Management of Ovarian Cancer in the Elderly Population

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Abstract

Ovarian cancer is the second leading cause of female-specific cancer death in women over the age of 65 years, and almost half of newly diagnosed cases are in this age group. Many elderly people live with disability and various comorbidities and are vulnerable to stressors. Primary cytoreductive surgery followed by adjuvant chemotherapy is the conventional treatment strategy for advanced ovarian cancer. The increased likelihood of physical comorbidities in elderly patients is thought to be associated with a higher risk of postoperative morbidities and severe side effects from cytotoxic agents. Therefore, elderly patients might be undertreated and miss the opportunity to receive the conventional treatment because of concern about its risks on the part of clinicians. However, guidelines specific for the treatment of elderly patients with ovarian cancer have not been adequately developed. Although treatment strategies for these patients need to be based on relatively limited evidence, appropriate criteria for decision-making regarding treatment have been studied. Appropriate assessments of geriatric patients with cancer to predict the risks of treatment have also been proposed. In this chapter, we outline the current evidence for surgery, chemotherapy, the newer anticancer agents, and comprehensive geriatric assessment to assist gynecologists treating elderly patients with ovarian cancer.

Keywords

Ovarian cancer • Elderly • Cytoreduction • Chemotherapy • Geriatric assessment

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H. Katabuchi (ed.), *Frontiers in Ovarian Cancer Science*, Comprehensive Gynecology and Obstetrics, DOI 10.1007/978-981-10-4160-0_16

16.1 Introduction

Ovarian cancer is the second leading cause of female-specific cancer death in women over the age of 65 years in both the USA and Japan. The most recent Surveillance, Epidemiology, and End Results (SEER) data indicate that the age-adjusted incidence rate of ovarian cancer was 11.9 per 100,000 women per year in 2009–2013 and that the number of deaths in this period was 7.5 per 100,000 women per year [1]. The median age at diagnosis of ovarian cancer was 63 years, and 45.2% of newly diagnosed cases were in women aged ≥65 years. The Japan Society of Obstetrics and Gynecology (JSOG) reported similar trends in their annual report of the committee on gynecologic oncology. Patients aged 60–69 and ≥70 years accounted for 26.9% and 17.4%, respectively, of all patients [2]. Although the World Health Organization does not define a clear cutoff point for chronological old age because of regional variations in factors affecting aging, 65 years is commonly accepted as elderly in most developed countries [3]. Therefore, it is considered that almost half of cases of ovarian cancer occur in older women.

Nearly half of ovarian cancer are diagnosed in the advanced stages and have peritoneal carcinomatosis at this time. The mainstay of treatment for advanced ovarian cancer continues to be maximal PCS (primary cytoreductive surgery) followed by adjuvant chemotherapy. These aggressive treatments have the possibility to increase the risk of peri-treatment morbidities for elderly patients, because elderly people are often in the state of frailty, living with disability and various comorbidities, and are vulnerable to stressors. Although evidences to define the treatment strategies for these patients are still limited, appropriate guidelines or criteria for decision-making regarding treatment have been studied. We would like to describe the current evidences and researches in treatment and geriatric assessment for elderly women with ovarian cancer.

16.2 Treatment-Related Risks in the Elderly

The risk of treatment-related complications increases in the elderly. Conditions such as hypertension, hypercholesterolemia, and hyperglycemia become more common as people age and increase the risk of postoperative morbidity, including delirium, infection, cardiac disease, and venous thromboembolism. There have been reports of significantly higher postoperative morbidity and mortality rates in men and women aged ≥80 years undergoing various types of surgery when compared with their younger counterparts [4, 5]. The increased likelihood of physical comorbidities in elderly patients is also associated with a greater risk of side effects from cytotoxic agents because of the altered pharmacokinetics in this age group. Therefore, conventional chemotherapy might be inadvisable in older patients with comorbidities. Further, even in the absence of definite comorbidity, elderly patients are potentially more vulnerable to physical and psychological stressors. A recent retrospective study of patients with stage III ovarian cancer in six of the Gynecologic Oncology Group (GOG) trials showed that 267 (14.1%) of 1895 enrolled patients

who underwent primary cytoreductive surgery (PCS) followed by chemotherapy including paclitaxel plus cisplatin were aged ≥70 years [6]. This study showed that increasing age was associated with increased risks of disease progression (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.02–1.11 for every 10-year increment in age) and death (HR 1.12, 95% CI 1.06–1.18). This study also showed that chronological age was an independent risk factor for a poorer outcome over and above the factors already known to be associated with a poorer prognosis, namely, the histology of the cancer and size of the residual tumor after primary surgery. However, the evidence is mixed in this regard, and it is still unclear whether chronological age itself should be considered a risk factor in the context of treatment of ovarian cancer. Either way, there is concern that elderly patients with cancer might be undertreated and miss the opportunity for outcomes similar to those that can be achieved in younger patients because of concern about the risks of treatment on the part of clinicians.

16.3 Primary Therapy for Elderly Women with Ovarian Cancer

16.3.1 Primary Cytoreductive Surgery

Over half of patients diagnosed with epithelial ovarian cancer have peritoneal carcinomatosis. Therefore, complete PCS is considered key in treatment of the disease. A systematic review of studies about postoperative mortality after PCS for advanced ovarian cancer reported a mean postoperative mortality rate of 3.7% (range 2.5–4.8%) in population-based studies and an overall mean postoperative mortality rate of 2.8% [7]. Another cohort study reported that patients aged ≥65 years with stage III or IV ovarian cancer who underwent PCS had an overall 30-day mortality rate of 8.2% [8]. Although the 30-day mortality rate was 5.6% in patients in the above studies who underwent elective surgery, it was 12.7% in those aged ≥75 years. Compared with the overall average mortality rate shown in the systematic review [7], the mortality rate of the elderly patients in this cohort study was high, especially in the patients aged ≥75 years.

There is a significant relationship between the volume of residual cancer and survival after cytoreductive surgery in patients with advanced ovarian cancer. Therefore, the question arises regarding how radical cytoreductive surgery should be in this age group, given that elderly patients are considered to be at a generally increased risk of perioperative morbidity and mortality. There is some evidence that surgical treatment may be less radical in older women with ovarian cancer. A review of the SEER database found that the rate of optimal cytoreduction for advanced ovarian cancer decreased from 43.7% in women aged <60 years to 29.5 and 21.7% in those aged 60–79 years and ≥80 years, respectively [9]. However, there are reports showing that similar levels of cytoreductive surgery can be achieved in both younger and older patients [10, 11]. An analysis of 2870 patients who underwent surgery for ovarian cancer in the National Surgical Quality Improvement Program

database for 2005–2012, 701 (24.4%) of whom were aged ≥70 years, showed perioperative complication rates of 9.5, 9.7, 13.4, and 14.6% in patients aged <50, 50–59, 60–69, and ≥70 years, respectively [12]. Compared with patients aged ≤50 years, those aged ≥70 years had a significantly higher rate of prolonged hospitalization (16.5% vs. 32.5%, $P < 0.0001$), nonroutine discharge (2.2% vs. 16.8%, $P < 0.0001$), transfusion (26.1% vs. 39.2%, $P < 0.0001$), and death (0.9% vs. 2.7%, $P < 0.001$). Although advanced age alone was not associated with an increased rate of perioperative complications, age ≥ 70 years and a higher American Society of Anesthesiologists score were significantly associated with prolonged hospitalization and nonroutine discharge ($P < 0.05$).

Given the abovementioned increased risks of perioperative morbidity and mortality and the evidence suggesting an increased probability of incomplete cytoreductive surgery in the elderly, it would seem preferable that these high-risk patients be treated in specialized high-volume hospitals. There is some evidence in support of this concept. In one study, 58, 51, and 40% of cytoreductive surgical procedures undertaken in patients aged ≥65 years with advanced ovarian cancer were performed by gynecologic oncologists, general gynecologists, and general surgeons, respectively [13]. Although surgeons specialized in gynecologic oncology were significantly more likely to perform radical surgery in these patients, there was no significant difference in survival between patients treated by gynecologic oncology surgeons and those treated by general gynecologists. Further, in the patients with stage III ovarian cancer, the rate of complete cytoreductive surgery achieved by gynecologic oncology surgeons was significantly higher than that achieved by general gynecologists (24% vs. 12%; $P = 0.02$). There has also been a report of a significantly improved 5-year survival rate in patients treated by gynecologic oncology surgeons, but only when patients aged >75 years were excluded from this analysis [14]. A meta-analysis of 19 studies demonstrated a better outcome in patients with ovarian cancer treated by a gynecologic oncology surgeon or in a specialized hospital, but with the caveats of potential publication bias, insufficient information provided about the effect of specialized care and hospital characteristics, and heterogeneity in each study [15]. However, given the potential disadvantages of this type of surgery, which are unpredictable in nature, it would be difficult to perform a randomized controlled study. However, there is a report showing that elderly patients (≥75 years) were just as likely as younger patients to want curative surgery [16]. Considering recent developments in anesthesiology and in surgical techniques and devices, we should seek to perform cytoreductive surgery for advanced ovarian cancer in all patients, regardless of age.

16.3.2 Chemotherapy

16.3.2.1 Concerns About Chemotherapy in Elderly Patients

Chemotherapy has a key role in the treatment of ovarian cancer, particularly in advanced disease. However, because aging is associated with decreased renal, hepatic, and/or bone marrow function, there are inevitable concerns about

potentially severe side effects of cytotoxic agents in the elderly. Several analyses of the SEER-Medicare database have highlighted the disadvantages of chemotherapy in elderly patients with ovarian cancer. One analysis, which included 9361 patients aged ≥65 years with stage I–IV ovarian cancer identified between 1991 and 2002, showed that patients aged ≥80 years accounted for 47.2% of all patients who did not receive chemotherapy and only 16.0–19.2% of those who did receive chemotherapy [17]. A more recent analysis of the SEER database identified 4617 patients with stage II–IV ovarian cancer diagnosed between 2001 and 2005, and showed that 28.8% of those aged ≥65 years received no chemotherapy, 24.7% received a partial course of chemotherapy, and only 46.5% received a full course of chemotherapy [18]. This report also showed that chemotherapy was more likely to be incomplete in patients aged ≥75 years than in those aged 65–74 years (odds ratio [OR] 1.64; 95% CI 1.33–2.04). Analysis of a Phase III clinical trial of triplet chemotherapy (GOG 182) reported that being aged ≥70 years was associated with less likelihood of receiving all eight cycles of chemotherapy [19]. As mentioned earlier, it is generally believed that older women with a diagnosis of ovarian cancer are likely to have more comorbidities present. A significant association between the presence of two or more comorbidities and incomplete chemotherapy (OR 1.83, 95% CI 1.34–2.50) was also reported [18]. Another study, albeit in a small number of patients (90 aged 70–79 years and 41 aged ≥80 years) covering the period 1996–2004 showed that 87% of patients aged 70–79 years received combination chemotherapy (a taxane and platinum) and only 46% of those aged ≥80 years received combination chemotherapy even though the comorbidities in the two age groups were similar [20]. The abovementioned reports consistently indicate that elderly patients are less likely to receive standard chemotherapy.

16.3.2.2 Primary Intravenous Chemotherapy

The current standard chemotherapeutic regimen for ovarian cancer is a combination of intravenous carboplatin and paclitaxel [21, 22]. Until the late 1990s, a combination of cisplatin (or carboplatin) and cyclophosphamide was the preferred regimen. In Europe, Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO) performed a prospective study in elderly women treated for advanced ovarian cancer between 1998 and 2000 to determine the feasibility of chemotherapy in this age group [22]. Eighty-three patients aged >70 (median 76) years received six cycles of intravenous carboplatin (area under the curve [AUC] 5) and cyclophosphamide (600 mg/m^2) every 4 weeks. Sixty (72%) of the 83 patients received their six cycles of chemotherapy without severe toxicity or tumor progression. Multivariate analysis showed that symptoms of depression at baseline ($P = 0.006$), dependence ($P = 0.048$), and a performance status ≤2 ($P = 0.026$) were independent predictors of severe toxicity. Symptoms of depression ($P = 0.003$), FIGO (International Federation of Gynecology and Obstetrics) stage IV ($P = 0.007$), and more than six different comedications per day ($P = 0.043$) were identified as independent prognostic factors for overall survival (OS). This study concluded that the comprehensive geriatric assessment tool, which includes evaluation of comorbidities, comedications per day, and patient autonomy, could predict severe toxicity and

OS in elderly patients with advanced ovarian cancer. GINECO went on to perform a retrospective extension of this study using the same eligibility criteria to add a further 75 patients from 2001–2004 who were treated with combination chemotherapy consisting of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) every 3 weeks [24]. Among the observed grade 3–4 toxicities, rates of leucopenia and neutropenia were significantly higher in the carboplatin-paclitaxel (CP) group than in the carboplatin-cyclophosphamide (CC) group (27.4 and 52.8% vs. 14.0 and 8.1%, respectively). Thrombocytopenia was observed more often in the CC group than in the CP group (39.5% vs. 9.7%). Among the non-hematologic toxicities, alopecia and sensory neuropathy were observed more frequently in the CP group. Although several characteristic toxicities were noted in the CP group, there was no significant difference in the rate of completion of six cycles of chemotherapy without severe toxicities or disease progression between the CC group and the CP group (75.6% and 68.1%, respectively). Therefore, the CP regimen was considered to be as feasible for elderly patients as the CC regimen. However, multivariate analysis indicated that not only age ($P = 0.013$), stage IV disease ($P = 0.001$), and symptoms of depression ($P < 0.001$) but also the CP regimen itself ($P = 0.025$) were independent prognostic factors for poorer OS in this study. The authors speculated that this result might be attributable to the higher rate of toxicities with paclitaxel and administration of chemotherapy for a shorter interval (3 weeks rather than 4 weeks).

The above findings raised the question of whether a decreased dose of chemotherapy with a shorter interval between treatments might be able to improve the safety of a taxane-carboplatin regimen. The Phase II Multicentre Italian Trial in Ovarian cancer (MITO-5) study performed in 2003–2005 investigated the tolerability of a weekly schedule of CP in 26 patients aged ≥70 (median 77) years [25]. The patients received intravenous carboplatin (AUC 2) and paclitaxel (60 mg/m^2) on days 1, 8, and 15 every 4 weeks. Seventeen (65%) of the patients completed six cycles of chemotherapy. Fourteen patients had two or more comorbidities. Although no febrile neutropenia was observed, grade 3–4 neutropenia was observed in 6 (23%) of the patients. Sensory neuropathy was observed in two patients (8%); however, the severity of neurotoxicity was grade 1. Median estimated progression-free survival (PFS) was 13.6 months and median OS was 32.0 months. The authors concluded that weekly administration of CP had a favorable toxicity profile. Another multicenter study retrospectively compared the toxicity profiles and outcomes in 100 patients aged ≥70 years with stage II–IV ovarian or primary peritoneal cancer treated with a standard-dose CP regimen (carboplatin AUC 5–6 and paclitaxel 175 mg/m^2 every 3 weeks) or a reduced-dose CP regimen (carboplatin AUC 4–5 and paclitaxel 135 mg/m^2 every 3 weeks) from 1994 to 2005 [26]. Twenty-six patients (median age 77.0 years) received the reduced-dose regimen, and 74 patients (median age 74.7 years) received the standard-dose regimen. Significant higher rates of grade 3–4 neutropenia, cumulative toxicities, and delays in therapy were observed in the patients who received standard-dose chemotherapy ($P = 0.002$, $P = 0.003$, and $P = 0.05$, respectively). However, there was no significant difference in PFS or OS between the two regimens. Although the number of patients included in this study was small, it appeared that the reduced-dose CP regimen had an acceptable safety

profile and was as effective as the standard CP regimen for elderly patients. Similar results were obtained in studies of patients aged ≥65 years [27] and ≥70 years [28] who received platinum-taxane chemotherapy for advanced ovarian cancer. A Phase III study (MITO-7) then compared the efficacy of carboplatin (AUC 6) and paclitaxel (175 mg/m^2) every 3 weeks (tri-weekly CP) for six cycles with that of weekly carboplatin (AUC 2) and weekly paclitaxel (60 mg/m^2) for 18 weeks (weekly CP) [29]. Of the 822 patients enrolled, data for 404 patients (median age 59 years, 86% with stage III or IV disease) who received tri-weekly CP and 406 patients (median age 60 years, 85% with stage III or IV disease) who received weekly CP were available for analysis. The study included 151 patients aged ≥70 years. There was no significant difference in PFS between the tri-weekly and weekly regimens (17.3 months vs. 18.3 months, $P = 0.066$). Evaluation of quality of life (QoL) using the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire showed that the weekly CP regimen was more feasible than the tri-weekly CP regimen. Moreover, the weekly CP regimen was associated with a significant lower risk of febrile neutropenia (0.5% vs. 3%), grade ≥ 3 thrombocytopenia (1% vs. 7%), and grade ≥ 2 neuropathy (6% vs. 17%). Subgroup analysis revealed no heterogeneity of treatment effect according to patient age (younger or older than 70 years) or size of the treating institution (large, ≥90 patients; intermediate, 20–89 patients; small, <20 patients). The authors commented that a weekly regimen of CP might be a reasonable first-line treatment option for women with advanced ovarian cancer. Although the MITO-7 study did not include a specific analysis of data for elderly patients, it suggested that a weekly chemotherapy regimen may be appropriate for this age group. Of note, weekly administration of the CP regimen has since been mentioned as a promising regimen for elderly patients and those with poorer performance status in the National Comprehensive Cancer Network (NCCN) guidelines [21].

Thus far, there has been limited prospective elderly-specific research on ovarian cancer. The first such trial in the USA is GOG 273, which was initiated in 2011 to assess both tolerance of chemotherapy and the characteristics predictive of the ability to complete chemotherapy in women aged ≥70 years with stage III–IV ovarian cancer. A geriatric assessment scoring tool is included to predict toxicity and assess QoL. In this study, the physician can choose between two treatment regimens (carboplatin AUC 5 and paclitaxel 135 mg/m^2 every 3 weeks or carboplatin AUC 5 every 3 weeks). The preliminary data suggested that women who received CP every 3 weeks had better rates of completion without dose delay or reductions than those who received carboplatin alone. A multivariate analysis showed that treatment with carboplatin alone, administration of neoadjuvant chemotherapy (NAC), and limited participation in social activities were associated with less likelihood of completion of 4 cycles of chemotherapy. However, given that both treatments improved QoL in these elderly patients, there may be a good chance of benefit using either of these treatment regimens in this age group. In 2013, a further choice of chemotherapeutic regimen (paclitaxel 60 mg/m^2 weekly and carboplatin AUC 5 every 3 weeks) was added. The GOG 273 trial has now reached its accrual target and is closed to further recruitment [19, 30, 31]. Further analyses of this trial are awaited.

16.3.2.3 Neoadjuvant Chemotherapy

Maximum cytoreductive surgery to decrease the residual tumor volume is important in the treatment of advanced ovarian cancer. Aggressive surgical resection, including resection of the bowel and/or other organs is often needed, and high-risk patients (including the elderly and those with multiple comorbidities) are less likely to be considered for such extensive surgery because of the increased risk of perioperative morbidity. Therefore, NAC may be performed to reduce the tumor volume before radical surgery to improve the completeness of cytoreductive surgery and might be considered an attractive treatment approach by both patients and their treating clinicians.

Unfortunately, meta-analyses assessing the benefits of NAC in advanced ovarian cancer have not shown a definite conclusion. One meta-analysis reported that NAC was associated with inferior OS when compared with upfront surgery and suggested that the likely reason for this was that definitive operative intervention was not undertaken sooner [32]. However, another meta-analysis reported that NAC contributed to an increased rate of optimal cytoreduction and that survival outcomes were non-inferior to those achieved by upfront PCS [33].

The European Organization for Research and Treatment of Cancer (EORTC) performed a randomized prospective study (EORTC 55971) to compare the effectiveness of NAC followed by interval cytoreductive surgery with that of PCS followed by adjuvant chemotherapy [34]. Although a higher rate of complete cytoreduction and lower postoperative morbidity and mortality rates were achieved in the NAC group, no significant difference in OS or PFS was found between the group that underwent NAC followed by interval cytoreductive surgery and the group that underwent PCS followed by adjuvant chemotherapy (29 months and 30 months, respectively, for OS, and 12 months for PFS in both groups). This finding indicated that NAC followed by interval cytoreductive surgery was non-inferior to PCS followed by chemotherapy as a treatment option for patients with advanced ovarian cancer. This study included patients aged ≥70 years (55 in the PCS group and 70 in the NAC group). Although analysis of the elderly age group in this study was limited, there did not appear to any difference in OS between NAC and PCS in the older women.

Further, there has been a retrospective study that used inclusion criteria similar to those in EORTC 55971 and reported better survival outcomes after PCS than after NAC [35]. In this study, 285 (90%) of 316 enrolled patients received PCS. Although 87% of the patients had stage IIIC ovarian cancer, optimal cytoreduction (residual tumor diameter ≤1 cm) was achieved in 71% of cases, with a median OS of 50 months and a median PFS of 17 months. The authors mentioned that the higher rate of optimal cytoreduction achieved in their study when compared with that in EORTC 55971 (71% vs. 42%) might have accounted for their results. Their conclusion was that PCS should continue to be the preferred initial management for advanced ovarian cancer and that NAC followed by interval cytoreductive surgery should be reserved for patients who are unlikely to tolerate PCS and/or for whom optimal cytoreduction is not feasible. A retrospective study from a single institution also showed achieving better median OS and PFS with PCS followed by

platinum-based chemotherapy than with NAC followed by cytoreductive surgery (72 months and 22 months vs. 43 months and 14 months, respectively) [36]. In this institution, the proportion of patients who received NAC increased significantly from 22% before publication of the results of the EORTC trial to 30% afterward when the selection criteria for each treatment strategy became more stringent. Therefore, the better survival outcomes reported for PCS in that study might stem from high-risk patients being selected more effectively for NAC.

Recently, contrary to the reports described above, association of NAC treatment with shorter OS compared to PCS for stage IIIC ovarian cancer (33 months vs. 43 months of median OS; HR 1.40, 95% CI 1.11–1.77) was shown in the multi-institutional study of NCCN ovarian cancer outcomes database project [37]. Because this was retrospective analysis differently from EORTIC trial, further studies to evaluate the effectiveness of NAC treatment will be needed. It was also shown in this study that proportion of NAC treatment for stage IIIC and IV ovarian cancer significantly increased from 16% to 34% similarly to the above report [36]. In total, patients aged >74 years received NAC more frequently compared to patients aged 18–54 years in both stage IIIC (33% vs. 23%; OR 2.25, 95% CI 1.21–4.16) and IV (56% vs. 36%; OR 2.64, 95% CI 1.14–6.10) [37]. Although no precise description about this trend was shown, it might be the result of attending doctor's decision considering chronological age and/or higher risk of perioperative morbidity in elderly patients.

There have been a few retrospective elderly-specific studies of the effectiveness of NAC, albeit from single institutions with small patient numbers. A retrospective analysis comparing the therapeutic outcome of NAC with that of PCS in 175 patients aged ≥65 years treated between 1997 and 2007 was reported [38]. This study included 141 (81%) patients aged 65–79 years and 34 (19%) aged ≥80 years. A comparison of PCS and NAC found no significant difference in surgical complication rates (58.8% vs. 64.0%; OR 0.80, 95% CI 0.37–1.75) or in chemotherapy-related complication rates (55.2% vs. 60.3%; OR 0.79, 95% CI 0.34–1.90). There was also no significant difference in surgical complication rates between patients aged 65–79 years and those aged ≥80 years (63.1% vs. 52.9%; OR 1.01, 95% CI 0.79–1.18) or in chemotherapy-related complication rates (57.1% vs. 32.2%; OR 1.04, 95% CI 0.82–1.27). Further, there was no significant difference in median disease-specific survival between patients aged ≥80 years and those aged 65–79 years (24 months vs. 35 months, $P = 0.15$). The findings of this study suggest that patients aged ≥80 years and those aged 65–79 years have a similar risk of surgical and chemotherapeutic complications and comparable survival. Another retrospective cohort analysis also reported the benefit of NAC in 104 patients aged ≥70 years who were treated with PCS ($n = 62$, 60%, mean age 75.9 years) or NAC (n = 42, 40%, mean age 76.9 years) for stage III or IV ovarian cancer between 1996 and 2009 [39]. The rate of complete cytoreduction with no macroscopic residual tumor was significantly higher in the NAC group (71.4%) than in the PCS group (28.1%, $P < 0.001$). Further, NAC was associated with significantly fewer perioperative complications, including less blood loss ($P = 0.01$), less requirement for small bowel resection ($P = 0.009$), a shorter intensive care unit (ICU) stay ($P = 0.02$),

and a shorter hospital stay ($P = 0.04$). Median OS and PFS in the NAC group were not inferior to those in the PCS group (25 months vs. 39 months, $P = 0.947$, and 25 months vs. 19 months, $P = 0.078$, respectively). Interestingly, there has been a cost-utility analysis of NAC in elderly patients based on the randomized controlled study [34] comparing NAC and PCS that showed NAC to be a cost-saving treatment when compared with PCS for patients aged ≥65 years with ovarian cancer [40]. According to this analysis, if the survival effect is assumed to be equal for NAC and PCS, NAC yields a cost savings of US$5616.

As already mentioned, NAC followed by cytoreductive surgery is an attractive therapeutic option, but its efficacy remains controversial. The clinical practice guideline for NAC published by the Society of Gynecologic Oncology and the American Society of Clinical Oncology outlines appropriate criteria for identifying patients who are not suitable for PCS and in whom NAC could be considered and advises that chronological age should also be taken into account in the decision-making [41].

16.3.2.4 Intraperitoneal Chemotherapy

Intraperitoneal (IP) chemotherapy is considered to have pharmacokinetic characteristics that differ from those associated with intravenous chemotherapy, including a more direct effect on cancerous lesions. Therefore, IP administration of cytotoxic agents in patients with ovarian cancer and peritoneal carcinomatosis could be expected to have advantages. Two large Phase III studies investigated the survival outcomes in women who received IP taxane-platinum-based chemotherapy. One was the intergroup (a coalition of the GOG, Southwestern Oncology Group [SWOG], and Eastern Cooperative Oncology Group) Phase III (GOG 114/SWOG 9227) trial published in 2001 [42], and the other was the GOG 172 trial published in 2006 [43]. Both studies showed significantly better median OS and median PFS in the groups that received IP chemotherapy, although the rates of G3–G4 hematologic, gastrointestinal, and general toxicities were significantly higher than in those who received intravenous chemotherapy. However, controversy persists regarding whether the better survival outcomes and higher rates of treatment toxicity seen in these studies reflect the increased total amount of cytotoxic agents administered in the IP arms.

Although approximately 10% of the patients enrolled in the above two studies were aged ≥70 years, no elderly-specific analysis was performed in either study. Given the complicated nature of the procedure and the higher rates of toxicity involved, most oncologists would hesitate to administer chemotherapy via the IP route in their elderly patients, particularly at the doses described above. However, two studies have demonstrated that IP treatment is feasible in both younger and older patients. Both these studies used an IP regimen similar to that in the GOG 172 trial. A multi-institutional retrospective analysis was performed in 109 patients with ovarian, fallopian tube, or primary peritoneal cancer who received IP treatment from 2006 to 2009 [44]. Eighty-six patients were aged <70 years and 23 were aged ≥70 years. No significant increase in grade 3–4 chemotherapy-related complications was observed in the older patients. Further, although the older patients were

significantly less likely to complete their planned number of cycles (OR 0.30, 95% CI 0.10–0.87), there was no significant difference in OS or PFS between the patients aged <70 years and those who were older. The median PFS was 14.5 months in patients aged <70 years and 19.0 months in those who were older (P = 0.68). Therefore, the authors considered that chronological age alone should not limit access to IP chemotherapy. They also compared the toxicity of intravenous vs. IP treatment in their patients aged ≥70 years and found significantly more comorbidities in the intravenous group than in the IP group. However, the finding of less toxicity with IP chemotherapy might simply reflect the reluctance of physicians to embark on the IP route for fear of increased toxicity in patients with multiple comorbidities. Therefore, given the lack of significant differences in complication rates or survival outcomes, the intravenous route seems preferable to the IP route in elderly patients with multiple comorbidities. There is another report that showed the results similar to those of report shown above [44] for the IP chemotherapy route with regard to treatment completion rate, toxicity, and survival outcome in their analysis of 200 patients (100 aged <65 years and 100 aged ≥65 years) [45].

In a retrospective study of patients with stage III ovarian cancer in the two GOG trials, which enrolled a combined total of 845 patients who received optimal PCS followed by IP chemotherapy (paclitaxel plus cisplatin), chronological age was found to be a significant independent predictor of poorer OS (HR 1.00, 95% CI 1.02–1.03; P = 0.012) [46]. The authors found that the risk of death increased 1.01 times for each 1-year increment in age. However, the age range in the GOG trials was 49–64 years, so elderly patients were not actually included in this study. The results of recent trials from the Japan Gynecologic Oncology Group [47] and the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) [48], in which the same doses of cytotoxic agents administered via the intravenous route were given via the IP route, are eagerly awaited.

The NCCN guideline for ovarian cancer recommends IP treatment in patients with stage III disease who have undergone PCS and have a residual tumor diameter of <10 mm [21]. Therefore, we should not hesitate to provide IP treatment for elderly patients satisfying these criteria.

16.4 Treatment of Relapsed Ovarian Cancer

16.4.1 Secondary Cytoreductive Surgery

Secondary cytoreductive surgery (SCS) aims to achieve maximum resection of residual cancer after primary treatment or of relapsed cancer. The strategy used to treat relapsed disease depends on the time that has elapsed since treatment with a platinum-based agent. In general, a surgical approach is not recommended as the initial treatment for a relapse that is platinum refractory or resistant because the benefits are minimal [49, 50]. However, SCS has been reported to be beneficial for platinum-sensitive relapse in carefully selected patients [51, 52] and is now recommended for these patients in the NCCN guideline [21]. The *D*escriptive *E*valuation

of preoperative *S*election *KriT*eria for *OP*erability in recurrent *OVAR*ian cancer (DESKTOP OVAR) trial reported that a combination of good performance status (Eastern Cooperative Oncology Group 0), early FIGO stage (I or II) at initial diagnosis or no residual tumor after primary surgery, and an estimated low volume of ascites (<500 ml) can predict complete resection in 79% of patients [53]. A retrospective analysis performed at the Mayo Clinic showed that these criteria (together known as the AGO score) had a positive predictive value of 84.3% for complete SCS. However, complete SCS was also achieved in 64.4% of patients with a negative AGO score [54]. Phase III trials, including DESKTOP III and GOG 213, are presently further investigating the ability of the AGO score to select patients for SCS and the effectiveness of SCS followed by adjuvant chemotherapy [52].

To date, no trial has specifically investigated the feasibility or survival outcomes of SCS in elderly patients. Chronological age was not identified as a significant factor associated with completion of SCS in either univariate or multivariate analysis in the DESKTOP OVAR trial, so SCS might be an option for elderly patients who have platinum-sensitive relapse and meet the above criteria.

16.4.2 Chemotherapy

Platinum sensitivity is considered to be key in chemotherapy for relapsed ovarian cancer. For the treatment of platinum-sensitive relapsed ovarian cancer, combination chemotherapy that includes a platinum agent has been reported to be superior to chemotherapy using a platinum agent alone. The International Collaborative Ovarian Neoplasm 4 / Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (ICON4/AGO-OVAR-2.2)-2.2 trial evaluated the effectiveness of combination paclitaxel-platinum therapy in 802 women with platinum-sensitive relapsed ovarian cancer, 239 (29.8%) of whom were aged ≥65 years [55]. Both OS and PFS were significantly better in women who received combination chemotherapy than in those who received a platinum agent alone (HR 0.82, 95% CI 0.69–0.67; $P = 0.023$, and HR 0.76, 95% CI 0.66–0.89; $P = 0.0004$, respectively). Subgroup analysis showed no significant age-related difference in OS or PFS. The results for platinum-based combination chemotherapy containing gemcitabine are similar. An Intergroup (AGO-OVAR, NCIC CTG, EORTC GCG) trial reported significantly improved PFS in women who received gemcitabine-carboplatin chemotherapy when compared with those who received carboplatin alone (HR 0.72, 95% CI 0.58–0.90; $P = 0.0031$), but no significant improvement in OS (HR 0.96, 95% CI 0.75–1.23; $P = 0.735$) [56]. The response rate for gemcitabine-carboplatin chemotherapy was significantly higher than that for carboplatin alone (47.2% vs. 30.9%; $P = 0.0016$). Although hematologic toxicity and need for granulocyte-colony stimulating factor were significantly more frequent in the women who received combination chemotherapy, their QoL was not worsened. One hundred (28.1%) of the 356 patients enrolled in this study were aged ≥65 years, and subgroup analysis showed no significant age-related difference in PFS.

Comparisons of the effectiveness of other types of combination chemotherapy in women with relapsed ovarian cancer have also been reported. The Caelyx in Platinum Sensitive Ovarian patients (CALYPSO) trial compared the efficacy and

safety of combination chemotherapy containing pegylated liposomal doxorubicin and carboplatin (C-PLD) with that of a CP regimen in 976 women with platinum-sensitive relapsed ovarian cancer and demonstrated significantly better PFS in the C-PLD group (HR 082, 95% CI 0.72–0.94; $P = 0.005$) [57]. A subsequent analysis of the 157 patients (16.1%) in the CALYPSO trial who were aged ≥70 years showed no significant difference in hematologic toxicity between younger (<70 years) and older (≥70 years) patients in either treatment group [58]. Sensory neuropathy (grade ≥ 2) was significantly more common in the elderly patients (24.4% vs. 15.5%, $P = 0.007$), whereas allergic reactions were observed more frequently in the younger patients (13.9% vs. 5.8%, $P = 0.005$). The toxicity profile (i.e., grade ≥ 2 alopecia, sensory neuropathy, arthralgia, and hand-foot syndrome) in the elderly women was not different from that observed in the CALYPSO study population overall. Further, in the women aged ≥70 years, there was no significant difference in median PFS between the C-PLD and CP regimens (11.6 months vs. 10.3 months, $P = 0.44$). The authors concluded that chemotherapy containing carboplatin and pegylated liposomal doxorubicin achieved a survival outcome similar to that achieved by the CP regimen in elderly patients but with less toxicity.

Relapsed ovarian cancer refractory or resistant to platinum is usually treated with a single non-platinum agent [19, 21], such as pegylated liposomal doxorubicin, topotecan, irinotecan, gemcitabine, docetaxel, or weekly paclitaxel. However, as yet there is no definitive study performed in elderly patients with platinum-resistant relapsed ovarian cancer. In general, the response rate for these agents in platinum-resistant relapse is 20%–30% at most. Considering the poor prognosis in these patients, it might be better at this point to switch from chemotherapy to hospice care for maintenance of QoL, particularly in elderly patients.

16.5 Molecular Targeted Therapy for Ovarian Cancer

Bevacizumab (anti-vascular endothelial growth factor monoclonal antibody) is the only agent that has been demonstrated to improve survival in patients with advanced or recurrent ovarian cancer. The activity of bevacizumab as primary chemotherapy for ovarian cancer has been studied in two major Phase III trials, i.e., GOG 218 [59] and ICON-7 [60], which, respectively, included 430 (23%) and 150 (10%) women aged ≥70 years. In the bevacizumab arms of GOG 218 and ICON-7, the oldest patients were aged 89 years and 82 years, respectively. Two further Phase III trials in platinum-sensitive Ovarian Cancer Study Comparing Efficacy and Safety of Chemotherapy and Anti-Angiogenic Therapy in Platinum-Sensitive Recurrent Disease (OCEANS) [61] and platinum-resistant Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer (AURELIA) [62] relapsed ovarian cancer have also shown better PFS in patients treated with bevacizumab. However, none of these four trials performed a specific subset analysis for elderly patients. To date, no study has specifically investigated the effectiveness and feasibility of chemotherapy including bevacizumab for elderly patients with ovarian cancer. However, hypertension, proteinuria, thromboembolism, and hemorrhage are the well-known major toxicities of bevacizumab, and gastrointestinal perforation is reported to be the most life-threatening toxicity [63]. Clearly, these toxicities should be kept in mind when considering the use of bevacizumab in elderly patients with physical comorbidities.

Olaparib, a poly (ADP-ribose) polymerase inhibitor, has been reported to be a potentially effective agent in patients with ovarian cancer harboring BRCA mutations [64, 65]. Olaparib is now approved by the US Food and Drug Administration for patients who have received three or more lines of chemotherapy and is listed as one of the preferred agents in the NCCN guideline [21]. The results of further investigations showing the effectiveness and feasibility of this agent in elderly patients with ovarian cancer are awaited.

16.6 Comprehensive Geriatric Assessment

16.6.1 Frailty

Frailty in elderly people is defined as a state of vulnerability to various kinds of stressors and is attributable to the age-related decrease in physiological reserve. Frailty in an elderly person manifests as a number of symptoms and signs, including weakness, fatigue, weight loss, poor balance, low levels of physical activity, slowed motor processing and performance, social withdrawal, mild cognitive changes, and increased vulnerability to stressors, culminating in disability, loss of independence, diminished QoL, and mortality (Fig. 16.1) [66]. In the pathway to frailty, various molecular alterations and physiological reactions are considered to be associated (Fig. 16.2) [67]. Frailty may also be associated with psychological and financial problems.

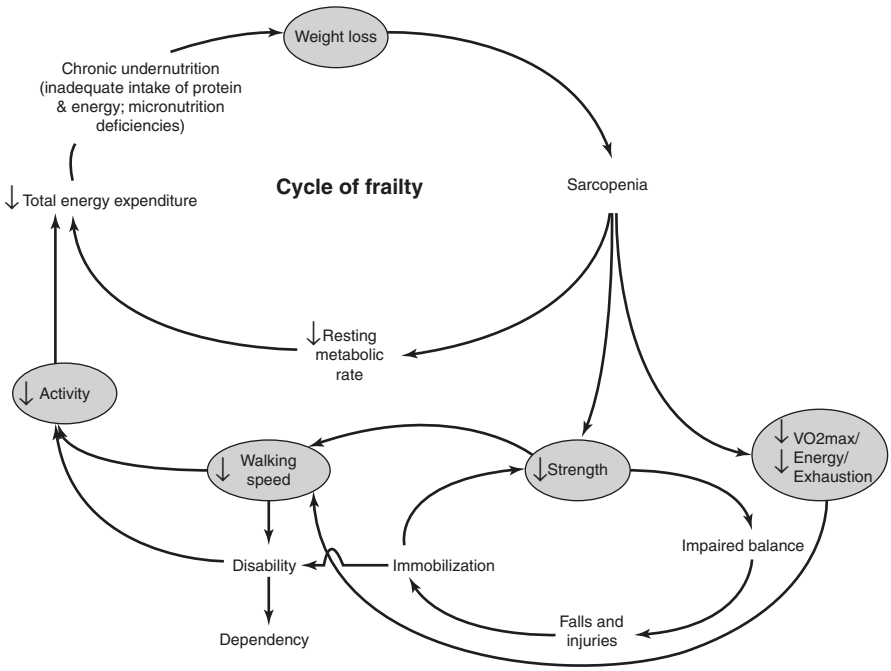

Fig. 16.1 Cycle of frailty [66], reprinted with permission of Oxford University Press

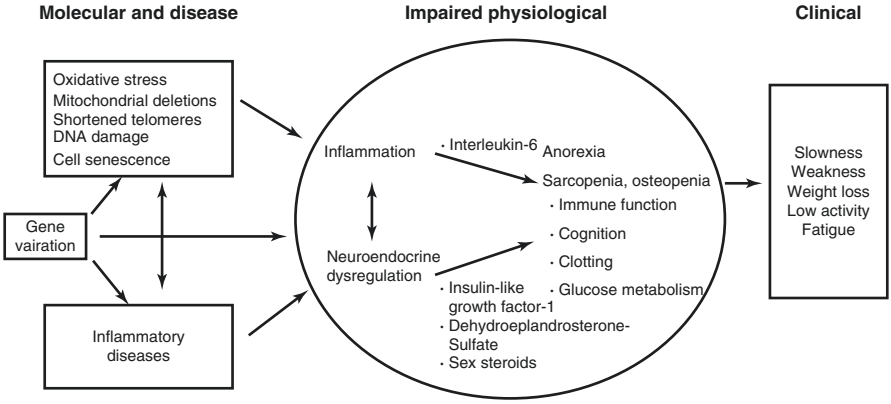

Fig. 16.2 Hypothesized molecular and physiological association with frailty [67], reprinted with permission of John Wiley and Sons

The question rises as to the best way of assessing elderly patients to determine if they are frail or not. Some useful criteria in this regard has been proposed based on the findings of the Cardiovascular Health Study, in which 5317 people aged 65–101 years (57.9% female, 14.8% African American) were evaluated to define the phenotype of frailty [68]. Five components of frailty were investigated, including unintentional weight loss (4.5 kg in the past year), weakness (grip strength, stratified by sex and body mass index), poor endurance (self-reported in response to two questions from the Center for Epidemiological Studies-Depression Scale [69]), slowness (walking speed, stratified by sex and height), and low physical activity (weighted score of kilocalories expended per week). Individuals who satisfied three or more of the above five criteria were defined as frail and those who met one or two criteria were categorized as pre-frail. Using these criteria, 368 people (6.9%) in this population were characterized as frail and 2480 (46.6%) as pre-frail. Mortality rates at 3 and 7 years in frail people were 18% and 43%, respectively, whereas those in non-frail people were 3 and 12%. This frailty phenotype could independently predict the risks of incident falls, worsened mobility or disability in activities of daily living, incident hospitalization, and death over 3 or 7 years, with hazard ratios ranging from 1.82 to 4.46 and from 1.28 to 2.10 for the frail and intermediate groups, respectively. Similar models of frailty have been proposed by the Women's Health and Aging Study [70], the Edmonton Frail Scale [71], and others [72].

16.6.2 Pretreatment Evaluation in Elderly Patients

16.6.2.1 Score to Predict Peri-treatment Morbidities

Although medical frailty is a concept with a relatively short history, a frail state is clearly associated with poorer health outcomes in the elderly. Therefore, appropriate assessment of elderly patients is necessary to predict the risk of severe peri-treatment morbidities or an unexpected worse outcome when considering treatment for any type of cancer. Several systematic reviews have revealed that appropriate

assessment has adequate feasibility and high sensitivity for predicting frailty in elderly patients with cancer. However, the types of assessment used have not always been useful for prediction of adverse outcomes or had high specificity or negative predictive value [73–75]. Therefore, it is possible that the assessment methods presently used to guide therapeutic decision-making may be inadequate for elderly patients with cancer.

16.6.2.2 Assessment to Predict Perioperative Morbidities

Efforts to evaluate the effectiveness of the assessment protocols proposed for elderly patients with ovarian cancer are ongoing. The Modified Frailty Index (mFI) consists of 11 variables derived from the Canadian Study of Health and Aging Frailty Index and was reported to predict morbidities requiring ICU admission in patients scheduled for colectomy (Table 16.1) [76]. The usefulness of the mFI as a predictor of the risk of morbidities has also been investigated in a retrospective study of 6551 patients who were identified in the National Surgical Quality Improvement Program data for 2008–2011 as having undergone surgery for gynecologic cancer (although the exact number with ovarian cancer was not reported) [77]. One hundred and eighty-eight (2.9%) of these women developed life-threatening complications requiring management in ICU or resulting in death within 30 days postoperatively. The complication rates were 2, 2.7, 4.4, 7.4, and 24.4% for mFI scores of 0, 1, 2, 3, and ≥4, respectively, and were significantly higher in patients with a score ≥ 3 than those with a score ≤ 2 ($P < 0.001$). In multivariate analysis, significant predictors of severe complications were a preoperative albumin level < 3 g/dl (OR 6.5, 95% CI 4.31–9.96), longer operating time (OR 1.003 per minute increase, 95% CI 1.001–1.004), non-laparoscopic surgery (OR 3.3, 95% CI 1.56–8.83), and an mFI score ≥ 2 (score 2, OR 1.91, 95% CI 1.17–3.11; score 3, OR 2.33, 95% CI 1.05–5.19; score ≥ 4, OR 12.5, 95% CI 4.77–32.76). When the women were categorized as low-risk and high-risk groups on the basis of a preoperative albumin level ≤ 3 g/dl

Table 16.1 Eleven variables to calculate Modified Frailty Index (mFI) based upon patient's medical record [76, 77]

Variables for Modified Frailty Index (mFI)	
1.	Nonindependent functional status
2.	History of diabetes mellitus
3.	History of either chronic obstructive pulmonary disease or pneumonia
4.	History of congestive heart failure
5.	History of myocardial infarction
6.	History of percutaneous coronary intervention, cardiac surgery, or angina
7.	Hypertension requiring the use of medications
8.	Peripheral vascular disease or rest pain
9.	Impaired sensorium
10.	Transient ischemic attack or cerebrovascular accident without deficit
11.	Cerebrovascular accident with deficit

and/or an mFI score ≥ 4, the high-risk group showed a higher (≥10%) rate of severe perioperative complications when compared with the low-risk group (≤10%). The authors concluded that the mFI criteria could identify patients with gynecologic malignancy who were at high risk for perioperative complications that require management in ICU or are fatal.

An ovarian cancer-specific investigation has since been performed for 751 patients aged ≥65 years identified in the National Surgical Quality Improvement Program database as having undergone PCS between 2005 and 2016 [78]. One hundred and twenty-three (16.4%) of these patients encountered complications of the same level of severity as those described in the previous report [77]. A number of variables, including patient demographics (age, body mass index, race), preoperative laboratory values (creatinine, hematocrit, platelet count, white blood cell count, albumin), and comorbidities (hypertension, cigarette smoking, diabetes, chronic obstructive pulmonary disease, history of cerebrovascular accident, myocardial infarction within the previous 6 months, history of transient ischemic attack), were compared between patients with and without severe morbidities. Eight variables identified to be significant were chosen for a model to predict the probability of postoperative complications in patients aged ≥65 years undergoing PCS for ovarian cancer (Table.16.2). The variables chosen for the proposed predictive model were ascites (present or absent), current smoking (yes or no), race (white vs. nonwhite), preoperative creatinine (≥1.5 mg/dL or <1.5 mg/dL), preoperative platelet count (≥450 × 10^9/L or <450 × 10^9/L), preoperative hematocrit (≥30% or <30%), preoperative white blood cell count (≥10 × 10^9/L or <10 × 10^9/L), and preoperative albumin (≥3.5 g/dL or <3.5 g/dL). The area under the receiver-operating characteristic curve for the model was 0.725, indicating fair (not poor but not good) performance. This model could predict a 35% probability of severe postoperative complications with 21.8% sensitivity and 92.6% specificity. When the threshold of prediction was decreased to 50% probability, the sensitivity decreased to 9.8% although specificity increased to 98.0%. These findings indicate that preoperative evaluation to identify patients with the highest risk of severe postoperative complications is not easy. However, the high specificity of this model means that patients who can undergo PCS safely could be identified, including those who are elderly.

Table. 16.2 Eight variables for the model to predict the major postoperative complication [78]

Variables for the predictive model	
Physical status or habit	
Ascites	Yes or No
Current smoker	Yes or No
Race	White or Non-white
Preoperative laboratory data	
Creatinine (mg/dL)	<1.5 or ≥1.5
Platelet (×10^9/L)	<450 or ≥450
Hematocrit (%)	<30 or ≥30
White blood cell (×10^9/L)	<10 or ≥10
Albumin (g/dL)	<3.5 or ≥3.5

16.6.2.3 Assessment to Predict Tolerance of Chemotherapy

A GINECO study has reported a comprehensive geriatric assessment tool that can predict the risk of severe treatment-related toxicities in elderly patients with ovarian cancer [23]. Based on their study findings, the authors devised a geriatric vulnerability score (GVS), calculated from five criteria, namely, a low activities of daily living score (<6), a low instrumental activities of daily living score (<25), hypoalbuminemia (<3.5 g/dL), lymphopenia at inclusion ($<1 \times 10^9$/L), and a high Hospital Anxiety and Depression Scale score (>14). GVS is sum of these variables of each patient. The patients aged ≥70 years with ovarian cancer were separated into two groups using a cutoff point of 3. Patients with a GVS ≥3 were significantly less likely to complete their planned chemotherapy than those with a GVS <3 (OR 0.41, 95% CI 0.17–0.99; $P = 0.044$) and were significantly more likely to have more severe (grade ≥ 3) non-hematologic toxicities (OR 4.40; 95% CI 1.92–10.08; $P = 0.0002$), more serious adverse events (OR 2.79, 95% CI 1.27–6.11; $P = 0.009$), and more unplanned hospital admissions (OR 2.57, 95% CI 1.17–5.63; $P = 0.017$) [79]. Since the chemotherapy administered in this study was carboplatin alone, further investigation is needed to evaluate the predictive accuracy of the GVS in elderly patients with ovarian cancer who receive combination chemotherapy with a taxane and a platinum agent.

Conclusion

Nearly half of all patients with ovarian cancer are diagnosed in the advanced stages of the disease and have peritoneal carcinomatosis at this time. The mainstay of treatment for advanced ovarian cancer continues to be maximal PCS followed by adjuvant chemotherapy. Clearly, the improvements in supportive care for patients and in the surgical devices available, as well as innovative cytotoxic and supportive agents, have contributed to the improved treatment of ovarian cancer. However, it should be acknowledged that the development of clinical guidelines has played a very important part in these improvements. Clinical evidence concerning the treatment of various types of cancer in the elderly has been steadily accumulating in recent years, and general guidelines for geriatric medicine have been proposed [80–82]. However, guidelines specific for the treatment of each type of cancer have not been adequately developed for elderly patients because of the difficulties inherent in performing clinical trials in this age group. Therefore, our treatment strategies for these patients have to be based on relatively limited evidence from analyses of subgroups in the major clinical trials.

The current evidence indicates that every effort should be made to perform PCS followed by chemotherapy in patients with advanced ovarian cancer, regardless of the patient's chronological age. A weekly chemotherapeutic regimen or single-agent chemotherapy is recommended for elderly patients and those with poorer performance status. However, the issues of frailty and the higher risk of peri-treatment morbidities do need to be considered in these patients. There is increasing awareness of the importance of appropriate assessment of geriatric patients with cancer, and a variety of scoring systems to predict the risks of treatment have been proposed.

It is now time to leave behind the concept that elderly patients are only eligible for palliative treatment because of their chronological age. Further studies, based on the accumulation of evidence from clinical trials that have included elderly patients, will be invaluable for increasing the reliability of geriatric assessment protocols and for predicting patients who can tolerate standard treatments.

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