Epithelial Ovarian Cancer: Not So Asymptomatic

It is imperative to correlate the potential symptoms of ovarian cancer and make a prompt diagnosis of this often aggressive disease.

By Diane M. Provencher, MD

Part I: Anatomy and Biomechanics – Hip Anatomy

In industrialized countries, epithelial ovarian cancer is the fifth most frequent cancer in women, next to breast, lung, colorectal and endometrial cancer. It is, however, the most lethal form of gynecological cancer. Risk factors include: infertility; number of ovulation; family history of ovarian, breast, or colon cancer; caucasian, use of talcum powder in personal hygiene. Oral contraceptives, multiple pregnancies and hysterectomy also seem to have a protective effect.

Ovarian cancer develops slowly. The average age of onset is 56, and, in many cases, patients are already at stage III or stage IV at the time of diagnosis. Despite a broad therapeutic arsenal, the mortality rate has remained stable over the past 20 years. Fewer than 20% of women afflicted with invasive epithelial ovarian cancer live more than five years after diagnosis. Since the introduction of the paclitaxel/platinum combination as a first-line adjuvant therapy, the median survival rate has jumped from 24 to 36 months. Access to second, third- and fourth-line treatment will yield valuable therapeutic options, which, depending on the clinical context, may allow patients to maintain a better quality of life and to live longer.

A subset of ovarian cancer has presented the challenge of identifying and managing individuals or families where ovarian cancer is hereditary. Roughly 8% to 10% of all

ovarian cancers fall into this category. Currently, individuals and families at risk are identified based on a patient's maternal and paternal family history, going back at least three generations. There is a pressing need to determine the natural history of this subgroup, measure the impact of medical interventions and dispel the uncertainty surrounding the bio-psycho-socio-legal intricacies that accompany the disease.

With the emergence of molecular biology as a dominant force in the field of clinical medicine, the future is promising. Genealogical trees, molecular histopathology and gene intervention testify to the progress this discipline has achieved. At the same time, legal, social and ethical issues are becoming increasingly important. No matter how complex ovarian cancer is, it deserves the research support offered by various funding organizations, in an effort to eradicate this disease.

Asymptomatic Screening versus Early Screening

Early diagnostic methods of screening for ovarian cancer are limited. Abdomino-pelvic ultrasounds combined with measurements of blood antibodies, (e.g., Ca-125) in 22,000 asymptomatic post-menopausal women detected 11 cases of ovarian cancer, including only three early-stage cases.[1,2] Nevertheless, these screening techniques are being assessed for women in whom there is a suspected family predisposition. Unfortunately, we currently are too often faced with a fait accompli (i.e., widely disseminated ovarian cancer to the abdominal cavity).

Over the course of a six- to 12-month period preceding the diagnosis of ovarian cancer, more than 95% of women describe multiple symptoms, including, abdominal discomfort (77%), gastrointestinal problems (70%), pain (58%), discomfort (50%), urinary dysfunction (34%) and vaginal discomfort (26%).[3] It is, therefore, erroneous to believe that ovarian cancer is asymptomatic. Any woman who has vague abdominal or pelvic discomfort that she has not felt before, particularly if she is in her perimenopausal or menopausal stage of life, should undergo at least an abdominal and pelvic clinical examination (i.e., vaginal and rectovaginal), or have a workup with ultrasound or a computerized tomography (CT) scan done, along with the blood marker Ca 125.

The treatment scenario for a presumed urinary tract infection, followed by an investigation for diverticulosis or irritable bowel, stress, fatigue, gastritis and possible depression, combined with appointment delays, means that the patient may not be operated on until six months, or a year, following diagnosis.

By this time, the patient may present with deterioration in her nutritional condition, in addition to progressing ovarian cancer. These delays reinforce the idea that ovarian cancer can be detected only at a late stage, leading to a shortened life expectancy.

Dr. Provencher is assistant professor, department of obstetrics and gynecology, division of gynecology, Universite de Montreal, and gynecologist/oncologist, CHUM, Notre-Dame Hospital, Montreal, Quebec. She specializes in molecular factors of ovarian cancer and clinico-molecular impact of familial predisposition.

Ovarian Cancer Management

When one or more adnexal masses are discovered, surgical management should be rigorous, and, preferably, carried out by a specialized team. Whether this involves a laparoscopy or a laparotomy, the challenge remains the same—histological confirmation of the diagnosis, accurate staging, maximum cytoreduction, and, in certain cases, interval surgery following neoadjuvant chemotherapy.

The technical criteria for these procedures are well defined,[4,5] and observing them will optimize your patients' survival and quality of life.

Prognosis and Treatment

Making an accurate prognosis is important, given the limited survival rate for advanced ovarian cancer. The following is a review a number of prognostic factors, some of which can be modified by the attending team:

- Stage[6]
- Post-surgical residual disease
- Tumor characteristics[7]
- Ca 125 result after three treatment cycles[8]
- Age and level of performance at time of diagnosis[9,10]
- Adjuvant therapy

Staging. The International Federation of Gynecology and Obstetrics (FIGO) described the possible clinical extension of ovarian cancer in 1964.

In 1985, it reviewed its considerations, and tried to describe ovarian cancer as evaluated at the time of surgery. Staging allows one to compare the results of various studies, evaluate the choice of treatment and determine a prognosis. It should be noted that, at the beginning of an investigation, when a stage has been assigned to a patient's cancer, it remains unchanged

Table 1

Survival at 5 Years and Stage-By-Stage Frequency At Time of Presentation

Stage	Survival at 5 Years (%) (Borderline Tumor Included)	% Frequency
I	82.4 - 92.1	30.1
II	51.4 - 69.0	9.9
III	17.1 - 39.3	31.7
IV	11.6	28.3

Adapted from Nugyen HN, et al. Cancer 1993; 72:3007(5).

throughout the disease. A recurrent ovarian cancer will be referred to as stage I-C, for instance, rather than as a carcinoma that has become stage III.

The statistics presented in Table 1 include ovarian cancers of low potential malignancy, or borderline tumors. The borderline tumor is a pathology that behaves in a different manner, and, which, in itself, could be the subject of an entire presentation. Dr. Alex Ferenczy described it, saying: "If a patient dies from a borderline cancer, you can be sure that she had a borderline pathologist." If borderline cancers are omitted from these statistics, the overall survival rate at five years drops from 35% to 20%.

The stage of the disease has an important impact on the choice of adjuvant treatment. It is particularly important, therefore, to determine the stage of the cancer. Guidelines for surgical staging have been published.[4] It appears that only between 52% or 35% of patients operated on by generally trained gynecologists and general surgeons are evaluated correctly.[5,11] All too often, inaccurate surgical staging leads to suboptimal adjuvant treatment, false reassurance, or needless, and potentially dangerous, treatment. In this respect, the appearance of leukemia in 5% of patients who have received cis-platinum/cyclophosphamide or etoposide (VP-16) is significant. Multidisciplinary specialized teams should be called upon when fighting ovarian cancer. This recommendation applies to both early-stage and late-stage ovarian cancer. In the former case, oncological principles must be adhered to, so as not to underestimate, or overestimate, the stage of the disease. In the event of late-stage cancer, it is a matter of providing optimal cytoreduction (surgical with adjuvant treatment) and quality of life, while limiting morbidity.

Tumor Characteristics may be studied under various angles: cell aspect, histology, grade, ploidy and the presence of dense adhesions or ascites.[6] It seems that only the

morphometric aspects of a cell (i.e., its average nuclear surface) have statistically significant prognostic values in ovarian cancer cases.[7]

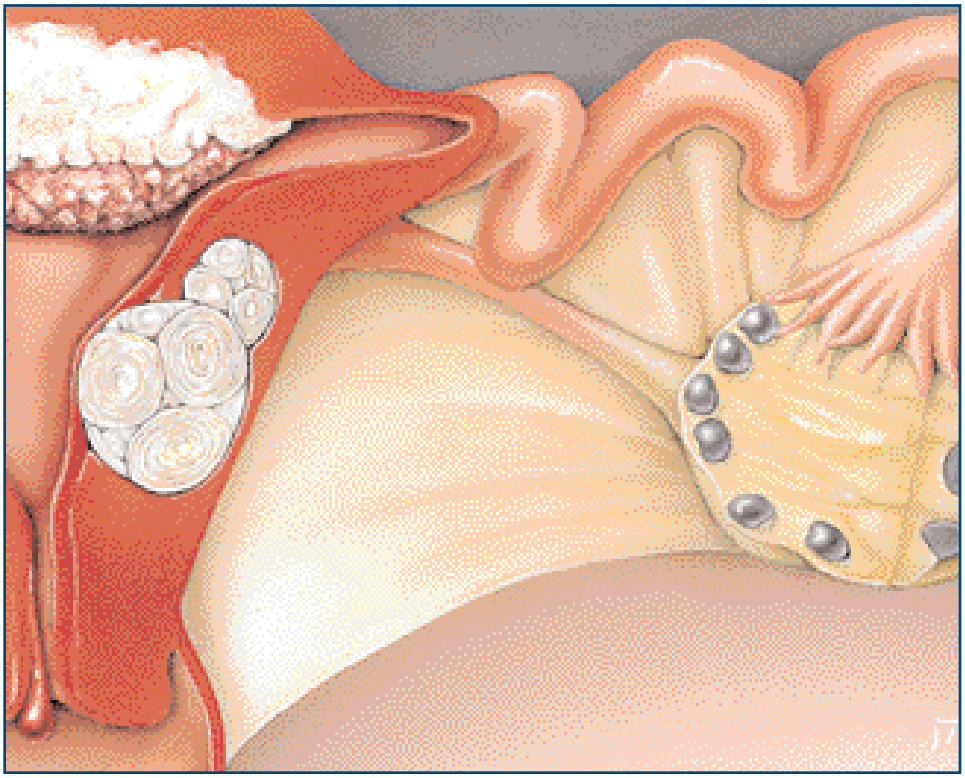
Diploid tumors seem to have a certain advantage, as compared to aneuploid tumors. This variable was confirmed prognostically by a number of brief clinical studies, however, such evaluations are rarely available.

The World Health Organization (WHO) has identified histological subtypes, based on whether tumors affect the tube, endometrium or endocervical epithelium, or upper vaginal wall. Determining a histological subtype is somewhat subjective. Apart from clear cell tumors, the histological subtype, currently, has no prognostic value in itself, but it does have biological characteristics. These subtypes will not be considered when choosing adjuvant therapy. For instance, mucinous and endometrioid tumors often are confined to the ovaries, where a more complete resection can be performed. Serous subtypes also show a number of psammoma bodies, as well as more aggressive tumor behavior with frequent and voluminous ascite formation.

While "stage" refers to the anatomical extensions of the disease, the term "grade" reflects cellular morphology and percentage of solid epithelial growth of a tumor. Broder's grades also have been defined by the WHO.[12] The grade, however, is subject to too much variability of interpretation to have an independent prognostic value. On the other hand, it has a special value for stage I tumors, in which grade I and II tumors often do not involve adjuvant treatment, provided the staging is complete.

Post-surgical Residual Disease. When it was discovered that ovarian cancer was chemosensitive, the door was opened to surgical cytoreduction.[13] This type of surgery differs from classic oncological surgery, where tumors are removed in toto, with an adequate margin of safety. Ovarian cancer is a peritoneal-surface disease, which allows no adequate margin of safety, except in the case of ovarian tumor masses. The high incidence of post-surgical residual tumors is a significant independent prognostic factor. The largest residual disease correlates to poorer survival. It may reflect a tumor's intrinsic biology, or the surgeon's skill.[14] So-called dense adherences (i.e., those bands requiring sharp dissection and containing microscopic neoplastic elements), as well as ascites, are controversial elements with respect to prognostic value.[3,15,16]

For patients who have undergone only "open-close" type surgery, the prognosis is not encouraging. For this situation, initial cytoreduction versus post-neoadjuvant chemotherapy interval cytoreduction is a concept that is generating much enthusiasm, and, currently, is being studied.[17] It is hoped that gynecologists/oncologists will be able to identify respectability indices, which would enable them to better select optimal used clinical strategies. For instance, a patient with a serious medical condition, or one who shows radiological evidence of a major disease affecting the suspensory ligaments of the liver, could benefit from interval surgery. This type of surgery would allow for delayed, complete cytoreduction with less morbidity and what is believed to be just as good a chance of survival with the same progression-free interval (i.e., the interval prior to recur-



rence).[17] The benefits of maximum cytoreduction (initial or interval) are evident as an independent prognostic factor. The benefits also are apparent in terms of median survival, subsequent response to chemotherapy, progression-free interval and quality of life, even in the case of stage IV ovarian cancer. A second screening is no longer needed as part of routine ovarian cancer management, since it does not alter survival. It may, however, be justified in special situations.

Ca 125 after three treatment cycles. Ca 125 is elevated in 75% to 90% of ovarian cancer patients.[18] Ca 125 is a glycoprotein consisting of two antigen fields (A and B) recognized by OC 125, a murine antibody produced in BALB/c-type mice that have been immunized with OVCA-433 cell line, derived from ovarian cancer cells from the tumor of a serous papillary-type ovarian cancer patient.[18]

In the pre-operative period, the Ca 125 has a sensitivity of 80% and a positive predictive value of 73%. Its value, however, is proportional to the size and grade of the tumor mass. More than 50% of patients with stage I ovarian cancer will have a normal Ca 125,[18] which means the test does not provide effective screening, even when combined with a pelvic ultrasound.[1] An elevated Ca 125 value can be used as an independent prognosis marker in patients with a stage I carcinoma. If in excess of 65 U/mL prior to surgery, such patients may need adjuvant treatment.[18]

Following surgery, the Ca 125 correlates with clinical progression. It is useful to monitor response and follow-up. Normal readings within three treatment cycles are

associated with better survival. After two chemotherapy cycles, if the Ca 125 is higher than 70 U/mL, survival is estimated at 12 months. If over 100 U/mL after three cycles, the survival estimate is seven months. If under 10, survival can reach five years or more. Conversely, a value that declines, but remains high after three treatment cycles does not justify changing treatment once chemotherapy is completed.

In the observation period, a normal value offers no higher than 40% of sensitivity. An elevation of Ca 125 seems to precede the emergence of clinical signs of recurrence by three to eight months (sensitivity of 96%).[18] The impact of early ovarian cancer recurrence treatment in cases where the Ca 125 is increasing, but where there is no demonstrable disease, is controversial within the medical practice, as well as an emotionally charged issue for patients, to say the least. The addition of other tumor markers is being investigated, both for screening and early detection of recurrence.

Age at Diagnosis. A patient's age and how well she copes physically correlate with survival. A woman under the age of 69, with a Karnofsky score of higher than 70%, will be more likely to respond to treatment. She will suffer less toxicity and have a better survival rate.[9]

Adjuvant Treatments. Maximum cytoreductive surgery (initial or interval) remains the best treatment approach in patients with ovarian cancer. It has an undeniable impact on chemotherapy, even if treatment is limited to removing necrotic tissue or tumor cells in the quiescent phase (G0 phase), and increasing vascular perfusion to help diffuse the agents.

Patients often worry when they hear the term "chemotherapy." Paradoxically, ovarian cancer chemotherapy improves a patient's quality of life by reducing the number, and intensity, of intestinal subocclusion attacks that are so typical of the disease.

Since cis-platinum became available for ovarian cancer treatment in 1979, many efforts have gone into improving patients' survival. Today, the initial treatment standard is based on a combination of paclitaxel 135 mg/m2 over three hours/platinum (cis-platinum or carboplatin AUC $\geq$ 4) for four to eight cycles. Attempts to increase doses, even with marrow support, have failed to increase survival. New agents that inhibit deoxyribonucleic acid (DNA) repair, such as topotecan, gemcitabine and liposomal/daunorubicin are believed to be effective when taken with platinum, and are under evaluation as the initial treatment of ovarian cancer. They are good substitute agents in cases of recurrence, with response rates for sensitive or resistant pathology (defined whether recurrence is observed prior to or after six months from completion of initial therapy) varying from 17% to 34%. Despite a fairly good response rate, long-acting oral etoposide (VP16, 50 mg/m2/day x 21 days), poses a risk of secondary myelodysplasia and acute leukemia. The level of risk varies according to the cumulative dose and treatment duration. All these agents can be toxic. It is, therefore, strongly suggested that only specialized health-care teams be responsible for such patients.

Currently, loco-regional radiotherapy is seldom used in the treatment of ovarian cancer, due to its toxicity. It is expected to become increasingly important, given the

interesting developments in that area.

Hormone Treatment

Hormone replacement therapy (HRT). There is controversy over the data correlating HRT with the risk of ovarian cancer. It is currently widely believed that women who have had ovarian cancer should not be prevented from taking HRT after appropriate counselling.[19] Research is rare when it comes to guiding the decision for, or against, the use of HRT in women who are genetically predisposed to ovarian cancer. It is known that these women have an even higher predisposition to breast cancer. As a result, decisions on HRT are made strictly on an individual basis.

Contraception. The use of oral contraceptives reduces the risk of ovarian and endometrial cancer in women who have a family predisposition to carcinoma of the ovary.[20] According to retrospective studies, oral contraceptives do not raise the overall risk of breast cancer.[21]

Genetic screening

Among all known factors, family history and age pose the greatest risks of developing ovarian cancer. Approximately 8% to 10% of all epithelial ovarian carcinomas are the result of a familial predisposition due to so far few known genes that have already a mutation on one allele at birth, leading to increased dominant autosomal susceptibility. These genes are involved in the cell cycle, but their precise functions are highly variable and remain unexplained.

A distinction should be made between two main hereditary manifestations of ovarian cancer:

- The family breast/ovary syndrome (BRCA1-2 genes); and
- Hereditary nonpolyposis colorectal cancer (HNPCC) (also known as Lynch's syndrome).

In more than 70% of cases, family ovarian cancer is attributable to a mutation in the BRCA1 or BRCA2 genes, which were discovered in 1994 and 1995. Their phenotypes correspond to a histological subtype, which is usually seropapillary or endometrioid, and seldom affects younger women. On rare occasion, it can be manifested as a borderline tumor, or Fallopian tube cancer. There is a strong association (90%) with breast cancer (i.e., hereditary breast/ovarian cancer syndrome). If ovarian cancer appears in the context of family colon and endometrial cancer before the age of 45, it points to HNPCC syndrome.

A review of the family history (both maternal and paternal) across three generations is now considered standard practice. The level of suspicion should go up if a patient:

1) Has at least one premenopausal women in her family diagnosed with breast cancer;

2) Has two relatives with breast and/or ovarian cancer;

3) Has multiple carcinomas in her family, one of which is breast cancer;

4) Has a family member has or has had colon cancer at an early age (< age 45);

5) Has rare types of cancer in her family (e.g., Fallopian tube carcinoma);

6) Has breast cancer in male members of her family; and

7) Is an Ashkenazy Jew.

The risk of neoplasia inherent in these mutations will be based on the penetrance of the gene and the target population (e.g.,

French Canadian, Ashkenazy, etc.). The risk perceived by the patient, however, is often quite different. The phrase: "The risk is in the eye of the beholder" has never been so true. Risk perception, the degree of cancerophobia, defense mechanisms, culture and instinct or individual projection, greatly contribute to the treatment decisions made by the patient. Interventions should aim at reducing anxiety, so that a truly enlightened decision can be made, based on the available clinical options. It is also important that we soon resolve patients' and physicians' uncertainty about the impact of prophylactic surgery, preventive chemotherapy and early detection tools. Treating these individuals is a challenge, especially since the clinical and biological-psychological-social-legal parameters of this hereditary predisposition are poorly defined.

Recommendations

• Keep a high level of suspicion: Any woman presenting with de novo abdominal or pelvic discomfort, particularly in pre-menopause or menopause, should be given an abdominal and/or pelvic examination (vaginal and rectovaginal) or an ultrasound/CT scan, and Ca 125 testing to rule out ovarian cancer.

• Surgical management should be rigorous, both for staging and cytoreduction. The established criteria must be observed.

• A patient with ovarian cancer (with or without a family history of the disease) should be treated by a specialized team.

• Expert opinion suggests that women who have had ovarian cancer should not be deprived of HRT after appropriate counselling.

• Obtaining a family history (both maternal and paternal) across three generations is now standard practice. Dx

References

1. Jacobs I, Davies AP, Bridges J, et al: Prevalence screening for ovarian cancer in post-menopausal women by Ca 125 measurement and ultrasonography. Brit Med J 1993; 306:1030-4.
2. Dembo AJ, Davy M, Stenwig AE, et al: Prognostic factors in patients with stage I epithelial ovarian cancer. Obstet Gynecol 1990; 75:263-73.
3. Déclaration de principes: Directives concernant la laparoscopie de la masse annexielle. SOGC, septembre 1998, numéro 76.
4. Goff B: SGO Communication. Abstract. Gynecol Oncol, San Diego, March 2000.
5. Young RC, Decker DG, Wharton JT, et al: Staging laparotomy in early ovarian cancer. JAMA 1983; 250:3072.
6. Ngyen NH, Averette HE, Hosking W, et al: National survey of ovarian carcinoma VI. Critical assessment of current International Federation of Gynaecology and Obstetrics staging system. Cancer 1993; 72:3007.
7. Geisler JP, Geisler HE, Wiemannt MC, et al: Nuclear shape; an independent predictor of survival in patients with ovarian carcinoma. Int J Gynecol Cancer 1998; 8:164.
8. Morgensen O: Prognostic value of Ca 125 in advanced ovarian cancer. Gynecol Oncol 1992; 44:207-12.
9. Thigpen T, Brady MF, Omura GA, et al: Age as prognostic factor in ovarian carcinoma. The Gynaecological Oncology Group Experience. Cancer 1993; 71:S606.
10. Ries LAG: Ovarian cancer: Survival and treatment differences by age. Cancer 1993; 71:524-9.
11. Mc Gowan L: Patterns of care in carcinoma of the ovary. Cancer 1993; 71(S2):628.
12. Broders AC: Carcinoma: Grading and practical application. Arch Pathol 1926; 2:376-81.
13. Griffiths CT: Surgical resection of tumour bulk in the primary treatment of ovarian cancer. Nat Cancer Inst Mon 1975; 42:101.
14. Smith-Sorensen B, Kaern J, Holm R, et al: Therapy effect of either paclitaxel or cyclophosphamide combination treatment in patients with epithelial ovarian cancer and relation to TP53 gene status, Br J Cancer 1998; 78(Suppl.3):375-381.
15. Vergote I, Fyles A, Bertelsen K, et al: Analysis of prognostic factors in 1287 patients with FIGO Stage I invasive ovarian cancer. Proc ASCO 1999; p. 1389.
16. Makar AP, Baekelandt MD, Tropé C, et al: The prognostic significance of residual disease, FIGO substage, tumour histology and grade in patients with FIGO stage III ovarian cancer. Gynecol Oncol 1995; 56:175-80.
17. Van der Burg MEL, Van Lent M, Buyse MBA, et al: The effect of debulking surgery after induction chemotherapy on prognosis in advanced epithelial ovarian cancer. N Engl J Med 1995; 332:629.
18. Prognostic factors in epithelial ovarian cancer. CME J Gynecol Oncol. Eds Peter Bosze, Georges D. Wilbauls et Terezia Barabas. Volume dedicated to Women's Cancer. Budapest, vol 4(1), 1999.
19. Conférence canadienne de consensus sur la ménopause et l'ostéoporose (The Canadian Consensus Conference on Menopause and Osteoporosis. SOGC), November 1998, Vol. 20, No. 13; December 1998, Vol. 20, No. 14.
20. Narod SA, Risch H, Moslehi R, et al: Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998; 33 :424-8.
21. Conférence canadienne de consensus sur la contraception. (The Canadian Consensus Conference on Contraception and Osteoporosis. SOGC), May 1998, Vol. 20, No. 5,6, June 1998, Vol. 20 No. 7, July 1998, Vol. 20, No. 8.