Distinguished Expert Series

Progress in epithelial ovarian carcinoma. Has the outcome been improved?

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Introduction

Ovarian cancer is a complex neoplasm composed of different histological grades and types, and is the leading cause of death from gynecologic malignancies in Western countries. Epithelial ovarian cancer (EOC) is the most common histological type of ovarian malignancy. In some areas of this malignancy considerable progress has been made during the past 30 years, in others there is stagnation. Has the outcome been improved?

Progress

Although the etiology of the disease is still mostly obscure, several involved risk factors are known. Certain reproductive factors, such as age at menopause and infertility, and lifestyle factors as cigarette smoking, obesity, diet and hormone replacement therapy may contribute to a greater risk of ovarian cancer, whereas pregnancy, pelvic surgery and oral contraceptive use, reduce the risk. Advances in cancer genetics has allowed the identification of mutations within the BRCA1 and BRCA2 genes. Women who have these mutations have a significantly increased lifetime risk (range 15-60%) of ovarian malignancies. Subsequent clinical genetic testing for mutations in the genes associated with hereditary breast-ovarian cancer and Lynch/hereditary nonpolyposis colorectal cancer syndrome were made available. About 5-10% of ovarian cancers are due to a hereditary risk. Risk-reducing surgery consisting of bilateral salpingo-oophorectomy is offered to women who carry the BRCA mutations. Chemoprevention (mainly oral contraceptive use) and/or intensified surveillance are alternative approaches.

Some understanding has been gained of the proteins and pathways involved in the early stages of malignant transformation and metastasis of ovarian carcinoma [1]. Multiple recent publications deal with clinical proteomics [2] and its possible relevance for risk assessment, early detection and management of ovarian cancer, though the new discoveries are not yet clinically applicable.

Transvaginal sonography and the serum CA125 biomarker are currently helpful in distinguishing benign from malignant adnexal masses. CA125 is extremely valuable for monitoring treatment response and diagnosis of recurrent disease. In addition, modern imaging modalities, such as PET/CT, greatly assist in the preoperative evaluation and follow-up of ovarian cancer patients.

In 1988 the FIGO surgical staging system was introduced. Among its advantages was the more accurate identification of malignancies truly confined to the ovaries. Several prognostic factors of ovarian carcinoma, in addition to stage, have been identified and include age, performance status, presence of large volume of ascites, histological tumor type, grade and microvessel density analysis.

In the surgical management of ovarian cancer the concept of cytoreduction (debulking) has been introduced and accepted based on numerous retrospective studies that indicate that patients with optimal cytoreduction have a better prognosis. Throughout the years the definition of optimal cytoreduction has been modified and today consists of residual tumor nodules of up to 1 cm and preferably of no macroscopic residual disease. Several studies indicate that women operated on by gynecologic oncologists have a more favorable outcome.

Based on phase III trials the standard adjuvant chemotherapy has been established as well [3]. According to the guidelines of the 1994 NIH Consensus Conference [4] management of advanced ovarian carcinoma should include surgical staging, optimal cytoreduction followed by chemotherapy with platinum combined with taxane. It has been recognized that surgically determined early ovarian cancer patients can be treated conservatively. In young women, the uterus and in some instances the uninvolved ovary may be retained thus preserving fertility. Such patients do not require postoperative chemotherapy. Using currently available assisted reproductive technology pregnancies and term deliveries have been reported in these cases.

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Following initial surgery, the great majority of patients with epithelial ovarian carcinoma will receive standard combined chemotherapy i.e., platinum (carboplatin or cisplatin) and a taxane (paclitaxel or docetaxel). Patients with recurrence are usually treated with several additional chemotherapy regimens during the course of the disease. They include newly developed chemotherapy agents such as etoposide, liposomal doxorubicin, gemcitabine, and topotecan.

Several treatment modifications are currently practiced. Neoadjuvant chemotherapy prior to cytoreductive surgery is used in selective cases of advanced ovarian cancer. Phase III trials have confirmed a significant advantage in progression-free and overall survival for initial adjuvant intraperitoneal chemotherapy in optimally cytoreduced advanced ovarian cancer. This treatment combined with postoperative IV chemotherapy was endorsed in January 2006 by the National Cancer Institute in the USA as the preferred treatment method for advanced ovarian cancer. However, it is noteworthy that this treatment regimen is more toxic and is associated with reduced short-term quality of life.

Novel treatments are being explored including immunotherapy, gene therapy, anti-angiogenic therapy and treatment by signal transduction inhibitors. Extreme drug resistance-directed chemotherapy may improve outcome in recurrent ovarian carcinoma patients [5]. Attempted approaches to achieve longer clinical complete remissions include consolidation and maintenance therapy. Microarray technologies may in the future provide valuable expression data for classifying ovarian cancer and insight into molecular changes in ovarian cancer that could be exploited in new treatment strategies.

Stagnation

Only 25% of ovarian cancers are detected in Stage I. However, when diagnosed in this stage, up to 90% of patients can be cured with conventional therapy. Therefore early diagnosis could markedly improve the overall survival of ovarian cancer patients.

Although transvaginal ultrasound and the marker CA125 are very useful in the diagnosis of ovarian malignancy, each of these modalities lacks the sensitivity and specificity to serve alone or in combination as a screening test. Currently no screening test for ovarian carcinoma with a high sensitivity and high enough specificity to avoid the harmful effects of false-positive results is available [6].

The quest for optimal cytoreduction in ovarian carcinoma is well ingrained in the gynecologic oncology community although no prospective randomized trials have ever been performed to show whether the benefit of this procedure is due to the aggressive surgery or to inherent biological properties of the tumor that allow cytoreduction. The concept of cytoreduction is not unchallenged. The results of some investigations do not support this surgical approach [7]. Therefore the justification for radical operations that often consist of procedures that involve other organ systems and that may be followed by a non-negligible complication rate is still debated. The Scottish Randomised Trial in Ovarian Cancer surgical study examined the impact on progression-free survival (PFS) of cytoreductive surgery and international variations in surgical practice in 889 patients [8]. One of the main conclusions of this study was that the increased PFS associated with optimal surgery is limited to patients with less advanced disease, supporting case selection rather than aggressive cytoreduction in all patients irrespective of disease extent. As so eloquently worded by two most prominent gynecologic oncologists [9]: “Many feel that the pendulum is now swinging toward … either neoadjuvant chemotherapy or less than ultraradical debulking among women with advanced ovarian cancer”.

Survival is not compromised with neoadjuvant chemotherapy but there is as yet no good evidence that for women with advanced epithelial ovarian cancer, it is superior to conventional cytoreductive surgery and platinum-based chemotherapy. Yet this approach does distinguish between responders and nonresponders to standard platin/taxan chemotherapy. Whether cytoreductive surgery is of value in nonresponders or whether they should be offered alternative chemotherapeutic agents or experimental treatment modalities remains to be proven.

Currently, objective responses are observed in approximately 60-80% of patients after initial surgery and standard adjuvant chemotherapy, but ultimately more than 80% of them recur. Each one of the subsequent lines of chemotherapy regimens has a different toxicity profile, and requires intensive monitoring and frequent hospitalizations for management of side-effects. The response rates to additional chemotherapy regimens are similarly low and can induce tumor remission in 20% to 30% of patients but after relapse the median survival time is only about two years. Patients with recurrence are not curable, complete responses are very rarely reported and long lasting responses are very seldom observed. Therefore the goal of salvage chemotherapy is palliation. How many additional cycles of chemotherapy should be used in patients with platinum-refractory or platinum-resistant recurrence has not been prospectively studied and their benefits over palliation have not been proven [10]. Some authors are of the opinion that continuous provision of futile cure-oriented therapy at the end of life is rarely justified [11] and that it involves significant cost increase with no appreciable improvement in survival [12].

The relatively few studies that assessed effect of ovarian cancer and its treatment on the patients and their caregivers [13] indicate that significant alterations occur in the quality of life of patients during treatment and follow-up. Long-term survivors of ovarian cancer frequently experience chronic fear of disease recurrence, significant sexual dysfunction, and identity disturbances [14]. Today many aspects of patient care such as emotional support, helping with daily activities, administration of medications and of special nutrition, rely on family, community, and social service

resources. These stressful demands and responsibilities have major emotional and physical impact on caregivers as well. Quality of life endpoints should be included in clinical trials of cancer therapies to supplement standard endpoints such as tumor response and overall survival.

How much have the aggressive surgical approach and modern initial and salvage chemotherapy regimens contributed to an improvement in outcome?

The US Survival, Epidemiology and End Results (SEER) cancer database is the most comprehensive source of information on cancer incidence and survival in the USA. It covers about 26% of the United States population, uses several quality control measures, ensures accuracy, completeness of reporting and is considered the standard for quality in cancer registries around the world.

Barnholtz *et al.* [15] used the SEER database to examine overall survival in 32,845 EOC patients from 1973 to 1997, with follow-up through the end of 1999.

Only a 4% increase in 5-year relative survival from 39% in 1980-1989 to 43% in 1990-1997 ($p \leq 0.05$) was observed. Women who were older than 60 years had a significantly worse prognosis than those who were younger than 60 years at the time of diagnosis. Chan JK *et al.* [16] also estimated the change in the 5-year disease-specific survival rates of 26,753 women with non-clear cell EOC during the14-year period 1988-2001 (across three intervals, 1988-1992, 1993-1997, and 1998-2001) registered in the SEER database. An overall increase in overall survival from 42.5% to 45.8% and in patients with advanced stage (III-IV) disease from 25.4% to 29.4% ($p < .001$) was observed. No improvements were observed for clear cell carcinoma. Although the increases in both studies are statistically significant they are small, consist of only about 4-5%, and may not be clinically notable. Chan *et al.* [17] also analyzed the outcome of 6,152 early stage (I-II) EOC patients during 1988-2001 obtained from the SEER database. A non significant ($p = 0.076$) increase in the 3-year disease-specific survivals across the above-mentioned three intervals (from 86.1 to 87.2 to 88.8%) was observed. Of those early-stage patients who underwent staging procedures with lymphadenectomy, there was also no improvement in survival over the three study period intervals (from 93.2 to 93.5 to 93.1%; $p = 0.978$). This is in line with a recent prospective randomized study that found that in women with advanced ovarian carcinoma who were optimally debulked systematic pelvic and aortic lymphadenectomy improves PFS but not overall survival [18].

The SEER cancer database demonstrates a marginal improvement in the death rate of women with ovarian cancer from 10 per 100,000 of the population to just over 9 per 100,000 [19] over the 30 years preceding 2003.

Similar outcome results were seen in smaller European registries. Data of 4,564 ovarian cancer patients (including non EOCs) documented from 1978 to 2000 in the Munich Cancer Registry [20] showed an improvement in survival in Stage I and II. However only a 6% improvement was seen in overall relative 5-year survival of ovarian cancer. It increased from 42.9 during 1978-1988 to 49.0% after 1998. As in other studies relative survival decreased with increasing age at time of diagnosis. Gondos A *et al.* [21] examined age-specific trends in 5-year relative survival of 2,260 ovarian cancer patients from 1979 to 2003, using data from the population-based Cancer Registry of Saarland, Germany. They found an improvement of 14%, mainly due to increased survival in the younger age groups (< 54 years). Analysis according to stage and histological type, important confounders that might influence outcome, is not reported in this study. Thus the improvement in the younger age group is possibly due to the modern effective treatment of non-EOC tumors prevalent in this age group.

According to the latest ovarian cancer statistics from the statistics team of GLOBOCAN 2002, a hardly noticeable decrease in mortality throughout the period from 1975 to 2005 is seen in the United Kingdom (Figure 1).

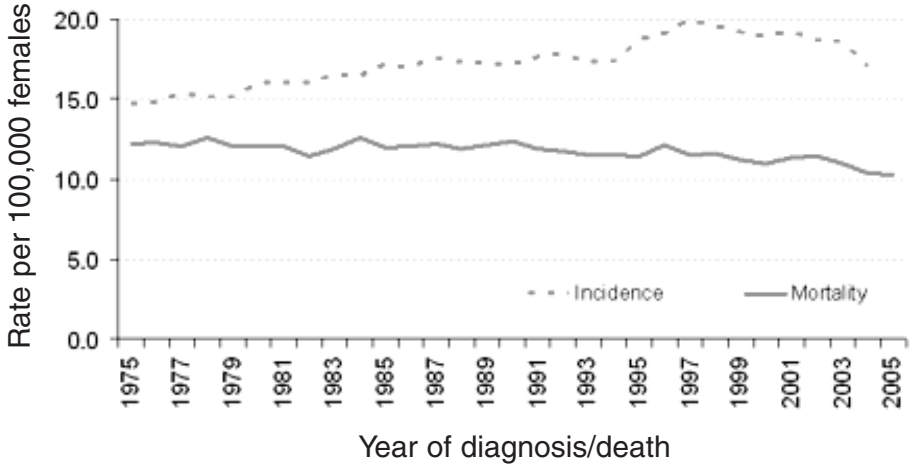

Figure 1. — Age-standardized (European) incidence and mortality rates, ovarian cancer, GB, 1975-2005.

The FIGO Annual Report on the results of treatment in gynecological cancer includes survival results of EOC from individual institutions in five continents. The overall absolute survival of patients during the period 1990-1992 was 41.6% and during the period 1996-1998 it increased by about 5% and was 46.4% [22].

In Israel during the period 1998-2004 about 300 new ovarian malignancies were diagnosed yearly and about 230 deaths from this malignancy occurred each year [23].

It thus seems that the advances in ovarian cancer have not translated into a considerable increased survival and most patients with epithelial ovarian cancer still die of their disease.

These gloomy results of the treatment outcome of ovarian cancer are not presented in order to dishearten gynecologic oncologists who daily relentlessly deal with ovarian cancer, but are intended to encourage accelerated research leading to the detection of 1) Highly specific effective methods for early detection of ovarian cancer; 2) A better understanding of the natural history of ovarian cancer, the biological and immunological processes leading to its oncogenesis and to the ability to harness them for prevention and treatment of this malignancy and 3) Identification of novel effective drugs and methods that will allow more effective individualization of treatment according to biological properties of the tumor.

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