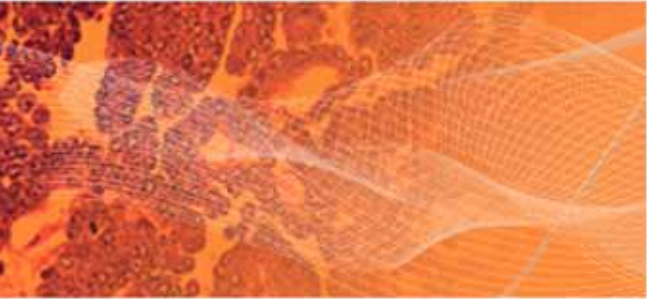


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Ovarian Cancer:

Updates from the 16th International Meeting of the
European Society of Gynaecological Oncology

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TARGET AUDIENCE

The target audience for the program will include gynecologic oncologists, medical oncologists, surgical oncologists, pathologists, and allied healthcare professionals caring for patients with ovarian cancer.

LEARNING OBJECTIVES

Upon completion of this educational activity, participants should be better able to:

- Recognize biologic pathways of significance in ovarian cancer pathogenesis and resistance
- Examine current treatment options in the management of ovarian cancer
- Propose an appropriate regimen for patients with either newly diagnosed or recurrent ovarian cancer
- Discuss toxicity prevention, identification, and management strategies for patients receiving therapy for ovarian cancer

STATEMENT OF NEED

New therapies, new combinations of existing chemotherapies, and new methods of delivery of local and systemic therapies have been shown to improve survival for patients with ovarian cancer. While improvements are being realized, many issues surrounding the management of ovarian cancer remain. Included are the utility of CA125 within clinical trials as a means of assessing clinically significant progression, choice of agent(s), use of monotherapy versus combination regimens, and the timing of salvage therapy. This educational program will provide medical oncologists, gynecologic oncologists, and healthcare professionals caring for patients with ovarian cancer with pertinent information about advances in the management of ovarian cancer.

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INTRODUCTION

Ovarian cancer is a considerable therapeutic challenge for clinicians and outcomes for the disease have not changed dramatically for several decades. This year, more than 20,000 women in the United States will be diagnosed with ovarian cancer, and nearly 15,000 will succumb to the disease.¹ The 16th International Meeting of the European Society of Gynaecological Oncology (ESGO), held in Belgrade, Serbia provided an excellent forum to discuss, debate, and disseminate much needed new clinical and scientific information. Highlights from novel ovarian cancer presentations are outlined in this newsletter.

RISK ASSESSMENT

The 5-year survival rate for women diagnosed with early stage ovarian cancer is over 90%. Unfortunately, nearly 80% of ovarian cancer patients are diagnosed with disseminated disease, where the 5-year survival rate is low. Several approaches have been taken to improve patient survival, but the general consensus is that screening and early detection offer the most promising avenue for reduction in mortality. The challenge is to identify ovarian cancer at early stage presentation, where the disease is more amenable to curative intervention, without subjecting healthy women to unnecessary surgery and extensive toxicity from chemotherapy. Risk assessment will likely need to take place on several levels to identify women most in need of screening or preventative measures.

Risk of Malignancy, HE4 and CA125

Currently, differentiation of benign and malignant tumors in women presenting with ovarian masses is challenging. Risk of malignancy is generally assessed using ultrasound and CA125 levels. However, significant limitations, especially with regard to sensitivity and specificity, exist with this methodology. The Risk of Ovarian Malignancy Algorithm (ROMA) was recently published.² ROMA stratifies patients into high- and low-risk of malignancy and is based on the serum levels of CA125 combined with human epididymis secretory protein 4 (HE4), which is expressed in serous, endometrioid, and clear cell cancer tissues.

In order to validate the ROMA algorithm, Van Gorp, et al conducted a prospective study on women about to undergo surgery for removal of an ovarian mass.³ Entrance criteria included women over the age of 18 with an adnexal mass who had at least one ovary at study entry and were fit to undergo surgery. Serum CA125 and HE4 levels were detected by enzyme-linked immunosorbent assay (ELISA). Serum samples were available from 413 patients, and 389 of those patients underwent surgery. For pre-menopausal and post-menopausal women combined, the area under the curve (AUC) was better with ROMA compared to either CA125 or HE4 alone in all malignant tumors (epithelial ovarian cancer [EOC], non-EOC, and metastatic disease) versus benign, EOC versus benign, stage I EOC versus benign, and borderline ovarian cancer versus benign (**Table 1**). ROMA yielded 75% specificity and 92.3% sensitivity in post-menopausal women and 74.8% specificity and 76.5% sensitivity in pre-menopausal women. For all patients and all malignant tumors ROMA yielded better sensitivity than the risk of malignancy index (RMI), which is based upon menopausal status, ultrasound findings, and serum CA125 levels, with a cutoff of 200 (84% for ROMA versus 78% for RMI) and slightly lower specificity (74% for ROMA versus 80% for RMI) (**Table 2**). The authors concluded that ROMA is a simple quantitative method that performs similar to other risk of malignancy models, although risk assessment of stage I EOC and borderline ovarian cancer remains challenging.

Table 1: Pathologic AUC versus benign AUC for ROMA, CA125 alone, and HE4 alone.

	All malignant vs Benign	EOC vs Benign	Stage I OC vs Benign	Borderline OC vs Benign
ROMA	89.5%	91%	81.1%	77.6%
CA125	87.7%	88.6%	75.5%	72.6%
HE-4	85.7%	87.1%	76.7%	73.7%

AUC, area under the curve; EOC, epithelial ovarian cancer; OC, ovarian cancer; ROMA, risk of ovarian malignancy algorithm; CA125, cancer antigen 125; HE4, human epididymis protein 4.



Table 2: Specificity and sensitivity of ROMA compared to other risk assessment tools.

Method	AUC	Sensitivity	Specificity
New IOTA log regression	0.94	93%	76%
Old IOTA log regression	0.90	80%	81%
ROMA	0.90	84%	74%
RMI (cut off 200)	0.87	78%	80%

AUC, area under curve; IOTA, International ovarian tumor analysis; RMI, risk of malignancy index; ROMA, risk of ovarian malignancy algorithm.

Penetrance of BRCA1 and BRCA2

Women who carry genetic mutations in breast cancer associated gene 1 (*BRCA1*) and 2 (*BRCA2*) are at significantly greater risk of both breast and ovarian cancers. de Bock, et al examined the penetrance of *BRCA1* and *BRCA2* mutations.⁴ The study analyzed 185 families for mutations in *BRCA1* or *BRCA2*. First degree relatives were screened and age-related penetrance was calculated by Kaplan Meier analysis for mutation carriers, proven non-carriers, and patients who were not tested.

A total of 1188 women from 185 families with pathogenic *BRCA1* (111 families) or *BRCA2* (74 families) mutations were included in the study. From the *BRCA1* families, 308 *BRCA1* carriers, 319 individuals who were not tested, and 128 proven non-*BRCA1* carriers were identified. From the *BRCA2* families, 178 carriers, 181 untested individuals, and 74 non-carriers were identified. In the *BRCA1* families, the risk of developing breast cancer by the age of 70 was 71.4% for mutation carriers, 35.1% for those who were not tested, and 8.6% for proven non-carriers. The risk of developing ovarian cancer in *BRCA1* families was 58.9% for mutation carriers with a steep rise even after the age of 60, 28.7% in those women not tested for mutation, and 0% in non-carriers. For *BRCA2* families, the risk of breast cancer was 87.5% with a steep rise even after the age of 60 for proven carriers, 34.7% in patients who were not tested, and 16.1% for proven non-carriers. The incidence of ovarian cancer in *BRCA2*-carrying families

was 34.5%, with a steep rise even after the age of 60, 12.8% for women who were not tested, and 0% for non-carriers (**Figure 1**). The incidence of contra-lateral breast cancer for patients with *BRCA1* was 34.2% within 10 years of diagnosis and 42% for the lifetime. For *BRCA2* patients the incidence was 29.2% within 10 years of diagnosis and 49.8% for lifetime (**Table 3**).

The authors recommended prophylactic bilateral salpingo-oophorectomy before the age of 40 for patients with proven mutations in *BRCA1* and before the age of 50 for patients with proven *BRCA2*-inactivating mutations. Continuing intensive breast cancer screening until age 70 in *BRCA2* mutation-positive women was also recommended. Taken together, these data underscore the high risk that *BRCA1* and *BRCA2* mutation carriers have for breast and ovarian cancer and emphasize the need this risk group has for special clinical considerations, follow-up, and preventative measures.

Table 3: Incidence of breast and ovarian cancer in confirmed mutation carriers, confirmed non-carriers, and not-tested first degree relatives of BRCA1 or BRCA2 carriers.

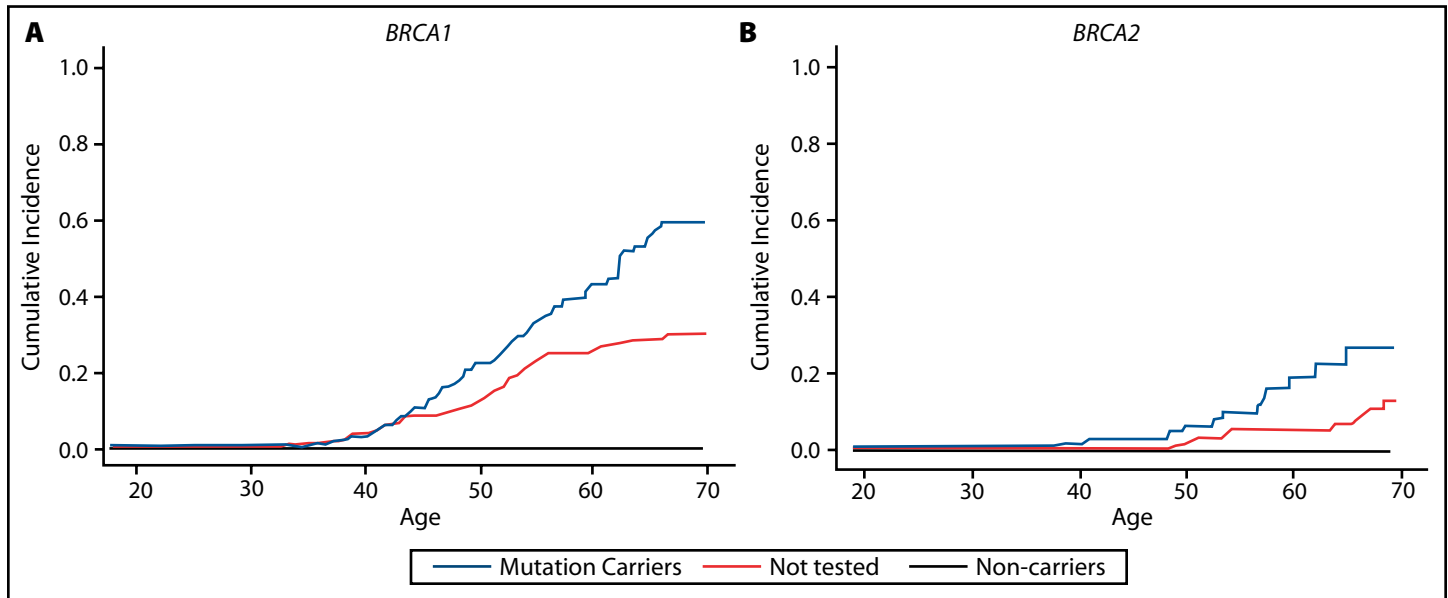
	Carrier	Not tested	Non-carrier
Breast Cancer			
<i>BRCA1</i>	71.4%	35.1%	8.6%
<i>BRCA2</i>	87.5%	34.7%	16.1%
Ovarian Cancer			
<i>BRCA1</i>	58.9%	28.7%	0%
<i>BRCA2</i>	34.5%	12.8%	0%

BRCA1, breast cancer associated gene 1; *BRCA2*, breast cancer associated gene 2.

VEGF Expression as a Predictor for Response to Bevacizumab

Angiogenesis is an essential component of tumor growth and development. The main molecular mediator of angiogenesis is vascular endothelial growth factor (VEGF), which stimulates proliferation and migration of endothelial cells. Bevacizumab,

Figure 1: Cumulative incidence by age of ovarian cancer in first degree relatives of *BRCA1* (A) and *BRCA2* (B) mutation carriers.



a humanized monoclonal antibody to VEGF, has potent anti-angiogenic effects and clinical efficacy in a number of human cancers, including ovarian cancer. Currently there are known predictive markers for response to bevacizumab therapy. Smerdel and colleagues investigated the predictive value of baseline serum VEGF and VEGF receptor 1 (VEGFR1) and 2 (VEGFR2) levels.⁵

Patients with multi-resistant ovarian cancer received single-agent bevacizumab at 10 mg/kg every 3 weeks. All patients were monitored for CA125, VEGF, VEGFR1, and VEGFR2 prior to bevacizumab administration. Response rates were assessed according to GCIg CA125 criteria. Thirty-eight patients were included in the study and 30 were evaluable for response. The median patient age was 54 years (range, 27-73 years). The majority of patients (92%) had serous tumor and most were grade 2 (40%) or grade 3 (42%). The population was heavily pre-treated with a median of 5 prior chemotherapy regimens (range, 2-9), and the median number of bevacizumab infusions was 4 (range, 1-24).

Nine patients (30%) responded to therapy. Median progression-free survival (PFS) was 5.9 months (95% CI, 3.5-9.4 months) and median overall survival (OS) was 8.6 months (95% CI, 6.6-12.8 months). Adverse events included gastrointestinal perforation (5%), ileovaginal fistula (2.5%), thromboembolism (5%), and grade 2 hypertension (2.5%). Serum VEGF levels declined by more than 98% after initiation of therapy and remained low throughout treatment. VEGFR2 levels increased modestly after initiation of therapy and VEGFR1 levels were relatively unchanged with bevacizumab treatment. Patients were stratified by baseline serum VEGF levels. High VEGF expressers were defined as those patients with serum levels greater than 540 pg/mL at baseline, and low expressers had baseline VEGF levels less than 540 pg/mL. Sixty percent of the low VEGF patients responded to bevacizumab. No patient with high serum VEGF levels at baseline responded to bevacizumab ($P = 0.0007$) (Table 4). In addition, patients with lower serum VEGF levels at baseline had better PFS ($P = 0.047$) and better OS ($P = 0.01$) (Figure 2). Five known VEGF polymorphisms and baseline VEGFR1 or 2 expression levels did not influence PFS or OS.



Although validation in a larger study is needed, these data suggest that pre-treatment serum levels of VEGF may be predictive of response to bevacizumab. Further studies will be needed to determine if increased doses of bevacizumab can safely overcome this effect.

Table 4: Response of ovarian cancer patients to bevacizumab according to baseline serum VEGF expression levels.

	Response n (%)	No response n (%)
N	9 (30%)	21 (70%)
Low VEGF (< 540 pg/mL)	9 (60%)	6 (40%)
High VEGF (> 540 pg/mL)	0 (0%)	15 (100%)

VEGF, vascular endothelial growth factor.

FIRST-LINE TREATMENT

Surgery

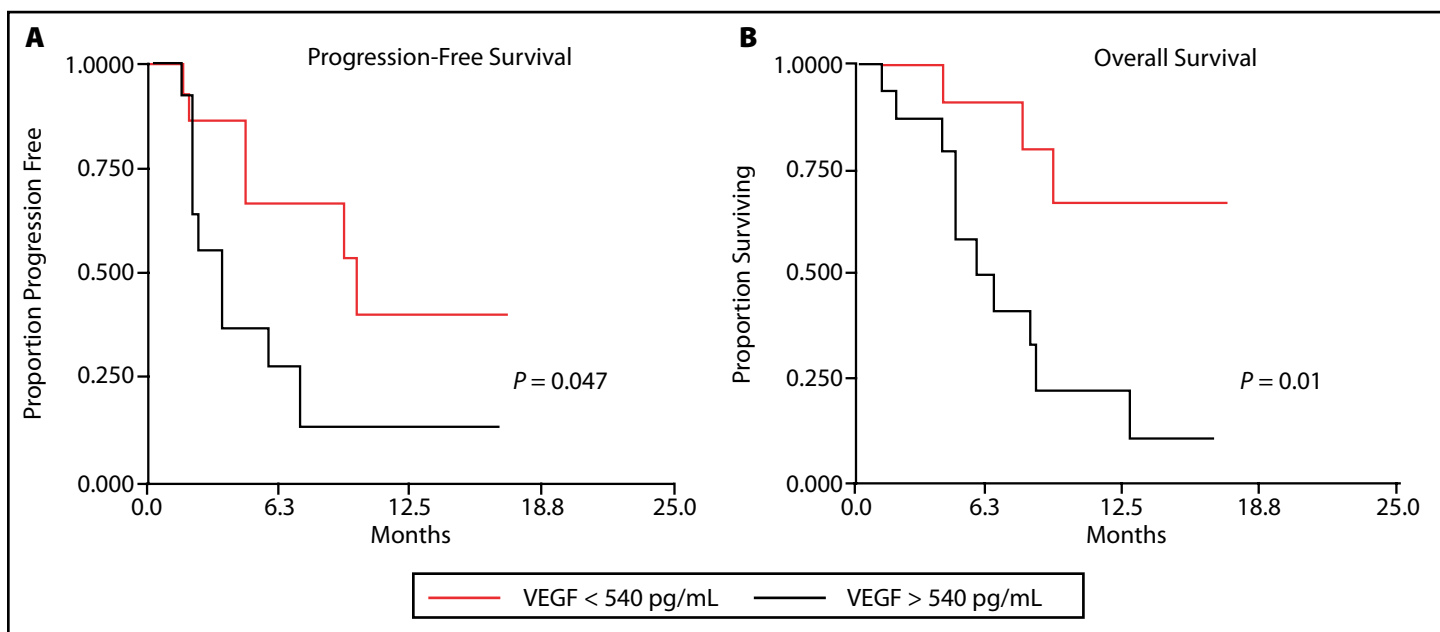
The Role of Lymphadenectomy

The standard of care for patients with advanced ovarian cancer is surgery followed by platinum/taxane-based chemotherapy. Residual tumor size is a significant prognostic factor, second only to disease stage.

Microscopic lymph node metastases, however, occur in approximately one-third of patients who appear to have complete intra-abdominal debulking,⁶ but the clinical impact of systematic pelvic and para-aortic lymphadenectomy has not been fully evaluated. du Bois, et al investigated the impact of lymphadenectomy on OS in 996 patients with no visible residual tumor and 946 patients with 0.1-1 cm residual tumor from 3 prospective trials (AGO-OVAR 3, 5, 7).⁷

In patients with residual tumors, multivariate analysis demonstrated a benefit of complete lymphadenectomy (pelvic + para-aortic) (HR = 0.78, 95% CI [0.64-0.96], $P = 0.0174$), but incomplete lymphadenectomy did not yield a benefit. Analysis of patients with residual tumors by clinical lymph node status found no impact in node-negative patients, but patients with palpable nodes benefited from lymphadenectomy ($P = 0.0038$). In patients with no residual disease univariate analysis found that lymphadenectomy resulted in an 11% impact on 5-year OS (log rank $P = 0.0081$), but was not significant in multivariate analysis (HR = 0.81, 95% CI [0.62-1.04], $P = 0.1008$). Therefore, the data suggest that some

Figure 2: Progression-free (A) and overall survival (B) by baseline serum VEGF levels.



subgroups may benefit from lymphadenectomy; however, further analysis is needed to assess the role and benefit of lymphadenectomy. A prospective randomized trial, AGO-OVAR OP.3, comparing systematic lymphadenectomy to no lymphadenectomy, is currently accruing patients.

Morbidity and Mortality in Debulking Surgery

Significant morbidity and mortality can be associated with debulking surgery for ovarian cancer. Ruffi and colleagues conducted a multicenter audit of 6 French Cancer Centers.⁸ The last 30 cases of patients with advanced ovarian cancer FIGO stage IIIc or IV who underwent optimal cytoreductive surgery achieving negative macroscopic residual disease and standard platinum/taxane-based chemotherapy at each center were audited. Events were graded by the Memorial Sloan-Kettering Cancer Center surgical secondary events grading system. Overall, 180 patients were evaluated and complications were observed in 33% of patients including 22% low-grade complications and 11% high-grade complications. Radical surgeries generated significantly more complications compared to standard surgery and centers performing more than 50% radical surgeries had significantly higher complications (76% vs 24%, $P = 0.01$). One death occurred within 30 days. Overall, high-grade morbidity was 10.5% and low-grade morbidity was 22.1%, suggesting that morbidity associated with debulking surgery, may be higher than what is reported in the literature.

Morbidity of Diaphragmatic Surgery

Surgical management of advanced stage ovarian cancer may require diaphragmatic surgery to achieve complete cytoreduction; however, the role of diaphragmatic surgery has not been thoroughly evaluated. Gouy, et al examined modalities and morbidities of diaphragmatic surgery in a retrospective review of 116 patients.⁹ Of those 116 patients, 63 patients underwent unilateral or bilateral diaphragmatic surgery at the time of initial (22 patients) or interval (41 patients) debulking surgery. Diaphragmatic surgery was performed in 54% of the cases and complete cytoreduction was achieved

in 95% of patients. The morbidity rate was similar between initial and interval surgery and was relatively low. Therefore, diaphragmatic surgery may safely aid in achieving optimal cytoreduction in some cases.

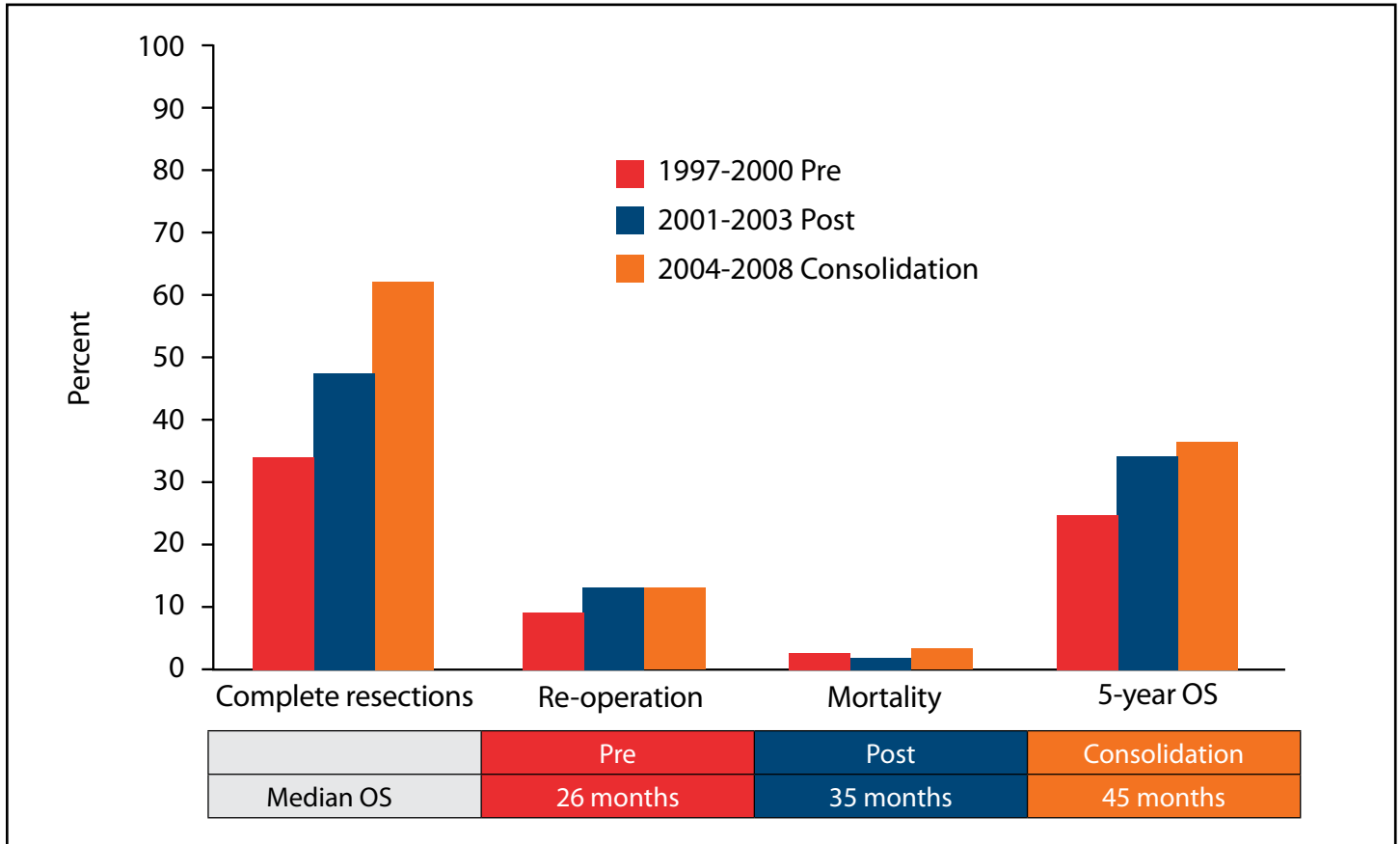
The Impact of Quality Management On Surgical Outcomes

Complete surgical resection significantly impacts outcomes of patients with advanced ovarian cancer. Improvements in the rate of complete surgical resection should impact patient survival. Muallem, et al presented results from a quality surgical management program for advanced ovarian cancer implemented at the Horst Schmidt Clinic in Wiesbaden, Germany in 2001.¹⁰ The quality management program included operation by dedicated surgical teams only, routine interdisciplinary pre- and intra-operating consultations, second opinion intra-operating consultation before closure in all patients with macroscopic residual disease, and annual quality conferences. A total of 438 patients with primary surgery for stage IIB-IV ovarian cancer were analyzed. The study was broken down into 3 phases, 1997-2000 (pre), 2001-2003 (post), and 2004-2008 (consolidation) and included 57, 94, and 287 patients, respectively.

Implementation of the quality management initiative resulted in significant increases in advanced surgical procedures such as para-aortic lymphadenectomy, intestinal surgery, diaphragmatic resection, splenectomy, and liver capsule resection. The proportion of patients achieving complete cytoreductive resections (0 mm residual tumor) increased from 33% pre, to 47% post, and 62% in the consolidation phase. Morbidity increased slightly mainly due to hemorrhage and re-operation. Median survival increased from a median of 26 months pre, to 37 months post, and 45 months in the consolidation phase. Five-year OS also increased (**Figure 3**). Taken together these data suggest that the incorporation of extensive upper abdominal procedures along with a systematic quality improvement initiative significantly improved cytoreduction and OS without significant increases in preoperative morbidity or mortality.



Figure 3: Outcomes before (pre) and after (post and consolidation) implementation of a quality surgical management program for advanced ovarian cancer.



CHEMOTHERAPY

Gemcitabine/Carboplatin/Paclitaxel vs Carboplatin/Paclitaxel, Phase III

The survival rates are low for patients with ovarian cancer detected at advanced stage. Unfortunately, nearly 80% of all ovarian cancers are detected at late stages. In an attempt to improve survival a number of agents have been added to the standard paclitaxel/carboplatin doublet, but, to date, no additional agents have conferred a survival advantage. Hardy-Bessard, et al presented the results of a randomized phase III trial by the GCIIG Intergroup comparing the triplet combination gemcitabine (800 mg/m² on d1, 8), paclitaxel (175 mg/m² over 3 hours), and carboplatin

(AUC 5) to paclitaxel (175 mg/m² over 3 hours) and carboplatin (AUC 5) (**Figure 4**).¹¹ Patients were stratified by stage and tumor size. Stratum 1 consisting of FIGO stage IA/B G3, IC-IIA, stratum 2 was FIGO stage IIB-IIIC and tumor size < 1 cm, and stratum 3 was FIGO stage IV or residual tumor size > 1 cm. The primary endpoint was the OS in stratum 2 and 3 and secondary endpoints included PFS, response rate, toxicity, and quality of life.

In total, 1742 patients were randomized between the 2 treatment arms. Baseline characteristics were similar between the 2 arms. More dose reductions occurred in one or more of the gemcitabine/carboplatin/paclitaxel arm (1.9% vs 3.4%, *P* < 0.0001) and the day 8 gemcitabine dose was omitted in 46.8% of

patients. More grade 3/4 hematologic toxicities occurred in the gemcitabine/carboplatin/paclitaxel arm including significantly higher rates of anemia, thrombocytopenia, leukopenia, neutropenia, and febrile neutropenia. Grade 3/4 fatigue was also significantly higher in the gemcitabine/carboplatin/paclitaxel arm.

Overall response, as assessed in patients with measurable disease, was better with gemcitabine/paclitaxel/carboplatin (77.5% vs 86.2%, $P = 0.039$), but this did not translate into a difference in OS (HR = 1.06). Moreover, PFS was actually better in the carboplatin/paclitaxel arm (HR = 1.17, $P = 0.0066$). Analysis of the 3 strata found that the addition of gemcitabine to carboplatin/paclitaxel did not improve PFS or OS in any of the strata (Table 5). Therefore, the addition of gemcitabine to carboplatin/paclitaxel yielded increased toxicity and did not benefit any patient subgroups. To date, all randomized studies testing the addition of agents, either in combination or sequentially, to carboplatin/paclitaxel have been negative. The current clinical outcome for advanced ovarian cancer requires improvement; however, alternative methodologies such as dose dense chemotherapy or targeted therapies, are needed.

Figure 4: GCIg study design, gemcitabine/carboplatin/paclitaxel versus carboplatin/paclitaxel in newly diagnosed epithelial ovarian cancer, phase III.

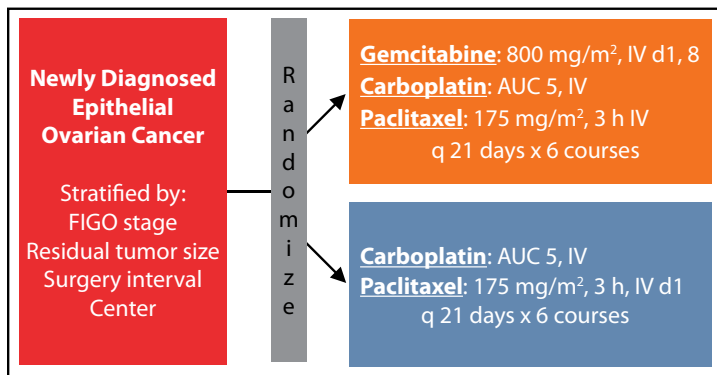


Table 5: Outcomes for gemcitabine/carboplatin/paclitaxel vs carboplatin/paclitaxel in patients with advanced ovarian cancer.

	Carboplatin/ paclitaxel	Gemcitabine/ carboplatin/paclitaxel	<i>P</i>
ORR*	77.5%	86.2%	0.039
Median OS	52.5 mo	49.3 mo	0.380
Median PFS	19.3 mo	17.8 mo	0.007
Stratum 1 PFS	NR	NR	0.750
Stratum 2 PFS	22.4 mo	20.1 mo	0.0265
Stratum 3 PFS	13.9 mo	13.0 mo	0.0365

*Measurable disease patients only.

ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Weekly Cisplatin, Phase III

The addition of a number of agents to paclitaxel/carboplatin has, to date, failed to improve survival in patients with advanced stage ovarian cancer. Unfortunately, survival in those patients is very low and improvement over the current standard of care is needed. The use of alternative doses and schedules is one avenue under investigation. Recently, one report suggested that dose dense paclitaxel plus carboplatin improves outcomes for patients with advanced ovarian cancer.¹² Fruscio, et al reported long-term outcomes of dose dense (weekly infusions vs every 3-week infusion) and dose intense (higher dose per week per cycle) cisplatin compared to standard cisplatin.¹³

A total of 285 patients with FIGO stage III or IV ovarian cancer were randomized to receive either 9 courses of weekly cisplatin at 50 mg/m² or 6 courses of cisplatin at 75 mg/m² every 3 weeks (the total overall dose intensity for both arms was 450 mg/m² over the intended treatment period). The median dose intensity achieved on the weekly cisplatin arm was 47 mg/m²/week compared to the 24 mg/m²/week in the cisplatin administered every 3 weeks. Median follow-up was 18.2 years.

The median number of weekly cisplatin cycles was 9, and 89% of patients received 7 or more cycles. Treatment was discontinued in 4 patients because of disease progression and 10 patients due to toxicity. The median number of cycles for patients on every 3 weeks cisplatin was 4, and 90% of patients received 4 or more cycles. Treatment was discontinued in the weekly arm for 9 patients because of disease progression and in 8 patients because of toxicity. Hematological toxicity was higher in the weekly cisplatin group with the incidence of leukopenia significantly higher ($P = 0.03$).

Overall and progression-free survival were similar (**Table 6**). The median OS for weekly cisplatin was 34 months compared to 32 months with standard cisplatin. Taken together, these data suggest that weekly cisplatin is feasible and manageable. However, intensification of cisplatin does not improve outcomes or offer any clinical advantages.

Table 6: Progression-free and overall survival with intensified or standard dose cisplatin.

	Weekly cisplatin (50 mg/m ²) n = 146	Cisplatin every 3 weeks (74 mg/m ²) n = 139
PFS (months)	17	18
OS (months)	34	32

PFS, progression-free survival; OS, overall survival.

Oxaliplatin, Docetaxel, and Bevacizumab

Given the high rates of relapse and mortality, the current standard of care for first-line treatment of advanced ovarian cancer is clearly limited. Therefore, Herzog and colleagues evaluated the safety and efficacy of the novel platinum/taxane doublet, docetaxel and oxaliplatin, in combination with bevacizumab as primary therapy for women with advanced ovary, peritoneum, or fallopian tube cancer following initial debulking surgery in a prospective, noncomparative study.¹⁴ The primary endpoint of the study was PFS at 1 year. Secondary endpoints included safety, response rates, and recurrence-free

survival (RFS). Patients were treated with 6 cycles of oxaliplatin (85 mg/m²), docetaxel (75 mg/m²), and bevacizumab (15 mg/kg) every 3 weeks, followed by maintenance with bevacizumab (15 mg/kg every 3 weeks) up to one year of therapy. Of the 110 evaluable patients, 84% had ovarian cancer (68.2% stage IIIC, 14.6% stage IV), and 61% were optimally debulked. Ninety percent of patients completed all 6 cycles, and 39%, 30%, and 52% of patients were dose reduced for docetaxel, oxaliplatin, and bevacizumab, respectively. Serious adverse events included neutropenia (43%), leukopenia (12%), hypertension (9%), febrile neutropenia (3.6%), vomiting (3.6%), pulmonary embolism (2.7%), dehydration (1.8%), and peripheral sensory neuropathy (1.8%). One patient had a colonic perforation and one patient died during cycle 9 of bevacizumab maintenance due to a subdural hematoma. In the 70 patients with measurable disease 34% achieved a CR, 46% a PR, 6% stable disease, and 13% progressed. One-year PFS was 68.1% (95% CI, 56.1-80.1) and median PFS was 69.1 weeks (95% CI, 53.6-106.1 weeks). Median RFS was 83.9 weeks (95% CI, 46.0-NR) and the probability of 1 year RFS was 59.2% (95% CI, 43.1-76.2). These results suggest that this novel combination is active and safe, and provides grounds for further clinical evaluation.

CHEMOTHERAPY IN RECURRENT DISEASE

Platinum Sensitive, Phase III

Carboplatin/PLD vs Carboplatin/Paclitaxel, CALYPSO

Most patients with advanced ovarian cancer who respond to first-line therapy relapse. Carboplatin and paclitaxel or carboplatin and gemcitabine are the current standard of care for platinum-sensitive (relapse-free interval > 6 months) relapsed ovarian cancer. Toxicities associated with the carboplatin/paclitaxel combination include cumulative neuropathy and alopecia; and toxicities for the carboplatin/gemcitabine combination are high rates of neutropenia and often thrombocytopenia. Phase II studies combining pegylated liposomal doxorubicin (PLD) with carboplatin suggested that carboplatin/PLD

is safe and active in relapsed ovarian cancer. Therefore, an international multicenter, open label, randomized phase III trial of non-inferiority design was conducted on ovarian cancer patients in late relapse (> 6 months) (Figure 5).¹⁵ Carboplatin/PLD was compared to carboplatin/paclitaxel in women progressing after first- or second-line therapy. The primary endpoint was PFS, and the study was powered for non-inferiority. Baseline characteristics were similar between study arms, with the exception that more patients in the carboplatin/paclitaxel arm had 2 previous therapies (17% vs 12%). Treatment with carboplatin/PLD resulted in a longer median duration of treatment (21 weeks vs 16 weeks) with more patients receiving 6 or more cycles of chemotherapy (85% vs 78%). Neuropathy, carboplatin hypersensitivity, myalgia, alopecia, and grade 4 neutropenia were more common with carboplatin/paclitaxel. Grade 3/4 thrombocytopenia and grade 2 nausea, hand-foot syndrome, and mucositis were more common in the carboplatin/PLD arm. More patients on the paclitaxel/carboplatin arm discontinued therapy early because of toxicity (15% vs 6%) (Table 7).

Progression-free survival was significantly better with carboplatin/PLD (11.3 months vs 9.4 months, HR = 0.82) and multivariate analysis indicated that the treatment arm was the only predictive factor for PFS, ($P = 0.003$) (Table 8). Therefore, carboplatin/PLD demonstrated a superior therapeutic index compared to the current standard, carboplatin/paclitaxel and offers another evidence-based option for patients with platinum-sensitive recurrent ovarian cancer.

Figure 5: CALYPSO study design, carboplatin/peglylated liposomal doxorubicin (PLD) versus carboplatin/paclitaxel in relapsed ovarian cancer, phase III.

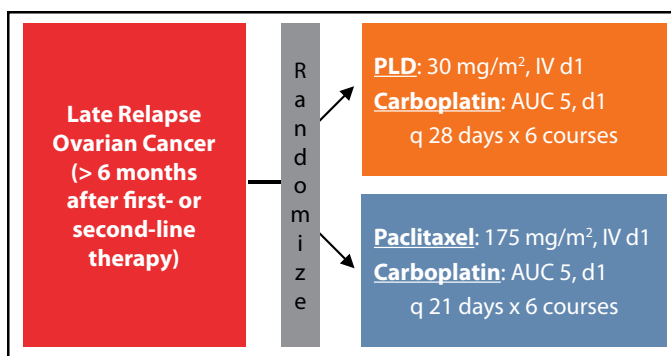


Table 7: Adverse events ≥ grade 3 that were significantly different between study arms.

Toxicity	Carboplatin/ PLD n = 464, %	Carboplatin/ paclitaxel n = 500, %	P
Neutropenia, gr 3	31	24	< 0.01
gr 4	4	22	< 0.01
Thrombocytopenia	16	6	< 0.01
Neuropathy, gr 2	4	24	< 0.001
gr 3/5	1	4	< 0.001
Carboplatin hypersensitivity, gr 2	3	10	< 0.001
gr 3/5	2	9	< 0.001

PLD, peglylated liposomal doxorubicin; gr, grade.


Table 8: Progression-free survival of carboplatin/PLD vs carboplatin/paclitaxel.

	Carboplatin/PLD n = 464	Carboplatin/paclitaxel n = 500
Median PFS, months	11.3	9.4
HR (95% CI)	0.82 (0.72-0.94)	
Log rank P value (superiority)	0.005	
P value (non-inferiority)	< 0.001	

PLD, peglylated liposomal doxorubicin; PFS, progression-free survival; HR, hazard ratio.

**Platinum Sensitive, Phase II
Farletuzumab, Platinum, and Taxane**

Farletuzumab (MORAb-003), a humanized monoclonal antibody to folate receptor alpha (FRα) is over-expressed on most EOC cells, but largely absent on normal tissue. Farletuzumab has also demonstrated activity against EOC cells in preclinical studies and efficacy and safety in phase I studies. Coleman, et al conducted a phase II study of farletuzumab in patients with platinum-sensitive ovarian cancer in first relapse.¹⁶ Patients undergoing symptomatic relapse were placed on their original carboplatin/taxane



regimen with farletuzumab at 100 mg/m² weekly. Patients experiencing asymptomatic relapse received single-agent farletuzumab until progression. Upon progression the original platinum/taxane regimen was added to farletuzumab. Forty-seven patients received platinum and taxane and farletuzumab and 44 subjects were evaluable. Median PFS was 13.6 months and the ORR was 69.8% with 7% of patients attaining a CR, 62.8% a PR, 23.2% SD, and 7% of patients progressing. The combination was well tolerated and additive toxicity to carboplatin/taxane was not observed. Nine patients (20.5%) had a second progression-free interval equal to or greater than their first progression-free interval and CA125 levels normalized in 92% of patients who had a first progression-free interval of less than 12 months. These data suggest that farletuzumab plus platinum/taxane-based chemotherapy is safe and active in patients undergoing first relapse for advanced ovarian cancer and supports expansion to a larger randomized trial.

PALLIATIVE CARE

Aflibercept and Malignant Ascites

Malignant ascites is a challenging comorbidity that significantly impacts the quality of life for ovarian cancer patients. The VEGF pathway has been shown to contribute to malignant ascites through enhancement of vascular permeability. Aflibercept is a recombinant fusion protein designed to bind VEGF family members including all VEGFA isoforms, VEGFB, and placental growth factor with high affinity, blocking downstream VEGF signaling. Vergote, et al tested the effect of aflibercept on advanced ovarian cancer patients with recurrent symptomatic malignant ascites requiring 1 to 4 paracentesis per month.¹⁷ Fifty-four patients were randomized between intravenous aflibercept at 4.0 mg/kg every 2 weeks and placebo. Patients were blinded for at least 60 days and then given an option to cross over. The primary objective of the study was effect on time to next paracentesis. Secondary

endpoints included safety and efficacy of aflibercept. The median number of cycles was 4 for the aflibercept group and 3 for the placebo group. The mean duration of exposure was 10.6 weeks on aflibercept compared to 6.4 weeks on placebo. The average time to repeat paracentesis was significantly longer in the aflibercept group compared to the placebo group (55 days vs 23 days, $P = 0.0019$). Median OS, however, was not significantly different between the 2 groups. Three patients (10%) in the aflibercept group and 1 patient (4%) in the placebo group had grade 3/4 intestinal perforation; all of which were terminal events. Hypertension and thromboembolic events were also more common with aflibercept. Overall, in this heavily pre-treated population, aflibercept prolonged the time to repeat paracentesis. However, fatal intestinal perforation was more common in the aflibercept group. Therefore, further evaluation and determination of the patient type most likely to benefit from this treatment will be needed.

GYNECOLOGICAL ONCOLOGISTS MAKE A DIFFERENCE

Ovarian cancer represents a unique clinical challenge that requires specific expertise. Stirling, et al reported data from 912 ovarian cancer patients treated in the West of Scotland Managed Clinical Network. The study found that women treated by gynecological oncologists compared to general gynecologists had a 24% lower risk of death. These data emphasize the importance of specialized care for ovarian cancer patients.¹⁸ The unique training of gynecological oncologists likely contributes to the improved outcomes for their patients. As demonstrated by the studies discussed in this newsletter, forums, such as the ESGO Congress, provide an excellent medium for these highly specialized clinicians to share, learn, and debate novel clinical information.

RESOURCES

European Society of Gynaecological Oncology:

<http://www.esgo.org/>.

Society of Gynecologic Oncologists:

<http://www.sgo.org/>.

Women's Cancer Network:

<http://www.wcn.org/>.

Gynecologic Cancer Foundation:

<http://www.thegcf.org/>.

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