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Malignant Epithelial Ovarian Tumours

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Ovarian cancer continues to have the highest mortality of all gynecological malignancies and is the least able to be diagnosed at an early stage. It is the fourth most common cause of cancer death in women, and the leading cause of gynecologic cancer death in the developed world (Boring et al 1994). Approximately 90% are epithelial carcinomas, and nearly 75% will have spread beyond the ovaries at the time of diagnosis (Young et al 1993). Since only a minority of women present with surgically curable localised disease, systemic chemotherapy has become the mainstay of treatment. Although much progress has been made in this regard over the last 20 years, the high response rates observed with chemotherapy have not readily translated into major long-term survival gains, and the overall 5-year survival is still less than 30% (Neijt et al 1991). The need for new therapeutic strategies is therefore paramount.

Etiopathology: The risk for developing ovarian cancer increases after 40 years of age, with the peak incidence between the ages of 50 and 55, and a median age of 59. General trends of higher incidence in the upper middle class especially in industrialised countries suggest environmental, dietary or pregnancy practices as possible etiologic factors in ovarian cancer. Environmental factors such as industrial pollutants, talc and asbestos have been implicated. So are a high-fat diet, hormonal, genetic and hereditary factors, number of pregnancies and, to a lesser degree, specific blood group factors and viruses have all been believed to contribute to the cause. In an attempt to unite several theories of the development of ovarian carcinoma, a theory of pathogenesis has been suggested (Cramer and Welch 1983).

Epithelial ovarian tumours arise from surface epithelium of the ovary which develops from the celomic epithelium (mesothelium) of the embryonic gonad. The latter epithelium is continuous with the celomic epithelium that penetrates the underlying mesenchyme to form the müllerian duct. This proximity is reflected in the various directions of müllerian differentiation pursued by the surface epithelium when it undergoes neoplasia in the postnatal ovary, that is fallopian tube epithelium, in cases of serous neoplasia, endometrial epithelium in case of endometroid tumours, and endocervical epithelium in cases of mucinous neoplasia. Although common epithelial tumours (Table 22.1) may arise directly from the surface epithelium and grow exophytically, more commonly, they appear to originate from its

TABLE 22.1: COMMON EPITHELIAL TUMOURS—HISTOLOGICAL WHO CLASSIFICATION OF OVARIAN TUMOURS

	Type	*Borderline*	*Malignant*
A	Serous tumours	serous cystadenoma, papillary serous cystadenoma, surface papilloma	cystadenocarcinoma, papillary serous cystadenocarcinomama, papillary adenocarcinoma;
		adenofibroma cystadenofibroma	malignant adenofibroma,cystadenofibroma
B	Mucinous	mucinous cystadenoma, adenofibroma cystadenifibroma	cystadenocarcinoma, cystadenocarcinoma; malignant adenofibroma,cystadenofibroma
C	Endometroid	adenoma, cystadenoma adenofibroma, cystadenofibroma	adenocarcinoma, adenoacanthoma, malignant adenofibroma and cystadeno fibroma; endometrial stromal sarcoma; mixed mesodermal tumours-homologous and heterologous
D	Clear cell (Mesonephroid)	clear cell adenoma	carcinoma, adenocarcinoma
E	Brenner	proliferating tumour	malignant tumour
F	Undifferentiated	-	carcinoma
G	Mixed	borderline tumour	malignant tumour
H	Unclassified	-	-

(Source: Serov et al, 1973)

inclusion glands, accounting for the basically cystic or endophytic nature of most of these tumours. Initially, inclusion cysts containing surface epithelium are formed by entrapment of ovarian surface epithelium in the ovarian stroma. This is followed by abnormal proliferation and malignant transformation of the epithelial lining of the inclusion cyst. They become solid when they contain a large component of ovarian stromal origin or when malignant neoplastic cells proliferate to form masses containing varying amounts of tumour cells and stroma. The abnormal proliferation of epithelial lining of inclusion cysts and to some extent, their malignant transformation, may occur by stimulation of high levels of gonadotrophins or estrogens. Both oral contraceptive use and pregnancy decrease the pituitary gonadotrophin excretion, and are associated with significantly lower incidence of ovarian cancer. These may exert their protective effects by inhibiting incessant ovulation, a proposed cause of inclusion cyst formation. High gonadotrophins increase with age, and reach their peak at the age when the incidence of ovarian cancer is highest. Premature ovarian failure, such as depletion of oocytes from mumps virus or chemicals such as talc or asbestos, would also be associated with high levels of gonadotrophin early in life. High levels of gonadotrophins could reflect estrogen degradation in the liver caused by exogenous toxic chemicals or drugs. High estrogen sources could be exogenous, non-contraceptive estrogens, or endogenous in diseases that cause high estrogen levels

from extra-glandular sources secondary to increased estrogen stores in adipose tissue in obese individuals.

Compiling the family cancer history through second degree relatives could, in certain circumstances, show at a glance that one may be dealing with a cancer aggregation consonant with hereditary cancer.

Screening: Screening for epithelial ovarian tumours remains one of medicine's greatest challenges after enormous advances in tumour marker and ultrasound technology, combined with sophisticated statistical analysis. A premalignant precursor lesion for ovarian cancer has not been identified, limiting the focus of screening at present to detection of asymptomatic, early stage disease. The relationship between stage at presentation and survival in ovarian cancer has long provided a rationale for efforts to improve outcome by detection of early stage disease. An attempt has been made to apply WHO screening criteria to ovarian cancer to assess the potential for early detection of the disease (Rosenthal and Jacobs 1998).

Specificity is a major consideration in ovarian cancer screening because the majority of women who test positive will require exploratory surgery. A variety of different modalities have been used to detect ovarian cancer in asymptomatic women. Although vaginal examination remains important in the assessment of women presenting with gynecological symptoms, it cannot be recommended as a first line screening tool in asymptomatic women (MacFarlane et al 1955; Andolf et al 1986; Jacob and Oram 1990).

A variety of ovarian tumour markers have been studied. The most extensively investigated of these is measurement of the tumour marker cancer antigen 125 (CA125) in serum. The use of combination of markers to increase the sensitivity and specificity has been widely investigated. The marker that appeared to exhibit complementarity to CA125 was OVX1 (Xu et al 1993; Woolas et al 1993), a monoclonal antibody developed using sequential immunisation with three different ovarian cancer cell lines. It is unstable unless serum is rapidly separated: a viable humoral marker has not yet been found. Ovarian Cancer Activating Factor, a species of lysophosphatidic acids capable of stimulating cancer cell proliferation which correlates with surgical stage did promise, but the procedure is quite involved for a screening test (Xu et al 1998). Serum analysed by an iterative searching algorithm that identified a proteomic pattern, could completely distinguish patients with cancer from those without with 100% sensitivity (95% CI 93–100) and 95% specificity (Petricoin III et al 2002; Singh et al 2006). Prostacin, a potential serum marker for ovarian cancer identified through microarray technology, demonstrates utility of expression arrays in identifying genes that may lead to the discovery of novel tumour markers (Mok et al 2001). Digital analysis of single nucleotide polymorphism (SNP) appears to detect ovarian cancer very well and is far more precise than other available tests. It is claimed to detect "allelic imbalance" in 87% of early disease, 95% of late disease and none in healthy controls (Chang et al 2002). However, as of now it is expensive and labour intensive.

Current screening methods include transvaginal ultrasound scanning of the ovaries and measurement of CA125 in serum. Although several other tumour markers have been associated with ovarian cancer, they have not been widely tested for screening purposes. When used for screening, CA125 measurement

is usually followed by ultrasound scanning in women with abnormal levels. The definition of abnormal level varies with menopausal status. The presence of rising CA125 levels obtained by serial measurements has also been used to indicate possible tumour activity. A sophisticated approach to interpretation of CA125 using an algorithm incorporating age and rate of change of CA125 as well as absolute levels has been made. The algorithm uses an individual's sequential CA125 results, from which the slope and intercept are calculated. The higher the slope or intercept, the greater is the risk of ovarian cancer (Skates et al 1995).

Transvaginal ultrasound scanning which offers greater resolution by virtue of closer proximity of the probe to the ovaries would be a sensitive tool. There are no universally-accepted criteria for distinguishing between benign and malignant conditions on the basis of ultrasound findings. Several systems for classifying and scoring abnormalities in the form of a morphological index (Sassone et al 1991; Learner et al 1994; Bourne et al 1993; Ferrazzi et al 1997) have been described. At the moment, no test has been proved reliable enough to screen for ovarian cancer in the general population. Two distinct screening strategies have emerged, one ultrasound based and the other based on measurement of the serum tumour marker CA125, with ultrasound as the secondary test (multimodal screening). Overall, the interim data from large prospective studies of screening for ovarian cancer in the general population (UKCTOCS; US Preventive Services Task Force 2004) suggest that sequential multimodal screening has superior specificity and positive predictive value compared with strategies based on transvaginal ultrasound alone. However, ultrasound as a first-line test may offer greater sensitivity for early stage disease. Other high modalities, such as radioimmunoscintigraphy, may yet have a role as second- or third-line tests, but will never be practical for mass screening.

To help determine preoperatively the patients with adnexal mass(es) as benign or likely to be malignant, various scoring systems to calculate risk of malignancy index using menopausal status, CA125 value and ovarian morphological scores have been proposed (Jacobs et al 1990; Tingulstad et al 1996; Tingulstad et al 1999). The value of detection of normal ovarian tissue (ovarian crescent sign) in the differential diagnosis of adnexal masses is suggested (Hillaby et al 2004) and appears simple, immediate and comparable to the scorings of malignancy indices (Kalghatgi 2006).

Staging: In order to manage patients with ovarian cancer properly, surgical exploration of abdomen cavity is necessary at the outset of therapy, and surgical staging has become mandatory, by convention, to document the precise extent of disease prior to the recommendation of adjuvant therapy, because occult dissemination may have occurred in patients whose disease is apparently confined to the ovaries. It has been seen that in many patients who were not subjected to rigorous staging, the overall 5-year survival rates for patients with apparent early stages (stage I and II) was lesser, with relatively significant relapse in these patients (Buchsbaumm and Lifshitz 1984; Fisher and Young 1977). Transcelomic spread by exfoliation of cells is the most common mode, but the malignant cells can also metastasise via the lymphatic or blood vessels.

The staging according to the Federation of Obstetrics and Gynecology (FIGO) is listed in Table 22.2 (Benedet et al 2000).

While in some patients the diagnosis of a malignant ovarian neoplasm is strongly suspected preoperatively, the actual diagnosis is frequently not confirmed until after laparotomy. Often the diagnosis is an incidental or completely unexpected finding.

In older patients, particularly those who are postmenopausal, an adnexal mass must be presumed to be a malignancy until proved otherwise. For preoperative assessment, in addition to a complete blood count, renal and liver function tests should be obtained. Serum levels of CA125 and Carcinoembryo Antigen be obtained, and if the levels are found to be elevated they prove useful in following the progress of the disease during subsequent

TABLE 22.2: FIGO STAGING OF CARCINOMA OF THE OVARY

Staging is based on findings at clinical examination and surgical exploration. The final histologic findings (cytologic, when required) after surgery are to be considered in the staging			***TNM***
Stage I	Growth limited to ovaries		T1
	A	Growth limited to one ovary, no ascites containing malignant cells; no tumour on the external surface, capsule intact.	T1a
	B	Growth limited to both ovaries, no ascites containing malignant cells; no tumour on the external surface, capsule intact.	T1b
	C	Tumour either stage IA or IB, with any of the following: tumour on external surface of one or both ovaries, capsule ruptured or with ascites containing malignant cells or with positive peritoneal washings.	T1c
Stage II	Growth involving one or both ovaries with pelvic extension		T2
	A	Extension and/or metastasis to the uterus and/or fallopian tubes; no malignant cells in ascites or peritoneal washings	T2a
	B	Extension to other pelvic tissues; no malignant cells in ascites or peritoneal washings	T2b
	C	Tumour either stage IIA or IIB; malignant cells in ascites or peritoneal washings	T2c
Stage III	Growth involving one or both ovaries with microscopically confirmed peritoneal metastases outside the pelvis and/or regional lymph node metastases		T3 &/or N1
	A	Microscopic peritoneal metastases beyond pelvis	T3a
	B	Macroscopic peritoneal metastases beyond pelvis, 2 cm or less in greatest dimension	T3b
	C	Macroscopic peritoneal metastases beyond pelvis, more than 2 cm in greatest dimension and/or regional lymph node metastases	T3c and/or N1
Stage IV	Distant metastases beyond peritoneal cavity.		M

Note: Liver capsule metastases is Stage III; Liver parenchymal metastases is Stage IV; Pleural effusion must have positive cytology
Source: FIGO Committee on Gynecologic Oncology, 2000

chemotherapy. Radiographic studies should include a chest x-ray which may reveal pleural effusion or may suggest lung parenchymal metastatic disease that might alter the extent of attempted tumour resection in the peritoneal cavity. Pelvic and abdominal ultrasound is useful and necessary. CT or MRI scan are not mandatory, since surgical exploration and intravenous urogram are necessary. An upper gastrointestinal series and intestinal evaluation should be performed, if symptoms and signs suggest this or if stools are positive for occult blood. The technique of surgical staging (Table 22.3) is described very well in most textbooks.

If the gastrocolic ligament is palpably normal, it does not routinely require resection, since occult metastases are more often located in the infracolic omentum. The retroperitoneal spaces should be explored to document lymph node metastases. A particularly thorough dissection is warranted in lesions apparently confined to the ovary, because the discovery of disease in this situation will require adjuvant therapy.

Reports from literature document occult metastasis in over 25% of cytologic specimens, about 7% of diaphragm and periaortic lymph node biopsies, and 6% of pelvic lymph node and 8% of omental biopsies in apparent stages I and II epithelial ovarian malignancies (Berek and Hacker 1987).

Management

Despite advances, novel approaches and the wide variety of different therapies, surgery has been the cornerstone in all treatment modalities for ovarian cancers. The optimal surgical approach to a malignant tumour is resection of the tumour with wide margins of normal tissue. In many patients with ovarian cancer, it is not attainable because of the existence of early metastases. Hence, the concept of cyto (tumour) reductive surgery or debulking surgery is applied for these patients where tumour is partially removed without curative intent, in the hope of making subsequent therapy more effective (Silberman 1982). The rationale is mainly based on three theoretical considerations: first, tumour mass excision provides physiological benefit by restoring gastric function, improving nutritional status, and thereby improving the general condition of the patient, temporarily interrupting the natural course of the disease (Fuller and Griffiths 1979). Second, the cell kinetic and tumour perfusion considerations: cytoreductive surgery will remove poorly diffused masses that have tenuous vascularisation and oxygenation and decreased growth fraction rendering the tissue sensitive to carcinochemotherapeutic agents or radiotherapy. The possible role of the immune system in the defence against cancer is formulated. The surveillance hypothesis is based on the assumption that cancer cells have surface antigens and immune system producing antibodies which destroy these malignant cells as long as only a small number of such cells are present. Once the tumour has begun to grow, it starts to interfere with the host's immune mechanisms to facilitate its own growth. The role of the surgeon could be to lower the level of immune suppression by resecting the bulk of tumour.

The main goal of cytoreductive surgery is to resect all visible tumours. The benefit of reducing burden to an optimal status, if only incomplete resection is possible, is described by several authors. The considered optimal status of tumour reduction has varied from a maximum tumour diameter of as small than 5 mm (Griffiths 1975) to less than 15 mm (Hacker et al 1983).

TABLE 22.3: STAGING LAPAROTOMY	
Preoperative preparation	1. Mechanical and antibiotic bowel preparation 2. Systemic prophylactic antimicrobials
Incision	1. Midline or paramedian - preferred 2. Low transverse (inadvertent) - divide/detach rectus muscles from symphysis; may extend the incision upward on the right side
Exploration	Careful inspection and palpation of all intraabdominal surfaces and viscera proceeding in a clockwise fashion: cecum, pericolic gutter, right kidney, liver, gall bladder, right diaphragm, entrance to lesser sac at periaortic area, left side of falciform ligament, spleen, left kidney; entire length of small intestine from ligament of Trietz to cecum, including peritoneal surfaces of intestinal mesentery; ascending, transverse and sigmoid colon
Sampling	1. Malignancy confined to pelvic viscera or ovaries a. Sample all sites in upper abdomen b. Retrieve ascetic fluid if present c. Obtain peritoneal washings after instilling 50–100 ml normal saline in five sites i. Pelvic cul-de-sac ii. Each pericolic gutter iii. Under each half of diaphragm* 2. If no macroscopic evidence of disease a. Multiple intraperitoneal biopsies including pelvic cul de sac, pericolic gutters, peritoneum over bladder and rectum, small intestinal mesentery, under surfaces of diaphragm† b. Biopsy from adhesions, irregularities c. 'Pap' smear of diaphragm surface 3. All cases—exploration of retroperitoneal spaces: resection of enlarged nodes; if not enlarged, representative nodal tissue from a. Periaortic area b. Iliac area—along external, internal and common iliac vessels 4. Young patient, disease apparently confined to one ovary (stage 1A) where fertility preservation is planned—arrange for frozen section evaluation a. Biopsy from other ovary b. Plus as in (b) and (c) above
Procedures	Bilateral salpingoovariectomy, total hysterectomy, infracolic omentectomy, maximum tumour resection (in fertility-preserving surgery, only removal of affected ovary and infracolic omentectomy; other ovary, tube and uterus are preserved)

** Collection can be facilitated by the use of rubber catheters attached to bulb syringe*
† laparoscope facilitated biopsy

EARLY STAGE (STAGE I OR STAGE II DISEASE): Although the preliminary radiological findings may seem to corroborate with clinical findings of early disease, it is imperative that these patients still undergo a thorough surgical staging. The prognosis of adequately staged patients with Stage IA and Stage IB Grade I cystadenocarcinoma is extremely good:

adjuvant chemotherapy would not provide further benefits. For higher grade tumours and for patients with Stage IC, adjuvant platinum based chemotherapy should be considered, although this practice remains controversial. All patients with Stage II disease should receive adjuvant chemotherapy. The number of cycles of chemotherapy has also not been clarified but are usually 3–6 (Dembo et al 1990; Young et al 1990; DiSaia and Creasman 2002; Bell et al 2003). Although it is axiomatic that pelvic radiation therapy has no role in the treatment of early staged ovarian cancer, the role of whole-abdomen irradiation, either open field or moving strip, remains unclear.

Fertility sparing surgery: Conservative surgery for invasive epithelial ovarian cancer is controversial. However, epithelial ovarian cancer does arise in young women who have yet to complete childbearing, and conservation of the uterus and opposite ovary in stage IA cancer may be considered for these patients. The situation and surgical possibilities should be discussed preoperatively. First, frozen sections should be obtained from the involved ovary, followed by staging exploration as outlined in Table 22.3. Because of the problems associated with frozen section reporting, efforts are on to find an alternative method and evaluation of the tissues through optical diagnosis by Raman microspectroscopy and this has shown encouraging results (Muralikrishna et al 2005). If there are no high-risk features (Table 22.4) and contralateral ovary appears to be normal, then fertility sparing surgery may be an option. If high-risk features are discovered on the final histopathology, or completion of childbearing, consideration should be given to a completion hysterectomy and unilateral salpingo-ovariectomy.

Borderline tumours: Borderline tumours or those of low malignant potential tend to remain confined to the ovary for long periods and are associated with good prognosis. Although uncommon, metastatic implants may occur and these may be invasive or non-invasive. The diagnosis is based on histopathological features that is characterised by the absence of stromal invasion (Bell 1991). The principal treatment of borderline ovarian tumours is surgical resection of the primary tumour. There is no evidence that either subsequent chemotherapy or radiation therapy improve survival. For patients in whom an ovariectomy or cystectomy has been performed and a border tumour is later documented, no additional immediate surgery is necessary.

Advanced stage (Stage III and IV): The patients in advanced disease are usually quite symptomatic from the intra-abdominal disease. This may affect performance status and fitness for surgery. However, as mentioned above, one of the most critical prognostic indicators in patients with advanced stage ovarian cancer is the volume of residual disease. Therefore, all patients whose medical condition and fitness for surgery permits should undergo primary laparotomy, with maximal attempt at optimal cytoreduction (Omura 1991; DiSaia and Creasman 2002).

It should be remembered that even large epithelial ovarian cancers tend not to infiltrate deeply in the peritoneum of the pelvic wall, or invade the lumina of the colon or bladder. Hence, retroperitoneal approach for pelvic tumour dissection, entering the retroperitoneum laterally along the surface of the psoas makes surgery easier and helps to avoid the iliac vessels and the ureter. The technique of reverse hysterectomy, which uses

conventionally (Griffiths and Fuller 1978; Schwartz et al 1999). For adopting upfront chemotherapy, it is necessary that there is cytological or histopathological evidence of adenocarcinoma, at least sonographic information that it could be ovarian with extra-pelvic metastasis, and that serum CA125 levels are high.

Adjuvant chemotherapy: Patients who have had cytoreduction should receive adjuvant chemotherapy (Aabo et al 1998; DiSaia and Creasman 2002). Several combinations have been studied. Median and overall survival has improved, but the long-term survival rates have been disappointing. Thus, the priority is a more effective first-line therapy. For systemic chemotherapy, a combination of a Paclitaxel or Docetaxel with Carboplatin is the first choice. Docetaxel is considered because of its favourable neurotoxicity profile (Vasey 2002). It is hoped that gemicitabine, topotecan, doxorubicin, and prolonged use of etoposide will provide effective disease-free status.

Secondary cytoreduction: The term secondary cytoreductive surgery could be applied to cytoreductive operations performed on patients who have a recurrence after adequate initial surgery followed by complete first line chemotherapy. The term is also used by some authors to describe cytoreductive after-induction chemotherapy in patients in whom optimal cytoreductive surgery was not performed initially. Others use the name to describe tumour resections in patients who were partial responders on first-line therapy. It is preferable to restrict the use of term secondary cytoreductive surgery to those patients who undergo tumour debulking at the completion of the prescribed course of primary chemotherapy. In patients with residual lesions of more than 10 mm after primary cytoreductive surgery, secondary debulking significantly increases the progression-free and overall survival.

Second-look operation: The 'second-look' operation remains a technique for documenting response to therapy in those patients with ovarian cancer who are clinically free of disease at the time that reassessment is deemed necessary. A negative second-look operation is one that documents no pathologic evidence of persistent cancer, including all cytologic and histologic specimens. The achievement of a negative second-look is, unfortunately, no guarantee that the lesion will not recur. Indeed, the reported recurrence rates after negative second-look range from 12% to 30% over 1 to 2 years. There have been many trials studying the benefits of second-look operations. Patients who had residual disease at the end of chemotherapy treatment seem to benefit from second-look surgery while patients who were optimally debulked at initial diagnosis did not benefit. This strategy in the management of advanced ovarian cancer is therefore not considered standard (Nicoletto et al 1997; Hoskins et al 1989; Bertelsen 1990; Potter 1993). The principal value of the performance of second-look operation appears to determine when to discontinue therapy. However, if no subsequent therapy is planned, a case can be made for omission of the second-look surgery.

Laparoscopy in ovarian cancer: The role of the laparoscope in the management of patients with ovarian cancer is somewhat limited as of now. Possible uses for the

procedure are for second-look in patients who either refuse a laparotomy or are considered medically unfit to undergo a laparotomy, for the follow-up of patients with neoplasms of low malignant potential, for the evaluation of patients with low-grade stage I tumours who have received no adjuvant therapy, and for certain patients on treatment protocols which require some operative documentation of response, particularly to second line therapies (Berek and Hacker 1983). Laparoscopy has been used immediately before a planned laparotomy. If gross disease is detected and secondary dissection of the tumour is not possible, a laparotomy can be omitted. Analysing the series which report the findings of laparotomy performed immediately following a laparoscopy, it is projected that laparoscopy was able to detect disease in only two-thirds of the patients with persistent disease (Lele and Piver 1986).

Maintenance chemotherapy: At the end of six cycles of chemotherapy, maintenance chemotherapy with Paclitaxel has been shown to improve disease-free interval but not overall survival (Markman et al 2003). However, this treatment must only be offered if a patient achieves complete response to treatment, and understands the aim of treatment and its potential toxicities. There is no consensus in prolonging the treatment after complete response. Systemic chemotherapy, external radiation, intraperitoneal chemotherapy, use of radioisotopes and use of novel approaches such as biological agents and radioimmunotherapy are all suggested as measures to consolidate the disease free status after the initial treatment. The role of intraperitoneal chemotherapy remains controversial.

Monitoring after treatment

There is no evidence to show that intensive clinical monitoring in asymptomatic women has any positive impact on overall survival or on the quality of life. Nonetheless, early diagnosis of recurrence after a prolonged progression free interval is thought to offer the best results. The objectives of follow-up could be to determine patient's immediate response to the treatment employed, early recognition and prompt management of any treatment-related complications, including any psychological sequelae and early detection of persistent or recurrent disease. In general, during the first year following treatment, patients should be seen every three months with a gradual increase in intervals to every four to six months and annually after the fifth year. At each follow-up, the patient should have her history retaken; complete physical examination (including breast, pelvic and rectal examination) performed to exclude any clinical signs of recurrence. The CA125 may also be checked at regular intervals. It is unclear as to the utility of such a practice on survival impact (Bast et al 1998). Radiological tests such as ultrasonography of the pelvis, CT scans or MRI scans should only be performed when the clinical findings or the tumour markers suggest possible recurrences. All patients with intact cervix should receive a regular pap smear. All patients above the age of 40 should undergo an yearly routine mammogram, as should younger patients with a strong family history of breast cancer.

The treatment of an asymptomatic patient with recurrent disease based on tumour marker alone is difficult. When CA125 rises to twice the upper limit of normal, close observation or hormonal therapy with agents such as tamoxifen can be considered (Hatch et al 1991). In the former situation, their

treatment is deferred until clinical relapse. It is important that the patient understands that chemotherapy responses do not necessarily translate into meaningful survival prolongation. Often, improvement in quality of life and optimisation of functionality become the goals of treatment.

Management of recurrences: The majority of patients treated for advanced epithelial ovarian tumours will unfortunately relapse. Patients who had a disease-free interval of at least 6 months can be considered platinum sensitive and those patients whose disease-free interval is less than 6 months can be considered platinum refractory. Trials have also shown that the longer the platinum-free interval, the higher the response rate to further platinum, as well as non platinum treatment (Markman et al 1991; DiSaia and Creasman 2002). For patients who are platinum sensitive, Carboplatin or Cisplatin can be offered. Combination with other cytotoxic or non-cytotoxic agents may be preferable. But there are no randomised studies to suggest that combination therapy is superior to single agent platinum in terms of overall survival. Patients with localised recurrences after a long disease-free interval may benefit from a secondary cytoreduction. Repeat cytoreduction for this group of patients has hitherto been controversial.

The patients who are considered platinum refractory may be provided the option of further non-platinum chemotherapy. There are a number of choices for chemotherapy: liposomal doxorubicin, topotecan (Gordon et al 2001), etoposide (Hoskins and Swenerton 1994; Rose et al 1998) and gemcitabine (Shapiro et al 1996; Friedlander et al 1998) have all shown a response ranging between 10% and 15%, either as a single agent or in combination. There is a pressing need to evaluate the many biological or molecular-targeted agents such as inhibitors of angiogenesis (for example, the monoclonal antibody Bevacizimab), epidermal growth factor receptor tyrosine kinase inhibitors (for example, gefitinib, erlotinib, cetuximab) which are emerging rapidly from the pharmaceutical industry's drug development programmes.

Refractory ovarian cancer: The optimal management of a patient with refractory ovarian cancer requires careful assessment of the patient's physical, mental and spiritual condition. It is pertinent to identify any physical condition that may immediately affect a patient's survival or quality of life, so that adequate appropriate treatment can be given. Such physical conditions include systemic infections, intestinal obstruction, ascites, pleural effusion, and unusual metastases to organs such as the brain, liver or bone. The hitherto lack of quality of life and palliative index measurements in salvage chemotherapy treatment of these patients makes it difficult to recommend the best option. It is important to bear in mind the function of the bone marrow in the dosing of chemotherapy in patients who have had many lines of chemotherapy.

The prognosis for patients with epithelial ovarian cancer relates to several clinical variables such as the patient's age, tumour stage and tumour grade at the start of the chemotherapy, residual disease, status at second-look, patient performance status and above all, the tumour behaviour. One should remember that the patients in any particular stage do not behave as a homogenous group. They have different molecular biological characteristics. In the same vein, patients from different stages may have homogenous

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