Treatment Challenge of Advanced Cervical Cancer

Presented by
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Histology commentary by
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Case Presentation: History

- M.A. is a 39-year-old gravida 4, para 2, smoking, Caucasian woman with no significant past medical or surgical history except that related to her cervical cancer
  - Last Pap test with delivery of youngest child at age 21
  - October 2003: presented with bleeding and diagnosed with grade 3 FIGO stage IB2 (5-cm) squamous cervical cancer

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Case Presentation: History (cont)

- November 2003: radical abdominal hysterectomy, BSO, pelvic and aortic lymphadenectomy
  - Grade 3 squamous cell carcinoma
  - 4.1 tumor
  - Positive lymph vascular invasion
  - Invasion through entire wall of cervix
  - Parametrium, margins, vagina, and corpus negative
  - 2 right external iliac nodes positive, 1 left internal/obturator iliac node positive
  - 8 common iliac and aortic nodes negative

BSO = bilateral salpingo-oophorectomy.

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Case Presentation: History (cont)

Aortic nodes
Subaortic (presacral) nodes
Common iliac lateral & medial nodes
Ureter
Superior gluteal (hypogastric) nodes
External iliac node
Obturator nodes
Obturator n.
Deep circumflex iliac a
External iliac node
Inferior epigastric a
Hypogastric nodes
Ureteral node
Cardinal lig

Morrow, ed. *Gynecologic Cancer Surgery.* 1996.

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Case Presentation: History (cont)

- December 2003 to January 2004: treated with pelvic radiation and chemotherapy
  - 28 fractions x 180 cGy = 50.4 Gy
    - Whole pelvis
  - 6 doses of weekly IV cisplatin 40 mg/m²

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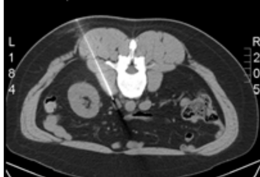
Case Presentation: History (cont)

- June 2005: physical exam normal except 3-cm fixed nontender left supra-clavicle node



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Case Presentation: Histology

Courtesy of Thomas C. Wright, MD.

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Issues

- What is her prognosis and what factors impact this?
- Does this patient need treatment?
  - If so, what are the goals?
- What is the optimal treatment?
  - Radiation therapy
  - Chemotherapy
  - Chemotherapy and radiation therapy

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GOG 179: Cisplatin vs Topotecan/Cisplatin

Cervical cancer, stage IV or recurrent → RANDOMIZE

→ Regimen 1
Cisplatin 50 mg/m²

→ Regimen 2
Topotecan 0.75 mg/m² d 1–3
Cisplatin 50 mg/m² d 1

Long et al. *Gynecol Oncol.* 2004;92:397.

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GOG 179: Cisplatin vs Topotecan/Cisplatin (cont)

- Opened 6/29/1999, closed 9/23/2002
- 294 patients
- Response rate
  - Cisplatin 13%
  - Cisplatin/topotecan 27%
- Median survival
  - Cisplatin 6.5 months
  - Cisplatin/topotecan 9.4 months

Long et al. *Gynecol Oncol.* 2004;92:397.

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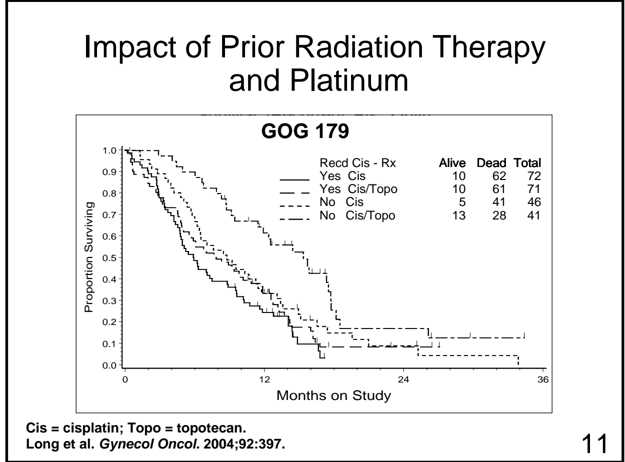
Impact of Prior Radiation Therapy and Platinum



Cis = cisplatin; Topo = topotecan.
Long et al. *Gynecol Oncol.* 2004;92:397.

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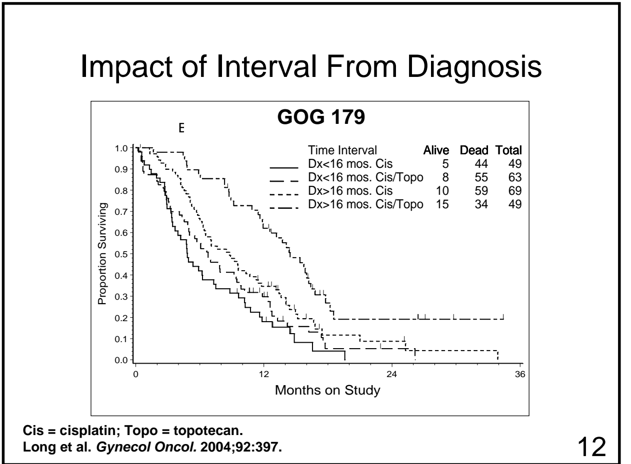
Impact of Interval From Diagnosis



Cis = cisplatin; Topo = topotecan.
Long et al. *Gynecol Oncol.* 2004;92:397.

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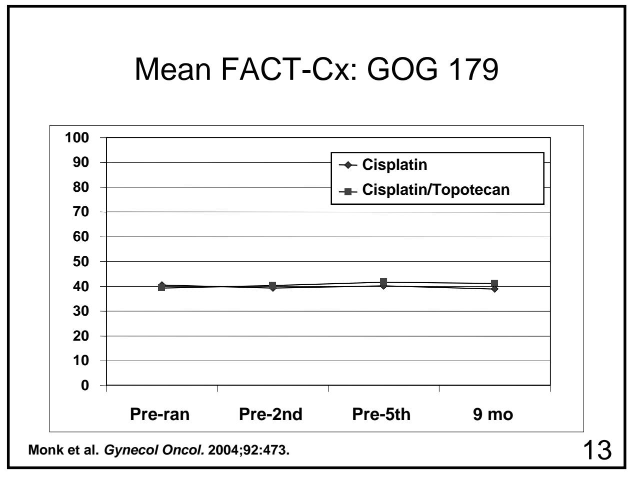
Mean FACT-Cx: GOG 179



Monk et al. *Gynecol Oncol.* 2004;92:473.

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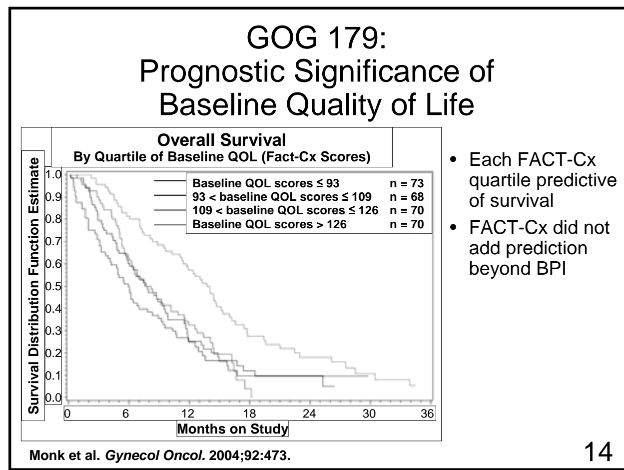
GOG 179: Prognostic Significance of Baseline Quality of Life



- Each FACT-Cx quartile predictive of survival
- FACT-Cx did not add prediction beyond BPI

Monk et al. *Gynecol Oncol.* 2004;92:473.

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Predictors of Response to Chemotherapy

- Previous radiosensitizing chemotherapy
- Interval from diagnosis
- Quality of life/pain/performance status
- Response more frequent in nonirradiated sites (70% vs 23%, $P = .008$) GOG 76X*
  - Will be prospectively evaluated in GOG 204

*Rose et al. *J Clin Oncol.* 1999;17:2676.

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GOG 204

Primary stage IVB or recurrent/persistent carcinoma of the cervix

- Measurable disease
- GOG performance status 0–1
- ANC ≥ 1500/μL
- Platelets ≥ 100,000/μL
- Serum creatinine ≤ 1.5 mg/dL
- No CNS disease
- No past or concomitant invasive cancer
- No prior chemotherapy (unless concurrent with radiation)

RANDOMIZE

Regimen 1
Paclitaxel 135 mg/m² over 24 hours and cisplatin 50 mg/m² repeated q 3 wk for 6 cycles

Regimen 2
Vinorelbine 30 mg/m² IV bolus days 1 and 8 and cisplatin 50 mg/m² IV day 1 repeated q 3 wk for 6 cycles

Regimen 3
Gemcitabine 1000 mg/m² IV days 1 and 8 and cisplatin 50 mg/m² IV day 1 repeated q 3 wk for 6 cycles

Regimen 4
Topotecan 0.75 mg/m² days 1, 2, and 3 and cisplatin 50 mg/m² IV day 1 repeated q 3 wk for 6 cycles

***Note*: all regimens included quality of life assessment.**

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Case 1: Discussion

- 39-year-old woman diagnosed with grade 3 FIGO stage IB2 (5-cm) squamous cell cervical cancer
- Issues
  - Surgery/radiation/chemotherapy
  - PET scanning

Panel

Case 1: Discussion (cont)

- 39-year-old woman diagnosed with grade 3 FIGO stage IB2 (5-cm) squamous cell cervical cancer
- Issues
  - Concurrent chemotherapy/radiation vs sequential radiation and chemotherapy
  - Adjuvant therapy

Panel

Case 1: Discussion (cont)

- 39-year-old woman diagnosed with grade 3 FIGO stage IB2 (5-cm) squamous cell cervical cancer
- Issue
  - Impact of surgery on overall treatment plan, survival, and quality of life

Panel

End of Presentation

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Dilemma: Ovarian Cancer Recurrence at 10 Months

Presented by
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and
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Histology and pathology commentary by
Thomas C. Wright, MD
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1

Case Presentation: History

- A 56-year-old woman develops abdominal pain and swelling
  - Physical exam reveals ascites and a pelvic mass
- Exploratory laparotomy, TAH/BSO, omentectomy, and tumor debulking
- Stage IIIC ovarian cancer
- Histology: clear cell carcinoma
- Residual after debulking:
  - Diffuse peritoneal metastases
  - Largest residual: 2 cm
  - PS = 0
  - CBC, metabolic panel WNL

TAH/BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

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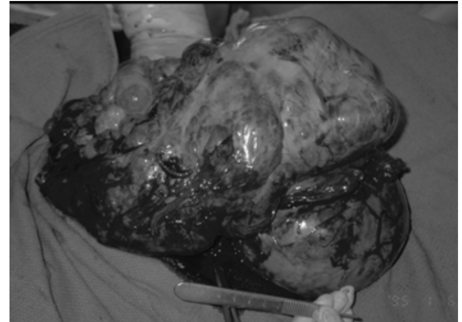
Gross Anatomy Pathology: Ovarian Tumor



Courtesy of Thomas J. Herzog, MD, FACOG, FACS.

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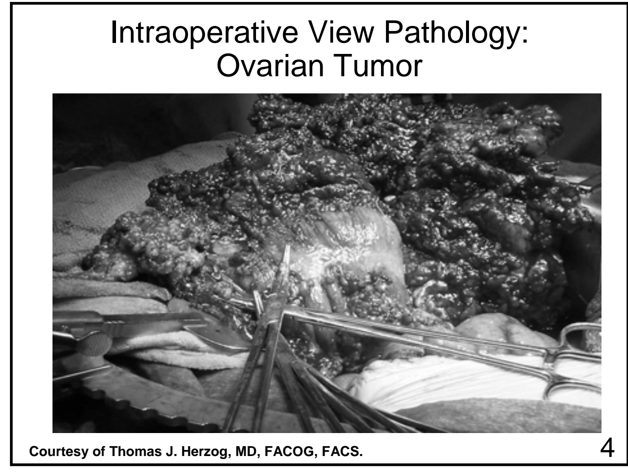
Intraoperative View Pathology:
Ovarian Tumor
Courtesy of Thomas J. Herzog, MD, FACOG, FACS.
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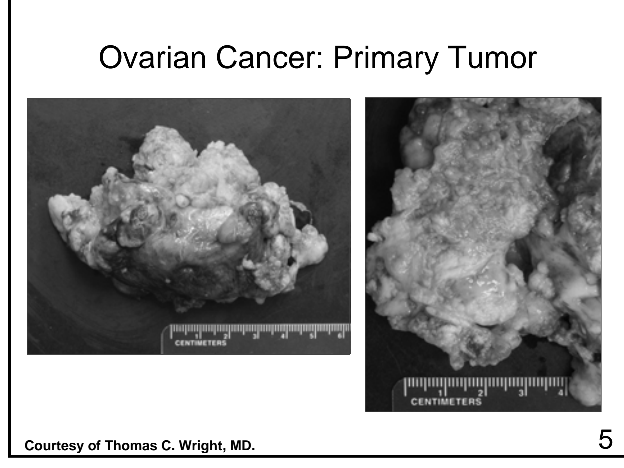
Ovarian Cancer: Primary Tumor
CENTIMETERS
CENTIMETERS
Courtesy of Thomas C. Wright, MD.
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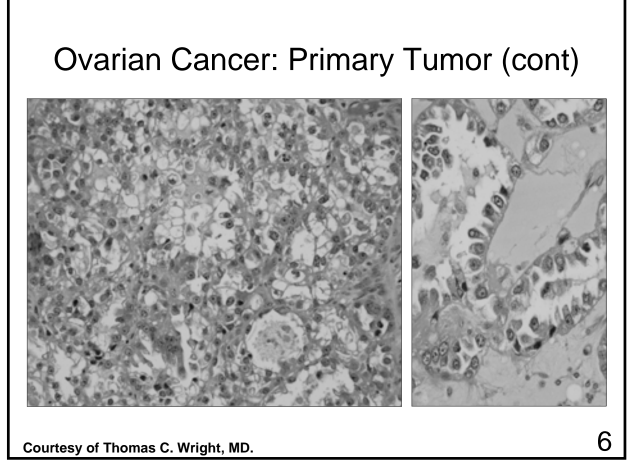
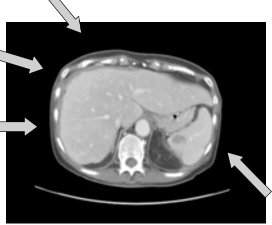

Ovarian Cancer: Primary Tumor (cont)
Courtesy of Thomas C. Wright, MD.
6

Case 2: Recurrence at 10 Months

- Receives paclitaxel and carboplatin x 6 cycles
- Achieves clinical CR
- Recurrence at 10 months
  - CA-125: 142
  - CT scan:
    - Several peritoneal and splenic masses
- Persistent grade 1 peripheral neuropathy
- PS: 0



CT Scan of Recurrence

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Considerations in Relapse

- Types and numbers of prior regimens
- Treatment-free (platinum-free) interval
- Current status:
  - Symptoms
  - Comorbidities
  - Performance status
  - Disease volume
  - Toxicity from prior treatment (growth factors, transfusion, hypersensitivity, etc)

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Ovarian Cancer: Salvage Therapy

	Response Rate, %	
Drug	**Platinum-Resistant**	**Platinum-Sensitive**
Docetaxel Liposomal doxorubicin* Etoposide Gemcitabine Paclitaxel* Platinum* Topotecan* Vinorelbine	10%–20%	20%–35%

*FDA approved.

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What Would Be Your Regimen of Choice for Therapy?

1. Carboplatin + paclitaxel
2. Carboplatin + gemcitabine
3. Carboplatin + docetaxel
4. Carboplatin + liposomal doxorubicin
5. Liposomal doxorubicin
6. Docetaxel
7. Paclitaxel
8. Topotecan
9. Gemcitabine
10. Oral etoposide

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Management: The Case for Single Agents

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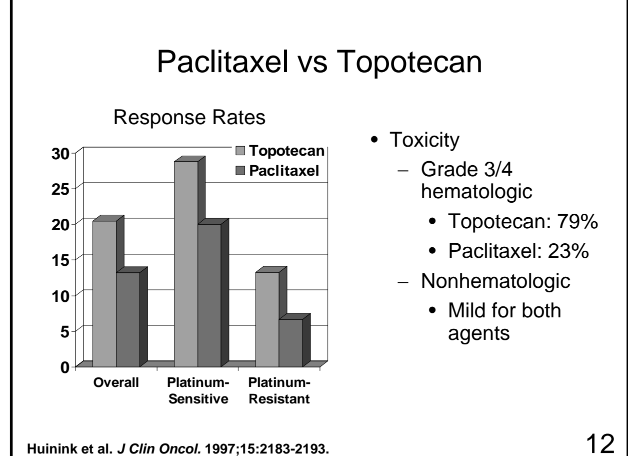
Paclitaxel vs Topotecan



- Toxicity
  - Grade 3/4 hematologic
    - Topotecan: 79%
    - Paclitaxel: 23%
  - Nonhematologic
    - Mild for both agents

Huinink et al. *J Clin Oncol.* 1997;15:2183-2193.

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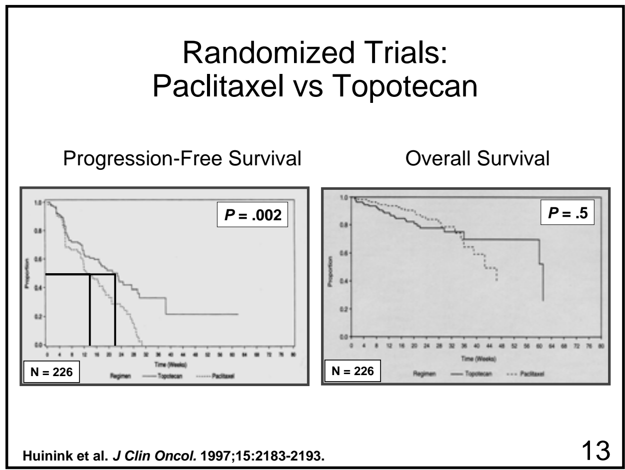

Randomized Trial: Liposomal Doxorubicin vs Topotecan in Recurrent Ovarian Cancer

	Liposomal Doxorubicin (N = 239)	Topotecan (N = 235)	*P* Value
Overall response	19.7%	17.0%	
Complete	3.8%	4.7%	0.390
Platinum-refractory	(N = 130)	(N = 124)	
CR + PR	12.3%	6.5%	0.118
Platinum-sensitive	(N = 109)	(N = 111)	
CR + PR	28.4%	28.8%	0.964
Time to progression	16.1 wk	17 wk	0.095

Gordon et. al. *J Clin Oncol.* 2001;19:3312-3322.

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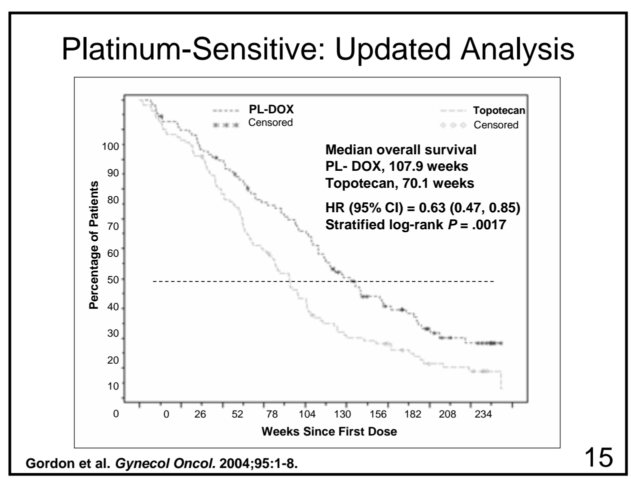
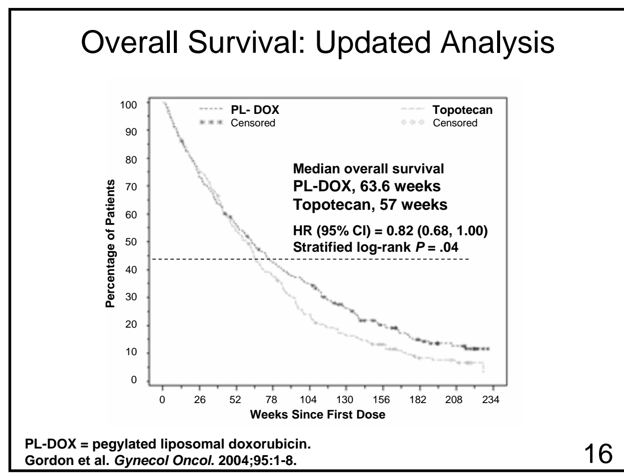


Overall Survival: Updated Analysis



PL-DOX = pegylated liposomal doxorubicin.
Gordon et al. *Gynecol Oncol.* 2004;95:1-8.

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Related Adverse Events

Overall			Grade 3/4	
Liposomal Doxorubicin (50 mg/m²) %	Topotecan (1.5 mg/m²/5 d) %	Characteristic	Liposomal Doxorubicin (50 mg/m²) %	Topotecan (1.5 mg/m²/5 d) %
35	81*	Neutropenia	12	77*
36	72	Anemia	5	28
13	65	Thrombocytopenia	1	34
36	63	Leukopenia	10	50
16	49	Alopecia	1	6
49	1	PPE	23	0
40	15	Stomatitis	8	0

P < .001 for all events, except alopecia *P* = .007.
*3 septic deaths.
Gordon et al. *J Clin Oncol.* 2001;19:3312-3322.

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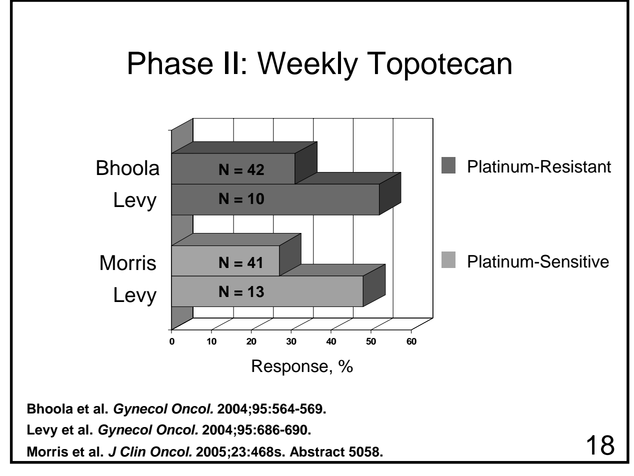
Phase II: Weekly Topotecan



Bhoola et al. *Gynecol Oncol.* 2004;95:564-569.
Levy et al. *Gynecol Oncol.* 2004;95:686-690.
Morris et al. *J Clin Oncol.* 2005;23:468s. Abstract 5058.

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Weekly Topotecan: Toxicity

Toxicity	Grade 3	Grade 4
Hematologic		
Neutropenia	7 (18%)	1 (3%)
Thrombocytopenia	3 (8%)	0
Anemia	4 (10%)	0
Nonhematologic		
Fatigue	7 (17%)	2 (5%)
Nausea/vomiting	3 (7%)	0
Dyspnea	3 (7%)	0
Pain	2 (5%)	0

Morris et al. *J Clin Oncol.* 2005;23:468s. Abstract 5058.

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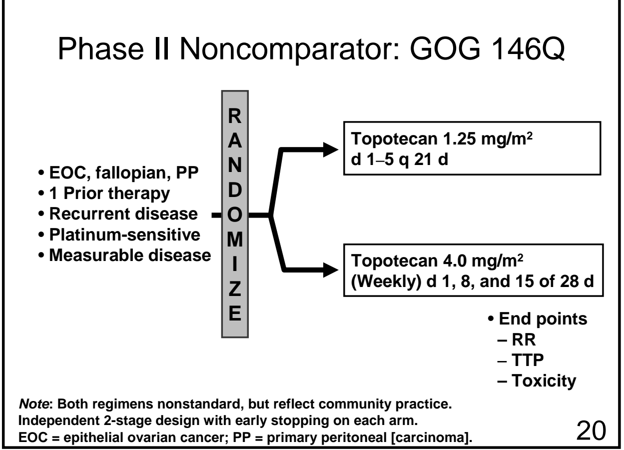
Phase II Noncomparator: GOG 146Q



• End points
- RR
- TTP
- Toxicity

Note: Both regimens nonstandard, but reflect community practice.
Independent 2-stage design with early stopping on each arm.
EOC = epithelial ovarian cancer; PP = primary peritoneal [carcinoma].

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Management: The Case for Platinum-Based Doublets

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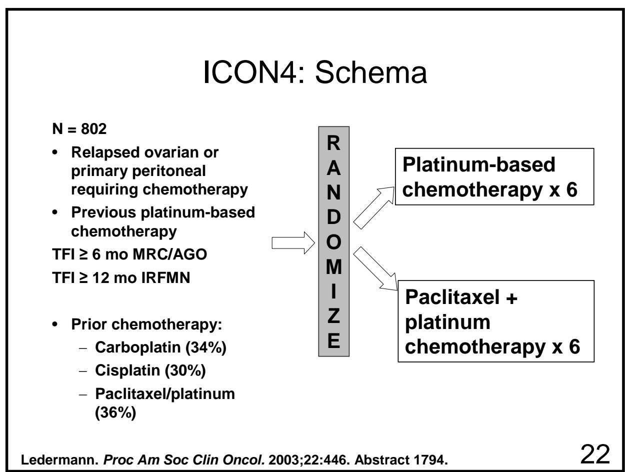
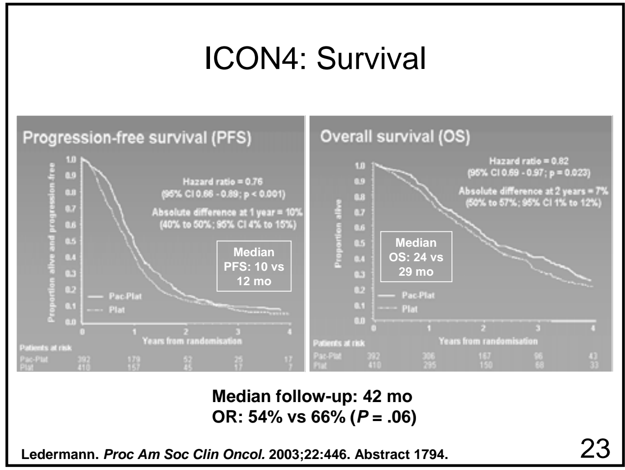
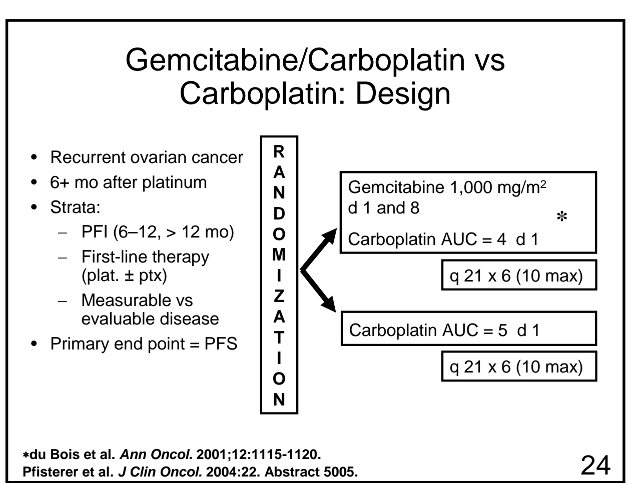

ICON4: Schema
N = 802
• Relapsed ovarian or primary peritoneal requiring chemotherapy
• Previous platinum-based chemotherapy
TFI ≥ 6 mo MRC/AGO
TFI ≥ 12 mo IRFMN
• Prior chemotherapy:
– Carboplatin (34%)
– Cisplatin (30%)
– Paclitaxel/platinum (36%)
RANDOMIZE
Platinum-based chemotherapy x 6
Paclitaxel + platinum chemotherapy x 6
Ledermann. Proc Am Soc Clin Oncol. 2003;22:446. Abstract 1794.
22


ICON4: Survival
Progression-free survival (PFS)
Median PFS: 10 vs 12 mo
Overall survival (OS)
Median OS: 24 vs 29 mo
Median follow-up: 42 mo
OR: 54% vs 66% (P = .06)
Ledermann. Proc Am Soc Clin Oncol. 2003;22:446. Abstract 1794.
23


Gemcitabine/Carboplatin vs Carboplatin: Design
• Recurrent ovarian cancer
• 6+ mo after platinum
• Strata:
– PFI (6–12, > 12 mo)
– First-line therapy (plat. ± ptx)
– Measurable vs evaluable disease
• Primary end point = PFS
RANDOMIZATION
Gemcitabine 1,000 mg/m2 d 1 and 8
Carboplatin AUC = 4 d 1
*
q 21 x 6 (10 max)
Carboplatin AUC = 5 d 1
q 21 x 6 (10 max)
*du Bois et al. Ann Oncol. 2001;12:1115-1120.
Pfisterer et al. J Clin Oncol. 2004:22. Abstract 5005.
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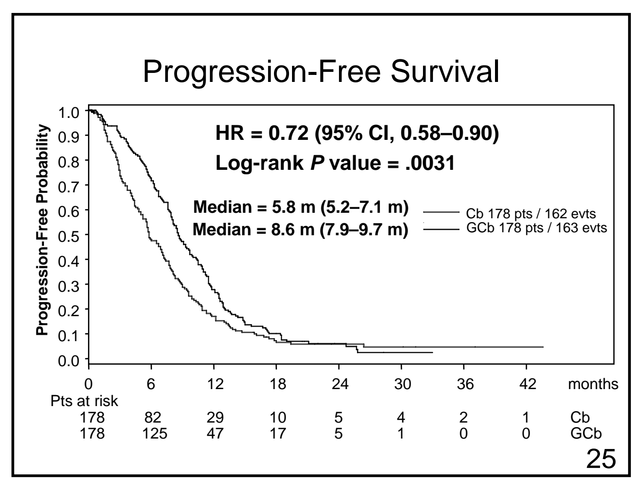

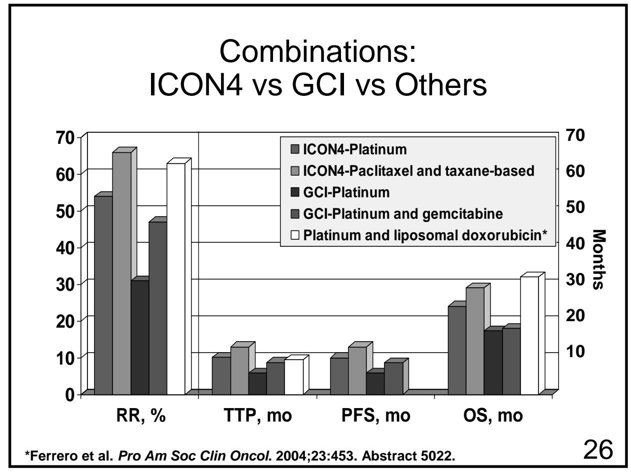

Ovarian Cancer: Conclusions

- Standards of when and how to treat recurrent ovarian cancer continue to evolve
- Novel chemotherapeutics and the future development of biologics provide multiple new options for adjuvant therapy
- Treatment selection for relapsed ovarian cancer must be based on patient-specific variables with the goals of extending survival and maximizing quality of life

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Case 2: Discussion

- 56-year-old woman diagnosed with stage IIIC clear cell ovarian cancer
  - Recurred at 10 months
- Issues
  - Bevacizumab in the treatment of gynecologic cancers
  - Doublet therapy

Panel

Discussion

- Stage III ovarian cancer, optimally debulked
  - CA-125 of 300 prior to surgery
    - CA-125 of 96 after surgery, 46 after 3 cycles of chemotherapy, and 12 after 6 cycles
- Issue
  - Maintenance therapy

Panel

End of Presentation

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Controversy: Radiation vs Chemotherapy in the Treatment of Advanced Stage IIIC Endometrial Cancer

Presented by
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Pathology commentary by
Thomas C. Wright, MD
College of Physicians and Surgeons of Columbia University
New York, New York

1

Case Presentation: History

- 63-year-old white female presenting with postmenopausal bleeding
- Endometrial biopsy, grade 3 adenocarcinoma
- Surgery: TAH/BSO and staging, including full node dissection and omental biopsy as well as washings

TAH/BSO = total abdominal hysterectomy and bilateral salpingo-oophorectomy.

2

Case Presentation: Pathology

- Uterus: adenocarcinoma, grade 3, invading 8 out of 15 mm of myometrium with LVSI
- Lymphadenopathy: 2/16 pelvic nodes positive and 0/8 para-aortic nodes positive
- Ovaries, fallopian tubes, washings, and omentum negative
- Surgical stage: FIGO IIIC

LVSI = lymphovascular invasion.

3

Pathology

Courtesy of Thomas C. Wright, MD.

4

Pathology

Courtesy of Thomas C. Wright, MD.

5

Adjuvant Treatment Options

- Pelvic radiation therapy
- Chemotherapy
- Combined chemotherapy and radiation therapy

6

Radiation Therapy for Stage IIIC: Retrospective Studies

Author	No. of Patients	3-Year Survival, %	5-Year Survival, %
Mundt, 2001*	30		55.8
McMeekin, 2001†	47	77	65
Nelson, 1999‡	77	81	72
Onda, 1997§	30		84
Morrow, 1991‖	63		71

*Mundt et al. *Int J Radiat Oncol Biol Phys.* 2001;50:1154-1160.
†McMeekin et al. *Gynecol Oncol.* 2001;81:273-278.
‡Nelson et al. *Gynecol Oncol.* 1999;75:211-214.
§Onda et al. *Br J Cancer.* 1997;75:1836-1841.
‖Morrow et al. *Gynecol Oncol.* 1991;40:55-65.

7

Stage IIIC Endometrioid Cancer of the Endometrium

- Peritoneal failure: 59% of stage IV but only 1% in stage I–III unless ≥ 2 risk factors (nonendometrioid, + cytol, + nodes, + cervix)

	Stage IIIC (nodes only)	Stage IIIC ("Plus") (nodes and perit, serosa, adnexa, vag)
Number	22*	24†
5-y CSS, %	72	33
5-y RFS, %	68	25

*Adj RT 21/22, CT/RT 1/22.
†Adj RT 16/24, CT/RT 1/24, CT 2/24, hormone therapy 4/24; distant failure predominated in IIIC ("Plus") but not in IIIC.
Mariani et al. *Gynecol Oncol.* 2002;87:112-117.
Mariani et al. *Gynecol Oncol.* 2003;89:236-242.

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Sites of Relapse: Radiation Therapy Studies

- Distant: most common
- Para-aortics: especially if not treated
- Pelvis

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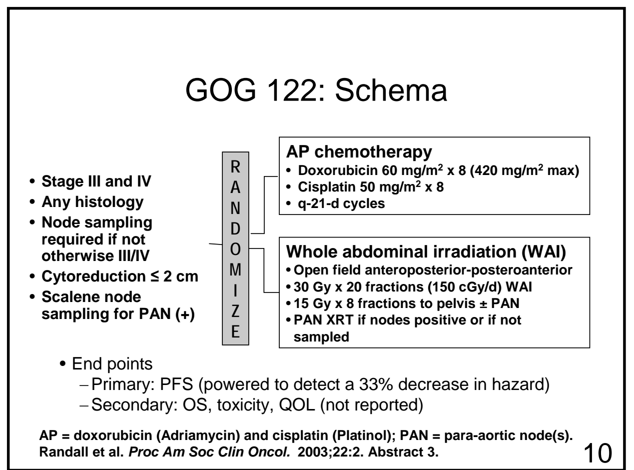

GOG 122: Patient Characteristics

Characteristics	WAI	AP
Race, %		
White	77.7	77.8
African American	14.9	17.0
Median age, y	63	63
Stage, %		
III	74.8	71.6
IV	25.2	28.5
Cell type, %		
Serous	21.3	20.3
Endometrioid	52.5	47.4
Clear cell	3.5	5.2
Mixed	9.4	16.0
Adenosquamous	5.9	6.2
Grade, %		
1	14.9	12.9
2	29.2	30.4
3	52.0	52.6

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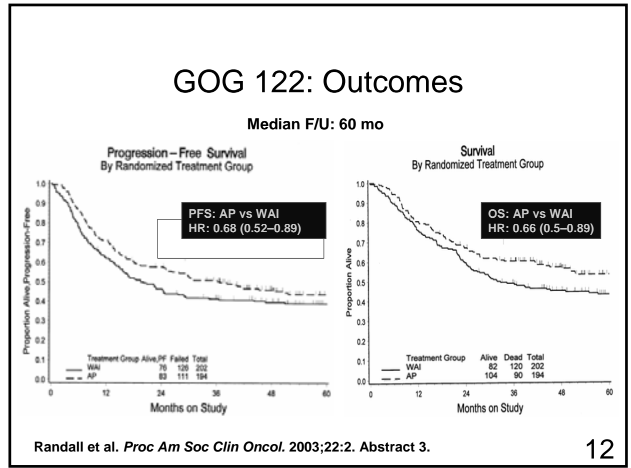

Treatment

Comparison	WAI	AP
Completed therapy, %	84	63
Stopped treatment due to toxicity, %	3	17
Median duration of treatment, mo	1.3	5.1
Did not receive protocol therapy, n	12	3

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GOG 122: Complications

Grade 3–4 Toxicity	WAI	AP
White blood cell count, %	4	62
Absolute neutrophil count, %	< 1	85
Gastrointestinal, %	13	20
Hepatic, %	3	1
Cardiac, %	0	15
Neurologic, %	< 1	7
Treatment-related deaths, n	4	8

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GOG 122: Sites of Initial Recurrence

Site	WAI, %	AP, %
Vagina	5.0	5.7
Pelvis	8.4	11.3
Retroperitoneum	0.0	2.1
Peritoneal cavity	16.3	11.3
Liver	3.5	7.2
Beyond the abdomen	18.3	9.8
Unknown	2.0	1.0
No evidence of recurrence	46.5	51.5

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GOG 122: Conclusions

- The risk of progression or death is reduced by 30% and the risk of death is reduced by 34%
- Toxicity is significantly increased with AP chemotherapy compared to WAI
- Recurrence rates were still significant:
  - 40%–50% in stage III, and 80%–90% in stage IV

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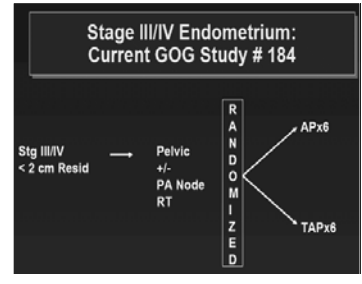
Current Trials: Advanced Disease

- Combination therapies
  - Chemoradiation
  - Volume-directed radiotherapy
- Biologics
- Less toxic chemotherapy



GOG 184. National Cancer Institute (Web site). Available at: http://ctep.cancer.gov/resources/gcig/activetrials.html. Accessed June 3, 2005.

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Treatment at M. D. Anderson Cancer Center

- Whole pelvic XRT—45–50 Gy—followed by 2–3 vaginal cuff boost with HDR
- Adjuvant chemotherapy: carboplatin and paclitaxel, 3–4 cycles every 3 weeks

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Radiation Treatment Plan

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Case 3: Discussion

- 63-year-old woman diagnosed with FIGO IIIC grade 3 endometrial adenocarcinoma
  - 2/16 pelvic nodes positive
  - 0/8 para-aortic nodes positive
- Issues
  - Distant vs local recurrence failure
  - Chemotherapy vs radiation

Panel

Discussion

- Issue
  - GOG 122
    - Patient population and response

Panel

End of Presentation

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