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Grand Rounds in Ovarian Cancer: Standards of Care and Novel Treatment Approaches

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Disclosure

- Dr. Dizon has nothing to disclose.
- Ms. Gahres has nothing to disclose.

Learning Objectives

- Describe the latest evidence-based therapy available in ovarian cancer
- Apply learning to the management of side effects from the latest treatments in patients with ovarian cancer
- Explain the focus of future research
- Develop and coordinate a multidisciplinary approach to patient care in the ovarian cancer setting

Which is the most common histologic subtype of epithelial ovarian cancer?

A. Serous
B. Endometrioid
C. Clear cell
D. Mucinous
E. Mixed epithelial
F. Small cell

A patient presents with ascites and a CA-125 level of 12,000 U/mL. CT shows omental caking and a right ovarian mass, consistent with advanced ovarian cancer. The most appropriate treatment at this time is:

A. Neoadjuvant chemotherapy
B. Exploratory surgery for staging and tumor debulking
C. A or B, depending on the feasibility of complete surgical cytoreduction
D. None of the above

A patient presents with advanced ovarian cancer and undergoes primary surgery. The operative report records she had stage IIIC ovarian cancer, resected to no gross residual disease. Your recommendation for adjuvant therapy is to administer:

A. Carboplatin alone, every 3 weeks for 6 cycles
B. Carboplatin plus paclitaxel, every 3 weeks for 6 cycles
C. Dose-dense paclitaxel (on days 1, 8, 15) plus carboplatin (on day 1), repeated every 3 weeks for 6 cycles
D. IV paclitaxel (day 1), IP cisplatin (day 2), and IP paclitaxel (day 8), repeated every 3 weeks for 6 cycles

A patient has been recommended to commence adjuvant chemotherapy after a diagnosis of stage IIIC ovarian cancer. Her family is interested in the addition of the angiogenesis inhibitor bevacizumab. The most appropriate statement regarding bevacizumab in this scenario is:

A. Bevacizumab improves progression-free survival (PFS) but has no impact on overall survival (OS)

B. Bevacizumab positively impacts both PFS and OS

C. Bevacizumab had no impact on PFS, but results in an improvement in OS

D. None of the above

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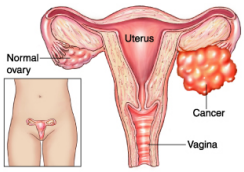
Outline

- Epidemiology of ovarian cancer
- Risk factors
- Histology
- Treatment options
  - Standard treatment
  - Novel approaches
- Case presentation



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Epidemiology

- Estimated new cases of ovarian cancer for 2014: 21,980
- Estimated deaths related to ovarian cancer for 2014: 14,270
- Median age at diagnosis: 63
- 5th leading cause of cancer-related death in women
- Diagnosis at stage III or IV
- 44% overall 5-yr survival

National Cancer Institute. Surveillance, Epidemiology, and End Results Program. SEER Stat Fact Sheets: Ovary Cancer.

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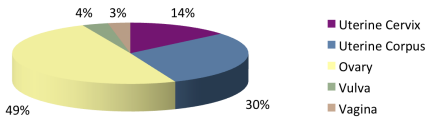
Gynecologic Cancer: U.S. Estimated Deaths in 2014



Siegel R, et al. *CA Cancer J Clin*. 2014;64:9–29.

Risk Factors

- Postmenopausal
- Obesity
- Nulliparous
- Hormone replacement therapy
- Family history of ovarian cancer
- *BRCA* mutation (5%–10% of cases)

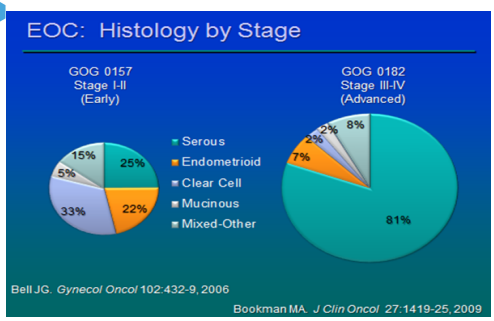
Histopathology

- High-grade serous carcinoma (70%–80%)
- Endometrioid carcinoma (10%)
- Clear cell carcinoma (10%)
- Mucinous carcinoma (3%)
- Low-grade serous carcinoma (< 5%)

Staging of Ovarian Cancer

Stage	Description
I	Confined to ovaries
II	Confined to pelvis
III	Spread IP or nodes
IV	Distant metastases

EOC: Histology by Stage



Approaching Primary Treatment

Surgery or Neoadjuvant Chemotherapy

- Initial decision point for most patients
- Rationale for neoadjuvant chemotherapy (NACT)
  - Reduce perioperative morbidity
  - Increase likelihood of a complete cytoreduction
  - Allows for evaluation of chemotherapy effectiveness
- In the US: Typically reserved for patients who are not candidates for surgery at the time of diagnosis and those deemed unresectable

Defining Unresectability

- Diffuse and/or deep infiltration of the small-bowel mesentery
- Carcinomatosis involving stomach and/or large portions of bowel
- Infiltration of duodenum and/or pancreas
- Involvement of the hepatoduodenal vessels, celiac trunk, or inferior to the porta hepatis
- Intraparenchymal hepatic metastases

Vergote I, et al. *Gynecol Oncol*. 2013;128:6–11.

NACT vs. Primary Surgery

- EORTC 559711: NACT resulted in
  - Less complications, including fewer postoperative deaths compared to primary surgery (0.6% vs. 2.5%)
  - A higher rate of optimal cytoreduction (81% vs. 42%)
  - No difference in PFS or OS
- CHORUS Trial 2: NACT resulted in
  - Higher rate of an optimal cytoreduction (35% vs. 15%)
  - No difference in PFS or OS

Vergote I, et al. *N Engl J Med*. 2010;363:943; Kehoe S, et al. ASCO 2013, Abstract 5500.

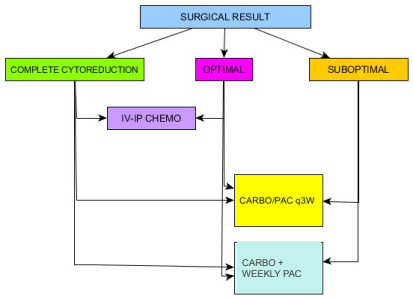
NACT vs. Primary Surgery (cont)

BOTTOM LINE

- No survival advantage to NACT
- Reserved for patients at risk for surgical complications

Vergote I, et al. *N Engl J Med*. 2010;363:943; Kehoe S, et al. ASCO 2013, Abstract 5500.

Adjuvant Therapy: An Algorithm

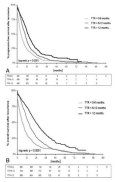


Prognosis Based on Surgical Outcome

- Residual disease at the end of surgery is prognostic
- AGO-OVAR: Analysis of three randomized trials (n = 3,126)

	OS (Median)	HR (95% CI)
Complete cytoreduction	99 mo	
Optimal cytoreduction (1–10 mm)	36 mo	2.12* (1.85–2.43)
Suboptimal cytoreduction (> 10 mm)	30 mo	1.20^ (1.08–1.33)

*Compares optimal vs. complete
^Compares suboptimal vs. optimal



Dubois A, et al. *Cancer*. 2009;115:1234–1244.

Prognosis and Surgical Cytoreduction

AGO study suggests…

- A subgroup of women with advanced ovarian cancer, cytoreduced to no residual disease, may be curable.

IV/IP Chemotherapy

- Eligibility: Up to 1 cm residual disease
- Cochrane meta-analysis of IV/IP vs. IV chemotherapy
  - 8 randomized trials (n = 1,800)
  - Compared to IV treatment
    - Reduction in the risk of death (HR 0.79, 95% CI 0.79–0.90)
    - Reduction in the risk of recurrence (HR 0.79, 95% CI 0.69–0.90)

Jaaback K et al. *Cochrane Database Syst Rev.* 2006.

Is It Utilized?

- NO, even among National Comprehensive Cancer Network institutions
  - N = 603 with stage III optimally cytoreduced ovarian cancer
  - IP usage
    - Between 2003 and 2006: 0% to 33%
    - 2007 to 2008: 50%
    - 2009 to 2012: 43%
  - 5-yr OS (IP vs. no IP): 57% vs. 44%
    - HR 0.69 (95% CI 0.50–0.94)

Wright AA, et al. ASCO 2014, Abstract 358.

Alternative Options Are Easier to Use

- Carboplatin plus weekly paclitaxel
  - Not compared to IP therapy in any of the published trials
- Conflicting data from two randomized trials

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Dose-Dense Paclitaxel With Carboplatin

JGOG 3016: RCT against every-3-week treatment (standard of care)
- Median follow-up 77 months, weekly dosing resulted in:
  - Higher PFS (median, 28 vs. 17.5 mo, HR 0.76, 95% CI 0.62–0.91)
  - Higher OS (median, 100.5 vs. 62 mo, HR 0.79, 95% CI 0.62–0.99)
  - Benefits best in suboptimally cytoreduced patients

RCT = randomized controlled trial
Katsumata N, et al. *Lancet Oncol*. 2013;14:1020.

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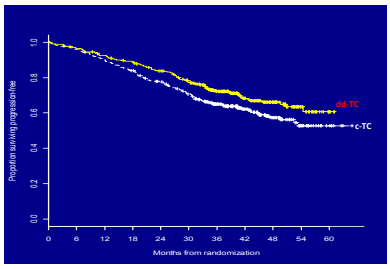
Overall Survival



Treatment	n	Event	3-yr survival	*p* value	HR	95% CI
c-TC	319	124	65.1%			
dd-TC	312	96	72.1%	.0325	0.749	0.574–0.976

Katsumata N, et al. *Lancet Oncol*. 2013;14:1020.

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Dose-Dense Paclitaxel Plus Carboplatin

- GOG 262: RCT against every-3-week treatment (standard of care) +/- bevacizumab
  - No difference in PFS (HR 0.97, 95% CI 0.79–1.18)
  - Among patients not treated with bevacizumab
    - Improvement in PFS with dose-dense therapy (median, 14 vs. 10 mo, HR 0.60, 95% CI 0.37–0.96)
    - This difference not seen if bevacizumab was given

Chan J, et al. ESGO 2013.

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Bottom Line

Dose-dense therapy appears to be of benefit, but benefit may depend on whether bevacizumab is also administered and on the surgical outcome

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Will We Have a Clearer Answer?

Maybe….

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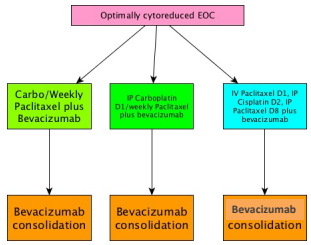
GOG 252

Eligibility: Optimally cytoreduced advanced ovarian cancer



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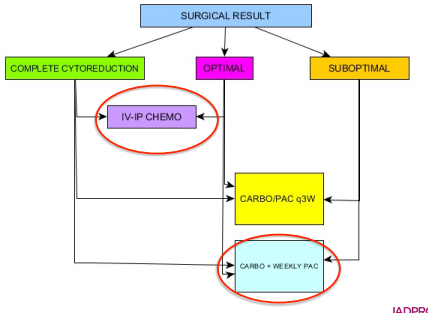
Adjuvant Therapy: An Algorithm



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Where Do We Go From Here?

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The Role of Angiogenesis Inhibitors

- Bevacizumab: No role in the adjuvant setting
  - Two randomized trials
    - GOG 2181: Bevacizumab improves PFS compared to standard treatment (14 vs.10 mo, HR 0.72, 95% CI 0.63–0.82), but no OS improvement (median, 39 mo across arms)
    - ICON72: Bevacizumab improved PFS (24 vs. 22 mo) but no improvement in OS
      - Women at "high risk": Bevacizumab improved PFS (18 vs. 14 mo) and OS (37 vs. 29 mo)
      - High risk: Suboptimal cytoreduction for stage III EOC, stage IV EOC at diagnosis

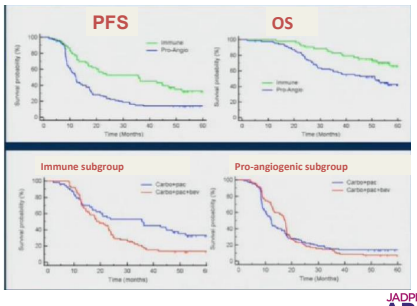
Burger RA, et al. *NEJM*. 2011;365: 2473; Perren TJ, et al. *NEJM*. 2011;365:2484.

Predicting Who Will Benefit From Angiogenesis Inhibitors

- Genomically predictive signatures of high-grade serous ovarian cancer re: bevacizumab might exist
- Gourley et al. (ASCO 2014)
  - Immune vs. proangiogenic signatures in ovarian cancer
  - Data from ICON7 clinical trial

Gourley C, et al. ASCO 2014, Abstract 5502.

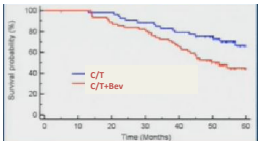
Gourley et al.



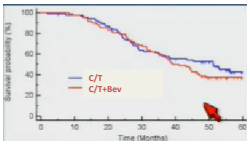
Gourley C, et al. ASCO 2014, Abstract 5502.

Gourley et al.: Overall survival

Immune subgroup



Pro-angiogenic subgroup



Gourley C, et al. ASCO 2014, Abstract 5502.

Significance

- Not all ovarian cancers are the same
- Immune genomic signature predicts harm
- Validation urgently needed

Pazopanib

AGO trial: Pazopanib as maintenance therapy

- All patients s/p chemotherapy without evidence of progression
- Compared to placebo, pazopanib resulted in:
  - Improvement in PFS (median, 18 vs. 12 mo; HR 0.77, 95% CI 0.64–0.91)
  - At first analysis: No improvement in OS
  - Worse toxicity: Hypertension, diarrhea, hepatotoxicity

Du Bois A, et al. ASCO 2013, LBA 5503.

Cediranib

- Oral VEGF TKI
- No data on adjuvant use, but provocative data for platinum-sensitive recurrent disease based on ICON 6
  - Chemotherapy +/- cediranib (with and/or following chemotherapy)
  - Compared to chemotherapy only, cediranib as maintenance treatment
    - Improved PFS (median, 12.5 vs. 9.4 mo)
    - Improved OS (median, 20.3 vs. 17.6 mo)

Ledermann JA, et al. ECC 2013.

PARP Inhibitors in Development

Agent	Phase of development
Olaparib	Phase III (newly diagnosed and in platinum-sensitive recurrent EOC)
Niraparib	Phase III (platinum-sensitive recurrent EOC)
BMN 673	Phase I
Rucaparib	Phase II (platinum-sensitive recurrent EOC)
Veliparib	Phase I (newly diagnosed)
CEP-9722	Phase I
E7016	Phase I

Olaparib

Study 19: Maintenance olaparib vs. placebo

- Eligibility: Platinum-sensitive recurrent EOC
  - All patients must have responded to most recent treatment
    - Median prior regimens: 3
    - PFI > 12 mo in 60% of patients
- Compared to placebo: Olaparib resulted in:
  - Improved PFS (median, 8 vs. 5 mo; HR 0.35, 95% CI 0.25–0.49)
  - No difference in OS (median, 30 mo)

EOC = epithelial ovarian cancer; PFI = progression-free interval.

Olaparib Benefits Women With mBRCA

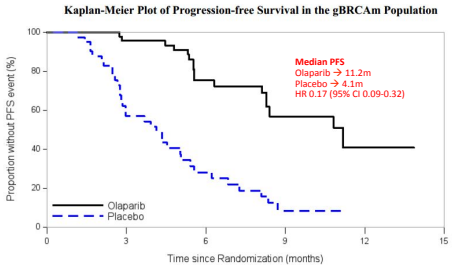
Preplanned analysis of Study 19

BRCA mutation+	Olaparib	Placebo
Known gBRCA+ at randomization	24%	22%
Identified gBRCA+ retrospectively	15%	12%
Total N	53	43
Somatic BRCA+*	6%	8%

*Patients with a wild-type BRCA in germline whose tumors had a somatic BRCA mutation identified using a different platform

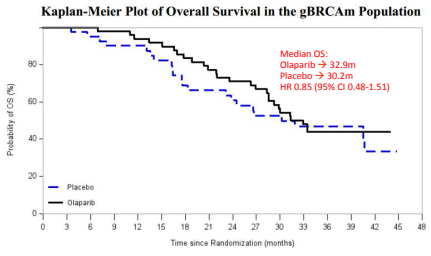
Ledermann JA, et al. ASCO 2013, Abstract 5505.

Study 19 Analysis by mBRCA Status



Ledermann JA, et al. ASCO 2013, Abstract 5505.

Study 19 Analysis by mBRCA Status (cont)



Ledermann JA, et al. ASCO 2013, Abstract 5505.

Study 19 Results: FDA Review

- Three olaparib-treated patients died within 30 days of last dose due to:
  - Hemorrhagic stroke
  - Cholestatic jaundice
- Myelodysplastic syndrome/AML
  - Incidence in Study 19: 2.2% (n = 3)
  - Estimate across trials: 0.8% (n = 21)
    - Risk with platinum: 0.03%

http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/oncologicdrugsadvisorycommittee/ucm402207.pdf

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Current Status of Olaparib

- ODAC review for accelerated approval: 6/25/2014
  - Committee vote: Disapproval
  - FDA final decision eagerly anticipated
- Studies of Olaparib in Ovarian cancer (SOLO)
  - SOLO1: mBRCA+, newly diagnosed EOC, responded to primary chemotherapy.
  - SOLO2: mBRCA+, platinum-sensitive recurrent EOC, responded to platinum-based chemotherapy

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Conclusions

- No singular standard of care for the first-line management of epithelial ovarian cancer
- Primary surgery is the preferred choice for most patients presenting with advanced disease
  - Neoadjuvant chemotherapy is not an unreasonable alternative
- Adjuvant treatment takes into account surgical results
  - No gross residual disease or optimal cytoreduction: IV/IP chemotherapy should be strongly considered
  - Suboptimal cytoreduction: Dose-dense paclitaxel with every-3-week carboplatin should be strongly considered

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Management of Ovarian Cancer

- Multidisciplinary
  - Care requires expertise in the **surgical** and the **medical** management of ovarian cancer
  - Gynecologic oncology spans both realms, but need not be a single provider
- Team-centric
  - Consistent approach to issues is needed
  - Advanced practice providers are well-positioned to ensure consistency and the quality of care are maintained
- Coordinated
  - Team members must understand the treatment plan and anticipate issues
  - MD, NP, PA, RN, PharmD: All important for coordination of care

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Coordinating Care Between the Physician and the Advanced Practitioner (AP)

- Clearly outline roles
  - Physicians must outline treatment plan
  - How will the AP assist in the execution of the plan?
    - Pretreatment clearance
    - Postoperative management
    - Inpatient responsibilities
    - Primary contact for other clinicians
  - Communicate who "WE" are to patients
    - Introduce patients to APs early
      - Website
      - Graphic display
      - In person
    - Create a place for the AP as part of the doctor-patient relationship

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Areas for Discussion

- Do not take on more responsibility than you are comfortable with
  - Radiology results
  - Changes in chemotherapy regimens
  - Delivering bad news
- Professional development
  - Access to CME
  - Conference coverage
- Institutional promotion
  - Pathway for promotion
  - Clear delineation of expectations
  - Annual reviews

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Advanced practitioners are essential to oncology…
when it works, it is fabulous.

So Make it Work

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Case Presentation

- 50-year-old new-onset pelvic pain and dysuria
- Treated for presumed UTI
- Follow-up pelvic ultrasound identified right ovary multiseptated cystic mass with severe nodular thickening
- CT scan A/P noted right complex mass in right cul-de-sac and omental masses
- Elevated CA-125: 317 (normal value < 35)

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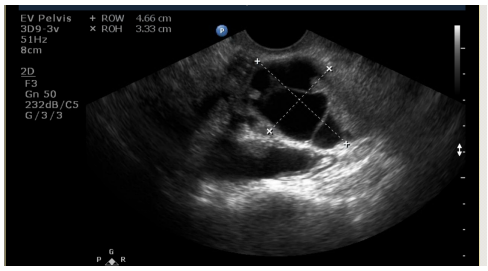
Transvaginal Ultrasound



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CT Scan C/A/P

History

- Past medical history: Hyperlipidemia, hypertension, hypothyroidism
- Meds: Levothyroxine 75 µg qd, Irbesartan 150 mg qd, Crestor 5 mg qd, MVI, ASA 81 mg qd
- Allergies: Sulfamethoxazole and trimethoprim, cephalexin
- Past surgeries: Subtotal thyroidectomy 2003, laparoscopy for endometriosis 1999, C-section 1994
- OB/GYN history: G1P2, IUD 2006, heavy menses, LMP 2012

History (cont)

Family history

- Mother with young-onset breast cancer (deceased age 32)
- Maternal aunt with breast cancer (alive)
- Recalls “distant aunts, 2 or 3 generations ago” probable ovarian cancer

Examination

- Review of systems: + abdominal pain
- Physical exam
  - Abd: Soft, non-distended, non-tender, no palpable masses
  - Gyn: Large somewhat mobile pelvic mass
  - Rectal: Identified rectal shelf c/w CDS disease

CDS = cul de sac

Preliminary Diagnosis

Advanced pelvic carcinoma, likely ovarian in origin

Primary Treatment: Surgery

- Surgery: Exploratory laparotomy with:
  - Total abdominal hysterectomy
  - Bilateral salpingo-oophorectomy
  - Nodal dissection
  - Omentectomy
- Pathology: High-grade serous ovarian cancer involving both tubes and ovaries, splenic capsule, diaphragm, colon, and left pelvic nodules
- FIGO diagnosis: Stage IIIC ovarian carcinoma

Adjuvant Treatment

Platinum plus paclitaxel

- IV paclitaxel d1, IP cisplatin d2, IP paclitaxel d8
- Six cycles administered

Thank you for listening!

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