Epithelial Ovarian Cancer in Older Women: Defining the Best Management Approach

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OVERVIEW

Epithelial ovarian cancer is a cancer of older women. In fact, almost half of women diagnosed with ovarian cancer will be older than age 64, and 25% will be older than age 74. Therefore, it is crucial to examine the available data in older populations to optimize the therapeutic approach without negatively affecting the quality of life permanently. Unfortunately, little prospective data are available in this under-represented population of women. Although ovarian cancer traditionally has been approached with aggressive cytoreductive surgery, older patients may benefit from a less aggressive surgical approach and, in some cases, may be candidates for neoadjuvant chemotherapy followed by an interval cytoreduction. Modalities do exist for assessing an older woman's ability to tolerate surgery and chemotherapy, and these tools should be familiar to clinicians who are caring for this population of women in making treatment decisions. Ongoing planned trials to evaluate pretreatment assessment for older patients will provide objective, feasible, clinical tools for applying our treatment-based knowledge. Future trials of both surgery and chemotherapy, including a focus on the sequence of these two treatment modalities, are crucial to guide decision making in this vulnerable population and to improve outcomes for all.

C lose to half (45%) of women diagnosed with ovarian cancer will be older than age 64, and 25% will be older than age 74 (20.7%, age 65 to 74; 16.6%, age 75 to 84; and 8.1%, older than age 84).1 The mean age at diagnosis of ovarian cancer is 63 years.1,2 In addition, the percentage of older women with ovarian cancer is expected to increase in the coming decades as our population ages and life expectancy improves.3,4 Unfortunately, as the age of the patients increases, cancer outcomes steadily worsen. One report showed age-standardized relative survival rates at 1 year of 57% for women age 65 to 69, 43% to 45% for those age 70 to 79, and 25% to 33% for those age 80 to 99.5 There have been various theories put forward to account for the decreased survival in older women, including the following: (1) more aggressive tumor biology, including higher grade and more advanced stage, (2) inherent resistance to chemotherapy, (3) individual patient factors, such as multiple concurrent medical problems, functional decline, and malnutrition leading to greater anticipated treatment toxicity, and (4) physician and health care biases toward older adults that lead to inadequate surgery, and suboptimal chemotherapy.6

To improve the outcomes of older women with ovarian cancer, we need to develop better decision aids to discriminate those patients who will and will not tolerate standard cytoreductive surgery (CRS) and chemotherapy. Our trials cannot continue to focus exclusively on younger, fit women and the healthiest subsection of older women. In the Southwest Oncology Group (SWOG) analysis of data on 16,396 patients enrolled in 164 trials during the 1990s, patients older than age 65 accounted for only 30% of all included patients.7 Similarly, in a recent Surveillance, Epidemiology, and End Results (SEER) survey, only 9% of patients older than age 75 who had cancer were included in clinical trials of new therapies.8 With a focus on improving under-represented populations, cooperative groups in the U.S. (Elderly Working Group in the NRG Gynecologic Oncology Group [GOG]) and Europe (Groupe d’Investigateurs Nationaux pour l’Etude des Cancers Ovariens, GINECO) are developing trials specific for older women with gynecologic cancer.

In this review, we will discuss currently available data regarding results of surgery and chemotherapy in the older woman with ovarian cancer as well as review geriatric assessment (GA) tools being developed to aid decision making regarding both surgical and chemotherapeutic interventions.

Ovarian Cancer Surgery in Older Women

The data for surgery in epithelial ovarian cancer (EOC), although retrospective, is clear: patients with advanced (stages III to IV disease) will experience an improved overall survival if they undergo an optimal CRS.9,10 The meaning of optimal has changed over time, with an accepted current definition in the platinum era of less than 1 cm of residual disease.11 Most recently, it has been suggested that no visible residual should be the goal of a cytoreductive surgery. The improved survival
associated with optimal CRS has been confirmed in recent prospective, randomized trials of chemotherapy.\textsuperscript{12-14}

There remains, however, controversy regarding the role of neoadjuvant chemotherapy (NACT) followed by an interval cytoreduction (iCRS) as a primary strategy for the treatment of ovarian cancer. The aggressive surgical effort that is required for an optimal primary surgery may result in postoperative morbidity; the interval surgery associated with NACT may be less extensive and, therefore, better tolerated.\textsuperscript{15} The idea that all patients, regardless of comorbidities, should be approached with a primary surgical effort has transformed into consideration of NACT with iCRS for those patients who may not tolerate an up-front maximal surgical effort.

Risk factors for postoperative morbidity after primary surgery for ovarian cancer have been identified. These include older age (older than age 75), poor performance status (PS), low serum albumin, the presence of ascites, and high preoperative CA 125.\textsuperscript{16} Thus, age becomes an important factor in determining the best first therapy for women who present with advanced disease when surgery and the timing of surgery are being considered.

Older studies noted that older women with ovarian cancer have a worse prognosis than younger women and suggested that this worse prognosis may be due to a less aggressive surgical approach to the disease. The American Cancer Society analysis from Hightower et al,\textsuperscript{17} for example, noted a significant reduction in survival for patients older than age 80 compared with their younger counterparts; this decrease was attributed to a less aggressive surgical approach.\textsuperscript{17} The older women were more likely to see a general surgeon rather than a gynecologic oncologist for their surgery and also were more likely to have a suboptimal CRS performed. In addition, older patients in this series were less likely to receive adjuvant chemotherapy (42% vs. 69%, p < 0.0001). The finding that older women are less likely to have an aggressive surgical effort also has been confirmed by other series.\textsuperscript{16-21} In part, this finding may be due to the observation that women older than age 70 are less likely to be seen by a gynecologic oncologist.\textsuperscript{22}

More recent studies consist of a series of single tertiary institution findings, reported by gynecologic oncologists, that are retrospective in nature and consequently affected by selection bias. The majority of these studies suggest that older women tolerate aggressive surgical effort well, with a consequent similar overall survival to their younger counterparts.\textsuperscript{23-25} However, a select few have noted significant morbidity in the cohort of very older ages (greater than 80).\textsuperscript{16,26,27} In particular, the report from Oklahoma noted a significant rate of death before hospital discharge and within 30 days of surgery in women older than age 80 who underwent primary cytoreduction.\textsuperscript{26} Although the authors were able to achieve a 74% rate of optimal cytoreduction in this group of patients (defined in this study as less than 1 cm of disease remaining), postoperative complications were common. In addition, and perhaps more significant, 13% were unable to receive adjuvant chemotherapy and, of those who were treated, only 57% completed more than three cycles.

Population-based studies have confirmed age as an independent risk factor for surgical morbidity. In the SEER analysis reported by Thrall et al,\textsuperscript{28} advancing age was associated with a significant increase in 30-day mortality. Among their sample of 5,475 patients, patients older than age 85 had five times the mortality risk as those age 65 to 69 (17.52% vs. 3.19%, respectively). When age was evaluated as a continuous variable, each year over age 65 was associated with a 7.5% increase in the risk of 30-day mortality. The authors performed further risk modeling, including stage and comorbidity, and found that women at the highest risk (more than 10%) for 30-day mortality after CRS were those older than age 75 with stage IV disease or those older than age 75 with stage III disease and a comorbidity score of +1.\textsuperscript{28} Another study using data from the Nationwide Inpatient Sample registry of patients admitted for ovarian cancer surgery also found that perioperative complications increased with age.\textsuperscript{29} Among the 28,651 patients included, those patients younger than age 50 had a 17.1% complication rate compared with rates of 29.7% in patients age 70 to 79 and 31.5% in patients older than age 80. Discharge to a facility also increased with age, from only 1.0% of patients younger than age 50 to 14.0% of patients age 70 to 79 and 33.3% of patients older than age 80. In the multivariate analysis, age, number of medical comorbidities, and number of radical procedures performed were the most important predictors of morbidity and mortality.

Finally, Wright et al\textsuperscript{30} reported SEER data for women age 65 years or older, this time with the primary goal of assessing reception of adjuvant therapy after primary surgery.\textsuperscript{30} In a multivariate model, older patients and those with comorbidities, mucinous tumors, and stage IV cancers were more likely to not receive chemotherapy after surgery, and age remained a predictor of delay of initiation of chemotherapy.\textsuperscript{30} These studies are shown in Fig. 1.

Likely, age alone cannot suffice as a measure of postoperative surgical morbidity and mortality. Instead, a combination of factors should be used to identify a group of patients for whom an up-front surgery will not be of benefit. The ability to assess who is fit enough to undergo aggressive CRS followed by chemotherapy and who should be offered an alternative pathway, such as NACT and iCRS or primary chemotherapy alone, is an unmet need. In the study from Aletti et al,\textsuperscript{16} when tumor distribution, age, and nutritional status were combined, the authors were able to identify a subgroup

**KEY POINTS**

- Almost half of women with ovarian cancer are older than age 64 years, and 25% are older than 74 years.
- Older patients may benefit from a less aggressive surgical approach and, in appropriate cases, may be candidates for neoadjuvant chemotherapy.
- Validated modalities exist for assessing an older woman’s ability to tolerate surgery and chemotherapy, and these tools should be utilized when caring for this population in making treatment decisions.
of patients for whom the benefits of an aggressive up-front surgery did not outweigh the risks. In addition, in this group of patients, aggressive surgery did not result in improved overall survival.

Further prospective study is warranted to identify those women for whom primary CRS is not indicated. If we use a generalized preoperative assessment for all patients, we may exclude many who might benefit from aggressive primary CRS. However, by not validating a preoperative tool in this vulnerable population, we risk excess morbidity and mortality in those patients with too little reserve to tolerate primary CRS followed by chemotherapy.

### Ovarian Cancer Chemotherapy in Older Women

**Timing of Chemotherapy: NACT**

NACT is the delivery of chemotherapy before a CRS. NACT use is gaining popularity in both the United States and Europe, particularly for older and frail patients. By shrinking cancer before surgery, several reports suggest that NACT increases the chance of an optimal CRS (defined as no gross residual disease postsurgery) with less surgical morbidity and no significant effect on survival.

The only published prospective, randomized study of NACT versus primary CRS followed by adjuvant chemotherapy is study 55971 from the European Organization for Research and Treatment of Cancer (EORTC). The 632 patients with newly diagnosed stage IIIC or IV EOC were randomly assigned to either primary CRS followed by six cycles of platinum-based chemotherapy or to three cycles of NACT platinum-based followed by an iCRS followed by an additional three cycles of platinum-based chemotherapy. The two cohorts had similar baseline characteristics (age, PS, histology type, grade, and stage). The median ages were 62 (range, ages 25 to 86) in the primary surgery group and 63 (range, ages 33 to 81) in the NACT group. No subgroup analysis was reported based on older age.

NACT was not inferior to primary surgery; the median overall survival times were 29 months in the primary debulking group and 30 months in those assigned to NACT. Although outcomes were equivalent, the median survival in each arm was relatively short, which suggests that the trial may have selected for a poor prognostic group of patients. The authors found that one of the main predictors of survival was no gross residual disease, so the question of NACT versus primary CRS remains controversial as it pertains to those patients for whom no gross residual disease is a reasonable expectation.

The CHORUS trial is another randomized, phase III trial with identical eligibility criteria to that of EORTC 55971. This study has only been reported in abstract form, but the primary endpoint of overall survival was not statistically different, at 22.8 versus 24.5 months for the pCRS and iCRS groups, respectively. These two studies were meant to be evaluated together; with combined data for this selected population, the overall estimate of the hazard ratio (HR) was 0.93 (95% CI, 0.81 to 1.06).

Several things are notable about these studies compared with the GOG studies, not specific to older women, that were described previously. First, the median age of the patients enrolled in EORTC 55971 and CHORUS were almost a decade older than those patients enrolled in the GOG studies. On the EORTC and CHORUS studies, 20% to 32% of patients had a PS of 2 to 3 compared with 8.5% of patients on the prior GOG studies, and approximately 25% of patients on the EORTC and CHORUS studies had stage IV disease compared with none in the prior GOG studies cited, which makes this a highly selected, poor-prognosis group of patients (Fig. 2).

Older women, particularly those with high comorbidities and frailty, are at the highest risk of surgical morbidity and may be the most appropriate candidates for NACT. Although each patient plan must be individualized, these criteria are reasonable to use as guidelines for an NACT approach.
Timing of Chemotherapy: After Primary Surgery

EOC is one of the most chemotherapy-sensitive diseases, with high initial response rates. The standard of care has evolved into taxane and platinum-based regimens that vary in schedule and route of administration. However, the studies that established these standards of care contained few older patients (here defined as age 70 or older), and the vast majority of those included would have been the most fit and had a high PS. For example, in GOG 158, which established paclitaxel and carboplatin as a standard of care, and GOG 172, which established intraperitoneal cisplatin and paclitaxel-based therapy as a standard for patients after optimal cytoreduction, only 12% of patients enrolled were older than age 70.13,35 Similarly, both GOG 218 and ICON 7, which evaluated the addition of bevacizumab to every-21-day paclitaxel and carboplatin, enrolled 23% and 10%, respectively, older than age 70.36,37 GOG 182, one of the largest randomized trials in EOC completed, with more than 4,000 enrolled patients, included 23% who were older than age 70.14 Although no subset analyses were done in the older population of patients in these trials, a post hoc analysis of the 620 patients age 70 or older enrolled in GOG 182 found that this group had a poorer PS, lower chemotherapy completion rates, increased toxicities (neuropathy and cytopenias) and an 8-month shorter overall survival after adjusting for other prognostic factors.38

These adverse outcomes, among highly selected older patients who were deemed fit enough to enroll in a prospective clinical trial, are significant and reflect the difficulty in assessing reserve for treatment in an older population. The uncertainty surrounding how much an older woman can tolerate, combined with competing comorbid and social conditions may explain the low percentage of older women receiving standard of care chemotherapy for ovarian cancer. In one SEER review of the use of chemotherapy in advanced EOC, the odds of chemotherapy being administered dropped with age compared with the reference group of ages 65 to 69.39 For example, women age 75 to 79 had a odds ratio (OR) of 0.65, women age 80 to 84 had an OR of 0.24, and women age 85 and older had an OR of 0.12.39 A second SEER analysis found that the women at greatest risk of incomplete chemotherapy (either not given or received an incomplete course) were those older than age 76 (OR, 1.64) and/or two or more medical comorbidities.40

Designated clinical trials for older women and PS-challenged women have been completed outside the United States. The first designated trial for this population (GOG 273) was completed in the United States and presented in abstract form in 2014, giving us useful guidelines on the selection of the best therapies for these patients.41

Front-line chemotherapy options. Because of concerns related to excess toxicity among older women, investigations have focused on improving tolerance while maintaining efficacy. There are three main foci of investigation: (1) initial dose modifications, (2) variations in scheduling, and (3) timing (neoadjuvant vs. primary chemotherapy). NACT is addressed above and will not be readdressed in this section.

Initial dose modification. In 1997, the GINECO group in France launched a dedicated older women ovarian cancer (EWOC) program. Between 1998 and 2003, two prospective studies were conducted to assess the tolerability of the current standard platinum-based chemotherapy regimens. Both studies enrolled women age 70 or older, with liberal inclusion

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**FIGURE 2. Surgery for Patients with Ovarian Cancer**

<table>
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<tr>
<th>AGO-OVAR</th>
<th>GOG</th>
<th>EORTC 55971</th>
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<tr>
<td>pCRs</td>
<td>iCRs</td>
<td></td>
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<tr>
<td>Suboptimal &gt; 1 cm</td>
<td>29.6 mos</td>
<td>35.0 mos</td>
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<tr>
<td>Gross optimal ≤ 1 cm</td>
<td>36.2 mos</td>
<td>42.4 mos</td>
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<tr>
<td>NGr</td>
<td>99 mos</td>
<td>71.9 mos</td>
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<tr>
<td>Age</td>
<td>58.9</td>
<td>57</td>
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<tr>
<td>PS</td>
<td>0 38%</td>
<td>0 41%</td>
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<tr>
<td>Stage</td>
<td>II 8.9%</td>
<td>III 100%</td>
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<td></td>
<td>III 74%</td>
<td>IV 22.9-24.3%</td>
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criteria, and a baseline GA was performed. In the first study (EWOC 1), 83 patients (median age, 76) with stage III/IV EOC received carboplatin (area under the curve [AUC] 5) and cyclophosphamide (600 mg/m²) in combination (i.e., CC) on day one every 28 days for six cycles. The rate of the completion of all six cycles of the CC regimen was 72%, with minimal toxicities. Moreover, GA predicted toxicity and overall survival. In the multivariate analysis, three factors appeared to have a prognostic value of toxicity: symptoms of depression at baseline (p = 0.006), dependence (p = 0.048), and PS of 2 or greater (p = 0.026). Independent prognostic factors identified for overall survival (Cox model) were depression (p = 0.003), International Federation of Gynecology and Obstetrics (FIGO) stage IV (p = 0.007), and more than six medications per day (p = 0.043). The second study (EWOC 2) assessed the feasibility of carboplatin (AUC 5) with paclitaxel (175 mg/m²) (CP) once every 3 weeks for six cycles in 75 older patients. The feasibility of completing all six cycles for patients receiving CP was 68%.43

These two studies were pooled in a retrospective, multivariate analysis (EWOC 1 plus EWOC2) to assess predictive factors of survival.43 Patients in the EWOC 2 study appeared to be younger and had better PS than those in the EWOC 1 study, which indicated a selection bias because of a concern that the CP regimen could be associated with higher toxicity. The CP regimen had more hematologic (grade 3 to 4) and neurologic toxicities. Despite the inclusion of a higher proportion of patients with optimal CRS (1 cm or less of residual disease) in the CP regimen (40% vs. 21% in the CC regimen), the survival curves were similar. Predictive factors of poor prognosis were advanced age, depression symptoms at baseline, and FIGO stage IV. The use of paclitaxel was found to be an independent factor for poor survival (HR = 2.42, p = 0.001).

However, given that this was a small, nonrandomized study, the validity of this finding is unclear. GOG 273 may address this issue when survival analyses are available. This study enrolled women older than age 70 with newly diagnosed EOC and allowed physicians to select treatment either with every-3-week paclitaxel (135 mg/m²) and carboplatin (AUC 5) plus pegfilgrastim support or with every-3-week carboplatin alone (AUC 5). The primary endpoint was the ability of independent activities of daily living (IADL) score to predict completion of four cycles of chemotherapy.

This study enrolled 153 women onto the combination arm and 59 onto the single-agent carboplatin arm. The study was not randomized, so it is not unexpected that the women in the single-agent arm were older (median age, 83 vs. 77), had a lower PS (PS of 2 to 3: 37% vs. 11%), were more likely to receive NACT (58% vs. 49%), and were less likely to complete all four cycles without a dose reduction or a more than 7-day delay (54% vs. 82%). However, overall completion of four cycles was high in both arms (92% and 75% in the combination and single-agent arms, respectively). Although the primary endpoint of the ability of IADL to predict completion of four cycles of chemotherapy was not met, patients in both arms reported improved quality of life, social activity, and function (i.e., activities of daily living [ADL]) with increasing cycles of chemotherapy.41

The EWOC 3 study evaluated the use of single-agent carboplatin AUC 5 in a highly selected, frail population. This study was used to validate the geriatric vulnerability score (GVS) developed during evaluation of the baseline GAs done for EWOC 1 and 2. The GVS will be discussed more in the section on GAs later in this chapter.44

**Variations in scheduling.** The MITO-5 (Multicenter Italian Trial in Ovarian cancer) phase II study assessed the tolerability of a weekly combination of carboplatin (AUC 2) plus paclitaxel (60 mg/m²) on days 1, 8, and 15, every 4 weeks for six cycles in a small trial of 26 patients age 70 or older with stage IC to IV disease and performance status up to or less than PS 2.45 In this study, 54% patients had at least two comorbidities and high functional dependency (ADL, 31%; IADL, 69%). The RECIST response rate was 38.5%, and the median overall survival was 32.0 months. Toxicity was low; 23 patients (89%) were treated without any defined-as-unacceptable toxicity (primary study endpoint).

The larger randomized, phase III trial (MITO-7) evaluated the same weekly regimen used in MITO-5 versus standard carboplatin (AUC 6) with paclitaxel (175 mg/m²) every 3 weeks in women with newly diagnosed EOC.46 Although this trial was not specifically for older women, it did confirm the possible advantages of the weekly regimen, because it was associated with better quality of life scores and lower toxicity, including lower incidence of neuropathy worse than grade 2 and fewer incidences of grade 3 to 4 hematologic toxicity. There was no survival advantage to the weekly regimen but no decrement either (median progression-free survival, 17.3 vs. 18.3 months), which supports this regimen as an alternative to every-21-day paclitaxel and carboplatin, especially among more vulnerable patients.

Because of the interest in weekly dosing generated by this and other phase III trials, GOG 273 added a weekly arm to evaluate carboplatin AUC 5 with weekly paclitaxel 60 mg/m². For this arm of the trial, the primary endpoint is to determine if an eight-point GA score could predict the ability to tolerate chemotherapy.47 This study has completed enrollment, and follow-up care is ongoing. In France, the most recent EWOC trial is enrolling as well. This randomized, phase II trial (NCT02001272) plans to enroll 264 patients, and treatment arms will encompass both initial dose modification strategies and weekly strategies (single-agent carboplatin, combination carboplatin and paclitaxel, and a weekly paclitaxel and carboplatin arm, similar to MITO-7). Eligibility for EWOC is defined by a GVS score greater than 3, again selecting for a very vulnerable population of older patients. A summary of clinical trials performed in the older patient with ovarian cancer is provided in Fig. 3.

**Is intraperitoneal chemotherapy a consideration for the older patient?** Cisplatin-based intraperitoneal chemotherapy has a demonstrated significant survival benefit for patients with an optimal CRS for stage III ovarian cancer and is a standard of
care at many U.S. cancer centers. Despite growing acceptance
of its superior survival advantages, several concerns remain,
including technical difficulties (intraperitoneal catheter
placement and complications) and increased toxicities (renal
dysfunction, neuropathy, hearing loss). In GOG 172, 39% of
the 205 women who received intraperitoneal cisplatin/pacli-
taxel were older: 26% were age 61 to 70, 12% were age 71 to
80, and 1% were older than age 80. Their functional status
was good (92% with a GOG PS of 0 to 1). Regardless of age, less
than 50% of all patients were able to complete four or more cy-
cles of the intraperitoneal regimen because of toxicity.
How does an oncologist apply these results to their older
population? First, the major limitation to the study was that
patients received intraperitoneal cisplatin. By age 70, renal
function may have declined by as much as 40%, and this re-
duction in glomerular filtration rate may lead to enhanced
toxicities, particularly those with significant renal ex-
creion, such as cisplatin. On GOG 172, patients were re-

<table>
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<tr>
<th>Study</th>
<th>Inclusion</th>
<th>Agents Used</th>
<th>Overall Survival (Median Months)</th>
<th>Discovery</th>
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<tbody>
<tr>
<td>EWOC-1 (83 patients, phase II, single arm)</td>
<td>Age &gt; 70, stage III/IV&lt;br&gt;Enrolled: (Age 70-90) Phase ≥ 2: 44% Stage IV: 24%</td>
<td>Carboplatin AUC 5 + cyclophosphamide 600 mg/m² q 28 days for 6 days</td>
<td>21.6</td>
<td>OS associated with: (1) depression (p = 0.003), (2) stage IV (p = 0.007), (3) &gt; 6 medications/day (p = 0.043). Toxicity associated with: (1) depression (p=0.006), (2) dependence of ADL or IADL (p=0.048), (3) PS ≥ 2.</td>
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<tr>
<td>EWOC-2 (75 patients, phase II, single arm)</td>
<td>Age &gt; 70, stage III/IV&lt;br&gt;Enrolled: (Age 70-89) Phase ≥ 2: 26% Stage IV: 22%</td>
<td>Carboplatin AUC 5 + paclitaxel q 21 days</td>
<td>25.9</td>
<td>OS associated with the HADS &gt; 15*</td>
</tr>
<tr>
<td>EWOC-3 (111 patients, phase II, single arm)</td>
<td>Age &gt; 70, stage III/IV</td>
<td>Carboplatin AUC 5</td>
<td>17.4</td>
<td>Validated the GVS**</td>
</tr>
<tr>
<td>MITO 5 (phase II, single arm)</td>
<td>Age ≥ 70, stage I-C-IV</td>
<td>Carboplatin AUC 2 + paclitaxel 60mg/m² day 1, 8, 15 every 28 days</td>
<td>32</td>
<td>89% of patients were treated without protocol defined unacceptable toxicity</td>
</tr>
<tr>
<td>GOG 273 (212 patients; includes only arms I and 2; phase II; multi-arm; not randomized)</td>
<td>Age ≥ 70, stage I-C-IV</td>
<td>Physician choice: (1) carboplatin AUC 5 + paclitaxel 135mg/m² + G-CSF q 21 days, (2) carboplatin AUC 5 q 21 days, (3) carboplatin AUC 5 every 21 days + paclitaxel 60mg/m² day 1, 8, 15 (results for this arm have not been presented)</td>
<td>Endpoint was trying to correlate IADLs with ability to complete 4 cycles of chemotherapy without delay &gt;7 days or dose modification. Arm 1: 82% completed without delay or dose mod. Arm 2: 54% completed without delay or dose mod. Patients in both arms reported improved quality of life, social activity, and ADL with increasing cycles of chemotherapy.</td>
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* HADS (Hospital Anxiety and Depression Scale).
** GVS (Geriatric Vulnerability Scale).
quired to have a serum creatinine less than 1.2 mg/dL; however, creatinine clearance is a more sensitive marker for renal dysfunction and should be used.\textsuperscript{48} The second limitation was the use of paclitaxel, because its drug clearance declines with age and its toxicities, such as neuropathy and cytopenias, heighten.\textsuperscript{49} Even with the overall survival benefit demonstrated with intraperitoneal therapy, widespread adoption of this modality has been slow secondary to the limitations discussed.

If intraperitoneal chemotherapy is offered as an option to older women, one needs to carefully select patients with good functional status, adequate kidney and hearing function, and an understanding that toxicities may arise earlier in the course of treatment compared with intravenous chemotherapy alone.

**Chemotherapy for recurrent disease.** Treatment for recurrent ovarian cancer is divided into relapse at 6 months or fewer since the last platinum-containing chemotherapy administration, as platinum resistant, and at greater than 6 months as platinum sensitive. For platinum-sensitive disease, trials show the survival advantage of a doublet combination with carboplatin and either paclitaxel, liposomal doxorubicin, or gemcitabine.\textsuperscript{50,51} The combination of carboplatin and paclitaxel (in CALYPSO) was significantly associated with a higher incidence of neurologic toxicity (neuropathy greater than grade 2) among patients older than age 70 (25% vs. 16%, respectively; \( p = 0.006 \)).\textsuperscript{52} Although the proportion of older patients (median age, 73) comprised only 16% of the study population, the prevention of severe neurologic toxicity would advocate for the use of pegylated liposomal doxorubicin rather than paclitaxel in older women.

For platinum-resistant disease, chemotherapy is typically given as single agent, with responses from 10% to 25% and a median duration of 4 to 8 months. Common options include liposomal doxorubicin, topotecan, gemcitabine, weekly paclitaxel, and single-agent bevacizumab.\textsuperscript{53} Unfortunately, few studies have been reported in older patients with ovarian cancer. Based on extensive studies from lung and breast cancer in older patients, most of these single-agent drugs are well tolerated.\textsuperscript{54,55} Gronlund et al\textsuperscript{56} described their experience with topotecan (1 mg/m\(^2\) over 5 days) in 57 older patients with platinum-resistant ovarian cancer and found no significant differences in the toxicity profile or response between an older (older than age 65) or younger (younger than 65) cohort.\textsuperscript{54} PS was a better predictor of response and survival in both cohorts. Currently, most oncologists use liposomal doxorubicin or weekly topotecan for older patients with platinum-resistant disease, given its improved toxicity profile.\textsuperscript{57,58}

The recent publication of the AURELIA trial and the subsequent U.S. Food and Drug Administration (FDA) label for bevacizumab 10 mg/kg every 2 weeks with either pegylated liposomal doxorubicin (PLD) 40 mg/m\(^2\), weekly paclitaxel 80 mg/m\(^2\) for four doses, or topotecan 4 mg/m\(^2\) weekly for three doses has created yet another option for the platinum-resistant population. The median age of patients on the chemotherapy/bevacizumab arm was 62, but the range was ages 25 to 80.\textsuperscript{59} There was criticism of this study because of the lack of a bevacizumab-alone arm, which is considered an effective agent but is not FDA approved for this indication on the basis of only phase II data.\textsuperscript{60} Hypertension and arterial thrombosis risk may be heightened in an older patient who has more comorbidities. Previously reported high bowel perforation rates (as high as 11%) have been greatly diminished, and recent data from a prospective, phase III trial demonstrated a 2.8% rate of perforation among those treated with bevacizumab compared with 1.2% in those treated without. Age was not mentioned as a risk for bowel perforation in this study.\textsuperscript{56}

Because these chemotherapy options offer primarily palliation, many argue for a focus on better supportive measures rather than more chemotherapy. In one study, there was a significant cost difference, with no appreciable improvement in survival in a comparison of patients with ovarian cancer treated aggressively with chemotherapy with those enrolled in hospice at the final months of their life. The authors suggest that earlier hospice enrollment is beneficial, particularly in the older frail patients who have poor prognoses.\textsuperscript{61}

**Assessment of the Older Woman for Ovarian Cancer Treatment: Making Data Driven Decisions**

Geriatric assessment (GA) provides information about a patient’s functional status (i.e., ability to live independently at home and in the community), comorbid medical conditions, cognition, psychologic status, social functioning support, and nutritional status. In the cancer setting, several studies have demonstrated the predictive value of GA for estimating the risk of severe toxicity from chemotherapy.\textsuperscript{47,62,63} A validated instrument for assessment specifically for the older patient with ovarian cancer does not yet exist. There are several assessments used in the older adult with cancer (Fig. 4), but further prospective studies are imperative to remove the guesswork from assessing a patient’s fitness for surgery or chemotherapy.

**Presurgery assessment.** Traditional models of preoperative assessment (e.g., Lee, Eagle, American Society of Anesthesiologists) do not consider the multisystem assessment needed to evaluate an older patient. The Preoperative Assessment of Cancer in the Elderly (PACE) tool was developed to combine elements of the comprehensive GA with surgical risk assessment tools in an older cancer population, although no gynecologic patients were included (Fig. 4). The authors found no significant association of age with postoperative complications. However, 30-day morbidity was predicted by IADL (i.e., more complex activities, such as managing finances and shopping), moderate to severely elevated scores on the Brief Fatigue Inventory (BFI), and abnormal PS. An extended hospital stay was predicted by lower scores in ADL (i.e., basic activities, such as eating, bathing, dressing), IADL, and worse PS.\textsuperscript{64,65}

A position paper was released in 2012 by the American College of Surgeons that outlined the best practices for optimal preoperative assessment of the geriatric patient with a
Timed Up & Go has been reported to predict 30-day surgical morbidity in patients age 70 or older who were undergoing cancer surgery (61% involved laparotomy). This was part of the PREOP study that was designed to assess a number of different presurgical assessments in older patients who had a variety of cancers and were undergoing a variety of different operations. A unique multicenter study (NRG-CC002) under accrual is focused exclusively on women older than age 70 at the time of diagnosis of a gynecologic cancer (advanced ovarian or en-
dometrical serous cancer). Before surgery or NACT, geriatric measures will be collected, to include the following: (1) function (ADL, IADL, PS, fall history), (2) comorbidity (physical health section of Older Americans Resources and Services), (3) psychologic (Mental Health Inventory-17), (4) social activity/support (Medical Outcomes Study survey), (5) nutrition (body mass index, weight loss), (6) Brief Fatigue Inventory, and (7) medications. A risk score will be calculated to determine its ability to predict major postoperative complications.

**Prechemotherapy assessment.** A simple and short screening test to assess toxicity risk for older vulnerable women with ovarian cancer undergoing chemotherapy is clearly needed, and a variety have been or are being tested (Fig. 4). Examples of short surveys used in various cancers are the Vulnerable Elders Survey (VES-13) and the Cancer and Aging Research Group (CARG)–GA and toxicity score. VES-13 is a self-administered survey that consists of one question for age and 12 additional questions that assess self-rated health, functional capacity, and physical performance. CARG-GA is a feasible assessment (mean time to completion is 27 minutes, mostly self-administered) with an 11-variable toxicity score (Fig. 4). The score predicted grade 3 to 5 chemotherapy toxicity far better than PS. The CARG study did include a small proportion of women who had ovarian cancer (50 patients, 10%), and a retrospective subgroup analysis showed that grades 3 to 5 toxicity occurred in 19 patients (37%). Abnormal CA125 was associated with assistance with IADL, low PS, chemotherapy toxicity, and dose reductions.

The French GINECO group has developed a GVS from a series of up-front trials in older women with ovarian cancer. The GVS includes the high-risk variables of low albumin (less than 35 g/L), low ADL score (less than 6), low IADL score (less than 25), lymphopenia (less than 1G/L), and a high hospital anxiety and depression (HADS) score (greater than 14). Women with a high GVS score (3 or greater) had a worse overall survival (11.5 vs. 21.7 months; HR, 2.94; p < 0.001), experienced a lower rate of chemotherapy completion (65% vs. 82%; OR = 0.41; p = 0.04), had higher incidences of severe adverse events (53% vs. 29%; OR = 2.8; p = 0.009), and more unplanned hospitalizations (53% vs. 30%; OR = 2.6, p = 0.02). The use of the GVS appears helpful in selecting those at greatest risk; validation studies with larger cohorts are underway.

**CONCLUSION**

As designated treatment trials for the older and performance-challenged woman with ovarian cancer increase, our understanding of and ability to discern best practices for treatment planning increase. In addition, the ongoing planned trials evaluating pretreatment assessment for older patients will provide objective, feasible, clinical tools for applying our treatment-based knowledge. These important works will hopefully eliminate much of the gestalt decision making in this potentially vulnerable population and improve outcomes for all.

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**Disclosures of Potential Conflicts of Interest**

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