

The current management of primary ovarian cancer: a review

Review Article

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Abbreviations: cancer services collaborative, (CSC); carcino-embryonic antigen, (CEA); Chemotherapy OR Upfront Surgery, (CHORUS); Computed tomography, (CT); Epithelial Ovarian Cancers, (EOC); European Organisation for Research and Treatment of Cancer, (EORTC); human milk factor globulins, (HMFGB); intra-peritoneal, (i.p); intra-venous, (i.v); macrophage colony stimulating factor, (M-CSF); magnetic resonance imaging, (MRI); National Cancer Research Network, (NCRN); National Institute of Clinical Excellence, (NICE); negative predictive value, (NPV); placental alkaline phosphatase, (PLAP); positive predictive value, (PPV); positron emission tomography, (PET); Risk of Malignancy Index, (RMI); risk of ovarian cancer, (ROC); tumour suppressor genes, (TSG)

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Summary

Traditionally ovarian cancer has been thought of as the 'silent killer'. In developed countries it is the leading cause of cancer related mortality among women with gynaecological cancers. In the UK several approaches are being followed that encompass provision of cancer care within the remit of the National Health Service, screening trials such as UKCTOCS, and randomisation of patients on well constructed clinical trials to improve the outcome from this disease. Established surgical and adjuvant treatments are discussed as are the various on-going clinical and experimental trials in combating this disease.

I. Introduction

Ovarian cancer affects one in seventy women and is the 4th leading cause of cancer related mortality amongst women in developed countries. Typically this cancer has an insidious onset and over 70% of women present with disease that has spread beyond the ovary and in this population, the 5-year survival is approximately 30% despite optimal surgery and aggressive chemotherapy. Each year in the UK there are 6000 new cases of ovarian cancer and 4500 deaths.

In the UK, with the development of national cancer networks providing a comprehensive care package, a multidisciplinary approach and recruitment of patients onto well-constructed clinical trials, significant inroads are being made to improve the overall and palliative outcome of patients with ovarian cancer. In addition, a better understanding of cancer aetiology is emerging with a flourish of activity in the fields of cancer genetics and molecular biology.

The remit of this review is to provide an overview of recent advances in the diagnosis and management of ovarian cancer. Epithelial cancer is the most common variant and is the primary focus of this review. The management of rare ovarian malignancies, such as germ cell tumours, hereditary ovarian cancer and recurrent disease is not described.

II. Organisation of care

In 1995, the Calman/Hine report "A policy framework for commissioning cancer services" was published in response to concerns about variations in treatment policies across the UK (A report by the expert advisory group on cancer to the chief medical officers of England and Wales. 1995; www.doh.gov.uk). In order to provide high quality cancer care, it recommended that cancer services be delivered at three levels - primary care based in the community, cancer units based in district/local hospitals, and cancer centres mainly in larger teaching hospitals. A multidisciplinary approach was

recommended in all settings. It envisaged the less common cancers and more advanced cancers be referred and treated at the cancer centres where affiliated services such as radiotherapy and advanced chemotherapy was readily available. In October 1999 delivery of this "hub and spoke" model of cancer care provision was identified as top priority by the government, so as to raise the standard and quality of cancer care across the country. To implement the necessary infrastructure, development of 34 cancer networks became mandatory, each serving a population of 1 to 2 million people.

In 2001, the Cancer Services Collaborative (CSC) published its experience of working with 9 cancer networks in redesigning services necessary to achieve the required changes (Cancer Services Collaborative: Ovarian cancer-Service improvement guide. 2001; www.nhs.npat). In summary, the CSC were able to demonstrate a significant reduction in the waiting times for diagnosis and treatment of patients with suspected ovarian cancer, an improved and standardised management of patients by the formal introduction of multidisciplinary teams, and a much greater patient satisfaction with care. Although multidisciplinary care for challenging cases has always existed in the National Health Service (NHS), a formal specialised multidisciplinary team for each cancer type is being established in all cancer units and cancer centres. For gynaecological malignancies these teams in general consist of specialist surgeons, medical and clinical oncologists, dedicated radiologists and pathologists, clinical nurse specialists, dieticians and psychosexual/social counselors.

Ovarian cancer is now largely managed within the remit of a cancer centre. It is recommended that all patients with pelvic masses suspicious of ovarian cancer be referred to the cancer centre for further surgical and possibly medical intervention. On completion of their initial treatment, continued follow up of patients is generally provided within the cancer units.

III. Pathology

Ninety to ninety-five percent of ovarian cancer is sporadic in nature with the remainder being familial. Of the sporadic cases, 90% are defined as Epithelial Ovarian Cancers (EOC), denoting their origin from the surface epithelium of the ovary or its corresponding invaginations into the ovarian stroma. Histologically EOC's comprise of Serous, Endometrioid, Mucinous, Clear Cell and Brenner subtypes, with the first being the most common. In relation to surgical and medical management of ovarian cancer this review refers to sporadic epithelial ovarian neoplasia.

Although the aetiology of sporadic ovarian cancer is unknown, epidemiological studies identify numerous factors that may influence the risk of developing it. The number of ovulatory cycles in a women's reproductive lifetime is the most significant of these associations giving rise to the "incessant ovulation" hypothesis (Fathalla, 1971). Theoretically, the repetitive disruption and repair of the surface epithelium of the ovary during ovulation may lead to spontaneous genetic mutations that in turn may confer an oncogenic genotype to the epithelial cells. Therefore, reducing the number of ovulatory cycles may

result in a decreased risk of developing this disease. Indeed multiparity, breast feeding, late menarche and early menopause, that all result in decreased ovulation, have all been shown to confer a protective effect. Use of the combined oral contraceptive pill is associated with up to a 70% reduction in developing EOC after 10 years or more of use compared with no-use, although this reduction appears to be vastly disproportionate to the decrease in number of ovulations inhibited (Gross and Schlesselman, 1994). Progestins have a potent apoptotic effect on ovarian epithelium as demonstrated in a study of primates receiving either combined oestrogen and progestin or progestin alone as opposed to oestrogen only therapy. A four to six-fold increase in the apoptotic activity of ovarian epithelium was noted in primates receiving a combined or single progestin regime (Rodriguez et al, 1998). Pathways regulating progestin induced apoptosis is complex, with evidence suggesting a role of differential regulation of *p53* and *TGF 11* in this process (Rodriguez et al, 2002). More recently, epidemiological data suggest an increase in the risk ratio of ovarian cancer amongst women taking oestrogen replacement in the menopause compared to those who are not (Noller, 2002). Studies have also demonstrated a small increased risk in those women taking sequential progestins along with oestrogen as compared to those taking a continuous combined form of HRT. One possible mechanism accounting for this increased risk may be the direct effect of oestrogen on epithelial ovarian cells. In cell line experiments, exposure to oestrogen results in a rapid increase in the proliferation of ovarian cancer cells (Chein et al, 1994). In addition, tamoxifen, an anti-oestrogen, has been reported to have beneficial effects in a few women with ovarian cancer.

Hereditary ovarian cancer is uncommon. Germline mutations in the *BRCA1* and *BRCA2* breast/ovarian susceptibility genes overwhelmingly account for most hereditary subtypes. *BRCA1* is located on chromosome 17q21 and encodes a large 220KDa protein expressed abundantly in testis, breast and ovarian tissue. *BRCA1* is thought to function as a tumour suppressor gene and carriers of a germline mutation have a 30-80% life time risk of developing ovarian or breast cancer. Similarly ovarian cancer has been reported to occur in 10-35% of carriers with *BRCA2* mutation located on chromosome 13 (Venkaraman, 2002). In hereditary nonpolyposis colorectal cancer, women with a mismatch repair gene mutation have been reported to have cumulative lifetime risk of 8-12% for ovarian cancer. The surveillance options and the preventative medical and surgical management of these high risk individuals are not discussed within this remit.

IV. Prognostic markers

Numerous clinicopathological variables have been identified that impact on the overall and disease-free survival of patients with ovarian cancer. These include clinical stage; volume of post-operative residual disease; histological grade including mitotic index, DNA ploidy, and cell type; presence of ascites; pre-operative rupture of ovarian tumour; pre-treatment level of serum CA125 and age and performance status of the patient. Whilst most

factors in various settings have been shown to be independent predictors of survival, the most important remain clinical stage and residual disease. The FIGO staging for ovarian cancer is shown in **Table 1**. Many oncogenes and tumour suppressor genes (TSG) have been implicated in the pathogenesis of ovarian cancer. Several of these genes are important in cell cycle regulation, in particular G₁ to S phase transition, and their aberrant expression is associated with poor prognosis. In various settings, the loss of cyclin dependent kinase inhibitors such as p21^{Waf1/Cip1}, p27^{Kip1}, inactivation of wild type p53 and overexpression of cyclin D1 have all been implicated

as markers of poor outcome in ovarian cancer. Other genetic mutations that present in ovarian cancer include overexpression/amplification of HER-2/*neu*, *c-MYC*, *BAX* and *c-FMS*. With the recent completion of the human genome and utilisation of complimentary techniques, such as oligonucleotide microarrays, the list of novel genes implicated in ovarian tumourigenesis is likely to grow. **Table 2** summarises the clinically useful prognostic variables predictive of disease outcome in ovarian cancer at various time points during treatment (Eisenhauer et al, 1999).

Table 1. FIGO staging system for ovarian cancer.

Stage I	Growth limited to ovaries
Ia	Growth limited to one ovary, no malignant cells in ascitic fluid or peritoneal washings; no tumour on external surface; capsule intact
Ib	Growth limited to both ovaries, no malignant cells in ascitic fluid or peritoneal washings; no tumour on external surface; capsule intact
Ic	As with 1a or 1b but with tumour on the surface of one or both ovaries; or with malignant cells in ascitic fluid or peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
IIa	Extension and/or metastases to the tubes and/or uterus No malignant cells in ascitic fluid or peritoneal washings
IIb	Extension to other pelvic tissues No malignant cells in ascitic fluid or peritoneal washings
IIc	As with 2a or 2b but with tumour on the surface of one or both ovaries; or with malignant cells in ascitic fluid or peritoneal washings
Stage III	Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal lymph nodes Superficial liver metastases equals stage 3
IIIa	Tumour grossly limited to true pelvis with negative nodes but histologically confirmed microscopic seeding of abdominal peritoneal surfaces
IIIb	Histologically confirmed tumour implants of abdominal peritoneal surfaces, none exceeding 2 cm in diameter Nodes negative
IIIc	Abdominal tumour implants exceeding 2 cm in greatest dimension and/or positive retroperitoneal or inguinal lymph nodes
Stage IV	Growth involving one or both ovaries with distant metastases Positive pleural effusions and/or parenchymal liver disease

Table 2. Prognostic variables predictive of disease outcome in ovarian cancer at indicated time points (modified table from Eisenhauer et al, 1999).

Events	Surgery	Post surgery	During	Relapse
Prognostic variables	Specialty of surgeon	Pre-chemotherapy	chemotherapy	
	Adequacy of surgery	Age	Type of chemotherapy	Time since last chemotherapy treatment
		Performance status	CA125 decrease	Disease bulk
		Stage		Number of disease sites
		Grade		Performance status
		Histology - cell type		Histology
		Residual disease		Time since diagnosis
		Ascites		Haemoglobin
		DNA ploidy		
		Capsule rupture (stage 1 disease)		
		CA125 level		
		Albumin level		

V. Diagnosis

A. Symptoms and signs

As previously mentioned, 70% of patients with ovarian cancer are diagnosed when the disease has spread beyond the ovary. Symptoms are generally vague, often resulting in a lengthy delay in diagnosis. A survey of 1700 patients carried out in the USA and Canada showed that 22% of women ignored their symptoms for a significant length of time prior to presentation to their local health authority. Subsequently, a further delay in diagnosis of 2 months occurred in 55% of women, 3-6 months in 19%, 7-12 months in 15% and more than 12 months in 11%. Patients frequently present with a history of indigestion (30%), non-specific abdominal discomfort (40%), abdominal distension (60%), lethargy (50%), urinary frequency (30%) and, more rarely, with weight loss, abnormal menses and post menopausal bleeding (Griffith RW, The not-so-silent killer. www.healthandage.com /Phome/gid2=1056).

Abdominal examination may reveal a mass arising from the pelvis, although the presence of a smaller pelvic mass can only be revealed by combined vaginal and rectal examination. However, vaginal examination lacks the sensitivity and specificity, even when carried out by experienced clinicians to differentiate between benign adnexal masses and malignant ones. The presence of ascites is highly suggestive of malignancy and with late stage disease there may be a pleural effusion, palpable disease in the recto-vaginal septum or supra-clavicular or inguinal lymphadenopathy.

B. Ultrasound

Ultrasound remains the most important form of radiological imaging in the initial evaluation of adnexal masses. Transvaginal ultrasound provides higher resolution in delineating the characteristics and site of smaller adnexal masses, whereas transabdominal ultrasound remains important for assessing larger cystic masses, the upper abdomen and other intra-abdominal organs. Architectural features consistent with malignant ovarian pathology include the size of the mass, multiloculated cysts with septae measuring > 3mm, solid components, papillary excrescences and the presence of ascites. When used in conjunction with Doppler colour flow, pelvic ultrasound is useful in determining the blood flow within ovarian tumours. Characteristically, malignant

tumours have increased blood flow associated with neovascularity and a low resistivity index due to a lack of smooth muscle support. However, combining Doppler colour flow or Doppler arterial resistance with morphology does not appear to significantly improve the sensitivity or specificity of ultrasound in determining malignant from benign ovarian masses. Combining these techniques requires additional expertise, is expensive, and vastly more time consuming. In addition, the reproducibility of Doppler arterial resistance measurements in ovarian masses has not been verified (Kinkel et al, 2000).

The use of ultrasound in determining the morphology of ovarian masses has been studied extensively. Taken in isolation, and depending on the scoring system used, studies have reported a sensitivity of 60 – 100%, specificity of 70 – 95%, positive predictive value (PPV) of 30 – 88% and negative predictive value (NPV) of 80 – 100% in determining the probability of malignant ovarian pathology. **Table 3** gives one example of a scoring system which was developed by Sassone et al, (1991) for a study population of 143 patients. This scoring system achieved a sensitivity of 100% and specificity of 83%, although the PPV remained low at 37%. High scores for many benign masses such as teratomas, endometriomas and ovarian fibromas contributed to the low PPV. This scoring system was later modified by Lerner (by removing wall thickness and adding shadowing defined as loss of acoustic echo), but with disappointing results (Lehner et al, 1998). To overcome this problem, research has focused on combining demographic, clinical, biochemical and radiological features to distinguish benign from malignant pathology. An example is an algorithm developed by Jacobs et al, (1991). The algorithm, termed Risk of Malignancy Index (RMI) is the product of serum CA125 level, the ultrasound score (expressed as 0,1 or 3 - **Table 4**) and the menopausal status. A sensitivity of 85% and specificity of 97% was reported with an RMI score of 200 or more in predicting ovarian malignancy. With a RMI cut-off at 50 the sensitivity improved to 95% but the specificity decreased to 76%. The RMI in this study was derived from the same population that was used to evaluate it. In 1993, these results were validated in a new study population that reported 87% sensitivity, 89% specificity and 75% PPV with a RMI cut-off level of 200 (Davies et al, 1993)

Table 3

Value	Inner wall structure	Wall thickness (mm)	Septa (mm)	Echogenicity
1	Smooth	Thin 3mm	No septae	Sonolucent
2	Irregularities 3mm	Thick > 3mm	Thin 3mm	Low echogenicity
3	Papillarities > 3mm	Not applicable, mostly solid	Thick > 3mm	Low echogenicity with echogenic core
4	Not applicable, mostly solid			Mixed echogenicity
5				High echogenicity
Maximum	4	3	3	5

Reproduced from Sassone et al, 1991 with kind permission from Obstetrics & Gynecology

Table 4

Ultrasound (1 point for each characteristic)	Ultrasound score (U)
Multilocular cyst	0 for 0 points
Evidence of solid areas	1 for 1 point
Evidence of metastases	3 for 2-5 points
Presence of ascites	
Bilateral lesions	
Menopausal status	Menopausal status score (M)
Premenopausal	1
Postmenopausal	3
RMI = U x M x serum CA125 level	

Reproduced from Jacobs and Oram, 1990 with kind permission by Charman & Hall

More recently use of artificial neural networks and logistic regression models have been introduced, although their value remains to be proven. The rationale of developing an ideal scoring system would be that appropriate referral to a specialist oncology centre could be triggered quickly and appropriately, ensuring optimal treatment for that individual.

C. Computed tomography (CT) and magnetic resonance imaging (MRI)

The use of cross-sectional imaging in the pre-operative assessment of primary ovarian cancer remains unclear. Important issues that need to be addressed are whether these modalities can:

- 1) Better distinguish between benign and malignant adnexal pathology than ultrasound.
- 2) Accurately stage the disease and improve the preoperative predictability of achieving optimal and gross tumour resectability.
- 3) Accurately evaluate retroperitoneal lymph node status, thereby allowing conservative surgery in early stage disease without compromising optimal surgical staging and subsequent treatment.

To date there are no prospective trials comparing the use of gray-scale ultrasound to CT or contrast-enhanced MRI in distinguishing benign from malignant adnexal masses. Morphological features of malignant change on non-enhanced MRI and contrast enhanced CT are similar to those used in ultrasound, and have roughly equivalent ability in predicting disease, but the cost and time differential vastly favours the use of ultrasound. Recent advances in MRI such as the use of paramagnetic contrast agents (gadolinium) and multicoils have dramatically improved its specificity, and this examination may have a role to play in the second-line evaluation of patients suspected of ovarian malignancy on the basis of ultrasound alone or in combination with other parameters. Using gadolinium enhanced MRI in a study population of 128 patients with 187 adnexal masses, Hricak et al, (2000) reported 93% and 95% accuracy in defining benign and malignant ovarian masses respectively. Inter and Intra observer agreement was extremely high, and the lesions that were not detected were generally less than 2cm in maximum dimension. Similar findings have also been published by Sohaib et al, (2003) in 104 patients. The

overall accuracy for the diagnosis of malignancy was reported as 91%. One particular subset of patients that prove difficult, and a diagnostic dilemma, are premenopausal women in whom there are multiple reasons for an elevated CA125 and an adnexal mass. Subgroup analyses were not performed in above-mentioned studies and the potential use of MRI in the premenopausal patient remains unanswered.

Several small studies have addressed pre-operative staging of ovarian cancer using cross-sectional imaging with reported accuracy of 70 – 85%. One limitation is the unreliable detection of lesions less than 1cm located on the bowel surface, mesentery or peritoneum, and of lymph node involvement in early stage disease. The use of positron emission tomography (PET), spiral scanning CT and fat-suppressed, gadolinium-enhanced studies and phased array multicoils with MRI may improve the detection rate but have yet to be tested in clinical trials. Surgical intervention carries a degree of morbidity, and in those patients who have been sub-optimally or minimally debulked (the “open-close” laparotomy), this morbidity significantly delays the initiation of adjuvant chemotherapy. Forstner et al. reported high positive and negative predictive values for CT and MRI in predicting tumour resectability (Forstner et al, 1995). The criteria used for non-resectability had been derived from an earlier study by Nelson et al, (1993). These included tumour deposits > 2 cm at the root of the mesentery, in the porta hepatis, the lesser sac of the omentum, gastro-splenic ligament, diaphragm, dome of liver and lymph nodes > 1cm at or superior to the celiac axis (Nelson et al, 1993). With current trials examining the role of neoadjuvant chemotherapy for patients with advanced ovarian cancer, the issue of operability needs to be formalised.

D. Serum tumour markers

Bast et al, (1983), first described the use of CA125 for ovarian cancer. In a population of 101 patients, 82% were found to have elevated levels of CA125 >35u/ml as compared with 6% of patients with non-malignant disease (Bast 1983). This high molecular weight glycoprotein is secreted by endothelial cells of most pelvic organs including normal ovary, and by mesothelial cells of peritoneum, pericardium and pleura. Levels are elevated in 1% of the normal population, 6% of patients with benign disease such as endometriosis and pelvic infections and

28% of patients with non-gynaecological intra-abdominal malignancies. In EOC, levels are raised in 90% of stage II, III and IV tumours but in only 50% of stage I tumours. Therefore, the specificity of using CA125 as a solitary diagnostic test in detecting ovarian malignancy is poor. To improve this specificity, the addition of one or more tumour markers to CA125 has been examined. These include placental alkaline phosphatase (PLAP), macrophage colony stimulating factor (M-CSF), OVX1 and human milk factor globulins (HMFG). However, only a modest improvement in specificity is achieved and the addition of other tumour markers is not routine. In the UK, a prospective randomised controlled trial involving 200,000 women is presently underway examining the roles of CA125 measurements and ultrasound in screening for ovarian cancer. This multimodel screening strategy has been optimised by use of a sophisticated way to interpret CA125 levels. The risk of ovarian cancer (ROC) is calculated using an algorithm based on Bayes theorem, which compare each individual's serial CA125 levels to the pattern in cases and controls. The UKCTOCS (UK Collaborative Trial of Ovarian Cancer Screening) trial is still underway but depending upon results may alter the manner in which patients present with ovarian cancer. Presently in all patients with suspected ovarian malignancy, serum HCG and FP should be taken to diagnose germ cell tumours and carcino-embryonic antigen (CEA) to exclude other primaries, in particular from the gastro-intestinal tract. However CEA may also be raised in ovarian mucinous cystadenocarcinomas.

VI. Treatment

A. Surgery

The role of primary surgery for ovarian cancer can be broadly classified into 3 categories:

1) Diagnosis - to establish a definitive diagnosis of ovarian cancer. Although the presence of a pelvic mass with ascites is highly suggestive of ovarian malignancy, surgical resection is required to confirm this diagnosis. Consequently the histological cell type and grade of tumour can be confirmed by pathological analysis.

2) Staging - accurate surgical staging requires a systematic examination of the pelvic organs, the peritoneal surfaces of the abdominal cavity including the paracolic gutters and subdiaphragmatic area, the surfaces of the small and large bowel, liver and omentum, and palpation with resection of any suspicious pelvic and/or para-aortic lymph nodes.

3) Therapy - cytoreductive surgery with the aim of leaving < 1 cm of macroscopic disease. There are now several published series confirming an advantage in disease-free interval and overall survival for patients that have been optimal debulked and indeed even further benefit of leaving no macroscopically visible disease. There are also theoretical benefits for successful delivery of chemotherapeutic agents to small volume disease. Small well perfused tumour beds, with high cell growth fraction, may favor increased cell kill to cytotoxic agents, as might the removal of large, poorly vascularised tissue which may not respond to drug manipulation. The possible use of fewer cycles of chemotherapy would reduce the

likelihood of side effects and development of chemoresistant disease. In addition, surgery offers the immediate relief of pressure symptoms, although the long-term quality of life of patients that have been successfully debulked compared to those that have not has not been adequately addressed.

Adequate intra-abdominal exposure is achieved through a vertical incision. A sample of ascites or peritoneal washings using saline is taken and sent for cytological evaluation. This step is unnecessary when widespread intra-abdominal disease is visualized. Following this, a systematic exploration of the intra-abdominal contents is performed as described above. Cytoreductive surgery typically involves a total hysterectomy, bilateral salpingo-oophorectomy, infra-colic omentectomy and resection of any bulky disease from the peritoneal surfaces or from the intestines. For stage Ia and Ib disease where no other indications for chemotherapy exist (such as adverse histopathological cell type or grade of tumour) and bulky nodal disease, retroperitoneal lymph node dissection should be performed, the value of which is discussed later. If there is no evidence of macroscopic metastatic disease, biopsies or scrapings of the peritoneal surfaces including the area under the diaphragm should be performed. All intraabdominal adhesions should also be biopsied. Ultraradical surgery involving peritoneal stripping, splenectomy and en-bloc resection of the sigmoid colon with the reproductive organs to attain optimal debulking is questionable. Morbidity from these procedures is high and there is no good evidence of a survival benefit for patients (Bristow, 2000).

Conservative surgery can be considered for young women wishing to preserve their fertility. These patients need to as thoroughly staged as possible and unilateral oophorectomy only considered for presumed stage I, grade I tumours. Careful follow up is essential, arguably in the form of transvaginal ultrasound surveillance and CA125 monitoring, as recurrence rates of up to 9% in the remaining ovary have been reported. Consideration should be given to removal of the uterus and remaining ovary once child-bearing has been completed (Zanetta et al, 1997).

The use of minimally invasive surgery in gynaecological practice has grown rapidly in the past decade. Possible benefits include shorter hospitalisation and time to recovery, less patient discomfort and analgesic requirements and, importantly, decreased cost. Laparoscopic surgery for a presumed benign mass has become routine. Data suggests that 10% of presumed 'benign' masses will appear suspicious on laparoscopy and of these 50% will be malignant (Manolitsas and Fowler, 2001). Therefore the unexpected malignant mass encountered during laparoscopy is not uncommon, and to date there are no clear recommendations for the subsequent management of such patients. What is not in doubt is that full surgical staging should be performed, as up to 25% of apparent stage I ovarian cancers are actually stage III disease on account of retroperitoneal lymph node involvement. In a retrospective study of 192 patients, Kindermann et al. reported that a delay in staging laparotomy of greater than 8 days after laparoscopy was

associated with significant adverse effects (Kindermann et al, 1996). Port site metastases occurred in 56% of apparent stage IC-II cancers and in 47% of stage III cancers. In addition, there also appeared a rapid progression to stage III disease in 39% of presumed stage I cancers. However, interpretation of this data is difficult. The majority of cases were associated with capsule rupture as techniques such as aspiration, biopsy and morcellation were used, with only 7% of masses being removed intact in an endobag. Research also suggests that carbon dioxide, used routinely to create a pneumoperitoneum, may have a growth stimulating effect on tumour cells and intra-peritoneal dissemination (Volz et al, 1999).

There are no well constructed prospective trials examining the short term morbidity and long term prognosis of patients with ovarian malignancy managed by laparoscopy as compared to those managed by laparotomy. With advancing technology and growing expertise in pelvic and paraaortic lymph node dissection, adequate staging for apparent stage I ovarian cancer by laparoscopy is possible (Pomel et al, 1995). The adequacy of lymph node yields by laparoscopic surgery has been addressed in several studies. These studies are limited to cases of cervical cancer, and there are only anecdotal reports of laparoscopic restaging of ovarian malignancies (i.e. for cases referred for definitive management when malignancy had been diagnosed unexpectedly elsewhere). Nevertheless, in laparoscopic lymphadenectomy for cervical cancer the average node count appears to be only marginally less than that removed by an open approach (Childers et al, 1992). As more post menopausal women are now entering ovarian cancer screening trials, laparoscopic oophorectomy has become the norm for those who fall into the moderate or high risk categories. Hence, the finding of an incidental malignant mass at laparoscopy is likely to increase, and there is need to examine the role of minimal access surgery in the complete management of patients with stage I disease. The interval to completion staging also needs to be addressed as does the disease-free interval and overall survival of such patients.

B. Chemotherapy

Chemotherapy plays a central role in the management of EOC and adjuvant combination therapy is usually given after the surgical treatment and accurate staging of this disease (Harries and Gore, 2002). As a result of numerous prospective randomised clinical trials, the combination of a platinum based agent (Cisplatin / Carboplatin) and paclitaxel has become the standardised therapy for ovarian cancer in developed countries. The role of neo-adjuvant chemotherapy for advanced disease and adjuvant chemotherapy for early stage disease is controversial and is discussed later.

1. Platinum drugs

Cisplatin was first introduced in the treatment for ovarian cancer in the 1970's for patients who had failed to respond to alkylating agents such as melphalan and chlorambucil. Subsequently clinical trials examining the role of cisplatin as first-line treatment, either in combination with alkylating agents or as a single agent,

failed to demonstrate a survival advantage, although initial clinical response was much greater with platinum therapy, and the quality of life for patients was improved. A significant survival benefit for platinum was finally demonstrated by results of a meta-analysis in 1998, which showed a 5% improvement in survival of patients at 2 years (45%-50%) and 5 years (25%-30%) (Aabo et al, 1998).

The two platinum drugs currently in use are cisplatin and carboplatin. Carboplatin developed in the 1980's, has significantly fewer side effects than cisplatin with almost no renal or neurotoxicity and a decreased frequency of nausea and vomiting. Trials, such as ICON2, comparing the use of these two drugs in over 2000 patients have shown no difference in efficacy between them, and given that carboplatin is significantly better tolerated than cisplatin, carboplatin alone or in combination have become adopted for first-line therapy for ovarian cancer (The ICON collaborators, 1998).

2. Taxane drugs

Paclitaxel is derived from the bark of the pacific yew tree and was first introduced in the treatment for ovarian cancer in the 1990's. Side effects of paclitaxel include total hair loss, hypersensitivity reactions, myelosuppression and sensory neuropathy. Nausea and vomiting are generally mild. The first trial examining the efficacy of paclitaxel was the GOG111 trial (McGuire et al, 1996). Four hundred and ten women with suboptimally debulked stage III/IV disease were recruited from 1990 to 1992 and were randomised to receive, cisplatin plus cyclophosphamide or cisplatin plus paclitaxel. An improvement of 5 months in the progression free interval (13 vs. 18 months) and 14 months in overall survival (24 vs. 38 months) was observed in those receiving cisplatin plus paclitaxel. A further randomised trial (OV10) with a similar design to GOG111 supported these finding in a group of 680 women (Piccart et al, 2000). An absolute improvement of 4 and 10 months was observed in progression free survival and overall survival respectively in patients receiving a paclitaxel regime. In contrast to these findings, the results of GOG132 and ICON3 show no survival advantage for patients receiving paclitaxel. In the GOG132 trial, a large number of the 645 participants in all arms crossed to alternative treatments before progression, thus confounding the results and making interpretations difficult (Muggia et al, 2000). For the ICON3 trial, 2074 patients were recruited between 1995 and 1998 (The ICON collaborators, 2002). Entry criteria included patients with all stages of ovarian cancer requiring chemotherapy. Patients were randomised to receive paclitaxel plus carboplatin or a control (either carboplatin alone or cyclophosphamide, doxorubicin and cisplatin). Meaningful comparison of this trial to the previously published positive data on paclitaxel is immediately difficult due to the broad entry criteria in ICON3. Although clinical significance is not reached, subgroup analysis of non-optimally debulked stage III/IV cancer patients in ICON3, does demonstrate a trend towards improved survival with paclitaxel. These are the only group of patients that can be compared with those

participants in GOG111 and OV10 trials. Further confounding factors may include a combination of paclitaxel with carboplatin rather than cisplatin, and the differing time and dose regimes of the various chemotherapeutic agents. Despite the conflicting results, paclitaxel may have a role in the management of ovarian cancer although its use may have to be tailored to those with poor risk advanced disease.

The National Institute of Clinical Excellence (NICE) in the UK offers guidance on the use of taxanes for ovarian cancer. Paclitaxel is licensed for use in the UK and is recommended for treatment in combination with cisplatin in patients with advanced disease or residual disease after initial surgical management. Docetaxel, a more recent family member of the taxane group with fewer side effects, is not licensed for use, though there is a trial underway comparing the use of docetaxel/platinum versus paclitaxel/platinum.

3. Neoadjuvant chemotherapy

The role of neoadjuvant chemotherapy in the treatment of ovarian cancer is yet to be established. There is evidence to suggest that interval debulking may be technically easier, with less intra-operative and post-operative morbidity, in patients with advanced FIGO stage ovarian cancer. In addition, this modality of treatment may also offer a better quality of life for patients without significantly compromising their disease-free interval and overall survival.

In a retrospective study by Schwartz et al, (1999) 59 women were identified having received neoadjuvant chemotherapy on the basis of clinical and radiological evidence of advanced ovarian cancer and in whom optimal debulking surgery would be unlikely. The outcome of this cohort was compared to that of 206 patients over a similar time frame receiving conventional treatment (i.e. cytoreductive surgery followed by adjuvant chemotherapy). The three surgical parameters measured were estimated blood loss, intensive care days and post-operative hospital days. All parameters favoured the neoadjuvant chemotherapy group without altering the overall and disease-free survival of patients. In contrast, a smaller but more recent prospective trial demonstrated a significantly higher median survival time for patients with advanced disease treated with neoadjuvant chemotherapy compared to those treated conventionally (42 months vs. 23 months). Time spent in surgery, the requirement for blood transfusion and the intra-operative morbidity and mortality were not significantly different between the two groups (Kuhu et al, 2001).

In the UK, the overall benefits of neoadjuvant chemotherapy are currently being studied in a randomised feasibility trial of 150 patients organised and funded by the clinical trials unit of the medical research council. This pilot study termed CHORUS (Chemotherapy OR Upfront Surgery) will investigate the impact of timing of surgery and chemotherapy in newly diagnosed patients with advanced ovarian, peritoneal or fallopian tube cancer, in terms of overall and progression free survival, and quality of life. Eligible patients will receive either up front surgery or interval debulking after 3 cycles of carboplatin based

chemotherapy. The trial is currently open and recruitment will hopefully be complete in 18 months. A similar trial in 800 patients organised by the European Organisation for Research and Treatment of Cancer (EORTC) is also currently underway. Once again the questions being addressed include: the quality of life of patients receiving either treatment, whether optimal debulking is more frequent in those treated with neoadjuvant chemotherapy and if this translates to a prolonged disease-free interval and overall survival of patients.

4. Adjuvant chemotherapy for early stage ovarian cancer

Stages I – IIa ovarian cancers account for 30% of all EOC. Over the past decade there has been limited and controversial data regarding the impact of adjuvant chemotherapy in such cases on the disease-free interval and overall survival of patients. The ACTION and ICON1 trials were initiated by the EORTC and MRC respectively to address these questions and were closed in January 2000. The individual and combined results of these trials were published in January 2003 (The ICON collaborators, 2003a, 2003b; Trimbos et al, 2003). In brief, patients were randomised to platinum based chemotherapy or no treatment following surgery. Both trials allowed considerable flexibility about the chemotherapy regimes used as long as a platinum drug was included. The recruitment criteria for patients entered in the ACTION trial were strict. Optimal staging surgery was required and only those with stages Ia and Ib, grade 2 and 3, Ic and IIa, all grades were entered. ICON1 recruitment was more liberal, not requiring adequate staging and randomising all cases of early stage ovarian cancer on the basis of the physician's uncertainty about the need for chemotherapy.

In the combined analysis of the 925 patients entered (477 in ICON1 and 448 in ACTION), overall survival at 5 years was 82% in the chemotherapy arm and 74% in the observation arm. Recurrence free survival at 5 years also followed a similar and significant trend (76% in the chemotherapy arm and 65% in the observation arm). However, these results need to be interpreted with caution. In ICON1, with its liberal entry criteria, many patients with good prognostic factors were included, as were poor prognosis patients with possible occult stage 3 disease. Indeed, ICON1 reported an increase of 7% (82% vs. 75%) in overall 5 year survival for patients receiving chemotherapy. In contrast, the ACTION trial with its strict entry criteria showed no overall survival advantage and only a marginal benefit in recurrence free survival with adjuvant chemotherapy. However this benefit appeared to be limited to patients with non-optimal staging. In this trial four staging categories were defined ranging from optimal to inadequate, and on closure, only one-third of patients were deemed to have been optimally staged. Certainly lymph node involvement is present in 14% - 20% of apparent stage I disease, which under current FIGO staging would upgrade these tumours to stage III. Retroperitoneal pelvic and paraaortic lymph node sampling or indeed full systematic lymphadenectomy requires considerable expertise and increases patient morbidity. This needs to be balanced against a possibly

unnecessary use of chemotherapy in cases where the disease is actually confined to the ovary. Prior to the publication of the above data and despite the increased morbidity, there has already been a shift to performing optimal surgical staging for apparent early stage disease thereby permitting a logical argument for the use of adjuvant chemotherapy. This is likely to continue. Subsequent studies need to focus on molecular markers and microarray profiles that may further distinguish between good and bad prognosis in early stage ovarian cancer thereby allowing even more tailored treatments.

5. New chemotherapy agents

Numerous drugs have shown activity in recurrent ovarian cancer. Some of these are now being evaluated as first-line agents in treating patients with ovarian cancer. A large five-arm phase III randomized trial is currently underway comparing 4 experimental drug regimes to the standard treatment with paclitaxel and carboplatin. This international collaborative trial funded by the MRC in the UK and the NIH in the USA (Protocol identification: GOG0182, ICON5, SWOG-GO182) will better define the role of these agents. The recruitment target is estimated at 5000 patients and is some years away to completion. The various arms of this trial are summarised below. Doses and intervals can be obtained from the MRC.

<i>ARM I</i>	Carboplatin + Paclitaxel	8 cycles (every 3 weeks)	(Paclitaxel IV over 3 hours and Carboplatin IV over 30 minutes – Day 1)
<i>ARM II</i>	Carboplatin + Paclitaxel + Gemcitabine	8 cycles	(Chemotherapy as in arm 1. Gemcitabine IV over 30 minutes days 1 and 8)
<i>ARM III</i>	Carboplatin + Paclitaxel + Doxorubicin	8 cycles	(Chemotherapy as in arm 1. Doxorubicin IV over 1 hour cycles 1,3,5 and 7)
<i>ARM IV</i>	Carboplatin + Topotecan	4 cycles	(Topotecan IV over 30 minutes on days 1-3. Carboplatin IV over 30 minutes on day 3)
Followed by			
	Carboplatin + Paclitaxel	4 cycles	(Chemotherapy as in arm 1)
<i>ARM IV</i>	Carboplatin + Gemcitabine	4 cycles	(Gemcitabine IV over 30 minutes on days 1 and 8, Carboplatin IV over 30 minutes day 8)
Followed by			
	Carboplatin + Paclitaxel	4 cycles	(Chemotherapy as in arm 1)

The sequential delivery of these drugs either as a single agent or in pairs is aimed at reducing the toxic side effects associated with triple therapy. Research examining the combination of other new regimes is also continuing. The Scottish Randomised Trials in Ovarian Cancer (SCOTROC) has recently reported on the use of docetaxel in combination with carboplatin in advanced diseased compared to standard paclitaxel and carboplatin (Vasey, 2002). Docetaxel is a semi-synthetic taxane with a different toxicity profile to paclitaxel, but with at least similar efficacy. Although survival data are not yet available, the disease-free interval is not significantly different. The use of Docetaxel appears to be associated with less neurotoxicity but greater myelosuppression. The use of epirubicin in combination with carboplatin and paclitaxel as first-line treatment has also been disappointing with a significant increase in toxicity, and has largely been abandoned.

6. Intra-peritoneal therapy

Few studies have evaluated the use of intra-peritoneal (i.p) therapy in ovarian cancer. Due to the limited penetration of drugs used in this manner, only patients optimally debulked have been assessed in clinical trials. The rationale for this route of therapy is that ovarian

cancer tends to remain confined to the abdominal cavity and spread superficially. A direct effect on the cancer cells would possibly limit systemic side-effects as compared to those treated with high dose intra-venous (i.v) therapy. In addition there may be a pharmacokinetic advantage of IP delivery of some agents such as paclitaxel where IP delivery results in > 1000 fold higher than achieved with IV delivery of the same drug. However, practical difficulties in administering IP chemotherapy remain, including catheter insertion, intra-peritoneal infections and acceptability to patients.

In 1996, a combined SWOG and GOG trial reported a significant improvement in the median survival and in the reported and measured side effects of women receiving 6 cycles of intra-peritoneal cisplatin compared to those receiving it via the IV route (Markman et al, 2001). Patients in both arms of this trial received concomitant IV cyclophosphamide. Of the 546 patients eligible for evaluation, median survival was significantly longer in the IP group versus the IV group (49 months vs. 42 months). In addition, those in the IP arm suffered fewer and milder neurotoxic events relating to tinnitus, hearing loss and neuromuscular effects. A further GOG study (GOG 172) has recently been reported (Armstrong et al, 2002). Four hundred and seventeen patients were randomised to receive 6 cycles of either IV paclitaxel and cisplatin or IV

paclitaxel followed by IP cisplatin and IP paclitaxel on day 8. Although the data reported are very immature, there appears to be an improvement in disease-free survival in the IP group (24.3 months vs. 19.3 months) and a trend towards improved overall survival. Interestingly, however, there does appear to be more neurological, gastrointestinal, renal and haematological side effects in the IP treated group. The use of IP chemotherapy remains experimental but given the results of these recent trials further investigation is warranted.

C. Gene therapy

Cancer development and progression is thought to arise from an accumulation of mutations in multiple genes that are important for normal cellular function resulting in uncontrolled proliferation and tumour growth. Therefore the rationale for using gene therapy to treat cancer is the potential targeting of cells at a molecular level. Current gene therapy approaches involve introduction of TSG, pro-apoptotic genes, or factors blocking oncogenic effect with a wide range of viral factors. Different vectors provide different benefits / problems, such as integration of the desired gene into the host genome, limitation of gene size for transfer, induction of host immune response and so on.

Gene mutations and/or overexpression of mutated p53 (a TSG) have been reported in 30% - 80% of EOC's. Accumulation of this aberrant protein is associated with reduced disease-free interval and overall survival of patients with ovarian cancer. In addition, a few studies also report a significant relationship between loss of functional wild-type p53 and chemoresistant disease. Long term follow up of a phase I/II trial using recombinant wild-type p53 gene replacement with an adenoviral vector has been recently reported (Buller et al, 2002). Patients with recurrent disease in a heavily pretreated population were given either a single dose or multiple doses of IP p53 gene replacement with concurrent Paclitaxel and Carboplatin. Median survival was significantly longer in those receiving multiple doses, and almost double that of those treated with palliative radiotherapy or following paclitaxel failure (Buller, 2002). Other genes being targeted include Her-2/neu and BRCA1. Although expertise in this field is expanding, numerous obstacles remain which include the identification of an ideal vector, efficient gene transfer, effective transgene expression and reduction in the host immune response (Russell, 2002).

VII. Conclusion

Ovarian cancer is the 4th most common cancer amongst women in the UK, and is the leading cause of gynaecological cancer related death in this country. Many women are still managed outside the setting of a cancer centre without appropriate multidisciplinary support and treatment, although various steps to rectify this are underway. The majority of patients with early and advanced disease are not recruited for prospective clinical trials, which may reflect the poor co-ordination of trials at a national level in the UK. With several of these issues now being addressed and anticipated completion of some

large prospective trials examining the role of new chemotherapeutic agents in treating advanced malignancy and the value of complete surgical staging in early disease, the next few years are likely to change the shape of current management in ovarian cancer. Listed below are some of the recent and anticipated advances in the management of patients presenting with ovarian cancer.

All patients suspected to have ovarian cancer should be referred to and managed in cancer centres. This would allow rapid and appropriate recourse to all cancer services that include dedicated radiology, pathology, nursing, oncology and social support.

1) All patients should be considered for recruitment onto clinical trials whether they are locally or nationally run. The National Cancer Research Network (NCRN) in England was established April 2001 to provide the NHS with an infrastructure to support prospective trials of cancer treatments and well designed studies. By improving the speed, quality and integration of research undertaken on a national basis the overall aim is to provide better patient care.

2) The routine use of cross-sectional imaging in ovarian cancer requires further assessment, and given cost and time implications its use should be tailored to individual cases.

3) In light of recent data, selected cases with presumed stage I ovarian cancer should have appropriate surgical staging that includes pelvic and para-aortic lymphadenectomy.

The use of new chemotherapeutic agents (in addition to standard Paclitaxel and Platinum drugs) should only be considered in the setting of clinical trials. An example of such a trial is the five-arm randomised trial funded by the MRC and NIH, examining the efficacy and side effects of new chemotherapy treatments. There are also trials examining the impact of neoadjuvant chemotherapy although selected patients are offered this outside the setting of a trial (for example those deemed unfit for appropriate surgery or those presenting with stage IV disease).

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References

- Aabo K, Adams M, Adnitt P et al, (1998) Chemotherapy in advanced ovarian cancer: Four systematic meta-analyses of individual patient data from 37 randomized trials. **Br J Cancer** 78, 1479-1487.
- A report by the expert advisory group on cancer to the chief medical officers of England and Wales. 1995; www.doh.gov.uk
- Armstrong DK, Bundy BN, Baergen R et al, (2002) Randomized phase II study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): A Gynecologic Oncology Group trial (GOG 172). **Proc Am Soc Clin Oncol** (Abstr 803).

- Bast RC, Klug TL, St John E, Jenison E et al, (1983) A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. **N Engl J Med** 309, 883-887.
- Bristow RE (2000) Surgical standards in the management of ovarian cancer. **Curr Opin Oncol** 12, 474-80.
- Buller RE, Shahin MS, Horowitz JA et al, (2002) Long term follow-up of patients with recurrent ovarian cancer after Ad p53 gene replacement with SCH 58500. **Cancer Gene Ther** 9, 567-572.
- Cancer Services Collaborative: Ovarian cancer-Service improvement guide. 2001; www.nhs.npat
- Chein CH, Wang FF, Hamilton TC (1994) Transcriptional activation of c-myc proto-oncogene by estrogen in human ovarian cancer cell lines. **Mol Cell Endocrinol** 99, 11-19.
- Childers J, Hatch K, Surwit E (1992) The role of laparoscopic lymphadenectomy in the management of cervical carcinoma. **Gynecol Oncol** 47, 38-43.
- Davies AP, Jacobs I, Woolas R, Fish A, Oram D (1993) The adnexal mass: benign or malignant? Evaluation of a risk of malignancy index. **Br J Obstet Gynaecol** 100, 927-931.
- Eisenhauer EA, Gore M, Neijt JP (1999) Ovarian cancer: should we be managing patients with good and bad prognostic factors in the same manner? **Ann Oncol** 10, 9-15.
- Fathalla MF (1971) Incessant ovulation-a factor in ovarian neoplasia? **Lancet** 17, 163.
- Forstner R, Hricak H, Occhipinti KA et al, (1995) Ovarian cancer: Staging with CT and MR imaging. **Radiology** 197, 619-626.
- Griffith RW. The not-so-silent killer. www.healthandage.com/Phome/gid2=1056
- Gross TP, Schlesselman JJ (1994) The estimated risk of oral contraceptive use on the cumulative risk of epithelial ovarian cancer. **Obstet Gynecol** 83, 419-424.
- Harries M, Gore M (2002) Part I: Chemotherapy for epithelial ovarian cancer-treatment at first diagnosis. **Lancet Oncol** 3, 529-536.
- Hricak H, Chen M, Coakley FV et al, (2000) Complex adnexal masses: Detection and characterization with MR Imaging – multivariate analysis. **Radiology** 214, 39-46.
- Jacobs IJ, Oram DH (1990) Potential screening tests for ovarian cancer. Sharp F, Mason WP, Leake RE (eds). **Ovarian cancer**. Charman & Hall: 197-205.
- Kindermann G, Massen V, Kuhn W et al, (1996) Laparoscopic management of ovarian tumours subsequently diagnosed as malignant. **J Pelvic Surg** 2, 245-251.
- Kinkel K, Hricak H, Lu Y et al, (2000) US characterization of ovarian masses: a meta-analysis. **Radiology** 217, 803-811.
- Kuhu W, Rutke S, Spathe K et al, (2001) Neoadjuvant chemotherapy followed by tumour debulking prolongs survival for patients with poor prognosis in international federation of gynecology and obstetrics stage IIIc ovarian carcinoma. **Cancer** 92, 2585-2591.
- Lehner R, Wenzl R, Heinzl H et al, (1998) Influence of delayed staging laparotomy after laparoscopic removal of ovarian masses later found malignant. **Obstet Gynecol** 92, 967-971.
- Manolitsas TP, Fowler JM (2001) Role of laparoscopy in the management of the adnexal mass and staging of gynecologic cancers. **Clin Obstet Gynecol** 44, 495-520.
- Markman M, Bundy BN, Alberts DS et al, (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. **J Clin Oncol** 19, 1001-1007.
- McGuire WP, Hoskins WJ, Brady MF et al, (1996) Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. **N Engl J Med** 334, 1-6.
- Muggia FM, Braly PS, Brady MF et al, (2000) Phase III randomised study of cisplatin-paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or stage IV ovarian cancer: a Gynecologic oncology group study. **J Clin Oncol** 18, 106-115.
- Nelson BE, Rosenfield AT, Schwartz PE (1993) Preoperative abdominopelvic computed tomographic prediction of optimal cytoreduction in epithelial carcinoma. **J Clin Oncol** 11, 166-172.
- Noller KL (2002) Estrogen replacement therapy and risk of ovarian cancer. **JAMA** 288, 368-377.
- Piccart MJ, Bertelsen K, James K et al, (2000) Randomised intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced ovarian cancer: Three-year result. **J Natl Cancer I** 92, 699-708.
- Pomel C, Provencher D, Dauplat J et al, (1995) Laparoscopic staging of early ovarian cancer. **Gynecol Oncol** 58, 301-306.
- Rodriguez GC, Nagarsheth NP, Lee KL et al, (2002) Progesterin-induced apoptosis in the macaque ovarian epithelium: Differential regulation of transforming growth factor- β . **J Natl Cancer I** 94, 50-60.
- Rodriguez GC, Walmer DK, Cline M et al, (1998) Effect of progesterin on the ovarian epithelium of macaques: cancer prevention through apoptosis? **J Soc Gynecol Investig** 5, 271-276.
- Russell W (2002) Adenovirus gene therapy for ovarian cancer. **J Natl Cancer I** 94, 706-707.
- Sassone AM, Timor-Tritsch IE, Artner A et al, (1991) Transvaginal sonographic characterization of ovarian disease. **Ostet Gynecol** 78, 70-76.
- Schwartz PE, Rutherford MD, Chambers JT et al, (1999) Neoadjuvant chemotherapy for advanced ovarian cancer: Long-term survival. **Gynecol Oncol** 72, 93-99.
- Sohaib SA, Sahdev A, Van Trappen P, Jacobs IJ, Reznick RH (2003) Characterization of adnexal mass lesions on MR imaging. **AJR Am J Roentgenol** 180, 1297-304.
- The ICON collaborators (1998) ICON2: Randomised trial of single agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin and cisplatin) in women with ovarian cancer. **Lancet** 352, 1571-1576.
- The ICON collaborators (2002) ICON3: Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin and cisplatin in women with ovarian cancer: the ICON3 randomised trial. **Lancet** 36, 505-515.
- The ICON collaborators (2003a) International collaborative ovarian neoplasm trial 1 and adjuvant chemotherapy in ovarian neoplasm trial: Two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma. **J Natl Cancer I** 95, 105-112
- The ICON collaborators (2003b) International collaborative ovarian neoplasm trial 1: A randomised trial of adjuvant chemotherapy in women with early-stage ovarian cancer. **J Natl Cancer I** 95, 125-132.
- Trimbos JB, Vergote I, Bolis G et al. (2003) Impact of adjuvant chemotherapy and surgical staging in early ovarian carcinoma: European organisation for research and treatment of cancer-Adjuvant chemotherapy in ovarian neoplasm trial. **J Natl Cancer I** 95, 113-125.
- Vasey PA (2002) Survival and longer-term toxicity results of the SCOTROC study: docetaxel-carboplatin (DC) vs. paclitaxel-carboplatin (PC) in epithelial ovarian cancer (EOC). **Proc Am Soc Clin Oncol** (Abstr 804).

- Venktaraman AR (2002) Cancer susceptibility and the functions of BRCA1 and BRCA2. **Cell** 108, 171-182.
- Volz J, Koster S, Spacek Z et al, (1999) The influence of pneumoperitoneum used in laparoscopic surgery on an intraabdominal tumour growth. **Cancer** 86, 770-774.
- Zanetta G, Chiari S, Rota S et al, (1997) Conservative surgery for stage 1 ovarian cancer in women of childbearing age. **Br J Obstet Gynaecol** 104, 1030-1035.



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