21st Century Challenge of Ovarian Cancer in the Elderly

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Given that in the 21st century many believe 70 years of age is the new 60 and 80 years of age is the new 70, any article on ovarian cancer in the elderly depends on one’s definition of elderly. To put this in a 21st century perspective, in a thoughtful article on aging in The New Yorker (“The Way We Age Now,” April 30, 2007), Atul Gawande points out, “for most of our hundred-thousand-year existence—all but the past couple of hundred years—the average life span of human beings has been 30 years or less (research suggests that subjects of the Roman Empire had an average life expectancy of 28 years).

ABSTRACT: The incidence of ovarian cancer is highest in women over 70 years old, and the disease is the leading cause of death from gynecologic malignancies in the United States and Europe. Nevertheless, improving the quality of medical care for elderly women with ovarian cancer continues to be a challenge. This paper presents the major issues related to the surgical management of presumed early-stage ovarian cancer, surgery and chemotherapy for advanced-stage ovarian cancer in the elderly, and a proposed 21st century algorithm for dealing with these major issues in ovarian cancer in the elderly.

Ovarian Cancer in the Elderly

Ovarian cancer peaks in incidence during the ages of 75 to 79.[1] As a result, a significant number of women in their 70s and 80s will present with presumed ovarian cancer, requiring a dramatic change in our approach to “elderly” women with this disease. Therefore, it is reasonable in the 21st century to define elderly relative to ovarian cancer as women in their 70s and 80s.

TABLE 1

FIGO Staging of Early-Stage Ovarian Carcinoma

At this point, certain facts seem fairly clear:
(1) In the United States and Western Europe, the incidence of ovarian cancer is highest in women over 70 years of age.[2]
(2) Ovarian cancer is the leading cause of death from gynecologic malignancies in the United States and Europe.[2]
(3) Approximately 70% of epithelial ovarian cancer at presentation are in International Federation of Gynecology and Obstetrics (FIGO) stage III or IV (Table 1) with disease above the pelvis involving the peritoneal cavity.[3]
(4) The ultimate length of survival for women with presumed early-stage disease at presentation (FIGO stage I or II) to a great extent depends on careful surgical staging.[4]
(5) The duration of survival of women with FIGO stage III/IV disease depends largely on cytoreductive surgery that leaves no residual disease > 1 cm and preferably < 5 mm, followed by taxane/platinum chemotherapy.[5]
(6) To achieve optimal debulking, approximately 25% of patients with FIGO stage III/IV will require intestinal resection and, in some, more radical procedures.[6]
(7) Renal function is less than optimal in many patients in their 70s and 80s, and thus, cytotoxic chemotherapy has the potential to be more toxic.[7]
(8) Comorbidities in this age group make the management of ovarian cancer in the elderly a true 21st century challenge. With the recent emphasis on improvements in preventive care in medicine, significantly more people are living longer. But with the increase in longevity comes a combination of chronic diseases and organ impairments, not all of which are clinically readily apparent in the elderly.

The purpose of this paper is to present the major issues related to the surgical management of presumed early-stage ovarian cancer, surgery and chemotherapy for advanced-stage ovarian cancer in the elderly, and a proposed 21st century algorithm for dealing with these major issues in ovarian cancer in the elderly.

**Surgery for Presumed FIGO Stage I/II Ovarian Cancer**

For almost all cancers, patients with presumed early-stage disease—especially stage I—have significantly superior survival to patients presenting with more advanced-stage disease. In 1972, Bagley and coauthors best framed the problem as it relates to the early-stage ovarian cancer setting, in an article published in the New England Journal of Medicine.[8] These authors reported that the mean 5-year survival for patients with stage IA ovarian cancer limited to one ovary was 63%, or conversely, that approximately 40% were dead with recurrent ovarian cancer in less than 5 years from the earliest-stage disease. Therapy at the time of that review consisted primarily of total abdominal hysterectomy and bilateral salpingo-oophorectomy with or without pelvic or abdominal radiation therapy.

<table>
<thead>
<tr>
<th>Site</th>
<th>Number</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>Malignant washings</td>
<td>79</td>
<td>33%</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>44</td>
<td>11%</td>
</tr>
<tr>
<td>Aortic nodes</td>
<td>58</td>
<td>10%</td>
</tr>
<tr>
<td>Pelvic nodes</td>
<td>37</td>
<td>8%</td>
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<tr>
<td>Omentum</td>
<td>27</td>
<td>3%</td>
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Subclinical Metastases Found by Staging Laparotomy in Stage I Ovarian Cancer Patients

As early as 1940, Penberton advocated that “when an operation for cancer of the ovaries is done it would be wise to remove the omentum, regardless of whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrence later.”[9]

As evidenced by the report by Bagley et al in 1972, little had changed in the surgery and treatment of presumed early-stage ovarian cancer up to that time. In the mid-1970s, however, reports started to emerge that there were previously unrecognized or subclinical areas of metastasis when an ovarian cancer at surgery appeared clinically to be limited to the ovary. These areas included the undersurface of the diaphragm, pelvic lymph nodes, para-aortic lymph nodes, omentum, and tumor cells in a saline lavage of the peritoneal cavity.

In 1978, we reported our results and a collective review of the literature of subclinical or microscopic metastasis in patients with presumed stage I ovarian cancer on five areas of subclinical metastasis from presumed stage I ovarian cancer.[4] In descending order of prevalence, these areas included malignant peritoneal washings (33%), diaphragm metastasis (11%), para-aortic lymph node involvement (10%), pelvic lymph node metastasis (8%), and omental metastasis (3%). Although the
percentages have varied in subsequent reports, these five areas need to be evaluated at time of surgery for presumed early-stage ovarian cancer (Table 2, Figure 1). Some authors also include random peritoneal biopsies as a part of the surgical staging for presumed stage I/II ovarian cancer. We now know that for women with presumed ovarian cancer clinically limited to the ovary, surgical staging will identify subclinical metastasis in 20% to 25% of cases and thus result in important treatment decisions.

FIGURE 1

Ovarian Cancer Spread

The challenge, however, for the 21st century is that most women with a pelvic mass—a small percentage of which will subsequently be found to be ovarian cancer—are still not operated on by surgeons trained especially in pelvic lymphadenectomy (with removal of lymph nodes from the common iliac vessels, the external iliac artery and vein, the internal iliac vessels, and the obturator fossa) as well as para-aortic lymphadenectomy (with removal of lymph nodes along the aorta and vena cava from the lower aorta to the renal vessel). While this situation is understandable in the United States, gynecologic oncology and surgical oncology programs do prepare surgeons for this important part of the surgical staging of presumed early-stage ovarian cancer.

Another challenge for the 21st century is the need to develop improved transvaginal ultrasound and color doppler with significantly improved sensitivity and specificity for malignancy involving a pelvic mass. We will also need to discover additional tumor markers to serum CA-125 with a higher sensitivity than 50% in stage I ovarian cancer. Such developments will allow for referral of patients preoperatively to centers with a high volume of ovarian cancer cases.

Surgery for Stage III/IV Ovarian Cancer

Surgery for the elderly patient with presumed advanced-stage ovarian cancer presents the biggest challenge facing the treating oncologist. First, elderly women with advanced-stage ovarian cancer have a significantly lower survival than younger patients, which is thought to be, in part, secondary to less aggressive surgery and chemotherapy in this age group.[10] Moreover, as stated earlier, 70% will present with FIGO stage III/IV ovarian cancer, with the ultimate length of survival largely dependent on radical cancer surgery leaving no residual disease ≥ 1 cm in largest diameter followed by taxane/platinum chemotherapy.[5] Finally, and equally important, the elderly have comorbidities that make extensive radical cancer surgery more problematic.

Most oncologists use the Gynecologic Oncology Group (GOG) definition of optimal cytoreductive surgery as residual disease ≤ 1 cm at the completion of surgery. Support for the GOG definition of optimal surgery is seen in the report by Winters and coauthors, who reviewed six different GOG protocols involving 1,895 patients with FIGO stage III ovarian cancer, all of which used cisplatin and paclitaxel chemotherapy at the same dosages.[11] For patients with no microscopic residual disease, the progression-free survival of 33 months and overall survival of 71.9 months was statistically significantly better (P < .01) than outcomes for patients with residual disease but ≤ 1 cm (16.8 and 42.4 months, respectively), and patients with residual disease > 1 cm (14.1 and 35.0 months, respectively).

As pointed out by Earle and coauthors, elderly women with advanced-stage ovarian cancer are significantly more likely to have optimal cytoreductive surgery if it is performed by a gynecologic oncologist.[12] We reported on evidence for the concept of surgery in advanced ovarian cancer by gynecologic oncologists over 2 decades ago.[6] In a prospective study of 50 consecutive previously untreated patients with FIGO stage III/IV ovarian cancer, we evaluated what percentage of such
patients could have their tumors optimally cytoreduced (at that time, the definition of optimal surgery was ≤ 2 cm residual disease). Optimal cytoreduction was achieved in 76% of 50 cases and 77% of 18 cases referred by the original surgeon as “inoperable.” To achieve this goal, the six most common operations performed in descending order of frequency was bilateral salpingo-oophorectomy (100%), hysterectomy (98%), omental tumor resection (86%), peritoneal tumor resection (40%), intestinal resection (36%) and gastrocolic ligament resection (16%). Not only has it been documented that optimal cytoreductive surgery occurs significantly more frequently when performed by a gynecologic oncologist, but as Hillner and coauthors reported, outcome for most cancers is improved with increased volume of patients cared for and specialization of the treating physician.[13]

As stated regarding women with presumed early-stage ovarian cancer, the 21st century surgical challenge for women with presumed advanced-stage ovarian cancer is the development of improved imaging studies and serum tumor markers that allow for a higher degree of diagnostic certainty, which would allow for centralization of surgery in high-volume specialized centers.

**Chemotherapy for Advanced Disease**

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Elements of the Comprehensive Geriatric Assessment and Potential Clinical Applications

The 21st century challenge of chemotherapy in the elderly patient with advanced-stage ovarian cancer is complex for many reasons. First, elderly patients with advanced-stage ovarian cancer are significantly underrepresented in clinical trials, and therefore, therapeutic decisions must be made based on less than adequate data.[14] Second, there is a progressive decline in glomerular filtration with increasing age, thus leading to an increase in major toxicities.[7] This frequently results in elderly patients receiving less than optimal treatment, with a predictable decline in overall survival.[10] Finally, since the 1996 seminal report by McGuire et al established intravenous (IV) platinum and taxane as standard and best therapy, there has been no improvement in either the progression-free or overall survival of patients with advanced-stage ovarian cancer.[15]

It has been argued, however, that survival has improved in patients with ovarian cancer since McGuire’s report, as shown by Armstrong and coauthors in their phase III trial published in the New England Journal of Medicine in 2006.[16] This trial purported to demonstrate a significant advantage in progression-free and overall survival (by approximately 15 months) in optimally debulked stage III ovarian cancer with the use of intraperitoneal (IP) and IV cisplatin and paclitaxel, as compared to IV cisplatin and paclitaxel. That same year, this study resulted in the National Cancer Institute (NCI) issuing a Clinical Announcement recommending that “consideration should be given to a regimen containing IP cisplatin (100 mg/m2) and a taxane” for a patient with optimally debulked stage III ovarian cancer.[17]

Despite the NCI’s recommendation, IP chemotherapy in such instances has become neither standard nor even widely adopted. Reasons for not widely utilizing IP chemotherapy in this scenario are that many clinicians do not believe that the Armstrong paper (GOG protocol 172) actually documented superior survival. This conclusion is based on the fact that only 42% of patients in the IP arm of GOG 172 completed the assigned number of courses; patients in the IP arm had to have their treatment reduced or changed to IV chemotherapy or less toxic drugs because of the excessive toxicity; and,
many believe, the wrong control arm (IV cisplatin and paclitaxel) was used, given that standard chemotherapy for advanced ovarian cancer was IV carboplatin and paclitaxel. Moreover, not only is IP chemotherapy more toxic and more costly, it is technically more complicated to administer, making it problematic for elderly patients with advanced-staged ovarian cancer. Another 21st century chemotherapy challenge in the elderly could be the adoption and wider use of the comprehensive geriatric assessment (CGA), as described by Balducci in a 2006 article in ONCOLOGY.[18] The oncologist treating a patient with advanced-stage ovarian cancer could then better decide whether to use (1) full-dose chemotherapy, (2) reduced or even single-agent chemotherapy, or (3) just symptom management (Table 3, Figure 2).

**Pretherapy Use of the Comprehensive Geriatric Assessment**

![Pretherapy Use of the Comprehensive Geriatric Assessment](image1)

**Treatment of Older Cancer Patients**

Arguably, 21st century best medical care for the preoperative assessment of the elderly woman with a presumptive diagnosis of ovarian cancer is best done by a geriatrician. However, as pointed out by Gawande, the number of board-certified geriatricians has decreased in the United States by one-third from 1988 to 2004. He postulated that this partly “had to do with money—incomes in geriatrics and adult primary care are among the lowest in medicine. And partly, whether we admit it or not, most doctors don’t like taking care of the elderly.” However, some progress is being made. In 2000, the International Society of Geriatric Oncology was formed, followed by the creation of the Geriatric Oncology Consortium for the cooperative study of the elderly patient with cancer. In 2003, Repetto and colleagues pointed out that “as age from a clinical perspective is highly heterogeneous and poorly reflected by chronologic age, the clinical evaluation of the older person is influenced by several factors and is a key step in the clinical decision process.”[19] A geriatric consultation provides a variety of relevant information and enables the health-care team to manage the complexity of health-care in the elderly. This process is referred to as the comprehensive geriatric assessment.[18] Whether the CGA is a useful tool in the pretherapy surgical assessment of the elderly patient with presumed ovarian cancer is unclear. However, it has been evaluated in the use of chemotherapy in the elderly patient with advanced-stage ovarian cancer. In a prospective trial using the CGA in 83 stage III/IV ovarian cancer patients aged over 70 and treated with carboplatin and cyclophosphamide, Freyer and coauthors demonstrated three independent factors related to severe toxicity from chemotherapy: (1) symptoms of depression (P = .006), (2) loss of autonomy (full autonomy at home vs dependent living, living at home with assistance, living with medical assistance in a specialized institution; P = .048), and (3) performance status ≥ 2 (P = .026) prior to chemotherapy.[20] The question addressed in their study was whether the CGA would identify subgroups of elderly patients who should receive standard combination chemotherapy, dose-reduced therapy, or no chemotherapy at all. The authors admitted that, by necessity, they did not enroll the very fragile elderly. They also conceded that carboplatin/cyclophosphamide is not the same as the current gold standard of carboplatin and a taxane. Nevertheless, they felt that the CGA did allow oncologists to decide which elderly patients with advanced ovarian cancer were candidates for standard combination chemotherapy, single-agent chemotherapy, or no therapy.**FIGURE 3**

![FIGURE 3](image2)
Treatment of Older Cancer Patients, Modified

Although the CGA has not been evaluated in the preoperative surgical assessment of the elderly patient with presumed advanced-stage ovarian cancer, a modification of the algorithm for the treatment of the elderly cancer patient has been proposed by Balducci (Figure 3), which would better allow the surgical oncologist to decide on standard cytoreductive surgery, less radical surgery, or chemotherapy alone vs symptom control.

Conclusions

With more and more women living into their 7th and 8th decades of life with the attendant and inescapable physiologic changes of aging, improving the quality of medical care for those elderly women who develop ovarian cancer will be difficult at best. However, the 21st century challenge is to not accept the 20th century results of less aggressive therapy and lower survival in all elderly patients as compared with younger ovarian cancer patients. Instead, we need to develop improved imaging systems for differentiating the benign from the possibly malignant pelvic mass, find more sensitive and specific tumor markers, and promote the wider use of such instruments as the CGA, while encouraging the training of more gerontologists.

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References:
chemotherapy and survival in elderly patients with advanced ovarian carcinoma: A GINECO study.

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