OVARIAN CANCER: A THERAPEUTIC MODEL

by

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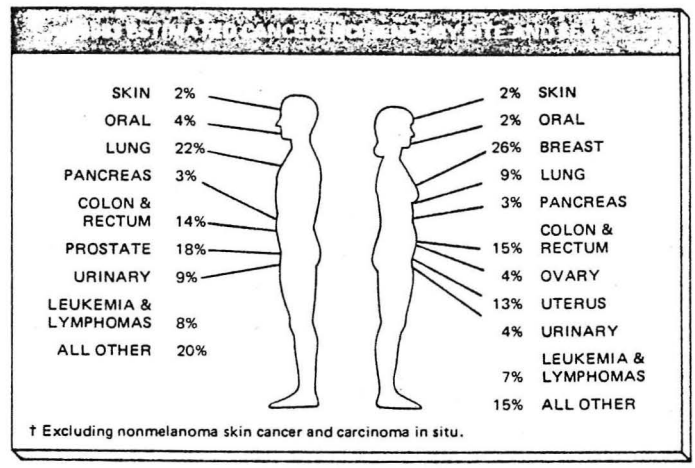
I. INTRODUCTION

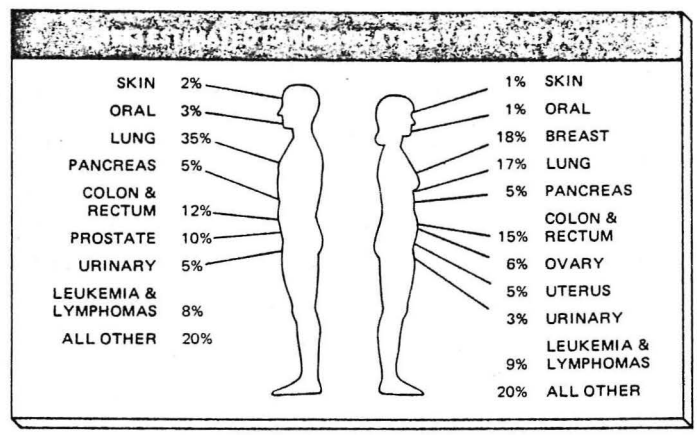
Ovarian cancer is the second most frequent invasive gynecologic cancer with an incidence of approximately 18,000 new cases diagnosed each year (Fig. 1) (1). This represents one fifth of all pathologically documented ovarian masses; it is the most frequent ovarian mass detected in post-menopausal woman. Ovarian cancer affects approximately one in seventy woman with a peak incidence in the sixth and seventh decade. Its incidence and death rate have remained fairly constant over the last 20 years at a rate of 14 and 9, respectively, per 100,000 woman each year. This is despite major advances in the diagnosis and treatment of ovarian cancer. Because of its biology and mode of spread, ovarian cancer is most commonly insidious in its earliest stages. This results in its being the most frequent cause of gynecologic cancer-related deaths at a rate of about 11,500 deaths per year (Table 1).

Figure 1

Cancer Statistics, 1983



† Excluding nonmelanoma skin cancer and carcinoma in situ.



The estimates of the incidence of cancer are based upon data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program (1973-1979). Nonmelanoma skin cancer and carcinoma in situ have not been included in the statistics. The incidence of nonmelanoma skin cancer is estimated to be about 400,000. Prepared by Edwin Silverberg, Supervisor, Statistical Information Services, Department of Epidemiology and Statistics, American Cancer Society, New York, New York.

Malignant Tumors of the ovary can arise from all of its component cell origins: epithelial, stromal, and germinal cells. Eighty-five percent of ovarian carcinomas are of epithelial cell origin; the remaining 15% of ovarian tumors encompass a wide variety of cell types (Table 2). The non-epithelial tumors are much more uncommon and differ greatly in their biology, prognosis, and responses to therapy. For these reasons this protocol will deal entirely with epithelial ovarian cancer.

TABLE 1

Gynecologic Cancer

Tissue	Incidence	Deaths
Ovarian	18,200	11,500
Cervix, invasive	16,000	7,500
Uterine corpus & endometrium	39,000	3,000
Others	4,400	1,000

TABLE 2

Ovarian Cancer

Cell Type	Incidence (%)
Epithelial	85
Germ	8
Granulosa	3
Sertoli-Leydig	1
Sarcomas	1
Others	2

Ovarian Cancer is of interest and concern to the internist because of its high incidence, the difficulties associated with early diagnosis, and its high death rate. Since the disease most commonly affects post-menopausal women with non-specific symptomatology, it is a gynecologic malignancy which may first be recognized or misdiagnosed by the internist. Ovarian cancer interests us at this forum because it is an excellent model for exploring modern approaches and principles of cancer diagnosis and therapy. Recent developments in these areas have led investigators to turn from the pessimism expressed by Tobias and Griffiths in 1976 (2).

> "Despite many dramatic and rapid advances in the treatment of cancer during the last 20 years, the management of ovarian cancer remains unsatisfactory. Although surgical and radiotherapeutic technics have improved, the survival figures for ovarian cancer have not."

These advances have led to a renewed interest in ovarian cancer with many investigators beginning to think in terms of curing patients with far advanced disease. This protocol will be devoted to the role of important oncologic concepts--tumor burden, histologic grade, and biologic markers--as prognostic factors and their relationship to the curability of ovarian cancer. For a more complete discussions of ovarian cancer, the reader is referred to other reviews (3,4,5,6).

II. PROGNOSTIC FACTORS

A. Staging

Epithelial ovarian cancer tends to be a disease of the abdominal cavity. The tumor tends to spread to the retroperitoneal lymph nodes. The disease often involves the retroperitoneal lymph nodes. Unlike most other malignancies involving these nodes, the tumor is postulated to cause an obstruction of lymphatic flow with the fairly early development of ascites (7). It is obvious in patients with bulky disease that lymphatics are obstructed with tumor contributing to the development of ascites. There are, however, a group of carefully staged patients with stage Ic and IIc disease who have ascites without incidence of extension to retroperitoneal nodes; this suggests that there may be other mechanisms for ascites formation. Once malignant ascites develops, the tumor spreads rapidly throughout the entire abdominal cavity in the ascitic fluid implanting on peritoneal surfaces, including the serosal surface of the liver and intestines.

To correlate the extent of disease with prognosis, the International Federation of Gynecology and Obstetrics (FIGO) developed a uniform staging system for ovarian cancer in the 1960's (8). Table 3 represents the scheme with patient prognosis (9). The classification scheme was based primarily on end results with epithelial tumors and, unfortunately, has been utilized for classification of both epithelial and non-epithelial tumors. Although in its original format it was probably too complex for evaluation of most patient populations, it focused the physician on the relationship of disease spread at the time of diagnosis to prognosis. This has become the key prognostic factor: the relationship with the stage of the disease and five years survival is obvious. If the disease is confined to the ovaries, about 60% of the patients are cured.[1] Whereas patients

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[1]Since epithelial ovarian tumors tend to recur within 1-3 years from the

with the disease extending out of the ovaries into the true pelvis do much worse. And once the disease has metastasized to nodes, rectum, or bowel patients are essentially not curable. The data supporting these conclusions was compiled by Tobias and Griffiths in 1976 and is based on the survival in six series comprising a total of 1792 patients (2). Thus, extent of disease (i.e., the stage of the patient at diagnosis) has a direct correlation with the prognosis and survival of the patient.

TABLE 3

Staging scheme of the International Federation of Gynecology and Obstetrics for ovarian cancer and survival rates following surgery ± irradiation and/or single agent chemotherapy

Stage	Five-year survival (%)
I. Growth limited to ovaries	60
A. Growth limited to one ovary; no ascites	
B. Growth limited to both ovaries; no ascites	
C. Tumor Stage IA or IB plus ascites or malignant cells in peritoneal washings	
II. Growth involving one or both ovaries with pelvic extension	39
A. Extension or metastases or both to uterus or tubes or both	
B. Extension to other pelvic tissues	
C. Tumor Stage IIA or IIB plus ascites or malignant cells in peritoneal washings	
III. Growth involving one or both ovaries with intraperitoneal metastases outside the pelvis or positive retroperitoneal nodes, or both; tumor limited to true pelvis with histologically proven malignant extension to small bowel or omentum	6
IV. Growth involving one or both ovaries with distant metastases; pleural effusion must contain malignant cells to indicate Stage IV disease; parenchymal liver metastases indicate Stage IV disease	4

It is important to note that this data was generated prior to the development of many diagnostic and therapeutic approaches that are presently available. Many investigators believe that with modern approaches the cure rate of true stage I (Ia only) may be as high as 70-80% (10,11). When disease was found outside of one ovary, it was rarely confined to the true pelvis. Once malignant cells were detected in the abdomen, the patient's prognosis decreased markedly and only a small fraction was cured. These observations have led to more aggressive staging procedures (see following section) to determine the true extent of malignancy (12,13). With this approach the percentage of patients having stage I and II disease has dropped dramatically; in essence most patients with apparent Ib, Ic, and IIc disease when carefully staged are now at least stage III, and those with IIa and IIb disease (tumors extending only to the oviduct and uterine corpus) have been greatly reduced (Fig. 3). By removing those patients with advanced disease from earlier stages, prognosis in stage I and II has been greatly improved (Fig. 2). Similarly, the prognosis of patients with stage III disease has improved because patients with less bulk disease have

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time of primary surgery, a patient surviving 5 years is presumed to be cured.

been added to this stage. These points are not moot since new studies often compare results with older studies where patients have not been properly staged. Large studies are not as yet available with more aggressive staging so that the true incidence of limited ovarian cancer can only be surmised at between 20-30%. Another concept which developed from the analysis of carefully staged patients was that disease confined, although "bulky," did considerably better than disease of similar tumor burden which also had a diffusely distributed component. For example, if one compares the survival of patients that are Ia with Ic or IIa,b with IIc, there are considerable differences in prognosis. And when one compares disease that is confined to the true pelvis (stage Ia or IIa,b), there are survival benefits, but these appear less significant than the presence of diffuse disease which has a much poorer prognosis. This has led investigators to stress the importance of "debulking" the primary tumor (i.e., reducing the residual tumor mass); this will be discussed in detail in section IIIc).

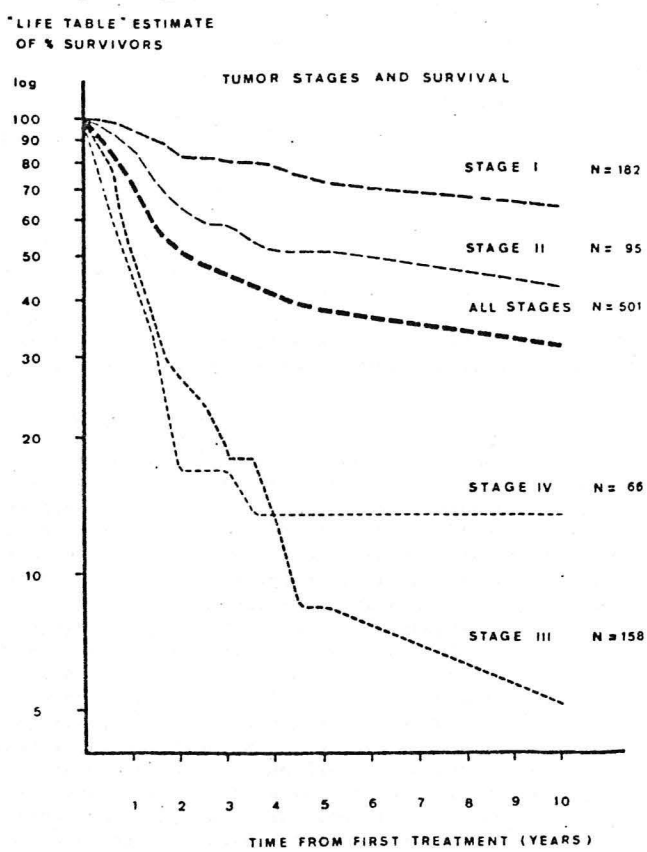


Figure 2

Life-table survival for the complete series (N=501) and for subgroupings into different tumor stages.

CHANGES IN STAGE RESULTING FROM COMPREHENSIVE RESTAGING
(100 patients referred as stage Ia - IIb)

Final Stage

	Ia	Ib	Ic	IIa	IIb	IIc	III	% Upstaged
Ia	31				3		3	6/37 (16%)
Ib		7	1		1		1	3/10 (30%)
Ic			2					0/2
IIa				0			4	4/4 (100%)
IIb					23	3	12	15/38 (39%)
IIc						6	3	3/9 (33%)

Total Upstaged 31/100 (31%)
Upstaged to Stage III 23/31 (77%)

Figure 3

Therefore, the extent of the patient's disease in ovarian carcinoma has a critical effect on prognosis. There are two major factors which determine the extent of disease: 1) where the disease is located (stage) and 2) the bulk of disease. These factors define the Tumor Burden.

Staging Evaluation:

The importance of determining the extent of disease has been emphasized. In section IIIc the importance of reducing the tumor burden will be discussed in detail. The data suggests that the smaller the amount of tumor mass present following surgery, the better the prognosis (14,15). Hence, it is critical to aggressively locate the tumor, and it is probably equally important to aggressively remove the tumor which is present whenever possible. Non-invasive diagnostic studies--i.e., computerized tomography, (sonography), lymphoangiography, nuclide scanning--are of limited usefulness in detecting diffuse abdominal involvement. However, CT scanning and sonography are useful in characterizing an ovarian or abdominal mass at presentation (16). Intravenous pyelograms and barium enemas are an important aspect of the presurgical evaluation but do not augment diagnosis and staging. Tumor markers have considerable potential (see section III), but have not as yet been helpful in detecting the extent of disease. Peritoneoscopy has been very helpful in detecting disease involving the diaphragm, sampling suspicious lesions, and sampling intra-abdominal fluid and washings for cytologic examination (10,17,18,19). The role of peritoneoscopy in the inital staging is probably limited to those patients in whom primary surgery has been done and the patient has been reported to

have been rendered "free of disease," but adequate observation of the omentum and diaphragms and cytologic examination of abdominal fluid has not been performed.

TABLE 4

AN APPROACH TO STAGING EPITHELIAL OVARIAN CARCINOMA

1. History and Physical Examination
2. Ultrasound and/or Computerized Tomography
3. Surgery
   a. Bilateral salpingo-oophorectomy
      Total abdominal hysterectomy
   b. Infracolic omentectomy, inspectin of small bowel
   c. Periaortic node sampling
   d. Biopsy of liver, diaphragm, peritoneal gutters
   e. Peritoneal surface washing for cytologic examination

The present approach to staging an ovarian mass is to go directly to surgery once the clinician becomes suspicious of the diagnosis. The mass should be defined by either sonography or CT scan prior to surgery, and these studies will also demonstrate whether bulk disease is present or absent. The surgery should include: 1) a bilateral salpingo-oophorectomy, 2) hysterectomy, 3) omentectomy, 4) inspection and biopsy of the liver, diaphragmatic surfaces, and peritoneal gutters, and 5) cytologic examination of abdominal fluid and washings. If mass disease is present, attempts should be made to remove all bulk disease (see section IIIc). The only exception to this approach should be when the tumor appears to be of low malignant potential (histologic grade 0 or 1) or of non-epithelial origin where the disease does not typically spread to either the other ovary or adjacent tissues. Then a unilateral oophorectomy may be appropriate with a blind biopsy of the second ovary. This approach should be considered in premenopausal women who may wish to become pregnant in the future. When patients present following a TAH-BSO procedure and bulk disease is present by history or diagnostic studies, the patient should undergo an aggressive surgical procedure prior to either chemotherapy and/or radiation therapy (see Section IIIc). When the patient presents with data suggesting that there is no metastatic or bulk disease, peritoneoscopy should be the next invasive procedure in these patients. However, if omental or bulk disease were observed at peritoneoscopy, then a second surgical procedure would be indicated prior to additional therapy for complete staging and debulking.

B. Histologic Grade

Histologic grade is as significant a prognostic factor as the extent of disease (stage) and the amount of residual disease following resection of the primary tumor (9). There is a significant correlation between histologic grade and survival (11,20,21,22). Histologic grade pre-

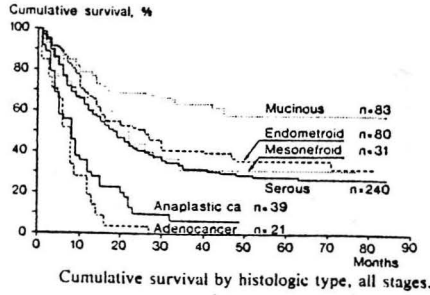
dicts response to therapeutic manipulations--i.e., those patients with lower histologic grade do better than the patients with more aggressive tumors (23,24,25). Two histologic grading systems have been employed which follow either the pattern of tumor growth (21) or the degree of cellular atypia (Broder's Classification) (23,24,25,26).

Histologic grading, however, had not been universally accepted as an important prognostic factor until the last five years. Its significance was down played or overlooked because the histologic type, the stage of disease, and, more recently, the extent of residual disease were of such obvious significance. Another reason was the difficulty pathologists have had in assigning consistent tumor grades. Probably the most important reason histologic grade was overlooked was that survival in advanced disease was so poor, making discrimination of other prognostic factors impossible. With better staging and better therapy, histologic grade may have become as important a factor as the histologic type and the extent of disease. The difficulties in the consistency of pathologic interpretation has been alleviated by the modification of Broder's classification as advocated by Young and his colleagues at the National Cancer Institute (24,25). This approach requires at least two reviewers with observation of all tissue blocks to get a spectrum of tumor differentiations in the entire mass. Since the degree of differentiation is often variable within a tumor, pathologists usually assign a grade on the basis of the most "aggressive" component present and the extent to which it is present. As one would predict, this is the most subjective aspect of grading. Institutions which are referral centers for ovarian cancer have a uniformity of results based on tumor grade, implying a consistency of diagnosis.

Figures 4 and 5 illustrate the stratification of patients which can be achieved using histologic type and differentiation (22). When these patients are further segregated on the basis of stage, the correlation persists except in patients with stage IV disease (Tables 5,6,7). The proportion of differentiated tumors decreases with increasing stage. This data suggests that stage, histologic type, and differentiation are independent variables. Correlating all three will give the patient the best determination of prognosis.

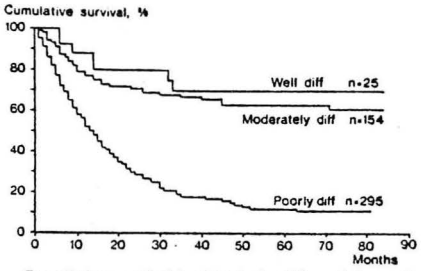
As mentioned above, the histologic grade correlates well with response to therapy. Dembo et al, have shown this in patients treated with radiation therapy (Fig. 6) (23). Similar results have been obtained in patients treated with chemotherapy (Fig. 7 & 8) (25). More recently investigators have criticized the importance of the results obtained using the multiagent regimen Hexa-CAF (27) because the study had a high percentage of patients with more differientiated tumors in advanced stage lesion and lack of response to Hexa-CAF in these patients with Broder's grade IV lesions (24,25). This line of reasoning suggests that studies in ovarian cancer are comparable only when patients have been stratified on the basis of stage and histologic grade. This greatly increases the number of patients to achieve required meaningful statistical analysis.

PROGNOSTIC FACTORS IN CARCINOMA OF THE OVARY



Cumulative survival by histologic type, all stages.

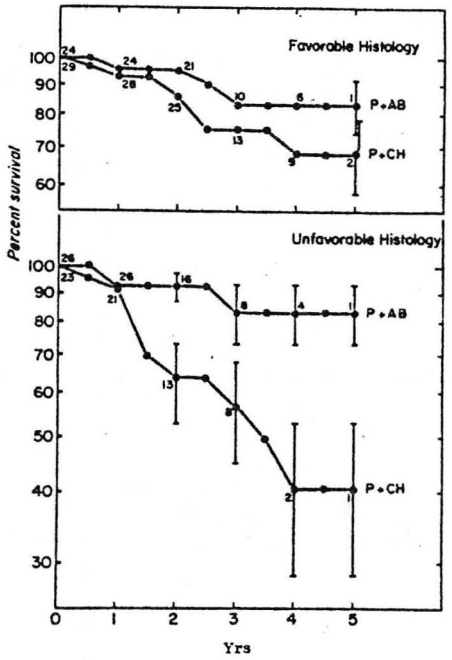
Figure 4



Cumulative survival by histologic differentiation, all stages.

Figure 5

Figure 6



—Actuarial survival curves by treatment and histology in BSOH-completed stage IB, II, and asymptomatic III patients.

TABLE 5

THE DISTRIBUTION OF HISTOLOGIC DIFFERENTIATION IN THE DIFFERENT STAGE GROUPS AND THE *P* VALUE FOR SURVIVAL

	Histologic grade				
	Poorly differ.		Well–moderately differ.		
Stage	No.	5-year survival (%)	No.	5-year survival (%)	*P*-value for cumulative survival
I–IIa	47	(53)	86	(95)	<0.0001
IIb, IIc	38	(21)	30	(68)	<0.01
III	182	(3)	54	(24)	<0.005
IV	48	(2)	9	(0)	>0.5

TABLE 6

DISTRIBUTION OF HISTOLOGIC TYPE AND DIFFERENTIATION IN STAGES I–IIa AND IIb AND IIc TUMORS

	Histologic grade					
	Stages I–IIa			Stages IIb, IIc		
Histologic type	Poorly (%)	Well–moderately (%)	Total	Poorly (%)	Well–moderately (%)	Total
Serous	22 (41)	32 (59)	54	18 (62)	11 (38)	29
Mucinous	5 (11)	40 (89)	45	1 (12)	7 (88)	8
Endometrioid	10 (42)	14 (58)	24	10 (56)	8 (44)	18
Mesonefroid	8 (100)		8	6 (60)	4 (40)	10
Anaplastic	2 (100)		2	3 (100)		3
Total	47 (35)	86 (65)	133	38 (56)	30 (44)	68

TABLE 7

DISTRIBUTION OF HISTOLOGIC TYPE AND DIFFERENTIATION IN STAGE III AND IV TUMORS

	Histologic grade					
	Stage III			Stage IV		
Histologic type	Poorly (%)	Well–moderately (%)	Total	Poorly (%)	Well–moderately (%)	Total
Serous	100 (77)	30 (23)	130	23 (85)	4 (15)	27
Mucinous	7 (33)	14 (67)	21	5 (56)	4 (44)	9
Endometrioid	26 (74)	9 (26)	35	2 (67)	1 (33)	3
Mesonefroid	10 (100)		10	3 (100)		3
Anaplastic	24 (100)		24	10 (100)		10
Adenocancer (ungraded)	15 (94)	1 (6)	16	5 (100)		5
Total	182 (77)	54 (23)	236	48 (84)	9 (16)	57

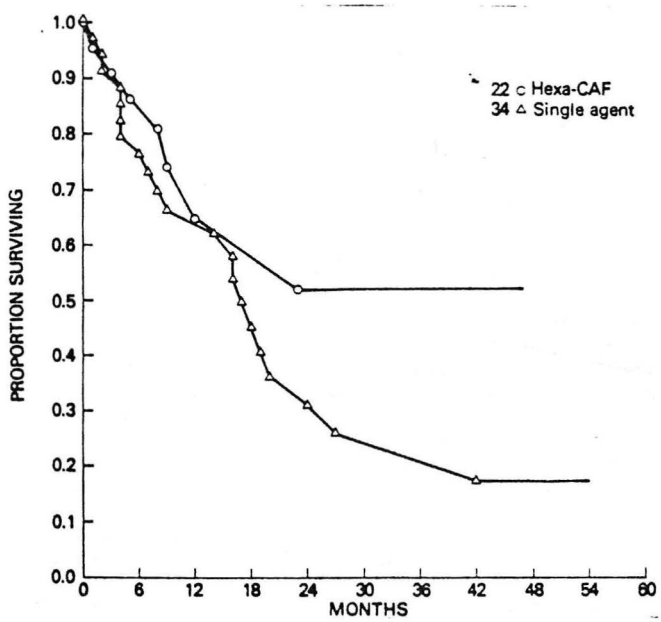
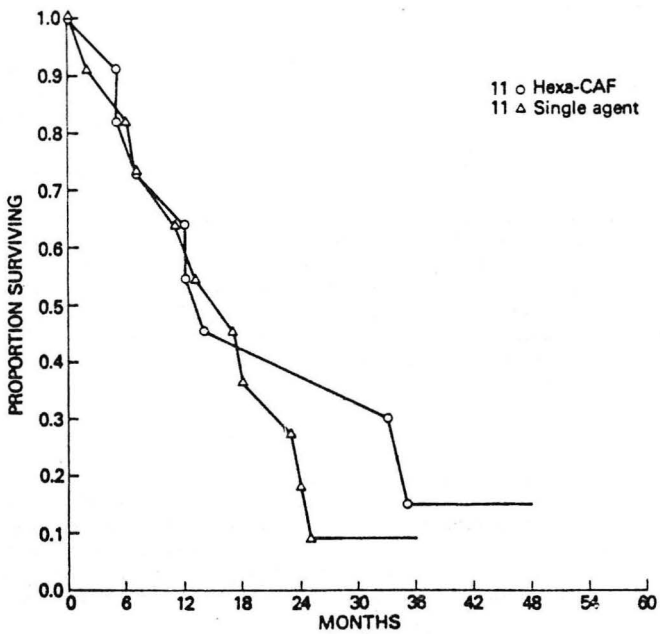


Figure 7

Survival of patients with advanced-stage ovarian cancer and modified Broders' Grades 2–3 as a function of single-agent or combination chemotherapy.

Figure 8

Survival of patients with advanced-stage ovarian cancer and modified Broders' Grade 4 as a function of single-agent or combination chemotherapy.



Pathologic Evaluation:

Appropriate pathologic evaluation should include the following:

1. Review of all tissue and peritoneal fluid cell blocks by at least two independent observers
2. Determination of histologic type
3. Determination of histologic grade
4. Review by ovarian cancer referral center

C. Biologic Markers: Tumor Antigens

Since at least 70% of patients with ovarian carcinoma present with advanced disease at the time of diagnosis, there is vital need for the identification of tumor markers specific for ovarian cancer. Tumor specific markers, alpha-fetoprotein and beta-hCG, have been particularly useful in the detection of testicular germ cell tumors, monitoring the response to therapy, and, more recently, for immunodetection of tumor masses. Both these markers have proven useful only in ovarian germ cell tumors but are not present in epithelial ovarian carcinoma. A variety of markers have been identified in patients with ovarian carcinoma, some of which may be of limited usefulness. None of these meet the ideal criteria listed below (Table 8); most of them lack specificity.

TABLE 8

CRITERIA FOR OVARIAN TUMOR MARKERS

1. Present in serum
2. Detectable at low levels
3. Detectable in Stage I/II
4. Specific for ovarian cancer
5. Level reflects tumor burden

1. Ovarian Cystadenocarcinoma-Associated Antigens (OCAA)

The antigen was initially isolated from an ovarian carcinoma, and it is present in 70% of patients (28,29). The antigen is polyclonal. The antigen is not specific for gynecologic tissue, having been found at least in colon, breast, and cervical malignancies. It probably is not detectable in limited ovarian malignancies (30). Battacharya and Barlow have shown a "reasonable" correlation with the extent of disease and the circulating antigen level (27). The antibody which is presently available appears to be of limited usefulness.

2. Ovarian Tumor Associated Fraction (OCA)

Knauf and Umbach have isolated antigen that can be detected in the plasma of patients with early and advanced ovarian cancer regardless of the pathologic type or the degree of differentiation (31,32). Unfortunately, OCA antibody and the antibody for CEA (carcinoembryonal antigen) cross react. An antigen, NB/70K, which does not react with CEA has been isolated from OCA; to date there are no reports of its usefulness in ovarian cancer (33).

3. OC125

OC125 is a murine monoclonal antibody derived from a human ovarian carcinoma cell line OVCA433. It recognizes a glycoprotein antigen of approximately 110,000 daltons which is present in cells of mullerian related differentiation (34,35). The antigen is elevated in approximately 70% of patients with advanced ovarian cancer. It appears to be rather specific for ovarian carcinoma but does cross react with at least one melanoma cell line (34). The antigen is present in low levels in normal controls and can be elevated in serum from patients with pancreatic carcinoma (36). Bast et al has recently demonstrated that the antigen level correlates with the extent of disease and disease recurrence (36). CEA levels did not correlate with either the extent of disease or disease recurrence in the same patients. OC125 is by far the most promising marker for monitoring the extent of disease and response to therapy. In view of its possitivity in pancreatic cancer, it will not be helpful in discriminating the origin of carcinomas of unknown primary in women presenting with ascites. It may be useful for detection of metastatic disease, but will not be useful for immunotoxin therapy.

4. Pregnancy-Associated α_2-glycoprotein (α_2-PAG)

This antigen or group of antigens has been isolated by many investigators (37). Elevated levels are present in 80% of patients with epithelial ovarian carcinomas; lower levels of the antigen are present in controls and patients with benign tumors. Although there is a statistically significant difference in levels of patients with and without ovarian cancer, considerable overlap of these groups occurs. Thus, these antigens are of questionable use as tumor markers because of poor sensitivity.

5. Carcinoembryonic Antigen (CEA)

CEA appears to be an antigen associated with mucinons carcinoma. Its role in ovarian carcinoma is severely limited. It is found in 30-50% of the patients with ovarian carcinoma, and its level does not correlate well with the extent of disease (35,36,37). However, an increase in the level of the antigen does suggest disease progression. It, thus, may be somewhat useful in patients who have been shown to be CEA positive as a means of crudely monitoring the extent of disease.

III. THERAPEUTIC CONSIDERATIONS: The Curability of Ovarian Cancer

Because ovarian cancer is typically not resectable at the time of presentation and because the rate of cure is so low, gynecologic oncologists have historically used multi-modal and novel approaches to therapy. The chronic lack of success has made investigators more adventurous and more aggressive. The present schema of therapy is based on the prognostic factors, stage and histologic type and grade, and the amount of residual tumor that is present. The rational application of treatment based on the biological principles of the tumor growth and spread makes ovarian cancer an excellent model which can be applied similarly to other tumors. Because the prognostic factors are so important, therapy will be discussed on the basis of stage and histologic grading. In the discussion that follows, the underlying assumption will be that the patient has been adequately staged and that the histologic grade is correct.

A. Stage I: "Only Surgery?"

In section II the importance of adequate staging and pathologic review was stressed; these are the paramount considerations in a rational treatment of stage I tumors. Surgery is the primary mode of therapy. Almost all investigators agree that stage Ia disease should be treated by a bilateral saligingo-oophorectomy (BSO) and total abdominal hysterectomy (TAH) (10,38). When the lesion is a borderline grade malignancy and the patient is premenopausal and desirous of having children, most surgeons would be willing to remove the involved ovary and biopsy the remaining ovary (38). If the lesion involved the second ovary as well (Ib) or if there were ascites, the surgeon would proceed to do a complete staging procedure (see section II). All postmenopausal patients would undergo a BSO-TAH as there is no need for preservation of ovarian or uterine function. All clinical stage Ib and Ic cell patients require a complete staging procedure since at least 30% will be converted to a more extensive pathologic stage (10).

The issues of controversy are what additional therapy is required following surgery. Certainly low grade or borderline malignant lesions require none since at least 87% have a 5 year survival without further therapy (20). Four major studies have evaluated postoperative radiation therapy in stage I disease, none of which demonstrated an effect (23,39, 40,41). The role of chemotherapy appears equally as useless (9). In those few randomized studies (23,41) survival is not different in those patients who received further therapy. The chemotherapy used was typically a single alkylating agent which has been shown to be less effective than more aggressive multiagent therapy in more advanced disease. Since the results in stage I with no further therapy are so good and the number of patients with stage I so few, it is unlikely that any of these studies would have been able to demonstate a statistical difference in survival discriminating among the therapeutic approaches. When the histologic grade is considered as another variable, even larger patient populations are required to prove significance. Presently, the Ovarian Cancer Study Group and the Gynecologic Oncology Group are investigating the role of intracavitary ^{32}P or melphelan in patients with stage I with extra ovarian capsule extension, ascites, and/or unfavorable histologic grade.

Recommendations:

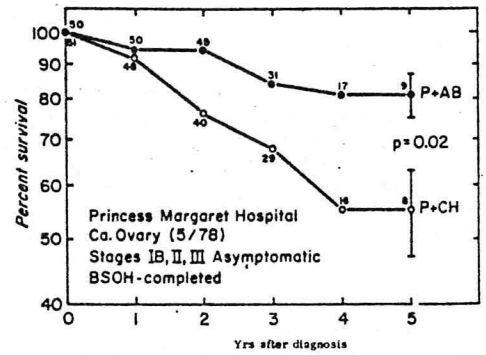
For stage I lesions with a well differentiated or moderate tumor grade, a complete staging procedure appears appropriate. When ascites (Ic) or extracapsular extension is present or the tumor is poorly differentiated, then additional therapy is probably indicated. No one knows which therapeutic approach should be used. Since patients with carefully evaluated aggressive stage I disease are rare, we recommend that the patient be referred to the Gynecologic Oncology Group (Dr. Herbert Buchsbaum, Department of Obstetrics and Gynecology, UTHSCD) for entry onto their protocol.

B. Stage II: "Anxious Waiting"

With careful staging the percentage of patients who remain stage II is quite small, probably less than 10% (10). The group of true stage II tumors becomes even smaller if one presumes that patients with IIc disease

(extension to other pelvic structure with malignant ascites) are really stage III without biopsy proof of malignant invasion of peritoneal or seronal surfaces. The therapeutic approach reflects this dilemma. The recurrence for survival of pathologic stage II patients at five years is about 60% (42). In order to achieve this rate, a complete surgical staging procedure is required. None of the prospective randomized trials document a role for pelvic irradiation in stage II. In poorly staged patients the group from the Princess Margaret Hospital have shown that strip irradiation of the entire abdomen has a survival benefit in stage I, II, and asymptomatic III disease (23); single agent chemotherapy had little effect (Fig. 9). Unfortunately, because of the inadequate staging in this study, it is impossible to determine which stages are benefitted from the radiation therapy. Clearly, those with a more aggressive histologic grade do worse (Fig. 6). Chemotherapy in this stage is poorly defined as stage I. Most studies have included radiation therapy with chemotherapy and no survival benefits have been demonstrated (23,41).

Figure 9



—Actuarial survival curves of BSOH-completed patients, stages IB, II, and asymptomatic III, by treatment.

Recommendations:

All patients should have a complete staging procedure (Table 4). In reviewing the literature it is difficult to prove a significant survival benefit in carefully staged patients with either postoperative radiation or chemotherapy. Considering the proven high rate of second malignancies in patients treated with either or both alkylating agents and radiotherapy, it is probably inappropriate to recommend indiscriminate use of either or both modalities (43). If one could predict which patients would recur following either radiation or chemotherapy (40% of patients), our recommendation would be to be more aggressive in this group of patients following surgery. Possibly, tumor markers will be useful in discriminating these patients. Probably only twenty percent of patients are affected by either the radiation or single agent chemotherapy. By treating all patients we are reducing the ability of patients to respond to more aggressive therapies in the future as a result of decreased bone marrow reserve or the selection of drug resistant tumor cells (9). Since patients can now be followed with periodic peritoneoscopy and cytologic examination of peritoneal washings

(9), it is appropriate to consider aggressively following stage IIb patients after a complete staging procedure (monthly physical examination and tumor markers and peritoneoscopy every six months) and to wait for intra-abdominal recurrence before treating. This would alleviate the risk of second malignancies in patients who would be cured of ovarian cancer by surgery alone. One would only treat those patients who had actually recurred. Considering the successful results in patients presenting with minimal stage III disease, this would be the least morbid approach.

C. Stage III and IV: "Try to Cure"

At least seventy percent of patients with ovarian cancer present with stage III and rarely stage IV disease. Once disease has spread throughout the abdomen the two important prognostic factors are the extent of residual disease following cytoreductive surgery (19,44) and the histologic grade of the tumor. Initial studies demonstrated a survival benefit with reduction of the total measurable tumor mass to less than 2 cm (19,44). Considering the massive disease with which most stage III and IV patients present, surgery requires removing kilograms of tumors as well as the involved viscera. The literature is replete with reports of bowel obstruction (45) and urinary tract obstruction (46) being associated with worse survival than those patients with similar tumor burden without obstruction. But prophylactic bowel resection and urinary diversion are common events in cytoreduction. Even if bowel resection is not required, tumor masses must be removed or stripped from the serosal surfaces. A recent paper from UCLA suggests a survival benefit if the total tumor mass can be reduced to microscopic disease with an intermediate benefit for patients with residual masses of 0.5-1.5 cm (Fig. 10). The mass of tumor present preoperatively did correlate with survival (Fig. 11) (15). Reports presented at the 1983 American Society of Clinical Oncology meeting suggest that if there is any microscopic disease present following cytoreduction surgery, patients could not be cured with the addition of multiagent chemotherapy (47,48). Similarly, in patients in whom a complete remission could not be induced, further cytoreductive surgery to achieve no residual disease prolonged survival but has not resulted in curing patients (48,49).

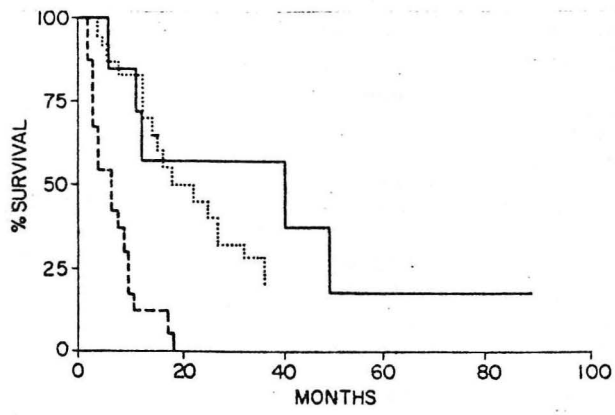


Figure 10

Survival versus diameter of largest residual disease. Broken line = diameter > 1.5 cm, 16 patients with median survival six months; dotted line = diameter 0.5–1.5 cm, 24 patients with median survival 18 months; solid line = diameter < 0.5 cm, seven patients with median survival 40 months. $P < .001$.

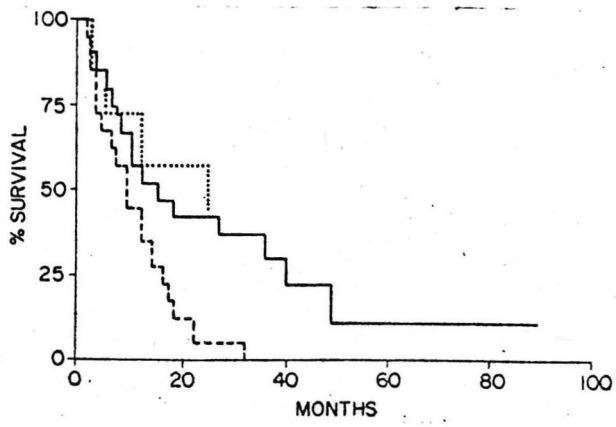


Figure 11

Survival versus diameter of largest metastatic disease before cytoreduction. Broken line = diameter > 10 cm, 19 patients with median survival nine months; solid line = diameter 1.5–10 cm, 21 patients with median survival 15 months; dotted line = diameter < 1.5 cm, seven patients with median survival 25 months. $P < .03$.

TABLE 9

Single agents active in advanced ovarian adenocarcinoma

Drug	Schedule	Patients (no.)	Response rate (%)
Alkylating agents			
Melphalan	0.2 mg/kg/day X 5 p.o. or i.v. q 35 wk	494	47 (20 complete)
Chlorambucil	0.2 mg/kg/day p.o.	280	50
Thiotepa	10 mg/day X 15 courses i.v.	144	65
Cyclophosphamide	50–150 mg/day p.o.	126	49
	400 mg/day X 4 days i.v. then 50–150 mg/day p.o.	104	37
Mechlorethamine	0.2 mg/kg/day X 2 i.v. then chlorambucil 8–14 mg/day p.o.	81	35
Antimetabolites			
5-Fluorouracil	15 mg/kg/day X 5 then 7.5 mg/kg q.o.d./34 wk	81	32 (18–20)
	15 mg/kg i.v./wk	21	33
Methotrexate	5 mg/day X 5–10 p.o. or i.v. 3–4 wk	16	25
	1–7.5 gm/m^2 i.v. wk with leukovorin rescue	23	13
Vinca alkaloids			
Vinblastine	0.1–0.15 mg/kg/day X 1–3 i.v.	16	13
Miscellaneous			
Hexamethylmelamine	8 mg/kg/day p.o. or 6 mg/kg/day p.o. X 14 days q 4 wk	53	41
Doxorubicin hydrochloride	30 mg/m^2/day X 3 i.v.	18	28
	50 mg/m^2 i.v. q 3 wk	33	36
Progestogens	200–600 mg/wk i.m.	50	10
Cisplatin	30 mg/m^2 daily i.v. X 3 q 28 days	34	27

An alternative approach would be to treat patients with stage III and IV disease with chemotherapy followed by cytoreduction surgery when bulk disease remains, a scheme which has been most successful in treating germ cell tumors. This plan might obviate the need for massive surgery. Unfortunately, that data which exists suggest that preoperative chemotherapy will not apparently work in ovarian cancer. This is supported by our inability to attain cures in patients undergoing cytoreductive therapy following primary surgery and chemotherapy. However, no study has examined preoperative chemotherapy prospectively. It is possible that chemotherapy might be more successful in controlling disease if there had been no surgical disruption of the vascular supply to the tumor. A second point is that the chemotherapy presently used in ovarian cancer is not as successful as germ cell neoplasm; a 60-70% complete response rate cannot be achieved with any chemotherapy. Histologic grade IV tumors respond poorly to chemotherapy (27); high grade tumors may be the ones with the residual disease following chemotherapy. Therefore, preoperative chemotherapy may become important with patient selection according to histologic grade or when better drug schedules or drugs become available.

Chemotherapy has been used as an adjunct to surgery and/or radiation therapy in advanced ovarian cancer essentially since it became available. The drugs which have some therapeutic efficacy as single agents in this disease are listed in Table 9. An important point to consider when evaluating the usefulness of drugs in ovarian cancer is that older agents were given to patients who had never received chemotherapy, whereas newer agents were studied in patients who had failed at least alkylating agents. Young and his colleagues have demonstrated almost universal drug resistance to active combination therapy in patients who have been previously treated with alkylating agents (27). This is not the experience of oncologists in treating most other tumors which respond well to single agents, like lymphoma, breast, testicular, and leukemia, but it is similar to that which is observed in oat cell carcinoma of the lung. The most active agents available are alkylating agents (melphelan, chlorambucil, cyclophosphamide), 5 fluorouracil, methotrexate, hexametheylmelamine, adriamycin, and cisplatinum (9). The first randomized trial comparing multiagent therapy with single agents in ovarian cancer was reported by the National Cancer Institute in 1978 (27). It compared Hexa-CAF (hexamethylmelamine, cyclophosphamide, adriamycin, and 5-FU) with standard therapy in advanced disease, single agent melphelan. It was important because patients were meticulously staged preoperatively and at the completion of six months of chemotherapy. It demonstrated the efficacy of multiagent over single agent therapy (Fig. 7), but it also showed that ultimate survival did not change in patients with advanced disease (Fig. 8). As mentioned previously, this study has been criticized because of the large proportion of histologic grade II and III tumors. Later studies without this random selection have had difficulty duplicating these results (47,50,51). In addition, using Hexa-CAF Young et al showed the importance of residual tumor burden following cytoreductive therapy as a predictor of response to chemotherapy (27). Table 10 is a compilation of results obtained with Hexa-CAF and other drugs with respect to residual tumor burden (52).

TABLE 10

OVARIAN CANCER: EFFECT OF RESIDUAL DISEASE ON RESPONSE TO CHEMOTHERAPY

Drug Regimen	Disease Status after Laparotomy (<3 cm masses) % CR : Pathologic	(>3 cm masses) % CR
Hexa-CAF (NCI)[48]	100% (8/8)	16% (5/32)
CHex-UP (NCI)[53]	36% (5/14)	14% (5/37)
H-CAP (Vanderbilt)[54]	86% (18/21)	11% (3/29)
A-C (Sidney Farber)[55]	92% (11/12)	4% (1/24)
PAC (Indiana)[56]	30% (5/17)	13% (5/39)
Mean:	69% (30-100%)	11% (4-16%)
CHAD (ECOG)[57]	100% (5/5)*	48% (10/21)*

*Clinical CR

Recommendations:

Cytoreductive surgery is critical. It appears that it must be done prior to chemotherapy. Since the presently available chemotherapeutic regimens cannot attain cures in patients who have macroscopic residual disease, cytoreductive therapy must if possible reduce the residual disease to microscopic levels. Therefore, cytoreductive therapy must be as aggressive as the patient can tolerate. It must also be emphasized that there is a group of patients with massive disease in whom a significant debulking procedure cannot be done. When considering the results of the ability to achieve complete responses and cures in patients, a primary debulking procedure which cannot reduce the tumor mass to less than 2 cm should not be done. When this can be determined preoperatively in patients, it is more cogent to take a palliative approach and treat with preoperative chemotherapy.

Because there are so many active agents in ovarian cancer, it is difficult to determine the most active combination. Most randomized trials comparing multiple agents have been presented only in abstract and, as such, have too few patients entered, do not stratify their groups according to histologic grade, and, often in cooperative group trials, do not require second or third laparotomies to document complete response. Thus, the reviewer is often comparing apples and oranges. Although many multi-drug regimens are active, none to date appears optimal. There are three approaches available to the gynecologic oncologist. The first is that it doesn't matter. These nihilists will treat patients with bulky residual disease with single agent therapy since the patients will die anyway, and this approach is relatively nontoxic. They will use radiation therapy for bulky residual disease. In patients with little or no residual tumors following cytoreductive surgery, these oncologists will use the least toxic

multiagent regimen available with decent response rates--which is probably adriamycin plus cytoxan (55). This avoids the use of hexamethylmelamine and cisplatinum, the two most effective single agents which are not tolerated because of severe emesis. The second group of oncologists will be very aggressive--using the latest, most complex regimens with drugs which have no proven efficacy over previous regimens using fewer drugs on the assumption that more is better (58). Unfortunately, the patient under most circumstances is subjected to maximal toxicity without achieving additional benefits. The third alternative is to enter the patient in a clinical trial. Being an academic oncologist, it is my bias that this is the most appropriate approach. It is especially important in ovarian carcinoma where tremendous advances have been made toward curing patients with very few patients extended into trials. It is conceivable that with greater patient accession, advanced ovarian cancer could become curable in the near future.

Residual Disease: Palliation

Following the completion of a chemotherapeutic regimen, usually 6 months of therapy, the patient must be extensively reevaluated to determine if a complete response has been obtained. If a complete response has not been obtained then, additional therapy is probably indicated:

1) cytoreduction therapy for bulk disease,
2) more systemic chemotherapy,
3) local-regional therapies.

As discussed earlier, cytoreduction surgery does improve survival but does not increase the cure rate (49). Young et al have achieved complete response with additional chemotherapy in approximately one fourth of patients with microscopic residual disease following Hexa-CAF therapy. But it is clear that patients who do not achieve a complete remission with the initial therapy are not likely to achieve a complete response with additional chemotherapy (9). For this reason other approaches have been considered which include intraperitoneal chemotherapy (59) and total abdominal radiation (60). The intraperitoneal infusion studies have shown tumors to be responsive if the drug had not been given intravenously. No long term complete remissions have been achieved with this technique, but it is presently under active investigation (59). Fuks et al have shown that stage III minimum residual disease can be controlled with radiation therapy (60). Their results do not appear quite as good as chemotherapy. However, these results have prompted a number of studies which combine radiation therapy with chemotherapy in patients with residual disease following cytoreductive surgery. Radiation sensitizers are also being studied as means of increasing the therapeutic efficacy of the radiation therapy.

Another approach in patients with residual disease has been to study tumor cells in the human tumor clonogenic assay (61,62,63). Because the cells are viable in ascitic fluid, they are relatively easy to clone and can be tested against many drugs. Using this technique to select therapy, Alberts et al were able to demonstrate improved survival (63).

Recommendations:

The approach to residual disease is palliative. Most therapies are experimental and have considerable associated morbidity and little likelihood of improved survival. The alternatives available to the oncologist

are to recommend local/regional radiation therapy, to treat the patient symptomatically, or to enter the patient in an experimental trial. This decision must be individualized on the basis of the patient's extent of disease, performance status, and desire for additional therapy.

IV. CONCLUSIONS

The preceding discussion has focused on those factors in epithelial ovarian cancer which affect the patient's prognosis, the extent of disease as determined by pathological staging, the histologic grade or type of tumor, and the amount of residual disease following staging procedures. These prognostic indicators have been integrated into a rational treatment program. The direct correspondence of these oncologic principles with response to therapy has made ovarian cancer an excellent therapeutic model for study in lecture halls, classrooms, laboratories, and patients. If the recent progress in understanding the biologic behavior and in the treatment of ovarian cancer continues, it may indeed become a curable malignancy in the very near future.

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