

Epithelial Ovarian Cancer: Prevention, Diagnosis, and Treatment

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Abstract

The leading cause of death from gynecologic malignancies in the United States is epithelial ovarian cancer. The significant risk factor for development of ovarian cancer is advancing age, although there is clearly a genetic predisposition—often associated with the BRCA1 and BRCA2 genes—in at least 5% to 10% of all epithelial ovarian cancers.

Oral contraceptives are known to reduce the risk for development of ovarian cancer and should be considered as a method of birth control in women at increased risk. Currently, there is no acceptable method of screening for this disease, although measurement of CA-125 level and transvaginal ultrasound have been utilized.

Ovarian cancer is a surgically staged disease. In apparent early-stage disease, complete surgical staging is critical for the selection of adjunctive therapy. In advanced-stage disease, the goal is primary cytoreduction.

Standard postoperative therapy for advanced-stage ovarian cancer includes platinum-based chemotherapy with the substitution of paclitaxel for cyclophos-

phamide occurring in the last decade. Despite these advances in chemotherapy, ovarian cancer continues to be fatal in far too many cases. (CA Cancer J Clin 1999;49:297-320.)

Introduction

Epithelial ovarian cancer continues to be the leading cause of death from gynecologic malignancies in the United States. The American Cancer Society estimates that in 1999, 25,200 new cases will be diagnosed and that 14,500 women will die of this disease.¹ In the past decade, the number of ovarian cancers has increased 30% and the number of ovarian cancer deaths has increased 18%.²

Ovarian cancer is difficult to diagnose at an early stage. Thus, most are at an advanced stage when discovered. Histologic confirmation of the diagnosis, surgical staging, and aggressive surgical debulking, when possible, are all part of the initial evaluation and treatment of this disease. In most cases, surgery is followed by chemotherapy.

Ovarian cancer usually portends a grave prognosis; however, in contrast to many metastatic epithelial cancers, a cure is possible in a subset of patients with advanced disease. In addition, the advent of effective chemotherapy that can be administered with less toxicity has provided an improved sense of well-being for many patients who are not ultimately cured.

It is important that physicians and other allied health personnel who provide care to women be familiar with ovarian cancer. This article reviews the im-

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portant points in prevention, diagnosis and treatment of this disease.

Risk Factors

As with many cancers, advancing age is the most significant risk factor for the development of ovarian cancer. The risk increases from 15.7 to 54 per 100,000 as one ages from 40 to 79 years.³ The mean age at diagnosis is 59.⁴ In the United States, approximately one woman in 70 develops ovarian cancer.

Other than age, the strongest risk factor for the development of ovarian cancer is a familial history of the disease. It is estimated that at least 5% to 10% of all epithelial ovarian cancers result from a hereditary predisposition in which germline inheritance of a mutant gene confers autosomal dominant susceptibility with high penetrance.⁵⁻⁷ The average age of onset for ovarian cancers thought to be familial in origin is significantly lower, up to 10 years, than that of ovarian cancer in the general population.^{7,8}

Analysis of familial ovarian cancer pedigrees and other epidemiologic studies have confirmed the existence of three ovarian cancer hereditary syndromes. All physicians should be aware of these hereditary manifestations because two of these syndromes include diseases not traditionally cared for by a gynecologist. The syndromes are: (1) breast and ovarian cancer syndrome, in which both cancers occur at a higher rate than they do in the general population and both occasionally occur in the same individual; (2) ovarian cancers associated with a higher rate of colorectal and endometrial cancers that define the hereditary nonpolyposis colorectal cancer [HNPCC] syndrome;⁹⁻¹³ and (3) site-specific ovarian cancer syndrome.^{8,9,11,14,15}

The site-specific syndrome probably accounts for only 10% to 15% of ovarian cancers, whereas the breast and ovarian cancer syndrome is present in 65% to 75% of all cases of hereditary ovarian

cancer.^{9,14} HNPCC syndrome also accounts for 10% to 15% of all hereditary ovarian cancer cases.⁹

Most breast and ovarian cancer families are linked to the BRCA1 gene.^{16,17} Those that are not linked to BRCA1 are probably linked to the BRCA2 gene.^{18,19} At least one study shows that essentially all families with site-specific ovarian cancer syndrome are linked to the BRCA1 gene, suggesting that these cancers are likely to represent manifestations of the breast and ovarian cancer syndrome in which early onset breast cancer has not yet appeared.¹⁵

The penetrance of BRCA1 mutations was estimated to be about 95%, providing a cumulative risk of about 63% for the development of ovarian cancer by age 70.⁸ More recent information, indicates that penetrance is not as great as initially thought and that modifying genetic loci may affect penetrance. Current estimates have been revised downward considerably and suggest a lifetime ovarian cancer risk of only 16% for carriers of either BRCA1 or BRCA2.²⁰

Another risk factor for this disease includes nulliparity, each pregnancy reducing the chance of developing ovarian cancer by 10%.²¹ Early menarche and late menopause are also known to increase the risk of development of this disease.²²

Oral contraceptive use reduces the risk for the development of ovarian cancer by 30% to 60%. A World Health Organization Study showed that the relative risk of ovarian cancer decreased as the duration of oral contraceptive use increased, with women using oral contraceptives for five or more years decreasing their risk by 50%.²³

Because lactation, pregnancy, and use of oral contraceptives reduce the risk of ovarian cancer whereas early menarche and late menopause increase the risk, it has been postulated that a greater number of ovulations leads to a greater number of repairs of the ovarian epithelium.

This results in a high risk for inadequate or aberrant repair, leading, in turn, to carcinogenesis. The observation that both tubal ligation and hysterectomy reduce the risk of ovarian cancer lends some credence to this theory.²⁴ It may be that this reduction is secondary to either an interruption of the ability of co-carcinogens to get to the ovary via the genital tract or a change in the hormonal milieu that in some way reduces the risk of carcinogenesis in the disrupted epithelium.

Prevention

Advancing age, the major risk factor for the development of ovarian cancer is, of course, unalterable. However, all physicians caring for women should consider ways to reduce the risk of developing ovarian cancer, especially because no effective screening method for this disease exists.

Because oral contraceptive use is known to decrease the risk for the development of ovarian cancer, it should be strongly considered as a method of birth control, particularly in women believed to be at increased risk. When permanent sterilization is contemplated, both tubal ligation and hysterectomy should be considered in light of some evidence that these procedures reduce the risk of developing this disease.

Prophylactic oophorectomy should be a consideration in women with a hereditary predisposition to ovarian cancer. Although an earlier study suggested that in these women the risk of developing intraperitoneal carcinomatosis after oophorectomy was substantial (as high as 10%),²⁵ a more recent report on a larger group of women suggests a rate closer to 1.8%.²⁶

A recent multi-institutional study suggested a 24-fold increase in "ovarian" cancer for women at risk who had not undergone oophorectomy compared with a 13-fold increase in "ovarian" cancer among women at risk who had under-

gone oophorectomy.²⁷ Because BRCA1 carriers have a substantially increased risk of developing of ovarian cancer, it seems clear that prophylactic oophorectomy can prevent ovarian cancer in these women.

The issues related to genetic testing—technical, ethical, legal, and psychosocial—are formidable and will continue to evolve over the next several decades. It has been suggested that families with a total of five or more breast or ovarian cancers in first- or second-degree relatives qualify as having the breast and ovarian cancer syndrome,¹⁶ as do families with at least three cases of early onset (before age 60) breast or ovarian cancer.¹⁷

Genetic testing should be considered in these families; however, it should be performed in conjunction with established research programs that have a certified laboratory, pre- and post-test counseling, and continued emphasis on the ethical, legal, and psychosocial aspects of genetic testing.

The American College of Obstetricians and Gynecologists suggested in 1994 that prophylactic oophorectomy should be considered in any woman with (1) two or more first-degree relatives with epithelial ovarian carcinoma; (2) a pedigree of multiple occurrences of nonpolyposis colon cancer, endometrial cancer, and ovarian cancer; and (3) a pedigree of multiple cases of breast and ovarian cancer.

In view of more recent findings, however, recommending referral of these women to established genetic research programs for evaluation and development of options now seems more prudent. This not only provides these women with evaluation by experts in the field but also allows a more rapid accumulation of knowledge in all aspects of genetic testing.

Screening

The five-year survival rate for ovarian carcinoma varies from 87.8% for stage IA disease to 18% for stage IV, suggest-

ing that early detection can decrease mortality.³

Early detection requires a reliable screening test. An optimal screening test has high sensitivity, specificity, patient acceptance and is easy to perform. The three screening techniques available at this time (pelvic examination, CA-125 level, and vaginal ultrasound) do not actually diagnose ovarian cancer but only suggest its presence; laparotomy is required for definitive diagnosis.

Based on the prevalence of ovarian cancer in the population, the positive predictive value of a screening test for ovarian cancer with a 99% specificity in women 45 to 75 years of age is estimated to be approximately 4%. This would lead to 24 negative laparotomies for each case of ovarian cancer detected. None of the single tests mentioned reaches this level of specificity.

PELVIC EXAMINATION

The pelvic examination, which is the current standard for screening women with ovarian cancer, has limited value because its sensitivity for detecting a mass measuring 4 by 6 centimeters is only 67%. A 15-year study evaluating pelvic examinations found six ovarian cancers in 1,319 women who underwent 18,753 pelvic examinations, further demonstrating the inadequacy of this method of screening.²⁸

CA-125 LEVEL

The most extensively studied tumor marker used in screening for ovarian cancer is CA-125, a high molecular weight glycoprotein recognized by the murine OC-125 monoclonal antibody as an immunogen. The normal level is 35 U/ml. CA-125 levels are elevated (greater than 35 U/ml) in 85% of epithelial ovarian cancers but in only 50% of patients with stage I disease, the stage at which intervention is most likely to have an impact on mortality.

The CA-125 can be elevated in several other disease processes, including endometriosis, pelvic inflammatory disease,

adenomyosis, liver disease, pancreatitis, peritonitis, and many other benign processes. It also may be elevated in a number of other malignant processes, including endometrial adenocarcinoma; biliary tract tumors; and hepatic, pancreatic, breast, and colon carcinomas. A recent review of several large studies using CA-125 and other markers concluded that the CA-125 does not have adequate specificity to warrant its use in mass screening for ovarian cancer.²⁹

The addition of other serum markers complementary to CA-125 may increase sensitivity, specificity, and positive predictive value.^{30,31} However, these other markers have not been tested in large trials and certainly increase the cost of screening.

It has also been suggested that serial determinations of a marker improve specificity and positive predictive value.³² A progressive increase in serum marker levels is more indicative of ovarian malignancy than is a single elevated marker level; however, this approach may prolong the detection of early-stage disease.

TRANSVAGINAL ULTRASOUND

Although transabdominal and transvaginal ultrasound have been investigated as noninvasive screening modalities, transvaginal ultrasound is the preferred method because of its superior ability to image the ovary. The major problem with transvaginal ultrasound is its lack of sufficient specificity. Morphologic scoring systems have been proposed to increase specificity. Criteria being studied include size/volume, papillary projections from the cyst wall, and cyst complexity. A large study of 3,220 women using transvaginal ultrasound and a morphologic index provided a specificity of 98.7% and a positive predictive value of 6.8%. Forty-four laparotomies were required to find three cancers, two of which were stage I.³³

Another proposed screening method is color Doppler imaging coupled with transvaginal ultrasound to de-

tect specific flow patterns related to malignant disease. The use of color flow Doppler is based on observed differences in vascularity associated with neoplasms. Low impedance in relation to flow, as reflected by a pulsatility index below 1.0, was demonstrated in 16 of 17 malignancies.³⁴ In contrast, the pulsatility index was 1.0 or higher in 35 of 36 cases of benign ovarian tumors. The sensitivity and specificity of the pulsatile index in identifying malignant tumors in this study were 94% and 97%, respectively.

A study of 1,600 women with a family history of ovarian cancer ended with 61 patients having a surgical procedure. Six ovarian cancers (five stage I, one stage III) and three tumors were considered to have low malignant potential.³⁵ Color flow Doppler is, of course, a more expensive technology, and its ability to differentiate early ovarian malignancies (stage I) from benign ovarian tumors is unknown.³⁶

A summary of five studies using transabdominal ultrasound, transvaginal ultrasound, morphologic index, and color Doppler indices in various combinations screened 11,283 women. Four hundred eighty-six of these women required laparotomy for definitive diagnosis. Twenty-two cases of cancer were found, 13 of which were stage I, five of which were invasive. This provides a specificity for ovarian cancer of 95.8% and a positive predictive value of 3.1.³⁷

Screening Recommendations

In 1994, a National Institutes of Health Consensus Conference on Ovarian Cancer concluded that there is no evidence that screening with CA-125 and/or transvaginal ultrasound can be used effectively to decrease ovarian cancer mortality or morbidity.³⁸ These tests are not recommended for routine screening at this time. The Prostate, Lung, Colon, and Ovary cancer screening trial sponsored by the National Cancer Institute is currently testing the efficacy of pelvic examination,

transvaginal ultrasound, and CA-125 level in detecting ovarian cancer in women between the ages of 55 and 74. Future recommendations await the completion of this prospective randomized trial.³⁹

WOMEN AT HIGH RISK

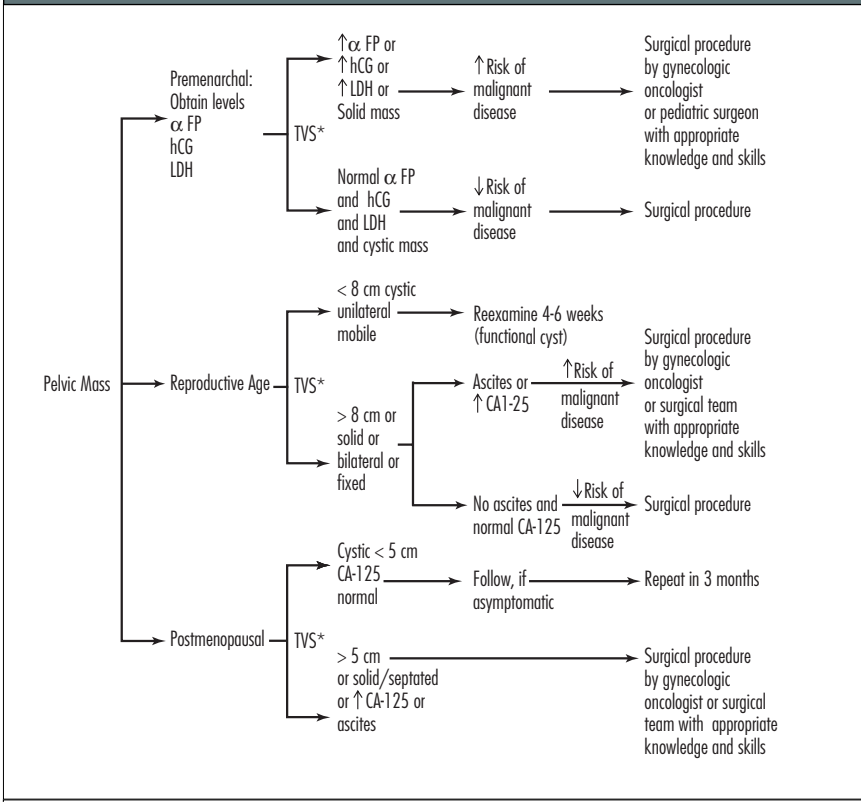
The appropriateness of screening women who are high risk based on genetic studies or family history continues to be debated. Measurement of serum CA-125 levels and transvaginal sonography have not been systematically studied in this group of women. Screening procedures may prove more effective in the early detection of ovarian cancer in women with genetic predisposition; however, clinical trials are needed to test this hypothesis. For now, the American College of Obstetricians and Gynecologists recommends an annual rectovaginal examination, CA-125 level, and transvaginal ultrasound in women at high risk until childbearing is complete or to age 35, at which point prophylactic oophorectomy should be considered.³⁸

Any physician who sees high-risk members of HNPCC families has an even more formidable challenge because of the numerous cancers seen in this group of patients. The consensus recommendations of the International Collaborative Group on HNPCC include the option of prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy in women who are undergoing subtotal colectomy following the diagnosis of colon cancer or in asymptomatic high-risk members of HNPCC families with severe cancer phobias.

Otherwise, surveillance guidelines for high-risk individuals include, in addition to colonoscopy procedures, endometrial curettage, transvaginal ultrasound, possibly Doppler color blood flow imaging of the ovaries, and serum CA-125 measurement annually after the age of 30.⁴⁰

The most recent recommendations for follow-up care in individuals with an inherited predisposition to cancer come from a task force convened by the Cancer

Figure 1
Management of a Woman with a Pelvic Mass



αFP=alpha-fetoprotein; hCG=human chonic gonadotropin; LDH=lactate dehydrogenase.
*Perform transvaginal ultrasound (TVS) only if needed to establish size or cystic nature of mass.

Genetics Studies Consortium, organized by the National Human Genome Research Institute.^{41,42} For patients with HNPCC-associated mutations, colonoscopy is recommended every one to three years starting at age 25. Endometrial cancer screening is also recommended.

The task force found insufficient evidence to recommend surveillance for ovarian cancer, but noted that some experts have recommended it. No recommendation was made for or against pro-

phylactic surgery (i.e., colectomy or hysterectomy), but such surgery is an option for mutation carriers.

Early breast cancer and ovarian cancer screening is recommended for individuals with BRCA1 mutations and early breast cancer screening for women with BRCA2 mutations. Again, no recommendation was made for or against prophylactic surgery (i.e., mastectomy or oophorectomy), although it remains an option for mutation carriers.

Signs and Symptoms

Traditionally, both lay and medical communities believed that early-stage ovarian cancer is usually asymptomatic. Thus, it has become known as the "silent killer."

Several studies, however, suggest that women with localized disease have symptoms that are quite similar to and frequent as those in women with advanced disease.^{43,44} Indeed, only 10% of patients are without any symptoms.

The most common symptoms are abdominal swelling, abdominal pain, intestinal symptoms, and vaginal bleeding. Almost all of these symptoms are non-specific. Therefore, all providers of care for women should consider the possibility of ovarian neoplasms when these symptoms persist. Diagnostic tests to be considered in addition to a pelvic examination include measurement of CA-125 and transvaginal ultrasound in patients whose symptoms persist and who have an otherwise normal pelvic examination.

Diagnostic Tests

The evaluation of a suspected pelvic mass should help determine whether the mass is likely to be malignant and who is the appropriate surgeon to perform diagnostic laparotomy when indicated (Fig. 1).

PREMENARCHAL GIRLS AND POSTMENOPAUSAL WOMEN

All masses, solid or cystic, found in premenarchal children and adolescents and in postmenopausal women should be considered abnormal and potentially malignant. Surgery is indicated in all of these patients. The only exception occurs when ultrasound in a postmenopausal woman with a normal CA-125 level reveals a completely cystic mass, smaller than 5 cm in diameter with no septations. When these criteria are met, the patient may be followed conservatively without laparotomy be-

cause the likelihood of malignancy is quite low. The tests should be repeated in three months to confirm that no change has occurred.⁴⁵

In premenarchal girls, all solid masses have the potential to be neoplastic. Germ cell tumors, not discussed in this review, should be strongly considered in this age group.

Tumor markers, including alpha-fetoprotein (α FP), human chorionic gonadotropin (HCG), CA-125, and lactate dehydrogenase (LDH), can help guide the surgeon to the most likely diagnosis. The level of α FP is elevated in endodermal sinus tumors, HCG is elevated in choriocarcinoma, and both are elevated in embryonal cell tumors. LDH and low levels of HCG are present in dysgerminomas. Surgical procedures in children and young women with solid masses and elevated tumor markers should be performed by gynecologic oncologists, or pediatric surgeons.

WOMEN OF REPRODUCTIVE AGE

Pelvic masses found in women of reproductive and postmenopausal age must be evaluated preoperatively to determine the probability of malignancy. This is important to ensure that the surgeon who performs the laparotomy has the appropriate skills and training to complete the necessary procedures.

A pelvic mass in a woman of reproductive age may be a functional cyst, particularly if the mass is cystic, less than 6 to 8 centimeters in diameter, unilateral, and mobile. If all of these criteria are present, it is appropriate to reexamine the patient in four to six weeks. If the mass persists or has grown, exploratory laparotomy is indicated.

A pelvic mass in a patient with a markedly elevated CA-125 level is likely to be cancer whatever the age of the patient. Certainly, a solid or partially cystic mass in a postmenopausal woman should be considered malignant until proven otherwise. A woman with a solid or par-

Table 1
International Federation of Gynecology and Obstetrics (FIGO)
American Joint Committee on Cancer (AJCC)
Staging Systems for Ovarian Carcinoma

Staging of ovarian carcinoma is based on findings at clinical examination and by surgical exploration. The histologic findings are to be considered in the staging, as are the cytologic findings of any effusions. Biopsy should be obtained from suspicious areas outside of the pelvis.

TNM	FIGO	
T1	Stage I	Tumor limited to the ovaries (one or both)
T1a	Stage IA	Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant cells in ascites or peritoneal washings*
T1b	Stage IB	Tumor limited to both ovaries; capsules intact, no tumor on the ovarian surface; no malignant cells in ascites or peritoneal washings*
T1c	Stage IC	Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
T2	Stage II	Tumor involves one or both ovaries with pelvic extension
T2a	Stage IIA	Extension and/or implants on uterus and/or tube(s). No malignant cells in ascites or peritoneal washings
T2b	Stage IIB	Extension to other pelvic tissues. No malignant cells in ascites or peritoneal washings
T2c	Stage IIC	Pelvic extension (2a or 2b) with malignant cells in ascites or peritoneal washings
T3 and/or N1	Stage III	Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis and/or regional lymph node metastasis
T3a	Stage IIIA	Microscopic peritoneal metastasis beyond pelvis
T3b	Stage IIIB	Macroscopic peritoneal metastasis beyond pelvis 2 cm or less in greatest dimension
T3c and/or N1	Stage IIIC	Peritoneal metastasis beyond pelvis more than 2 cm in greatest dimension and/or regional lymph node metastasis
M1	Stage IV	Distant metastasis (excludes peritoneal metastasis)

*The presence of nonmalignant ascites is not classified. The presence of ascites does not affect staging unless malignant cells are present.

Note: Liver capsule metastases are T3/stage III; liver parenchymal metastasis, M1/stage IV. Pleural effusion must have positive cytology results for M1/stage IV.

tially cystic mass, ascites, and/or an elevated CA-125 level should be operated on by a gynecologic oncologist or by a surgical team with the necessary skills to surgically stage or debulk the disease appropriately as well as knowledge of the natural history of the disease and the surgical approach to be taken in each case.

All surgeons who attend women with suspected ovarian malignancy must understand the need for and be able to perform appropriate surgical staging and debulking of ovarian cancer. The appropriate operative procedures for early- and advanced-stage ovarian cancer are discussed later in this article.

Staging

Ovarian cancer is a surgically staged disease. Most ovarian cancers are approached operatively unless a significant medical contraindication to the procedure exists. The staging schema is shown in Table 1. Since 1988, stage III disease has been subdivided into three substages based on the greatest dimension of upper abdominal disease prior to cytoreductive surgery. This information should be recorded in the operative report. It is essential that the appropriate staging procedures be performed, particularly in women with early-stage disease.

Surgical Treatment

The initial approach to the treatment of ovarian cancer is almost always surgical. The purpose of surgery is to establish or confirm the suspected diagnosis; to surgically stage the patient with apparent early-stage disease; and in the event of advanced-stage disease, to remove as much disease as possible—i.e., debulk or cytoreduce the tumor.

EARLY-STAGE DISEASE

Of paramount importance is the proper staging of women with malignant ovarian neoplasms visibly confined to one or both

ovaries or to the pelvis only. Prognosis is established and therapeutic decisions are made on the basis of the information obtained by this procedure. A thorough inspection and surgical evaluation of the upper abdomen and pelvis are necessary.

An organized approach to laparotomy is presented in Table 2. Any ascitic fluid should be removed and sent for cytologic study. In the absence of obvious ascites, peritoneal washings should be obtained from the right and left paracolic gutters, the pelvis, and the subdiaphragmatic areas.

The primary mass should be removed and sent for frozen section, if necessary, to establish the diagnosis. If fertility is not an issue, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed. Any masses or implants in the pelvis should be removed. If no mass is present in this area, biopsy samples of the right and left pelvic peritoneum, cul-de-sac, and bladder peritoneum should be obtained. When disease is confined to one or both ovaries or the pelvis, biopsy samples must be obtained from the pelvic and para-aortic nodes to complete the surgical staging and guide postsurgical treatment. Any disease noted in the omentum should be removed and, in the absence of gross disease, an infracolic omentectomy should be performed. A biopsy sample should be taken from the right hemidiaphragm or a scraping should be made with a sterile tongue blade, fixed to a glass slide, and sent for cytologic study.

Removal of a unilateral adnexa with preservation of the contralateral adnexa and uterus is appropriate in patients with apparent stage IA disease who want to maintain fertility. This conservative approach can be considered in women with epithelial cancers, borderline tumors, stromal tumors, and malignant germ cell tumors confined to one ovary (Fig. 2).

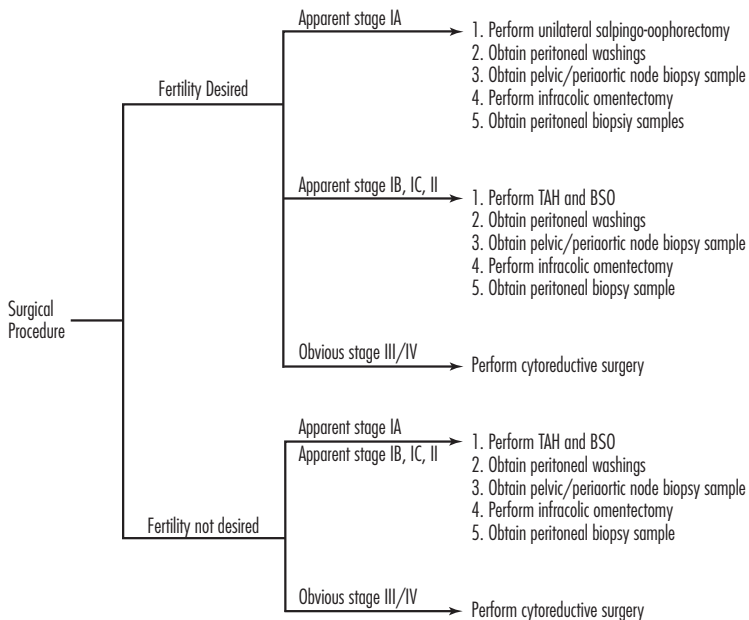
Surgical staging that includes all of these steps is essential in the care of

Table 2
Surgical Staging Procedure for Apparent Early-Stage Disease

Remove primary tumor intact, and send for frozen section evaluation, if necessary.
 If disease is apparently confined to the ovaries or pelvis:

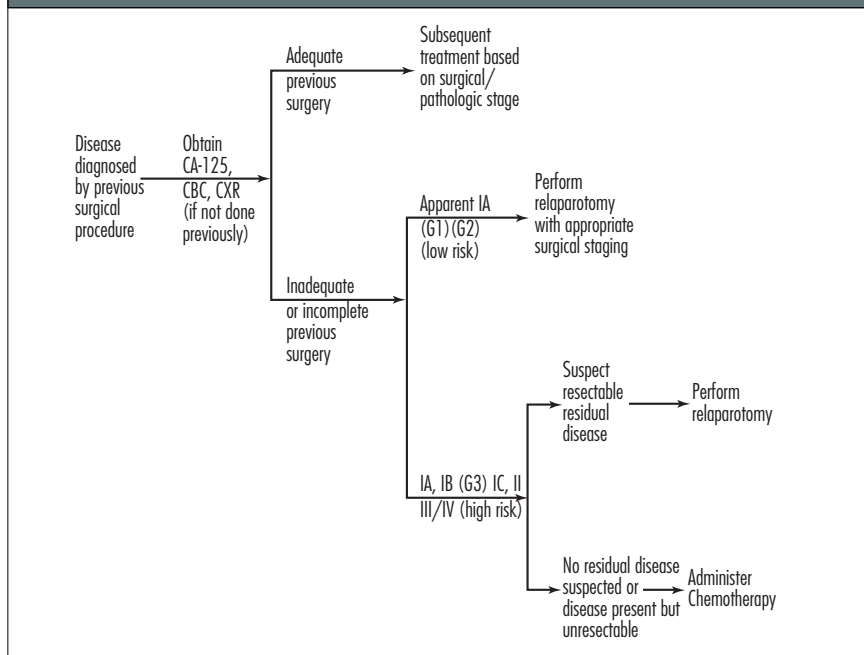
1. Thoroughly inspect pelvis and upper abdomen
2. Submit any free fluid for cytologic study
3. If no free fluid is present, obtain peritoneal washings
4. Obtain biopsy samples of any adhesions or suspicious areas. If none, biopsy multiple areas of the peritoneum
5. Evaluate the right diaphragm by biopsy or by cytologic study of scrapings
6. Perform infracolic omentectomy
7. Obtain biopsy samples of pelvic and periaortic lymph nodes

Figure 2
Selection of Surgical Procedure for Ovarian Cancer



BSO=bilateral salpingo-oophorectomy
 TAH=total abdominal hysterectomy

Figure 3
Management Algorithm for Patients Diagnosed with Ovarian Cancer by Previous Surgery



CBC=complete blood count; CXR=chest radiograph

women with early-stage disease. If the status of residual disease is unclear from the operative note or pathology report, reexploration with the appropriate evaluation should be considered before making definitive decisions about administering either adjunctive therapy or no treatment (Fig. 3).

Laparoscopy

Laparoscopy has been used as an alternative to open laparotomy even when masses are suspected of being malignant. In one study, laparoscopy was performed on 138 patients with suspicious adnexal masses based upon a combination of elevated CA-125 values, abnormal ultrasound findings, or a mass larger than 10

centimeters. Malignancies were found in 19 patients, and 14 (74%) were able to have surgery completed via the laparoscope.⁴⁶ The laparoscopic approach does increase the chance of rupturing the primary tumor and should be performed only by surgeons who are skilled in the open approach. More data are needed about the efficacy and safety of this approach before it is widely adopted.

ADVANCED DISEASE

In contrast to early-stage disease, the goal of surgery in obviously advanced disease is primary cytoreduction. Because ovarian cancer tends to remain confined to the peritoneal cavity and not to invade deeply or into the hollow or-

gans, it is often amenable to surgical resection. The superficial nature of the disease allows it to be removed in many cases without resection of major organs.

Patients whose largest residual disease is less than 1 to 2 centimeters in diameter have survival rates superior to those with a larger volume disease. Several retrospective studies have demonstrated this difference. A summary of these studies showed a median survival of 36.7 months in 388 patients whose tumors were cytoreduced to the optimal level versus 16.6 months in 537 patients with large-volume residual disease.⁴⁷

Unfortunately, these studies do not prove beyond question that cytoreductive surgery that leads to small-volume disease is the key element in increased survival. The ability to adequately debulk, and subsequent survival, may reflect the biology of the disease. However, given the preponderance of retrospective evidence that cytoreductive surgery is beneficial, most gynecologic oncologists and others who treat this disease regularly believe in its value. Only a randomized, prospective clinical trial could definitively answer the question, but practical and ethical problems make such a trial unlikely.

The definition of optimal cytoreduction has ranged from 5 millimeters to 3 centimeters. It has been demonstrated by the Gynecologic Oncology Group (GOG) that survival for patients with advanced ovarian cancer progressively decreases as the maximum residual disease increases from microscopic to 2 cm.⁴⁸ The GOG also found that the upper threshold at which no survival improvement takes place is 2 centimeters. Thus, 2 centimeters or less is accepted by most as the goal of cytoreduction.

The removal of all tumor should, of course, be the surgeon's initial goal; however, if this is not technically feasible, an attempt should be made to reduce residual disease to 2 centimeters or less. If this goal (i.e., 2 centimeters or less) is not pos-

sible, bowel resections or other aggressive surgical procedures should not be attempted.

The aggressiveness, patience, and training of the surgeon and his/her belief in the value of debulking determine the percentage of patients with advanced ovarian cancer who are optimally debulked. A summary of nine retrospective studies reveals that 42% of 925 patients were optimally cytoreduced;⁴⁷ however, in the most contemporary of these series, 87% of the patients were optimally cytoreduced.⁴⁹

Disease located in the pelvis can usually be optimally resected. Many patients will require only a total abdominal hysterectomy and bilateral salpingo-oophorectomy to accomplish this goal. Others, however, particularly patients with a "socked in" pelvis, will require radical pelvic surgery. This type of surgery includes a retroperitoneal approach and requires resection of pelvic peritoneum, cardinal ligaments, uterosacral ligaments, a portion of the sigmoid colon or rectum, and possibly partial resection of the lower urinary tract. Such surgery has been called radical oophorectomy, modified posterior exenteration, and reverse hysterocolposigmoidectomy.^{50,51}

Resection of a portion of the sigmoid colon and/or rectum is the most frequent ancillary component to total abdominal hysterectomy and bilateral salpingo-oophorectomy when pelvic disease is resected. With modern surgical stapling devices, most patients do not require a colostomy, and every consideration should be given to reanastomosis of the resected area.^{50,51} The bowel should be prepared both mechanically and with antibiotics before surgery.

The value of cytoreduction of the pelvic and paraaortic nodes in ovarian cancer is not completely clear. At least two studies have demonstrated a survival advantage in patients with advanced disease undergoing a lymphadenectomy.^{52,53} Another report, however, demonstrated

no difference in survival in patients with stage III and IV disease with negative, microscopically positive, or macroscopically positive nodes.⁵⁴

Although a randomized clinical trial would be required to prove the benefit of nodal resection in advanced ovarian cancer, performing a pelvic and paraaortic lymphadenectomy is probably reasonable in patients in whom optimal intraperitoneal resection has been performed.

Areas that cannot be entirely cytoreduced from a technical standpoint include liver and diaphragm agglutinated with disease, extensively diseased liver parenchyma, positive nodes above the level of the renal vessels with involvement of the superior mesenteric artery, an extensively diseased lesser sac of the omentum, and diseased mesentery of the small bowel causing agglutination of the mesentery in the central abdomen.

SECONDARY CYTOREDUCTION

Secondary cytoreductive surgery, defined as surgery performed following some form of chemotherapy, continues to be controversial. However, this situation can include a number of clinical scenarios, including repeat debulking after two to three courses of chemotherapy in patients whose initial debulking was suboptimal; resection of gross disease at second-look laparotomy following a completed course of chemotherapy; and resection of recurrent disease present at a time distant from that of primary chemotherapy.

Several studies have demonstrated a median survival benefit to optimal versus suboptimal resection in patients with gross residual disease at the time of second look, with the most dramatic differences seen in women in whom all gross residual disease was removed.⁵⁵⁻⁵⁸ However, again, in the absence of randomized clinical trials, it is unclear whether the surgical resection itself or the biologic nature of the disease leads to

increased median survival.

Patients with clinical evidence of disease immediately following a course of chemotherapy almost certainly do not benefit from secondary cytoreduction. No difference was seen in median survival in 32 patients optimally cytoreduced versus 45 patients with suboptimal cytoreduction at second-look laparotomy when clinical disease was present prior to the procedure.⁵⁹

Secondary cytoreduction may be beneficial in patients who have a significant disease-free interval following chemotherapy. Aggressive debulking in 30 patients who fit this category led to increased median survival in the 14 patients who could be completely resected. Significant factors for survival included absence of gross residual disease following secondary cytoreduction and a disease-free interval of 12 months or greater after initial therapy.⁶⁰

The issue of interval secondary cytoreduction after a response to a short initial course of chemotherapy in patients whose initial debulking was suboptimal awaits the results of a GOG randomized trial. A European study, however, suggests that interval debulking does increase survival.⁶¹

Currently, secondary cytoreductive surgery should be limited to patients being evaluated on protocol and those who have recurrent disease one year or more after initial treatment.

SECOND-LOOK SURGERY

The true second-look operation is a systematic surgical exploration in an asymptomatic patient who has completed a course of chemotherapy, has no clinical evidence of disease by physical examination and/or radiographic studies, and a normal level of CA-125. The rationale for this surgical procedure is to accurately determine the disease status so that appropriate subsequent therapy can be selected or first-line chemotherapy safely terminated.

There is no evidence, however, that second-look laparotomy is a therapeutic procedure. Retrospective studies comparing patients who underwent a second-look laparotomy with those who did not failed to show a difference in survival.⁶²

Many gynecologic oncologists no longer consider second-look laparotomy part of the routine care of women with ovarian cancer. Their position is strengthened by the realization that current standard second-line therapies are largely ineffective. Thus, second-look laparotomies are now confined to clinical trials evaluating innovative therapies and are not justified if only standard salvage management is anticipated.

Chemotherapy for Ovarian Cancer

EARLY-STAGE DISEASE

Two randomized clinical trials initiated in 1976 and 1978, respectively, examined the use of adjuvant therapy in early-stage disease.⁶³ The first trial included patients with stage IA and IB, grade 1 and grade 2 tumors. These patients were randomized to no further treatment or oral melphalan for 12 cycles. There were no significant differences in either five-year disease-free survival (91% versus 98%) or overall survival (94% versus 98%).

In the second trial, patients with stage I, grade 3 tumors and stage II tumors were randomized to 12 cycles of oral melphalan versus a single intraperitoneal dose of radioactive phosphorous (32P). Again, no difference was noted in five-year disease-free survival (80% in both groups) or overall survival (81% versus 78%).⁶³

Following the identification of platinum compounds as active agents in ovarian cancer, cisplatin was compared with 32P in two randomized trials. In the first trial, patients with stage IC disease were randomized to six cycles of cisplatin or a single dose of intraperitoneal 32P. No difference in overall five-year survival was demonstrated (81% versus

79%). However, patients who received cisplatin remained disease-free longer than those who received 32P, and patients in the 32P arm whose disease recurred were salvaged with cisplatin and attained the same five-year survival rate seen in other patients in the study. This suggests that platinum is the superior agent in early-stage disease.⁶⁴

In a second trial, patients with stages I, II and IIIA ovarian cancer received either six cycles of cisplatin or one dose of 32P. Again, no difference in five-year disease-free survival was noted (81% versus 75%).⁶⁵ The GOG randomized patients with high-risk, early-stage disease to three cycles of cisplatin/cyclophosphamide or a single dose of intraperitoneal 32P. While final results have not been reported, preliminary data suggest no difference in survival between the two groups.⁶⁶ A current GOG trial randomizes patients with stages I, II, and IIIA ovarian cancer who are at high risk for recurrence to three or six cycles of carboplatin and paclitaxel.

Based on the available data, several conclusions can be made regarding the management of early-stage disease. Appropriate surgical staging is critical in determining which patients can forego adjuvant therapy. Patients who have stage IA and IB, grade 1 and grade 2 disease do not require adjuvant chemotherapy and can anticipate long-term survival. Patients with stage IA and IB, grade 3, stage IC, or stage II disease should be treated with either three to six cycles of platinum-based chemotherapy or a single dose of intraperitoneal 32P.

A critical question that remains to be answered is whether adjuvant therapy is better for patients with high-risk early-stage disease than is continued observation with chemotherapy only for those who relapse. While the trials completed to date have not had an untreated control arm, a current study by the Italian Gruppo Interregionale Collaborativo in Ginecologia Oncologia randomizes patients to

observation versus six cycles of platinum. Preliminary results from this provocative trial suggest similar overall survival for the two arms.⁶⁷

***Quality of life issues
should be given strong
consideration in light of
the lack of data
demonstrating a clear
survival advantage for
second-line chemotherapy.***

ADVANCED DISEASE

Once a tumor has spread beyond the confines of the ovary, surgery alone is unlikely to provide adequate therapy. Chemotherapy is therefore used in addition to surgical resection. The most obvious effect of chemotherapy in the past 30 years has been an increase in the median survival from 10 to 12 months in the 1970s to 37.5 months with current combination regimens.⁶⁸ Although a temporary response rate to chemotherapy of 70% can be anticipated, the age-adjusted death rate for ovarian cancer has changed little since 1960.¹ Therefore, the optimal strategy for the management of advanced ovarian carcinoma leading to long-term survival is yet to be defined.

Combination Regimens

Epithelial ovarian carcinoma is a chemosensitive tumor. The use of single alkylating agents was emphasized until 1978, when the superiority of a combination regimen over single-agent melphalan was demonstrated. This randomized clinical trial compared melphalan with hexamethylmelamine, cyclophos-

phamide, methotrexate⁶⁹ and 5-fluorouracil (Hexa CAF).⁷⁰ Treatment with the four-drug regimen demonstrated an increased response rate (75% versus 54%) as well as longer median survival (29 versus 17 months).

Cisplatin and Doxorubicin

The late 1970s also witnessed the emergence of cisplatin as an active agent in the treatment of ovarian cancer. A GOG study reported in 1987 compared doxorubicin/cyclophosphamide with doxorubicin/cyclophosphamide plus cisplatin. The inclusion of cisplatin resulted in significantly increased response rate (76% versus 48% percent), progression-free interval (15 versus 9 months) and median survival (20 versus 16 months).⁷⁰

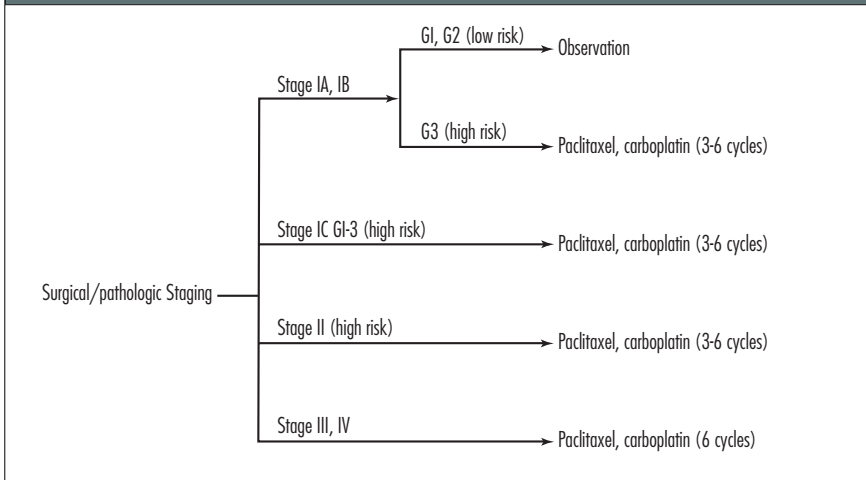
Four large randomized clinical trials subsequently examined the need to include doxorubicin in combination regimens, and all failed to demonstrate a significant survival benefit for this agent.⁷¹⁻⁷⁵ However, the contribution of doxorubicin in combination regimens continues to be debated.

A recent meta-analysis comparing cisplatin/cyclophosphamide with cisplatin/doxorubicin/cyclophosphamide has suggested a significant survival advantage, increased complete response rate, and increased frequency of negative findings at second-look surgery for doxorubicin-containing regimens.⁷⁶ These benefits must be weighed against the increased toxicity of doxorubicin. For this reason, the two-drug regimen of cisplatin and cyclophosphamide continued to be the regimen of choice.

Paclitaxel

In 1989, paclitaxel was reported to produce a 28% response rate in patients previously treated with platinum.⁷⁷ Based on this encouraging finding, cisplatin plus paclitaxel was compared with cisplatin plus cyclophosphamide in previously untreated patients with advanced ovarian

Figure 4
Postsurgical Treatment



cancer.⁶⁸ The results of this trial showed a significantly increased overall response rate (73% versus 60%), progression-free survival (18 versus 13 months), and median survival (38 versus 24 months) in the cisplatin/paclitaxel arm. The regimen of cisplatin (75 mg/m²) and paclitaxel (135 mg/m²) given every three weeks for a total of six cycles should be considered first-line chemotherapy following surgical exploration.

Several studies attempted to further document the superiority of combination chemotherapy over single-agent therapy. A GOG study compared melphalan alone with either melphalan plus hexamethylmelamine or doxorubicin plus cyclophosphamide.⁷⁸ Overall median survival was not influenced by the use of a combination regimen. The superiority of nonplatinum-containing combination therapy over single-agent therapy must therefore be viewed critically. Indeed, a meta-analysis by the Advanced Ovarian Cancer Trialists Group of 16 randomized studies comparing single nonplatinum regimens with combination nonplatinum

regimens showed no survival difference.⁷⁹

The Gruppo Interregionale Collaborativo in Ginecologia Oncologica compared cisplatin alone (P) or in combination with either cyclophosphamide (PC) or cyclophosphamide and doxorubicin (PAC). Progression-free survival was significantly increased in the combination regimens (PAC 21% versus PC 16% versus P 12%) and a trend toward increased overall survival was also noted with the combination regimens. A subsequent meta-analysis then demonstrated a significant survival advantage in favor of a platinum-containing combination regimen.⁷⁹

These data demonstrate that the addition of platinum to a combination regimen enhances response rate, progression-free interval and, in all likelihood, increases median survival.⁸⁰

Carboplatin

Carboplatin is often substituted for cisplatin in combination with paclitaxel. It is associated with less neurotoxicity and nephrotoxicity than is cisplatin. An additional advantage of carboplatin is that it

can be administered as an outpatient infusion and does not require intravenous hydration. Several prospective randomized trials demonstrate that carboplatin and cisplatin are equally effective. These results are supported by a Medical Research Council overview of 11 randomized clinical trials involving 2,061 patients.⁷⁹ A GOG trial comparing cisplatin (75 mg/m²) and paclitaxel (135 mg/m² over 24 hours) with carboplatin (area under the curve [AUC] 7.5) and paclitaxel (175 mg/m² over three hours) should help determine which of these compounds has the best therapeutic index.

Two randomized trials have investigated the appropriate duration of therapy in cisplatin-containing regimens. No significant survival difference was noted with five to 10 cycles or six to 12 cycles.^{81,82} While patients are generally treated with six cycles of combination chemotherapy, duration of therapy has not been definitively established with paclitaxel-based regimens.

In summary, the available data indicate that platinum should be included in the treatment of ovarian cancer, and platinum-containing combinations are more effective than nonplatinum-containing regimens. First line therapy should include cisplatin (75 mg/m²) and paclitaxel (135 mg/m²) infused over 24 hours every three weeks for six cycles. An alternative regimen is carboplatin (AUC 7.5) and paclitaxel (175 mg/m²) infused over three hours every three weeks for six cycles (Fig. 4).

Radiation Therapy for Ovarian Cancer

Radiation therapy for ovarian cancer remains controversial in the United States. The consensus panel for establishing ovarian cancer guidelines for the National Comprehensive Cancer Network (NCCN) described this as an area of considerable disagreement but listed whole abdominopelvic radiation therapy as an

acceptable alternative to chemotherapy in patients with low-bulk disease.⁸³

A review of the evidence of the effectiveness of radiation therapy revealed that a combination of the independent prognostic factors of grade, stage, and residual disease defines an "intermediate" risk group with long-term survival rates after abdominopelvic radiation therapy of 62% to 91%. The group that seems to benefit from abdominopelvic radiation consists mostly of patients with stage II disease of all grades with no or small volume residual disease in the pelvis and selected optional stage III patients with low-grade tumors.⁸⁴

Monitoring Response to Therapy

Most recommendations for follow-up include physical examinations every three to six months with measurement of CA-125 level.⁸⁵ If this tumor marker is positive at initial diagnosis, a persistently elevated value always indicates the presence of disease. An increased CA-125 has been shown to predict persistent disease at second look in 97% of cases.⁸⁶ It has also been shown that if the level was normal, (less than 35 U/ml), disease was still present in 44% of patients.⁸⁷

Follow-up recommendations are further complicated by the fact that no evidence exists that initiating salvage chemotherapy at the time of subclinical recurrence (elevated CA-125 level) results in improved survival compared with reserving therapy reserved for the onset of clinical manifestations of recurrence. In fact, it is unclear whether any cancer-directed treatment following recurrent disease improves overall survival.

Management of Recurrent Ovarian Cancer

NO THERAPY

Women with recurrent or persistent ovarian cancer following a platinum-based regimen usually ultimately succumb to

Table 3
Phase II Trials of Single Agent Chemotherapy
for Recurrent Ovarian Cancer (1990-1997)

Agent	N	RR(%)	MS(mo)	Author
Iproplatin	101	12	NS	Weiss ⁹⁹
Zeniplatin	25	16	9	Wilemse ¹⁰⁰
Zeniplatin	31	19	NS	Markman ¹⁰¹
Lobaplatin		22	8	Gietema ¹⁰²
Etoposide (oral)	31	26	NS	Hoskins ¹⁰³
Etoposide (oral)	41	24	10	Seymour ¹⁰⁴
Etoposide (oral)	28	16	NS	deWit ¹⁰⁵
Paclitaxel	1,000	22	9	Trimble ¹⁰⁶
Paclitaxel	43	37	16	Thigpen ¹⁰⁷
Paclitaxel	39	13	6	Bruzzone ¹⁰⁸
Paclitaxel	33	33	NS	Nardi ¹⁰⁹
Docetaxol	76	24	8	Piccart ¹¹⁰
Topotecan	48	25	NS	Armstrong ¹¹¹
Topotecan	92	16	NS	Creemers ¹¹²
Topotecan	28	14	10	Kudelka ¹¹³
Topotecan	28	14	6	Swisher ¹¹⁴
Gemcitabine	50	19	6	Lund ⁹⁴
Fazarabine	22	0	NS	Manetta ¹¹⁵
Vinorelbine	33	15	4	Bajetta ⁹⁵
Epirubicin	118	20	NS	Vermorken ¹¹⁶
Altretamine	51	14	7	Vergote ¹¹⁷
Ifosfamide	57	12	NS	Markman ¹¹⁸
Trimelamol	42	10	NS	Judson ¹¹⁹
Edatrexate	22	0	NS	Broun ¹²⁰
Doxifluridine	35	17	6	Van Oostrom ¹²¹
Merbarone	24	10	NS	Look ¹²²
Piroxantrone	16	0	6	Albain ¹²³
Didemnin B	16	0	NS	Malfetano ¹²⁴

MS(mo)=median survival (months); N=number of patients in study; NS=not stated
 RR=response rate

their disease. Standard second-line chemotherapy regimens rarely, if ever, cure patients. It is, indeed, open for debate whether these regimens actually

prolong survival. Data from recent phase II trials demonstrate no correlation between response rate and median survival (Table 3), suggesting a limited duration

of survival benefit. To date, there have been no prospective trials of second-line therapy versus supportive care that evaluated median survival and quality of life.

The physician's primary goal is to restore the patient's health; that is, to cure when possible. If cure is not possible, prolongation of life becomes the secondary goal. It is important, however, that the intended treatment to prolong life is acceptable to the patient and maintains dignity, humanity, and well-being. It is thus important that the potential benefits, risks, and burdens of the proposed salvage or secondary therapy be discussed frankly with the patient.

With no solid evidence to support prolongation of life with secondary chemotherapy, offering supportive care only as an option to women with recurrent ovarian cancer is appropriate. If therapy is considered by the physician or insisted upon by the patient, investigational or protocol therapy should be the primary choice.

CHEMOTHERAPY

If "standard" second-line chemotherapy is administered for recurrent disease, several points, some of which have already been discussed, should be understood as follows:

1) There is no compelling evidence that chemotherapy for recurrent ovarian cancer is associated with a survival advantage over supportive care only.

2) Administration of cytotoxic agents is costly and potentially burdensome.

3) No evidence exists that initiating second-line chemotherapy when subclinical disease is detected is superior to beginning therapy at onset of symptoms.

4) Intraperitoneal chemotherapy for recurrent disease has not been shown to be superior to systemic therapy.

5) Dose intensification has not been shown to be superior to "standard dose" therapy.

6) No evidence exists that combination regimens are superior to single

agents in this setting.

A recent NCCN panel observed that there is no single chemotherapeutic agent of choice in the setting of recurrent disease.⁸³ Recent phase II trials have yielded a number of options with varying response rates (Table 3).

Patients who have responded to prior platinum-based chemotherapy and whose disease recurs more than six months after initial chemotherapy can be considered to be drug sensitive. Several studies have reported response rates from 21% to 100% when patients are retreated with cisplatin or carboplatin.⁸⁸⁻⁹² Although paclitaxel has not been extensively evaluated, the ability of this agent to induce a second remission is probably similar to that of platinum compounds.⁶⁶ Therefore, retreatment with a platinum compound should be considered in this platinum-sensitive patient population. If no response is noted following three cycles, retreatment with paclitaxel is an option.

Patients whose disease recurs within six months of completing therapy or who experience progression while on primary chemotherapy have a very poor prognosis. The likelihood of a response to a second platinum compound is small, secondary to cross-resistance. Therefore, nonplatinum compounds should be emphasized.⁶⁴

Acceptable nonplatinum regimens for recurrent ovarian cancer outlined by the NCCN panel include topotecan, gemcitabine, vinorelbine, liposomal doxorubicin, and oral etoposide.⁸³ These agents have been selected on the basis of increased response rates in phase II trials: topotecan (25%), gemcitabine (19%), vinorelbine (15%), liposomal doxorubicin (26%), and oral etoposide (26%). As noted previously, increased response rate has not reliably translated into prolonged median survival.

Topotecan was compared with paclitaxel in patients with recurrent ovarian

cancer who had been previously treated with platinum.⁹³ Patients receiving topotecan had a better response rate (21% versus 13%) and a longer median survival (61 versus 43 weeks). However, these differences were not statistically significant, and any benefit must be weighed against the increased toxicity and longer infusion times required for topotecan.

Enthusiasm for gemcitabine and vinorelbine was generated secondary to observed responses in a group of heavily pretreated patients with platinum resistance with short treatment-free intervals.^{94,95} Modest toxicity was also noted.

Liposomal doxorubicin was associated with a response rate of 26% and median survival of 11 months in a phase II trial of patients previously treated with platinum/paclitaxel.⁹⁶ While stomatitis was noted, no associated nausea, hair loss, or decreased ejection fraction occurred.

The use of oral etoposide in the setting of recurrent cancer has been supported by a recent GOG trial demonstrating a response rate of 27% in platinum-resistant patients and 35% in platinum-sensitive patients.⁹⁷ Importantly, most of the patients in the study were previously treated with paclitaxel.

To summarize, patients with recurrent ovarian cancer have a poor prognosis. Quality of life issues should be given strong consideration in light of the lack of data demonstrating a clear survival advantage for second-line chemotherapy. When treatment decisions are made, first consideration should be given to protocol or investigational therapy.

Patients who have evidence of recurrence more than six months after initial chemotherapy may benefit from retreatment with single-agent platinum or paclitaxel. Women in whom initial chemother-

apy fails during therapy or within six months of its completion should be considered platinum resistant, and selection of an alternative agent as recommended by the NCCN panel seems reasonable.

RADIATION THERAPY

As with primary adjuvant treatment, the use of radiation therapy in recurrent disease remains controversial. The NCCN panel listed radiation therapy as an alternative salvage regimen.⁸³ A modest (25% to 30%) disease-free survival is seen in patients treated with whole abdominopelvic radiation therapy whose persistent or recurrent disease is small volume, low-to-intermediate grade, and whose disease was low bulk at termination of the initial surgical procedure.⁹⁸ The application of radiotherapy in this setting has been limited in the United States.

Summary

Epithelial ovarian cancer continues to be a deadly disease. Because no effective screening procedure exists, physicians who see women with persistent lower abdominal symptoms must maintain a high index of suspicion. The diagnosis and initial treatment include surgery and, in most cases, chemotherapy. Areas for future investigation include the development of effective prevention and screening strategies, the incorporation of genetic testing into management, and the development of more effective chemotherapy or other strategies for primary treatment and treatment of recurrent disease. **CA**

References

1. Landis SH, Murray T, Bolden S, Wingo PA: Cancer statistics, 1999. *CA Cancer J Clin* 1999;49:8-31.
2. Wingo PA, Tong T, Bolden S: Cancer statistics, 1995. *CA Cancer J Clin* 1995;45:8-30.
3. Fiorca JV, Roberts WS: Screening for ovarian

cancer. *Cancer Control* 1996;3:120-129.

4. Kerlikowske K, Brown JS, Grady DG: Should women with familial ovarian cancer undergo prophylactic oophorectomy? *Obstet Gynecol* 1992;80:700-707.
5. Gregg S, Genuardi M, Benedetti-Panici P, et al: Analysis of 138 consecutive ovarian cancer patients: Incidence and characteristics of familial cases. *Gynecol Oncol* 1990;39:300-304.
6. Houlston RS, Collins A, Slack J, et al: Genetic epidemiology of ovarian cancer: Segregation analysis. *Ann Hum Genet* 1991;55:291-299.
7. Piver MS, Baker TR, Jishi MF, et al: Familial ovarian cancer: A report of 658 families from the Gilda Radner Familial Ovarian Cancer Registry 1981-1991. *Cancer* 1993;71(Suppl 2): 582-588.
8. Lynch HT, Watson P, Bewtra C, et al: Hereditary ovarian cancer: Heterogeneity in age at diagnosis. *Cancer* 1991;67:1460-1466.
9. Bewtra C, Watson P, Conway T, et al: Hereditary ovarian cancer: A clinicopathological study. *Int J Gynecol Pathol* 1992;11:180-187.
10. Schildkraut JM, Risch N, Thompson WD: Evaluating genetic association among ovarian, breast, and endometrial cancer: Evidence for a breast/ovarian cancer relationship. *Am J Hum Genet* 1989;45:521-529.
11. Lynch HT, Conway T, Lynch J: Hereditary ovarian cancer: Pedigree studies, part II. *Cancer Genet Cytogenet* 1991;53:161-183.
12. Watson P, Lynch HT: Extracolonic cancer in hereditary nonpolyposis colorectal cancer. *Cancer* 1993;71:677-685.
13. Lynch HT, Lemon SJ, Karr B, et al: Etiology, natural history, management, and molecular genetics of hereditary nonpolyposis colorectal cancer (Lynch Syndromes): Genetic counseling implications. *Cancer Epidemiol Biomarkers Prev* 1997;6:987-991.
14. Narod SA, Madlensky L, Bradley L, et al: Hereditary and familial ovarian cancer in southern Ontario. *Cancer* 1994;74:2341-2346.
15. Steichen-Gersdorf E, Gallion HH, Ford D, et al: Familial site-specific ovarian cancer is linked to BRCA1 on 17q12-21. *Am J Hum Genet* 1994;55:870-875.
16. Easton DF, Bishop DT, Ford D, et al: Genetic linkage analysis in familial breast and ovarian cancer: Results from 214 families. The Breast Cancer Linkage Consortium. *Am J Hum Genet* 1993;52:678-701.
17. Narod SA, Ford D, Devilee P, et al: An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. *Am J Hum Genet* 1995;56:254-264.
18. Wooster R, Neuhausen S, Mangion J, et al: Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13. *Science* 1994;208:2088-2090.
19. Narod S, Ford D, Devilee P, et al: Genetic heterogeneity of breast-ovarian cancer revisited. *Am J Hum Genet* 1995;57:957-958. Letter.
20. Boyd J: Molecular genetics of hereditary ovarian cancer. *Oncology* 1998;12:399-406.
21. Young RC, Perez CA, Hoskins WJ: Cancer of the ovary, in Devita VT Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles & Practice of Oncology*, ed 4. Philadelphia, JP Lippincott Co, 1993, pp 1226-1263.
22. Ozols RF: Ovarian cancer, part II: Treatment. *Curr Probl Cancer* 1992;16:61-126.
23. The WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Epithelial ovarian cancer and combined oral contraceptives. *Int J Epidemiol* 1989;18:538-545.
24. Hankinson SE, Hunter DJ, Colditz GA, et al: Tubal ligation, hysterectomy, and risk of ovarian cancer: A prospective study. *JAMA* 1993;270:2813-2818.
25. Tobacman JK, Green MH, Tucker MA, et al: Intra-abdominal carcinomatosis after prophylactic oophorectomy in ovarian-cancer-prone families. *Lancet* 1982;2:795-797.
26. Piver MS, Jishi MF, Tsukada Y, et al: Primary peritoneal carcinoma after prophylactic oophorectomy in women with a family history of ovarian cancer. A report of the Gilda Radner Familial Ovarian Cancer Registry. *Cancer* 1993;71:2751-2755.
27. Struewing JP, Watson P, Easton DF, et al: Prophylactic oophorectomy in inherited breast/ovarian cancer families. *J Natl Cancer Inst* 1995;17:33-35.
28. McFarlane C, Sturgis MD, Fetterman FC: Results of an experience in the control of cancer of the female pelvic organs: A report of a 15-year research. *Am J Obstet Gynecol* 1956;69:294-301.
29. Squatrito RC, Buller RE: Use of serum CA-125 for monitoring and prognosticating outcome in patients with epithelial ovarian cancer. *The Female Patient* 1994;19:14.
30. Gadducci A, Ferdeghini M, Prontera C, et al: The concomitant determination of different tumor markers in patients with epithelial ovarian cancer and benign ovarian masses: Relevance for differential diagnosis. *Gynecol Oncol* 1992;44:147-154.
31. Berek J, Bast RC Jr: Ovarian cancer screening: The use of serial complementary tumor markers to improve sensitivity and specificity for early detection. *Cancer* 1995;76(Suppl 10):2092-2096.
32. Zurawski V, Sjoval K, Schoenfeld D, et al: Prospective evaluation of serum CA-125 levels in a normal population, Phase I: The specificities of single and serial determinations in testing for ovarian cancer. *Gynecol Oncol* 1990;36:299-305.
33. DePriest PD, van Nagel Jr, Gallion HH, et al: Ovarian cancer screening in asymptomatic postmenopausal women. *Gynecol Oncol* 1993;51:205-209.
34. Weiner Z, Thaler I, Beck D, et al: Differentiating malignant from benign ovarian tumors with transvaginal color flow imaging. *Obstet Gynecol* 1992;79:159-162.
35. Bourne TH, Campbell S, Reynolds KM, et al: Screening for early familial ovarian cancer with transvaginal ultrasonography and colour flow imaging. *BMJ* 1993;306:1025-1029.
36. Caruso A, Caforio L, Testa A, et al:

Transvaginal color Doppler ultrasonography in the presurgical characterization of adnexal masses. *Gynecol Oncol* 1996;63:184-191.

37. Karlan BY, Platt LD: The current status of ultrasound and color Doppler imaging in screening for ovarian cancer. *Gynecol Oncol* 1994;55:S28-S33.

38. NIH Consensus Development Conference Panel. Ovarian Cancer: Screening, Treatment, and Follow-up. Washington DC, National Institutes of Health, April 5-7, 1994. NIH Consensus Statement 12.

39. Kramer BS, Gohagan J, Propok PC, et al: A National Cancer Institute sponsored screening trial for prostatic, lung, colorectal, and ovarian cancers. *Cancer* 1993;71(Suppl 2):589-593.

40. Menko FH, Wijnen JT, Khan PM, et al: Genetic counseling in hereditary nonpolyposis colorectal cancer. *Oncology* 1996;10:71-76.

41. Burke W, Petersen G, Lynch P, et al: Recommendations for follow-up care of individuals with an inherited predisposition to cancer. I. Hereditary nonpolyposis colon cancer. *JAMA* 1997;277:915-919.

42. Burke W, Daly M, Garber J, et al: Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. *JAMA* 1997;277:997-1003.

43. Flam F, Einhorn N, Sjøvall K: Symptomatology of ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* 1988;27:53-57.

44. Finn CB, Luesley DM, Buxton EJ, et al: Is stage I epithelial ovarian cancer overtreated both surgically and systemically? Results of a five-year cancer registry review. *Br J Obstet Gynecol* 1992;99:54-58.

45. Goldstein SR: Postmenopausal adnexal cysts: How clinical management has evolved. *Am J Obstet Gynecol* 1996;175:1498-1501.

46. Childers JM, Nasser A, Surwit EA: Laparoscopic management of suspicious adnexal masses. *Am J Obstet Gynecol* 1996;175:1451-1457.

47. Hoskins WJ: Epithelial ovarian carcinoma: Principles of primary surgery. *Gynecol Oncol* 1994;55:S91-S96.

48. Hoskins WJ, McGuire WP, Brady MF, et al: The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. *Am J Obstet Gynecol* 1994;170:974-979.

49. Piver MS, Lele SB, Marchetti DL, et al: The impact of aggressive debulking surgery and cisplatin-based chemotherapy on progression-free survival in stage III and IV ovarian carcinoma. *J Clin Oncol* 1988;6:983-989.

50. Eisenkop SM, Nalick RH, Teng NN: Modified posterior exenteration for ovarian cancer. *Obstet Gynecol* 1991;78:879-885.

51. Barnes W, Johnson J, Waggoner S, et al: Reverse hysterocolpogmoidectomy (RHCS) for resection of panpelvic tumors. *Gynecol Oncol* 1991;42:151-155.

52. Burghardt E, Pickel H, Lahousen M, et al: Pelvic lymphadenectomy in operative treatment of ovarian cancer. *Am J Gynecol* 1986;155:315-319.

53. Kigawa J, Minagawa Y, Ishihara H, et al: Evaluation of cytoreductive surgery with lymphadenectomy including para-aortic nodes for advanced ovarian cancer. *Eur J Surg Oncol* 1993;19:273-278.

54. Spirtos NM, Gross GM, Freddo JL, et al: Cytoreductive surgery in advanced epithelial cancer of the ovary: The impact of aortic and pelvic lymphadenectomy. *Gynecol Oncol* 1995;56:345-352.

55. Lippman SM, Alberts DS, Slymen DJ, et al: Second-look laparotomy in epithelial ovarian carcinoma: Prognostic factors associated with survival duration. *Cancer* 1988;61:2571-2577.

56. Luesley D, Lawton F, Blackledge G, et al: Failure of second-look laparotomy to influence survival in epithelial ovarian cancer. *Lancet* 1988;2:599-603.

57. Hoskins WJ, Rubin SC, Dulaney E, et al: Influence of secondary cytoreduction at the time of second-look laparotomy on the survival of patients with epithelial ovarian cancer. *Gynecol Oncol* 1989;34:365-371.

58. Podratz KC, Schray MF, Wieand HS, et al: Evaluation of treatment and survival after positive second-look laparotomy. *Gynecol Oncol* 1988;31:9-24.

59. Michel G, Zarca D, Castaigne D, et al: Secondary cytoreductive surgery in ovarian cancer. *Eur J Surg Oncol* 1989;15:201-204.

60. Janicke F, Holscher M, Kuhn W, et al: Radical surgical procedure improves survival time in patients with recurrent ovarian cancer. *Cancer* 1992;70:2129-2136.

61. van der Burg ME, van Lent M, Buyse M, et al: The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med* 1995;332:629-634.

62. Ozols RF, Rubin SC, Dembo AJ, et al: Epithelial ovarian cancer, in Hoskins WJ, Perez CA, Young RC, (eds): Principles and Practice of Gynecologic Oncology, Philadelphia, JB Lippincott, 1992, pp 731-781.

63. Young RC, Walton LA, Ellenberg SS, et al: Adjuvant therapy in stage I and stage II epithelial ovarian cancer: Results of two prospective randomized trials. *N Engl J Med* 1990;322:1021-1027.

64. Bolis G, Colombo N, Pecorelli S, et al: Adjuvant treatment for early epithelial ovarian cancer: Results of two randomized clinical trials comparing cisplatin to no further treatment or chronic phosphate. *Ann Oncol* 1995;6:887-893.

65. Vergote IB, Vertooge-DeVos LN, Abeler VM, et al: Randomized trial comparing cisplatin with radioactive phosphorus or whole-abdomen irradiation as adjuvant treatment of ovarian cancer. *Cancer* 1992;69:741-749.

66. Ozols R, Rubin S, Thomas G, et al: Epithelial ovarian cancer, in Hoskins WJ, Perez CA, Young RC (eds) Principles and Practice of Gynecologic Oncology, ed 2. Philadelphia, Lippincott-Raven Publishers, 1997, p 947.

67. Bolis G, Colombo N, Pecorelli S, et al: Adjuvant treatment for early epithelial ovarian cancer: Results of two randomised clinical trials comparing cisplatin to no further treatment or chronic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo in Ginecologia Oncologica. *Ann Oncol* 1995;6:887-893.
68. McGuire WP, Hoskins WJ, Brady MF, et al: Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1-6.
69. Young RC, Chabner BA, Hubbard SP, et al: Advanced ovarian adenocarcinoma: A prospective clinical trial of melphalan (L-PAM) versus combination chemotherapy. *N Engl J Med* 1978;299:1261-1266.
70. Omura GA, Blessing JA, Ehrlich CE, et al: A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. *Cancer* 1986;57:1725-1730.
71. Omura GA, Siller BS: Primary chemotherapy of epithelial ovarian carcinoma. *Semin Surg Oncol* 1994;10:283-287.
72. Gruppo Interregionale Collaborativo in Ginecologia Oncologica: Randomized comparison of cisplatin with cyclophosphamide/cisplatin and with cyclophosphamide/doxorubicin/cisplatin in advanced ovarian cancer. *Lancet* 1987;2:353-359.
73. Omura GA, Bundy BN, Berek JS, et al: Randomized trial of cyclophosphamide plus cisplatin with or without doxorubicin in ovarian carcinoma: A Gynecologic Oncology Group study. *J Clin Oncol* 1989;7:457-465.
74. Bertelsen K, Jakobsen A, Andersen J, et al: A randomized study of cyclophosphamide and cisplatin with or without doxorubicin in advanced ovarian carcinoma. *Gynecol Oncol* 1987;28:161-169.
75. Conte PF, Bruzzone M, Chiara S, et al: A randomized trial comparing cisplatin plus cyclophosphamide versus cisplatin, doxorubicin, and cyclophosphamide in advanced ovarian cancer. *J Clin Oncol* 1986;4:965-971.
76. Ovarian Cancer Meta-Analysis Project: Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin, and cisplatin chemotherapy of ovarian carcinoma: A meta-analysis. *J Clin Oncol* 1991;9:1668-1674.
77. McGuire WP, Rowinsky EK, Rosenshein NB, et al: Taxol: A unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989;111:273-279.
78. Omura GA, Morrow CP, Blessing JA, et al: A randomized comparison of melphalan versus melphalan plus hexamethylmelamine versus adriamycin plus cyclophosphamide in ovarian carcinoma. *Cancer* 1983;51:783-789.
79. Advanced Ovarian Cancer Trialists Group: Chemotherapy in advanced ovarian cancer: An overview of randomised clinical trials. *BMJ* 1991;303:884-893.
80. Thigpen T, Vance R, Punecky L, et al: Chemotherapy in advanced ovarian carcinoma: Current standards of care based on randomized trials. *Gynecol Oncol* 1994;55: S97-S107.
81. Bertelsen K, Jakobsen A, Stroyer J, et al: A prospective randomized comparison of 6 and 12 cycles of cyclophosphamide, adriamycin, and cisplatin in advanced epithelial ovarian cancer: A Danish Ovarian Study Group trial. *Gynecol Oncol* 1993;49:30-36.
82. Hakes TB, Chalas E, Hoskins WJ, et al: Randomized prospective trial of 5 versus 10 cycles of cyclophosphamide, doxorubicin, and cisplatin in advanced ovarian carcinoma. *Gynecol Oncol* 1992;45:284-289.
83. Ozols RF: Update of the NCCN ovarian cancer practice guidelines. *Oncology* 1997;11:95-105.
84. Thomas GM: Radiotherapy in early ovarian cancer. *Gynecol Oncol* 1994;55:S73-S79.
85. Morrow CP, Curtin JP, Townsend DE: Tumors of the ovary: Neoplasms derived from coelomic epithelium, in Morrow CP, Curtin JP, Townsend DE (eds): *Synopsis of Gynecologic Oncology*, ed 4. New York, Churchill Livingstone, 1993, p 265.
86. Jacobs I, Bast RC Jr: The CA 125 tumor-associated antigen: A review of the literature. *Hum Reprod* 1989;4:1-12.
87. Berek JS, Knapp RC, Malkasian GD, et al: CA 125 serum levels correlated with second-look operations among ovarian cancer patients. *Obstet Gynecol* 1986;69:685-689.
88. Ozols RF, Ostchega M, Myers CE, et al: High-dose cisplatin in hypertonic saline in refractory ovarian cancer. *J Clin Oncol* 1985;3:1246-1250.
89. Gershenson DM, Kavanaugh JJ, Copeland LJ, et al: Retreatment of patients with recurrent epithelial ovarian cancer with cisplatin-based chemotherapy. *Obstet Gynecol* 1989;73:798-802.
90. Markman M, Rothman R, Hakes T, et al: Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9:389-393.
91. Ozols RF, Ostchega Y, Curt G, et al: High-dose carboplatin in refractory ovarian cancer patients. *J Clin Oncol* 1987;5:197-201.
92. Kavanaugh J, Tresukosol D, Edwards C, et al: Carboplatin reinduction after taxane in patients with platinum-refractory epithelial ovarian cancer. *J Clin Oncol* 1995;13:1584-1588.
93. ten Bokkel Huinink W, Gore M, Carmichael J, et al: Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997;15: 2183-2193.
94. Lund B, Hansen OP, Theilade K, et al: Phase II study of gemcitabine (2', 2'-difluorodeoxycytidine) in previously treated ovarian cancer patients. *J Natl Cancer Inst* 1994;86:1530-1533.
95. Bajetta E, Di Leo A, Bignanzoli L, et al: Phase II study of vinorelbine in patients with pretreated advanced ovarian cancer: Activity in platinum resistant disease. *J Clin Oncol* 1996;14:2546-2551.
96. Muggia FM, Hainsworth JP, Jeffers S, et al: Phase II study of liposomal doxorubicin in refractory ovarian cancer: Antitumor activity and toxicity modification by liposomal encapsulation. *J Clin*

- Oncol 1997;15:987-993.
97. Rose PG, Blessing JA, Mayer AR, et al: Prolonged oral etoposide as second line therapy for platinum resistant (PLATR) and platinum sensitive (PLATS) ovarian carcinoma: A Gynecologic Oncology Group study. *Proc Am Soc Clin Oncol* 1996;15:282. Abstract.
 98. Schray MF, Martinez A, Howes AE, et al: Advanced epithelial ovarian cancer: Salvage whole abdominal irradiation for patients with recurrent or persistent disease after combination chemotherapy. *J Clin Oncol* 1988;6:1433-1439.
 99. Weiss G, Green S, Alberts DS, et al: Second-line treatment of advanced measurable ovarian cancer with iproplatin: A Southwest Oncology Group study. *Eur J Cancer* 1991;27:135-138.
 100. Willemsse PHA, Gietema AJ, Mulder NH, et al: Zeiniplatin in patients with advanced ovarian cancer: A Phase II study with a third generation platinum complex. *Eur J Cancer* 1993;29:359-362.
 101. Markman M, DeMarco LC, Birkhofer M, et al: Phase II trial of zeiniplatin (CL 286558) a new platinum compound in patients with advanced ovarian cancer previously treated with organoplatinum based therapy. *J Cancer Res Clin Oncol* 1993;119:234-236.
 102. Gietema JA, Veldhuis GJ, Guchelaar HJ, et al: Phase II and pharmacokinetic study of lobaplatin in patients with relapsed ovarian cancer. *Br J Cancer* 1995;71:1302-1307.
 103. Hoskins PJ, Swenerton KD: Oral etoposide is active against platinum-resistant epithelial ovarian cancer. *J Clin Oncol* 1994;12:60-63.
 104. Seymour MT, Mansi JL, Gallagher CJ, et al: Protracted oral etoposide in epithelial ovarian cancer: A phase II study in patients with relapsed or platinum-resistant disease. *Br J Cancer* 1994;69:191-195.
 105. de Wit R, van der Burg M, van den Gaast A, et al: Phase II study of prolonged oral etoposide in patients with ovarian cancer refractory to or relapsing within 12 months after platinum-containing chemotherapy. *Ann Oncol* 1994;5:656-657.
 106. Trimble EL, Adams JD, Vena D, et al: Paclitaxel for platinum-refractory ovarian cancer: Results from the first 1000 patients registered to National Cancer Institute treatment referral center 9103. *J Clin Oncol* 1993;11:2405-2410.
 107. Thiipen JT, Blessing JA, Ball H, et al: Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: A Gynecologic Oncology Group study. *J Clin Oncol* 1994;12:1748-1753.
 108. Bruzzone M, Catsafados E, Miglietta L: Salvage chemotherapy with paclitaxel in platinum-resistant advanced ovarian cancer patients. *Oncology* 1996;53:349-356.
 109. Nardi M, Aloe A, DeMarco S, et al: Paclitaxel as salvage therapy in advanced pretreated ovarian cancer: A phase II study. *Am J Clin Oncol* 1997;20:230-232.
 110. Piccart MJ, Gore M, ten Bokkel Huinink W, et al: Docetaxel: An active new drug for treatment of advanced epithelial ovarian cancer. *J Natl Cancer Inst* 1995;87:676-681.
 111. Armstrong D, Rowinsky E, Donehower R, et al: A phase II trial of topotecan as salvage therapy in epithelial ovarian cancer. *Proc Am Soc Clin Oncol* 1995;14:275. Abstract.
 112. Creemers GJ, Bolis G, Gore M, et al: Topotecan, an active drug in the second-line treatment of epithelial ovarian cancer: Results of a large European phase II study. *J Clin Oncol* 1996;14:3056-3061.
 113. Kudelka AP, Treskosol D, Edwards CL, et al: Phase II study of intravenous topotecan as a 5-day infusion for refractory epithelial ovarian carcinoma. *J Clin Oncol* 1996;14:1552-1557.
 114. Swisher EM, Mutch DG, Rader JS, et al: Topotecan in platinum- and paclitaxel-resistant ovarian cancer. *Gynecol Oncol* 1997;66:480-486.
 115. Manetta A, Blessing JA, Look KY: A phase II study of Fazarabine in patients with advanced ovarian cancer: A Gynecologic Oncology Group study. *Am J Clin Oncol* 1995;8:156-157.
 116. Vermorken JB, Kobierska A, van der Burg ME, et al: High-dose epirubicin in platinum-pretreated patients with ovarian carcinoma: The EORTC-GCCG experience. *Eur J Gynaecol/Oncol* 1995;16:433-438.
 117. Vergote I, Himmelmann A, Frankendal B, et al: Hexamethylmelamine as a second-line therapy in platinum resistant ovarian cancer. *Gynecol Oncol* 1992;47:282-286.
 118. Markman M, Hakes T, Reichman B, et al: Ifosfamide and mesna in previously treated advanced epithelial ovarian cancer: Activity in platinum-resistant disease. *J Clin Oncol* 1992;10:243-248.
 119. Judson I, Calvert AH, Gore ME, et al: Phase II trial of trimelamol in refractory ovarian cancer. *Br J Cancer* 1991;63:311-313.
 120. Broun ER, Iseminger KA, Bookman M: A phase II trial of edatrexate in previously treated ovarian cancer: A Gynecologic Oncology Group study. *Am J Clin Oncol* 1995;18:164-166.
 121. Van Oosterom AT, ten Bokkel Huinink W, van der Burg ME, et al: Phase II clinical trial of doxifluridine in patients with advanced ovarian cancer. *Eur J Cancer* 1991;27:747-749.
 122. Look KY, Blessing JA, Adelson MD, et al: A phase II trial of merbarone (NSC 336628) in the treatment of recurrent epithelial ovarian carcinoma: A Gynecologic Group study. *Am J Clin Oncol* 1996;19:7-9.
 123. Albain KS, Liu PY, Hantel A, et al: A phase II trial of piroxantrone in advanced ovarian carcinoma after failure of platinum-based chemotherapy: Southwest Oncology Group Study 8904. *Gynecol Oncol* 1995;57:407-411.
 124. Malfetano JH, Blessing JA, Jacobs A: A phase II trial of Didemnin B (NSC #335319) in patients with previously treated epithelial ovarian cancer: A Gynecologic Oncology Group study. *Am J Clin Oncol* 1993;16:47-9.