Chapter 3
Geriatric Issues in Ovarian Cancer

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Abstract Older age is an independent prognostic indicator in ovarian cancer. Population data and case series over recent decades show poorer survival of older women regardless of stage. In Western countries, older women are less likely to receive the optimal surgery and standard chemotherapy established in clinical trials. However, in some series older women do well, and in some they do not tolerate standard of care if it is given. This chapter presents geriatric measures that may help in selecting which older women will be fit for standard surgical and medical therapy, geriatric management principles which modulate risk factors for adverse treatment effects, and direct supportive measures for older women with advanced disease.

Keywords Ovarian cancer • Elderly patients • Clinical oncology • Operative mortality • Chemotherapy

Introduction

Ovarian cancer is one in which stage at diagnosis and survival by stage is strongly influenced by age. Marked differences in tumor biology as, for example, in breast cancer or hematologic malignancies do not appear to explain the magnitude of the age disadvantage. Differences in the receipt of standard surgical and cytotoxic chemotherapy are evident in most European and American population-based data and in case series. The data on how well elderly women tolerate standard therapy is inconsistent and likely represents both referral and selection biases. Nonetheless,

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some do well. Some ideas are presented for how adopting geriatric management practices may improve treatment tolerance and potentially increase appropriate optimism in treating ovarian cancer in elderly women.

Incidence, Survival, and Disparities

Ovarian cancer has not proven to be one of the great success stories in clinical oncology, but there has been slow and steady progress with this stealthy disease. The median age at diagnosis is 63 years, so just under half of the affected women are Medicare age [1]. Incidence rates rise steadily with each decade of age, beginning in the perimenopausal decade between 45 and 54 (14.8–22.0/100,000) and continuing through age 85 (55.5/100,000) according to age- and race-adjusted SEER data through 2008 [1]. An apparent slight drop in incidence among women over 85 may well represent underdiagnosis bias on death certificates. Mortality among diagnosed cases rises steadily to 56.3/100,000 among women over 85 [1]. Viewed over 50 years, incidence rates for new ovarian cancers have leveled off and may even have declined slightly by about 1.6 % since the 1990s [1]. There is as yet no convincing explanation for this good news. There is another hopeful information in the numbers.

Looking at it from the cup half-full perspective of survival, the good news is a small but steady improvement in 5-year survival for all women with ovarian cancer, from 36.1 % in 1975–1977 to 43.6 % in 2001–2007 [1]. But this positive trend obscures several marked and growing disparities. For white women under age 65, survival has improved from 43.6 % in 1975–1977 to 56.9 % in 2001–2007, over 13 %. Survival for white women over 65 during the same period has improved by only 5.1 % and remains 30 % lower than the younger cohort. Among Black women, in 1975–1977, both older and younger women had 5-year survival rates about equal to white women. Instead of improving over time, survival rates have declined for both younger and older Black women. In 2001–2007 Black women's survival was 4 % worse in both age groups than they had been 30 years earlier [1].

Stage at diagnosis does not explain this disparity. Older Black women were only slightly more likely to be diagnosed at a more advanced stage, but stage for their survival is worse. Five-year survival for younger vs. older women of both races with localized disease was not markedly different in these most recent data [1]. Among women with advanced stage disease, 5-year survival was good: 79.9 % for younger women with regional disease compared with 55.6 % for older women. Women with distant metastasis fared poorly regardless of age, 35.6 % compared with 18.1 % 5-year survival, respectively, among young and old [1].

In summary we see a familiar epidemiologic picture in ovarian cancer. Incidence rises with age regardless of race. Absolute mortality is somewhat lower in Black women at all ages because their incidence rates are lower. However, improvements in 5-year survival have been essentially confined to younger white women. Late diagnosis among Black and elderly women does not appear to explain these

disparities. We wonder whether disparities in treatment may in part explain the observed differences in survivorship. The role of age in treatment decisions and treatment response will be the subject of the next discussion.

What Is the Standard of Care?

As shown in Table 3.1, ovarian cancer, specifically ovarian epithelial cancer, is the fifth leading cause of female death in the USA. Among the 11 most common malignancies, ovarian cancer ranks seventh in percent for 5-year survival (see Table 3.2) [2].

The most common histology over all is ovarian epithelial. Less common neoplasms of low malignant potential include serous and mucinous histologies which occur in elderly women about as often as in younger women. There are other uncommon histologies, including germ cell tumors, ovarian stromal tumors, Mullerian tumors, and carcinosarcomas. The survival statistics are different for each type of tumor [3]. Among older women, the epithelial histology is most common.

Table 3.1 Five most common sites of cancer mortality: U.S. older adults, 2009 [2]

Ages	60–79 years		>80 years	
Sex	Men	Women	Men	Women
Site	Lung	Lung	Lung	Lung
	Colon	Breast	Prostate	Colon
	Prostate	Colon	Colon	Breast
	Pancreas	Pancreas	Urinary bladder	Pancreas
	Esophagus	Ovary	Pancreas	NH lymphoma

Table 3.2 Median age at diagnosis and percent 5-year survival: U.S. women by age and cancer site, 2005–2009 [1]

		5-Year survival by age at diagnosis		
Site	Median age	<65	65–74	>75
All cancers	65	75.3	59.7	47.4
Breast	61	89.2	90.4	86.8
Urinary bladder	74	82.8	75.3	62.4
NH lymphoma	68	80.6	72.1	53.0
Colon	73	74.5	68.0	53.3
Ovary	*63*	*56.4*	*36.0*	*20.2*
Lung and bronchus	71	25.3	21.9	14.2
Esophagus	72	21.9	19.2	10.1
Pancreas	74	11.3	5.6	2.9

Guidelines have been published on-line [4]. They reflect the common scenario in which a tissue diagnosis has been made, but the clinical staging is unclear. The guideline is based on the consistent finding that optimal debulking surgery, that is, the complete removal (CR) of all abdominal reproductive organs, peritoneum, lymph nodes, and other visible tumor deposits whether primarily or after neoadjuvant chemotherapy offers the best survival outcomes. There is no other validated method to measure intraabdominal tumor mass except by laparotomy performed by an expert surgeon. Thus, optimal surgical treatment will often involve two surgical procedures, at least one of which is considered intermediate to high risk by standard stratification systems [4].

Cytoreductive Surgery and the Elderly Woman

There are four questions to ask. First, are older women equally or less likely to receive recommended surgery? If they do receive guideline driven surgery, do they achieve equivalent benefit for the risk? If they do not, do we know why age is associated with less definitive surgery? Should surgical risk for elderly women with ovarian cancer be assessed differently than for any other elective abdominal procedure?

Examining data from Olmstead County, 280 women over age 65 were more likely to have had increased risk for surgery based on low albumin [5]. This risk factor and age were independently associated with survival, but neither was independently associated with the extent of debulking surgery. Less extensive surgery was not associated with age in these data. The proportion of women with residual disease (RD) after debulking surgery was approximately the same among women aged 65–69 as among those aged 80 or more. Survival was independently predicted by age and extent of surgery. In other words, surgical risk and age were independent and neither was associated with how aggressively surgery was pursued. But older women and women who received more extensive surgery had lower survival. They noted over 1/3 of women over 75 experienced postoperative complications. The reasons for less than complete surgery were not reported, and the authors concluded that such studies are needed.

Other population-based studies similarly have observed higher 30-day postoperative mortality among women aged over 75 with advanced disease and comorbidities [6]. Using the SEER-Medicare data, Janda et al. [7] risk stratified women over 80, finding 0, 8, and 21 % postoperative mortality based on their algorithm of age, comorbidities, and organ function. An analysis of state level hospital discharge data found that age, race, low income, and treatment at a low-volume or non-teaching hospital were associated with less complete surgery [8]. These findings were confirmed by an American College of Surgeons multi-institution survey in which 1,115 women over 80 had poorer survival at any stage of disease and were less likely to receive complete (CR) surgery from a specialist surgeon and less adjuvant or neoadjuvant chemotherapy [9]. A meta-analysis of 23 acceptable quality reports

estimated very low overall postoperative mortality for cytoreductive surgery but higher mortality with older age and more extensive surgery [10].

The problem with this literature is that the majority of studies are retrospective; single institution studies with small numbers of women over 70 accumulated over ten or more years during which surgical and anesthesia practice may have changed. When the samples are large enough, as in the population-based studies, to compare young-older women 65–74 with women over 75 or 80, the women under the 75–80-year age barrier generally do well, but administrative data give only limited insight into surgical decision-making with very old women. The scatter among the small series is considerable, reflecting the quality of institutions' care, individual surgeons' risk tolerance, underlying referral bias for more or less fit women, and technical differences in the surgeries performed. Few studies give details about how patients and surgeons decided on whether, how, or when to proceed. The small series studies fall essentially into two groups. One group of studies reports few complications and improved overall survival (OS) for women over 70 who receive optimal debulking [11–17]. A second group of studies finds that older women are in poorer health when they present for surgery and have less definitive surgery [18–21]. However, all the studies agree that even over 80 years of age selected, healthy women can withstand optimal CR and benefit with improved OS [22–24].

Single institution case series and population studies confirm the observation that older women are less likely to receive definitive complete reductive surgery (CR). Although on the one hand it may seem obvious that older, sicker women would appropriately receive palliative rather than definitive surgery, it is very difficult to pull this out of the published data. The extent of multidisciplinary consultation between medical oncologists and surgeons is not always documented outside of multidisciplinary cancer centers where it is assumed [9]. In the Netherlands [20] reported improved survival with CR regardless of age, but that women over 70 were less likely to receive CR. A Greek series reported on 170 women over 70. Compared to women under 70, they had poorer performance status, less CR surgery, less chemotherapy, higher grade tumors, and poorer survival [18]. By contrast a series reported from a comprehensive cancer center indicated no such differences [23]. From these data the relative contributions of patient characteristics and treatment given to OS survival cannot be separated, and both appear to be strongly related to whether women are referred to specialized cancer care. Few studies examine the medical decision-making process, whether less aggressive surgery, or no surgery, is the doctors' recommendation or the patients' choice [25].

Once older women do undergo surgery, they are less likely to receive optimal debulking. From available data we cannot determine whether patient safety concerns for surgical complications explain surgeons' reluctance to undertake CR in older women or whether intraoperative factors cause surgeries to be scaled down. Single institution series are unlikely to answer these questions. Earle et al. [26] addressed whether the process of cancer surgery affected the outcomes. Using the Medicare-SEER files, 33 % of women over 65 were operated on by gyne-oncology surgeons, 45 % by general gynecologists, and 22 % by general surgeons. The outcome measures in median survival were clearly superior for both gynecological sur-

geons compared to general surgeons and not markedly different by oncology as a focus of practice. However, the association is confounded with the referral patterns that may direct healthier women to specialists and older, sicker women to more convenient local surgeons [25, 26]. Other process measures include how smoothly transitions between surgical and medical oncology care are accomplished. In at least one study, transition processes appear to be less standardized for older women [17]. Indeed one large single institution study limited the analysis only to patients who were successfully transitioned from CR to standard chemotherapy [22].

There is currently a great deal of interest in surgical risk stratification for older cancer patients and whether the standard preoperative schemes capture the appropriate measures of fitness. An important reason for questioning whether cardiac risk and general ASA risk stratification is generalizable to cancer surgery because the cancer patient does not have surgery to repair the problem and then go home. Cancer patients must be fit enough to withstand neoadjuvant chemotherapy and then surgery, or recover quickly enough from surgery to undergo adjuvant therapy. Perhaps the bar is higher. One forum in which these concerns have been studied and discussed is the PACE (Preoperative Assessment of Cancer surgery in the Elderly project) [27]. Studies are emerging in the literature in which geriatric measures such as cognitive screening, functional assessment of ADL and IADL performance, depression screening, and nutritional status improve the predictive value of "standard" preoperative indicators such as albumin, GFR, and comorbidity scores [27–29]. In single institution studies there are some suggestions that these measures stand up to statistical adjustment, but how they might affect the process of surgical care specifically for ovarian cancer has yet to be described and would be a welcome addition to the literature.

Key Points
Older women with ovarian cancer:
1. Experience lower OS regardless of stage of OC.
2. Are less likely to receive definitive CR surgery.
3. Who undergo definitive CR surgery have improved OS compared to those who do not.
4. In unselected populations surgical complications are higher among older women.
5. Research is needed to determine whether geriatric measures improve operative risk stratification above that of existing risk stratification tools.

Chemotherapy and the Older Woman with Ovarian Cancer

Overall survival for women with ovarian cancer has improved in recent decades largely due to the introduction of platinum and taxane chemotherapy [30]. The influential clinical trials have generally excluded elderly women [31]. The reasons

are complex including patient preferences and physician reluctance [32]. A review of available studies examines the extent to which older women are likely to receive standard therapy as initial therapy and on reports of the effectiveness of first-line chemotherapy compared to less treatment. Finally, the studies will be reviewed for predictors of treatment toxicity, the presumed most common cause of treatment reduction and abandonment. For reference, shows the current NCCN Guideline for chemotherapy in ovarian cancer [4].

The SEER-Medicare data set for 1992–1996 for Stage II [33] and Stages III–IV [34] OC showed about 50 % of women received recommended platinum treatments. Age was an independent predictor for not receiving platinum. Platinum treatment produced a small, several-month benefit in 5-year survival among women who completed all or most cycles regardless of age. The OVAR-3 Phase III trial from the same period using platinum and taxane combination therapy enrolled 103 women over age 70. The EORTC-QoL was included in baseline and continuing assessments. Older women did not differ in any significant way from younger women in terms of disease characteristics, EORTC-QoL subscale scores, or non-hematological toxicities. The older women however had less complete CR going into the trial, that is, more RD before chemotherapy, and a higher proportion with ECOG-PS 1–2 as compared with ECOG-PS = 0, no performance limitations among the younger women. 26 % of the older women were withdrawn early due to toxicity, mainly febrile neutropenia and fatigue [35].

Intraperitoneal therapy (IP) was introduced as a way to deliver drug directly to the tumor while limiting whole body toxicity from IV drug. Recent data from a small series showed that 23 women over 70 were less likely to complete a combined IV/IP protocol than younger women even though there was no difference in the total IV dose delivered. The investigators had no explanation [36]. However, a GOG study, which enrolled women over 60 with PS <2 included 27 women over 70, reported very high levels of abdominal discomfort and poorer function among IP patients regardless of age, and only 50 % of the experimental patients could complete the study [37].

Standard geriatric measures were gathered in a French study which included 83 women over age 70. Only 21 % had had optimal CR surgery, of this select group, 72 % tolerated all planned 6 cycles of platinum and cyclophosphamide. That is, only 15 % of the older women enrolled in this trial completed recommended combined treatment. We do not know if the same factors which predicted less complete CR also predicted chemotoxicity. Severe toxicity was predicted by preoperative depression, ADL dependence, and PS >0. OS was associated with disease stage, depression, and >6 prescribed medications [38]. A second GINECO study enrolled 158 Frenchwomen over 70. Nearly 1/3 was IADL dependent in at least one domain, and 15 % had lower than normal cognitive screening scores. In this trial depression and anxiety were stronger predictors of OS than the chemotherapy regimen [39]. Again, relatively few of the women in a small cohort had measureable geriatric impairments, so the statistical power of any individual indicator to detect vulnerability is low.

At each step of multidisciplinary cancer treatment, the published research shows that age plays a critical role in the receipt of optimal therapy. One series of 131

women over age 70 included 41 over age 80. Surgical debulking was complete for 80 % of the women under 80 but for only 25 % of those over 80. The women over 80 were equally as likely to complete platinum treatment but half as likely to complete combined platinum-taxane treatment. Both age groups were about equally likely to experience dose reductions and dose delays. With such small numbers, only the difference in surgery by age was statistically significant [40]. In another, similar series, investigators specifically tried to identify toxicities associated with treatment termination. Women over 80 were less likely to get combination therapy and even then were only half as likely to complete it with no particular differences in self-reported toxicity [41]. The toxicity measures were standardized, and these measures typically inquire about specific adverse events, such as neutropenia and symptoms, such as neuropathic pain. It may be that despite the theoretical likelihood that older women will experience more neuropathy, for example, the actual event is the cumulative toll of several toxicities.

Oncologists have many choices within the platinum-taxane paradigm. Drug can be delivered before surgery to reduce the volume of tumor to be removed, or it can be delivered after surgery to treat visible or microscopic RD [42]. Dosing can be done IV or with a combination of IP and IV to reduce toxicity. If necessary, doses can be reduced or spaced out in time, but treatment effectiveness is strongly associated with tolerating the full dose of combination therapy delivered on schedule. If necessary, single agent treatment can be given. How age affects these decisions has been studied [44–46]. In one surgical series, the timing of chemotherapy did not affect disease or survival outcomes nor was there any difference in dose delivered to women over and under age 80 [15].

Most chemotherapy for OC is given as outpatient infusions. Unfortunately delayed toxicity may lead to unplanned hospitalizations for which the elderly are at increased risk [43]. Examination of SEER-Medicare data sought to identify whether there were any differences among the various OC regimens for this level of severe toxicity. The chemotherapy patterns identified were platinum alone, platinum-taxane combination therapy, other non-platinum therapy, and no chemotherapy. The highest rates of hospitalization were among those receiving non-platinum, that is, nonstandard therapy. Comorbidity and age were associated with infections and cardiovascular hospitalizations, but age was not associated with gastrointestinal or hematological toxicity in these population data [43]. This study cannot determine to what degree less fit women were given less than standard chemotherapy in an unsuccessful attempt to reduce toxicity, or whether nonstandard chemotherapy was indicative of system and provider characteristics such as nonurban residence, low-volume practice, or absence of community support resources for the elderly. These system and provider factors have been shown to predict cardiovascular outcomes, and it would not be surprising that similar systems characteristics affect oncology outcomes.

Current practice favors neoadjuvant to adjuvant chemotherapy after complete CR surgery. Current practice also favors IP with IV infusion of 6 cycles of platinum-taxane combined therapy. Evaluation of surgical outcomes is confounded by the type of chemotherapy delivered, and evaluation of chemotherapeutic regimens must make adjustments for the surgical results [46]. In order to evaluate therapy then, it

takes a number studies, none individually definitive, in order to triangulate an optimal approach. Thus far, clinical trial evidence supports the idea that fit women, and some over age 80, derive benefit from standard therapy without unacceptable toxicity. More often, older women are not offered standard therapy or do not tolerate it.

Where women are treated appears to be a strong predictor of treatment given. Age, comorbidities, and PS are routinely recorded, and so they are easier to study, but new studies indicate that many different geriatric measures can predict treatment intolerance [41]. Examples include the inclusion of standardized geriatric scores in the protocols of the CALGB breast cancer trials group. At least in the setting of dedicated cancer centers, it was feasible to collect multiple geriatric measures of fitness. Recently, these data were used to create a multifactorial algorithm that included traditional physiologic measures, comorbidities, tumor characteristics, and many geriatric measures [47]. The algorithm performed well in predicting which women would go on to experience grade 3–5 toxicities. As a proof of concept then, this algorithm or others incorporating geriatric measures might more accurately identify women at high vs. low risk for treatment-limiting toxicities in ovarian cancer as well. Having such a tool would set the stage for interventions to improve treatment tolerance and thus outcomes for older women with OC.

Key Points

Older women with ovarian cancer:

1. Achieve a relative improvement in OS from receiving standard combined chemotherapy.
2. Women over age 80 appear less able to tolerate standard protocols of chemotherapy.
3. Neoadjuvant and adjuvant chemotherapy appear to be equally efficacious in the elderly.
4. IP chemotherapy does not appear to be well tolerated by the elderly.
5. Chemotoxicities in the elderly do not appear to be qualitatively different; however, reduced renal function, neutropenic fever, and bone marrow suppression are more likely.
6. Toxicity is associated with age, comorbidity, polypharmacy, decreased cognition, depression, anxiety, ADL, IADL, reduced CrCl, low albumin, and poorer ECOG-PS.

Contradictions and Questions

Reviewing the chemotherapy and the surgical literature leads us to ask whether elderly women with ovarian cancer who would benefit from standard therapy are being systematically undertreated. Equally we should ask whether women who receive less than standard treatment have been appropriately identified as being unlikely to tolerate standard treatment. It has been reported that women who are not

optimally debulked also are less likely to receive any or standard chemotherapy. Surgical oncologists and medical oncologists seem to be identifying the same patients, or there is systematic migration of the fit patients to the highest quality centers. The published literature does not directly answer these follow-up questions. Perhaps promulgating a standard assessment that is sufficiently robust to identify women who regardless of age are physiologically fit to withstand standard therapy and linking this to more integrated cancer treatment would address the questions about age-related disparity or age-related fitness. Are there reliable ways to lower the risks of surgery and chemotherapy to increase the pool of fit elderly women? If so, are these individual interventions, changes to practice, or systems interventions? Although there are presently no trials specifically designed for ovarian cancer patients, there are studies of cancer patients that report results of geriatric multidisciplinary interventions [48].

Geriatrics in Ovarian Cancer Care

There is a strong referral bias for more fit elderly in cancer clinical samples [7], and clinical trials have usually excluded or not been able to recruit older participants for many practical reasons including transportation. Extrapolating from clinical trials to clinical practice is thus somewhat subjective. Analyses of population treatment data through the linked SEER-Medicare database suggest that frail elderly are unlikely to be referred to specialty cancer centers from community practices. The geriatric concept of frailty describes a phenotype of slowness, weakness, subjective exhaustion, and slow weight loss [49]. It is distinct from the assessment of functional status which seeks to inventory exactly what an elderly woman can and cannot do to take care of herself while enduring cancer treatment. The geriatric approach includes individual interventions to improve performance and environmental interventions to lower the demand to what the patient can do. Thus, frailty alone is not a complete picture of what is possible with an elderly patient.

Balducci has adapted the consensus frailty phenotype as defined by Fried and colleagues to making decisions about cancer therapy [50]. He also includes ADL and IADL disability, non-cancer severe comorbidity, and presence of "geriatric syndromes." Geriatric syndromes are easily recognized [51]. Most lists include cognitive impairment, falls, delirium, and preexisting severe weakness as probably excluding an older cancer patient from receiving full dose or, depending on the situation, any chemotherapy [50]. The frailty model explains in terms of cancer-related life expectancy why the allostatic load of surgical, disease, and chemotherapy stressors can overwhelm the homeostatic reserve of apparently well elderly and, even in the absence of specific organ toxicities, result in geriatric syndromes and physiologic collapse. There appears to be a tacit agreement in community practice not to subject obviously frail and otherwise incapacitated elderly to toxic therapy. Primary frailty and terminal disease are recognizable in a common sense way. Geriatricians on the other hand are interested in identifying markers of impending disability that

can be remediated. Geriatricians are also interested in early risk factors for decline and assessing the likely impact on recovery from stress of illness. There are two adverse scenarios with respect to recognition of vulnerability. In the first, an elderly patient who might benefit from treatment by having an extended period of symptom-free survival is not treated due to concern for toxicity. In the second instance, for a patients who will likely die from the cancer whether or not it is treated, we should consider whether the risks of the treatment will shorten survival or impair the quality of remaining time with friends and family.

Functional status as used by geriatricians refers to activities of daily living (ADL), the ability to care for oneself at home, and instrumental ADL (IADL), the ability to live alone and manage one's own household affairs. Very frail, cognitively intact women can often perform these tasks for years, slowly and perhaps not up to their own expectations, but well enough to keep "help" out of the house. This is different from the oncologists' construct of performance status which has more to do with grading activity levels from fully physically active outside the home to bedbound. Using a summary Karnofsky Performance Score or Eastern Cooperative Oncology Group Performance Score (ECOG-PS), oncologists make very accurate predictions about survival and ability to tolerate further toxic therapies. These are rapid, intuitive, and can be serially performed over the course of treatment. Summary KPS or ECOG scores describe present status but do not predict risk for future functional decline, and they fail to identify the so-called vulnerable elderly who look good but are high risk for catastrophic decline [52]. The summary scores do not identify specific functional disabilities that might be reversible, nor do they suggest how that might be done. These scores miss important nonphysical performance measures such as cognition, fatigue, anorexia, mood, and social support. If not specifically asked, this useful information is missing. Furthermore, the hallmark of aging is loss of reserve, the ability to meet increased demand [53]. That may refer to a specific organ including pulmonary, renal, and cardiac response to fever, anemia, and toxins. Delirium is essentially brain failure as a result of similar stressors.

A short functionally based screening such as the ACOVE VES-13 has been proposed as a quick way to select apparently fit elderly cancer patients who may be at risk for functional failure for further evaluation [55, 56]. A more extensive battery of screening tools has been shown to be quite feasible to perform in the outpatient oncology setting [57]. Several studies have suggested that abbreviated geriatric measures of function provide actionable data [58, 59]. For example, a fall risk audit for hospitalized cancer patients reported profiles consistent with those in the geriatrics fall literature [60]. An outpatient survey identified a high prevalence of previously underreported falls among prostate cancer patients on hormonal deprivation therapy [61]. Fall risk should be routinely assessed among elderly cancer patients. Ovarian cancer patients in particular are at risk due to the double challenge of abdominal surgery and chemotherapy on cognition, nutrition, gait and balance, mood, sleep, elimination, and pain.

Functional status has been measured a number of different ways using different scales and observational data points. There are many, many validated and widely used rating scales for each of several domains important to determining the ability

of an elderly ovarian cancer patient to live alone or with only limited support [62]. The specific tool is not in my opinion critical, but the sampling of the several domains that contribute to functional independence is critical. And the use of standardized scales improves communication between team members and consultants. As summarized by the NCCN expert panel, key assessments include scores for physical, psychological, and cognitive impairment and instrumental social supports and environmental demand [48]. The various domains sampled in a CGA and the specific tools were developed for determining rehabilitation needs and need for external supports for elderly people. They will not calculate chemotherapy doses. They will identify patients who if they do develop toxicities are at substantial risk of unplanned hospitalization or catastrophic events including injurious falls. Awareness of the likelihood of injurious falls should guide clinical decisions about full or reduced dose regimens.

There has been increasing interest in identifying tools with particularly good performance with the elderly cancer patient. Any battery must meet the criteria of being acceptable to oncology providers, and easily scored and interpreted. Assessments should lead to actions including other medical referrals, rehabilitation, social and home care services, and polypharmacy review. Oncologists should approach geriatric patients with preemptive supportive measures including GCF, nutrition, and control of specific toxicities including mucositis, bowel function, nausea, and painful neuropathy. For an elderly patient with arthritis and a slow gait, the accumulation of several low-grade toxicities even if none is rated as 4 or 5 can lead to the development of geriatric syndromes, such as delirium, incontinence and falls, and unplanned hospitalizations.

The concept of limited homeostatic reserve explains this “unraveling.” We can measure cardiac output and renal function, single organ functions. The geriatric concept of homeostatic reserve also applies to the integrated function of organs needed to perform the activities of daily living safely and consistently. Normally, an elderly woman has the cardiac function to go about her daily activities. In the presence of fever and anemia, she will go into congestive failure. An elderly woman may be able to shop with her daughter and fix her own meals. If she is feeling queasy and fatigued, she may not eat the food that is brought in and a little diarrhea will lead to dehydration. If she is cognitively intact but she is unable to sleep and is taking several prns for symptoms, she might develop a low-grade delirium, become confused about time of day, and forget important medications and meals. Polypharmacy taxes the memory, and the sheer number of pills increases the likelihood of nonspecific drug interactions that cloud the sensorium and disrupt appetite and sleep.

Because of this, an expert panel of the NCCN developed guidelines for assessing elderly cancer patients; similar considerations were addressed by the European collaboration (EORTC) [63]. The NCCN Clinical Practice Guidelines offer a decision tree based on their assessment of the strength of the evidence for routine use of geriatric assessments in a variety of tumor types. The expert panel grades the evidence 2A, that is, acceptable quality with no dissent among the panel members [48]. A significant limitation at this time is that we have few trials or demonstration

projects showing the impact of applying the methods. It is hoped that this will soon be remediated.

Step 1 is to determine whether the patient's pre-cancer life expectancy would have been long enough to benefit from treatment. For example, with advanced ovarian cancer (based on stage and malignant potential), what is the predicted best outcome of treatment?

This is actually the most difficult question. Data on median survival has been previously reviewed, and we see that published survival figures are based on clinical trials with few elderly women or small series collected over a decade in single institutions or from population databases such as the SEER-Medicare files from which few direct measures of functional status are available [64, 65]. In other words, in a patient with similar disease and similar comorbidities and similar functional limitations who receives standard therapy, how likely is she to live another 2 years? Another 5 years? Oncologists routinely use their optimism and experience to match the patient with the pattern. Walter and Covinsky published a now well-known graph showing median survival by age and quartile of health as a guideline [66]. It remains useful but the underlying data and assumptions should be interpreted for individuals as probabilistic rather than prognostic. Survival was calculated using historical cohorts and comorbidity estimated from administrative data. It remains an extremely useful heuristic tool. Balducci suggests that oncologists make treatment decisions based on their estimate of the best probable, not possible, outcome based on the stage/grade of disease in 3 prognostic groups: patients with estimated RLE >5 years if they receive best treatment with best response, patients who may live 2–5 years with treatment, and those will live <2 years with or without treatment such as patients who are already nursing home-confined [50]. He thus recommends staging the aging as carefully as the malignancy as shown in Table 3.3.

Example: An 82-year-old woman is diagnosed by CT-guided biopsy with epithelial ovarian cancer. Radiologically it appears to be Stage IIIb. She takes medications for HTN and coronary artery disease although she has no clinical history of infarction or stroke. Her renal function is mildly impaired, with eGFR 48 mg/ml/min.

Her cardiac risk factors for noncardiac surgery are age over 75 and HTN. The surgeon would also take into account chronic renal insufficiency. She is at slightly

Table 3.3 Staging the aging [50]

Stage of aging	Probable RLE (years)	Treatment approach
Fit	>5	Standard therapy NCCN guidelines [4]
Vulnerable	2–5	Comprehensive assessment reveals physiological, functional, psychological, and social risk factors. Multidisciplinary interventions for a pretreatment tune-up include rationalizing polypharmacy, optimizing cardiovascular and pulmonary condition, optimizing nutritional status, analysis of home supports and instrumental needs, and gentle conditioning [67]
Frail	<2	Palliation based on symptoms

increased risk for cardiac events in an intermediate risk noncardiac surgery. Her anesthesia risk also includes renal impairment. Again her risk is intermediate and not unacceptably high. Her 30-day surgical mortality risk in a high volume center should be <3 % [7]. Using population estimates of remaining life expectancy (RLE) according to overall health status [66], before the diagnosis of ovarian cancer, she would be in average health, median RLE of about 6 years. After the diagnosis she would be classified as poor health, and median RLE would be around 3.5 years. Based on these tools, she would benefit from standard treatment.

There are several key aspects of geriatric assessment that are particularly salient for surgical cancer treatment. In addition to standard preoperative risk stratification, preoperative assessments should be able to anticipate whether recuperation at home or at a long-term care facility (LTCF) will be needed. Will she be ambulatory and performing ADLs within a week of surgery? Will she have complex wound care needs? Has the decision been made about placing an IP catheter? Excellent surgical and anesthesia technique reduce operating time, blood loss, and infection. Excellent postoperative care includes strict nursing protocols for mobilization, bowel, nutrition, and pain management. Nonetheless, a major postoperative complication such as delirium has significant adverse impact on surgical outcomes in oncology and often can be predicted by CGA. Delirium is very common on oncology floors, and it is important to recognize it and manage it appropriately [68–70].

Delirium guidelines for hospital inpatients are now available. Environmental adjustments to hospital routines should promote normal day-night sleep-wake entrainment and mobilization, and nutritional supplementation is feasible [54]. When the example patient is postoperative, vitals and medications should be restricted to only those that are absolutely necessary during the night shift. Unless there is hemodynamic instability, it is not necessary to obtain blood pressures at 2 a.m. nor should blood draws be timed at 5 a.m. per hospital routine. Labs drawn at 7 or 8 will be resulted during the day shift. Patients should be encouraged to get out of their rooms as early as the first postoperative day if they are able. Physical and occupational therapy evaluations should not be delayed. Appetite is a key vital sign. There is a delicate balance between appropriate pain management and over sedation that should be re-evaluated with physician, nursing, and pharmacy input.

The most consistent toxicities for the elderly are platinum renal toxicity and taxane neuro- and marrow toxicity [44–46]. Several chemotherapy studies have included elderly women. Median survival for women over 70 who completed standard treatment was 33 months in one series [71]. Women over 70 had about an 18 % 5-year survival in another series [72]. In any series, there are long-term survivors. Optimally, median survival data should be presented by stratum of age and stratum of age by health status but these data not readily available for ovarian cancer for women over 70. If the data do not calculate survival by age, I would suggest that overall median survival is an appropriate measure to extrapolate to elderly women with no severe risk factors. Study results expressed as hazard ratios and percentage difference in 1 and 5-year survival are difficult to translate into life expectancy. Returning to the example, available data suggest that if optimally treated this patient could have 3 years survival. This agrees with general population estimates [66] and

at least one published series [71] and places her in the vulnerable group according the Balducci stratification [50]. Thus, she should have a comprehensive geriatric assessment during the course of her treatment planning.

Step 2: Geriatric Assessment. The NCCN Guidelines for Senior Oncology list functional risk factors and suggest alternative screening tools. The purpose of these assessments is to identify risk factors that can be modified or compensated for. If no risk factors are identified, the recommendation is to proceed to standard therapy.

The example patient is living alone in a senior citizen building. Also she does not use an assistive device; her gait is slow, <1 m/s on the timed-up-and-go; and she wobbled briefly rising from the examining table. Her daughter who lives 15 miles away takes her shopping every Saturday and calls every evening. When asked, she denies previous falls but admits to reaching the wall the steady herself if she gets up quickly. Her ECOG-PS = 1. The church van picks her up every Sunday for services and supper.

Step 3: Risk factors are identified and addressed:

1. Fixable: She will need transportation. Social work can apply for senior transportation if she lives within the transportation zone. If she is out of zone, she may have to continue treatment elsewhere.
2. Not fixable: She does not have absolute contraindications to standard platinum-taxane therapy: advanced dementia, nursing home residence, or renal insufficiency.
3. Remediable: Multidisciplinary staffing to determine how risk factors will respond to targeted individual interventions.
   The patient's blood pressure medications are making her orthostatic. Her blood pressure regimen is changed. She has a PT/OT evaluation that focuses on household task performance and gentle conditioning.
4. Modifications of the patient's environment during the treatment period, by reducing environmental demand and constructing a safety net: Delirium protocols for postoperative patients, short stay in a rehabilitation facility, home health services, and electronic fall monitors [73].

The example patient did not want to move in with her daughter. Homemaker services were initiated to reduce housekeeping burdens, a visiting nurse was instituted, and physical therapy was started. This provided someone in the apartment 4 days a week. The building manager was advised of her health status so the doorman could keep an eye out for changes in her routine. The patient was given a fall monitor. Hospital-based transportation took her to and from appointments.

The resources required to screen for vulnerability are modest, as shown by several studies [55, 56, 58]. However once vulnerability is suspected, a comprehensive assessment is more time consuming than small oncology practices can undertake. A multidisciplinary approach to older women with advanced ovarian cancer and one or more risk factors requires ready access to and a willingness to engage with rehabilitation, social work, consulting pharmacists, psychiatry and nutritionists. We have few models for how to do this specifically for older cancer patients. Most cancer centers have these ancillary services but they may not be

specialized in the elderly. We do not know the extent to which local oncology providers are aware of or use ancillary geriatric resources. There are few well-described programs in geriatric oncology and fewer outcome studies on which to base specific recommendations.

The geriatric literature is consistent in showing that performing assessments by themselves has no benefit. However, implementation of recommendations especially when part of an organized system of transitions has shown benefit [74]. A clinical trial of continuity of care randomized several thousand geriatric veterans to inpatient geriatric assessment and intervention with follow-up in outpatient GEMs and home-based care [75]. Post hoc subgroup analysis revealed that older veterans with a cancer diagnosis benefitted the most from an integrated continuum of geriatric care. Although they did not live longer, quality of life measures were statistically significantly improved [76]. So mainstreaming elderly cancer patients through a continuum of geriatric care had a measureable benefit.

The patient in the example we are discussing has several medical risk factors, notably renal function, individual risk including gait and balance problems, and safety net risks including living alone and relying on a distant support person. Each risk factor requires a different discipline to be involved and to be serially reassessing the patient's status. The goal is to prevent unplanned hospitalizations that result in permanent nursing home placement. This is different from a planned short SNF stay following surgery. Shopping for acceptable facilities should begin early. It is upsetting to patients and families to be handed these decisions on the day of discharge. Precipitous discharges are also fraught with risks associated with transitions of care. The transitions should be carefully orchestrated with specific instructions regarding diagnosis, plan for further treatment, nutritional support, mobilization, and wound care [77]. Cancer surgery outcomes for the elderly are improved by early mobilization and early nutritional support [78].

Restaging the Aging: Use Structured Methods Serially to Assess the Functional Impact of Treatment

Just as the oncology team restages the tumor after a trial of therapy, it is necessary as well to restage the aging over the course of therapy. The tumor board coordinates disease-oriented care plans and should also serially restage the aging. The short-term impact of chemotherapy on functional capacity should be assessed proactively. Is the patient at risk for delirium? Did the patient experience postoperative delirium? Has the patient's baseline cognitive function and decisional capacity been documented in a standard format? [79] This bears directly on the patient's ability to self-manage over the typical course of 6 cycles of chemotherapy. An elderly person living alone who manages quite well in their usual state of health is judged fit for chemotherapy by having an ECOG-PS of 2 or less. They are likely to do well in the infusion suite but develop delayed toxicities and become ill a week later. An extensive summary of the evidence for the NCCN guidelines summarized above has been

prepared by the International Society for Geriatric Oncology (SIOG) based in Geneva [80]. This document identifies a number of validated standardized assessment tools. It remains to be shown however which assessments are most sensitive and specific for anticipating clinically significant adverse events.

Part of treatment planning is to establish the patient's goals for ovarian cancer treatment. Neither SIOG nor NCCN guidelines suggest specific ways to periodically revisit patient goals and expectations over the course of treatment. Older patients are open to discussing their prognosis and making plans for their own care ahead of the need. Advance directives should be part of the initial and ongoing conversation. In one study over 65 % oncologists report that they do not routinely discuss prognosis, advance directives, or end-of-life until the patient is within days to weeks of death. This contrasts with younger and non-oncology physicians who report having these discussions before the need [81]. There is an interesting correspondence with patient preference in this study. A similar >60 % of cancer patients preferred not to have these discussions with their oncologists; rather, they expressed no unwillingness to discuss advance directives and end-of-life with hospital doctors, that means typically hospitalists and house staff [81]. However, the conversation is broached it should be documented.

Supportive Management During Cancer Treatment Is Just Good Geriatric Care

Supportive oncology is the management of symptoms due to cancer and to the effects of cancer treatment with the goal of maintaining patients' quality of life. All major cancer centers have invested in supportive care because it offers the best chance for patients to be able to complete treatment. Often palliative care is thought of as end-of-life care, but aggressive supportive care uses essentially the same modalities whether in parallel with or when efforts at disease management are no longer desired.

Four randomized clinical trials have compared palliative care delivered with cancer treatment to usual care with optional palliative referral as determined by the treating physician. 322 patients with advanced cancer in rural Vermont, mean age about 65 years, were randomized to monthly telephone follow-up by nurses. At the end of the study, quality of life and mood scores were higher in the intervention group, but there was no difference in symptom intensity or hospital days [82]. Two additional trials also showed improvements in self-reported quality of life among patients randomized to palliative care along with usual cancer care, but the differences were not statistically significant [83, 84]. Similarly a Norwegian trial was suggestive but inconclusive [85]. Part of the weakness of such designs is that inherently the specific interventions are individualized, not standardized, and most of the studies included several cancer types with different symptom patterns. In other words, the inherent methodological limitations of the randomized clinical trial are similar in palliative care and in geriatric interventions [86]. The interventions are

inherently not standardized. There is no "dose" of palliative or geriatric care. The spectrum of disease, the combinations of symptoms and disabilities, cannot be totally standardized the way tumors can be graded and staged. It is therefore very impressive that positive results are obtained when studies are powered to perform.

A recent study had the methodological advantage of strictly staged patients all receiving care at the same cancer center. 151 advanced stage non-small cell lung cancer outpatients were randomized to concurrent palliative care or usual care. The mean age was about 65 years. Mean change scores on symptom scales and quality of life scales favored the experimental group, but the differences were not statistically significant. However, the experimental group survived on average 2.7 months (30 %) longer and used fewer hospital days at the end-of-life [87]. Similarly designed studies of supportive and geriatric interventions for ovarian cancer patients may reproduce the finding of less hospitalization, less cost, and improved subjective quality of life. If survival is longer as well, this is hard evidence.

In the palliative care and supportive oncology literature, it is clear that the burden of symptoms as well as the stage of disease drive functional status. Targeting the most troublesome symptoms should improve functional status. In most studies the numbers are small, patients are not particularly old, and a variety of tumor types and stages are included. Furthermore, the definition of quality of life is rather broad and includes everything from psychological well-being, social connection, energy levels, spiritual peace, functional status, and freedom from symptoms. One review enumerated over 100 different definitions of quality of life [88]. It is easier to focus on studies of specific symptoms [89], but new designs will be needed to understand how complex interventions such as geriatric team management affect the balance of clusters of symptoms and to see if and how these interventions improve ovarian cancer treatment outcomes for elderly women.

Key Points

1. Geriatric tools and best oncology evidence should be combined to classify ovarian cancer patients as fit, vulnerable, or frail.
2. Vulnerabilities should be addressed by multidisciplinary interventions and serially reassessed throughout treatment.
3. Geriatric assessments should be directed to anticipating toxicities.
4. Concurrent supportive care is good geriatric care.
5. New research designs are needed to evaluate complex multidisciplinary interventions.

Conclusions

Disparities in treatment and disparities in outcomes for older women with ovarian cancer have been inadequately explained. A systematic approach including concurrent medical and surgical preoperative consultation should thoroughly evaluate

patients' fitness for combined surgical and chemotherapy. These evaluations should systematically inventory comorbidity and also functional and instrumental assets and deficits. So before surgery both surgical risk and chemotoxicity risk need to be assessed. A systematic approach must include risk stratifying the patient based on standard risks, seeing if that can be improved by medically optimizing comorbidities and by geriatric interventions to optimize functional status. The best way to do this is within the clinical trials groups, opening Phase II and III trials to risk stratified vulnerable women. I agree with Balducci that truly frail women, women confined to nursing homes or requiring aid and attendance in their homes, cannot be enrolled in trials for a number of practical and ethical reasons. We can obtain a set of standardized measures to broaden patient eligibility and representativeness. Clinical trials groups are a platform to disseminate best patient selection practices. The extent to which disease characteristics and treatment are standardized, evaluation of the impact of geriatric and supportive interventions will be improved. The immense influence of the trial groups on community practice can then be harnessed to promote appropriate care for older women. We need to identify and document functional measures for use in community practice recognizing that non-CCC providers can deliver this kind of care. Patient education should encourage older women to seek ovarian cancer care at centers that have high volume, specialist care, and multidisciplinary senior care even if the latter is not necessarily housed within the cancer practice.

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