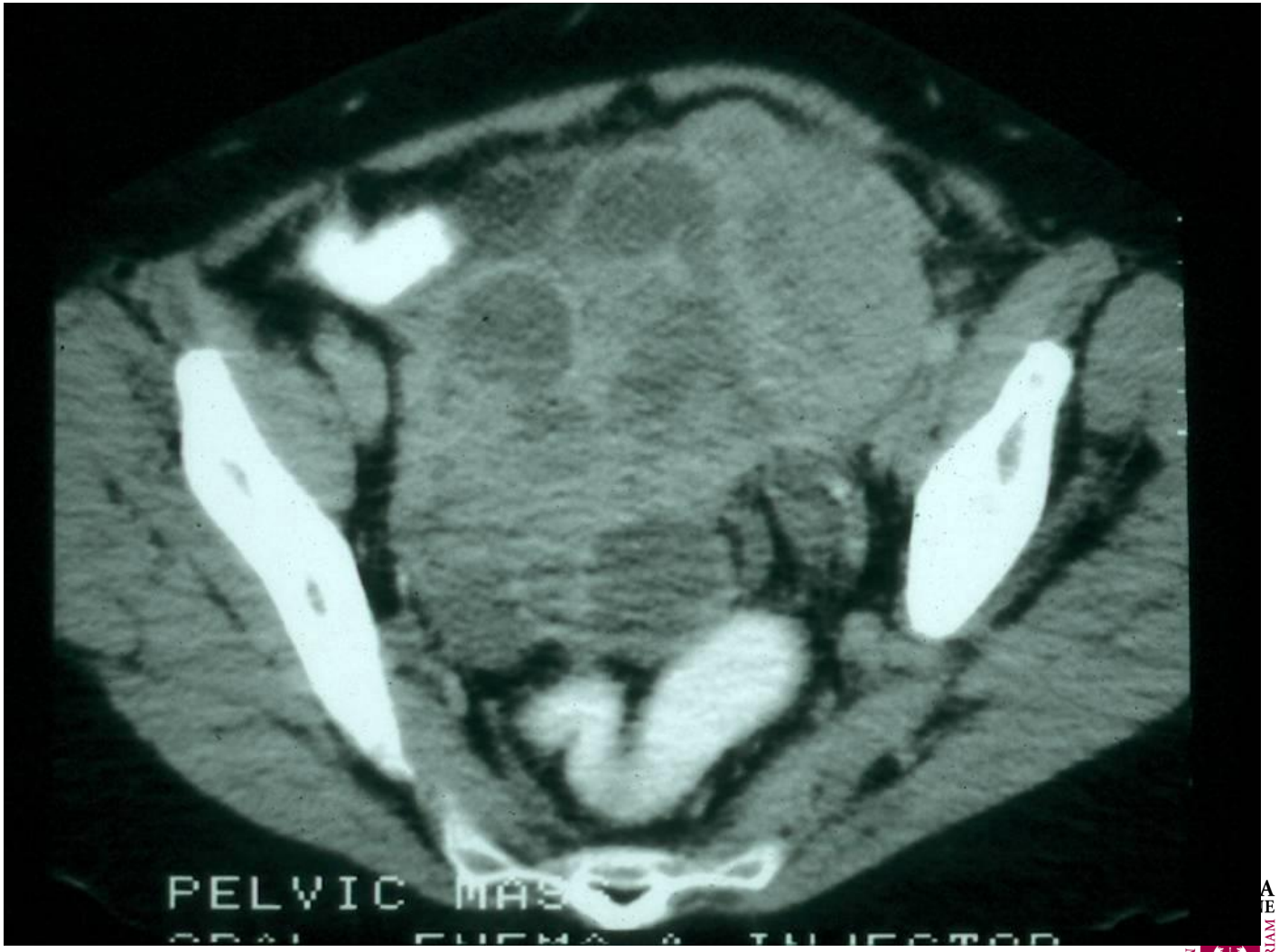

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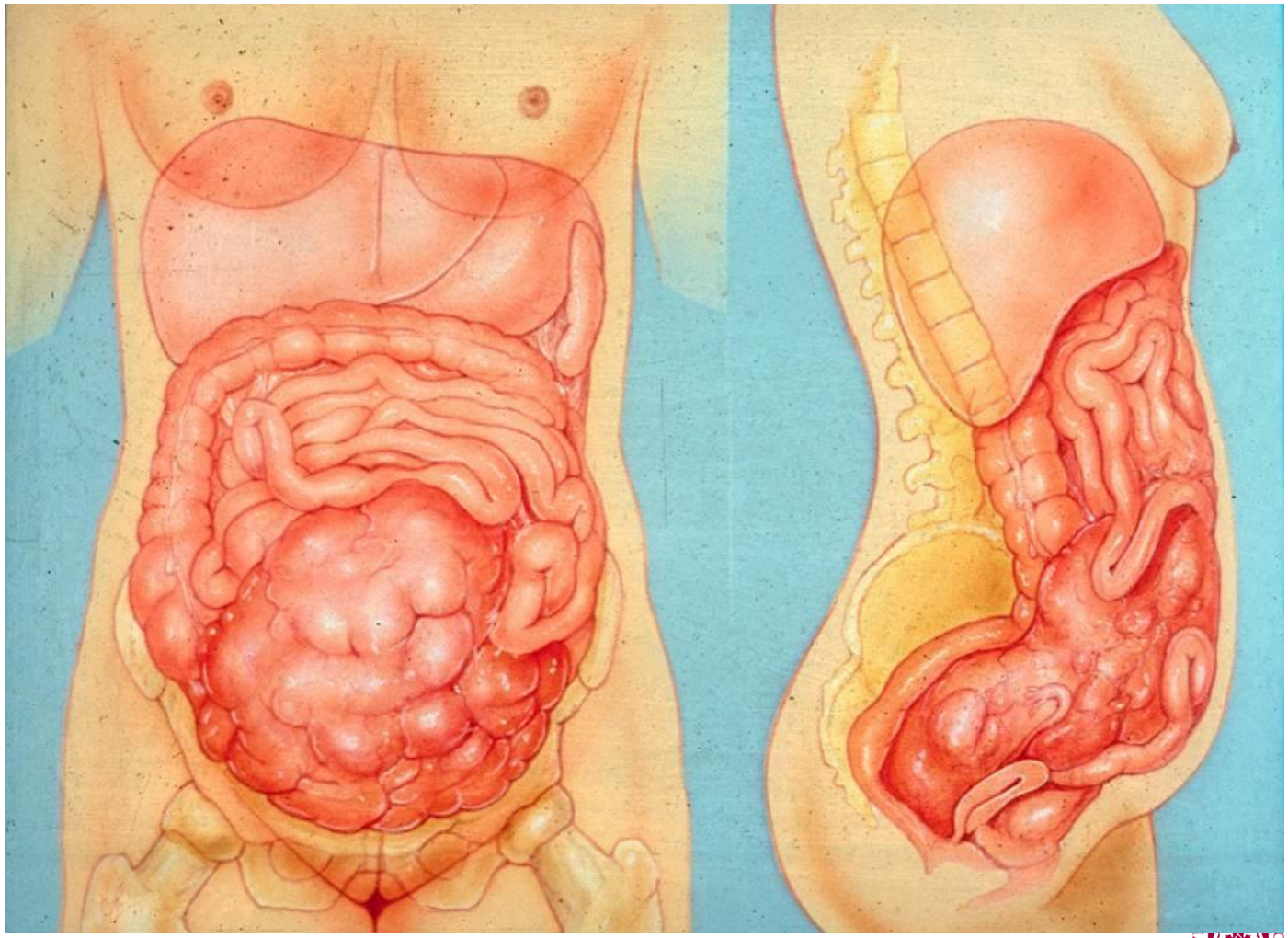

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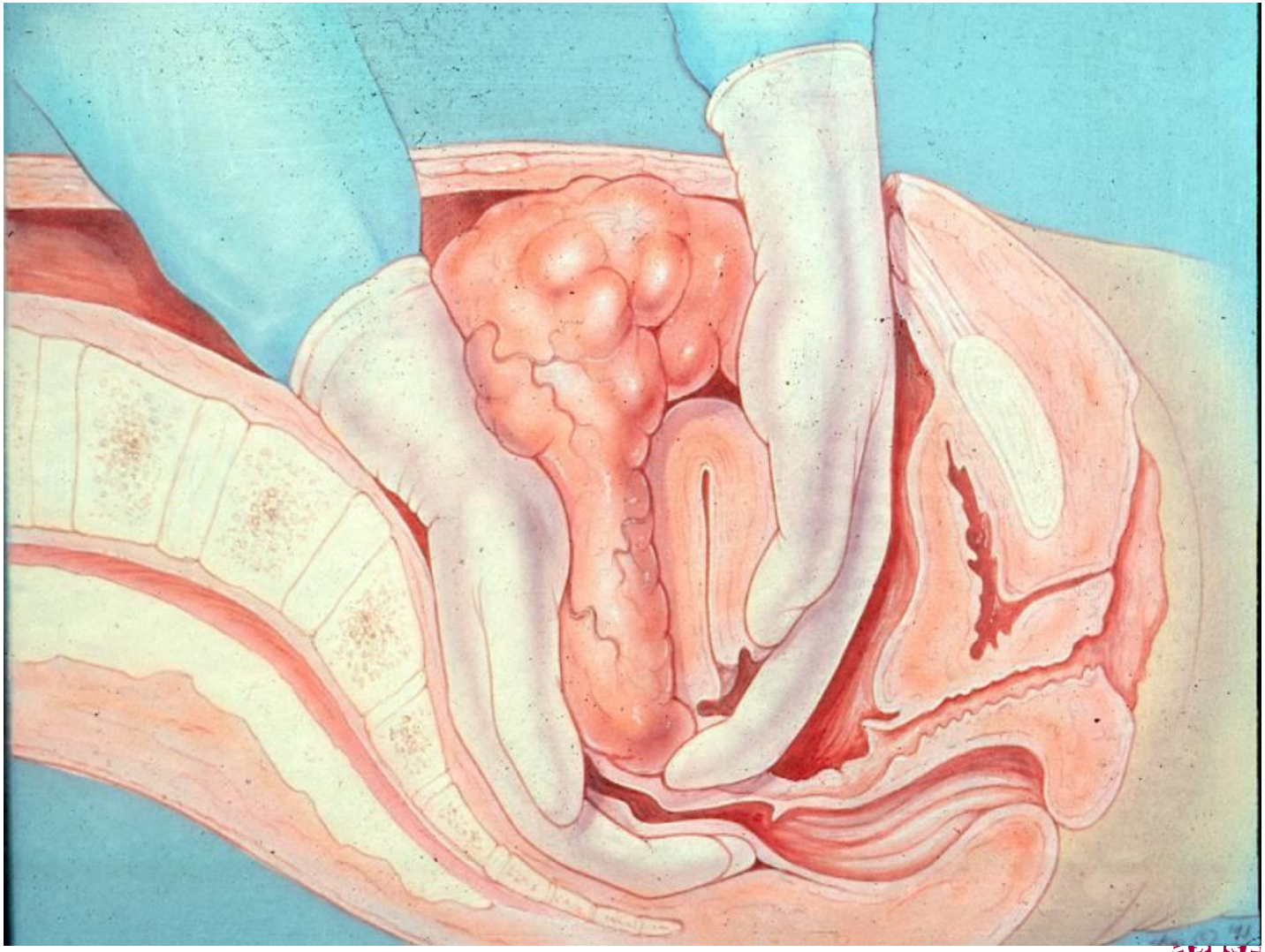

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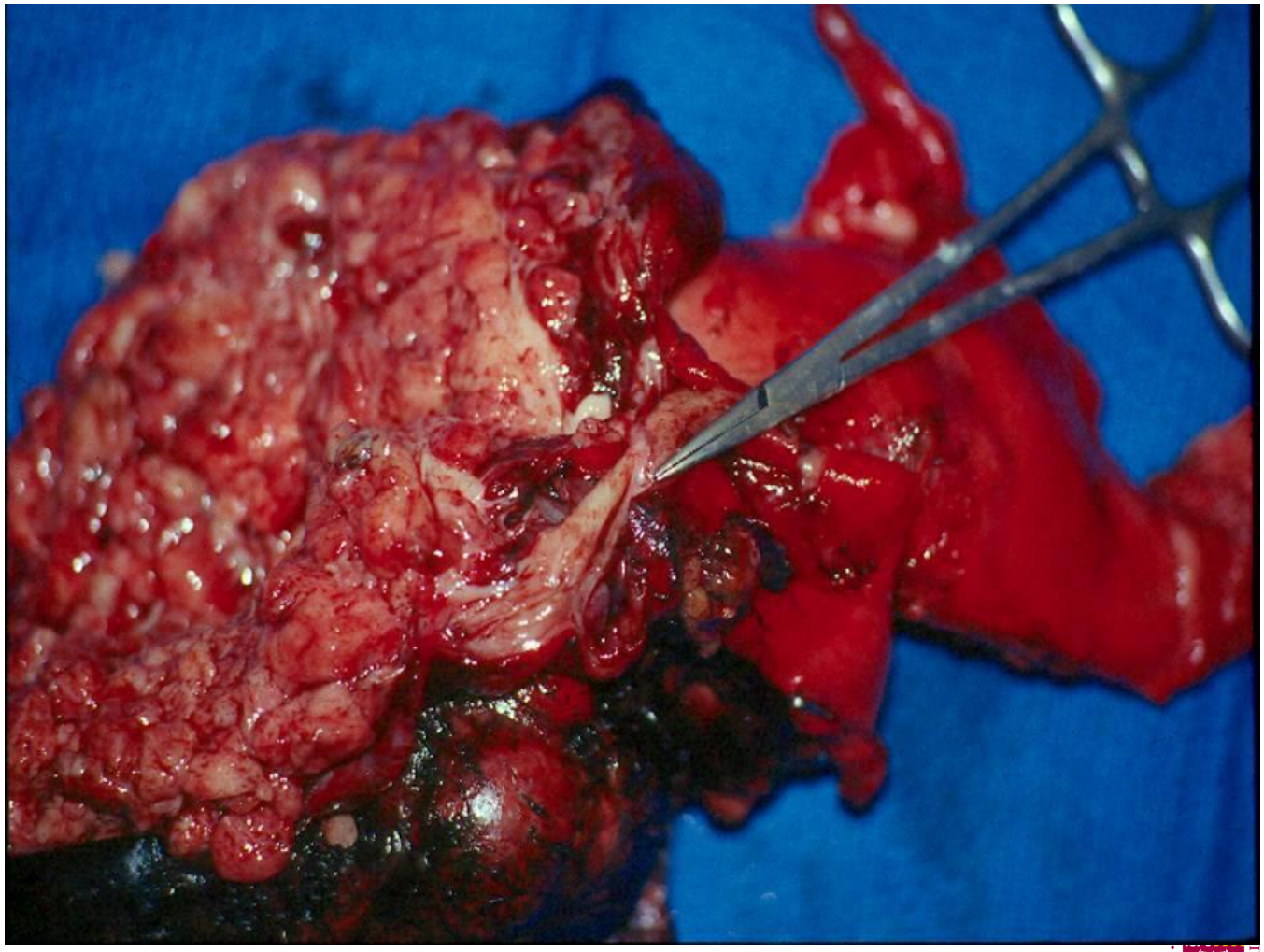

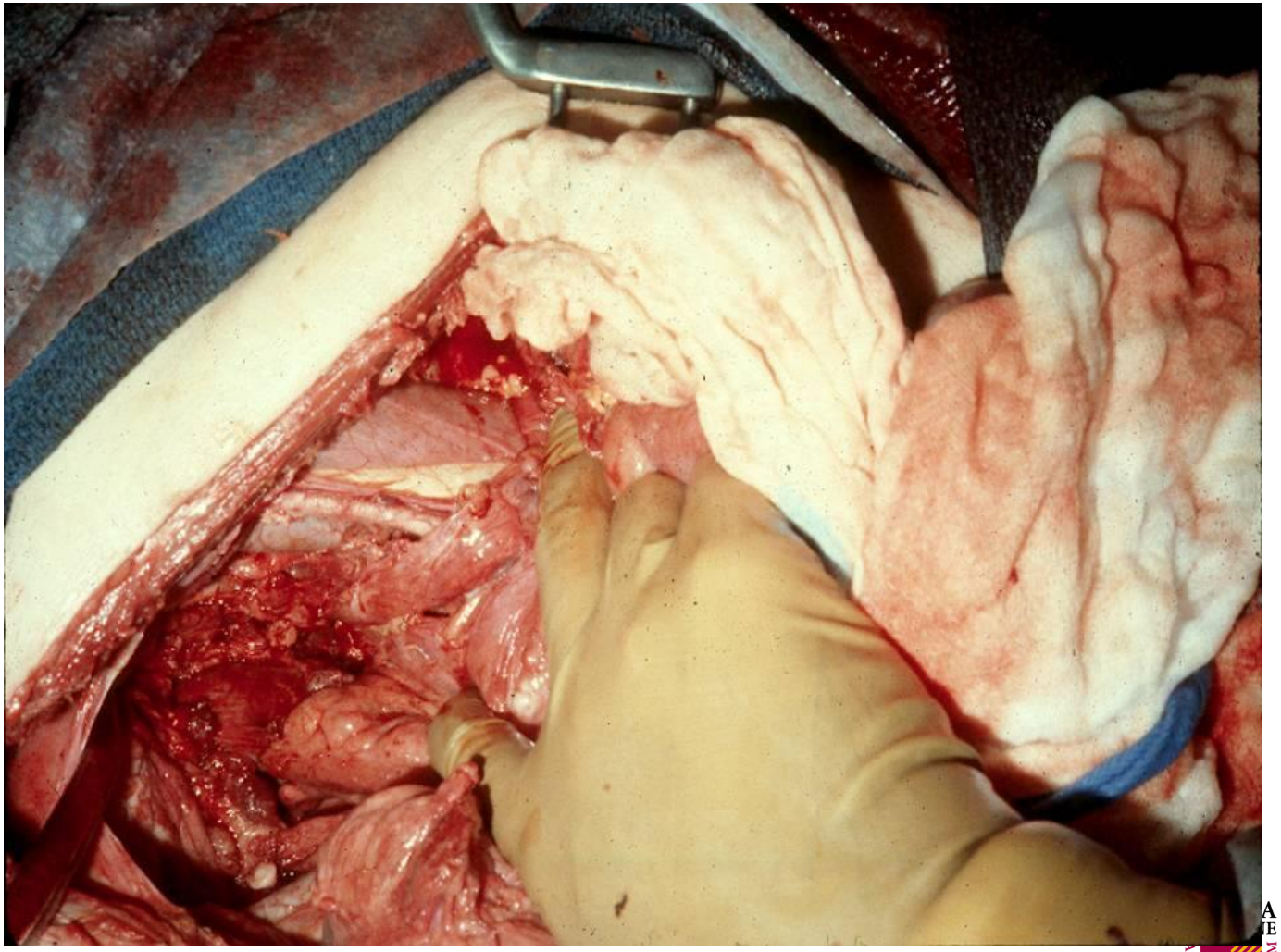

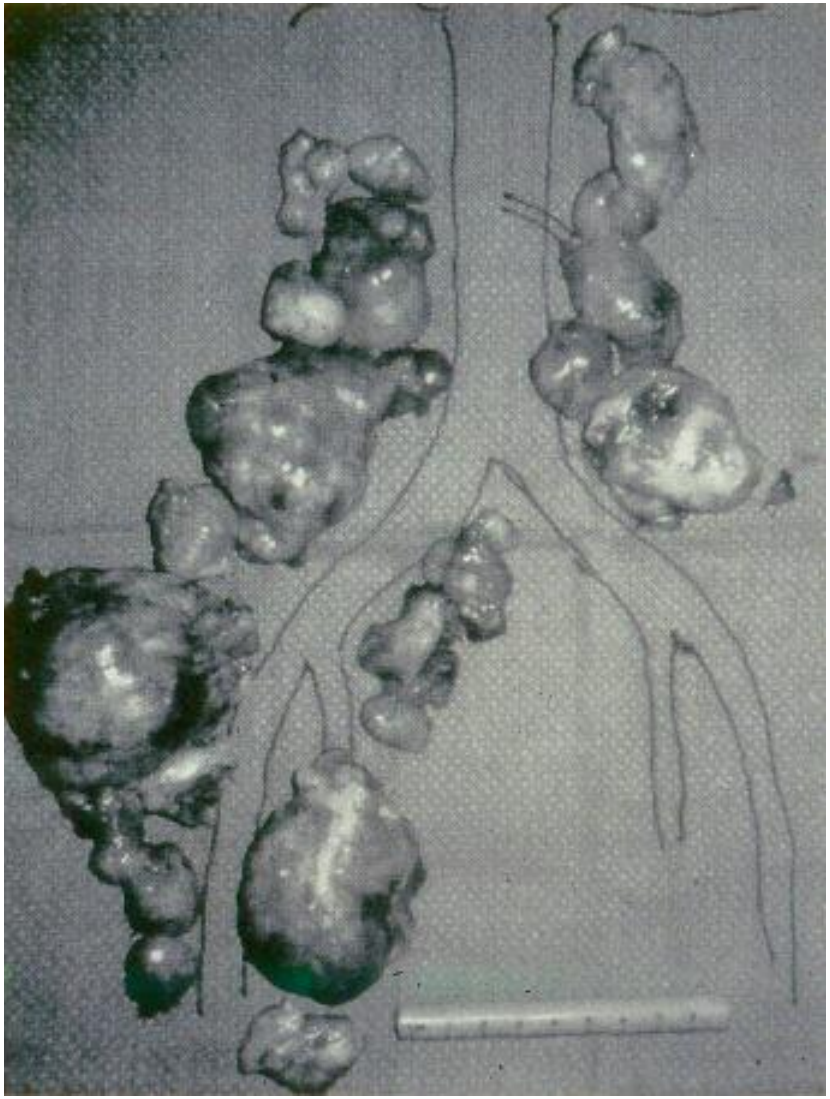

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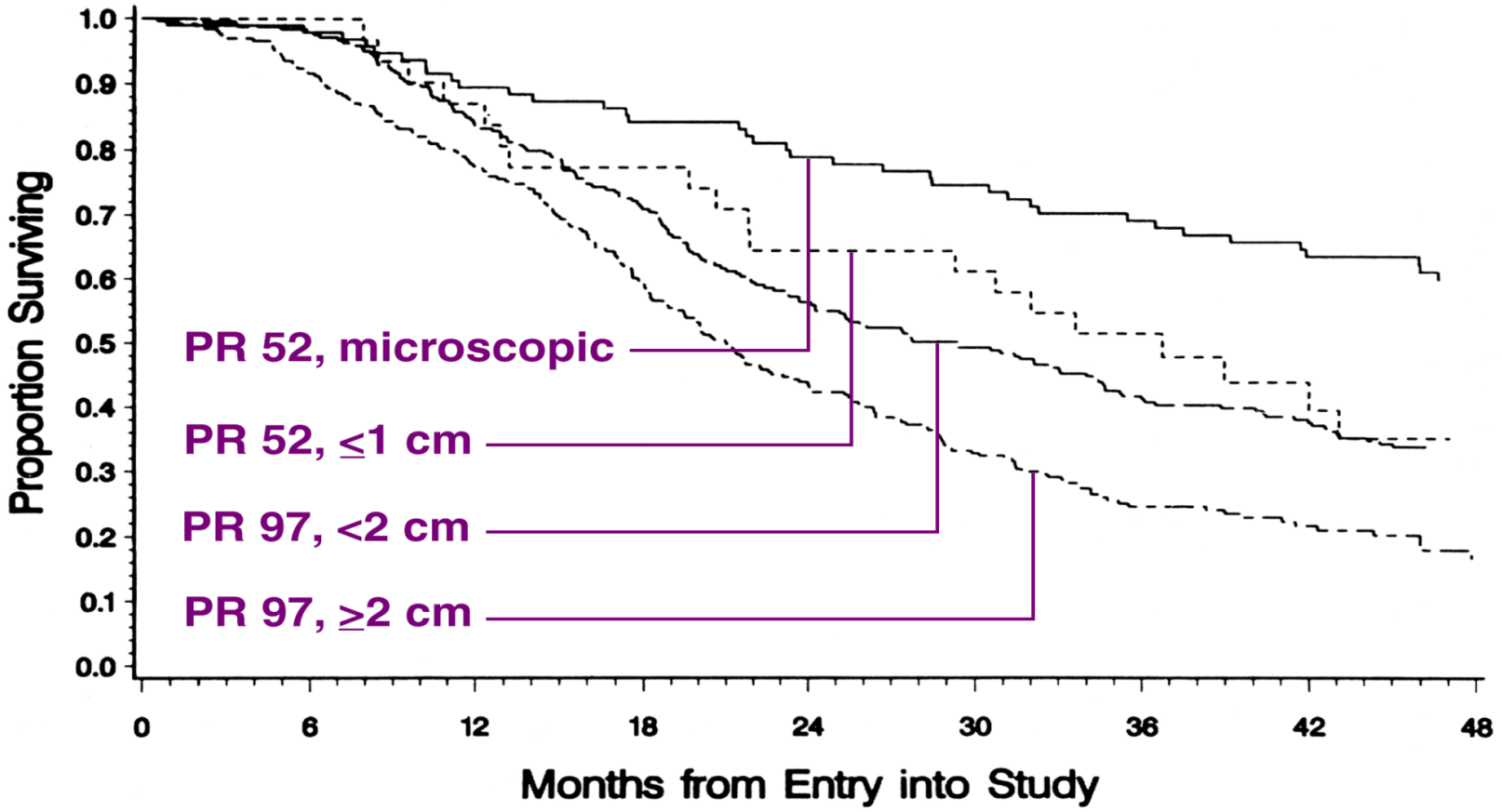
Ovarian Cancer: Survival by Residual Disease



GOG Protocols (PR) 52 and 97

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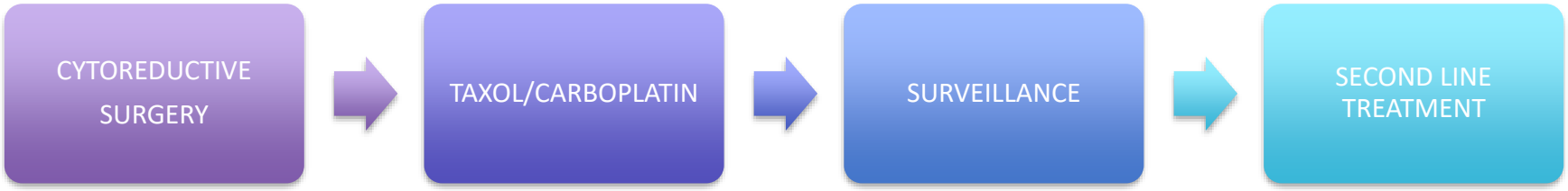
Natural History



Neoadjuvant Chemotherapy

- giving pts 3-4 cycles of chemotherapy prior to debulking surgery
- Easier surgery
- Less hospital days
- Survival data mixed

Neoadjuvant Chemotherapy

- Reserved for patients unfit for primary debulking surgery
  - Poor performance status
  - Medical comorbidities
  - Widely metastatic disease that is believed to be unresectable to optimal

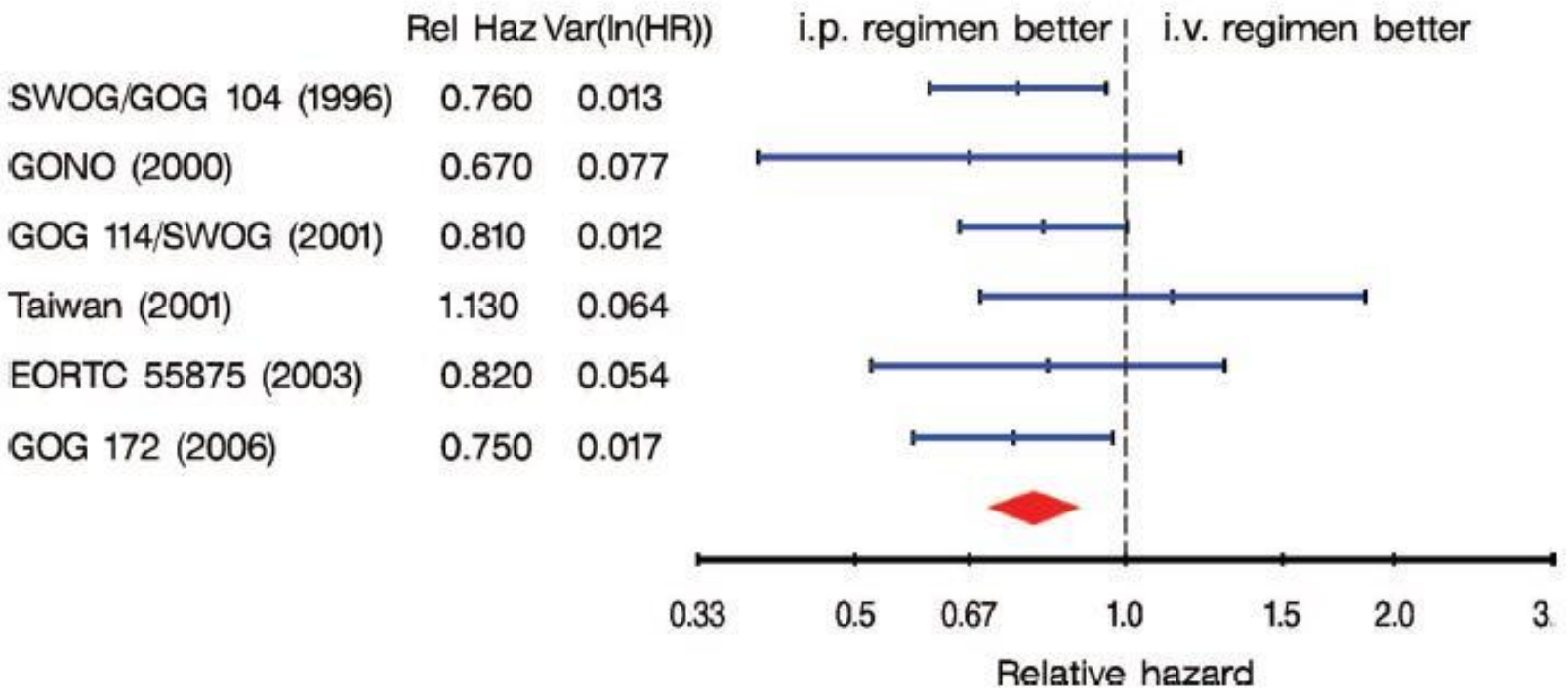
Drug Delivery for Ovarian Cancer: Intraperitoneal Therapy

- 1950's: First use of IP for malignant ascites
- 1968: Long-term peritoneal access device
- 1978: Demonstration of slow peritoneal clearance of some drugs
- 1984: Feasibility of intermittent large volume intraperitoneal therapy
- 1996: First report of a survival benefit for IP vs. IV chemotherapy in advanced ovarian cancer

Intraperitoneal Chemotherapy

- Rationale for IP therapy
  - Ovarian cancer is an intraperitoneal disease
  - Cisplatin and Taxol have a pharmacologic advantage when given IP
    - High IP concentration of drugs
    - Longer half-life of drug IP compared to IV
    - Longer systemic exposure to chemo drugs
    - Cisplatin achieves 10 – 20x greater exposure IP than IV

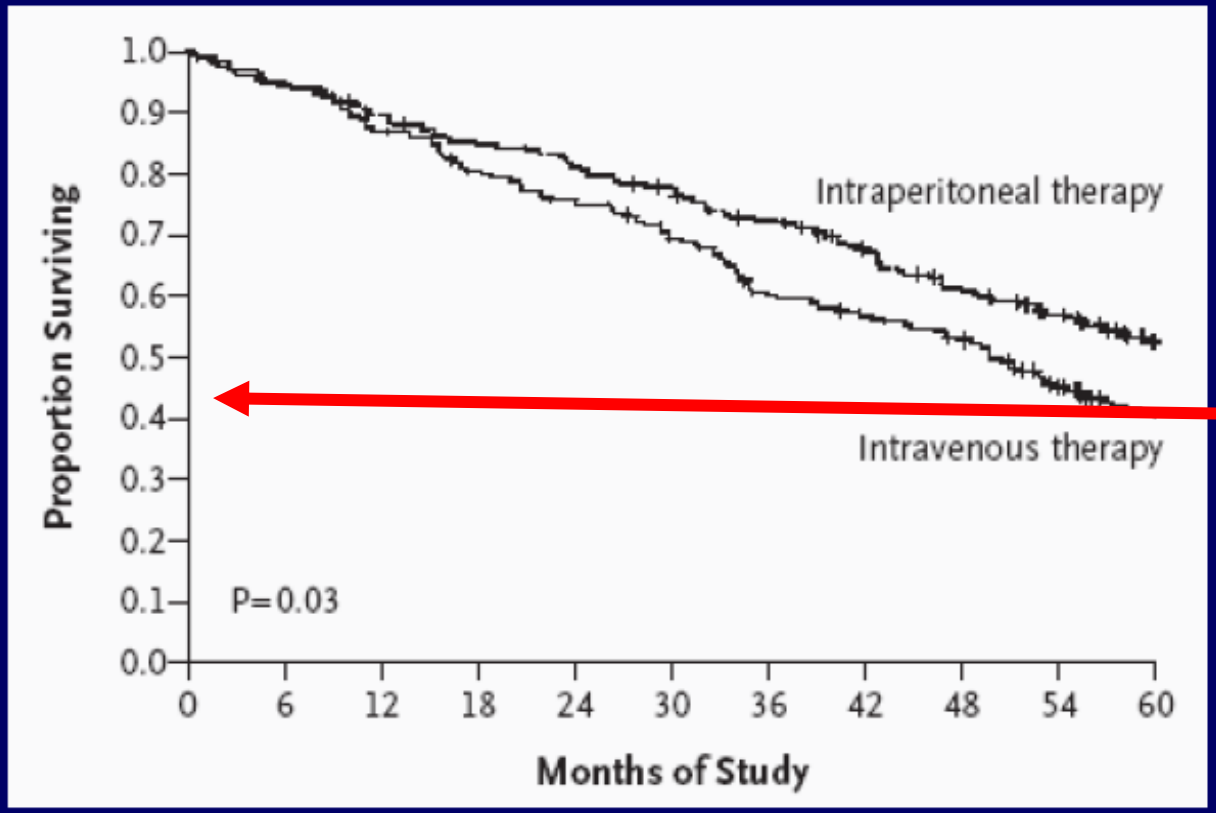
Overall Survival IP vs. IV chemo



Trimble *Oncologist* 2008

GOG #172: Overall Survival

Armstrong et.al. N Engl J Med 2006;354:34-43



GOG Gynecologic Oncology Group

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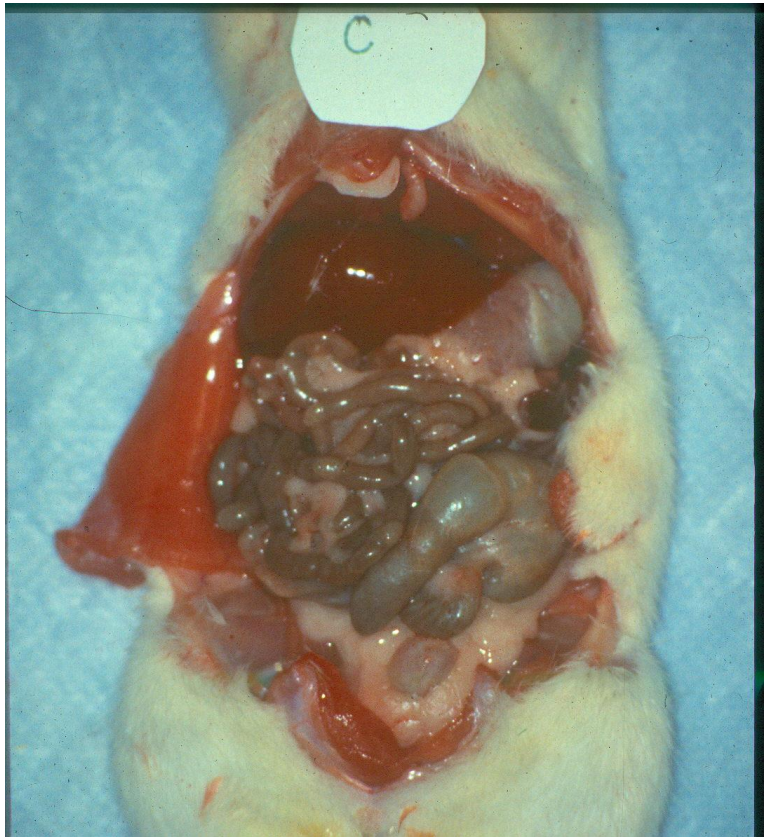
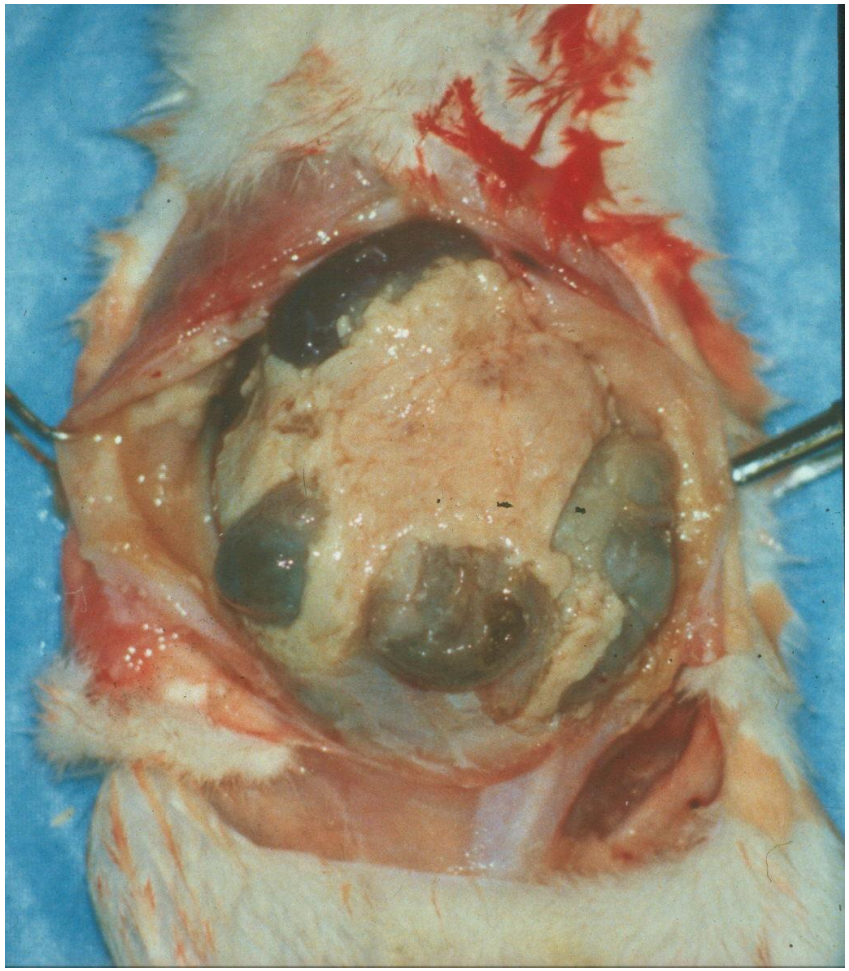
GOG 172: Toxicity

Grade 3/4 Toxicity	IV	IP
Leukopenia	64%	76%
Thrombocytopenia	4%	12%
Gastrointestinal	24%	46%
Renal/GU	2%	7%
Neurologic	9%	19%
Fever	4%	9%
Infection	6%	16%
Fatigue	4%	18%
Metabolic	7%	27%
Pain	1%	11%

Armstrong *NEJM* 200

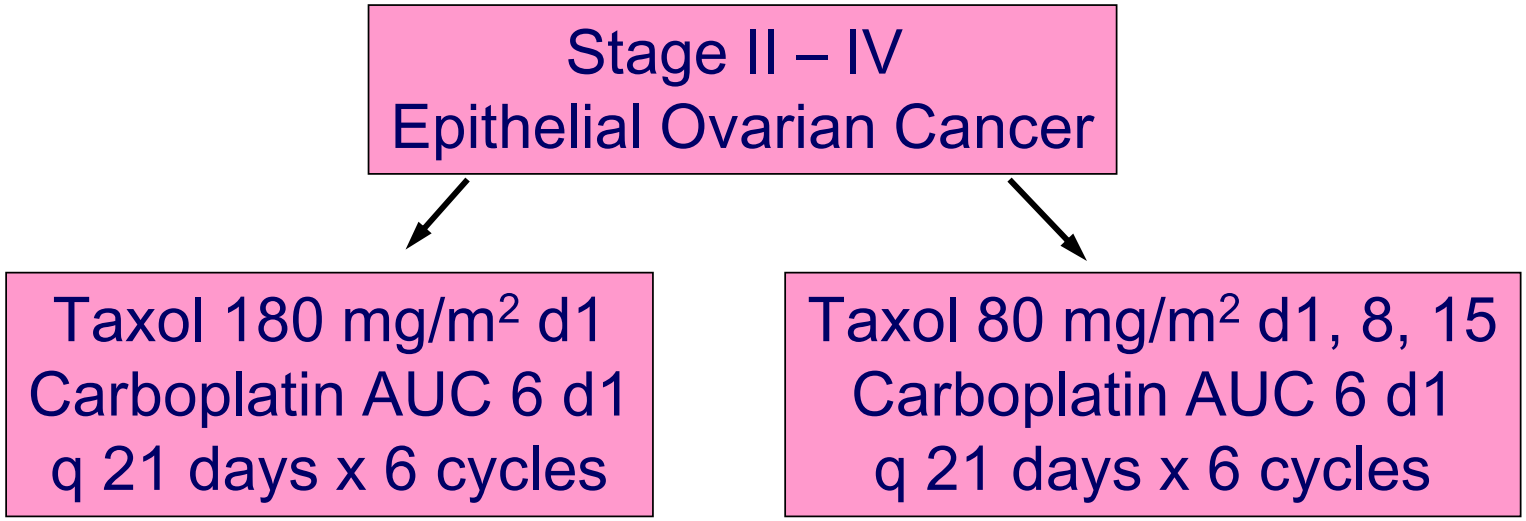




Dose-Dense Taxol

- Preclinical studies suggest that duration of exposure is an important determinant of the cytotoxic activity of paclitaxel

JGOG 3016

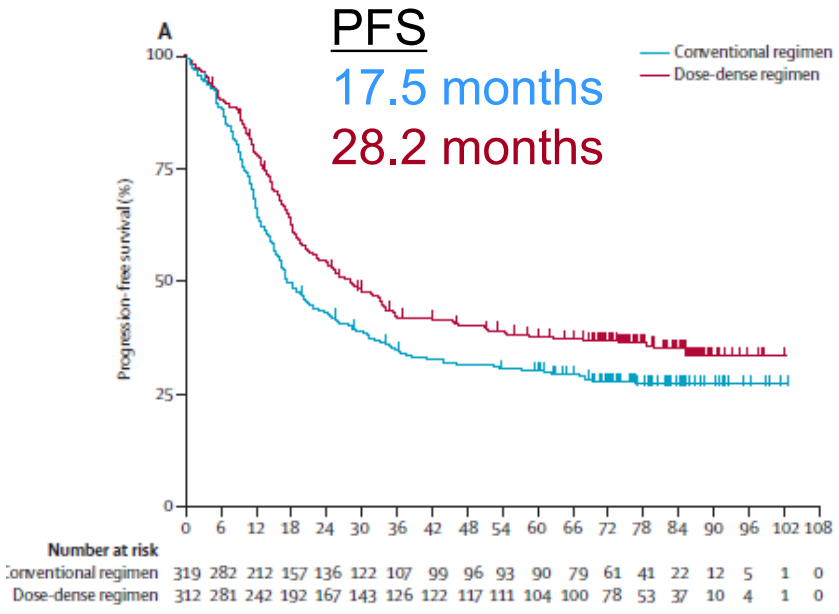


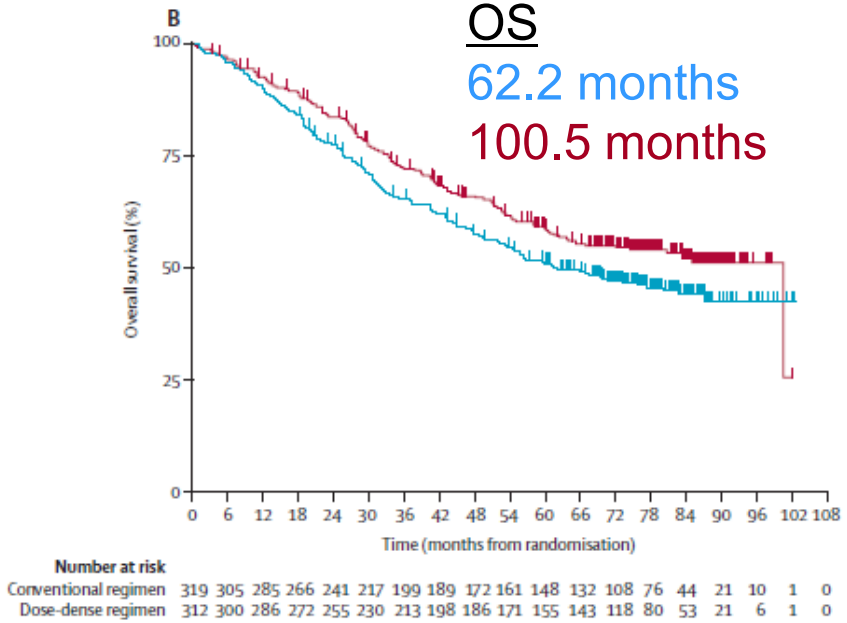
Katsumata *Lancet* 2013

Dose Dense Taxol

JGOG 3016: Dose Dense Taxol

Survival





Katsumata *Lancet* 2013

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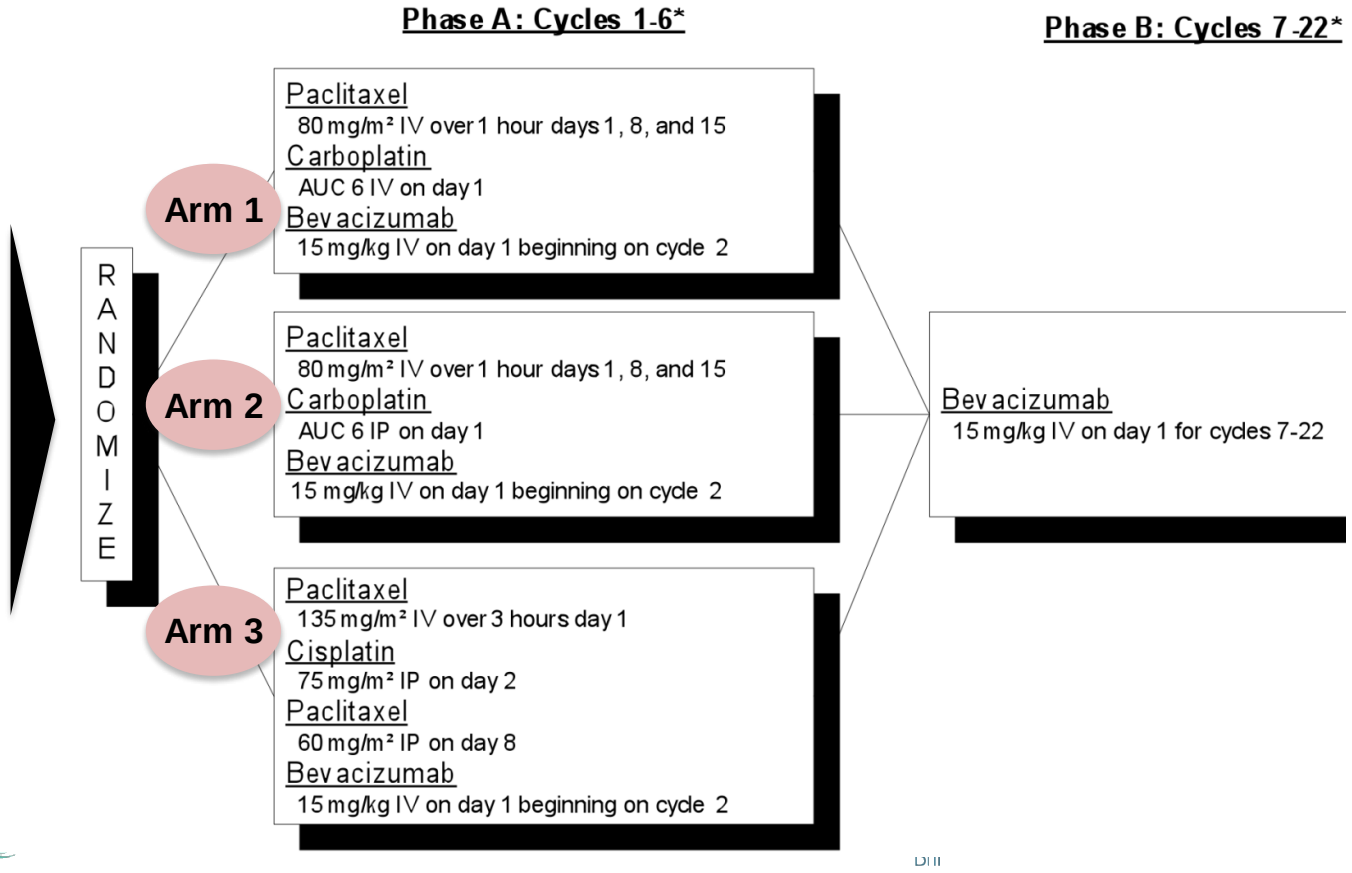
GOG 252: Schema

Eligibility

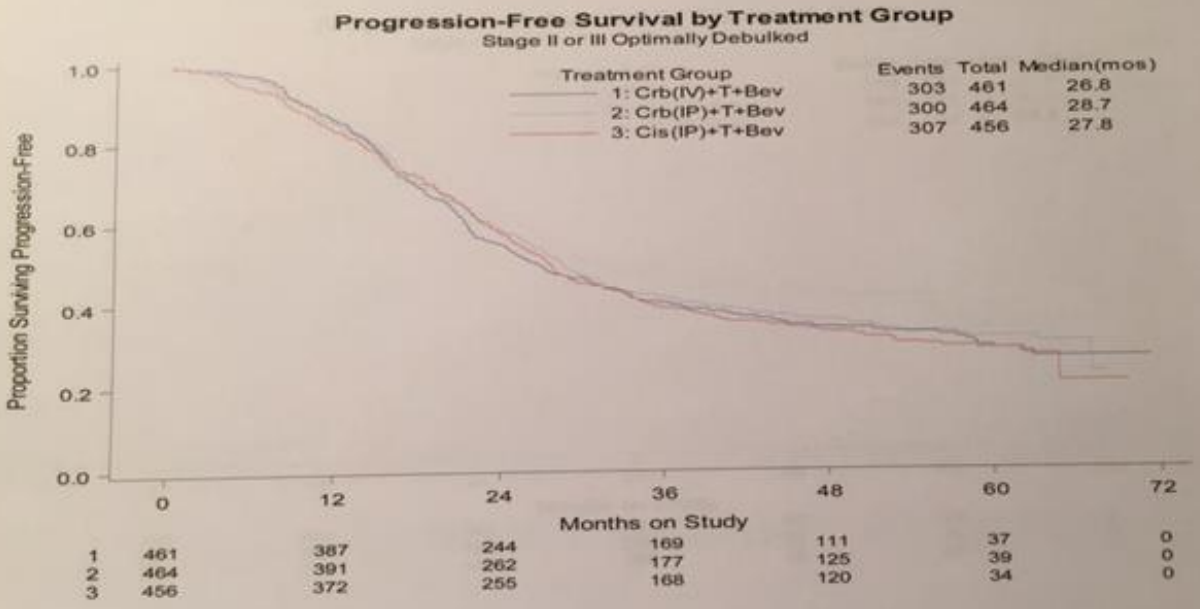
Stage II-III Epithelial Carcinoma: Ovary, Fallopian Tube, Peritoneal

Resected to optimal: less than or equal to 1 cm visible tumor by surgeon report

Exploratory: suboptimal (7%) and Stage IV (5%)



Progression Free Survival Optimal Stage II-III



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PRINCIPLES OF SYSTEMIC THERAPY (3 of 8)
Primary Systemic Therapy Regimens[a]
Epithelial Ovarian (including LCOH)/Fallopian Tube/Primary Peritoneal

Stage II-IV

- **IP/IV Regimen (for optimally debulked stage II-III disease)**
  - **Paclitaxel 135 mg/m² IV continuous infusion over 3 or 24 h[b] Day 1; cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; paclitaxel 60 mg/m² IP Day 8. Repeat every 3 weeks x 6 cycles. (category 1)**
- **IV Regimens**
  - **Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[c] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
  - **Dose-dense paclitaxel 80 mg/m² IV over 1 hour Days 1, 8, and 15 followed by carboplatin[c] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
  - **Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes. Weekly for 18 weeks.[d] (category 1)**
  - **Docetaxel 60–75 mg/m² IV over 1 hour followed by carboplatin[c] AUC 5–6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. (category 1)**
  - **Carboplatin AUC 5 + pegylated liposomal doxorubicin 30 mg/m² every 4 weeks for 6 cycles.**
  - **Bevacizumab-containing regimens per ICON-7 and GOG-218:**
    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[c] AUC 5–6 IV over 1 hour, and bevacizumab 7.5 mg/kg IV over 30–90 minutes Day 1. Repeat every 3 weeks x 5–6 cycles. Continue bevacizumab for up to 12 additional cycles. (category 2B)
    or
    Paclitaxel 175 mg/m² IV over 3 hours followed by carboplatin[c] AUC 6 IV over 1 hour Day 1. Repeat every 3 weeks x 6 cycles. Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV over 30–90 minutes every 3 weeks for up to 22 cycles. (category 2B)

Neoadjuvant Therapy

- **Any of the above IV regimens can be used as neoadjuvant therapy before IDS.**
- **Bevacizumab-containing regimens should be used with caution before IDS due to potential interference with postoperative healing.**
- **After neoadjuvant therapy and IDS any of the above regimens (IV or IP/IV) can be considered as adjuvant therapy options.**
- **There are limited data for the use of IP chemotherapy regimens after neoadjuvant therapy and IDS. The following is an additional IP option after IDS: IV paclitaxel 135 mg/m² over 3 hours on Day 1, IP carboplatin AUC 6 IP Day 1, paclitaxel 60 mg/m² IP Day 8.[e]**
- **A minimum of 6 cycles of treatment is recommended, including at least three cycles of adjuvant therapy after IDS.**

[a]See Discussion for references.
[b]The published randomized trial regimen used IV continuous infusion paclitaxel over 24 h.
[c]Due to changes in creatinine methodology, changes regarding carboplatin dosing can be considered. See FDA carboplatin dosing statement.
[d]This regimen may be considered for elderly patients or those with poor performance status.
[e]Mackay H, Gallagher CJ, Parulekar WR, et al. OV21/PETROC: A randomized Gynecologic Cancer Intergroup (GCIG) phase II study of intraperitoneal (IP) versus intravenous (IV) chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer (EOC) [abstract]. J Clin Oncol 2016;34: Abstract LBA5503.

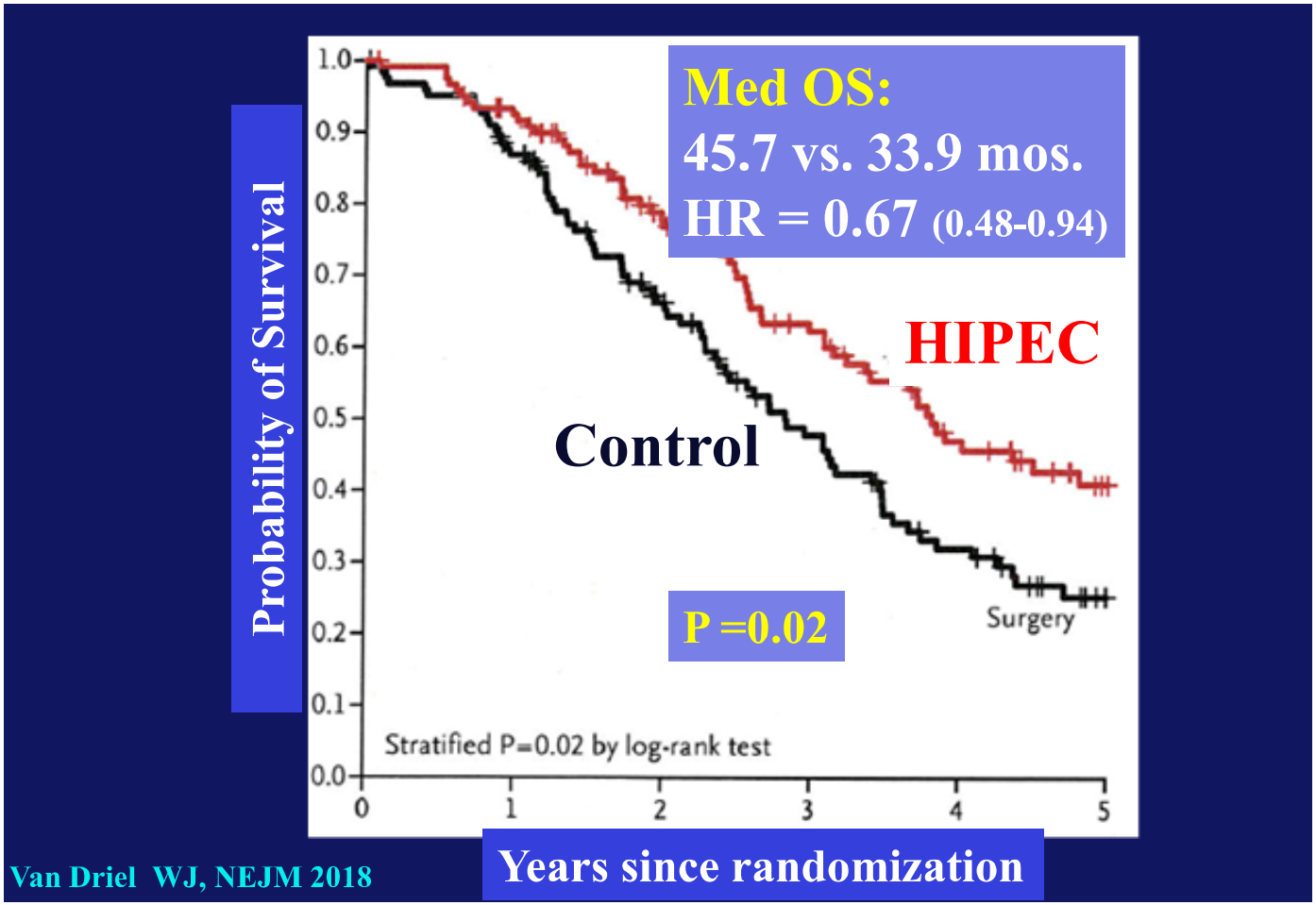
Continued

HIPEC

- Phase III RCT, Netherlands
- 245 patients, stable disease after neoadjuvant chemotherapy (carbo/taxol)
- Interval cytoreductive surgery followed by HIPEC-cisplatin 100 mg/m^2
- Followed by 3 cycles of carbo/taxol
- Primary endpoint RFS, secondary OS

van Driel, NEJM 2018

HIPEC Overall Survival



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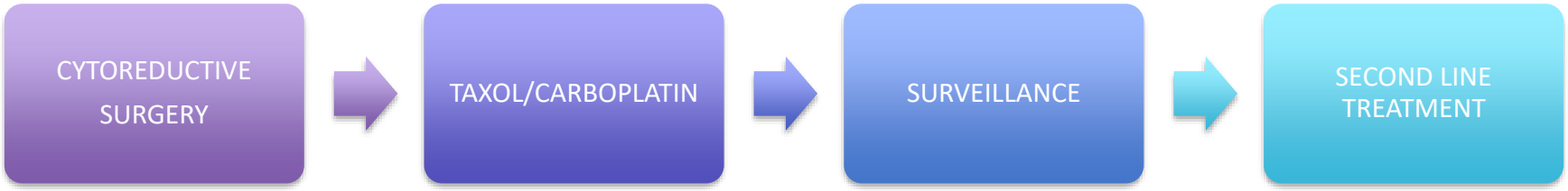
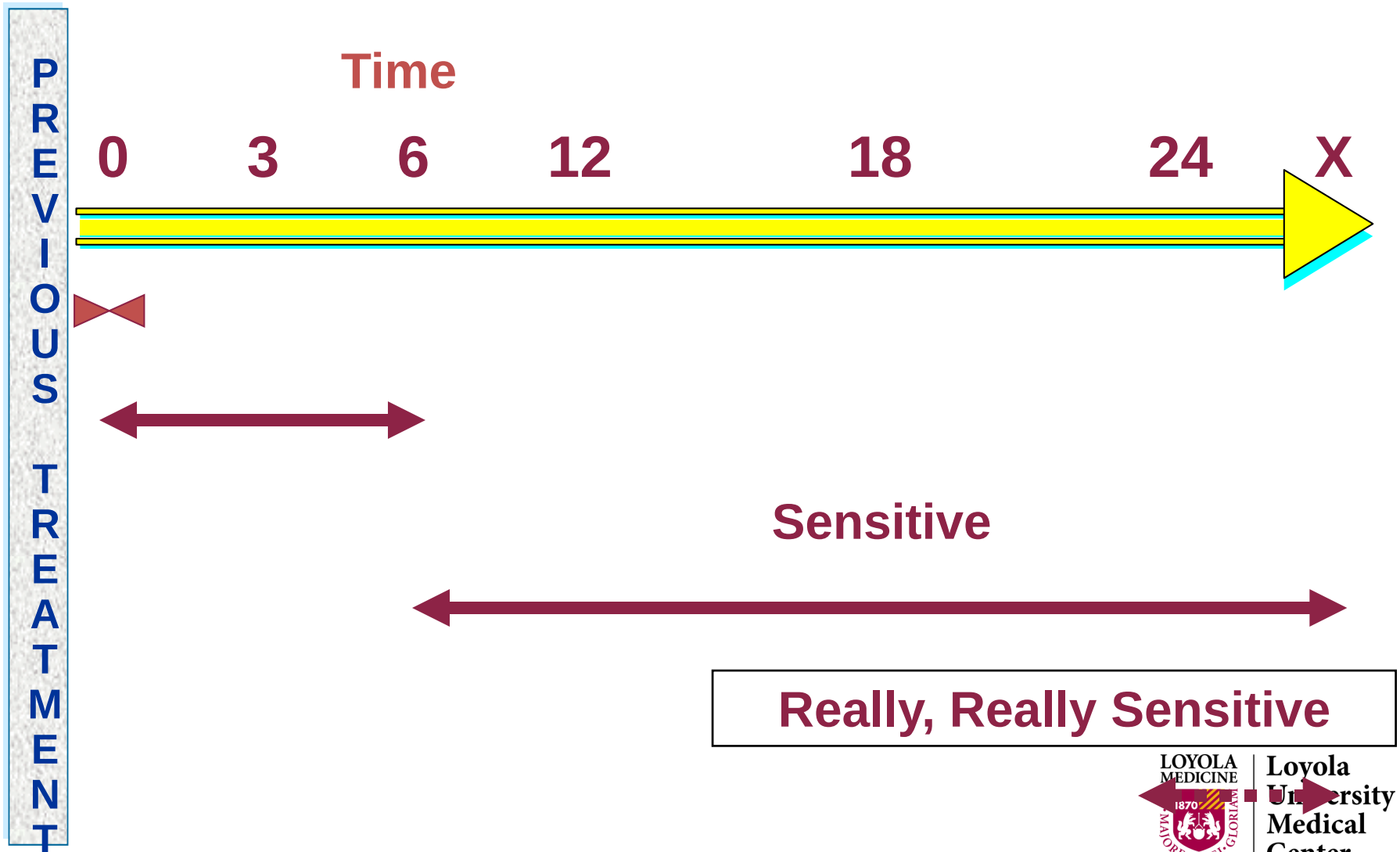
Natural History



Recurrent Ovarian Cancer: Definition of Disease Sensitivity



2006 meta-analysis

- included 60 trials in women (n=15,609) with EOC
- A platinum-based combination was better than platinum monotherapy (hazard ratio [HR] favoring the combination 1.16, 95% CI 0.86-1.58)
- A platinum-taxane combination was better than a platinum plus non-taxane combination (HR favoring platinum plus taxane 1.28, 95% CI 1.07-1.53)

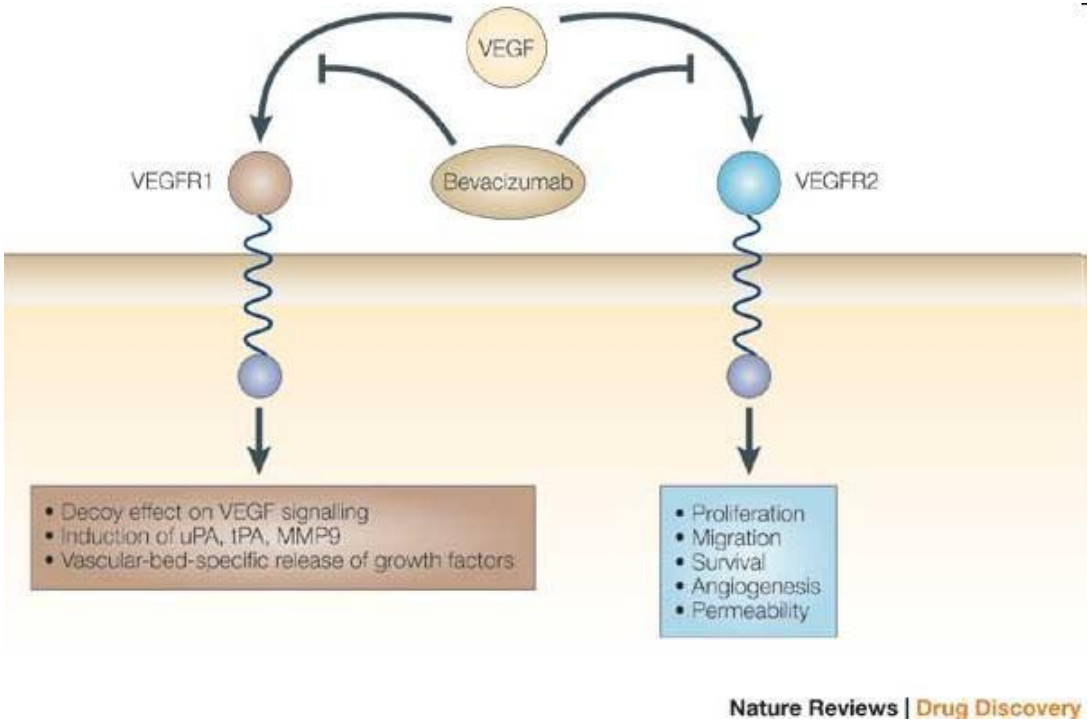
J Natl Cancer Inst 2006; 98:1655.

Take Home Points: Platinum Resistant EOC

- Goal setting:
  - Incurable disease
  - Balance toxicity with efficacy
  - Maximize quality of life while attempting disease control
- Strong Consideration of Clinical trial:
  - If performance status allows
  - Platinum Resistance is a global adaption by tumor
    - Novel combinations are likely to be necessary to overcome this
    - PARPi, DDR agents, IO, anti-angiogenics, epigenetics
  - Development of functional biomarker assays needed
- Single Agent therapy:
  - Addition of Bevacizumab improves response and PFS for those eligible

Adding a Biologic Agent

Monoclonal antibody to VEGF-A that inhibits angiogenesis



Nature Reviews | Drug Discovery

Targeting Angiogenesis:

- **Aurelia Trial:**
  - **Open label Phase III RCT**
  - 361 patients; Physician's Choice Chemo vs **Chemo+ Bevacizumab**
  - Platinum-resistant disease
  - No bowel obstruction within 6 mos, no malignant bowel involvement
  - No more than 2 prior lines
    - Weekly paclitaxel 80mg/m2 (day 1, 8, 15, 22) every 4 wks
    - Pegylated Liposomal Doxirubicin 40mg/m2 every 4 wks
    - Topotecan 4mg/m2 weekly every 4 wks OR 1.25mg/m2 day 1-5 every 3 wks

Aurelia Trial:

Improving chemotherapy sensitivity in platinum resistant EOC

- **Physician choice chemo + bevacizumab:**
  - 31% ORR vs 13% chemo alone (13.5 mos follow up)
  - *Decrease recurrence HR 0.48 (CI 0.38-0.60)*
  - *PFS 6.7mos vs 3.6 mos*
  - Grade 2 HTN, proteinuria
  - GI perf 2.2% (4 pts)
- **Impact of Bevacizumab:**
  - *Paclitaxel+ Bev: ORR 53% vs 30% Taxol alone*
    - PFS 10 mos vs 4 mos; HR 0.46 (0.30-0.71)
  - Topo+ Bev: ORR 17% vs 0%
    - PFS 6 mos vs 2 mos HR 0.32 (0.21-0.49)
  - PLD + Bev: ORR 14% vs 8%
    - PFS 5 mos vs 4 mos (0.39-0.83)

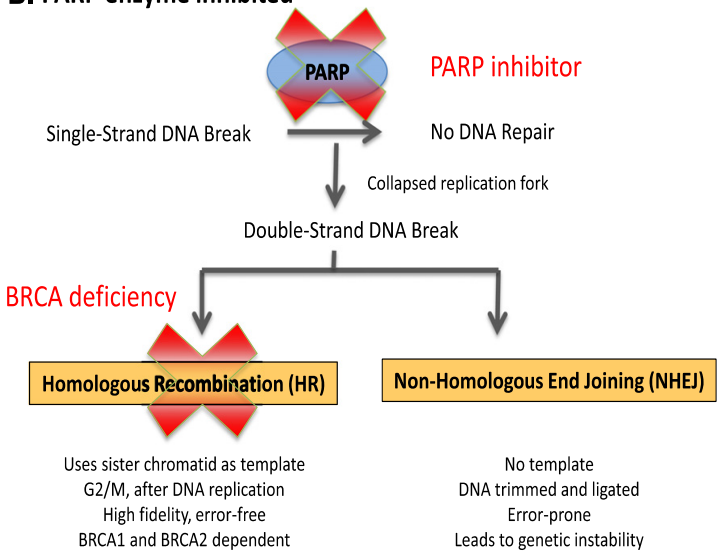
**Not powered to discern difference between chemotherapy backbones

PARPi

- Mechanism of action works on principle of synthetic lethality
- Inherent vulnerability that when combined with a genetic event may become lethal
- HRD can happen via BRCA mutations or mutations and epigenetic changes in genes involved in HR can lead to HRD

A. Functioning PARP enzyme

B. PARP enzyme inhibited



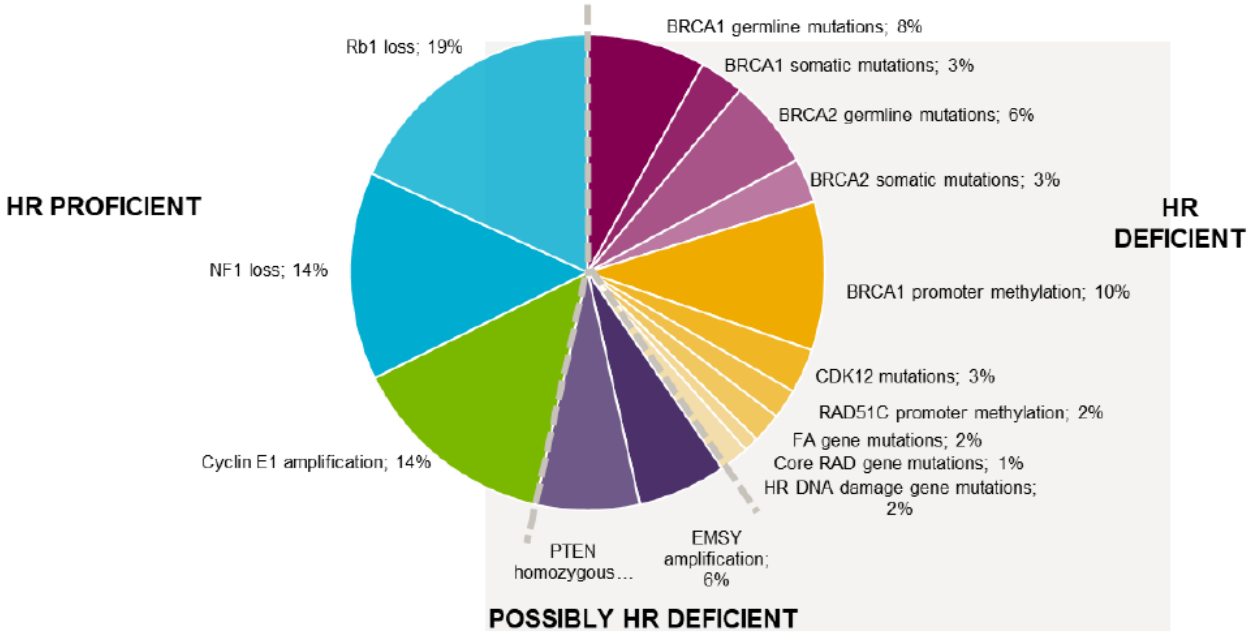
C. Deficiency in HR and BER together lead to synthetic lethality

Condition	HR	BER	Outcome
Normal cells	+	+	Viable
BRCA deficient	-	+	Viable
Normal cells, PARP inhibitor	+	-	Viable
BRCA deficient, PARP inhibitor	-	-	Cell Death

Walsh, et. Al. Gyne Oncol, 2015

Why Does PARPi Work? We know the HRD Rationale for Efficacy in treatment

General assumption 1: HR deficiency = PARP inhibitor sensitivity



Konstantinopoulos et al, Canc Disc 2015 and Patch et al, Nature 2015

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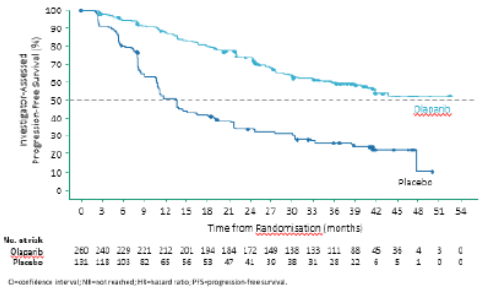
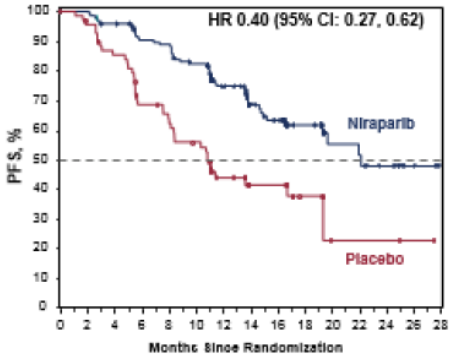
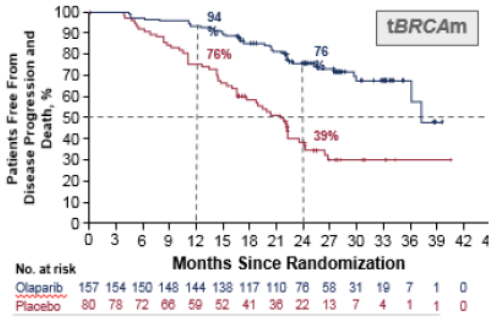
Drug	FDA Approval	Indication
Olaparib	Dec 2014	Patients with deleterious or suspected deleterious **germline BRCA-mutated** advanced ovarian cancer who have been treated with **three or more** prior lines of chemotherapy
	Aug 2017	**Maintenance treatment** of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in **a complete or partial response to platinum-based chemotherapy**
Rucaparib	Dec 2016	Patients with deleterious BRCA mutation (**germline and/or somatic)** associated advanced ovarian cancer who have been treated with **two or more** chemotherapies
	Dec 2017 Priority review	**Maintenance** treatment for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in **a complete or partial response to platinum-based chemotherapy**,
Niraparib	Mar 2017	**Maintenance** treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in **complete or partial response to platinum-based chemotherapy**

Why Maintenance?

- Recurrence after clinical CR: 50-80%
- Recurrence after pathological CR: 40-60%
- Prognostic factors for recurrence:
  - Tumor burden = residual disease
  - Response to therapy = "biology"
  - Unknowns
- Cure after Recurrence: ***Rare***

BRCAm Front Line Maintenance: 4 POSITIVE RANDOMIZED TRIALS

Primary endpoint: PFS

SOLO1 - gBRCAm[a]	PRIMA - gBRCAm[b]	PAOLA-1[c]	
			
NR mo vs 13 mo HR 0.30 (95% CI: 0.23, 0.41)		37.2 vs 17.7 mo HR 0.33 (95% CI 0.25-0.45)	INV REVIEW
NR vs. 14.1 mo HR 0.28 (95% CI 0.2-0.39)	21.9 vs. 10.4 HR 0.43 (95% CI 0.31-0.59)		BICR REVIEW

a. Moore K, et al. *N Engl J Med.* 2018;379:2495-2505. b. Gonzalez Martin A, et al. NEJM. 2019: 381(25):2391-2402. c. Ray-Coquard I, et al. NEJM. 2019: 381(25):2416-2428.

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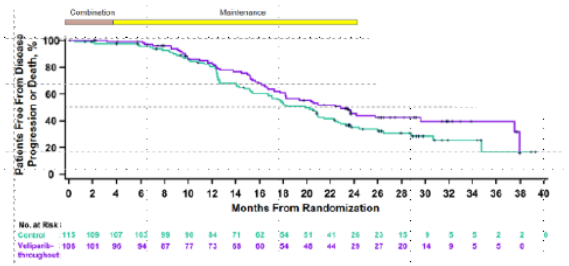
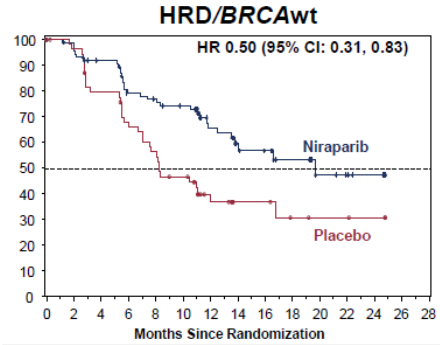
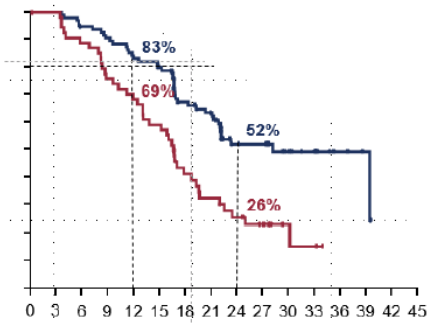
HRD+ Front Line Maintenance: 3 POSITIVE RANDOMIZED TRIALS

Primary endpoint: PFS

VELIA [a]	PRIMA [b]	PAOLA-1 [c]	
			
22.9- 19.8 mo HR 0.74(95% CI: 0.52- 1.06)		28.1 vs 16.6 mo HR 0.43 (95% CI 0.28-0.66)	INV REVIEW
	20 vs. 8 mo HR 0.50 (95% CI 0.31-0.83)		BICR REVIEW

- a. Coleman R et al. NEJM. 2019: 381 (25): 2403-2415. b. Gonzalez Martin A, et al. NEJM. 2019: 381(25):2391-2402. c. Ray-Coquard I, et al. NEJM. 2019: 381(25):2416-2428.

Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer

BRCA mutation	PFS	34.7 m vs 22.0 m
HRD	PFS	31.9 m vs 20.5 m
WT	PFS	23.5 m vs 17.3 m

Coleman **N Engl J Med 2019;381:2403-15**

Front Line Maintenance Therapy With PARPi Should be the SOC!

- 4 Randomized Trials, all positive, why is there any controversy?
  - No OS data
    - True – patients have done so well that OS is years away – you want to wait?
    - Benefit of PARPi is an early effect - clonality
  - HR in second line is as good or better than front line so "I'm going to wait"
    - Understand HR in context
    - Biomarkers are key here
  - Toxicity

PARPi side effects

Adverse events noted with PARP inhibitors.

	Anemia G1-4/G3-4	Neutropenia G1-4/G3-4	Low Plts G1-4/G3-4	Fatigue G1-4/G3-4	Nausea G1-4/G3-4	Vomiting G1-4/G3-4	Diarrhea G1-4/G3-4	Elevated Cr G1-4/G3-4	Elevated LFTs G1-4/G3-4
Olaparib (phase 2; FDA label)	90%/15%	25%/7%	30%/3%	66%/8%	64%/3%	43%/4%	31%/1%	30%/2%	NR/NR
Rucaparib (phase 3) [73]	37%/19%	18%/7%	28%/5%	69%/7%	75%/4%	37%/4%	32%1%	15%/1%	34%/10%
Niraparib (phase 3) [57]	50%/25%	30%/20%	61%/34%	60%/8%	74%/3%	34%/2%	19%/0%	NR	NR

Gunderson, et. Al 2018 Gyn Oncolo

DFS

- Stage I & 2 65-90%
- Stage III optimal 40%
- Stage III sub optimal 5-10%
- Stage IV 5-10%

Screening

- **Unknown precancer condition**
- **Low detection**
- **High mortality**
- **No screening has yet proven to be effective**

Prevention

- OCP
- Tubal Ligation
- Prophylactic Salpingo-Oophorectomy

OCP

- 6 years of use
- 60% Reduction

Tubal Ligation

- ↓ Risk in General Population
- BRCA1 .39 (.22 - .70)
- Both TL + OCP .28 (.15 -.50)

Risk of Ovarian Cancer

General Population	**1.4%**
BRCA1	**16-60%**
BRCA2	**10-25%**

Prophylactic Salpingo-Oophorectomy

551 Women w/ BRCA1 or 2 mutation

- **292 Control Group**
  - 58 Cancers
  - 6/58 Stage I (11%)
- **259 PO**
  - 6 Stage I Ovarian Ca
  - 2 Additional Peritoneal Ca
- **Risk Decreased from 20% to < 1%**
- **RR Breast CA .45 (.29 - .77)**

Rebbeck NEJM 2002

3 Unanswered Issues:

1) **Optimal Time**
2) **Should Hysterectomy be included**
3) **Role of HRT**

Optimal Time

- **Deferred until childbearing complete**
- **BRCA 1 patients – 11-21% CA risk by age 50**
- **Defer till > 40 may lose breast protection**
- **2- 4 % rate of occult invasive carcinoma**

Hysterectomy

- No consensus
- Should include bilateral salpingectomy
- Argue… portion of tube in uterus is at theoretical risk
- Uterine cancer not over represented in BRCA2
- Uterine cancer may be increased in BRCA1
  - (3-4%)
- Increase morbidity


Estrogens
I just don't know what to think

HRT Effect on Breast Cancer Reduction

- **Cohort of never users** **RR 0.42**
- **Cohort of users & nonusers** **RR 0.53**

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