



**NATIONAL BREAST
CANCER CENTRE**

Incorporating the
Ovarian Cancer Program

Clinical practice guidelines for the management of women with epithelial ovarian cancer

Approved by



Australian Government

National Health and Medical Research Council



Clinical practice guidelines for the management of women with epithelial ovarian cancer

Prepared by the Australian Cancer Network and
the National Breast Cancer Centre

(incorporating the Ovarian Cancer Program)

Funded by the Department of Health and Ageing
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Australian Government

National Health and Medical Research Council

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These guidelines were approved by the National Health and Medical Research Council at its 152nd Session on 18 March 2004, under section 14A of the National Health and Medical Research Council Act 1992. Approval for the guidelines by NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years. Readers should check with the National Breast Cancer Centre for any reviews or updates of these guidelines.

The strategic intent of the NHMRC is to provide leadership and work with other relevant organisations to improve the health of all Australians by:

- fostering and supporting a high quality and internationally recognised research base;
- providing evidence based advice;
- applying research evidence to health issues thus translating research into better health practice and outcomes; and
- promoting informed debate on health and medical research, health ethics and related issues.

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of publication.

This is the first edition of the *Clinical practice guidelines for the management of women with epithelial ovarian cancer*.

It is planned to review this Clinical Practice Guideline in 2009. For further information regarding the status of this document, please refer to the NHMRC web address: <http://www.nhmrc.gov.au>

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FOREWORD

“The ovary is small, homely, and innocuous at first glance, but its tumors of gigantic proportion and exotic appearance continually widen the eye of the most jaded gynecologist as they exert fascinating effects upon his patient. Such an organ deserves respect”, wrote Kraus in his 1967 textbook of pathology.¹

The lifetime risk of ovarian cancer for Australian women to age 74 is one percent (1%),² but the impact on society is far greater than this figure implies. Ovarian cancer is the most common cause of death from gynaecological malignancy. For the majority of women who develop ovarian cancer, it will ultimately be lethal. This is due to a large extent to our current inability to readily diagnose ovarian cancer at an early stage, where cure might be achievable. No algorithm for early detection has yet been developed. The symptoms are frequently vague and non specific, so that in about three-quarters of cases, diagnosis is only made when the disease is advanced, thus overall outcomes are poor.

There is a distinct lack of awareness, both on the part of women and also health professionals, about symptomatology and triage for women who might have ovarian cancer. In spite of the high mortality rate, the majority of women do not receive optimal staging or treatment.^{3,4}

We are eagerly awaiting the results of several large international studies on population screening. These will not be available for another year or so at the earliest. Meanwhile routine screening has not been proven to be efficacious, at this stage, for the general population. (*See chapter 3 – Screening for ovarian cancer.*)

Interpretation of the histological findings is crucial to determining prognosis, and thus influences treatment decisions. Expert pathology review is a vital component of the overall management process. (*See chapter 5 – The biology and pathology of ovarian cancer and chapter 6 – Multidisciplinary management of women with ovarian cancer.*)

There is evidence that prognosis is directly related to the training of the treating surgeon, who understands the natural history of the disease, and is also trained formally to deal with any situation which might be found at the time of surgery. The Certified Gynaecological Oncologist has a three year post-specialty training in this area. (*See chapter 6 – Multidisciplinary management of women with ovarian cancer.*) Incomplete staging gives incomplete information about the extent of the disease. If staging is not complete then there is a strong chance that the woman will not be adequately treated and the chance of subsequent death is increased.

These guidelines, based upon a review of evidence-based information, have been specifically confined to the dominant group of ovarian malignancies - the so-called epithelial tumours. This group accounts for over 90% of primary ovarian cancers and represents the common usage of the term ‘ovarian cancer’. Neither germ cell malignancies nor sex cord stromal tumours have been addressed. These groups, which account for less than 10% of primary ovarian cancers, have very different patterns of pathogenesis, epidemiology, clinical management and outcomes and have therefore not been included.⁵

The guidelines are formulated with the aim of closing the gap on information for clinicians (both specialists and general practitioners) and other health professionals, so that awareness of ovarian cancer is raised and the possibility of earlier diagnosis and optimal treatment is realised. Consumers and consumer groups frequently show interest in the clinical document, however, it is planned to subsequently develop a consumer guide, based on the evidence in the guidelines.

The best available evidence has been collated and while much of it is level IV, there is a substantial component of level III evidence, with some level II and level I evidence. As the levels of evidence are low for most situations, more research is required. We have included suggestions for where research can be directed to improve the evidentiary base (*See Appendix 6*).

Dr Margaret Davy AM

Chair, Working Party

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EXECUTIVE SUMMARY

- Cancer of the ovary is a significant malignancy in Australian women, being the eighth most common cancer and the sixth most common cause of death. It is the most common cause of death from gynaecological malignancy.
- In Australia in 1999 the age-standardised incidence rate was 10.6 per 100,000 female population. There has been a decline in mortality since 1983, most notable for women less than 55 years of age. Possible explanations for the trend include differences in histological types and prognosis of tumours occurring in the younger age groups, protective effects of oral contraceptive use and improvements in treatment.
- The established risk factors for ovarian cancer are strongly related to family history and increasing age, neither of which is readily modifiable through prevention strategies.
- Specific strategies may be considered to reduce the risk of ovarian cancer for women with one of the familial cancer syndromes.
- Protective factors for ovarian cancer include increasing parity, hysterectomy, tubal ligation and oral contraceptive use.
- The issues around screening for ovarian cancer are not yet resolved and the results of three large randomised, controlled trials are awaited.
- The vagueness of initial symptoms of ovarian cancer requires that clinicians be alert to their significance during examination and investigation.
- The surgical approach is the cornerstone of all subsequent treatment and management of ovarian cancers, as the careful and accurate surgical procedure will determine the true stage. Optimal benefits result when all gross malignancy can be excised safely. Chemotherapy is available for the treatment of any residual disease.
- Radiation therapy may be used in certain circumstances.
- Accurate histopathological and clinical staging provide prognostic indices for gynaecological oncologists and women.
- To achieve best outcomes for women with ovarian cancer the ideal is that they be treated by a multidisciplinary team that includes a gynaecological oncologist.
- Attention to psychosocial issues, quality of life and palliative care is an essential part of multidisciplinary care.
- Better outcomes have been reported for those cancer patients taking part in clinical trials.
- Emphasis must be placed on optimal use of available resources and the collection of comprehensive and consistent data to plan future strategies in prevention and to achieve a reduction in mortality.

SUMMARY OF GUIDELINES

Guideline	Level of Evidence	Chapter/ Reference number	Page
Familial aspects of ovarian cancer		Chapter 4	
Bilateral risk reducing salpingo-oophorectomy in carriers of BRCA1 and BRCA2 mutations reduces the risk of epithelial ovarian cancer by at least 90%. It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. It may also halve the risk of breast cancer in mutation carriers. Ideally, risk reducing surgery should always be discussed with women at potentially high risk of ovarian cancer.	III-2	26,27,28	37
The biology and pathology of ovarian tumours		Chapter 5	
It is recommended to sample several areas from any suspected borderline ovarian tumour (eg highly complex cystic tumours), to reduce sampling error; especially for tumours that are, or appear to be, mucinous or which are over 1 kg.	III-3	7	45
The use of the Universal Grading System is recommended and addresses some of the limitations of other methods for histological grading. There is good predictive power across most stages and types.	III-3	11,12	47
When considering the prognostic indicators for serous borderline tumours, surgical pathological stage and sub-classification of extra-ovarian disease into invasive and non-invasive implants are the most important indicators.	IV	18	49

Guideline	Level of Evidence	Chapter/ Reference number	Page
Use of the term 'high grade proliferating' as an alternative to 'carcinoma in situ' or 'intraepithelial carcinoma' within a borderline neoplasm is recommended for mucinous tumours with no evidence of stromal invasion, if they show more than four layers of nuclei and marked nuclear atypia.	IV	24	50
The multidisciplinary management of women with ovarian cancer		Chapter 6	
There is a growing body of evidence to suggest that outcomes for a woman with ovarian cancer are improved if she is referred to be managed under the care of a Multidisciplinary Care team. The ideal situation is for referral of the woman to a centre where all aspects of management, including surgery, pathology review, chemotherapy and on-going psychosocial support are available.	IV	1,7	58
Survival for women with ovarian cancer has been shown to be improved when the initial surgery has been done by a gynaecological oncologist. The surgical care of women with ovarian cancer is best directed, whenever possible, by a gynaecological oncologist.	IV	2,4,5,13,15	61

Guideline	Level of Evidence	Chapter/ Reference number	Page
Management of a pelvic mass		Chapter 8	
<p>Surgical staging for ovarian cancer always includes:</p> <ul style="list-style-type: none"> • peritoneal washings for cytology; • exploration of all peritoneal surfaces including the diaphragm, bowel serosa and Pouch of Douglas; • biopsy of any suspicious nodules; • infracolic omentectomy, multiple peritoneal biopsies; and • at least adequate sampling of pelvic and para-aortic lymph nodes. 	IV	7,8,9	73
<p>In premenopausal women, with invasive adenocarcinomas, early disease and favourable pathology (Grade I or Grade II, Stage IA or IB tumours) fertility-preserving surgery in association with appropriate follow-up can be safely undertaken, if child bearing is desired.</p>	IV	10-13	74
<p>In the event of an unexpected diagnosis of ovarian cancer at the time of surgery for other purposes:</p> <ul style="list-style-type: none"> • diagnosis should be confirmed with a biopsy; • minimal additional surgery should be undertaken; • postoperative referral to a gynaecological oncology unit for definitive treatment should be arranged. 	IV	14	75
The management of borderline ovarian tumours		Chapter 9	
<p>There is no role for adjuvant therapy for Stage I borderline ovarian tumours.</p>	I	7	79

Guideline	Level of Evidence	Chapter/ Reference number	Page
Surgery for invasive ovarian cancer		Chapter 10	
<p>Primary cytoreduction is considered the initial treatment of choice for women with ovarian cancer and typically includes:</p> <ul style="list-style-type: none"> • total abdominal hysterectomy; • bilateral salpingo-oophorectomy; • omentectomy; and • resection of metastatic lesions from the peritoneal surfaces or from the bowel. 	IV	1,2,3	81
Neoadjuvant chemotherapy and interval cytoreduction may be considered if optimal primary cytoreduction was not achieved.	II	13	83
Surgery has no place for women who develop progressive disease during their initial chemotherapy program.	IV	15,16	84
Chemotherapy - Early ovarian cancer		Chapter 11	
Adjuvant chemotherapy with a platinum agent is recommended for patients with high grade or clear cell histology because they are known to have a higher relapse rate.	II	1	90
Patients with stage IA or IB well or moderately differentiated tumours do not require adjuvant chemotherapy because their risk of relapse is low, and the toxicity not justified.	II	2	90
Adjuvant chemotherapy is not indicated in patients with borderline tumours (unless invasive implants are confirmed histologically).	II	3	90

Guideline	Level of Evidence	Chapter/ Reference number	Page
Platinum-based adjuvant chemotherapy improves recurrence-free and overall survival in women with surgically resected early ovarian cancer who are at high risk of relapse.	II	6,7	90
Chemotherapy - Advanced ovarian cancer		Chapter 11	
The first line treatment of advanced ovarian cancer ideally should include a platinum compound.	I	9	91
It is currently recommended that standard first line chemotherapy should be a combination of carboplatin (AUC × 6) and paclitaxel (175 mg/ m ²) given every three weeks.	II	10,12	93
In patients unsuitable for combination therapy (on the basis of either concurrent medical conditions, performance status or by patient preference) single agent carboplatin is an effective and acceptable treatment for advanced ovarian cancer.	II	14	93
Although intraperitoneal chemotherapy is not recommended as standard therapy its use may be considered on an individual patient basis at a designated cancer centre.	II	27	95
The use of chemotherapy protocols utilising high dose therapy should only be offered as part of an appropriately designed clinical trial.	IV	34	96
The use of maintenance or consolidation chemotherapy should only be offered as part of an appropriately designed clinical trial.	II	38,39	97

Guideline	Level of Evidence	Chapter/ Reference number	Page
Patients relapsing more than 6 months after a confirmed response to initial treatment with platinum compounds should be considered for re-treatment.	IV	40,41	98
Radiation therapy		Chapter 12	
Whole Abdominal Radiation Therapy (WART) should be considered in Stage III ovarian cancer patients with complete surgical and pathologic remission at second-look laparotomy.	II	12	105
Symptomatic relief and palliation in women with metastatic or recurrent disease can be achieved with radiation therapy.	IV	15,16, 17	106
Quality of life and psychosocial issues		Chapter 13	
Psychosocial interventions can result in lower rates of anxiety and depression, reduced mood disturbances, nausea and vomiting and enhanced knowledge for cancer patients.	I	9	109
Psychosocial interventions that can improve physical, functional and psychological adjustment and may be considered for women with ovarian cancer; include: <ul style="list-style-type: none"> • Counselling and relaxation therapy • Education programs to improve pain control • Cognitive behavioural interventions 	I II III-2	9 16 17	110

Guideline	Level of Evidence	Chapter/ Reference number	Page
Alternative and complementary therapies		Chapter 14	
Relaxation therapy has been shown to be effective and non-harmful in managing patients with cancer pain.	I	5	121
Palliative care		Chapter 16	
Specialist palliative care services can improve outcomes in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction and control of pain, symptoms and family anxiety.	I	4	132
Clinical trials		Chapter 17	
Cancer patients who participate in clinical trials may have better outcomes than those given the same treatment outside a clinical trial setting. It is appropriate for clinicians to discuss participation in clinical trials with women who have ovarian cancer.	III- I	4	140

INTRODUCTION

Research has shown that clinical practice guidelines can be effective in bringing about change and improving health outcomes.¹ In November 2000, the Australian Cancer Network established a multidisciplinary working party to develop clinical practice guidelines for the management of women with epithelial ovarian cancer. With the establishment of the National Ovarian Cancer Program in 2001, the National Breast Cancer Centre worked collaboratively with the Australian Cancer Network to develop, revise and complete the guidelines.

The working party comprised representatives from the disciplines of:

- Gynaecological Oncology
- Medical Oncology
- Pathology
- Radiation Oncology
- Nursing
- General Practice
- Epidemiology; and
- Consumers

The *Clinical practice guidelines for the management of women with epithelial ovarian cancer*, aim to:

- improve the quality of healthcare for women;
- educate those involved in the care of women with epithelial ovarian cancer;
- assist the decision-making process by women with epithelial ovarian cancer and their doctors; and
- facilitate the optimal treatment of women with epithelial ovarian cancer.

In the first chapter of these guidelines, *Ovarian cancer in Australian women*, the data provided covers all types of ovarian cancer. In the following chapters, the information provided will be for epithelial ovarian cancer (borderline and invasive) only. Most information will be about invasive epithelial ovarian cancer.

The *Clinical practice guidelines for the management of women with epithelial ovarian cancer* are based on the best available evidence, and readers can judge the level of the evidence on which assertions are based.

The process employed to develop the guidelines is described in Appendix 6.

These guidelines are not rigid procedural paths. They are one element of good medical decision-making, which takes account of patients' preferences and values, clinicians' experience, and the availability of resources.²

The guidelines use a rating system to identify the evidence base for key recommendations. The rating system is recommended by the Quality of Care and Health Outcomes Committee (QCHOC) and has been adapted from the system developed by the US Preventive Services Task Force and recommended by the National Health and Medical Research Council (NHMRC).²

- Level I** evidence obtained from a systematic review of all relevant randomised controlled trials.
- Level II** evidence obtained from at least one properly designed randomised controlled trial.
- Level III-1** evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
- Level III-2** evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
- Level III-3** evidence obtained from comparative studies with a historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
- Level IV** evidence obtained from case series, either post-test or pre-test and post-test

Level I evidence represents the gold standard.

'Guidelines' are boxed throughout the text and are summarised at the beginning under 'Summary of Guidelines'. These are all evidence-based and the level of evidence and appropriate references are denoted.

There are also 'Key points' to draw the reader's attention to other issues of importance that may be of interest, but which are not clinical practice recommendations. Levels of evidence were able to be attributed for some of these, while others refer to areas for which there is no 'hard' evidence, but which the working party nevertheless considered to be worthy of consideration by clinicians.

These guidelines highlight areas of established knowledge, but also areas where knowledge is poor. They provide guidance for research. The guidelines will be evaluated to determine their impact and their effects on patient outcomes.

A consumer booklet will be developed by the Ovarian Cancer Program of the National Breast Cancer Centre, based on the clinical practice guidelines. This booklet will be for use by women with epithelial ovarian cancer and their families, as well as for discussion between the woman and her doctor.

STAGING

Management decisions are made based on the diagnosis and prognostic indices. The guidelines used for staging are presented here for reference and should be used in conjunction with the information provided in the chapter on *Management of a Pelvic Mass* (Chapter 7). Ovarian cancers are staged surgically, based on the extent of growth of the disease. Guidelines for staging have been established by the *Federation Internationale de Gynecologie et d'Obstetrique (FIGO)*. The *Annual Report on the Results of Treatment in Gynaecological Cancer* is published triennially to coincide with the scientific meeting of FIGO. This is a collection of data from many countries world-wide to give a world picture of the incidence and the outcomes of treatment in gynaecological malignancies. The concept began in 1928 when Heyman, Lacassagne and Voltz were given the task to explore a system to give uniform statistical information on the results of radiation therapy in cervix cancer. Their system was adopted in 1929. It was not until 1973 in the 15th Annual Report that ovarian cancer was included.³

Stage I Growth limited to ovaries

- Ia Growth limited to one ovary; no ascites present containing malignant cells. No tumour on external surface; capsule intact.
- Ib Growth limited to both ovaries; no ascites present containing malignant cells. No tumour on external surfaces; capsules intact.
- Ic* Tumour either stage Ia or Ib, but with tumour on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.

Stage II Growth involving one or both ovaries with pelvic extension

- IIa Extension and/or metastases to the uterus and/or tubes.
- IIb Extension to other pelvic tissues.
- IIc* Tumour either stage IIa or IIb, but with tumour on the surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.

Stage III Tumour involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals Stage III. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.

- IIIa Tumour grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery.
- IIIb Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastases of abdominal peritoneal surfaces, none exceeding 2cm in diameter; nodes are negative.

IIIC Peritoneal metastases beyond the pelvis >2cm in diameter and /or positive retroperitoneal or inguinal nodes.

Stage IV Growth involving one or both ovaries with distant metastases.

If pleural effusion is present, there must be positive cytology to allot a case to stage IV. Parenchymal liver metastases equal Stage IV.

* In order to evaluate the impact on prognosis of the different criteria for allotting cases to Stage Ic or IIc, it would be of value to know if rupture of the capsule was spontaneous, or caused by the surgeon; and if the source of the malignant cells detected was peritoneal washings, or ascites.

The role of surgical staging is the cornerstone of all subsequent treatment discussions in ovarian cancer. Careful and accurate surgical procedure will determine the true stage. (*See chapter 10 on Surgery for invasive ovarian cancer*). The task forces of FIGO endorse the histologic typing of ovarian tumours, as presented by the World Health Organization (WHO). (*See Appendix 2*).

References

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3. FIGO Annual Report on the Results of Treatment in Gynaecological Cancer. Vol 24. Division of Epidemiology and Biostatistics. European Institute of Oncology. 2000

I. OVARIAN CANCER IN AUSTRALIAN WOMEN

INTRODUCTION

Routine statistics do not separate epithelial, germ cell and sex cord-stromal tumours. However, as the great majority of ovarian cancers are epithelial (>90%), rates of epithelial tumours are closely approximated by ovarian cancer rates overall. The only exception is at young ages (below the age of 40) where epithelial tumours are rare and germ-cell tumours relatively more common. The data reported in this chapter will refer to all types of ovarian cancer unless indicated otherwise.

Ovarian cancer in Australian women in 1999¹

- 1,173 women diagnosed with ovarian cancer
- 731 women died from ovarian cancer
- 5,948 years of life lost under the age of 75
- relative survival nationally of 42% at five years after diagnosis in 1992-1997
- the most common cause of death from gynaecological malignancy

In 1999, cancer of the ovary was the eighth most common cancer (the seventh most common cancer excluding cancers of unknown site) and the sixth most common cause of death from cancer (the fifth most common cause of death excluding cancers of unknown site) in Australian women.¹ The ranking of the most frequently occurring cancers based on the number of new cases and deaths in Australian women is shown in Figures 1 and 2.

Figure 1 Most frequently occurring cancers. Numbers of new cases in Australian women, 1999. (NHL refers to Non-Hodgkin's lymphoma)

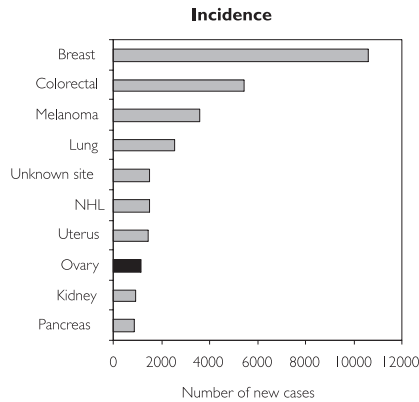
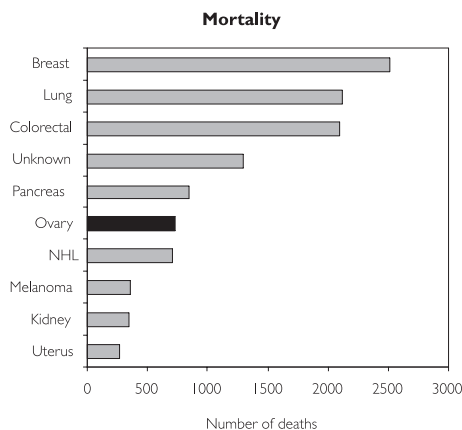


Figure 2 Most frequently occurring cancers. Numbers of deaths in Australian women, 1999. (NHL refers to Non-Hodgkin's lymphoma)



INTERNATIONAL COMPARISONS

Ovarian cancer incidence varies more than two fold around the world. Countries with a high incidence include the Scandinavian countries, the United Kingdom and the United States. Asian countries have relatively low rates of ovarian cancer, although there is evidence that rates have increased over recent years. Rates in Australia tend to be lower than those in the UK, USA and Northern Europe but higher than those in Southern Europe and Asia. Incidence rates probably reflect differences in diagnostic and registration accuracy in different populations as well as differences in the distribution of risk factors for ovarian cancer, particularly fertility patterns.

Examples of ovarian cancer incidence and mortality rates in different regions are shown in Figures 3 and 4.

Figure 3 Age standardised incidence of ovarian cancer per 100,000 in selected countries.²

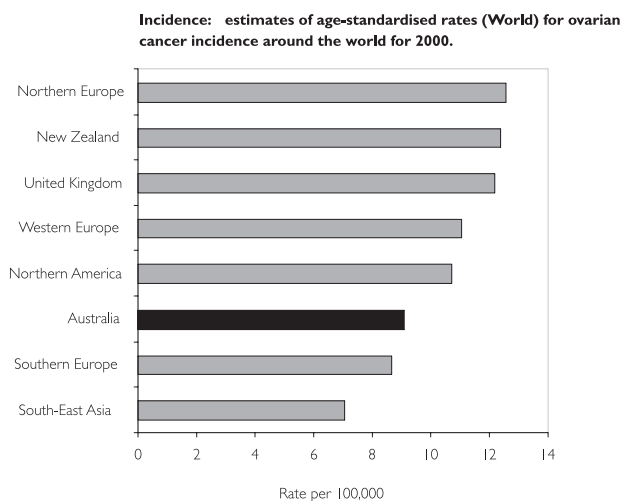
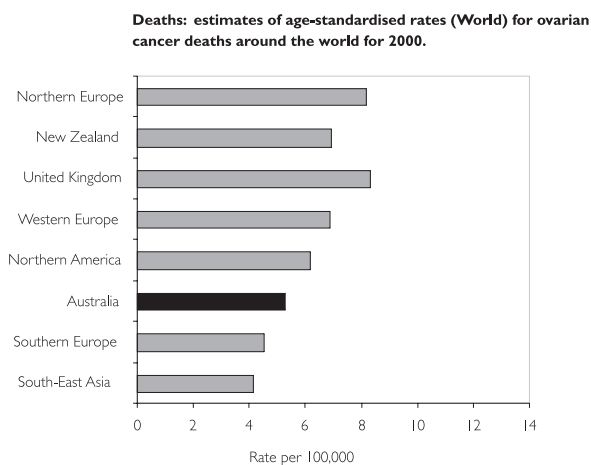


Figure 4 Age standardised mortality rates of ovarian cancer per 100,000 in selected countries.²

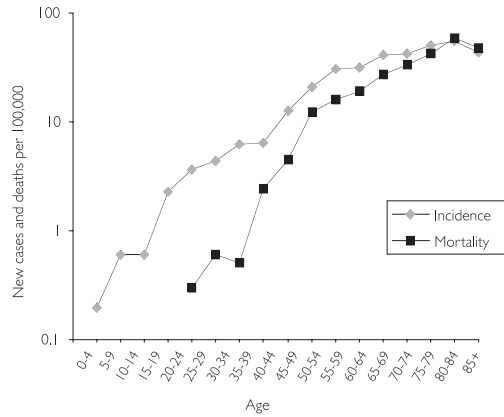


Note: the data from each country in Figures 3 and 4 are estimated for the middle of 2000 from the most recent data available, generally 3-5 years earlier.

AGE-SPECIFIC INCIDENCE AND MORTALITY RATES

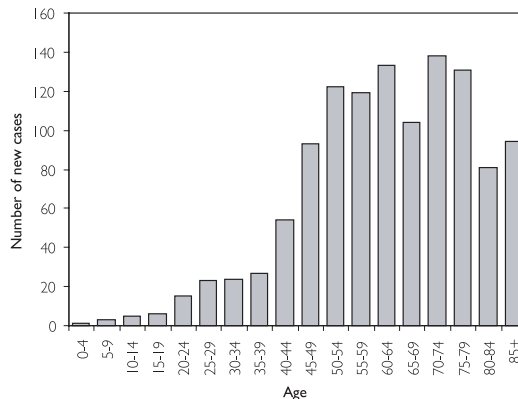
Ovarian cancer incidence and mortality rates increase with age as shown in Figure 5. Incidence increases steeply to 50 years of age and continues to increase, although more slowly, in women at older ages.

Figure 5 Age-specific incidence and mortality rates for ovarian cancer in Australian women 1999



The age distribution of women diagnosed with ovarian cancer in 1999 is shown in Figure 6. The distribution is skewed towards later life. The median age at diagnosis was 63 years. Overall, 87% of cancers are diagnosed among women over the age of 45 years and, as noted above, the majority of tumours in women under 40 years are germ-cell tumours and not epithelial cancers. For a detailed review of population and clinical cancer statistics, see the report *Ovarian Cancer in Australian Women*.³

Figure 6 Age distribution of new ovarian cancer cases, Australia, 1999

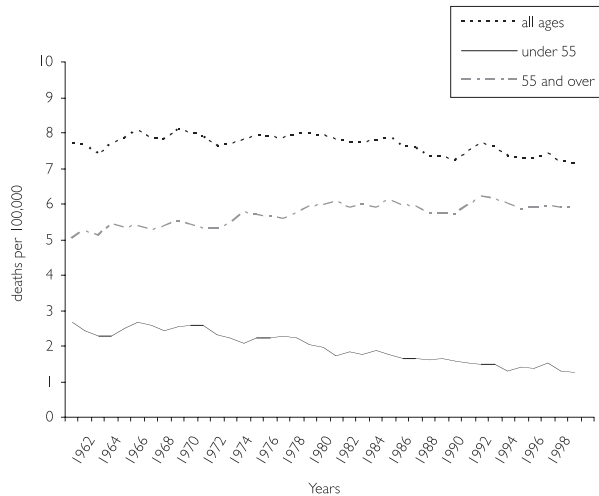


TRENDS IN OVARIAN CANCER INCIDENCE AND MORTALITY

In 1999 the age-standardised incidence rate was 10.6 per 100,000 female population and the lifetime risk to age 74 was 1 in 107; the age-standardised mortality rate was 6.3 per 100,000 women.¹

National cancer incidence data only became available in 1983 and since then the incidence of ovarian cancer has remained stable. In contrast, national mortality data have been available since 1921. Over the last 40 years there has been a decline in ovarian cancer mortality, most notably in women under the age of 55 (Figure 7). Similar trends have been seen in some other countries.^{4,5} Possible explanations for the trend include differences in the histological types and prognosis of tumours occurring in younger age groups, protective effects of oral contraceptive use and improvements in treatment.

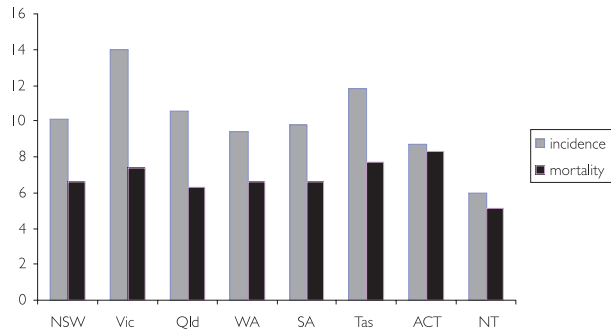
Figure 7 National trends in age-standardised mortality rates for ovarian cancer, 1958-98. (3-year leading averages)



DIFFERENCES IN STATE AND TERRITORY CANCER INCIDENCE AND MORTALITY RATES

In 1994-1998, incidence of ovarian cancer was highest in Victoria and Tasmania and mortality was highest in Victoria, Tasmania and the Australian Capital Territory (ACT). In general, differences in State and Territory cancer incidence rates may be explained by normal incidence rate fluctuations, the availability and utilisation of diagnostic procedures, and reporting and coding inconsistencies. It is also possible, however, that the differences could be due to geographic variations in the prevalence of risk factors for ovarian cancer.

Figure 8 Average annual incidence and mortality rates by State and Territory, Australia, 1995-1999

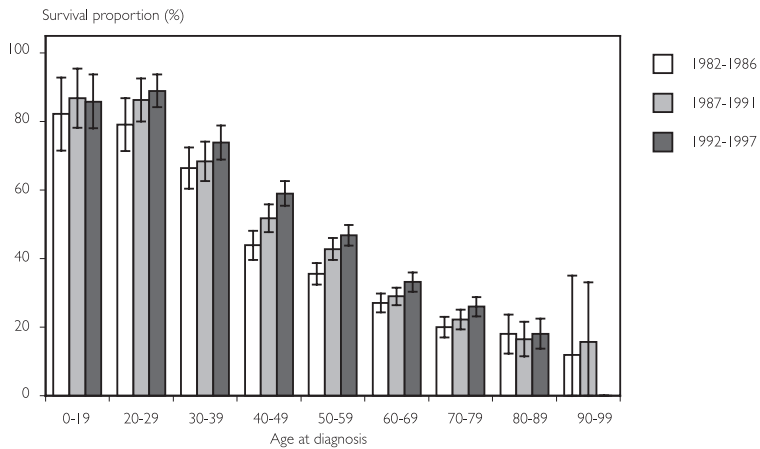


SURVIVAL FROM OVARIAN CANCER

Five-year relative survival for Australian women of all ages with ovarian cancer was 42% in 1992-1997. The data in Figure 9 show that five-year relative survival after a diagnosis of ovarian cancer increased between 1982-1986 and 1992-1997. Survival was highest in the younger age groups.

Note: 95% confidence intervals are shown for each age group.

Figure 9 Cancer of the ovary. Five-year relative survival proportions: age at diagnosis by period of diagnosis, Australia.⁶



Evidence of improved survival of women with ovarian cancer comes from relative survival analysis of national ovarian cancer data.⁶ Relative survival analysis compares the survival of persons diagnosed with cancer (observed) with that experienced by the general age and sex-matched population to which they belong (expected).⁶ Expressed as a percentage, it is the proportion of cancer patients that survives a specific number of years after the diagnosis of cancer divided by the general population that survives the same number of years. A survival rate of less than 100% indicates that the survival of women with ovarian cancer is less than expected for women in the general population of the same age.

Key points:

- Five-year relative survival after a diagnosis of ovarian cancer is highest in younger women and decreases with age.
- Five-year relative survival increased significantly between 1982-1986 and 1992-1997.

Increased survival from cancer may arise for a range of reasons. For ovarian cancer, these may include more effective and more widely available treatment, more effective investigation, diagnosis and staging of disease, and increased speed of referral. Clinical cancer registry data have made possible some comparisons of survival by clinical characteristics.

Information about tumour stage and grade is not available at the national level. Registries in South Australian teaching hospitals have, however, collected data about Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stage and tumour grade. Data from the South Australian Hospital-based Cancer Registries are used as an indication of the situation in the whole of Australia.

After adjusting for these characteristics and for age, women diagnosed between 1992-98 had a 21% lower risk of dying (Relative risk = 0.79; 95% Confidence interval 0.66 to 0.95) than women diagnosed between 1984-91.⁷ This was indicative of treatment gains. The registries also showed that five-year survival fell from 86% for women with FIGO stage IA tumours to 7% for women with stage IV tumours, and from 70% for low-grade tumours to 25% for high-grade tumours.⁷ Age at diagnosis was also an important predictor of outcome, with the five-year survival rates ranging from 74% for cases under 40 years at diagnosis to 18% for those aged 75 years or more. (In this instance, the survival proportions were not calculated as relative survival.) Similar figures have been reported by a study of ovarian cancer conducted in Queensland, New South Wales and Victoria between 1990 and 1993. Five year survival fell from 88% for stage 1 tumours to 12% for stage IV cancers; from 79% for low grade tumours to 30% for high grade tumours and from 67% for women diagnosed below the age of 40 to 29% among women diagnosed at age 70-79 years.⁸

Table 1 Five year survival rates for ovarian cancer in Australia by age at diagnosis, FIGO stage and tumour grade

	South Australia, 1984-1998 ⁷	Queensland, NSW & Victoria, 1992-1994 ⁸
Age		
Younger	74% (age <40)	67% (age < 40)
Older	18% (age 75+)	29% (age 70-79)
FIGO stage		
I	86% (IA)	88%
II		65%
III		27%
IV	7%	12%
Tumour grade		
Well-differentiated	70%	79%
Moderately differentiated		41%
Poorly differentiated		39%
Undifferentiated	25%	30%

Key points:

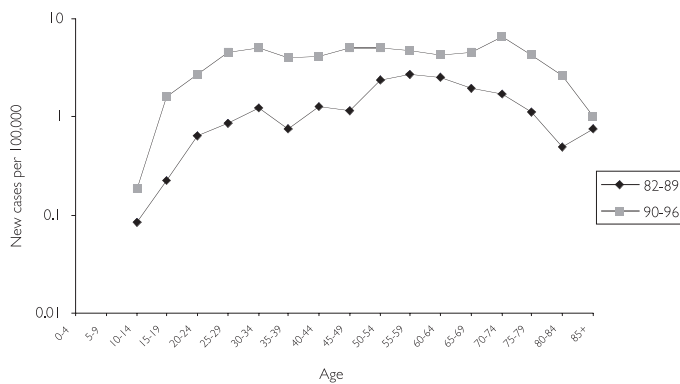
- Stage and grade of tumour at diagnosis are important predictors of five-year survival; FIGO stage 1A and low grade tumours have the highest survival rates.

BORDERLINE OVARIAN TUMOURS

One group of epithelial cancers, not as aggressive as others, are described as ‘borderline’ (or low malignant potential) ovarian cancers. They generally occur at younger ages and with a more favourable stage distribution than other ovarian cancers. (*See chapters on Risk factors for ovarian cancer, Chapter 3; The biology and pathology of ovarian tumours, Chapter 5; and Management of borderline ovarian tumours, Chapter 9*)

There are no national cancer registry data on borderline ovarian tumours. Few cancer registries in Australia enter data on borderline ovarian tumours into their registry databases (eg they are not registered in the NSW Central Cancer Registry). Data are available from the Victorian Cancer Registry although they are influenced by changes in coding as well as reporting and registration practices. Prior to 1995, borderline ovarian tumours were coded as International Classification of Disease (ICD) 236.2, neoplasms of uncertain behaviour - ovary. Since 1995, under ICD-O2 rules, borderline ovarian tumours are coded as malignant under ICD 183 and distinguished by separate morphology codes. Data presented in Figure 10 are from Victoria from 1982 to 1996.

Figure 10 Age specific incidence rates for borderline ovarian tumours, Victoria 1982-1996



Borderline ovarian tumours are less common than invasive ovarian cancers. The age-specific incidence of borderline ovarian tumours shows a different pattern from that of invasive ovarian tumours (see Figure 5). Incidence of borderline ovarian tumours increases to age 30 and then flattens with a fall in incidence from age 75. Incidence rates in 1990-1996 were higher than in 1982-89, reflecting both increased reporting and registration of borderline ovarian tumours, though the pattern of incidence with age was similar.

In a report from the USA, 10-years survival for 2818 women with borderline tumours was 95%⁹ although this figure fell from 97% among women with stage I tumours (82% of all borderline tumours) to 69% among the small group (3%) with stage IV tumours. Data from Switzerland¹⁰ and Norway¹¹ have also shown overall survival to be more than 90% after five years. A recent Australian study reported only two deaths during an average of seven years follow-up of 145 women with borderline epithelial ovarian tumours.⁸

Key point:

- Reliable national data on the incidence of borderline ovarian tumours and on the incidence of ovarian tumours by major histopathological type are not currently available and would be of value in monitoring trends and outcomes.

TECHNICAL GUIDE

CANCER REGISTRATION

Cancer registration is a legal requirement in all Australian States and Territories. Population-based data are collected by each State and Territory cancer registry to monitor cancer trends, increase understanding of the causes of cancer, and assist prevention efforts and treatment decisions. Population-based registries normally collect a limited range of data items only.^{12,13} Priority is placed on case ascertainment, rather than on collecting a broad range of data items. The data show the burden of cancer on the total population, and its component sub-groups, as indicated by incidence, mortality and survival data.¹²

Hospital-based registries can play an important role in collecting the clinical data that hospitals require for purposes such as monitoring care and survival by stage and other clinical characteristics to assess concordance with recommended protocols and expectations from the scientific literature. Data can be used for research purposes and to assess caseloads for planning and resource negotiation.⁷

NATIONAL POPULATION-BASED CANCER STATISTICS

Established in 1987, the National Cancer Statistics Clearing House (NCSCCH) compiles data produced by State and Territory registries and produces national cancer statistics.¹⁴ The Australian Institute of Health and Welfare (AIHW) operates the NCSCCH under the supervision of the Australasian Association of Cancer Registries. Although some State and Territory cancer registries have been operating for more than 20 years, registration was not universal in Australia until 1982.

National data on cancer deaths have been available for many years based on information provided to the Registrar of Births, Deaths and Marriages in each State and Territory.

The statistics presented here for ovarian cancer in Australia are derived from data collected by the NCSCCH and reported by the Australian Institute of Health and Welfare. Data are from 1999 except where numbers of cancers in particular sub-groups are small and data from several years are pooled. Incidence rates for borderline ovarian tumours come from the Victorian cancer registry.

HOSPITAL-BASED CANCER STATISTICS

Although there are currently no national clinical data collections on ovarian cancer, the National Cancer Control Initiative has released recommended minimum data sets for hospital and other clinical cancer registries.¹⁵ A standardised approach to the collection of clinical data would enable national patterns of cancer survival by stage at diagnosis and patterns of cancer care to be assessed.

Hospital-based cancer registries have a long history in the USA. In Australia, hospital-

based cancer registry data have been collected from South Australian teaching hospitals with specialist gynaecological oncology services. The data have been used for a broad range of purposes including monitoring clinical practice and outcomes and for planning health services.

DEFINITIONS

Rates are presented per 100,000 female population. Age-standardised rates have been calculated by the direct method using the 1991 Australian standard population.¹⁴ For international comparisons, the world standard population has been used.

CODING

Australian data for ovarian cancer in 1999 are presented for “malignant neoplasms of the ovary” (International Classification of Diseases revision 10, ICD-10 code C56). Prior to this date cancers were coded to ICD-9 and data are presented for “malignant neoplasms of the ovary and other uterine adnexa” as classified to the single three-digit code 183.¹⁶ The majority of neoplasms with this code are malignant neoplasms of the ovary. Coding at the four digit level of 183.0 to 183.9 distinguishes between different sites as follows: 183.0 ovary; 183.2 fallopian tube; 183.3 broad ligament; 183.4 parametrium; 183.5 round ligament; 183.8 other; 183.9 uterine adnexa, unspecified.

Cancers of the ovary comprised 97.3% of all cancers coded as ICD-9 183 malignant neoplasms of the ovary and uterine adnexa in 1992-1996. Malignant neoplasms of the broad ligament (ICD 183.3), parametrium (ICD 183.4) and round ligament (ICD 183.5) were very rare with fewer than ten cases in total diagnosed in the five-year period. The number of new cases and the age standardised incidence rates are shown in Table 2 for sites with more than five cases.

Table 2 Malignant neoplasms of the ovary and uterine adnexa in Australia 1992-1996 by site. (National Cancer Statistics Clearing House and Australian Institute of Health and Welfare: Personal Communication)

	Ovary 183.0	Fallopian tube 183.2	Other 183.8	Uterine adnexa, unspecified 183.9
Number of new cases	5,408	104	26	14
Age-standardised incidence rate per 100,000	11.1	0.2	0.1	<0.1

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2. RISK FACTORS FOR OVARIAN CANCER

Established risk factors for ovarian cancer have been identified in well-designed studies from multiple research groups around the world and observed in the pooled re-analysis of data from several studies. They include the increase in risk with age and a family history of ovarian cancer. Evidence for other risk factors has been less consistent. Important protective factors are parity and use of the oral contraceptive pill.

As a comprehensive review of recent research literature on risk factors for ovarian cancer has been commissioned by the National Breast Cancer Centre and detailed reviews of the epidemiology of ovarian cancer can be found elsewhere,^{1,2,3} these guidelines will provide a general overview.

The epidemiology of specific ovarian tumour types has not been well described and risk factors may differ. Some studies have focussed on the epidemiology of epithelial ovarian tumours while others have grouped together a broad range of histological types. There have been relatively few studies of the epidemiology of borderline ovarian tumours. Evidence to date suggests a similar pattern of risk factors to invasive ovarian tumours. Possible exceptions include weaker protection from oral contraceptive use, a stronger association with infertility and fertility drug use and a weaker association with family history.^{4,5}

AGE

Invasive ovarian cancer is rare among young women; the majority of cases are diagnosed in women over the age of 50. The pattern for borderline ovarian tumours is different (*see chapter 1 on Ovarian cancer in Australian women, Figure 10*).

FAMILY HISTORY

Familial clusters of ovarian cancer have been recognised for many years and family history has been identified as a risk factor in most epidemiological studies that have investigated its role.⁶ Between 5% and 10% of cases of ovarian cancer are believed to be attributable to hereditary factors.⁷ The proportion is higher in women of Ashkenazi Jewish descent - about 30%. Mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 have been identified as important. Although particular gene mutations, such as these, confer a high risk, the majority of ovarian cancers occur in women who do not have a family history of the disease (*see chapter 4 on Familial aspects of ovarian cancer*).

REPRODUCTIVE HISTORY

Infertility

The relationship between infertility and ovarian cancer risk is not well understood. Studies have had difficulty in separating the effects of low parity, infertility and its treatment with fertility drugs; few have distinguished between anovulatory infertility and infertility due to other causes.

Findings about ovarian cancer risk in women who have been treated with fertility drugs have been inconsistent.⁸ Follow-up of a large Australian cohort of In Vitro Fertilisation patients treated with fertility drugs to induce superovulation has, to date, shown no increase in ovarian cancer incidence.⁹ A recent pooled reanalysis of 8 case-control studies of ovarian cancer showed no increased risk of invasive ovarian cancer in women with a history of fertility drug use¹⁰ When the different histologic subtypes were considered separately an odds ratio of 2.4 (CI 1.0-5.9) for borderline serous ovarian tumours was seen among treated women who had never had children. However, this association could have been due to chance.

One study suggests a possible association between ovarian epithelial dysplasia and ovulation induction therapy, in accord with previous results of increased risk of ovarian cancer in women with a history of fertility treatment. The higher dysplasia score could be attributable to the drugs used to induce ovulation or to a genetic susceptibility of ovarian cancer.¹¹

Pregnancy

Evidence for the protective effect of pregnancy on ovarian cancer risk comes from analyses of population fertility rates and ovarian cancer mortality¹² and more recently from case-control studies, including a large Australian study.¹³ The combined analyses of 12 US case-control studies⁴ and 3 European case-control studies^{14,15} confirmed the protective effect of parity with a risk reduction of up to 50% depending on the study design and number of births women had experienced. One study notes that compared with women who have never had children (Relative Risk of 1.0), women with a single pregnancy have a lower relative risk (CI 0.6 to 0.8). Each additional pregnancy lowers risk by about 10 to 15 percent.¹⁶ The effect may be greatest for non-mucinous tumours.¹⁷ Increasing parity has also been shown to reduce the risk of borderline ovarian tumours in women aged 50-74.¹⁴

Greater age at first birth^{18,19} and greater age at last birth^{18,20,21} have both been associated with a reduced risk of ovarian cancer in some but not all studies. Multiple pregnancies may also confer increased protection compared to singleton births, particularly for non-mucinous tumours.²²

There has been some suggestion that incomplete pregnancies reduce ovarian cancer risk but the effect appears to be less than for complete pregnancies.^{3,4}

Hysterectomy and tubal ligation

Many studies have observed protective effects of hysterectomy (with bilateral ovarian conservation) and tubal ligation on ovarian cancer risk. Risk reductions of 35% - 40% were found in one case-control study.²³ The explanation for this finding is not clear, but it has been suggested that protection may result from reduced passage of carcinogens to the upper genital tract. Hormonal and circulatory sequelae of hysterectomy and tubal ligation have also been proposed as possible explanations.²⁴

OTHER REPRODUCTIVE FACTORS

There are other reproductive factors in determining ovarian cancer risk which are uncertain. Studies have reported no association with age at menarche^{18,13} and earlier age at natural menopause has been associated with both decreased¹⁸ and increased²⁵ risk. Among women with early onset disease, there is little evidence to suggest that early menopause is related to ovarian cancer.²⁵

Breastfeeding may, however, reduce the risk of ovarian cancer slightly.^{4,26} It has also been shown to reduce the risk of borderline ovarian tumours in women aged 50-74.¹⁴

EXOGENOUS HORMONES

The effect of hormone replacement therapy (HRT) on ovarian cancer risk has been controversial with some studies showing a significant increase in risk¹⁸ while others show no association or only a non-significant increase in risk.²⁷ A recent study of long term users of menopausal HRT by Lacey *et al.* showed an association between oestrogen only HRT and ovarian cancer, with Relative Risks, for 10-19 years of use and 20 or more years of use, of 1.8 and 3.2 respectively. There was no increased risk found for short-term use of combined progestin/oestrogen HRT.²⁸ However, in a study published shortly after this by Sit *et al.*, there was no association overall between any use of HRT and epithelial ovarian carcinoma.²⁹

Unopposed oestrogen replacement has been associated with a significant increase in relative risk of endometrioid and clear cell epithelial ovarian cancer (OR 2.56, CI 1.32 to 4.94).³⁰ This finding is consistent with the well-known association between oestrogen therapy and risk of endometrial cancer. A second study reported the greatest increase in risk for serous cancers.¹⁸ The association between HRT and risk of the different histologic subtypes of ovarian cancer needs to be investigated in larger studies.

Key point:

- Further studies are needed to establish whether there are associations between different types of hormone replacement therapy and different histological types of ovarian cancer.

ORAL CONTRACEPTIVE PILL

There has been consistent evidence of a protective effect of the combined oral contraceptive pill on ovarian cancer risk. Women who had ever used the oral contraceptive pill had a 50% reduction in risk compared to women who had never used the Pill in the Australian case-control study.¹³ Although there is evidence that the protective effect persists for up to 15 years,^{4,31} it may diminish in the longer term.³²

One study compared oral contraceptive oestrogen and progestin content for cases and controls, adjusted for current age, number of pregnancies, race and family history of ovarian cancer. Use of low-oestrogen/low-progestin pills afforded an estimated risk-reduction that was identical to that for high-oestrogen/high-progestin pills.³³

Suppression of ovulation has been believed to be the most likely explanation for the protective effect of oral contraceptives. However, there is increasing recognition of the role of hormones in the aetiology of ovarian cancer³⁴ and evidence that oral contraceptives are protective even after adjusting for the number of ovulatory cycles a woman has experienced.³⁵ Whether or not changes to the formulations of oral contraceptives in recent years has affected the degree of protection remains to be seen.

A recent Swedish case control study confirmed a long-lasting protective effect of oral contraceptive use against ovarian cancer, but noted some differences in odds ratio by histologic type, with no protective effect seen for mucinous carcinoma.¹⁸ Others have, however, reported similar benefits for both mucinous and non-mucinous cancers.¹⁷

A single study of borderline tumours reported no protective effect for oral contraceptive use¹⁴ but others have found similar protection for invasive and borderline tumours.⁴

OTHER FACTORS

It has been suggested that inflammation may play a part in ovarian cancer risk and that ovarian cysts and hyperthyroidism may be associated with inflammatory responses of the ovarian epithelium.³⁶ Endometriosis has been associated with an increased risk of ovarian cancer in a large Swedish cohort study³⁷ and in a pooled analysis of seven case-control studies,¹⁰ but has yet to be confirmed in other well-designed cohort studies. There is also clinical evidence indicating that deposits of endometriosis on the ovary may develop into epithelial ovarian cancer, and in particular the endometrioid and clear cell subtypes.^{38,39} The question of whether a history of benign ovarian cysts increases the risk of ovarian cancer has been addressed in only a small number of studies and there is currently little evidence to support an association.^{40,41}

BODY SIZE

Some data suggest that increasing body weight may confer a protection against cancer⁴² but taken together, the evidence is in favour of a small to moderate positive relation between high Body Mass Index (BMI) and occurrence of ovarian cancer.⁴³

LIFESTYLE FACTORS

Diet

While retrospective studies of dietary intake are notoriously difficult, the influence of dietary factors on ovarian cancer risk has been studied as a possible explanation for differences in incidence between countries and ethnic groups. Increased risks have been associated with the consumption of meat, whole milk⁴⁴ and animal fat in some studies; others have found no such associations.² It has been suggested that intake of low fat milk, calcium or lactose may reduce the risk of ovarian cancer.⁴⁵ Overall, results suggest no association between intake of any type of fat and ovarian cancer.⁴⁶ There has been more limited research on the effects of alcohol and coffee consumption with no consistent evidence of an increased risk.⁴⁷

Smoking

Some studies have shown an association between smoking and ovarian cancer.^{13,48,49} One study showed that women who had ever smoked were more likely to develop ovarian cancer than those who had never smoked.⁵⁰ The level of risk may vary according to the histologic type of tumour, with higher risk for borderline and mucinous ovarian cancer but not for non-mucinous tumours.^{50,49} A case-control study by Marchbanks *et al.* showed that the risk for mucinous epithelial ovarian cancer was more than doubled for women who had ever smoked and for current smokers. This elevated risk was regardless of years since the first cigarette or age at which women first smoked.⁴⁸

Physical activity

Overall results provide only limited support for an inverse association between recreational physical activity and risk of ovarian cancer.⁵¹

Use of talcum powder

An association between the use of talcum powder in the perineal area has been suggested in some studies,^{13,23} but not found in others.^{52,53}

Key points:

- Level III-2 evidence indicates that important risk factors for ovarian cancer include the increase in risk with age^{1,2} and a family history of ovarian cancer.⁶ Evidence for other risk factors has been less consistent.
- Protective factors include increasing parity and oral contraceptive use.
- The epidemiology of specific ovarian tumour types has not been well described and risk factors may differ.
- At present, the risk factors for ovarian cancer are not readily modifiable and have not been translated into primary prevention strategies.

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3. SCREENING FOR OVARIAN CANCER

INTEREST IN OVARIAN CANCER SCREENING

There is great interest in the feasibility and benefits of early detection of ovarian cancer through screening, defined as the investigation of asymptomatic women. In this chapter the focus will be on women at average or population risk. The management of women at high risk will be covered in chapter 4, *Familial aspects of ovarian cancer*.

The poor prognosis for women diagnosed with ovarian cancer is related to the fact that the disease is usually diagnosed at an advanced stage. By the time that the patient is investigated for often generalised symptoms, the disease has usually progressed and chances of a cure are reduced. Early stage disease, where the disease is confined to the ovaries, is associated with a 5-year survival rate of over 80%.¹

ISSUES FOR OVARIAN CANCER SCREENING

- No true precursor lesion has been identified (*see chapter 5 on The biology and pathology of ovarian tumours*)
- Any screening for ovarian cancer should ideally detect early, pre-clinical, asymptomatic disease to reduce morbidity and mortality
- To date there is no evidence to indicate a decrease in mortality as a consequence of ovarian cancer screening, although survival advantage has been found in two trials^{2,3}
- Any screening test will need to have an appropriate sensitivity (the ability to determine the presence of the disease in those who have it) and specificity (the ability to exclude the disease in those who do not)
- The benefits of any screening test should outweigh any chance of physical or psychological harm

(For the World Health Organization (WHO) criteria for screening, *see Appendix 3 - Principles of screening*).

TECHNIQUES FOR SCREENING FOR OVARIAN CANCER

BI-MANUAL PELVIC EXAMINATION

When used alone, bimanual pelvic examination lacks both the sensitivity and specificity to be effective and is not recommended as a screening method.⁴

ULTRASOUND

Transabdominal ultrasound

Transabdominal ultrasound has been used to detect changes in the ovaries which may be suggestive of the presence of a tumour, such as enlargement. Transabdominal ultrasound was used to screen over 7000 asymptomatic women or post menopausal women and showed a specificity ranging from 94% to 98%, with a positive predictive value ranging from 1.5% to 7.7%.^{5,6,7,8}

Transvaginal ultrasound (TVUS)

Transvaginal ultrasound provides increased proximity to the ovaries and allows for better visualisation of morphological changes than transabdominal ultrasound. While it does have the ability to detect the presence of ovarian disease, it gives rise to a large number of false positives, due to its inability to distinguish between benign and malignant masses.^{9,10} Studies with asymptomatic women showed that for those who had a positive ultrasound test, the proportion who correctly had ovarian cancer predicted was only between 6% and 9%.^{11,12,13,14}

Combination of transabdominal and transvaginal ultrasound

Studies that used a combination of transabdominal and transvaginal ultrasound in women with a family history of ovarian cancer have achieved a positive predictive value of between 7% and 9.8%.^{15,16}

Sonography may best be used as a secondary test due to its low positive predictive value, and its inability to accurately differentiate between benign and malignant disease (giving rise to false positives).

Doppler ultrasound

Colour Doppler ultrasound has been used singly or in conjunction with other techniques, to improve differentiation between benign and malignant disease through imaging of the blood flow characteristics. Results have been mixed and it has not been shown that this technique is a better differential test than transvaginal ultrasound or CA125.^{17,18,19,20}

CA125

CA125 is an ovarian cancer antigen which can be detected in blood serum. The levels present in the blood can be affected by a number of factors such as prior cancer diagnosis, regular smoking, caffeine consumption, age, and age at menarche, age at menopause and history of previous ovarian cyst.²¹ Elevated levels may also be associated with other malignancies or benign conditions. It is most often raised in serous and less frequently in mucinous cancer and is found in over 80% of non-mucinous epithelial ovarian cancers.²²

As a screening test, a cut-off value of 30U/ml-35U/ml is usually used. CA125 is elevated in 76% of women with FIGO stage II disease, over 90% of women with FIGO stage III and IV disease but only 49% of women with FIGO stage I disease.²³ As a stand-alone screening tool it lacks the specificity and sensitivity required.

Key point:

- Less than 50% of women presenting with FIGO stage 1 ovarian cancer have elevated levels of CA125.

Using CA125 in combination with other modalities such as ultrasound, as a serial measure or with complementary tumour markers, such as inhibin,²⁴ has been investigated in an attempt to increase its specificity and sensitivity.

FUTURE DIRECTIONS

Genomic and proteomic technologies²⁵ have the potential to identify specific genes and novel cancer-specific markers for ovarian cancer. The development of molecular profiles for ovarian cancer and a better understanding of the genetic and molecular origins of ovarian cancer may also be used for early detection.

RECOMMENDATIONS ABOUT SCREENING FOR OVARIAN CANCER

There is currently no national or international study which recommends routine screening for women in general. (For the management of women with a family history of ovarian cancer or with a hereditary cancer syndrome, *see chapter 4 on Familial aspects of ovarian cancer*).

FUTURE PROSPECTS IN OVARIAN CANCER SCREENING

Three large multi-centre, population-based randomised trials are in progress.

- St Bartholomew's trial (UK) commenced in 1995, plans to recruit 200,000 post-menopausal women over seven years, randomised to screening with CA125 followed by ultrasound, ultrasound only or a control group.
- Prostate, lung, colon-rectum and ovary trial (PLCO - USA) commenced around 1993 and has enrolled 37,000 women in each arm. The protocol involves a combination of transvaginal ultrasound, CA125 and pelvic examination conducted annually.
- European Organisation for Research and Treatment of Cancer trial (EORTC-UK and Europe) commenced in 1995 and the trial has 30,000 in each arm and 60,000 in the control arm. The protocol involves transvaginal ultrasound at either 18 or 36 month intervals, with repeat scans performed based on criteria which may indicate carcinoma.

The results of these trials will be used to frame a decision on the type of population screening test and the optimal screening interval.

Key points:

- None of the currently available screening tests, either singly or in combination, have been shown to be effective in reducing mortality from ovarian cancer.
- Population-based screening for ovarian cancer cannot be recommended at this time due to the absence of evidence for a reduction in morbidity or mortality.

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4. FAMILIAL ASPECTS OF OVARIAN CANCER

Up to 10% of all cases of epithelial ovarian cancer are thought to be due to the autosomal dominant inheritance of mutations in one of a small number of ovarian cancer-related genes (see Table 3).² Carriers of mutations in such genes have an increased risk of epithelial ovarian cancer of at least 10 fold. Some of these genes are also associated with an increased risk of female breast cancer, while others are associated with an increased risk of other cancers, such as male breast cancer and cancer involving other organs.³

These genetic factors are the strongest known risks for ovarian cancer, although they are rare and do not inevitably lead to disease.

Table 3 - Known genes responsible for hereditary ovarian cancer

Syndrome	Gene	Chromosome	Risk of other cancers
Hereditary breast/ovarian cancer	BRCA1	17q	Female breast, prostate, fallopian tube, primary peritoneal
	BRCA2	13q	Female breast, male breast, prostate, pancreas fallopian tube, primary peritoneal and other
Hereditary non-polyposis colorectal cancer	DNA mismatch repair genes (HNPCC)	Various	Colorectal, other gastrointestinal, endometrial, renal tract, ovarian

Two main hereditary ovarian cancer syndromes have been identified (*see Table 3*). These two syndromes account for about ten percent of all cases of ovarian cancer. They are:

- hereditary breast/ovarian cancer syndrome, which is characterised by susceptibility to both breast and ovarian cancer, cancer of the fallopian tube, primary peritoneal cancer, male breast, prostate and pancreatic cancer.
- hereditary non-polyposis colorectal cancer syndrome (HNPCC), which includes early onset colorectal cancer, other gastrointestinal cancers and cancer of the renal tract and an increased risk of extracolonic cancers, including endometrial and ovarian.

GENES ASSOCIATED WITH OVARIAN CANCER

Constitutive (germline) mutations in specific genes are associated, in carriers, with an increased risk of ovarian cancer. The degree of risk depends on the gene involved, and there is evidence that different mutations in the same gene may be associated with different risks of certain cancers.

The BRCA1 and BRCA2 breast/ovarian cancer susceptibility genes have been well studied because of their major role in the genetic predisposition to breast cancer. Carriers of a germline mutation in either BRCA1 or BRCA2 are also at increased risk of ovarian cancer.^{4,5} The risk of developing ovarian cancer by age 70 for female carriers of a mutation in BRCA1 or BRCA2 has been estimated to be between 15% and 66%,^{4,6,7} although the risk for BRCA2 mutation carriers is, on average, at a later age and less than for BRCA1 mutation carriers.^{4,5} The age at diagnosis of ovarian cancer in women with a BRCA1 mutation tends to be earlier than for women in the general population, with a median age at diagnosis of 48 years, while the average age at diagnosis of BRCA2-related ovarian cancer is similar to that for women without a genetic predisposition⁸ and usually in the late 50s or early 60s.

Key points:

- Female carriers of germline mutations in BRCA1 have a lifetime risk of ovarian cancer that may be as high as 60%,¹⁰ and in BRCA2 as high as 40%.⁵
- For women with a BRCA1 mutation, who develop ovarian cancer, the average age at diagnosis is earlier than for women in the general population.⁸

Neither BRCA1 nor BRCA2 appear to be associated with very early ovarian cancer (i.e. diagnosed before the age of 30 years). There is some evidence that some mutations in the BRCA2 gene are associated with a higher risk of ovarian cancer and a lower risk of breast cancer.⁹ There is ongoing Australian and international research investigating the frequency of BRCA1 and BRCA2 mutations in the population, their associated risks of different cancers (penetrances) and phenotypes, such as tumour morphology, and the effect on disease risk due to genes and/or environmental risk factors.

Between 1 in 500 and 1 in 1000 unaffected women carry a germline mutation in one of these genes. The founder mutations 185 del AG and 5382 ins C in BRCA1, and 6174 del T in BRCA2, are carried by about 2% of individuals of Ashkenazi Jewish ancestry. For this reason, a higher proportion of ovarian cancer cases in Ashkenazi Jewish women are due to germline mutations in these genes (estimated to be 40-60%).¹¹ Each of these mutations is associated with an increased risk of ovarian cancer.⁶ BRCA-associated invasive epithelial ovarian malignancy tends to be of the non-mucinous, mostly serous, subtype, as is the case for most ovarian cancers in the general population.¹² Cancers of the fallopian tube¹³ and primary peritoneal cancers are also associated with germline mutations in BRCA1 and BRCA2, though to a lesser extent.

In families with HNPCC due to a germline mutation in one of the DNA mismatch repair genes, mutation carriers have a 70-90% lifetime risk of developing any cancer.

There is a higher risk of colorectal cancer for men compared to women from HNPCC families. Women who carry a mismatch repair gene mutation have a lifetime risk of up to 40% for endometrial cancer and a lifetime risk for ovarian cancer of up to 10%.¹⁴ In a retrospective review of HNPCC-associated ovarian cancers, the mean age at diagnosis was relatively young at 42.7 years.¹⁵ There is a tendency for these cancers to be of lower grade and earlier stage, and synchronous ovarian/endometrial cancers may occur.

All the above risks for carriers of deleterious mutations in ovarian cancer-related genes are estimates, and have large confidence intervals. They are mostly derived from selected families with extensive family histories, and in which case the penetrance of the gene mutation may be particularly high. Increasingly, though, risk evidence is accumulating from families unselected for a strong family history.⁸

Finally, there may be many other genes, as yet undiscovered, which are associated with an increased risk of ovarian cancer.¹⁶

MUTATION TESTING FOR GENES ASSOCIATED WITH OVARIAN CANCER

Familial Cancer Clinics make a thorough assessment of the family's cancer history and determine the likelihood that a germline mutation in an ovarian cancer-related gene may be present. Genetic testing should only be offered with pre and post-test counselling, conducted in conjunction with a specialist genetics service for breast/ovarian cancer. The potential harms, benefits and limitations of genetic testing need to be considered.

The process of genetic testing usually begins with the analysis of ovarian cancer-related genes by taking a blood sample from an affected family member. Although it is technically possible to detect constitutive alterations in ovarian cancer-associated genes, genetic testing requires specialised laboratory techniques and the 'mutation search' is expensive and time consuming. It is possible that some disease-related genetic mutations may not be detected using current technology. Detection of a genetic mutation in an affected family member allows for further predictive genetic testing of adult, unaffected relatives. Some family cancer clinics are also involved in ongoing risk management.

Key point:

- The potential harms, benefits and limitations of genetic testing need to be considered. Genetic testing (mutation searching and predictive testing) should only be offered with pre- and post-test counselling, conducted in conjunction with a specialist genetics service for breast/ovarian cancer.

FAMILY HISTORY

Having a family history of ovarian cancer is an important risk factor for ovarian cancer.¹⁷ Similarly, having a family history of breast cancer, or of cancers associated with HNPCC, may be associated with an increased risk of ovarian cancer.

Epidemiological data (case-control studies) have found a 2-to-20-fold increase in risk of ovarian cancer associated with a family history of ovarian cancer.^{17,18} The risk increases with the number of affected first degree relatives. The lifetime risk of ovarian cancer for women with a single first degree relative with ovarian cancer may approach 3% (a 3 fold increase compared to the general population), while for a woman with a single first degree relative with breast cancer, it is less than 2%, (compared to the population risk of around 1%).¹⁹ The lifetime risk for women with two first degree relatives with ovarian cancer has been estimated to range between 7% and 20%.²⁰ It should be noted that estimates of risk for women with various combinations of multiple affected relatives on the same side of the family are often based on small numbers, and should be interpreted with caution.

For any woman of Ashkenazi Jewish origin with a family history of breast or ovarian cancer, her Jewish background should be considered as an additional risk factor.⁶

In estimating risk of ovarian cancer based on family history, it is essential to take an accurate family history, and update it regularly. Taking a family history involves asking about all cancers for all first and second-degree relatives, both male and female, on both the maternal and paternal sides of the family. Attempts should be made to verify all cancer reports.

Key points:

- A comprehensive cancer family history is essential to be able to estimate risk of ovarian cancer.
- Any Ashkenazi Jewish woman with a family history of breast or ovarian cancer should have her ancestry considered as an additional risk factor.

PREDICTING RISK BASED ON CANCER FAMILY HISTORY

The National Breast Cancer Centre has previously published guidelines for health professionals to assist in assessment of risk based on family history.²¹ The information about familial aspects of ovarian cancer has now been updated (*see Appendix 1*), and the changes are included in the section below. For the purpose of advising women about their risk of ovarian cancer, it is useful to divide women into TWO broad categories.

Category 1: This covers more than 99% of the female population and includes women with no family history of epithelial ovarian cancer, or a limited family history, who are at or at most moderately above average risk.

Category 2: This covers less than 1% of the female population and includes women at a potentially high risk of ovarian cancer. (*See Risk classification for women at potentially high risk of epithelial ovarian cancer p.36*)

Being in Category 2 suggests that there may be, within the family, a dominantly inherited mutation in a gene such as BRCA1 or BRCA2, which confers a high risk of breast cancer and an increased risk of ovarian cancer, or a dominantly inherited mutation in the mismatch repair genes involved in HNPCC. Women from families in which the presence of an ovarian cancer-associated gene mutation has been established also belong to this category, since they are at potentially high risk.

Generally, it would be appropriate to commence testing for a causative germline mutation in any affected individual (or obligate carrier) in a family that meets the criteria for Category 2 (potentially high risk). In an Ashkenazi Jewish family, if the family meets the criteria, but an affected family member is not available, germline testing may be offered to an unaffected individual, in order to test for any of the three founder mutations in BRCA1 and BRCA2 that are associated with familial breast/ovarian cancer in that particular background.

Key point:

- Women who are proven to carry an ovarian cancer-associated gene mutation should be considered at potentially high risk.

Note:

To make these risk categorisations the family history of ovarian cancer must not be considered in isolation. A family history of breast cancer, and of some other types of cancer, should also be taken into account. Ashkenazi Jewish background is also important. If these additional features are present, referral to a specialist cancer genetics service may be appropriate. Women should be encouraged to seek medical advice promptly if they develop symptoms or signs that could be related to any cancers. Women found to have a pelvic mass at any age should be referred for specialist opinion.

Key point:

- A family history of breast cancer and of some other types of cancer should be taken into account, to ensure that a family history of ovarian cancer is not considered in isolation. Ashkenazi Jewish background is also important.

RISK CLASSIFICATION FOR WOMEN AT POTENTIALLY HIGH RISK OF EPITHELIAL OVARIAN CANCER

(See Category 2 above)

The following women should be advised that they have a potentially high risk of developing ovarian cancer and perhaps other cancers. This group includes less than 1% of the population, and comprises women who have:

- One first degree relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry;
- Two first or second-degree relatives on the *same side* of the family diagnosed with breast or ovarian cancer, especially if one or more of the following features occurs on the same side of the family:
 - breast cancer diagnosed before the age of 40;
 - bilateral breast cancer;
 - breast **and** ovarian cancer in the same woman;
 - breast cancer in a male relative;

OR

- Three or more first or second degree relatives on the same side of the family diagnosed with any of the cancers associated with hereditary non-polyposis colorectal cancer (HNPCC): colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer, and cancers involving the renal tract;
- A member of a family in which the presence of a high risk ovarian cancer mutation in a gene such as BRCA1, BRCA2 or one of the DNA mismatch repair genes, has been demonstrated.

Women in this group should be advised that, although potentially at high risk for ovarian cancer, the majority of women in this group will not develop ovarian cancer. For a woman who has had genetic testing, the identification of a germline mutation in one of the ovarian cancer susceptibility genes, however, is associated with a high risk of ovarian cancer, and perhaps other cancers, depending on the gene.

Key point:

- For a woman who has had genetic testing, the identification of a germline mutation in one of the ovarian cancer susceptibility genes is associated with her having a high risk of ovarian cancer.

ISSUES TO CONSIDER IN THE MANAGEMENT OF WOMEN AT KNOWN OR POTENTIALLY HIGH RISK OF EPITHELIAL OVARIAN CANCER

There are limited data on which to base the management of women at known or potentially high risk of ovarian cancer, so precise protocols remain controversial.

Women from families with the breast/ovarian cancer syndrome should be considered at increased risk of breast cancer. Bilateral prophylactic (risk reducing) mastectomy, with or without reconstruction, should be considered as an option in the context of risk counselling and management. Women from families with suspected HNPCC may require screening for gastrointestinal and endometrial cancers, as well as screening for ovarian cancer.

Two observational studies of the effect of the oral contraceptive pill (OCP) on women with a mutation in BRCA1 or BRCA2 are conflicting; one study showed a protective effect,²² but there was no evidence for such an effect in a second study.²³ In addition, there is some evidence that the use of the OCP may increase the risk of breast cancer in mutation carriers.²⁴ To date this has only been demonstrated from a study of BRCA1 mutation carriers.²⁴ Although the increased risk for BRCA1 mutation carriers who used the OCP, compared to those who did not, was only 1.3-fold for OCP use for 5 or more years in BRCA1 carriers, the higher baseline risk of breast cancer in BRCA1 carriers means that even such small increases in risk may translate into substantial increases in absolute risk. Given these conflicting data, it is not possible to recommend the use of the OCP as a chemoprevention against ovarian cancer in women with a mutation in BRCA1 or BRCA2. Tubal ligation has been reported to reduce the risk of ovarian cancer in BRCA1 (but not BRCA2) mutation carriers²⁵ and could be considered as a means of contraception after childbearing had been completed.

In women who carry a germline mutation in BRCA1 or BRCA2, bilateral salpingo-oophorectomy (with or without hysterectomy) reduces the risk of epithelial ovarian cancer by at least 90%.^{26,27,28} It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. In addition, bilateral risk reducing salpingo-oophorectomy has been reported to be associated with at least a 50% reduction of risk of breast cancer in BRCA1 or BRCA2 mutation carriers.^{26,27,28}

Guideline - Risk reducing surgery	Level of Evidence	Refs
Bilateral risk reducing salpingo-oophorectomy in carriers of BRCA1 and BRCA2 mutations reduces the risk of epithelial ovarian cancer by at least 90%. It is the only proven method of reducing the risk of ovarian cancer and cancer of the fallopian tube. It may also halve the risk of breast cancer in mutation carriers. Ideally, risk reducing surgery should always be discussed with women at potentially high risk of ovarian cancer.	III-2	26,27,28

These findings support the practice of offering bilateral risk reducing salpingo-oophorectomy to carriers of a mutation in BRCA1 or BRCA2 after their childbearing is completed. The current practice, based on risk figures derived from mutation-carrying families, is to offer such surgery from about the age of 35–40 years in BRCA1 carriers and 40–45 years in BRCA2 mutation carriers. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member.

Women with germline HNPCC or women from HNPCC families (where definitive predictive testing is not possible) may also consider prophylactic (risk reducing) total hysterectomy once their child-bearing has been completed, from the age of 30–35 years. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member.

There are no data about the safety of combined short term hormone replacement therapy (HRT) or tibolone use for women at increase genetic risk. When making a decision about risk reducing salpingo-oophorectomy, either with or without hysterectomy, issues related to other health sequale need to be taken into account. For example, hormone replacement (HRT) issues such as the possible need for relief of symptoms such as hot flushes, as well as the prevention of osteoporosis, may be considered for pre-menopausal women.¹⁶ If the uterus remains intact, therapies other than HRT should be tried in the first instance, but if unsuccessful in controlling symptoms, combined (oestrogen/progesterone) HRT or tibolone might be offered in the short term for relief. The type of therapy recommended will depend on each woman's situation and the effect on her quality of life of menopausal symptoms, so it is appropriate that this is discussed on a case-by-case basis. Longer term use of combined hormone replacement therapy is associated with an increased risk of breast cancer in the general population,²⁹ although no specific data are available for women at high genetic risk. Recently, the use of tibolone has also been associated with an increased risk of breast cancer in women in the general population in a single large observational study that had several important methodological limitations.³⁰

Monitoring of bone density may also be appropriate, with treatment for reduced bone density, if required. If a total hysterectomy is performed (which removes also the small intramural uterine portion of the fallopian tube), then unopposed oestrogen might be considered for relief of menopausal symptoms, if required. Several studies have suggested that, in women in the general population, unopposed oestrogen results in a smaller risk for breast cancer compared to combined oestrogen and progesterone HRT. Thus the consequences of hysterectomy need to be weighed against the advantages of removal of the entire fallopian tube and the ability to use short-term unopposed oestrogen as HRT, if required.

In deciding whether women who have already had breast cancer should use post-operative HRT, the details of the breast cancer history and treatment should be considered. For those women who do not have a past history of breast cancer, details of any prophylactic breast surgery may also be relevant if considering HRT use.

The complexities associated with the decision to have bilateral risk reducing salpingo-oophorectomy (with or without hysterectomy) and the post-operative care decisions mean that this is best done in a multi-disciplinary environment.

Key points:

- Decisions about timing of risk reducing surgery also need to take into account the family history of ovarian cancer, particularly the earliest age at diagnosis in an affected family member, and other possible health sequelae of this surgery.
- The decision to have risk-reducing gynaecological surgery is complex and best made in a multi-disciplinary environment.

MANAGEMENT OF WOMEN AT POTENTIALLY HIGH RISK WHOSE OVARIAN CANCER-ASSOCIATED GENE STATUS IS UNKNOWN

The first step for women at potentially high risk, but whose ovarian cancer-associated gene status is not known, must be to exclude cancer. Thereafter early detection should be emphasised. While surveillance of women at increased risk may be appropriate, women should be made aware of the current limitations of such surveillance. It should be emphasised that there are no data which conclusively demonstrate that surveillance has a favourable impact on either the stage at diagnosis or the mortality from ovarian cancer in women at risk.³¹ Furthermore, women should be informed that unnecessary intervention can sometimes result after a false positive test, and that interval cancers can develop between tests.

Women in this group should be advised:

- that an appropriate surveillance program may include transvaginal ultrasonography, preferably with colour flow Doppler, although the age at which this could commence may depend on details of the family history and CA125 measurement
- bilateral salpingo-oophorectomy has been proven to reduce the risk of ovarian and breast cancers in women who carry a BRCA1 or BRCA2 mutation.^{32,33}

(See chapter 3 on Screening for ovarian cancer)

MANAGEMENT IN WOMEN WHO HAVE BEEN SHOWN BY GENETIC TESTING TO CARRY A HIGH RISK MUTATION IN A GENE WHICH PREDISPOSES TO OVARIAN CANCER

The first step for women in this group must be to exclude cancer. Following that, consideration should be given to advising women:

- that an appropriate surveillance program may include transvaginal ultrasonography, preferably with colour flow Doppler, although the age at which this could commence may depend on details of the family history and CA125 measurement.
- that because early detection may be important and risk reducing surgery (bilateral salpingo-oophorectomy) has been proven to reduce the risk of ovarian and breast cancer in women with a mutation in BRCA1 or BRCA2,^{32,33} she should see a gynaecological oncologist. The age at which risk reducing surgery may be considered depends on the details of her family history, but would generally be from about age 35-40 years and when her child-bearing has been completed in BRCA1 carriers. In BRCA2 carriers, whose risk of ovarian cancer rises later in life, this decision might be deferred until age 40-45 years, and when child-bearing has been completed. Decisions about timing of such surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member. Primary peritoneal carcinoma may occur despite prophylactic oophorectomy.³⁴
- that women in HNPCC families may also consider prophylactic total hysterectomy when their child-bearing has been completed, from the age of 30-35 years. Decisions about the timing of such surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member.
- to consider participation in a relevant approved clinical trial.

(See chapter 3 on Screening for ovarian cancer)

Key points:

- Decisions about timing of risk reducing surgery also need to take into account the family history of ovarian cancer, including the earliest age at diagnosis in an affected family member.
- Primary peritoneal carcinoma may occur despite risk reducing oophorectomy³⁴ but is uncommon.

CONCLUSION

The state of knowledge and technology as it applies to genetic and familial aspects of ovarian cancer are changing rapidly. The need for updating information, collection of relevant Australian data and links to new research are as important to this field as they are to breast cancer.

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5. THE BIOLOGY AND PATHOLOGY OF OVARIAN TUMOURS

INTRODUCTION TO OVARIAN CARCINOMA TYPES

These guidelines address the common types of ovarian malignancies, which fall into the category known as surface epithelial/stromal tumours. Collectively, they comprise almost 60% of all ovarian tumours and up to 90% of primary ovarian cancers in Australia. They are a heterogeneous group, many with homologues within the Müllerian duct derivatives and related structures. The terms commonly given to these tumours in the ovaries (eg serous, mucinous, endometrioid, clear cell and transitional cell) reflect this homology. This is a more important reason for grouping them together than their supposed common histogenesis and is the rationale for establishing common principles of tumour grading, staging and treatment for malignancies of the female genital tract. Such homologous tumours have been reported elsewhere in the female pelvis, quite commonly in the broad ligaments and widespread throughout the peritoneal cavity, and even in testicular and para-testicular tissues in men. Considering them as a single neoplastic spectrum, and as intrinsically ‘ovarian’, has led to blurring of well-defined patterns of genesis, metastasis, pathological correlates, therapeutic responses and clinical outcomes.

PRECURSOR LESIONS AND PATTERNS OF CARCINOGENESIS

There is good circumstantial evidence that ovarian epithelial/stromal malignancies arise, by progressive transformation, from the glandular cells of benign epithelial precursors (inclusion cysts or benign tumours). Serosal inclusions, surface proliferations, metaplasias or endometriosis in the ovary (and elsewhere) represent possible precursor lesions for surface epithelial/stromal tumours. The nature and distribution of these lesions are central to understanding such tumours, for they demonstrate the Müllerian potential of the surface ‘epithelium’ of the ovary that, in turn, may dictate the relative frequency and histological range of the neoplasms that develop. In this regard, very considerable research effort has been directed to the specific properties and dynamics of the surface epithelium of the ovaries, on the unproven assumption that such efforts will reveal the pathogenetic pathways of ovarian carcinoma – the characteristics of the ‘cancer prone ovary’.¹

BORDERLINE TUMOURS

There is uncertainty about the role of benign and so-called borderline or proliferating epithelial tumours (these latter two epithets are used interchangeably and also equate to the widely used term, ‘of low malignant potential or LMP’) as precursor lesions for epithelial malignancies. It seems that non-serous carcinomas regularly arise from

pre-existing benign neoplastic lesions (i.e. from 'benign' through 'proliferating' to 'malignant'), with an extended transit time, via a multi-step adenoma-carcinoma sequence, which usually preserves evidence of the pre-existing lower grade neoplasms. There is equally good circumstantial evidence that many high-grade (poorly differentiated) serous carcinomas arise de novo from non-neoplastic epithelial precursor lesions while most low grade (well differentiated) serous carcinomas arise from pre-existing proliferating neoplasms, but with a foreshortened transit time. Indeed evidence seems to indicate entirely different genetic mutational pathways for the development of proliferating (borderline) serous tumours and high-grade invasive serous carcinomas.²⁻⁴ It is speculated that the series of molecular genetic events necessary for this transformation may occur rapidly or more slowly.⁵ In the former event the transition from non-neoplastic inclusion cyst to carcinoma might occur in the absence of a benign tumour phase or, alternatively, it might not be appreciated pathologically. In the latter event, a benign or proliferating tumour might result, followed by a carcinoma only after further steps and only in some patients.

These concepts, if proven, have important consequences for the screening strategies for ovarian carcinoma in women, particularly in those at increased genetic risk of ovarian cancer, as the majority of women with germline mutations in BRCA1 /BRCA2 have high grade serous cancers that arise de novo, are often multifocal and appear to have a short sojourn time with rapid progression (*see chapter 2 on Risk factors for ovarian cancer, chapter 3 – Screening for ovarian cancer, chapter 4 – Familial aspects of ovarian cancer, and chapter 9 – The management of borderline ovarian tumours*).

Metastatic tumours from other sites are not addressed specifically in these guidelines, the exception being pseudomyxoma peritonei. This is an uncommon condition associated with both intra-abdominal and ovarian mucinous tumours, and is now thought to be almost always metastatic from the appendix. Correct assignment of this condition to the category of metastatic low-grade mucinous carcinoma (as it must be), has important implications for the remaining proliferating mucinous tumour group, relegating such tumours from being 'of low malignant potential' to benign/atypical and, at worst, premalignant (see below).

INTRAOPERATIVE CONSULTATION AND MANAGEMENT (INCLUDING FROZEN SECTION REPORTING)

Intraoperative pathological consultation is of value in cases where clinical management decisions may be altered depending on the histological type and grade of tumour, e.g. young women for whom continuing fertility is crucial. An experienced gynaecological pathologist should be able to assist with gross examination alone of the fresh specimen, while in other circumstances or with doubtful cases, a 'working' diagnosis can be made by either frozen section (FS), or cytological 'scrape' preparation.⁶ The latter technique, when the pathologist is familiar with the expected cytological appearances, has the advantage of not requiring a cryostat (i.e. can be offered to those patients who are HIV or HCV positive). Both techniques are prone to sampling and diagnostic error.

Specific intraoperative recommendations from the pathologist may include the following:

- removal of the appendix in all cases of pseudomyxoma peritonei, even if clinically normal
- endometrial curettage if conservative therapy is planned for an endometrioid ovarian tumour of any degree of proliferation
- careful examination of the large bowel if a mucinous ovarian carcinoma is diagnosed (most are metastatic rather than primary)

Frozen section (FS) is more reliable in separating benign from borderline tumours than borderline tumours from carcinomas. The former, however, is not a distinction that impacts on patient management. Sampling error is a significant problem in the latter differentiation, particularly in non-serous neoplasms, which are more heterogeneous, with benign, borderline and carcinomatous components often coexisting in the same lesion.⁷

Clinicians should be aware that a single sample may not provide adequate material for the histopathologist whereas, further sampling for paraffin sections may result in upgrading of a FS diagnosis of benign to borderline tumour (not significant) or of a high-grade borderline tumour to invasive carcinoma (significant). If any doubt is expressed by the pathologist on FS, the more conservative diagnosis must be the ‘working’ diagnosis for immediate patient management.

Guideline - Sampling of suspected borderline tumours	Level of Evidence	Refs
It is recommended to sample several areas from any suspected borderline ovarian tumour (eg highly complex cystic tumours) to reduce sampling error, especially for tumours that are, or appear to be, mucinous or which are over 1kg.	III-3	7

Fresh material can be taken for molecular and ploidy studies and for research (with patient consent), if appropriate. Consent is best obtained before rather than after surgery. Tumour impression smears or ‘scrape’ preparations may be made for subsequent comparison with peritoneal washing cytology.

SURGICAL CUT UP

It is desirable, in early FIGO stage cases, to mark the surface of the ovary/mass (eg with Alcian Blue) so that this can later be identified histologically as distinct from cyst lining epithelium. In cases of prophylactic oophorectomy in ‘high-risk’ patients, great care must be taken in the handling of the ovaries. The serosal surface layer is very fragile and may be the site of macroscopically invisible carcinoma-in-situ or lesser ‘dysplastic’ changes that should be documented.^{1,8} **In these cases, the entire ovary (and associated tube, if also removed) should be blocked for examination.**

PATHOLOGY BLOCK SELECTION

For suspected borderline tumours the accepted standard is one block of tumour per centimetre of maximum diameter of the 'solid' ovarian mass (i.e. exclude 'cysts' in measurement). This is to detect small areas of high-grade invasive carcinoma, which might otherwise be missed, and is particularly important in mucinous tumours.

In cases of pseudomyxoma peritonei the **entire appendix should be submitted**.

Transverse sections are best (apart from the actual tip), to allow assessment of degree of penetration through the wall of any tumour. Free mucin from the abdomen should be sampled in several blocks. A similar approach is merited in malignant mucinous tumours as signs of intra-abdominal dissemination and of appendiceal primaries may be very subtle macroscopically.

When the specimen includes a macroscopically normal contralateral ovary, this should be blocked in its entirety, as microscopic tumour is often found and affects both staging and assessment of likely primary site, where this is in doubt.

Macroscopically negative omentum often has microscopic deposits (22%) and these are commonly the only evidence for upstaging the patient and mandating adjuvant therapy. It is therefore recommended that a minimum of 4 blocks be submitted from macroscopically normal omenta in patients with no other macroscopic evidence of high stage disease.⁹

HISTOPATHOLOGY REPORTING

There is little scientific analysis of methods of histological typing of ovarian carcinomas, this still being based essentially on pattern recognition. Where there are mixed epithelial types identified, the percentages should be estimated, but no evidence exists on the best method of achieving this or on the clinical significance of mixed versus 'pure' types. Epithelial tumour type is a recognised prognostic variable for carcinomas, but it is unclear if this is independent of grade or stage. There is early evidence of some variation in chemo-responsiveness by histological type. A small percentage of tumours, despite expert assessment, will remain unclassifiable, although clearly 'Müllerian.'

NOTES ON HISTOLOGICAL TYPE OF THE PERITONEAL METASTASES

It should be noted if a significant component of the metastatic tumour is of a different histological type from the primary, especially one that is thought to have a worse prognosis or response to chemotherapy.¹⁰

RECOMMENDED GRADING SYSTEM FOR INVASIVE CARCINOMAS

There have been various methods for the histological grading of invasive carcinomas, many have been vague and showed poor reproducibility or were only limited to one carcinoma sub-type. The recently developed Universal Grading System addresses some of these limitations.¹¹ Although still cumbersome, it is said to be reproducible by the authors, and may be modified to compensate for variation from microscope to microscope (see below).

Guideline - Grading system for invasive carcinomas	Level of Evidence	Refs
The use of the Universal Grading System is recommended and addresses some of the limitations of other methods for histological grading. There is good predictive power across most stages and types.	III-3	11,12

The specific components of the Score must be recorded as well as the final grade, as different components have different prognostic value depending on stage.¹² The scoring system is summarised below:

Architectural pattern	Score
Predominantly glandular	1
Predominantly papillary	2
Predominantly solid	3
Nuclear pleomorphism	
Slight	1
Moderate	2
Marked	3
Mitotic activity in most active region (originally expressed as mitotic figures per 10 high-power fields where 1 HPF = 0.345 mm²):	
0-3/mm ²	1
4-8/mm ²	2
>8/mm ²	3
Add these three scores together for an individual tumour to give final grade.	
3-5	Grade 1
6-7	Grade 2
8-9	Grade 3

NB. Clear cell carcinomas and transitional cell carcinomas are not graded.

Key point:

- Good reproducibility in assessing mitotic activity requires careful attendance to a strict protocol, good quality sections and ongoing quality assurance feedback.¹³

GRADING OF PSEUDOMYXOMA PERITONEI

The cytological atypia and architectural features of the mucin-secreting cells in the peritoneal deposits and/or in the free floating mucinous ascites (histological or cytological assessment) have been found to correlate strongly with prognosis and a categorisation on this basis is recommended.^{14,15}

The peritoneal mucin may vary in features, which can have prognostic significance.¹⁶ It is not yet clear if this is independent of the cellular features as above. In pseudomyxoma peritonei, the tumours should be classified based on the resemblance of the peritoneal deposits to benign or borderline ovarian cystadenomas (peritoneal adenomucinosis) or to carcinoma (peritoneal mucinous carcinomatosis) as the prognosis has been found to differ accordingly.^{14,15}

CATEGORISATION OF BORDERLINE (PROLIFERATING) TUMOURS

Borderline tumours are distinguished from benign by the presence of at least two of the following four features in any one area of a tumour: 'budding' architectural pattern, multi-layering, at least mild nuclear atypia and increased mitoses. A small area of atypia (<10% of available material is a useful watershed) should not be sufficient to put the tumour into the borderline category¹⁷ remembering that the distinction between benign and proliferating has no bearing on clinical outcome.

Borderline (proliferating) tumours are not traditionally graded, although a simple grading of the architectural and cellular changes into low-grade and high-grade has considerable merit and may substitute for the plethora of confusing terms surrounding these neoplasms. The latter (high-grade) subgroup would include lesions up to 'carcinoma-in-situ' (so-called micropapillary serous carcinomas and 'intraepithelial carcinomas' of mucinous type), as discussed below.

SEROUS

An appreciation of serous borderline tumours is the key to understanding of where, in the scheme of ovarian neoplasms, this controversial group stands. Their historical importance¹⁷ is based on a long-term clinical outcome intermediate between benign and frankly malignant tumours, yet good evidence exists that, when confined to the ovaries, patient outcome is no different from that of benign neoplasms.¹⁸ Surgical pathological stage and sub-classification of extraovarian disease into invasive and non-invasive implants are the most important prognostic indicators for serous borderline tumours.

Survival for stage I tumours is 99.5%; survival for advanced stage tumours with non-invasive implants is 95.3%.

Guideline - Prognostic indicators for serous borderline tumours	Level of Evidence	Refs
When considering the prognostic indicators for serous borderline tumours, surgical pathological stage and sub-classification of extra-ovarian disease into invasive and non-invasive implants are the most important indicators.	IV	18

It is irrefutable that the clinical outcome for the patient depends on the presence and nature of the extra-ovarian lesions rather than the biological potential of the ‘ovarian’ mass per se. The controversy, which surrounds these tumours some three-quarters of a century after their original description, and remains unresolved, is the nature of the relationship between the ovarian and the extra-ovarian lesions. Some authorities argue fervently for ‘implantation’ as the sole or dominant process by which the peritoneal lesions arise from the ovarian masses, thus giving credence to the low malignant potential of the neoplastic process as a whole. Others propose equally vehemently for a ‘multifocal’ neoplastic process by which the peritoneal lesions arise independently, thus relegating the proliferating ovarian lesions to a subcategory of benign (i.e. ‘non-malignant’), and assessing the peritoneal lesions on their merits as benign, borderline or frankly malignant. It is inappropriate, here, to attempt to resolve this dilemma.

An observable architectural spectrum of proliferation and cellular changes is present within the category of proliferating serous tumours. No generally accepted guidelines for defining this spectrum exist. At the ‘high-grade’ end of the spectrum, however, an attempt to define a specific subcategory of ‘micropapillary serous carcinoma’ (despite the absence of invasive cancer) has been promoted.¹⁹ It is defensible to regard this end of the spectrum as representing serous papillary carcinoma in situ. An important observation is that small areas of invasive carcinoma (microinvasive carcinoma) do not adversely affect outcome in these or other borderline serous tumours. Microinvasion is defined as one or more foci, each no more than 10mm². Other authors have used the similar cut-off of 3mm greatest diameter, which is recommended as it is simpler to apply.^{20,21} These foci must show either single cells or small irregular solid islands of cells. They are usually multiple.

PERITONEAL IMPLANTS OF BORDERLINE SEROUS TUMOURS: NON-INVASIVE VERSUS INVASIVE

The careful histological assessment of extraovarian lesions (peritoneal ‘implants’) with the specific aim of separating out those showing locally invasive malignancy is crucially important as this feature is the predominant determinant of patient outcome. A recent study found that, even in the absence of destructive invasion of normal tissues, where the implants show both a micropapillary pattern and solid tumour islands surrounded by

clefts, the prognosis for the patient is worsened. In their group of 31 such patients, with a mean 5 year follow-up, 6 were dead of disease and 13 were alive with progressive disease.²²

Involved retroperitoneal lymph nodes (20% of such patients) are no less perplexing. Nodal involvement appears to affect intra-abdominal recurrence rates (presumably due to incomplete surgical resection) but not long-term clinical outcome,²³ and is usually a further manifestation of multifocal tumorigenesis, although true metastases from 'invasive peritoneal implants' may account for some cases. While they may be regarded as metastatic, they should not be interpreted as carcinoma and they do not mandate aggressive therapy.

The commonly encountered presence of a surface papillary component to the ovarian neoplasm correlates with an increased likelihood of extraovarian lesions being present in the peritoneal cavity, but does not, of itself, adversely affect patient outcome. It is likely that the so-called desmoplastic non-invasive subset of peritoneal lesions is specifically associated with proliferating serous tumours with a surface papillary component.

MUCINOUS

Extending the proliferating or borderline category to ovarian mucinous tumours was based on the assumption that certain non-invasive mucinous neoplasms could be accompanied by extraovarian manifestations, in this case pseudomyxoma peritonei, with adverse consequences for the patient. That is to say, pseudomyxoma peritonei was considered analogous to peritoneal implants of serous borderline tumours. As noted earlier, the majority of researchers in the field currently hold to the view that pseudomyxoma peritonei represents metastatic low grade mucinous carcinoma, most often arising in the appendix, and that concurrent ovarian involvement is also in the nature of metastatic epithelial neoplasia. Proliferating mucinous tumours, unassociated with pseudomyxoma peritonei at presentation, do NOT progress to later produce this condition. The very low risk of progression in these tumours (in the vicinity of 2-5%) is most probably due to tissue sampling which was insufficient to identify areas of invasive carcinoma. As with serous proliferating tumours, there is an observable spectrum of proliferative activity. This statistical risk is clearly greater in those proliferating mucinous tumours with high grade epithelial changes,²⁴ defined as showing more than four layers of nuclei and marked nuclear atypia, but still with no evidence of stromal invasion.

Guideline - Terminology in borderline neoplasm	Level of Evidence	Refs
Use of the term 'high grade proliferating' as an alternative to 'carcinoma in situ' or 'intraepithelial carcinoma' within a borderline neoplasm is recommended for mucinous tumours with no evidence of stromal invasion, if they show more than four layers of nuclei and marked nuclear atypia.	IV	24

Approximately 15% of proliferating mucinous tumours show features more closely resembling endocervical than intestinal epithelial differentiation. Of these, 10-15% are associated with small focal extraovarian lesions, akin to the peritoneal implants of serous borderline tumours. The presence of such lesions does not adversely affect patient outcome.

MICROINVASION ARISING IN BORDERLINE TUMOURS

This must not be confused either with frank carcinoma or with carcinoma in situ (see above) although it may overlap with the latter in some cases.

Similar criteria have been applied to both serous and mucinous types. The serous type is easier to identify as single cells, or small invasive papillae with their 'luminal' surface apposed to the stroma, and often apparently within tissue spaces. An inflammatory tissue response is characteristically, but not always, generated. Both serous and mucinous proliferating tumours displaying microinvasion have been found to have a clinical outcome not materially different from those which do not display this feature.²⁵ Thus, while immunostaining (cytokeratins) may assist in identifying such microfoci, their pursuit should be regarded as of academic rather than practical interest.

Note that a desmoplastic or inflammatory response to free mucin may occur and this should not be regarded as evidence of stromal invasion in mucinous proliferating tumours. Similarly, serous tumours may have plaques of desmoplastic fibrosis in the wall, with psammoma bodies. This also does not imply microinvasion.

SIMULTANEOUS ENDOMETRIAL AND OVARIAN CARCINOMAS

In this relatively common situation, the problem is to decide if one or the other or both are primaries, as this affects staging and may affect prognosis. A recent study of endometrioid carcinomas has shown that bilateral ovarian involvement does not necessarily indicate metastatic disease, two of three such cases were primary to the ovary by molecular analysis.²⁶ Furthermore, cases in which the ovary was monoclonal with an endometrial carcinoma, included examples with deep myometrial invasion as well as minimal invasion. Thus, this is also not a useful feature. The study confirmed that the presence of ovarian endometriosis supports the probability that the ovarian tumour is primary. The belief that the overall good prognosis of such tumours implied that most were double primaries received limited support. Approximately 60% of the informative cases were double primaries in a study where both were of the same endometrioid type - a higher percentage would be likely to be double primaries if cases with more disparate histological patterns of differentiation were included. Why independent tumours should so often arise in these two sites is an unanswered question, although a similar phenomenon is observed with independent primary carcinomas in cervix and ovaries.

THE ANATOMICAL PATHOLOGY REPORT

Synoptic reports have been advocated by many authorities,²⁷ as they promote a uniform and complete record of the surgical specimen and highlight prognostic parameters. The report should include:

- the histological type(s) of tumour;
- its grade, including the components of the score;
- the presence of any microinvasion, capsular/surface involvement;
- the presence and types of peritoneal implants; and
- involvement of other structures (fallopian tube, uterine serosa, lymph nodes etc).

Key points:

- It is strongly recommended that a synoptic proforma system be used for epithelial ovarian tumour reports to allow ease of finding and interpreting data consistently on ovarian cancer patients regardless of the laboratory or reporting pathologist.

HISTOPATHOLOGY CHALLENGES AND A CENTRAL REVIEW CENTRE

Studies of gynaecological cancer cases sent for ‘central review’, indicate that the diagnosis is changed in up to 33% of cases, with 12% of patients being given an altered management plan.²⁸ This is a reflection of the diagnostic difficulties in such cases and reinforces the principal of central review by a specialist gynaecological pathologist prior to management planning. The many variations in ovarian cancer types, and in related ovarian conditions, means that few pathologists can have extensive personal experience of all, or can conduct research on rare types, if limited to cases personally diagnosed (*see Foreword, pvii*).

Hence, best practice would suggest the desirability of a mechanism for central pathology review to which unusual, difficult or interesting cases can be referred for further assessment and categorisation. With current rapid improvements in digital technology, it may not be necessary for all, or even most cases, to be sent physically to a central laboratory (*see Appendix 6, p182- Future research needs*).

MOLECULAR BIOLOGY

Many advances in our understanding of molecular genetics of ovarian cancer have been made, but these are not yet affecting clinical practice. The interested reader is referred to the excellent reviews by Russell²⁹ and by Leary and Friedlander.³⁰

The oncogene with most promise of clinical relevance is p53. The p53 gene on chromosome 17p 13.1 is central to the control and regulation of DNA repair in cells.

Deletions and mutations of this gene are common in all human tumours. The protein causes arrest of cell cycle after DNA damage and triggers apoptosis if the damage is too great for repair. There have been many studies to determine the incidence and role of p53 in ovarian tumours. In a number of these studies p53 protein over expression alone was used as an indirect indicator of mutation and caution is needed in interpreting these results as there is not always a good correlation between immunohistochemical assessment of protein levels and mutation analysis to detect changes in the controlling gene segment.^{31,32,33,34,35}

p53 mutation and over expression is commonly observed in invasive serous ovarian tumours with an incidence ranging from 23 – 72%.^{36,37} Mutations are rarely observed in borderline serous ovarian tumours. Most studies suggest that p53 alterations are a late event in the development of ovarian tumours with evidence of loss of p53 function in about 15% of early stage tumours^{38,39} and over 50% of late stage disease.^{40,41} A number of studies have looked at the prognostic significance of p53 status in ovarian tumours but the findings are inconclusive.^{42,43} More recently there have been studies to suggest that p53 mutations are associated with platinum resistance, an area of current interest.⁴⁴

Other genetic mutations seem to operate in histological tumour types other than serous carcinomas. For example PTEN (Phosphatase and tensin homologue deleted on chromosome 10) is frequently altered in endometrioid neoplasms,^{45,46} and K-ras mutations have been identified with progressive frequency in mucinous ovarian tumours of increasing levels of proliferative activity.⁴⁷

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6. MULTIDISCIPLINARY MANAGEMENT OF WOMEN WITH OVARIAN CANCER

The goal of management in women who have epithelial ovarian cancer is to provide the best possible outcome. The major factors that determine outcome are:

- early and accurate diagnosis; and
- surgical care appropriate to the presenting disease

Both elements require to be addressed in a positive manner.

- Early and accurate diagnosis needs to be fostered through educating primary health carers to be aware of the nuances of clinical presentation of ovarian cancer to optimise their interpretation of these and to follow sound referral pathways
- There is evidence that outcomes are directly related to the training of the surgeon, who understands the natural history of the disease and who is also trained to deal with any clinico-pathological situation which might arise at the time of the laparotomy.¹⁻⁵ Improvements in survival have been found both in women with early stage and advanced disease

MULTIDISCIPLINARY CARE FOR OVARIAN CANCER

Many diseases, including ovarian cancer, require a range of treatment modalities for optimal outcomes. The concept of multidisciplinary care, as a co-ordinated approach using a collaborative group of health professionals for the diagnosis, continuing management and palliative care has been evolving for ovarian cancer over the last decade or more. The team as a whole is responsible for the diagnosis, continuing management and palliative care of the woman with ovarian cancer.

No randomised clinical trial has been undertaken to compare outcomes for women managed by multidisciplinary teams versus individual clinicians. Audits show shortcomings in clinical practice despite published guidelines.⁶ The best evidence is from a comparison of patient outcomes from teaching hospitals versus non-teaching centres. Junor's paper reports that the decrease in risk of death at five years is 40% for women treated in teaching hospitals. This is independent of optimal surgery and reflects presumed benefit of multi-disciplinary management.¹

There is, however, a growing body of evidence^{1,7} to suggest that outcomes for a woman with ovarian cancer are improved if she is referred to be managed under the care of a Multidisciplinary Care team including:

- pathologists and nursing staff specially trained in the management of ovarian cancer;
- subspecialty-trained gynaecological oncologists; and
- medical and radiation oncologists with expertise in the management of ovarian cancer.

In the UK, the *National Health Service Executive Report on The Management of Women with Gynaecological Cancer July 1999*,⁸ responsible for all commissioning of cancer services in the UK, announced:

“Dedicated diagnostic and assessment services should be established in cancer units to which all women with suspected gynaecological cancer should be referred. There should be specialist gynaecological oncology teams based at the referral centres ...who are responsible for the management of all women with gynaecological malignancy”

While the ideal situation is for referral of the woman to a centre where all aspects of management, including surgery, pathology review, chemotherapy and on-going psychosocial support are available, there are several reasons why women are not referred to a multidisciplinary team for primary management of ovarian cancer. These may include that the diagnosis is not anticipated by the surgeon, who is not well trained to deal with the situation. Some surgeons may feel that comprehensive surgery is excessive and not warranted, especially in early stage disease.⁹ A comprehensive understanding of the disease is important, together with the mindset to perform as complete surgery as is possible.

Guideline - Multidisciplinary care for women with ovarian cancer	Level of Evidence	Refs
There is a growing body of evidence to suggest that outcomes for a woman with ovarian cancer are improved if she is referred to be managed under the care of a Multidisciplinary Care team. The ideal situation is for referral of the woman to a centre where all aspects of management, including surgery, pathology review, chemotherapy and on-going psychosocial support are available.	IV	1,7

THE AUSTRALIAN CONTEXT

Multidisciplinary care is not uniform across Australia. There may be multiple models which are still acceptable for good practice, depending on the local availability of resources, and external arrangements with larger multidisciplinary care units in the capital cities but the principles of multidisciplinary care should be promoted. The minimum standard, regardless of location, includes the presentation and discussion of individual women’s cases at a Multidisciplinary Care meeting, with expert pathology review and input from a gynaecological oncologist. This may take the form of a letter or telemedicine conference and in all cases the outcome of the discussion should be relayed directly to the woman and her referring doctor.

WHAT GROUPS SHOULD BE INVOLVED IN THE MULTIDISCIPLINARY TEAM FOR THE MANAGEMENT OF OVARIAN CANCER?

The input of specialists from several disciplines offers a broader perspective for the derivation of a care plan for a given woman’s disease. Protocols are established by

consensus and in the setting of a formalised training program; the discipline of adhering to the plan is much stronger in these circumstances.¹⁰

Care of the gynaecological oncology patient relies on all partners in the team – no one team member being less important than the other. Each has a role to play in the management and support of the woman, from those who deliver the primary care, to the staff, both medical and paramedical, to the support team in the community. All are important and should not lose sight of either their own role or the importance of others around them. Any specialist is welcome to be part of the discussion about any given woman with ovarian cancer, as is the initial referring doctor. The team may offer advice and help, but is always willing and motivated to work as a teaching resource and for tertiary referrals.

In general, consumers are in favour of ‘multidisciplinary teams, good teamwork and communication between professionals’.¹¹ It is worthwhile taking time to discuss the role of the team and each of its members with the woman. She may feel more comfortable discussing the management of her care with one particular member of the team and needs to know that each member of the team is equally valued, that the team members communicate and discuss the options for her care, and that any one of them can provide her with the best available advice and opinion.

Key point:

- Any member of the multidisciplinary team may, with the woman’s approval, become the lead person for on-going communication about her care.

THE MULTIDISCIPLINARY CARE TEAM FOR WOMEN WITH OVARIAN CANCER

- Gynaecological oncologist
- Gynaecological pathologist
- Medical oncologist with special experience in ovarian cancer
- Radiation oncologist with special experience in ovarian cancer
- Radiologist with a special interest in ovarian cancer
- General practitioners
- Specialist nurses
- Physiotherapists
- Pharmacists
- Psychologists, social workers
- Palliative Care specialists
- Geneticist
- Genetic counsellors

Key point:

- The involvement of a broad range of staff considering the care plan requirements for each patient will result in a planned approach that takes into consideration all the nuances of the woman, her disease and psychosocial situation.

ROLE OF THE GYNAECOLOGICAL ONCOLOGIST

Gynaecological Oncology is a sub-specialty of obstetrics and gynaecology. It was recognised as a sub-speciality by the National Academic Specialist Qualifications Advisory Committee (NASQAC) in 1988, as an advanced speciality credentialing process.

Gynaecological Oncologists are specialists in Obstetrics and Gynaecology who:

- hold a Fellowship with the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (FRANZCOG);
- have completed a formal three year training program in gynaecological cancer care;
- have passed the examination for the Certificate of Gynaecological Oncology (CGO);
- are actively practising in the field of gynaecology, with at least 66% of time spent in gynaecological oncology;
- are competent in the comprehensive management of women with a genital malignancy; and
- must submit for re-certification every three years.

(See Appendix 4 - Gynaecological oncology training requirements.)

The role of the certified gynaecological oncologist is clearly significant in the management of epithelial ovarian cancer (*see chapter 7 – Assessment of initial symptoms, chapter 8 – Management of a pelvic mass and Chapter 10 – Surgery for invasive ovarian cancer*).

In the National Institutes of Health Consensus Statement on Ovarian Cancer, it was noted that for surgery for ovarian cancer ‘...the procedure is best conducted by a qualified gynaecologic oncologist’.¹²

There is Level IV evidence for the influence of training of the surgeon on outcomes of treatment, especially surgery. A study from Scotland found an improved patient survival independent of other prognostic factors if operated on by specialist gynaecologist or by a gynaecological oncologist.¹³

An Australian report² follows this same trend, whilst an American study suggests that adequate staging only occurs when patients are operated on by specialists.³

Mayer⁴ *et al.* found a significantly better survival for women with stage I and II disease when they were staged by a gynaecological oncologist compared with those women who were operated on by a non-oncologist. Five-year actuarial survival was 83 ± 7% for the gynaecological oncologist group and 59 ± 11% for the non-oncologist group (p<0.05) and disease-free survival was 76 ± 8% and 39 ± 11% respectively (p<0.03).

Key point:

- The training of the surgeon has an effect on prognosis, especially in early stage disease, where careful staging can determine whether a woman needs additional therapy or not.

In a recent review of patients in Utah with epithelial ovarian cancer from 1992-1998, it was shown that overall, a gynaecological oncologist saw only 39.3% of patients at some time during their diagnosis and/or treatment. Among cases diagnosed with advanced stage disease, those cases seen by gynaecologic oncologists had a significant survival advantage when compared to those who were not (median survival 26 and 15 months respectively, $p < 0.01$).⁵

A study of patterns of care in Victoria during 1993-1995,¹⁴ showed that primary surgery was performed by gynaecological oncologists in 47.2% of cases (205 women). Gynaecological oncologists were more likely to perform complete and adequate surgery; however the proportion of tumours optimally resected was relatively low, even when surgery was performed by gynaecological oncologists. The study did show, 'staging to be associated with improved survival when tumours were adequately staged'.

A population-based cohort study of all women undergoing surgery for ovarian cancer in Ontario, Canada between 1992 and 1998 showed there was a statistically significant association between 30-day postoperative survival, reoperation rate and overall survival and surgical specialty. The adjusted survival was improved if the initial surgery was done by a gynaecological oncologist (Hazard Reduction 0.70, CI 0.57 to 0.85) or by a gynaecologist (Hazard Reduction 0.65, CI 0.53 to 0.79).¹⁵

Guideline - Surgical care of women with ovarian cancer	Level of Evidence	Refs
Survival for women with ovarian cancer has been shown to be improved when the initial surgery has been done by a gynaecological oncologist. The surgical care of women with ovarian cancer is best directed, whenever possible, by a gynaecological oncologist.	IV	2,4,5, 13,15

The surgical care of the woman should be directed by state-of-the-art surgical staging. This is best directed, whenever possible, by a fully trained gynaecological oncologist, who has a full knowledge of the natural history of the disease, which includes an awareness of the likely sites of spread and who is trained to manage, intra-operatively, the range of pathology that may be encountered.

THE ROLE OF THE GENERAL PRACTITIONER

The general practitioner (GP) may play a number of roles in the management of the woman with ovarian cancer including: diagnosis, referral, treatment, and co-ordination of care, through all stages of the disease. The GP is also ideally placed to provide ongoing information and support to the woman with ovarian cancer and her family.

As a key member of the multidisciplinary team, the GP should provide all necessary information to specialists and allied health professionals involved in the care of the woman with ovarian cancer. The GP's role will be greatly supported by the receipt of timely letters from specialists involved in the woman's care, with adequate information about the management plan, pathology reports, other investigations etc.

THE ROLE OF THE GENERAL SURGEON

The general surgeon may encounter ovarian cancer unexpectedly or inadvertently at the time of laparotomy for other purposes in a rural or acute setting. In this case the minimum necessary surgery (e.g. relief of bowel obstruction) should be carried out. A biopsy should be undertaken for histological diagnosis and the woman referred for further evaluation and treatment recommended as appropriate by the multidisciplinary team (*see chapter 8 – Management of a pelvic mass*).

THE ROLE OF THE NURSE SPECIALIST

Nurses are essential to the delivery of a comprehensive service to women affected by ovarian cancer and play a significant part in the woman's cancer journey. Relatively little is known about women's experiences of having ovarian cancer or the impact of recurrent disease, and this limits the development and implementation of appropriate nursing interventions.¹⁶ A number of studies focussing on the care of women with breast cancer have shown that women cared for by a specialist nurse have better outcomes in relation to co-ordination of care, earlier referral to specialist services and improved psychological outcomes.^{17,18} These studies suggest that a similar outcome could be achieved by specialist gynaecological nurses.

There is limited information available about benefit of specialist nursing for gynaecological oncology patients, although a recent randomised controlled trial identified that sexual functioning and quality of life were improved for women in a specialist gynaecological nurse intervention group.¹⁹

ROLE OF THE PATHOLOGIST

Expert pathological reviews of ovarian cancers have found that 10% had a change in diagnosis, as a result of review. There was especial difficulty with borderline lesions.^{20,21} Cronje *et al.*²² reviewed 1718 slides from 454 patients with a diagnosis of granulosa cell tumours, and 111 (24%) were reclassified, mostly to classifications with a less good prognosis. In all, 206 were initially reported as granulosa cell tumours, but after review only 97 remained.

Patients referred to Johns Hopkins Hospital for definitive therapy for cancer were studied.²³ In 6171 cases, the diagnosis was changed in 1.4%, but in gynaecological cases, 5.1% ($p < 0.0001$) were changed.

Where any doubt exists, the second opinion of a specialist pathologist should be

mandatory if patient safety and quality control is to be maintained.²³ This would expedite timely decision-making by the multidisciplinary team.

To ensure that the multidisciplinary team can fully discuss all aspects of a woman's case, it is helpful for the pathologist to ensure that the relevant slides are available for each multidisciplinary team meeting.

Key point:

- A pathologist with extra training in gynaecological malignancy pathology is an integral member of the multidisciplinary team.

CLINICAL TRIAL PARTICIPATION

Better outcomes have been reported for patients with other cancers taking part in clinical trials.^{24,25} Teams who take part in clinical trials are at the forefront of new knowledge and treatments and can offer these to their patients (*see chapter 17 – Clinical trials*).

Key point:

- Better outcomes have been reported for cancer patients who take part in clinical trials.

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7. ASSESSMENT OF INITIAL SYMPTOMS

While it is commonly reported that the presenting symptoms of ovarian cancer are frequently vague, and do not point to the ovary as the primary problem, some small retrospective studies, which relied on chart review, suggest that most women diagnosed with ovarian carcinoma do report symptoms, although they are not usually gynaecological in nature.^{1,2}

Data obtained from a survey of 1725 women showed that 95% of women reported symptoms prior to diagnosis. Only 11% of stage I and II and 3% of stage III and IV reported no symptoms prior to their diagnosis.³ Using a structured questionnaire to conduct interviews with over 750 women diagnosed with borderline or invasive epithelial ovarian cancer, Vine *et al.* reported that 92% of women with invasive ovarian tumours and 84% of borderline cases have symptoms, with a median duration of four months.⁴ In a group of 168 women who were interviewed shortly after diagnosis, nearly all the cases (93%) reported at least one symptom, compared with 42% of controls.⁵ In a study of Canadian women only 9% reported experiencing no symptoms whatsoever prior to diagnosis.⁶

OVARIAN CANCER SYMPTOMS

- Abdominal bloating
- Increased abdominal girth
- Indigestion, lack of appetite
- Change in bowel habits
- Constipation
- Urinary frequency or incontinence
- Fatigue
- Abdominal and/or pelvic pain

SYMPTOM CATEGORIES³

77%	Abdominal symptoms
70%	Gastro-intestinal
50%	Constitutional (e.g. fatigue)
34%	Urinary
26%	Pelvic

While symptoms reported by women can be extremely difficult to differentiate from symptoms experienced by women with more benign conditions, one study indicated that bloating, fullness and pressure in the abdomen was much more likely to be constant, rather than intermittent, in proven cases of ovarian cancer, compared with controls.⁵

In the survey conducted by Goff and colleagues, when women were asked about the diagnosis offered prior to the diagnosis of ovarian cancer, 13% of the survey participants responded that they were told that nothing was wrong, 6% were told they had depression and 12% stress.³

Key points:

- Ovarian cancer symptoms are frequently vague and non-specific eg bloating, fullness and a feeling of pressure in the abdomen. Persistence of symptoms for greater than one month must promote a high index of suspicion.⁷
- The thought that a woman may have a psychosomatic problem should not overrule clinical suspicion of malignancy in women with persistent symptoms.
- A high level of suspicion is a useful adjunct in making the diagnosis of ovarian cancer, particularly:
 - in women with a family history of ovarian cancer;
 - in women who are older than 45; or
 - where symptoms appear to persist in the absence of any alternative explanation.

INVESTIGATION OF WOMEN WITH SYMPTOMS

The cornerstone to assessing initial symptoms that may be ovarian cancer is the taking of a careful clinical history. The clinician should seek information about symptoms which either persist or regularly recur. The physical examination is of equal importance and must not be neglected in favour of radiological or blood studies. It is important that the woman is undressed sufficiently to provide access to the whole of the abdomen, unrestricted by constricting clothing.

In women with ovarian cancer an omental mass may be felt as a firm resistance, or an unexpected fullness. Ascites may also be found as fullness which exhibits shifting dullness on percussion. A vaginal examination may also reveal a hard, irregular mass in the Pouch of Douglas, often more readily felt rectally, or adnexal masses.

Key points:

- The cornerstone to assessing initial symptoms that may be ovarian cancer is the taking of a careful clinical history. The physical examination is of equal importance and must not be neglected in favour of radiological or blood studies.
- It is important that the woman is undressed sufficiently to provide access to the whole of the abdomen, unrestricted by constricting clothing.

If on clinical examination, there is a suspicion of a mass, then radiological imaging, (using either ultrasound or CT, but not both), should be able to both confirm any findings, and also help elucidate its nature. The transvaginal ultrasound has a greater sensitivity for the detection of ovarian masses than transabdominal studies. Cysts less than 4 cm may be monitored, but cysts which are of a greater dimension, complex or solid should be referred for consideration of surgical exploration.

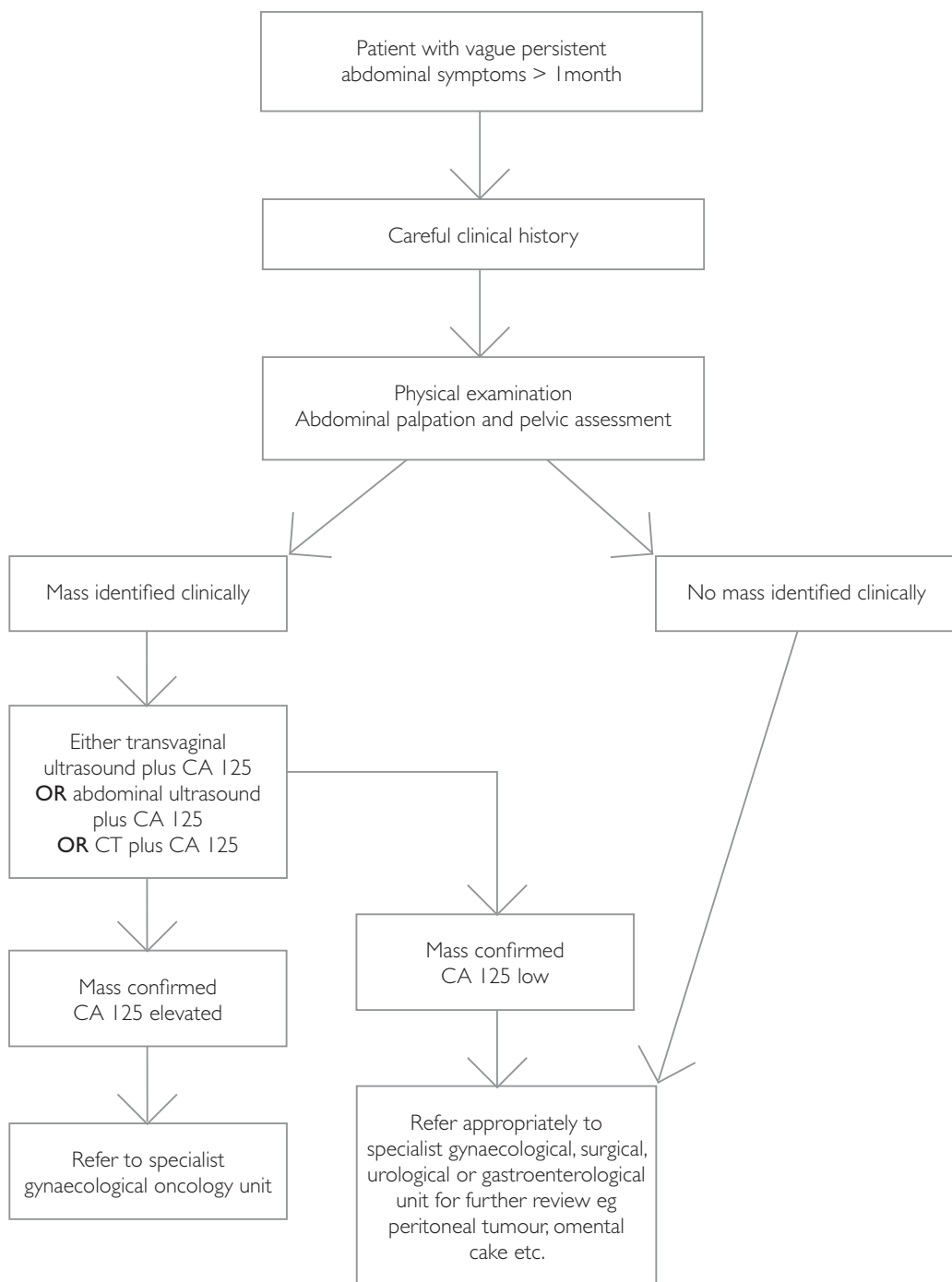
A blood test for CA125 may also contribute information, but whilst a very high value may assist in confirming the diagnosis, a low level is not helpful because of the non-specific nature of the test (*see chapter 3 – Screening for ovarian cancer and chapter 8 – Management of a pelvic mass*). CA125 should not be used to either rule in or rule out disease, as both false negative and false positive results can occur.

If all investigations and tests strongly suggest an ovarian malignancy, direct referral to a gynaecological oncology unit is the preferred option. If the CA125 is low, with a confirmed mass, one should consider other pelvic pathologies before deciding on the primary referral pathway; this might include colorectal and urological as well as gynaecological specialists. The final choice may still include a gynaecological oncologist, and will strongly be dependent on the presenting symptoms as well as any radiological findings. A woman with a suspicious or persistent complex adnexal mass needs surgical exploration. The surgeon of choice is one trained to understand the natural history of the disease who can anticipate and deal with any eventualities during surgery.⁸ Currently only a small percentage of women receive this optimal approach initially.

The more difficult situation is where the clinical examination is negative. The dilemma then is to decide which investigations to perform. Review of the symptoms and possibly radiological investigation of the whole abdomen may help suggest an appropriate referral line. Clinicians should be aware that primary peritoneal cancer may be a subtlety, whereby there are no pelvic masses, but ascites and an omental cake may still be found.

An algorithm has been developed to assist with an organised approach in assessing a woman presenting with vague and persistent abdominal symptoms. (*See Figure 11: Algorithm outlining the approach to assessment of women with vague and persistent abdominal symptoms*).

Figure 11 Algorithm outlining approach to assessment of women with vague and persistent abdominal symptoms



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8. MANAGEMENT OF A PELVIC MASS

When a woman presents with a pelvic mass, it is important to attempt to discriminate between a gynaecological and non-gynaecological mass in the first instance, and then whether the mass is benign or malignant.

Non-gynaecological masses will be diagnosed on the basis of history, physical findings, and special investigations such as colonoscopy.

If the mass is considered to be of ovarian origin, it is important to determine its likelihood of being malignant, because potentially malignant lesions should be referred to a gynaecological oncology unit where adequate surgical staging or cytoreduction can be performed (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*). The best way to detect early ovarian cancer is for both the woman and her clinician to have a high index of suspicion of the diagnosis in a symptomatic woman.¹

There are a series of warning signs on both clinical assessment, biochemistry (CA125) and imaging that should raise suspicion that a pelvic mass is malignant. (For assessment of symptoms and diagnostic pathway, *see chapter 7 – Assessment of initial symptoms*.)

CA125

The CA125 titre in pre-menopausal women is commonly elevated in association with benign conditions such as endometriosis, pelvic inflammatory disease, fibroids adenomyosis, pregnancy and menstruation. Elevated CA125 titres are more suspicious in a post-menopausal woman,² however a normal CA125 measurement alone does not rule out ovarian cancer as it may be normal in 50% of women with stage I ovarian cancer and 20-25% of advanced cancers are also associated with normal values.

ULTRASOUND

Features of cancer on the ultrasound images that suggest malignancy include:

- Septation
- Papillary projections
- Solid areas
- Ascites

The presence of ascites has a positive predictive value of 95%. The absence of ascites is far less reliable in predicting a benign lesion. Less than 20% of early stage ovarian cancers have ascites present.³

Key points:

- The risk for ovarian cancer being present is related to older age (greater than 45 years), family history (positive for breast/ovarian cancer) (*see chapter 2 - Risk factors for ovarian cancer and chapter 4 - Familial aspects of ovarian cancer*), the level of the CA125 titre (>35U/ml), and characteristics on transvaginal ultrasonography⁴
- Any woman with a pelvic mass, in association with the following features should be considered for referral to a gynaecological oncology unit¹
 - Ascites
 - Nodular or fixed pelvic mass
 - Any evidence of abdominal or distant metastases
 - Family history of one or more first degree relatives with breast or ovarian cancer
 - Raised CA125 (or a very raised CA125 (>200U/ml) in a premenopausal woman)

RISK OF MALIGNANCY INDEX⁵

Efforts to standardise the information obtained from each modality have resulted in scoring systems that can be applied as a method of triage. One of these methods (the Risk of Malignancy Index) is a scoring system devised by Jacobs that can be applied as a useful triage for a woman with a pelvic mass.⁵ The algorithm includes assessment of the woman's menopausal status, the ultrasonic features and the serum CA125.

Criteria	Scoring System	Score
Menopausal status: Premenopausal Postmenopausal	1 3	A (1 or 3)
Ultrasonic features: Multiloculated Solid areas Bilaterality Ascites Metastasis	no features = 0 one feature = 1 > 1 feature = 3	B (0, 1 or 3)
Serum CA125	Absolute level	C
Risk Of Malignancy Index (RMI)		A x B x C

If a cut off value of 200 is used to discriminate benign from malignant ovarian masses, there is a good correlation, with a sensitivity of 87% and a specificity of 97%.

Key point:

- Use of a Risk of Malignancy Index in the presence of a pelvic mass is a useful triage to help determine which women would benefit from direct referral to a gynaecological oncology unit.

SURGERY FOR A PELVIC MASS

A woman with a suspicious or persistent complex adnexal mass needs surgical exploration. The surgeon of choice is a clinician, such as a gynaecological oncologist, who is trained to understand the natural history of the disease, who can appropriately stage and debulk ovarian cancer, and anticipate and deal with any eventualities during surgery.⁶ Currently only a small percentage of women receive this optimal approach initially.

Surgery should be performed in a hospital facility, such as a gynaecological oncology unit, that has the necessary support and consultative services, which will optimise the patient's outcome, such as preoperative counselling, psychosocial support services and intraoperative pathology assessment.

Prior to surgery, the woman should be counselled about the risks of ovarian cancer, the plans and options available during surgery and the possible need for radical surgery and staging, including the possible effect on fertility and menopause. If appropriate, consent should be obtained for removal of the uterus, tubes and ovaries and complete surgical staging.

If the woman has her primary surgery in a gynaecological oncology unit, she should have removal of the pelvic mass, as far as is technically possible. If the mass is confirmed as ovarian cancer, she should undergo complete surgical staging⁷⁻⁹ (*see FIGO Staging, Introduction, p3*)

Guideline - Surgical staging	Level of Evidence	Refs
Surgical staging for ovarian cancer always includes: <ul style="list-style-type: none">• peritoneal washings for cytology;• exploration of all peritoneal surfaces including the diaphragm, bowel serosa and Pouch of Douglas;• biopsy of any suspicious nodules;• infracolic omentectomy, multiple peritoneal biopsies; and• at least adequate sampling of pelvic and para-aortic lymph nodes	IV	7,8,9

When these procedures are performed on women with disease apparently confined to the pelvis, 28% of women with apparent stage I disease and 43% of women with apparent stage II disease will be upstaged, usually to stage III disease.⁸ This upstaging increases from 16% for Grade I lesions to 34% for Grade II and 46% for Grade III. The most common sites of metastatic disease are the omentum, diaphragm and retroperitoneal lymph nodes.⁹

In postmenopausal women, total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed.

When ovarian cancer is encountered in premenopausal women who are desirous of retaining fertility, with early stage disease and favourable pathology (that is, Grade I or II tumours), fertility-preserving surgery in association with appropriate follow-up can be safely undertaken.¹⁰⁻¹³

Guideline - Retaining fertility for premenopausal women	Level of Evidence	Refs
In premenopausal women, with invasive adenocarcinomas, early disease and favourable pathology (grade I or grade II, stage IA or IB tumours) fertility-preserving surgery in association with appropriate follow-up can be safely undertaken, if child bearing is desired.	IV	10-13

FOLLOW UP POST-FERTILITY PRESERVING SURGERY

In cases where the uterus and contralateral ovary are preserved, the patient should undergo three monthly measurements of CA125 and the remaining ovary should be monitored with transvaginal ultrasonography every six months. Consideration to remove the contralateral ovary should be given when childbearing has been completed.

Key points:

- In cases where the uterus and contralateral ovary are preserved, the patient should undergo three monthly measurements of CA125 and the remaining ovary be monitored with transvaginal ultrasonography every six months.
- Consideration to remove the contralateral ovary should be given when childbearing has been completed.

If an adnexal mass is removed by a specialist other than a gynaecological oncologist and intraoperative assessment indicates that ovarian cancer is present, no further surgical excision should be performed, unless consent for removal of the uterus and contralateral ovary has been obtained. If histological evaluation reveals an ovarian malignancy, the patient (with her histopathology slides) should be referred to a Gynaecological Cancer Centre for appropriate multidisciplinary evaluation (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*). Avoidance of unnecessary fertility

destroying surgery is especially important in the case of younger women and in women where the final pathology may not confirm the indications for such treatment.

INADVERTENT DISCOVERY OF OVARIAN CANCER

There may be circumstances when the diagnosis of ovarian cancer is made unexpectedly or inadvertently at the time of laparotomy for other purposes, such as by general surgeons in rural or acute settings. If intraoperative consultation by a gynaecological oncologist is not available, it is suggested that the diagnosis be simply confirmed by appropriate biopsy such as of the omentum, that the acute situation be dealt with (for example, a bowel obstruction may be relieved), that minimal other surgery be carried out and that the patient be referred postoperatively to a gynaecological oncology unit.¹⁴ In such circumstances, good outcomes are obtained with individualised approaches such as using neoadjuvant chemotherapy and interval debulking surgery (*see chapter 10 – Surgery for invasive ovarian cancer and chapter 11 – Chemotherapy*). Referral also improves the opportunities for appropriate counselling and psychosocial support being made available to the patient.

Guideline - Inadvertent diagnosis of ovarian cancer	Level of Evidence	Refs
<p>In the event of an unexpected diagnosis of ovarian cancer at the time of surgery for other purposes:</p> <ul style="list-style-type: none"> • the diagnosis should be confirmed with a biopsy; • minimal additional surgery should be undertaken; • postoperative referral to a gynaecological oncology unit for definitive treatment should be arranged. 	IV	14

LAPAROSCOPIC SURGERY

Laparoscopic surgery is increasingly being used in the assessment of gynaecological symptoms. In recent years, reports have been published of undiagnosed ovarian cancer managed by laparoscopy with unfortunate consequences including dissemination of early stage disease and abdominal wall metastases. In view of these risks, laparoscopic surgery should not be performed when there is any significant risk of malignancy. If malignancy is encountered, then the patient should be referred promptly for immediate surgical staging and definitive treatment.^{15,16}

Key point:

- Laparoscopic surgery should not be performed when there is any significant risk of malignancy. If malignancy is encountered, then the patient should be referred promptly for immediate surgical staging and definitive treatment.

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9. THE MANAGEMENT OF BORDERLINE OVARIAN TUMOURS

BACKGROUND

Borderline ovarian tumours are also known as atypically proliferating epithelial ovarian tumours or tumours of low malignant potential. They account for about 15% of all epithelial ovarian malignancies.¹ They tend to occur in young women and around 75% are stage 1 at time of diagnosis. Bilateral ovarian involvement is present in one quarter to one third of cases, sometimes only microscopically. Serous tumours are the most common epithelial type. Histologically, they are characterised by cellular stratification, cytological atypia and epithelial tufting, but without evidence of destructive stromal invasion.

Key point:

- Ovarian tumours of borderline ovarian tumours, account for about 15% of all epithelial ovarian malignancies. They tend to occur in young women and around 75% are stage I at time of diagnosis.

Most women with borderline tumours present with disease confined to the ovary. Whilst these women may be surgically upstaged, the presence of non-invasive metastatic deposits does not apparently affect the outcome, provided the metastatic component is an implant as opposed to showing signs of invasion. These non-invasive metastatic deposits should probably be considered multifocal disease field change.

SURVIVAL RATES FOR BORDERLINE TUMOURS

A recent meta-analysis² suggests that survival for stage I tumours is virtually 100%, whilst survival for advanced stage tumours with non-invasive implants is 95% and survival for tumours with invasive implants is 66%, after 7.4 years of follow-up. Microinvasion in the primary ovarian tumour was associated with a 100% survival rate at 6.7 years of follow-up. A recent publication based on the Surveillance, Epidemiology and End Results (SEER) Program, looking at relative survival in over 2800 women with low malignant potential (LMP) tumours, demonstrated a 10 year relative survival of 95%. The authors felt that the diagnosis of an ovarian tumour of LMP conveys a relatively benign prognosis and recommended that conservative surgery be considered in younger women with early-stage disease.³

MANAGEMENT OF BORDERLINE OVARIAN TUMOURS

FERTILITY CONSERVING SURGERY

Management of low grade borderline tumours is dependent upon the woman's wishes for fertility. Where the tumour is confined to the ovary and fertility sparing surgery is appropriate, either a unilateral salpingo-oophorectomy or ovarian cystectomy is appropriate, minimising trauma to the contralateral ovary by unnecessary biopsy. Bilateral ovarian cystectomy is equally acceptable if both ovaries are involved. Limited surgical staging should be performed to include resection of any peritoneal deposits and an omental biopsy (*see chapter 8 – Management of a pelvic mass*).

Care must be taken with interpretation of frozen section reporting, particularly of mucinous tumours, which must await routine paraffin sectioning to exclude invasive mucinous adenocarcinoma. Where doubt exists and fertility is still an issue, fertility sparing surgery is indicated. Where frozen section has reported a high grade borderline mucinous tumour it is probably prudent to stage those patients as though they were an early stage invasive ovarian carcinoma (*see chapter 5 – The biology and pathology of ovarian tumours*).

All mucinous tumours should have appendicectomy included as part of their procedure. There is a 15% chance of synchronous tumours, as mucinous tumour may be as a result of appendiceal seeding as with pseudomyxoma peritonei. Lymphadenectomy or diaphragmatic scrapings are of no value unless suspicious disease exists. Pelvic lymphadenectomy was reported by Leake⁴ as revealing metastatic disease in 21% of cases but whilst these patients had a statistically higher chance of recurrence, it did not influence their survival. There appears to be no case to restage patients who have been referred from outlying centres without appropriate surgery, rather surveillance is appropriate.⁵ Bell *et al.*⁶ also suggested that residual tumour at completion of surgery was a poor prognostic factor.

SURGERY WHERE CONSERVATION OF FERTILITY IS NOT REQUIRED

Where patients have completed their childbearing then a complete hysterectomy with bilateral salpingo-oophorectomy and omentectomy together with resection of any obvious disease is the treatment of choice. Resection should be limited to removal of all obvious disease and again no benefit exists for lymphadenectomy or random peritoneal or diaphragmatic biopsies.

ADJUVANT THERAPY

There is no role for adjuvant therapy for borderline tumours. Survival for stage I disease with surgery alone, in four consecutive randomised trials is so high (99%) that adjuvant therapy is unlikely to offer a survival advantage.⁷

The adjuvant therapy in the four trials consisted of:

1. External irradiation combined with intraperitoneal instillation of radioactive gold or external irradiation alone;
2. Intraperitoneal radioactive therapy followed by N, N', N'', triethylenethiophosphoramidate (thio-TEPA) or no further treatment;
3. thio-TEPA or no adjuvant therapy; and
4. cisplatin or ³²P (colloidal chromic phosphate) treatment.

In advanced stage I tumours no survival advantage has been demonstrated for adjuvant therapy. Kaern *et al.*⁸ reported on 370 patients, some of who received adjuvant therapy. Those without residual disease performed equally or better than those without adjuvant therapy.⁸

Guideline - Role of adjuvant therapy for Stage I borderline ovarian tumours	Level of Evidence	Refs
There is no role for adjuvant therapy for Stage I borderline ovarian tumours.	I	7

FOLLOW UP

Surveillance of patients with stage I borderline ovarian disease in 164 patients reported by Zanetta *et al.*⁹ suggested a recurrence rate of 17% (28/ 164), five of whom had invasive disease. The CA125 estimation was only elevated in 8 patients, and so they recommend three monthly transvaginal ultrasound for 2 years, and six monthly thereafter. Long term review is indicated as it is recognised that late recurrence is common with borderline tumours. They report that 161 women are alive without disease after 71 months. Interestingly in women with stage IB disease 5 of 14 (36%) recurred although all were salvaged with further surgery. They concluded that ultrasound and CA125 estimation were the best method of continuing surveillance.

The role for completion hysterectomy and oophorectomy following completion of childbearing is controversial, in the absence of recurrent disease. Should recurrence occur secondary cytoreduction is treatment of choice.

Key point:

- The role for completion hysterectomy and oophorectomy following completion of childbearing is controversial, in the absence of recurrent disease. Should recurrence occur, secondary cytoreduction is treatment of choice.

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10. SURGERY FOR INVASIVE OVARIAN CANCER

The surgical approach is the cornerstone of all management of ovarian cancers.

Surgery has a major role in the initial cytoreduction, for interval cytoreduction, and also in the management of persistent or recurrent disease.

PRIMARY CYTOREDUCTIVE SURGERY

Primary cytoreductive surgery is used as the initial management of women with ovarian cancer. It is employed to facilitate and confirm the diagnosis, as well as being definitive in removing the tumour(s) as part of the initial therapy. Primary cytoreduction typically includes total abdominal hysterectomy; bilateral salpingo-oophorectomy; omentectomy; and resection of metastatic lesions from the peritoneal surfaces or from the bowel. A number of retrospective studies of cytoreductive surgery have shown the favourable prognostic effect of minimal residual disease in terms of median survival duration.^{1,2,3,4}

Guideline - Primary cytoreduction	Level of Evidence	Refs
Primary cytoreduction is considered the initial treatment of choice for women with ovarian cancer and typically includes: <ul style="list-style-type: none">• total abdominal hysterectomy;• bilateral salpingo-oophorectomy;• omentectomy; and• resection of metastatic lesions from the peritoneal surfaces or from the bowel.	IV	1,2,3

Key point:

- Primary cytoreduction is considered the treatment of choice for most patients who are initially referred to Gynaecological Cancer Centres.

Optimal benefit results when all gross tumours can be excised safely.¹ A meta-analysis of 58 studies found that maximum cytoreductive surgery produced a small improvement in median survival time.⁵ This study was biased against surgery by the inclusion of a number of studies which did not use optimal chemotherapy, and by the variable definitions of 'optimal' cytoreduction (*see chapter 11 – Chemotherapy*).

Key points:

Cytoreductive surgery is considered to offer three theoretical advantages:

- Removal of bulky tumour masses may improve the physiological status of the patient by alleviating the nausea and early satiety often associated with a large omental mass, improving bowel function, and decreasing the volume of ascites.
- Cytoreduction may eliminate the hypoxic areas of a tumour, thereby improving the perfusion of the residual tumour nodules, and increasing the growth fraction of the tumour. (Well perfused, actively divided cells are more likely to respond to chemotherapy or radiotherapy).⁶
- Resection of bulky disease enhances the immunological competence of the patient.

Primary cytoreduction typically includes resection of metastatic lesions from the peritoneal surfaces or from the bowel. The latter may necessitate bowel resection, so preoperative bowel preparation is necessary in all patients. Primary reanastomosis is always feasible following small bowel resections, and usually feasible following colonic resection.

Bulky pelvic or para-aortic lymph nodes should be resected if possible but whether or not there is benefit from systematic lymphadenectomy is being tested currently in an international randomised trial.⁷

The goal of cytoreduction should be to remove all macroscopic disease, but as this is seldom feasible, as much disease as possible should be removed. Optimal cytoreduction is usually defined as residual disease ≤ 2 cm. When performed by gynaecological oncologists, optimal cytoreduction can be achieved in 70-90% of patients^{2,8}, whereas resection of all macroscopic disease is feasible in only about 12% of cases. In those women for whom resection of all macroscopic disease is feasible, the 5-year survival rate is around 50%.⁹

Epithelial ovarian cancer is a tumour of intermediate chemosensitivity, with response rates to first line chemotherapy in the order of 70%. A meta-analysis of 38 chemotherapy studies reported that residual disease of ≤ 2 cm ($P = 0.011$) and the use of platinum chemotherapy, ($p=0.005$) were the only independent prognostic factors in multivariate analysis¹⁰ (*see chapter 11 – Chemotherapy*).

Morbidity from cytoreductive surgery is generally well tolerated. In a study of 472 primary cytoreductive operations for ovarian cancer from Helsinki, intraoperative bleeding in excess of 1000 ml occurred in 21% of cases. In addition, 18% of women had urinary tract infections, 7% had bowel complications (mainly prolonged ileus), 4% had fever, 3% had wound complications, and 2% developed thromboembolism. Only five women (1%) died post-operatively.¹¹

INTERVAL CYTOREDUCTIVE SURGERY

Interval cytoreductive surgery is defined as surgery undertaken after a period of neoadjuvant chemotherapy, which is given either because optimal primary cytoreduction (residual disease of ≤ 2 cm) was not achieved, or because the woman's general medical condition was too poor initially to undergo surgery.

If cytoreductive surgery is to be performed it should be undertaken by a specialist gynaecological oncologist in a specialist centre (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*).

Definitions of sub-optimal cytoreduction have varied within the literature, reflecting the difficulty of accurately describing residual tumour burden within the various peritoneal sites and lack of agreement on the amount of residual tumour that constitutes optimal cytoreduction.¹² Conventionally, women with tumour nodules of greater than 2 cm diameter at the completion of cytoreductive surgery are regarded as suboptimally cytoreduced.

There has only been one major prospective randomised trial of interval cytoreductive surgery. It was conducted by the European Organisation for Research and Treatment of Cancer (EORTC), and was a study of interval cytoreduction following three cycles of chemotherapy for women who had a suboptimal primary operation, defined in this study as tumour deposits greater than 1 cm remaining.¹³ Women whose tumour progressed on the three cycles of treatment were ineligible. There were 319 patients randomised, and both progression-free and overall survival were longer in the group having interval cytoreduction ($p = 0.01$). Although this is the only randomised prospective study of cytoreduction, it does not imply that all patients should have initial definitive surgery delayed until chemotherapy has been given.

Elective interval cytoreduction following neoadjuvant chemotherapy may also be indicated if the woman's general medical condition is poor, particularly in the presence of massive ascites and a large pleural effusion.

Randomised studies in this setting have not been conducted, but the use of neoadjuvant chemotherapy in selected cases has demonstrated comparable survival to patients treated with conventional cytoreductive surgery followed by chemotherapy.¹⁴ In the latter setting, a diagnosis of malignancy should be established cytologically prior to the initiation of chemotherapy. (*For management of borderline ovarian tumours, see chapter 9*).

Guideline - Interval cytoreduction	Level of Evidence	Refs
Neoadjuvant chemotherapy and interval cytoreduction may be considered if optimal primary cytoreduction was not achieved.	II	13

SECONDARY CYTOREDUCTIVE SURGERY

SURGERY FOR PERSISTENT OR RECURRENT DISEASE

Patients who develop progressive disease on chemotherapy have a very poor prognosis. Surgery in this context offers no survival advantage and should be limited to symptomatic care, for example, for the relief of an acute bowel obstruction (*see chapter 16 – Palliative care*).

Secondary cytoreductive surgery is confined to surgery undertaken to further debulk the cancer in women who have persistent disease, following a completed course of chemotherapy, or who subsequently experience biochemical and/or clinical relapse.

The outcomes for patients who have persistent disease at the end of the primary treatment and who then undergo surgery are poorer than for those who have a good initial surgically documented response to their chemotherapy and then later relapse. The longer the interval from complete remission to evidence of relapse, the more likely there will be a substantial benefit from a second attempt at surgery^{15,16,17,18,19,20,21} (*see chapter 11 – Chemotherapy*).

Guideline - Surgery in women who develop progressive disease during initial chemotherapy	Level of Evidence	Refs
Surgery has no place for women who develop progressive disease during their initial chemotherapy program.	IV	15, 16

A recent study by Tay *et al.*²² reviewed 336 patients treated by gynaecological oncologists between 1996 and 1998. Forty six patients underwent secondary cytoreductive surgery after a disease free interval. The authors report that in those women in whom all remaining disease could be cleared, and those who had a disease-free interval of at least 24 months after initial treatment, survival could be significantly prolonged.

Key points:

Secondary cytoreductive surgery may benefit women with^{23,24}:

- Long disease-free interval (especially >2 years)
- Younger age
- Good performance status
- Isolated recurrences, especially in the pelvis, if resection can be completed

In contradistinction to the situation in colon cancer, there are no data to substantiate the use of liver resection for recurrent disease. The most common clinical situation which women with ovarian cancer experience is disease in the upper abdomen,

usually involving the diaphragms and the liver parenchyma. This is equally difficult to manage surgically in the primary and recurrent disease. CT scanning and abdominal and transvaginal imaging studies are therefore mandatory prior to deciding on such surgery.

Data on the rate of success of attempted secondary debulking surgery are few. Most women who undergo such procedures opt for cytotoxic therapy following surgery although some have been reported to have a satisfactory response without postoperative therapy.²⁵ Therefore, the effect of the surgery itself is unclear.

Key point:

- A randomised trial is required to compare surgery plus chemotherapy, with chemotherapy alone, in disease which has relapsed more than 24 months since discontinuation of primary treatment.

SECOND-LOOK SURGERY

'Second-look' operations have been traditionally undertaken following the completion of the initial treatment program, which has usually involved a primary laparotomy, followed by six cycles of combination chemotherapy. The accuracy of laparoscopy and laparotomy in detection of disease seems comparable.^{26,27,28} Although it is clear that second-look surgery does provide reliable prognostic information,²⁹ it remains controversial whether such procedures improve survival.^{30,31,32,25,33} Although the data are conflicting, there are a number of publications, particularly about platinum-treated patients, suggesting a survival advantage 'when macroscopic residual disease can be reduced to microscopic'. The introduction of taxanes and other agents as possible second line treatment should stimulate the question to be revisited. A recent randomised controlled trial comparing WART, chemotherapy and no further treatment for advanced ovarian cancer (*see FIGO Staging, Introduction- p3*) in women with complete surgical and pathologic remission after induction chemotherapy, showed a survival advantage for WART,³⁴ although the numbers did not reach statistical significance (*see chapter 12 – Radiation Therapy*).

Key point:

- Second-look procedures should only be undertaken in the context of a research setting, to investigate further treatment such as chemotherapy or Whole Abdominal Radiation Therapy (WART).

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II. CHEMOTHERAPY

Surgical staging is the cornerstone to all subsequent treatment discussions in ovarian cancer. The careful and accurate surgical procedure will determine the true stage, and this must be performed meticulously (*see Introduction, chapter 10 – Surgery for invasive ovarian cancer and Appendix 4 - Gynaecological oncology training requirements*).

This is especially important for early stage disease, as stages IA and IB may not always require adjuvant chemotherapy, and one must be as certain as is possible, that there is no tumour in the ‘sanctuary’ or hidden sites, especially omentum, diaphragms and lymph nodes.

Outcomes of treatment are best for women managed in a multidisciplinary care setting, with medical, nursing and allied health staff specially trained in the management of patients with ovarian cancer (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*). Wherever possible, chemotherapeutic management of patients with ovarian cancer should be undertaken in conjunction with a major referral centre for the management of gynaecological malignancy.

Key points:

- Surgical staging is the cornerstone to all subsequent treatment discussions in ovarian cancer.
- Wherever possible chemotherapeutic management of patients with ovarian cancer should be undertaken in conjunction with a major referral centre for the management of gynaecologic malignancy.

WHICH PATIENTS WITH EARLY OVARIAN CANCER SHOULD RECEIVE CHEMOTHERAPY?

Provided that surgical staging is meticulous and follows all the guidelines, not all women with early stage ovarian cancer will benefit from chemotherapy.¹ If surgery is not optimal, chemotherapy can reduce the risk of recurrence and death in early ovarian cancer. The absolute benefit for an individual patient will vary according to their risk of relapse, which is closely related to their disease stage.^{1,2,3,4}

Patients with borderline tumours, even with documented metastases, have an excellent prognosis (*see chapter 5 – The biology and pathology of ovarian tumours, and chapter 9 – The management of borderline ovarian tumours*). In the absence of documented invasive implants, adjuvant chemotherapy is not indicated.⁵

Guideline - Adjuvant chemotherapy for women with early stage ovarian cancer	Level of Evidence	Refs
Adjuvant chemotherapy with a platinum agent is recommended for patients with high grade or clear cell histology because they are known to have a higher relapse rate.	II	1
Patients with stage IA or IB well or moderately differentiated tumours do not require adjuvant chemotherapy because their risk of relapse is low, and the toxicity not justified.	II	2
Adjuvant chemotherapy is not indicated in patients with borderline tumours (unless invasive implants are confirmed histologically).	II	3

ADJUVANT TREATMENT OF EARLY OVARIAN CANCER

Two recently reported randomised trials examined the effect of immediate chemotherapy after surgical resection of early ovarian cancer compared to a policy of delaying such treatment until clinically indicated by the development of symptoms. The ICON1 trial⁶ randomised 477 patients with histologically confirmed epithelial ovarian cancer on the pragmatic basis that the treating clinician was uncertain of the need for immediate adjuvant chemotherapy. Surgically, all visible tumour had to have been removed. Various platinum-based chemotherapy regimens were allowed. A parallel study¹ included 448 patients with a variety of FIGO stages after various degrees of surgical staging. Again the randomisation was between immediate and delayed chemotherapy, and chemotherapy had to consist of at least four courses (six were recommended) of a platinum-based chemotherapy.

Although results of the two trials have been presented separately, a prospectively designed combined analysis⁷ was also reported. Immediate chemotherapy compared to no (delayed) chemotherapy resulted in improved 5-year overall survival (82% vs. 74%; HR= 0.67, C.I 0.50 to 0.90; p=.008) and improved 5-year recurrence-free survival (76% vs. 65%; HR = 0.64, C.I 0.50 to 0.82, p= 0.001). In the combined analysis, the survival benefit was limited to those with non-optimal staging, suggesting that patients more at risk of unappreciated residual disease are more likely to benefit from chemotherapy.

Guideline - The effect of platinum based adjuvant chemotherapy on women with early stage ovarian cancer	Level of Evidence	Refs
Platinum-based adjuvant chemotherapy improves recurrence-free and overall survival in women with surgically resected early ovarian cancer, who are at high risk of relapse.	II	6, 7

FIRST LINE TREATMENT OF ADVANCED DISEASE

Two individual-patient-data meta-analyses and seven additional randomised trials investigated the survival benefits of various options for first-line systemic chemotherapy for advanced ovarian cancer. A meta-analysis based on these nine studies indicated that,

when compared to non-platinum-based regimens, platinum, alone or in combination with other agents, improves survival when used as a first-line treatment, with a Mortality Hazard Ratio (HR) of 0.88; 95% C.I 0.79 to 0.98; p=0.02; n=1704). This translates into an absolute improvement of approximately 5% in the survival rate at two years (35% without platinum versus 40% with platinum).⁸

Another meta-analysis⁹ has supported the use of a platinum compound as the standard chemotherapy for ovarian carcinoma.

Guideline - First line treatment of advanced ovarian cancer	Level of Evidence	Refs
The first line treatment of advanced ovarian cancer ideally should include a platinum compound.	I	9

CISPLATIN OR CARBOPLATIN

A meta-analysis was published in 1998,⁹ containing twelve trials of carboplatin versus cisplatin with 2219 patients. The trialists concluded that there was no evidence of any difference between cisplatin and carboplatin when given as a single agent or in combination. There was no evidence that any group of women (by age, stage, progression-free survival (PS), residual tumour bulk, histology or grade) would do better with cisplatin versus carboplatin.

Subsequent randomised trials of the combination of carboplatin and paclitaxel have been performed since the publication of this meta-analysis.^{10,11,12} The consistent findings are that there is no significant difference in progression free or overall survival when carboplatin is substituted for cisplatin. Given the favourable toxicity profile and ease of administration yet equivalent efficacy of carboplatin this agent has become generally accepted as the preferred first line treatment.

Key points:

- Carboplatin is well tolerated by the great majority of patients, and in trained hands can be given safely even in relatively frail and/or elderly patients.
- In patients who decline intravenous chemotherapy, or are otherwise unsuitable for carboplatin, oral alkylating agent therapy (eg chlorambucil or melphalan) is a reasonable alternative treatment.

SINGLE AGENT PLATINUM VS. PLATINUM PLUS OTHER DRUGS

Despite the recent publication of a number of large, well conducted randomised prospective trials, this issue has not been completely resolved.

A meta-analysis¹³ performed before the introduction of taxanes used individual patient data from 1095 patients in a total of nine randomised trials of single agent platinum

versus platinum containing combinations. Although the Hazard Ratio of 0.91 (95% C.I 0.80 to 1.05; $p=0.21$) slightly favoured combination treatment, this result was not statistically significant.

The International Collaborative Ovarian Neoplasm (ICON) 2 trial¹⁴ compared carboplatin (AUC=5) to cisplatin (50 mg/m²) + cyclophosphamide + doxorubicin. The median survival was 33 months and 2 year survival 60% in both arms (mortality HR, 1.0; 95% C.I 0.86 to 1.16; $p=0.98$).

The International Collaborative Ovarian Neoplasm (ICON) 3 trial¹⁵ included a comparison of single agent carboplatin (AUC = 5-6) with carboplatin (AUC = 5-6) and paclitaxel (175 mg/m² over 3 hours) in 1421 patients. The median overall survival was not significantly different in the two arms, Hazard Ratio 0.98 (95% C.I 0.85 to 1.12, $p=0.73$).

Some authorities have criticised the design of the ICON studies, suggesting that there is a potential for unrecognised biases in these trials. Others believe that their sheer size makes the results quite robust. Despite the ICON results, the global standard remains treatment with combination chemotherapy. Ongoing trials are testing the addition of new drugs such as gemcitabine and topotecan to the combination of carboplatin and paclitaxel. There are no single agent control arms in any of the currently ongoing randomised controlled trials.

WHICH COMBINATION?

In early studies, the addition of doxorubicin to platinum and cyclophosphamide was shown to be beneficial in terms of overall survival.^{16,17-19} This survival benefit is small and was only detected from pooled data, so that its clinical utility has been questioned.¹⁹

ROLE OF PACLITAXEL

Two large randomised trials have compared cisplatin plus cyclophosphamide versus cisplatin-paclitaxel. These studies demonstrate a statistically significant survival advantage for the combination of cisplatin and paclitaxel over cisplatin and cyclophosphamide.^{20,21}

WHICH PLATINUM WITH PACLITAXEL?

A number of other studies investigated the preferable platinum analogue and duration of infusion of paclitaxel. Regimens employing carboplatin produce overall survival results apparently equivalent to those employing cisplatin, but with significantly less toxicity. Regimens incorporating a three hour infusion are as effective as longer infusions and more acceptable to patients.^{22,23} Taken together these studies support the combination of carboplatin and paclitaxel as standard of care for first line therapy of epithelial ovarian cancer.

Guideline - Current practice for first line chemotherapy	Level of Evidence	Refs
It is currently recommended that standard first line chemotherapy should be a combination of carboplatin (AUC x 6) and paclitaxel (175 mg/m ²) given every three weeks.	II	10, 12

The use of platinum and paclitaxel is supported by the results from two randomised controlled trials (RCTs), Gynecologic Oncology Group (GOG) 111²⁰ and OV10²¹. A third trial, GOG 132, is essentially a trial of concurrent platinum/paclitaxel chemotherapy versus sequential platinum/paclitaxel chemotherapy.²⁴ No significant survival advantage was observed for the combination arm. However, the conclusions which might be drawn from this study are uncertain since many patients eventually received both drugs.

ICON 3, a trial of either carboplatin alone or CAP vs carboplatin/paclitaxel in over 2000 women, does not support the addition of paclitaxel to carboplatin. The difference in results from trials such as GOG111 and OV10 may be explained by the lower dose of platinum providing an inadequate control arm. A pooled analysis has been conducted in an attempt to explain trial heterogeneity.²⁵

Criticisms of ICON 3 include the difference seen in results from large and small treatment centres and the lack of audit in the UK Medical Research Council (MRC) trials. It is however the largest study of chemotherapy in ovarian cancer ever completed.

The apparently comparable results of combination therapy versus single agent carboplatin suggest that when patients are either unsuitable for combination therapy on the basis of their concurrent medical conditions or their poor performance status, or are unwilling to accept the toxicity of combination therapy, that single agent carboplatin is an acceptable alternative treatment regimen. Given the favourable toxicity profile of carboplatin as a single agent, there are very few patients who would not tolerate this treatment.

Guideline - Single agent carboplatin	Level of Evidence	Refs
In patients unsuitable for combination therapy (on the basis of either concurrent medical conditions, performance status or by patient preference) single agent carboplatin is an effective and acceptable treatment for advanced ovarian cancer.	II	14

NEWER AGENTS AND CURRENT RESEARCH

Current research strategies include substitution of taxotere for paclitaxel, addition of a third drug (eg gemcitabine, topotecan) in combinations or sequential patterns, or longer durations of therapy. Data from the randomised trial of docetaxel/carboplatin (DC) versus paclitaxel/carboplatin (PC) have only been reported in abstract form but early survival data suggest that docetaxel is an alternative to paclitaxel and produces a different toxicity profile.

Ongoing studies GOG182/ICON5 are comparing the addition of new agents to the standard of carboplatin and paclitaxel (gemcitabine, topotecan and pegylated liposomal doxorubicin) either concurrently or sequentially. All patients in this trial will receive at 8 cycles of chemotherapy.

WHEN TO COMMENCE CHEMOTHERAPY?

Chemotherapy does not delay the healing of uncomplicated wounds. There would appear to be no advantage and potential disadvantage to delay chemotherapy longer than is required to allow reasonable recovery after surgery. Chemotherapy should commence as soon as practical after bowel function has recovered following surgery, ideally within two weeks of surgery.

SPECIAL CHEMOTHERAPY STRATEGIES:

INTRAPERITONEAL THERAPY

Intraperitoneal (IP) therapy has been advocated because of a putative advantage derived from the high intraperitoneal drug concentrations achieved. One large randomised prospective trial²⁶ reported a survival advantage for IP cisplatin over systemic cisplatin (both used in combination with intravenous cyclophosphamide). A second study found no superiority for intraperitoneal over intravenous administration.²⁷ Median survival was 49 months versus 41 months ($p < 0.02$) with the same survival benefits for micro and various sizes of macro residual disease.

A subsequent study has reported small survival gains associated with intraperitoneal chemotherapy.²⁸ Survival difference was of borderline statistical significance (RR 0.89) for intraperitoneal versus intravenous administration with a Relative Risk of 0.78 survival advantage improvement in progression-free survival, compared with intravenous administration. This study also confirmed the relative safety of administering cisplatin to patients with small volume residual advanced ovarian cancer outside the clinical research setting.²⁸ Both of these studies were conducted in patients with stage III disease with minimal residual disease.

Although intraperitoneal chemotherapy has its advocates in particular centres, given the complexity of the technique and the conflicting data, this treatment has not yet been accepted as a standard of care.

Although not standard of care, its use may be considered on an individual patient basis in a designated cancer centre. The optimal drug and dose for intraperitoneal therapy have not yet been determined in this setting.

Guideline - Intraperitoneal chemotherapy	Level of Evidence	Refs
Although intraperitoneal chemotherapy is not recommended as standard therapy its use may be considered on an individual patient basis at a designated cancer centre.	II	27

DOSE INTENSE OR DOSE DENSE STRATEGIES:

Dose intensity was suggested as a strategy to improve the effectiveness of chemotherapy by Levin and Hryniuk based on retrospective studies. The question has now been addressed in a number of prospective studies.

A phase III 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 cancer showed superior progression free survival for patients randomised to the experimental treatment arm and borderline improvement in overall survival.

The West of Scotland trials group³⁰ studied patients (stage IC to IV) receiving either cisplatin 100 mg/m² plus cyclophosphamide 750 mg/m² High Dose (HD) or cisplatin 50 mg/m² plus cyclophosphamide 750 mg/m². There was thus a two-fold difference in the planned dose and total dose. A planned interim analysis (at n=165) showed a significant survival advantage for the HD arm (median survival 114 v 69 weeks, P=0.0008) and the trial was closed. Longer follow up to median observation of 57 months however shows a much reduced survival benefit, with the difference in favour of the HD arm being seen almost exclusively in the first year of follow up. Importantly, long term neurotoxicity is much more a problem in the HD arm. Interestingly the authors chose to recommend a dose of 75 mg/m² of cisplatin as optimal, and yet this dose was not formally tested.

The GOG31 performed a randomised trial in 458 suboptimally debulked patients with > 1 cm residual stage III and IV. The arms were 4 courses of dose intensified (HD) CisDDP 100 mg/m² plus cyclophosphamide 1000 mg/m² q 3 weekly for four cycles, and CisDDP 50 mg/m² plus cyclophosphamide 500 mg/m² for 8 cycles. The study achieved a doubling of dose intensity without a difference in the delivered total dose, as designed. No significant difference in response rate or median survival was seen.

Two other large studies^{32,33} have increased both dose intensity and total dose, demonstrating greater toxicity in the HD arm, but no response or survival advantage.

Most authorities recommend standard dose intensity for cisplatin of 25 mg/m²/week, as used in the classic GOG studies.

Key point:

- Most authorities recommend standard dose intensity for cisplatin of 25 mg/m²/week, for advanced ovarian cancer, as used in the classic GOG studies.

HIGH DOSE CHEMOTHERAPY WITH STEM CELL SUPPORT

The previous discussion refers to increased dose intensity/ total dose which can be achieved with standard chemotherapy without growth factor support. Apart from intraperitoneal therapy, the other option is very high dose therapy.

There are large numbers of Phase I and II trials reporting ‘feasibility’ of very high (i.e. 8 to 10 fold increase) in dose/intensity. High response rates are described, but a major issue is that the patient cohorts are usually poorly described in terms of their disease being likely to still be platinum sensitive or resistant. Until results from randomised trials underway to evaluate High Dose (HD) chemotherapy – as part of initial therapy or as consolidation therapy after initial response to therapy – and to compare HD with standard dose chemotherapy are reported, HD therapy remains limited to the clinical trial setting.³⁴

Guideline - High dose therapy	Level of Evidence	Refs
The use of chemotherapy protocols utilising high dose therapy should only be offered as part of an appropriately designed clinical trial.	IV	34

MONITORING DURING CHEMOTHERAPY

During chemotherapy tumour response is assessed by clinical measurement of evaluable tumour (when present). Serum CA125 level is an important marker of response (or otherwise) to treatment. A confirmed rise of serum CA125 level to more than twice the upper limit of normal during follow up after first line chemotherapy accurately predicts tumour relapse.³⁵ CA125 has a serum half-life of approximately 6 days. During the first few (probably 3) cycles of treatment, the CA125 level reflects the effects of debulking surgery as well as chemotherapy, so that a fall in CA125 cannot be taken as definite evidence of tumour response. However, if CA125 is falling, treatment should continue to six cycles.

HOW LONG SHOULD FIRST LINE CHEMOTHERAPY CONTINUE?

Three randomised trials have addressed this issue for intravenous chemotherapy.³⁶⁻³⁸

Overall none of the studies reported a difference in the rate of complete pathological response (CR) or median survival. Therefore, it is concluded that treatment beyond six cycles cannot be recommended. In practice, occasional patients show a slow but continued response to chemotherapy (manifest by a continuing drop in CA125) and require more than six cycles to achieve complete response. In these unusual cases, it is recommended to continue treatment until CR is achieved, as long as toxicity is acceptable.

Key point:

- While treatment beyond six cycles cannot be recommended, in unusual cases where there is slow but continued response to chemotherapy (manifest by a continuing drop in CA125) treatment can continue until complete pathological response is achieved, as long as toxicity is acceptable.

CONSOLIDATION TREATMENT

This approach addresses a different concept, i.e. does further chemotherapy after achieving a response to initial treatment confer a benefit. The available evidence is limited, but includes studies by the North Thames Group³⁸ and the Swedish-Norwegian Ovarian Cancer group.³⁹ At present, the evidence does not support the use of maintenance or consolidation therapy, outside the context of a properly designed clinical trial.

Guideline - Maintenance or consolidation chemotherapy	Level of Evidence	Refs
The use of maintenance or consolidation chemotherapy should only be offered as part of an appropriately designed clinical trial.	II	38,39

RELAPSED DISEASE

Patients with relapsed disease are incurable, but many such patients may still derive useful responses from further therapy. It is important to recognise the heterogeneity of this patient population, both in terms of patient's wishes and goals, and also in likelihood of response to further therapy.

There is evidence that the interval between the end of first-line therapy and relapse (the treatment-free interval) is an important predictor of likelihood of response. The longer the treatment-free interval, the higher the likelihood of worthwhile response.^{40,41} However (with the rare exception of patients whose disease progresses during primary platinum-based therapy), there is no absolute disease-free interval which can be arbitrarily used to exclude a response to carboplatin.

Patients who do not respond to initial therapy, or who progress during initial chemotherapy, are considered platinum refractory, and an argument can be made for not considering further treatment.

In contrast, the potential importance of retreating with carboplatin in women *who have responded* to platinum during first line therapy should be stressed. Clinical experience demonstrates that a significant number of patients derive worthwhile benefit from re-treatment with carboplatin (even with a platinum-free interval of less than 12 months). Worthwhile response is uncommon, but not unknown, in women with a disease-free interval of less than six months.

Given its ease of administration and low toxicity, the principle of therapy for relapsed disease should be that the potential utility of single agent carboplatin should be exhausted before moving on to other agents.

Guideline - Treatment of relapsing disease	Level of Evidence	Refs
Patients relapsing more than six months after a confirmed response to initial treatment with platinum compounds should be considered for re-treatment.	IV	40, 41

Response to such treatment must be carefully monitored however, and treatment is only continued past two or three courses if there is evidence of response and improvement in symptoms.

It is important not to be misled by a fall in CA125 levels after aspiration of pleural effusions or ascites.

THE TREATMENT OF OVARIAN CARCINOMA NO LONGER SENSITIVE TO PLATINUM

Topotecan and pegylated liposomal doxorubicin are cytotoxics with some efficacy in terms of response rate and survival times in platinum/taxane resistant disease.^{12,42,43} Topotecan is associated with more haematological toxicity and requirement for dosage modification. Liposomal doxorubicin commonly causes mucositis and may cause plantar-palmar erythrodysesthesia but only requires a four-weekly dosing.

Tamoxifen has limited but definite activity in otherwise drug-resistant disease. Given its low toxicity profile, it should be considered where chemotherapy is inappropriate.

Key point:

- In patients with relapsed ovarian cancer, quality of life must be a major component of assessment.

It is important to note that it is well recognised that occasional patients can have multiple responses to treatment, and a relatively protracted survival. These patients typically have a long treatment free interval. In patients in whom the treatment free interval is relatively prolonged (e.g. 18 months or more) consideration should be given to further debulking surgery.

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12. RADIATION THERAPY

The initial management of ovarian cancer is surgical, but most patients will require further treatment with chemotherapy, radiotherapy or both, because of the high risk of intra-abdominal recurrence. Systematic study of the role of radiation therapy in the management of ovarian cancer has been limited by poor accrual to large randomised trials in this area, by pre-existing prejudices regarding the outcomes of such studies, and by concerns about the toxicity of abdominal radiation therapy.

ADJUVANT RADIOTHERAPY

In a small number of treatment series, post-operative adjuvant treatment with Whole Abdominal Radiation Therapy (WART) appears to have achieved a cure in approximately 75% of suitably selected patients.¹

COMPARISON BETWEEN WHOLE ABDOMINAL RADIOTHERAPY AND ADJUVANT CHEMOTHERAPY

No well-designed prospective randomised clinical study has ever been completed to compare the efficacy and toxicity of Whole Abdominal Radiation Therapy (WART) alone versus chemotherapy alone as an adjuvant therapy. It is therefore not possible to provide evidence to support evidence-based guidelines that categorically demarcate the choice between radiotherapy and chemotherapy. The appropriate use of one or both of these treatments should be carefully considered in the multidisciplinary management of women with ovarian cancer.

The role of WART as adjuvant treatment is still an open subject deserving further study. Cardenes and Randall have written a useful review on current issues and future directions.²

EFFICACY OF WART

Patients most likely to benefit from post operative WART are those who have received optimal cytoreductive surgery, and are classified as 'intermediate risk' according to the criteria used at Princess Margaret Hospital (PMH) in Toronto.³ This classification which uses stage, grade and residuum of tumour as prognostic factors, (Figure 12), has been validated internationally.⁴⁻⁶

Figure 12 Prognostic Subgroupings According to Stage, Residuum and Grade in Patients with Stages I – III

Stage	Residuum	Grade 1	Grade2	Grade3
I	0	Low risk		
II	0		Intermediate risk	
II	< 2cm			
III	0		High risk	
III	< 2cm			

WART is indicated as primary post-operative therapy in patients with stage I, II and III disease having no macroscopic disease in the upper abdomen and small macroscopic (0-2cm) residual disease in the pelvis.

Low-risk patients with stage I disease completely resected, with well differentiated non adherent tumours and negative peritoneal cytology, are cured by operation alone in approximately 95% of cases, and do not require post-operative therapy.

Conversely, WART is inadequate treatment in the PMH 'high risk' category women, in whom only 20% remain free of disease at 10 years after WART alone. It has been known for many years that there is a relationship between tumour control probability, radiotherapy dose, and volume of disease for tumours of various histologies.⁷

For ovarian cancer the estimated relationship between tumour size and dose required to achieve any reasonable chance of tumour eradication (the 'cancericidal dose') is shown in Table 4.⁸

Table 4 Estimated relationship between tumour size and dose of radiation required to achieve reasonable chance of tumour eradication

Tumour Size	Cancericidal Dose
2cm	50 – 60Gy
0.5 – 2.0cm	45 – 50Gy
Microscopic	25 – 30Gy

ADJUVANT CHEMOTHERAPY FOLLOWED BY WART

The role of sequential chemotherapy followed by WART has been studied in two small prospective randomised studies.^{9,10} The available data suggest that WART is at least as effective as continued chemotherapy for women with advanced ovarian cancer and that long term survival may occur where consolidation WART is used for patients with negative second look laparotomy following chemotherapy.¹¹

A recent randomised controlled trial comparing WART, chemotherapy and no further treatment for advanced (FIGO stage III) ovarian cancer, showed a survival advantage for WART in women with complete surgical and pathologic remission after induction chemotherapy, although the difference did not reach statistical significance.¹² This lack of statistical significance may be explained by the small sample size and the survival advantage may be clinically important. It should also be noted that between-group difference at baseline in tumour grade (one of the prognostic factors for ovarian cancer) could explain some of the differences in the results. The proportion of women with well or moderately well differentiated tumours in the chemotherapy group was 26%, compared to 50% and 42% in the radiotherapy and control group respectively.

Guideline - WART for stage III patients	Level of Evidence	Refs
Whole Abdominal Radiation Therapy (WART) should be considered in stage III ovarian cancer patients with complete surgical and pathologic remission at second-look laparotomy.	II	12

COMPLICATIONS OF WART

There are limits to the radiation tolerance of normal organs included in the WART target volume, particularly in the upper abdomen.⁸ The complications of WART are acceptable as long as an open field technique is used, radiotherapy doses are limited to 45-50Gy in 1.8-2.0Gy fractions in the pelvis, and 22.5-27.5Gy in 1.0-1.2Gy fractions in the upper abdomen, and the dose to the kidneys is limited to < 20Gy by appropriate shielding.¹³ The radiotherapy protocol as set out by PMH Toronto is well tried and gives acceptable toxicity.^{3,8} Analysis of complications in 600 patients treated at PMH Toronto showed that most patients experience temporary acute side effects during WART, including

nausea, vomiting and diarrhoea. Myelosuppression was a common reason for treatment interruptions, and resulted in 10% of patients failing to complete WART.

The late complications of WART included chronic diarrhoea in 14% of patients, transient hepatic enzyme elevation (44%), symptomatic basal pneumonitis (4%), cystitis (2.8%) and bowel obstruction (4.2%), treated conservatively (1.5%) or with surgery (2.7%).

PMH Toronto conducted a randomised study of two doses of WART, which compared 22.5Gy in 22 fractions versus 27.5Gy in 27 fractions. A pelvic boost of 22.5Gy was used in both arms.¹⁴ The study involved 125 patients and concluded there was no difference in survival, tumour control or toxicity between the higher dose and lower dose of WART. Serious bowel toxicity was seen in three patients: two in the low dose and one in the high dose arm.

PALLIATIVE RADIOTHERAPY

Three studies have demonstrated the effectiveness of radiotherapy in the palliative treatment of brain metastases, vaginal bleeding, rectal bleeding, pelvic pain and other symptoms.

One study by Corn *et al.*¹⁵ evaluated 4027 women with ovarian cancer over a 30 year-period. Of these 32 were found to have cerebral metastases and each received fractionated whole-brain irradiation. Whole brain irradiation was found to be an effective means of palliating ovarian cancer metastatic to the brain, with symptomatic response achieved in 23 women, 16 of whom were palliated until death.

The role of selective irradiation in the management of recurrent or persistent ovarian cancer involving the vagina or rectum, after initial surgery or surgery with chemotherapy, was investigated by Firat and Erickson.¹⁶ Twenty eight women received selective irradiation and were evaluated for local control, survival and quality of life. Vaginal bleeding was controlled in all patients and a complete symptomatic response was achieved in 79% of symptomatic women. Vaginal bleeding or discharge can be palliated effectively in 71-90% of patients.¹⁷

Guideline - Radiation therapy for symptomatic relief and palliation	Level of Evidence	Refs
Symptomatic relief and palliation in women with metastatic or recurrent disease can be achieved with radiation therapy.	IV	15, 16, 17

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13. QUALITY OF LIFE AND PSYCHOSOCIAL ISSUES

BACKGROUND

Quality of life is a multi-dimensional construct that is generally accepted to include several important areas or domains of a person's life: physical functioning, psychological functioning, sexual functioning and spiritual and existential matters.^{1,2} There is support for the concept that cancer has a significant impact on all these major life domains.^{3,4} It has been suggested that using a brief, structured assessment of quality of life before a clinic appointment would be beneficial in identifying concerns in women with ovarian cancer.⁵

Key point:

- A brief structured assessment of quality of life before a clinical appointment may be beneficial in identifying concerns of a woman with ovarian cancer.

The diagnosis of ovarian cancer has a major impact on the quality of life of the woman, her family and friends. While there is evidence to support the use of psychosocial interventions to support the woman and to enhance her quality of life, the treatment team should not lose sight of the role played by the family and friends. Evidence from other cancers and chronic illnesses shows that family and friends can provide emotional and physical support and also provide an opportunity to discuss the disease and its impact.⁶⁻⁸

It is important for clinicians to be aware of the potential impact of the disease on women's quality of life and to have in place strategies for monitoring this, as there is evidence of the benefits of interventions. For example, a meta-analysis of 116 intervention studies showed that cancer patients receiving psycho-educational or psychosocial interventions had much lower rates of anxiety, depression, mood disturbances, nausea, vomiting and pain and, significantly greater knowledge about disease and treatment, than no intervention controls.⁹

Guideline - Psychosocial interventions	Level of Evidence	Refs
Psychosocial interventions can result in lower rates of anxiety and depression, reduced mood disturbances, nausea and vomiting and enhanced knowledge for cancer patients.	I	9

QUALITY OF LIFE ISSUES FOR WOMEN WITH OVARIAN CANCER

A Canadian study of older women's perspectives on living with ovarian cancer found that a significant difference was observed in quality of life before and after the diagnosis.¹⁰ Quality of life is likely to be significantly affected by both the symptoms of the disease and the side-effects of the chemotherapeutic agents used in treatment¹¹ with the severity of disease being cited as a crucial determinant of quality of life.¹²

The focus of management should be the minimisation of the physical and psychosocial impact of the cancer and its treatment, and promotion of optimal functioning. This is especially important in the case of metastatic disease. When ovarian cancer progresses, goals change from cure to prolongation of life, with the best possible quality of life for the patient.¹³

Key point:

- The focus of management should be minimisation of the physical and psychosocial impact of the cancer and its treatment.

Psychological interventions to provide support to ovarian cancer patients emotionally and to enhance their quality of life should be considered an important component of medical care. A multidisciplinary approach to cancer care that includes additional support, such as psychosocial counselling, could be beneficial.¹⁴ Interventions which have proven to be beneficial for other cancers include counselling,¹⁵ relaxation therapy,⁹ education programs¹⁶ and cognitive behavioural interventions.¹⁷ (*See chapter 6 – Multidisciplinary management of women with ovarian cancer*).

Support for women with ovarian cancer may also be found in groups such as peer support programs, telephone support programs and internet groups. (*Refer to the Clinical practice guidelines for the psychosocial care of adults with cancer*).¹⁸ The work of support groups in healthcare settings may be furthered by a multidisciplinary team approach, including psychiatry, social work, nursing and chaplaincy.¹⁹ In rural areas, the general practitioner can play a pivotal role in providing psychosocial support, as part of a multidisciplinary team.

Guideline - Psychosocial interventions that may be beneficial for women with ovarian cancer	Level of Evidence	Refs
Psychosocial interventions that can improve physical, functional and psychological adjustment and may be considered for women with ovarian cancer; include:		
• Counselling and relaxation therapy	I	9
• Education programs to improve pain control	II	16
• Cognitive behavioural interventions	III-2	17

SEXUAL ISSUES AND OVARIAN CANCER

Issues such as surgically-induced menopause, loss of child-bearing capacity, and the impact of a major life-threatening illness figure prominently in the psychological recuperation from ovarian cancer.²⁰ A survey of women with ovarian cancer, without evidence of active disease and not on treatment for at least 2 years, found that 57% reported that their sex lives had been negatively affected by cancer and its treatment. Women under 55 years of age reported a greater sense of loss about their sexual function and fertility.²¹ It is important to recognise that the impact on body image and sexual identity relates not just to the loss of body parts, but encompasses an altered sense of self as a social being.²²

Primary reanastomosis is always feasible following small bowel resection and is usually feasible following colonic resection. A stoma is a not uncommon issue for women with ovarian cancer. Evidence from colorectal cancer patients suggests that overall younger patients and women appear to experience higher levels of adjustment difficulties with a stoma.²³ It has been estimated that one-fifth of women whose sphincter function has been sacrificed suffer from dyspareunia.²³ For those patients who do not require a stoma but undergo ultra-low anastomosis, bowel and sexual function is also impaired.²⁴

A small, qualitative study in the United Kingdom²⁵ highlighted the need for healthcare professionals to be aware of concerns about sexual problems as they relate specifically to ovarian cancer. The recommendation from this study was that training be given to improve communication between women and their doctors in this area. A number of agencies provide communication skills training for doctors in Australia (*see Appendix 9*).

Key point:

- Doctors and other healthcare professionals should be aware of concerns about sexual issues as they relate specifically to ovarian cancer.

ANXIETY AND DEPRESSION

Data from a study of women with mainly advanced ovarian cancer suggest the need for an improved and more frequent assessment of ovarian cancer patients' psychological status, particularly as physical functioning declines, to improve early detection and referral for appropriate treatment.⁵ Impaired physical functioning was the most important predictor of heightened psychological distress, in an analysis involving medical/physical and socio-demographic predictors.⁵

Physiological stressors, such as surgically-induced menopause, steroid therapy and pain during active treatment, place women with ovarian cancer at high risk of depression and anxiety at this time.²⁶ It has been noted that clinically significant depression and anxiety may be more prevalent in patients with epithelial ovarian cancer than previously reported and that future studies of screening for and treating psychological distress are being designed to improve quality of life in these women.²⁷

A study of long term ovarian cancer survivors found that women continued to experience fear of follow-up diagnostic tests and fear of recurrence.²⁸ Another study reported that only one item, uncertainty about the future, negatively influenced quality of life.²⁹

A study of 60 women newly diagnosed with cervical, uterine and ovarian cancer found that the symptoms of depression experienced by women with ovarian cancer approached the level of acute symptoms typically reported by women entering outpatient psychiatric clinics.³⁰ Identification of those at risk of adverse psychosocial outcomes and its early detection and treatment is a crucial step in enhancing the quality of life of women with ovarian cancer.³¹

(Refer to 'Appropriate referral and specialised interventions for specific problems' –Table 5. Reproduced with permission, from the Clinical practice guidelines for the psychosocial care of adults with cancer).¹⁸

IMPACT ON THE FAMILY

Family members of newly diagnosed cancer patients report high levels of concern and psychological distress.³² Family studies where members have advanced cancer reveal that there may be significant anxiety, mood disturbance and poor mental health.³³ Psychiatric illness is reported in up to one-third of spouses and one-quarter of the offspring of men and women with advanced cancer.³¹ Although partners may feel highly anxious, only a small proportion actively seek out professional assistance.³⁴

Family reactions play a key role in the coping of women with cancer and promotion of more open communication and expression of feelings is generally helpful in adjustment.³¹

THE IMPACT ON HEALTH PROFESSIONALS

In dealing with oncology patients, many of whom have a poor prognosis, clinicians report experiencing frustration and a sense of professional failure.³⁵ Administering palliative or terminal care and a heavy work load have also been identified as contributing factors to professional 'burnout'.³⁵ Oncologists³⁵ and oncology nursing staff have reported high stress levels, with the levels being higher in those staff who are younger, who feel less supported in the ward,^{36,37} and more recent graduates.³⁸

Common sources of stress for clinicians are informing patients of the diagnosis of cancer³⁹ and providing emotional support for women and their families.⁴⁰ Decisions about complex and potentially toxic treatments⁴¹ and ethical and legal issues which arise in patient care add a further dimension of complexity to clinical work.

Clinical training often provides little preparation for the intensity of grief, anger, frustration and resentment displayed by patients and their families.⁴² Many clinicians may have unrealistic expectations about their role and how they cope. It has been found from areas such as Acquired Immune Deficiency Status (AIDS), that staff who have to

deal with the deaths of large numbers of patients faced an ‘accumulative loss’⁴³ and often feel immersed in suffering with little respite from the need to display warmth and empathy towards others.⁴⁴

It is also important for those working in oncology to be aware of and utilise the skills and expertise of members of multidisciplinary teams when dealing with complex clinical problems.⁴⁵ A study of breast cancer multidisciplinary teams in the United Kingdom found that teams with a number of leaders rather than just one, were most effective. The mental health of these team members was found to be significantly better than in other National Health Service (NHS) teams, those in previous studies of cancer clinicians and those in the general population.⁴⁶ One avenue for reduction of stress is enhancement of communication skills, as there is evidence that those who feel insufficiently trained in communication and management skills experience significantly higher levels of stress.⁴¹

Key point:

- Those who work in oncology should be aware of and utilise the skills and expertise of each member of a multidisciplinary team when dealing with complex clinical problems.

COMMUNICATION AND PROVISION OF INFORMATION

Women with cancer repeatedly report a desire to be well-informed.^{47,48} A Canadian study where 105 women from two university hospital oncology clinics were surveyed about their information needs, found that over 80% of these women wanted detailed information about ovarian cancer during the diagnosis, treatment and post-treatment stages of the disease and less than 1% wished for no explanation at any time point.⁴⁹ The top three categories concerning information were: the status and nature of the cancer, treatment concerns and self-care and empowerment issues.⁴⁹ (The authors noted that this sample consisted mainly of well-educated and urban women, but the issues of self care and empowerment should be considered for all women with ovarian cancer).

Effective communication involves more than the provision of information; it requires a process of individually-tailored explanation, problem-solving and acknowledgment of the woman’s feelings.

There are a number of communication skills that are relevant to any clinical situation and should be considered in any consultation with women with ovarian cancer. These are outlined below:

- Express empathy and listen effectively
- Avoid medical jargon and explain difficult terms
- Provide an interpreter if required
- Give clear specific information
- Actively encourage questions

- Actively check understanding
- Repeat important pieces of information
- Write down relevant information
- Tape the consultation as needed and if wanted
- Send a summary letter as follow up to both the woman and her treatment team

(Adapted from National Breast Cancer Centre's Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer.)⁵⁰

BREAKING THE NEWS ABOUT A DIAGNOSIS OF CANCER OR A RECURRENCE OF DISEASE

Breaking the news of a diagnosis or recurrence cancer can be difficult for both the woman and her doctor. For women with breast cancer it has been found that the way in which the news is given can affect the woman's understanding of the illness and impact on longer term psychological adjustment.⁵¹

Reaction to the diagnosis of a life-threatening illness has been accepted in the criteria for post traumatic stress disorder.⁵² Patients and families should be given time to assimilate information and the opportunity to ask questions and seek further information. One survey found that the diagnosis of persistent disease after conventional treatment for ovarian cancer proved more stressful for women than the diagnosis of the primary disease.⁵³ Some thought should be given as to how the news is provided, the setting and the woman's wishes in regard to support (see Cancer Council NSW booklet, *Breaking Bad News* 1997).⁵⁴

INVOLVEMENT IN DECISION MAKING

The National Health and Medical Research Council (NHMRC) notes that women with breast cancer are encouraged to make their own decisions about treatments or procedures and should be given adequate information on which to base those decisions.⁵⁵ Of women with ovarian cancer surveyed in two oncology clinics in Canada, the majority wanted to share cancer decision-making with their doctors - over 63% at diagnosis, 60% at treatment and 62% after treatment.⁴⁹

It is important to discuss with a woman the level at which she wants to be involved in decision-making. There may be some women who prefer to relinquish control over treatment decisions, particularly if faced with increasingly distressing and unfamiliar situations.⁵⁶ While some cancer patients with advanced disease and with a poorer health status were found to be least likely to seek involvement in their treatment decisions,⁵⁷ one study of women with ovarian cancer found that if the disease was perceived as very serious, or if metastases were present, women of all ages were much more likely ($p=0.001$) to prefer sharing decisions with their doctors, rather than autonomous or passive decision-making.⁴⁹

Key point:

- When ovarian cancer is perceived as being as very serious or when metastases occur, some women prefer to share decisions with doctors, rather than undertake autonomous or passive decision-making.

The following table is from the *Clinical practice guidelines for the psychosocial care of adults with cancer*.¹⁸

Table 5 Appropriate referral and specialised interventions for specific problems

Problem	Discipline to refer to	Specialised interventions with demonstrated effectiveness
Anxiety	Clinical psychologist/ Psychiatrist Social worker	Education; cognitive behavioural therapy including relaxation therapy or graded exposure; supportive psychotherapy (including existential therapy); crisis intervention; drug therapy; alone or in combination
Depression Suicidal ideation	Clinical psychologist/ Psychiatrist Social worker Psychiatrist	Education; cognitive behavioural therapy including problem-solving, and challenging negative cognitions; supportive psychotherapy (including existential therapy); often combined with antidepressant medication. In severe cases, ECT may be considered, or psycho-stimulants in those with advanced disease. Thorough assessment, identification and treatment of any specific stressors including pain, other physical symptoms, delirium. Treatment of identified depression, anxiety (see above)
Post Traumatic Stress Disorder (PTSD)	Clinical psychologist/ Psychiatrist	Cognitive behavioural therapy; supportive psychotherapy (including existential therapy), often in combination with antidepressants such as SSRIs
Body image concerns	Clinical psychologist/ Psychiatrist Social worker	Cognitive behavioural therapy; supportive psychotherapy; crisis interventions; complementary therapies, eg Exercise. Treatment of depression or anxiety which can compound the body image disturbance

Table 5 (contd)

Problem	Discipline to refer to	Specialised interventions with demonstrated effectiveness.
Sexuality concerns	Clinical psychologist/ Psychiatrist Social worker Endocrinologist	Personal and or couples counselling Endocrine assessment and or therapy if hormonal basis for the problem appears likely
Inter-personal problems	Clinical psychologist/ Psychiatrist/ Social Worker	Couples counselling; family counselling
Severe emotional problems	Clinical psychologist/ Psychiatrist	Cognitive behavioural therapy; supportive psychotherapy
Physical symptoms	Clinical psychologist/ Psychiatrist Other specialists	Education; cognitive behavioural therapy including relaxation therapy, guided imagery; supportive psychotherapy; speech therapy, physiotherapy, occupational therapy, nutritional services, dentistry, endocrinology, reconstructive surgery, specialist pain services, odour management
Fertility concerns	Clinical psychologist/ Psychiatrist Endocrinologist Fertility clinic/ Women's Health Nurse/Family Planning	Personal and or couples counselling Hormone assessment and or therapy Fertility counselling, storage of ovarian tissue/ oocytes/embryos and sperm, in vitro fertilisation

Notes:

In addition to the specialities listed above, there may be other local practitioners trained in the interventions listed eg. occupational therapists, specialist nurses. Many general practitioners will also have training in the above interventions.

For women experiencing sexual concerns referral to a gynaecologist/urologist is also recommended because of all the practical issues involved.

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14. ALTERNATIVE AND COMPLEMENTARY THERAPIES

The term ‘alternative therapies’ is used loosely to describe ‘anything outside the orthodox circle of surgery, radiation and chemotherapy’.¹ It can be used to cover a number of different approaches such as diet therapy, vitamins, herbs, relaxation, meditation and acupuncture (*see chapter 16 – Palliative Care*). However, an approach such as relaxation or meditation, which can work alongside conventional therapies, is usually known as a complementary therapy. The effect of many alternative therapies is unknown, and some may in fact cause harm. Most have not been examined rigorously, and some of those that have been examined have not been found effective.^{2,3,4}

Key point:

- There is little evidence that alternative therapies are effective in treating cancer.

Some complementary therapies, such as relaxation and meditation, have been shown to be effective, or at least not harmful, by conventional medical standards.⁵ Both relaxation and meditation are frequently and effectively used by general practitioners and palliative care teams. Complementary therapies, which concentrate on the mind-body relationships, such as prayer, laughter, relaxation and meditation, have been tested in the USA, through the National Institutes of Health, Office of Alternative Medicine and have been shown to be effective or valuable.^{6,7,8} There is evidence from randomised trials to support the value of hypnosis for cancer pain and nausea; relaxation therapy, music therapy, and massage for anxiety; and acupuncture for nausea.⁹

Guideline - Relaxation therapy	Level of Evidence	Refs
Relaxation therapy has been shown to be effective and non-harmful in managing patients with cancer pain.	I	5

Both alternative and complementary therapies are used by many Australians. Women are significantly more likely to use alternative products than men, especially vitamin and mineral supplements, evening primrose oil, aroma therapy oils and homeopathic medicines.¹⁰ Both in Australia and overseas, studies have demonstrated that up to 54% of adults with cancer use alternative therapies.^{11,12,13,14,15}

Amongst the users of alternative therapies in the study by Begbie *et al.*¹¹ the main reasons for using alternative therapies were:

- a new source of hope (49%);
- a preference for natural therapy (40%);
- the impression that it is a non toxic therapy (37%);
- a supportive alternative practitioner (29%);
- to try something different (23%); and
- a sense of greater personal involvement (14%)

The therapies often used by those using alternative therapies ¹¹ were:

- relaxation / meditation (59%);
- diet therapy (57%);
- megavitamins (43%);
- positive imagery (44%);
- aith/spiritual healing (30%);
- naturopathy (27%);
- immune therapy (17%);
- homeopathy (16%); and
- acupuncture (11%)

Seventy-five percent of people using alternative therapies used more than one (median 3, range 1-8).¹¹

USE OF ALTERNATIVE AND COMPLEMENTARY MEDICINE BY WOMEN WITH GYNAECOLOGIC CANCERS

A small American study (based on telephone interviews of women identified from a gynaecologic clinic) found that 51% of women had taken herbs sometime since they were diagnosed with ovarian cancer. Most herb use occurred concurrently with chemotherapy. Only 12% of women used a herbalist or other health practitioner for guidance in the use of the herbs.¹⁶

An outpatient study in a Midwestern university looked at use of complementary and alternative therapies (CAT) by patients with gynaecologic cancers over a 3 month period, using an anonymous questionnaire. There were 113 respondents. Of these 60% were being treated with chemotherapy with or without radiation therapy. Fifty-six (49.6%) had used CAT since their diagnosis. As expected, many women used multiple types of CAT, with 46% ingesting some kind of CAT. Products ingested included herbal therapies and plant extracts, high-dose vitamins and/or minerals, medicinal teas and shark cartilage.

Forty-four women (79% of users) used a psychological or spiritual therapy. The most common answer written in on the questionnaire was prayer. The majority of users hoped to achieve some benefit from CAT as an alternative therapy to directly fight the cancer (36%) or to increase the body's ability to fight the cancer (64%).¹⁷

COMMUNICATION ISSUES

Many cancer patients using alternative therapies do not discuss it with their doctor.¹¹ Presumably these patients are not asked or choose not to tell their doctors. It can be assumed that a negative attitude from health care providers about alternative therapies will inhibit frank discussion. Such inhibition means that women will not learn of support of, or concerns for, the way in which the alternative or complementary therapies may affect the conventional treatment patterns.

It has been suggested that doctors of women with gynaecologic cancer should ask these women early about CAT usage, during the initiation of cancer care.¹⁷ This could increase awareness of the potential for herb-drug interactions, such as the effect on chemotherapy and clarify the reasons why patients are using CAT. It may be able to shed light on issues not being addressed to the patient's satisfaction. 'An oncologist is likely to increase personal rapport and encourage patient trust by discussing this common practice'.¹⁷

Key point:

- **It is important for the clinician to be aware of all medication the patient is taking, to avoid adverse interactions with drugs.**

For many women, feeling that they can assume some control of the treatment of their disease is psychologically empowering. The physical problems that may arise from interference with conventional therapies may be attenuated by the strong psychological value of the alternative therapy. If conventional therapy holds little hope of cure for women, it is understandable that they seek other solutions. Clinicians should also be aware that the decision to use alternative therapies may not be based on the same philosophical approach as that used by their health care providers.

It is to everyone's advantage if women are able to discuss alternative therapies openly, knowing that they will continue to receive support and understanding from their health care providers, whether or not they agree with the therapy being used.

Key point:

- It is advantageous for a woman with ovarian cancer to be asked about her use of alternative and complementary treatments. This is even more important for women advanced and recurrent disease, as they may turn to these treatments when other conventional treatments fail to cure the disease.
- It is important for the clinician to be supportive of women taking alternative therapies, within the context of cost and safety issues.

SAFETY ISSUES

There are safety issues to be considered in the use of therapies that alter diet or introduce supplements into the diet. While the content of some substances is uncontrolled and has not been tested for safety, some may be intrinsically toxic. The safety of megavitamins, particularly those that are the fat-soluble has been questioned and there is the potential for high doses of vitamin A to cause headaches due to raised intracranial pressure.¹⁸

COST

The cost of alternative therapies needs to be explored with the woman. In a study in South Australia,¹ mean monthly expenditure on alternative therapies was \$10, with a range of \$1-\$500. However, some therapies are very expensive and the patient may be required to pay the full cost with no government subsidy/health fund rebate (*see chapter 18 – Economic implications for guideline implementation*).

(Adapted with permission from the National Breast Cancer Centre. Clinical practice guidelines for the management of advanced breast cancer.)¹⁹

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15. FOLLOW UP

FOLLOW UP POST-TREATMENT IN WOMEN WITH EPITHELIAL OVARIAN CANCER

Follow up is designed to provide appropriate medical review to support the physical and emotional needs of women following treatment. It can also establish a conduit through which a woman can communicate with an expert about her current health status, psychological issues, and the experience of the cancer journey. A definitive program is useful in providing this level of support. Women with ovarian cancer expect such a program, to offer continuity and support, regardless that the disease stage at diagnosis is predominantly advanced, and that the ultimate prognosis is usually poor.

The options for follow up, and the implications and possible consequences of these options should be discussed with the woman at the completion of the primary treatment. This discussion should include the option of no follow up. Some women will decide that the psychological trauma of follow up is too unsettling and opt to come only if they have symptoms. Others will be keen for surveillance – even though they may experience great anxiety prior to the follow-up visits.

There should also be time provided for personal discussion with the clinician about the implications of monitoring progress using CA125. The implications of stable, fluctuating and rising levels of CA125 should be discussed.

SURVIVORSHIP ISSUES

Some women who survive ovarian cancer, or who are living with ovarian cancer, have reported positive changes such as a new appreciation of life, a strengthening of relationships or family ties or a more “live for the moment” philosophy.¹ However, many women report issues related to survival. A small study of 18 Canadian women living with ovarian cancer, found that the most significant challenges faced by women with ovarian cancer could be grouped into three main themes: living with uncertainty, the stigma of cancer and facing death.²

The members of the treatment team should be aware that follow up visits may be a source of anxiety for women, with concerns about the testing involved and the possibility of a recurrence being diagnosed. Women surveyed about their experiences of recurrent disease have described the experience of waiting for a recurrence as frightening and the follow up appointments were anticipated with fear that their ovarian cancer had recurred. Tumour markers such as CA125 were a signal that their cancer was recurring and they found the periods of waiting difficult. A rising CA125 had significant meaning, and triggered panic, profound fear and devastation knowing it meant a recurrence of the cancer.³

In a study of women with stage I and II ovarian cancer, who had survived 5 years or more after completion of treatment, survivors reported significant amounts of distress related to fear of a second cancer, recurrence of the cancer, and future diagnostic tests. In relation to specific survivorship stressors, 18% reported continuing distress since the completion of treatment, and distress related to changes in their appearance as a result of the cancer and/or treatment.⁴ The diagnosis of persistent disease after treatment has been found to be more stressful for women than the initial diagnosis.⁵

TIMING OF FOLLOW UP CONSULTATIONS

COMMON PROGRAM

A woman may be reviewed by either a gynaecological oncologist or medical oncologist. If it is convenient for the woman, she may see her gynaecological oncologist and medical oncologist at alternate visits. The important factor is that follow up be offered regularly. There is no recommended frequency of follow up consultations, but a clear and mutually agreed arrangement, which acknowledges the benefits of an ongoing relationship and the opportunity to deal with issues as they arise, should be negotiated with the woman.

A common follow up program is:

- Review every 2-3 months for 2 years then;
- Review every four months for the next 2 years; and
- Review 6 monthly for a year before moving to annual review.^{6,7}

Key point:

- It is important that a clear and mutually agreed follow up routine be provided at appropriate intervals to all women who have been treated for epithelial ovarian cancer.

FORMAT FOR FOLLOW UP CONSULTATIONS

The basic format of consultation is to have the history updated, physical examination including pelvic examination undertaken and blood taken for CA125 cancer marker. In those women who initially had an elevated CA125, relapse of tumour can be accurately identified by the measurement of CA125 and this may be done at each visit.^{6,7,8} It should be noted that the woman's report to the clinician about how she feels will often contain the best index of recurrence for the clinician.

Radiological imaging should not be done routinely, but should be performed if there is clinical or CA125 evidence of recurrence. The rationale for not undertaking imaging should be discussed with the woman.

Key point:

- The CA125 level is an accurate predictor of relapse of epithelial ovarian cancer in those women who initially had a significantly raised CA125.

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16. PALLIATIVE CARE

PALLIATIVE CARE

Hospice and palliative care has been defined as a concept of care which provides coordinated medical, nursing and allied services for people who have a terminal illness, delivered where possible in the environment of the person's choice, and which provides physical, psychological, emotional and spiritual support for patients and for patients' families and friends. The provision of hospice and palliative care services includes grief and bereavement support for the family and other carers during the life of the patient, and continuing after death,¹ where appropriate.

Palliative care:

- stresses advanced planning rather than crisis intervention;
- offers a multidisciplinary model of care which is focussed on the whole person within their social and emotional context, rather than just the one disease; and
- requires a good knowledge of the natural history of the disease and relevant oncological practice.²

Ovarian cancer may affect women of all ages; including some women as young as in their 30s and 40s, creating additional distress in all areas. It is therefore desirable that there is an opportunity for early referral for psychological, emotional and social support for all women. Early attention to symptom control may alleviate many other problems which can cause distress.

The natural history of ovarian cancer, especially for women with stage III, stage IV and recurrent disease, is that there will be one or several remissions with therapy, before the final failure of treatment. Ovarian cancer frequently behaves as a chronic disease, with periods of disability and improvement, and a later final period of severely diminished personal function, prior to death. Thus, although cure may not be a realistic aim, significant long-term remissions mean that treatment should be recommended.

Key points:

- The history of advanced ovarian cancer is usually of one or several remissions to therapy before finally failure of treatment.
- Early attention to psychosocial support is important.

ORGANISATION OF PALLIATIVE CARE

Palliative care services have evolved in variety of ways, but in metropolitan areas specialist consultant palliative care services are generally available to give advice on symptom control and other problems, both in hospital and in the community. Access to hospice or specialist palliative care beds is also generally available.

In rural and remote areas access to specialist palliative care is limited. General practitioners will be able to supply significant support, further consultations may be by telephone or video conferencing and access to specialist inpatient care may be limited by distance.

Most palliative care will be provided by the existing network of carers, co-ordinated by either the general practitioner and/or treating gynaecology oncologist, who will draw on other health professionals as particular expertise is required. The National Strategy for Palliative Care encourages the use of existing networks and community services, working with palliative care specialists, to deliver palliative care.³

As the availability of specialist palliative care increases, and particularly with complex or difficult to resolve issues, specialist palliative care teams should be utilised to achieve optimum outcomes for the woman with ovarian cancer. Good communication at all times between all members of the treating team is essential.

The involvement of a specialist palliative care team in the care of patients with cancer in general increases patient and carer satisfaction, increases the amount of time spent at home by patients, reduces the time spent in hospital, reduces the overall cost of care and increases the likelihood of the patient dying where they wished to be.⁴

Guideline - Specialist palliative care services	Level of Evidence	Refs
Specialist palliative care services can improve outcomes in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction and control of pain, symptoms and family anxiety.	I	4

TIMING OF REFERRAL

Early referral will often be helpful. The precise timing at which the services of a palliative care specialist are introduced will depend predominantly on the patient's wishes, the individual illness, its varied symptom complexes; and psychosocial factors. Referral is facilitated if the palliative care professionals are already an integral part of the multidisciplinary treatment team.

Benefits from early referral include allowing the establishment of personal contact and exploration of options for future care, without any imperative for immediate decisions. This stresses active advanced planning, rather than crisis intervention.

The involvement of palliative care services does not preclude, and will frequently support, the continuation or commencement of active treatment programs.

Symptom relief, personal and family support and death preparation are a part of the care plan from the time of diagnosis, not merely introduced when active therapy options are not working.

SYMPTOM RELIEF

The principles of symptom control include:

- assessment of the symptom, including understanding the meaning ascribed by the patient. (This requires active listening on the part of the clinician, with allowance made for cultural factors);
- explanation of the likely cause;
- investigations (should be reserved for situations where a decision is required about continuing the same treatment plan or making a change);
- institution of treatment based on the known or likely causes of the symptoms, available options for treatment, and the wishes of the patient; and
- monitoring of the response to treatment and modification as necessary.

There is no set model of symptoms and progression of disease. In some cases, functional disturbance may precede structural change, as proven by clinical signs or radiological evidence of disease progression, but equally the reverse may apply, where an elevated tumour marker may precede by several months any objective evidence of recurrent or progressive disease.

Physical symptoms that are commonly reported in ovarian cancer are:

- Pain
- Fatigue
- Degrees of nausea and vomiting and constipation, culminating in malignant bowel obstruction
- Abdominal distension (from tumour, ascites or distended bowel)
- Dyspnoea (from pleural effusion or splinting of the diaphragm)

For guidelines on the management of symptoms not specifically addressed here, refer to *Therapeutic Guidelines: Palliative Care* (1st edition, Sept, 2001).⁵

PAIN

Over 70% of people with terminal cancer experience pain. Except in rare cases, cancer pain should be treatable.⁶ The pain management plan should aim to achieve pain relief both night and by day, at both rest and on movement.

Key point:

The pain management plan should aim to achieve pain relief both night and by day, at both rest and on movement.

It may include pharmacological and non-pharmacological methods. Some patients will benefit from non-pharmacological methods of pain relief such as relaxation⁷ or acupuncture.

Best care is provided when the woman and her family are offered as much information as possible about the cause of any pain experienced, and all help should be given to ensure that they understand and accept the recommended management plan. The management plan will need to include instructions for dealing with breakthrough or exceptional pain. All members of the treatment team should be aware of the management plan, to ensure a consistency of approach. As part of the plan, the woman and her supporters will need to be made aware of the mechanism for continued assessment and the follow up that is available. The details can be written down, if necessary.

RELIEF OF PAIN

If oral medications for pain have been in use, the route should be changed to a parenteral one. The subcutaneous route is frequently used for morphine, fentanyl or hydromorphone. Transdermal fentanyl¹ could be considered once stable pain control has been achieved and if the dose range is suitable.

RELIEF OF COLIC

Colicky pain may be a feature. Hyoscine butylbromide can be used subcutaneously. Its anti-cholinergic action may be helpful in reducing secretions and therefore reducing vomiting.

PAIN NOT CONTROLLED BY CONVENTIONAL ANALGESIA

The use of co-analgesics, nerve blocks or epidural delivery of analgesics, managed by a specialist in palliative care or pain management should be considered for women with uncontrolled pain.⁸

(For further information on the management of acute and severe pain in patients with cancer, see: *Acute pain management: scientific evidence.NHMRC.1998*⁹ and *Management of severe pain*. NHMRC. AGPS. 1998).¹⁰

BOWEL OBSTRUCTION

Bowel obstruction is a frequent complication of ovarian cancer, occurring in 15% -25% of patients overall, and in 45% of patients with advanced ovarian cancer. In localised disease, surgery may be considered, but the usual pattern of widespread peritoneal and omental disease leading to multiple sites of obstruction usually precludes this approach.

Medical management of bowel obstruction may include:

- **Relief of nausea and vomiting**

If obstruction is incomplete, use of a prokinetic anti-emetic such as metoclopramide can be considered as well as manoeuvres to clear the lower bowel of faecal material. If obstruction is complete, a centrally acting anti-emetic is recommended such as haloperidol (S/C) or prochlorperazine (PR).

- **Rehydration**

If the volume of loss can be reduced, reasonable levels of hydration for comfort can be maintained with S/C normal saline, 1 litre/24 hours, which can still allow care at home.¹¹

High dose steroids (S/C dexamethasone for 3-5 days) have been tried but there are no conclusive studies of efficacy.¹²

Octreotide has been used to reduce secretions and therefore reduce vomiting (or allow removal of nasogastric tube if one has been inserted).¹¹

- **Venting Gastrostomy**

In patients where vomiting is the major symptom, there may be a role for venting-gastrostomy. This can offer the patient a good quality of life, without vomiting or a nasogastric tube, as well as the possibility of eating and drinking for enjoyment, but not nutrition.¹³

ASCITES

Ascites continues to be an unsolved problem. Mechanical relief is often unavoidable, but is time limited, not least because of loss of protein.

Anecdotal mention of spironolactone, with or without steroids, may slow the rate of accumulation of ascites.

Evidence for shunting procedures is sparse, and experience is varied. The Le Vein shunt has been used in a series in Adelaide. The criteria for use have included:

- high production rate - at least one litre weekly;
- no particulate matter (i.e. bloody or chylous ascites);
- life expectancy of at least 2 months.

(For further information also see *Appendix 5*).

PERSONAL AND FAMILY SUPPORT

Both the woman and her family will need physical, emotional and psychosocial support during the course of her illness, but the extent or nature of that support will vary for a number of reasons, including the impact of the disease on functioning, psychological adjustment, individual differences in coping and the strategies used. Support may be provided by other members of the family, friends, members of the treatment team, peer group programs or through access to telephone or Internet programs.

(For further information about support services see *Appendix 9* and the *Clinical practice guidelines for the psychosocial support of adults with cancer*).¹⁴

DEATH PREPARATION

Death preparation involves initial recognition of imminent death (by patient, family, doctor) as a possible or likely outcome, which gives a perspective on:

- the value of time;
- priorities for action; and
- balancing losses and gains.

If the disease is clearly progressing, despite the best therapeutic efforts, the focus should change to death preparation, with strong emphasis on achievement of goals and ambitions and planning for later critical events, during a time when the patient's perspective is clear and well understood.

Prolongation of life strategies needs to be tempered by measures to maintain and improve quality of life by controlling functional disturbances caused by the cancer and by good symptom control. In some cases, when the disease has progressed faster than expected, the woman and her family may have some issues not completely resolved, such as regret about the late diagnosis.

On the death of the woman, a formal letter of condolence from the treating clinician is important in facilitating active bereavement.

Key points:

- Prolongation of life strategies needs to be tempered by measures to maintain and improve quality of life by controlling functional disturbances caused by the cancer and by good symptom control.
- On the death of the women, a formal letter of condolence from the treating clinician is important in facilitating active bereavement.

(For further information about end-of-life issues see the *Clinical practice guidelines for the psychosocial care of adults with cancer*).¹⁴

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17. CLINICAL TRIALS

The treatment of ovarian cancer is an evolving area and important clinical questions remain unanswered in the areas of surgery, chemotherapy and radiation therapy, at all stages from early disease to relapse. The gold standard test for new treatments must remain the randomised controlled trial. Clinical trials help to define new standards of care and are critical to improving standard therapy. The introduction of novel, target directed anticancer therapies requires new study designs as the phase I/II/III paradigm may not be relevant. Relapsed disease is seen as an important area for randomised controlled trials.¹

It has been noted that quality of life is an important end point,¹ although it is cautioned that quality of life measure in clinical trials should be interpreted carefully. All new clinical trials will include quality of life measures.

CLINICAL TRIALS

Clinical trials usually involve the testing of new treatments, or of new indications for treatments established for other indications. The development of a new treatment involves progression through three phases of clinical trials:

- Phase I trials are designed to evaluate the relationship between dose and toxicity, and aim to establish a tolerable schedule of administration. They usually include only small numbers of patients who have already received the standard treatments for their condition.
- Phase II trials are designed to screen new treatments for their anti-tumour effects, in order to identify those worthy of further evaluation. In phase II trials, a series of patients with a particular type of cancer receive the new treatment to determine the proportion in whom the tumours will shrink. If this proportion of patients responding compares favourably with other available treatments, then the usefulness of the treatment in patient management is assessed in a phase III trial.
- In phase III trials, patients are randomly allocated to receive either the new treatment or the best available standard treatment. Ideally the two arms of the treatment should be indistinguishable, so if possible an inactive placebo is used to mask the standard treatment arm. This is rarely possible in trials of chemotherapy drugs due to their side effects.

In Australia clinical trials must be approved by an Institutional Ethics Committee. Women must be provided with relevant information and complete information about the trial protocol and provide their written consent before they take part. Entry into a trial must be voluntary and refusal to enter a trial or a decision to withdraw later without giving a reason must not affect the woman's relationship with her treating practitioner.

(Acknowledgement: Clinical practice guidelines for the management of advanced breast cancer. National Breast Cancer Centre. 2001).²

PARTICIPATION IN CLINICAL TRIALS

Currently, only a few of all the patients suffering from any cancer participate in clinical trials. This may be a reflection of a lack of awareness by both clinicians and patients, although not all patients offered participation in a trial take part, commonly citing that they fear being used as a 'guinea pig'.

A participant survey conducted by the Coalition of National Cancer Cooperative Groups Survey in the USA (1998) showed that 85% of patients were not aware of the existence of clinical trials and that participation was an option.

The doctor most frequently does not offer the opportunity of participation. This may be because of a lack of awareness of the existence of the trial, or some clinicians fear that trial participation denies them individual clinical autonomy.

While the possibility of selection bias should be noted³, there is some indirect evidence to suggest that participation in clinical trials results in better outcomes when compared to patients given a similar treatment outside a clinical trial setting.^{4,5,6} This advantage is independent of stage. Treatment adherence may be sub-optimal outside the quality assurance framework of a clinical trial.

Guideline - Clinical trial participation	Level of Evidence	Refs
Cancer patients who participate in clinical trials may have better outcomes than those given the same treatment outside a clinical trial setting. It is appropriate for clinicians to discuss participation in clinical trials with women who have ovarian cancer.	III-I	4

Better outcomes may be due to:

- increased quality control mechanisms within the framework of controlled trials;
- standardised procedures;
- independent data review; and
- early relapse detection and treatment.

Patients who were surveyed by the Coalition of National Cancer Cooperative Groups and were treated as part of a trial reported this as a positive experience, and that the role of the doctor was pivotal to recruitment.

- 98% reported that they had received excellent care and were treated with dignity and respect, and that they viewed trial participation as a positive experience;
- 82% were happy that they did not perceive that they were treated as guinea pigs, nor were there unnecessary tests; and
- 78% would recommend trial participation to others.

When asked about their reasons for participating in a trial:

- 75% felt they were accessing best quality care;
- 62% cited that they were gaining access to newer or better treatment;
- 70% were happy to benefit others; and
- 40% felt that they got more care and attention.

The major focus of both the medical and consumer groups is to examine the overall value to the individual patients of participation in a clinical trial and comparing their survival rates with those patients treated outside trials with currently recognised standard therapy.

SOURCES OF INFORMATION ABOUT CLINICAL TRIALS

Information about clinical trials is available to patients and clinicians through a number of sources. The information provided covers aspects such as an explanation of clinical trials and issues of consent, as well as providing details of specific clinical trials being conducted.

Information may be obtained from:

- Australian and New Zealand Gynaecological Oncology Group (ANZGOG)
- National Health & Medical Research Council (NHMRC) Clinical Trials Centre
- Database of Cancer Research in Australia (CARA)
- The Cancer Council Australia
- State and Territory Cancer Councils
- Peter MacCallum Cancer Institute

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18. ECONOMIC IMPLICATIONS FOR GUIDELINE IMPLEMENTATION

While little formal research has been undertaken in relation to the costs of epithelial ovarian cancer, its economic impact would appear to be significant, particularly as so many cases are diagnosed too late for cure to be achieved. Economic factors can be identified in relation to direct and indirect costs, and to loss of quality of life and of loss of life itself. Due to the lack of economic data at this time, it may be useful to consider the economic impact of ovarian cancer in terms of present costs and then of future costs and benefits.

The first consideration of present costs relates to lives lost and to life years lost. Whatever measure is used, the costs of lost productivity include estimates of the value of paid work and the value of unpaid work, such as work in the household and voluntary work. These costs relating to women with ovarian cancer are borne by society.

An important component of present costs are treatment costs, which include medical and hospital services, drugs eg chemotherapy recommendations and tests, for example, those relating to surgical staging. These costs are primarily borne within the health care system, although co-payments and indirect costs such as time for treatment are borne by the patients themselves. The direct health care costs of malignant ovarian cancer were AU\$13.5 million in the 1993/94 financial year. Hospital costs were by far the greatest proportion (87%) of the direct costs of ovarian cancer in 1993/1994. This figure also includes medical services, pharmaceuticals, and allied health services. If all ovarian cancers are included (malignant, benign, in situ and uncertain) the cost was AU\$31.3 million. Ovarian cancer is estimated to be the fourteenth most costly cancer to treat with an estimated lifetime cost of nearly AU\$13,000 per new case.¹

Another component of present costs is that related to alternative and complementary therapies. While alternative and complementary therapies are widely used by people with cancer, there is very little information available on expenditure on alternative and complementary products and services. These costs are almost all out-of-pocket and borne by patients. In 1993 Australians spent an estimated AU\$309 million per year on alternative therapists and AU\$621 million per year on alternative therapies, which exceeds the patient contribution of AU\$360 million to standard pharmaceuticals in 1992/1993.² (*See chapter 14 – Alternative and complementary therapies*)

Current costs which have not been sufficiently documented include costs of home care provided by health professionals and informal care provided by family and friends,³ including time lost from employment when accompanying the woman with ovarian cancer to medical appointments.

FUTURE COSTS AND BENEFITS

When effective screening tests become available, economic evaluation will be required, including identification of the most appropriate target population, to ensure optimal use of resources. From an economic perspective, no implementable prevention strategies have yet been identified, so no prevention cost estimates are yet possible. Future

costs for best practice will include support for clinical trials, for example relating to radiation therapy. The development of national databases to provide comprehensive and consistent data should be accompanied by cost/benefit analysis.

IMPLICATIONS FOR IMPLEMENTATION

The implementation of the *Clinical practice guidelines for the management of women with epithelial ovarian cancer* may impact on future health care costs in a number of areas:

- the training of gynaecological oncologists (*see chapter 6 – Multidisciplinary management of women with ovarian cancer and Appendix 4, Gynaecological oncology training requirements*);
- the provision of nurses with appropriate skills in the area of gynaecological cancer (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*);
- the establishment of multidisciplinary care centres or the development of facilities to support access to the expertise of multidisciplinary care teams through methods such as video conferencing (*see chapter 6 – Multidisciplinary management of women with ovarian cancer*);
- the training of specialist gynaecological pathologists (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the cost of establishing centres for education and research in the histopathology of rare and variant ovarian tumours (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the cost of tests to confirm diagnosis of rare and variant ovarian tumours (*see chapter 5 – The biology and pathology of ovarian tumours*);
- the conduct of clinical trials of different treatment modalities such as chemotherapy and radiotherapy (*see chapter 17 – Clinical trials*);
- the provision of home support where a woman with ovarian cancer has a young family and;
- the provision of financial support when a woman with ovarian cancer is no longer able to work (*see chapter 13 – Quality of life and psychosocial issues*).

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GLOSSARY

Abdominal	The front portion of the body between the chest and the hips.
Abdominal palpation	A part of physical diagnosis where the hand applies light pressure to the abdomen to determine the condition of the parts beneath the surface.
Adjuvant therapy	A treatment that assists or aids another. The term is used to describe the use of chemotherapy or hormone treatment with or after primary surgery, the aim being to eradicate hidden cancer cells which were not removed at the operation.
Adenocarcinoma	Cancer derived from glandular tissue or in which cells form recognisable glandular structures.
Adnexa	Accessory organs - Fallopian tubes and ovaries.
Adnexal mass - uterine	A growth on an accessory organ such as fallopian tube or ovary.
Aetiology	Cause or causality.
Age-standardised rate	A procedure for adjusting rates eg death rates, designed to minimise the effects of differences in age composition when comparing rates for different populations.
Alcian blue	A dye used to mark tissue to distinguish it from other samples taken during an operation.
Alpha interferon	A glycoprotein used in the treatment of cancer. One of its effects is to inhibit cell growth.
Alternative therapies	A term used to loosely describe any type of therapy outside the orthodox circle of surgery, radiation or chemotherapy. Alternative therapies include things such as diet therapy, vitamins and herbs. (<i>See also Complementary therapies</i>)
Anastomosis	A surgical connection made between two normally distinct features, for example where repairs are necessary to the bowel following surgery.
Anovulatory	No release of egg from the ovary.
Anxiety	A diffuse highly unpleasant, often vague feeling of apprehension, accompanied by bodily sensations such as pounding heart or sweating. There is an associated anticipation of future misfortune or danger, external or internal.
Apoptosis	Process of cell death.

APRT	Abdomino-pelvic radiation therapy.
Ascites	Abnormal build up of fluid within the peritoneal cavity.
Atypia	Not regular or not conforming to type.
Autosome/autosomal	The chromosomes in the body not concerned with the determination of gender.
Basal pneumonitis	Low level inflammation of lung tissue. A side effect of radiation therapy.
Benign	Not malignant.
Bi-manual pelvic examination	An examination of the pelvis where the doctor feels the organs using fingers inserted into the vagina and/or the rectum.
Body mass index (BMI)	Ratio of weight in kilograms to height in metres ² . Used as an estimate of total body fat.
Borderline ovarian tumours	A group of epithelial tumours that are not as aggressive as other forms of ovarian cancer. Also referred to as low malignant potential tumours.
Bowel obstruction	A blockage of the bowel which may be the result of surgery or the growth of a tumour.
Brachytherapy	An implant of radioactive materials placed directly near the tumour.
Broad ligament (of uterus)	A band of tissues that connects bones or supports viscera. A double layer of peritoneum.
Brenner tumours	A rare type of epithelial ovarian cancer.
Budding	Asexual reproduction in which a portion of the cell body is thrust out and then becomes separated, forming a new individual.
CA125	A protein or tumour marker which can be detected in blood serum. Elevated levels may also be associated with other malignancies or benign conditions. It is most often raised in serous and less frequently in mucinous cancer and is found in over 80% of non-mucinous epithelial ovarian cancers.
Cancericidal	Destructive to cancer cells.
Cancer registry	A centre in each state and territory where details of cancers are collected to monitor trends.
Carcinoma	Malignant growth; cancer.
Carcinomatosis	The condition of widespread dissemination of cancer throughout the body.

Carboplatin	An anti-neoplastic agent which works by impairing the cancer cells' DNA function.
Case control study	A study that starts with the identification of people with the disease of interest and uses a suitable group without the disease for comparison to assess possible factors involved in the development of the disease. Such studies are often called retrospective as they look back from the outcome to its causes.
Cellular stratification	A pattern of cells where they are arranged in layers.
Chemo-responsiveness	The measure of how a tumour reacts when an anti-tumour drug is administered.
Chemotherapy	The use of drugs or a combination of drugs to kill cancer cells or prevent or slow their growth.
Cisplatin	Chemotherapy agent that works to prevent cancer cells dividing and multiplying.
Clear cell carcinoma	A form of cancer where the cytoplasm of the cell is clear.
Clinical practice guidelines	The bringing together by a central authority of the best available evidence to support recommendations for the prevention, diagnosis and treatment of cancer.
Complementary therapies	A term used to refer to therapies, such as meditation and relaxation therapy, that can work alongside conventional therapy.
Contralateral ovary	The ovary on the opposite side to that containing the tumour.
Counselling	Refers generically to a form of supportive care delivered by all health professionals. There are differing levels of sophistication depending on the training and experiences of the practitioner involved.
Curettage	Removal of growths or other material from wall of a cavity or other surface using a spoon-shaped instrument called a curet.
Cyclophosphamide	An agent used during chemotherapy to kill cancer cells.
Cystadenoma	A cystoma (a cystic tumour) blended with adenoma.
Cystectomy	Removal of an ovary.
Cystitis	Inflammation of the urinary bladder.
Cytokeratins	Any of a group of proteins found in keratin filaments.
Cytology	The study of the origin, structure, function and pathology of cells.

Cytological scraping	(See also diaphragmatic scrapings) Tissue from sites in the body to be tested for the presence of cancer cells.
Cytoreductive surgery	Surgery to remove as much of the tumour as possible to allow for the best possible outcome and to facilitate the effect of chemotherapy.
De novo	Arising as a separate entity, (as new).
Depression	A pervasive or sustained lowering of mood or the loss of interest in nearly all activities. When used clinically, it is a cluster of symptoms or a syndrome, whose other features may include: changes in appetite or weight, sleep or psychomotor activity; decreased energy; feelings of worthlessness or guilt; difficulty thinking, concentrating or making decisions; or recurrent thoughts of death or suicide ideation, plans or attempts.
Desmoplastic	Characterised by or causing the formation or development of fibrous tissue.
Diaphragmatic scrapings	Tissue collected from the diaphragm to be tested for the presence of cancer cells.
Docetaxel	Agent used in chemotherapy which inhibits cell division.
Doppler ultrasound	A technique that uses ultrasonic waves to identify abnormal blood flow patterns which may indicate the presence of a tumour.
Doxorubicin/liposomal doxorubicin	Agent used in chemotherapy.
Dysplasia	An abnormality in development.
Efficacy	The ability of a drug or intervention to produce the desired beneficial effect under ideal conditions.
Endocervix	The mucous membrane lining the canal of the cervix (neck of the womb); the region where the cervix opens into the uterine cavity.
Endometriosis	A condition where endometrial-like tissue is found in various locations within the pelvic cavity and elsewhere
Endometrioid	Resembling the endometrium.
Endometrium	The mucous membrane lining the uterus.
Epidemiology	The study of the distribution and determinants of health-related states or events in specified populations and the application of this study to the control of health problems.

Epithelial ovarian cancer	Cancer of the ovary arising in the epithelium (the 'skin' or outer cells) covering the ovary.
Epithelial tufting	Small clumps or clusters forming in the epithelium.
Epithelium	The cellular covering ('skin') of internal and external surfaces of the body consisting of cells joined by small amounts of cementing substances. It is classified according to the number of layers deep and the shape of the superficial cells.
Fat stains	Dyes used to demonstrate fat in tissue being examined under the microscope.
FIGO	Federation Internationale de Gynecologie et d'Obstetrique.
First line therapy	The first administration of therapy such as chemotherapy following surgical removal of the tumour.
Fistulisation	The surgical creation of a fistula; an abnormal tubelike passage within body tissue, usually between two internal organs or leading from an internal organ to the body surface.
Foci	The centre of a process.
Frozen section	A specimen of tissue that has been quick frozen, cut and stained immediately for rapid diagnosis of malignant tissue.
Gastroparesis	Partial or complete paralysis affecting the stomach.
Gemcitabine	An anti-neoplastic agent, given intravenously, which acts by inhibiting DNA and RNA synthesis in cancer cells.
Gene	One of the biologic units of heredity which are situated in specific locations on particular chromosomes in the body. Genes make up the DNA molecules that control cell reproduction and function.
Genesis	(see also histogenesis, pathogenesis, tumourgenesis) The start or origin of a process. Used to denote the production or development of an object or state eg tumorigenesis - the beginning of the development of a tumour.
Genome	A complete set of hereditary factors in the chromosomes.
Germline mutations	Changes in a particular sequence of cells that can be passed on to offspring.
GOG	Gynecologic Oncology Group (USA).
Grade	A score for the degree of cancer growth.

Gynaecological oncologist	A specialist in Obstetrics and Gynaecology awarded the Fellowship of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (FRANZCOG), who has completed a formal three year training program in gynaecological cancer care and has passed the examination for the Certificate of Gynaecological Oncology.
H&E sections	Use of a stain (Hematoxylin-eosin) for routine examination of tissue under a microscope. Cell nuclei are stained deep blue and the surrounds (cytoplasm) pink.
Hepatic enzyme elevation	Increase in the proteins in the liver which acts as catalysts for chemical reactions.
Hilum	Depression or pit at the part of an organ where the vessels and nerves enter.
Histogenesis	The differentiation of cells into specialised tissues forming various organs.
Histology	The study of the minute structure, composition and function of tissues.
HNPCC	Hereditary non-polyposis colorectal cancer. There are fewer polyps than in familial adenomatous polyposis and they tend to occur in the proximal colon.
Homologous	Corresponding in structure, position and origin.
Hypercoagulation	Excessive formation of clots in the blood.
Hyperthyroidism	Excessive activity of the thyroid gland producing symptoms such as weight loss, palpitations and weakness.
Hysterectomy	Surgical removal of the uterus (womb).
ICD	International Classification of Disease.
ICON	International Collaborative of Ovarian Neoplasm Trial.
Ileus	Failure of the appropriate forward movement of bowel contents.
Implants	Material grafted on to a new site or part of the body.
Inanition	Effect of prolonged malnutrition.
Incidence	The number of new cases of illness or disease during a given period in a specified population.
Inclusion cysts	A cyst formed by inclusion of a covering (skin) or lining (gut) in tissue along a line where the body fuses during development.

Infusion	Introduction of a fluid as a saline solution into the blood by gravity flow.
Inguinal	Relating to the groin.
Inhibin	A tumour marker.
Interval debulking	Surgery performed during the first-line chemotherapy but before the completion of the primary treatment.
Intraperitoneal (IP) chemotherapy	Chemotherapy administered through a catheter inserted into the peritoneal cavity
Intravenous (IV) chemotherapy	Administration of a chemotherapy using the veins.
Invasive	Infiltrating the surrounding tissues. A characteristic of malignant tumours.
K-ras	An oncogene mutation.
Laparoscopy	Examination by means of a laparoscope.
Laparotomy	Surgery where an incision is made through the abdominal wall to expose abdominal contents.
Luteinization	The process that takes place in the cells that have matured and discharged eggs.
Lymph nodes	Small, bean-shaped structures (found in the neck, armpit and groin) that filter lymph to prevent harmful agents entering the blood stream. May also be referred to as lymph glands.
Lymphadenectomy	Removal of one or more of the lymph nodes.
Macroscopic	Able to be seen with the naked eye.
Malignant/malignancy	Cancerous.
Malodorous	Having an unpleasant odour or smell.
Menarche	The start of monthly periods.
Menopause	The cessation of monthly periods. This may occur naturally or as a result of surgery or other treatment.
Mesentery	A fold of membrane attaching various organs to the body wall, especially the small intestine to the dorsal wall.
Meta-analysis	A statistical method used to combine the results of different studies on the same topic. Used to pool results from a number of small randomised controlled trials to provide an aggregate that will allow for demonstration of statistically significant results.

Microinvasion	Microscopic extension of malignant cells into adjacent tissue.
Miliary	Lesions resembling millet seeds.
Mitosis	The process of cell division where new cells are formed. Used by the body to replace dead cells.
Morbidity	Term used to report on illness. Can also be used to show persons who were ill, the period of illness and the duration of the illness.
Mortality	Death rate due to a particular cause or disease.
Mortality Hazard Ratio	The ratio of the mortality (hazard) in the treatment or control groups.
Mucinous	Secreting mucous.
Mucositis	Inflammation of the mucous membrane.
Müllerian duct	Paired embryonic ducts that develop into the vagina, uterus and uterine tubes in the female.
Multifocal disease field change	Neoplastic change occurring independently and simultaneously at many sites, in response to the same or related genetic alterations. It may occur as multiple discrete foci (multifocal disease) or as an apparently diffuse process (field effect or field change).
Multidisciplinary care	Multidisciplinary care is the co-ordinated approach using a collaborative group of health professionals and a range of treatment modalities. The team as a whole is responsible for the diagnosis, continuing management and palliative care of the woman with ovarian cancer.
Multidisciplinary team	A group of clinicians and health professionals, from a number of disciplines, working together to manage the care of a patient. The members of the team may include: a gynaecological oncologist, gynaecological pathologist, medical oncologist with special experience in ovarian cancer, radiation oncologist with special experience in ovarian cancer, radiologist with a special interest, general practitioners, specialist nurses, physiotherapists, pharmacists, psychologists, social workers, genetic counsellors, geneticists, and palliative care specialists.
Multi-step adenoma-carcinoma sequence	That sequence of genetic aberrations which predisposes or leads to sufficient genetic instability to cause a full malignant transformation of the affected cells. Conventionally, these steps include firstly a benign neoplastic lesion (ie adenoma) and secondly a malignant neoplastic lesion (i.e. carcinoma).

Mutation	A permanent and transmissible change in genetic material.
Myelosuppression	Suppression of bone marrow activity resulting in a decrease in the number of platelets, red cells and white cells.
Myometrial	The muscular structure of the uterus.
Non-polyposis	Without the formation of numerous polyps.
Nuclear atypia	Irregular or uncommon features in a nucleus.
Nuclei	Plural of nucleus. The body in a cell containing a number of its characteristics.
Nulligravid	Never having given birth.
Omentum	A protective layer of fatty tissue which covers the abdominal organs.
Oncogenes	A gene found in the chromosomes of tumour cells activated in the change of normal cells into cancer cells.
Oophorectomy	Surgical removal of the ovaries. May be bilateral (both ovaries) or unilateral (one ovary).
Open Field Technique	Whole abdominal radiation therapy given to the entire coelomic cavity using a single large portal extending from the domes of the diaphragm to the pelvic floor.
Optimal cytoreduction	Surgery where the residual disease is 2 cm or less.
Oral alkylating agent therapy	An anti-cancer or cytotoxic agent eg a platinum compound. An alkylating agent is one which substitutes an alkyl group for an active hydrogen in an organic compound.
Ovarian capsule	Covering (skin) of ovary.
Ovary	Part of the female reproductive system containing eggs (ova).
Ovulation	Release of egg from the ovary each month.
Paclitaxel	An anti-neoplastic agent, given intravenously, which acts by promoting and stabilising the polymerisation of microtubules.
Palliative care	The active total care of patients whose disease is not responsive to curative treatment. It encompasses the provision of co-ordinated medical, nursing and allied services to help relieve physical symptoms and to provide psychological, emotional and spiritual support.
Papillary	Small, nipple-shaped projections.
Paracentesis	The surgical puncture of a body cavity to collect fluid.

Parenchymal	The essential functioning elements of an organ.
Parity	The condition of a woman who has given birth.
Pathology block	A section outside the site of the tumour taken to test for invasion of cancer cells.
Pathogenesis	The development of a disease, specifically the cellular events, reactions and other pathologic mechanisms that occur.
Pelvis	The lower portion of the trunk forming a basin bounded by the hip bones, sacrum and tail bone.
Periodic acid Schiff (PAS)	Stain colouring sugars red – violet in tissues.
Peritoneal cancer	A variant of ovarian cancer which is found in the peritoneal surfaces.
Peritoneal implants	Growth or insertion of tissue into the peritoneum.
Peritoneal-venous shunt	A device whose purpose is to remove excess fluid (ascites) from the peritoneal cavity and return it to the venous system.
Peritoneal washings	Cells obtained by irrigating the abdominal cavity with saline.
Peritoneum	The serous membrane lining the walls of the abdominal and pelvic cavities.
Phase I, II, III trial	The different stages of a clinical trial. Phase I is designed to evaluate the relationship between dose and toxicity. In Phase II new treatments are screened for their anti-tumour effect, to see which are worthy of further evaluation and in Phase III patients are randomly allocated to receive the new treatment or the best available standard treatment.
Plantar-palmar erythrodyaesthesia	Condition caused by chemotherapy where the soles of the feet and palms of the hands are reddened and sensitive to touch.
Platinum analogue	An element with a similar structure to that of platinum but differing in some respects eg its metabolic action.
Platinum-based chemotherapy	Drugs used to treat ovarian cancer based on platinum eg cisplatin.
Platinum refractory	Disease progression whilst receiving platinum therapy.
Platinum resistant	Initial response to therapy with a platinum agent but with relapse occurring within six months of treatment.
Platinum sensitive	Responsiveness to the administration of platinum-based anti-tumour drug with relapse more than six months after treatment.

Pleomorphism	The assumption of various distinct forms by a single organism.
Pleural effusion	The collection of fluid in the lining of the lungs.
Ploidy studies	Identification of the number of genomes (complete set of chromosomes).
Pooled data	Data from a number of studies combined for analysis to look for an effect/result.
Pouch of Douglas	A sac or recess formed by a fold of the peritoneum dipping down between the rectum and uterus.
Precursor lesion	The forerunner of cancer.
Progression free interval/survival	Interval between the end of first line therapy and relapse.
Prognosis	A forecast as to the probable outcome of a disease and the prospect of recovery based on the nature of the case.
Proliferating	Growth by reproduction of similar cells.
Prophylactic	Something used to prevent disease.
Proportional hazards regression analysis	A mathematical model used to predict risk based on the effect on one variable of a number of independent variables.
Prospective trial/study	A study where subsets of a defined population are identified in relation to a factor/exposure hypothesised to influence the occurrence of a disease or some other outcome. The method used is to observe the population over a sufficient period of time to generate reliable incidence or mortality rates.
Proteomic	Protein patterns.
Psammoma bodies	Containing sand-like or calcareous matter.
Pseudomyxoma peritonei	An uncommon condition with both intra-abdominal and ovarian mucinous tumour present. There is a mass of jelly-like mucus in the pelvis and in many cases, in the upper abdomen.
PTEN	Phosphatase and tensin homologue deleted on chromosome 10. A tumour suppressor gene mutated frequently in a variety of human tumours. PTAN regulates cell growth, cell death and proliferation.
Putative	Commonly regarded as or reputed.

Quality of life	A person's view of their situation and well-being. It encompasses symptoms of disease, side effects of treatment, relationships, occupational and social functioning and a subjective evaluation of adjustment to daily life.
Radiation therapy	Use of X-rays/gamma rays to kill cancer cells.
Randomised controlled trial (RCT)	A study or experiment where subjects are allocated at random to receive or not receive the treatment, procedure or intervention. The results for each group are compared. Generally held to be the most scientifically rigorous method of testing an hypothesis.
Resection	Surgical removal of part of all of an organ or tissue.
Relapse	The return of cancer after it has apparently successful treatment.
Relative risk	The risk (of a disease or death) among those exposed to the risk compared to those who are not exposed to the risk.
Relative survival analysis	Statistical procedure for estimating time people survive with a particular disease when considering different treatments and other factors.
Residual disease	Disease not able to be removed as part of the surgical excision of the tumour.
Retroperitoneal lymph nodes	Lymph nodes situated external or posterior to the peritoneum.
Rhabdomyosarcoma	A highly malignant tumour arising in the muscle or embryonal connective tissue.
SAGE Analysis	Serial analysis of gene expression.
Salpingo-oophorectomy	Surgical removal of fallopian tube and ovary.
Salvage	Salvage (therapy) usually a therapeutic step taken late when other approaches have failed.
Screening	Testing of apparently well persons (those with no symptoms of the disease or condition) to determine whether a disease or condition is present or not.
Secondary cytoreduction	A second operation undertaken to further debulk a tumour in women with persistent disease following a complete course of chemotherapy, or after relapse.
Second-look surgery	Surgery performed after initial surgery or treatment to check on spread or recurrence of disease.
Seeding	The inoculation of other organs with tumour cells.

Sensitivity	The proportion of people who test positive for a disease who are found to truly have the disease.
Septation	The appearance of a wall or partition.
Sequelae	A condition following or occurring as a consequence of another condition.
Serous	Thin or watery like serum.
Serous papillary cystadenocarcinoma	An ovarian tumour derived from glandular tissue. It has features of both cystic and papillary tumours and contains both serum and some solid tissue.
SEST	Surface epithelial stromal tumours.
Specificity	The proportion of people who test negative for a disease who truly do not have the disease.
Surveillance	Watching or monitoring of a disease.
Stage/staging/ stage distribution	The classification of a tumour according to its extent.
Stem cell	Any precursor cell; a blood cell progenitor or 'mother' cell, having the capacity for both replication and differentiation.
Stoma	An opening created surgically from an internal organ to the surface of the body. It is kept open to allow for drainage or other purposes.
Stromal	The tissue forming the ground substance, framework or matrix of an organ as opposed to the functioning part.
Suboptimal debulking	Debulking surgery where residual disease is more than 2 cm.
Synchronous tumours	Tumours occurring at the same time.
Synoptic reporting	Use of pre-formatted reporting systems to capture all the information concerning a tumour.
Tamoxifen	A non-steroidal oral anti-oestrogen.
Taxanes	A group of chemical substances with varying degrees of anti-tumour activity, including paclitaxel, docetaxel and related compounds.
thio-TEPA	N, N', N'', triethylenethiophosphoramidate. A cancer chemotherapeutic agent that largely produces base damage to cells.
Thrombosis	Formation of a clot.

Thromboembolism	Obstruction of a blood vessel with thrombotic material carried by the blood from the site of origin to plug another vessel (blood clot).
Topotecan	A substance used in treatment of ovarian cancer that works by affecting the cancer cells' DNA.
Toxicity	The quality of being poisonous.
Transabdominal ultrasound	Use of high frequency sound waves to identify changes in organs through a hand held device passed over the abdomen.
Transudation	Passage of serum or other body fluid through a membrane or tissue surface.
Transitional carcinoma	That subset of epithelial malignancies that resembles carcinomas occurring in the upper urinary tract and derived from the lining transitional cells.
Transvaginal ultrasound	Use of high frequency sound waves to identify changes in organs through a device inserted into the vagina.
Tubal ligation	Tying off the fallopian tubes to prevent conception.
Tumour	Also called neoplasm. A new growth of tissue in which cell multiplication is uncontrolled and progressive. Tumours are classified in a number of ways the simplest being their origin and whether they are malignant or benign.
Tumour/tumourgenesis	The production of tumours.
Tumour marker	A substance found in the body that suggests the presence of a tumour.
Ultrasound	Use of very high frequency sound waves to examine the structures of the body. The sound is reflected back differently by different types of tissue.
WART	Whole Abdominal Radiotherapy.

ABBREVIATIONS

APRT	Abdomino-pelvic radiotherapy
BRCA1	
BRCA2	Breast cancer /ovarian cancer susceptibility genes
CA125	Cancer Antigen 125 (see Glossary)
CGO	Certificate of Gynaecological Oncology
CT	Computerised Tomography
FRANZCOG	Fellowship Royal Australian and New Zealand College of Obstetricians and Gynaecologists
FS	Frozen section
GOG	Gynecologic Oncology Group
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HNPPC	Hereditary non polyposis colorectal cancer
ICON	International Collaborative Ovarian Neoplasm Trial
NHS	National Health Service
NIH (USA)	National Institutes of Health, Bethesda, Maryland USA
PTEN	Phosphatase and tensin homologue deleted on chromosome 10 (see Glossary)
RMI	Risk of Malignancy Index
RPCT	Randomised prospective controlled trial
S/C	Subcutaneous
TVUS	Transvaginal ultrasound
WART	Whole Abdominal Radiotherapy

APPENDIX I - ADVICE ABOUT FAMILIAL ASPECTS OF OVARIAN CANCER

(NB: The following risk categories and management guide for ovarian cancer are based on the guide prepared by the National Breast Cancer Centre (NBCC) Genetics Working Group in 2000 and updated 18 September 2003, following a review of research).

FAMILIAL ASPECTS OF OVARIAN CANCER

The following categories apply to women **without** breast or ovarian cancer:

1° relatives = *parents, siblings, children*

2° relatives = *aunts, uncles, nieces, nephews, grandparents*

For most Australian women the risk of developing epithelial ovarian cancer to age 75 is approximately 1 in 100

CATEGORIES OF RISK	
<p>I. At or at most moderately above average risk</p> <p>Covers more than 99% of the female population</p> <ul style="list-style-type: none"> No confirmed family history of epithelial ovarian cancer. One 1° or 2° relative diagnosed with ovarian cancer at any age (provided the family is not of Ashkenazi Jewish ancestry*). Two 1° or 2° relatives diagnosed with ovarian cancer, but on different sides of the family (i.e. one on each side of the family). <p>Lifetime risk of ovarian cancer: 1 in 100 (for most women in this group) but not more than 1 in 30.</p> <p>Risk is no more than 3 times higher than the population average.</p> <p>* High-risk ovarian and breast gene mutations are more common in people of Ashkenazi Jewish ancestry.</p>	<p>2. Potentially high risk</p> <p>Covers less than 1% of the female population</p> <ul style="list-style-type: none"> One 1° relative diagnosed with epithelial ovarian cancer in a family of Ashkenazi Jewish ancestry*. Two 1° or 2° relatives on the same side of the family diagnosed with epithelial ovarian cancer; especially if one or more of the following features occurs on the same side of the family: <ul style="list-style-type: none"> - additional relative(s) with breast or ovarian cancer; - breast cancer diagnosed before the age of 40. - bilateral breast cancer. - breast and ovarian cancer in the same woman. - breast cancer in a male relative. Three or more 1° or 2° degree relatives on the same side of the family diagnosed with any cancers associated with hereditary non-polyposis colorectal cancer (HNPCC): colorectal cancer (particularly if diagnosed before the age of 50), endometrial cancer, ovarian cancer, gastric cancer; and cancers involving the renal tract. Member of a family in which the presence of a high-risk ovarian cancer gene mutation has been established. <p>Lifetime risk of ovarian cancer: From 1 in 30 up to 1 in 3, or possibly higher if shown to have a high-risk mutation.</p> <p>Risk may be more than 3 times higher than the population average.</p> <p>*High-risk ovarian and breast cancer gene mutations are more common in people of Ashkenazi Jewish ancestry.</p>

<h2>MANAGEMENT</h2>	<ol style="list-style-type: none"> 1. Reassure the woman that her risk is at or at most moderately above the average for the general population and that more than 97% of women in this group will not develop ovarian cancer. 2. Advise the woman about current best practice for the early detection of cancers for the population. 3. Advise the woman to visit her general practitioner promptly with any health changes. <p>Screening the general population for epithelial ovarian cancer cannot be justified on the basis of the low prevalence of ovarian cancer and the inadequate sensitivity of currently available tests.</p>	<ol style="list-style-type: none"> 1. Advise the woman that she has a potentially high risk of developing ovarian cancer and perhaps other cancers, such as breast cancer, but that the majority of women in this group will not develop ovarian cancer. 2. If the woman wishes to clarify her genetic risk or that of her family, or wishes to consider risk-reducing surgery, discuss referral to a specialist family cancer clinic for advice, appropriate counselling and management. 3. Because early detection may be important, and because bilateral salpingo-oophorectomy has been proven to reduce the risk of ovarian and breast cancer in women with a mutation in BRCA1 or BRCA2, advise the woman to see a gynaecological oncologist to discuss her options. <p>Should a women choose not to have risk-reducing surgery, an appropriate individualised surveillance program may include:</p> <ul style="list-style-type: none"> • visiting her general practitioner promptly with any health changes. • transvaginal ultrasonography.* (The age at which this commences may depend on the family cancer history and if a high-risk ovarian cancer gene mutation has been identified in the woman or her family). • CA125 measurement**. <p>* (There is no evidence that these tests reduce mortality from ovarian cancer but they may be considered for women who have not undergone risk-reducing salpingo-oophorectomy).</p> <ul style="list-style-type: none"> • surveillance relevant to other cancers (e.g. attending for clinical breast examination, mammography or other surveillance if the family cancer history is consistent with HNPCC). <ol style="list-style-type: none"> 4. Discuss possible participation in a relevant approved clinical trial.
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APPENDIX 2 - WORLD HEALTH ORGANIZATION HISTOLOGICAL CLASSIFICATION OF SURFACE EPITHELIAL- STROMAL TUMORS

Source: Sully RE, Young RH and Clemet P. Atlas of Tumour Pathology: Tumours of the Ovary, Maldeveloped Gonads, Fallopian tube and Broad Ligament. Armed Forces Institute of Pathology. Third Series. 1998; Fascicle 23: 28-31.

Serous Tumors

Benign

- Cystadenoma and papillary cystadenoma
- Surface papilloma
- Adenofibroma and cystadenofibroma

Of Borderline Malignancy (of low malignant potential)

- Cystic tumor and papillary cystic tumor
- Surface papillary tumor
- Adenofibroma and cystadenofibroma

Malignant

- Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
- Surface papillary adenocarcinoma
- Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

Mucinous Tumors, Endocervical-like and Intestinal Types

Benign

- Cystadenoma
- Adenofibroma and cystadenofibroma

Of Borderline Malignancy (of low malignant potential)

- Cystic tumor
- Adenofibroma and cystadenofibroma

Malignant

- Adenocarcinoma and cystadenocarcinoma
- Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

Endometrioid Tumors

Benign

- Cystadenoma
- Cystadenoma with squamous differentiation
- Adenofibroma and cystadenofibroma
- Adenofibroma and cystadenofibroma with squamous differentiation

Of Borderline Malignancy (of low malignant potential)

- Cystic tumor
- Cystic tumor with squamous differentiation
- Adenofibroma and cystadenofibroma
- Adenofibroma and cystadenofibroma with squamous differentiation

Malignant

- Adenocarcinoma and cystadenocarcinoma
- Adenocarcinoma and cystadenocarcinoma with squamous differentiation
- Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)
- Adenocarcinofibroma and cystadenocarcinofibroma with squamous differentiation (malignant adenofibroma and cystadenofibroma with squamous differentiation)

Epithelial-Stromal and Stromal

- Adenosarcoma, homologous and heterologous
- Mesodermal (mullerian) mixed tumor (carcinosarcoma), homologous and heterologous
- Stromal sarcoma

Clear Cell Tumors

Benign

- Cystadenoma
- Adenofibroma and cystadenofibroma

Of Borderline Malignancy (of low malignant potential)

- Cystic tumor
- Adenofibroma and cystadenofibroma

Malignant

- Adenocarcinoma
- Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

Transitional Cell Tumors

- Brenner Tumor
- Brenner Tumor of Borderline Malignancy (proliferating)
- Malignant Brenner Tumor
- Transitional Cell Carcinoma (non-Brenner type)

Squamous Cell Tumors

Mixed Epithelial Tumors (specify types)

- Benign
- Of Borderline Malignancy (of low malignant potential)
- Malignant

Undifferentiated Carcinoma

APPENDIX 3 - PRINCIPLES OF SCREENING

Although the concept of being able to detect ovarian cancer early and thereby reduce the morbidity and mortality from the disease is a highly attractive one, screening programs also have the potential to consume significant health resources and to cause harm to patients. Wilson and Jungner¹ have developed criteria for screening programs:

Principles of screening	
1	The condition should be an important health problem
2	The natural history of the disease should be well understood
3	There should be a recognisable latent or early asymptomatic stage
4	Treatment at an early stage should be of more benefit than treatment started at a later stage
5	There should be a suitable test or examination
6	The test should be acceptable to the population
7	Facilities should be available for the diagnosis and treatment
8	Screening should be repeated at intervals determined by the natural history of the disease
9	The chance of physical or psychological harm to those screened should be less than the chance of benefit
10	The cost of a screening program should be balanced against the benefit it provides.

SENSITIVITY AND SPECIFICITY OF A SCREENING TEST

Sensitivity - is the proportion of those persons who truly have the disease who are identified as having the disease by the screening test i.e. those who are truly positive who test positive. It is the probability that any given case will be identified by the screening test.

Specificity - is the proportion of those persons who truly do not have the disease and are so identified by the screening test eg those who are truly negative who test negative. It is the probability of correctly identifying a non-diseased person with a screening test.

A test that has a high sensitivity may give a false positive result. This may result in unnecessary intervention – surgical or otherwise – to establish the correct diagnosis.

'In terms of screening for ovarian cancer, the sensitivity of the test is particularly important, as delay in diagnosis may reduce survival. The specificity of the test also needs to be high, as a failure to differentiate benign disease from malignant disease will lead to unnecessary surgical intervention'.³

Tests may be combined or used in a serial fashion to improve the sensitivity and specificity of screening tests.

POSITIVE PREDICTIVE VALUE

The positive predictive value is the proportion of test results that are truly positive. The positive predictive value reflects not only the sensitivity and specificity of a test but also the prevalence of the disease in the population which is screened.

DISADVANTAGES OF SCREENING (AUSTOKER 1994)

- Longer morbidity in cases where prognosis is unaltered
- Overtreatment of questionable abnormalities
- False reassurance for those with false negative results
- Anxiety and sometimes morbidity in those with false positive results
- Unnecessary medical intervention in those with false positive results
- Hazard of screening test
- Resource cost: diversion of scarce resources to screening program

POTENTIAL FOR HARM

The principal ways in which a screening program can cause harm are:

- the adverse effects of the screening test(s);
- the psychological effects of a false positive test;
- the psychological effects of a diagnosis which is made earlier than otherwise with no effective change in health outcome;
- the adverse effects of on-going investigations in women with a false positive screening test results; and
- any delay in diagnosis due to false negative screening results.

References:

1. Wilson JM and Jungner JJ. Principles and practice of screening for disease. WHO Public Health Paper 34. Geneva: World Health Organization. 1968
2. J M Last. A Dictionary of Epidemiology. Second edition. Oxford University Press. 1988
3. Pearson VAH. Screening for ovarian cancer: a review. Public Health. 1994; 108: 367-382
4. Austoker J. Screening for ovarian, prostatic, and testicular cancers. British Medical Journal. 1994; 309: 315-320

APPENDIX 4 - GYNAECOLOGICAL ONCOLOGY TRAINING REQUIREMENTS

Gynaecological Oncology is a subspecialty of obstetrics and gynaecology.

Gynaecological Oncologists are specialists in Obstetrics and Gynaecology. In Australia they are awarded the Fellowship of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (FRANZCOG), having completed a formal three year training program in gynaecological cancer care and have passed the examination for the Certificate of Gynaecological Oncology (CGO).

Gynaecological oncologists are competent in the comprehensive management of women with a genital malignancy. The subspecialist will work in gynaecology with at least 66% of the time in gynaecological oncology. They will submit themselves for recertification every three years, and only those actively practising will continue to be certified.

PATHWAY TO CERTIFICATION AS A GYNAECOLOGICAL ONCOLOGY SUB SPECIALIST VIA THE ROYAL AUSTRALIAN AND NEW ZEALAND COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS (RANZCOG) TRAINING PROGRAM

The Gynaecological Oncology Training Program is of three year's duration and comprises clinical training and assessment requirements as follows.

<p>Clinical training program</p>	<ul style="list-style-type: none"> • must be prospectively approved • at least one year must be spent in a prospectively approved RANZCOG accredited CGO Subspecialty Training Post in Australia • desirable that part of the program is in a prospectively approved unit outside Australia (does not necessarily apply to trainees who have spent at least 12 months of their pre-CGO training in an overseas centre) • minimum number of procedures must be performed
<p>Training documentation</p>	<ul style="list-style-type: none"> • Trainee reports completed by Training Supervisor and submitted to the College for each 6-month period • Clinical summaries to be submitted for each 6-month period • All reports must be submitted within 8 weeks of completing each 6-month period
<p>Original research project and thesis</p>	<ul style="list-style-type: none"> • thesis must have been finally approved at least three months prior to the date of the oral examination • original research work of sufficient quality to be accepted in a peer-reviewed journal case reports and review articles not acceptable

Written examination	<ul style="list-style-type: none"> • applications close on 30 April each year • usually held in early August (at same time as MRANZCOG examination) • eligible only if satisfactory Training Assessment Record for 30 months of prospectively approved training • must be attempted for the first time within 2 years of completion of training • maximum of three consecutive attempts allowed • comprises twelve fifteen-minutes short answer questions
Oral Examination	<ul style="list-style-type: none"> • only eligible if written examination is passed and thesis has been finally approved at least three months prior to the date of the oral examination • usually held each year within six months of written examination • comprises six fifteen-minute and two twenty five-minute stations (with fifteen-minute break). Five minutes preparation before each station is allowed • Histological sections, laboratory worksheets, photographs, journal critiques may be included.

All RANZCOG Trainees must be supervised by an appointed Training Supervisor/ Program Director.

PROGRAM OUTLINE

1. The Trainee must have an understanding of the aetiology, epidemiology, screening and prevention of gynaecological malignancy.
2. Skills must be acquired in a wide range of investigative procedures - including cystoscopy, sigmoidoscopy, thoraco-centesis, paracentesis and the placement and care of permanent central intravenous lines. In addition, knowledge and interpretation of relevant ultrasonic, CT, lymphangiographic and other organ imaging techniques must be developed.
3. The Trainee must acquire a high level of skill in colposcopy and in the management of pre-invasive and micro-invasive lesions of the female genital tract.
4. The Trainee must acquire the necessary knowledge and skill to perform radical operations on reproductive organs, and operations on the intestine, urinary and vascular systems, as required in the management of gynaecological cancer and the complications of treatment. Surgical techniques must also be acquired for the dissection of inguinal, pelvic, paraaortic and supraclavicular lymph nodes and reconstructive procedures required for the restoration of pelvic organ function.
5. A sound knowledge of parenteral nutrition and intensive care management of the perioperative patient is required.

6. The Trainees must develop skills in the management of pain and the care of the terminally ill patient.
7. The Trainee must be well-informed about the methods and techniques of radiation therapy, including intracavity and interstitial brachytherapy, external beam therapy and intraperitoneal radioisotope therapy. The Trainee must be capable of participating in the planning of radiation treatment and must acquire an understanding of the principles of radiobiology and radiation physics. The Trainee must develop skills in the management of the side-effects and complications of radiotherapy.
8. The Trainee must acquire an advanced knowledge of the clinical pharmacology of cancer chemotherapy and the practical use of the various drugs required for treatment. The candidate should develop skills in the management of toxic side-effects.
9. The Trainee must develop competence in the assessment of the effects of treatment, and the long-term management of pre-invasive and invasive gynaecological malignancies.
10. The Trainee must develop a sound knowledge of gross and microscopic pathology relevant to gynaecological oncology. This knowledge must be sufficient for the candidate to interpret reports concerning gynaecological malignant histopathology.
11. The Trainee must develop skills in the planning, conduct and reporting of research in gynaecological oncology. In addition he/she must develop a high level of skill in the interpretation and evaluation of research reports.

ELEMENTS OF THE TRAINING PROGRAM

The Gynaecological Oncology Training Program will consist of **THREE CLINICAL YEARS**, all of which must be prospectively approved. It will include the following elements:

1. Active participation in the work of an approved gynaecological oncology unit for a minimum of TWO years. Because of difficulties in obtaining specific advanced training posts in 'general surgical units' (see below in Paragraph 3), it will be usual for trainees to spend THREE years in gynaecological oncology units.
2. At least ONE year of training will be in an accredited subspecialty training post in Australia.
3. It is desirable, but not mandatory, that there be participation in the work of a general surgical unit, particularly in the areas of gastrointestinal and urological surgery, for ONE year. The work should be at an advanced level and this should be reflected in a logbook of cases.
4. Sufficient participation in the medical oncology management of patients to provide an appropriate training. A specific attachment to a medical oncology unit is not required, but if obtained, no more than THREE months will be accredited.

5. Participation as member of a team planning radiotherapy and performing radiation treatment. A specific attachment to a radiation oncology unit is not required, but if obtained, no more than THREE months will be accredited.
6. Participation in pathology sessions, e.g. Tumour Board Meetings, as related to gynaecological oncology.
7. Participation in the planning, conduct, and reporting of research in gynaecological oncology.

Notes

- A:** A maximum of **3 months each** may be accredited for a specific rotation in medical oncology, radiation oncology, palliative medicine, or a related clinical discipline. No more than **two** such rotations will be accredited, i.e., a maximum of 6 months in total. Such a rotation should be for a minimum period of **3 months. Prospective approval should be sought for such a program.** A log book of cases seen, a weekly program, and a summary of training will need to be provided for this discretionary time to be accredited.
- B:** Specific training in research or for higher degrees not involving **clinical** gynaecological oncology is encouraged but not considered to be part of the training program and no reduction in the duration of the training program will be entertained in this respect.
- C:** Trainees commencing the CGO/DGO training program from 1 January 2000 should gain the following minimum number of surgical procedures over the 3 year training period. Trainees will be advised of these requirements at the time of commencement of training. These minimum numbers will be reviewed regularly in the light of submitted training documentation.

Radical hysterectomy & nodes	40
Pelvic nodes	50
Radical vulvar operations	20
Groin node dissections	20
Para-aortic node biopsies	30
Large bowel resections	20
Small bowel resections	20
Ovarian cancer debulking (advanced)	45

This provides a formalised program which gives as far as possible a standard of training. Equally, the College has initiated and pioneered a continuing accreditation program to ensure maintenance of standards.

Key point:

- There is a need to ensure that appropriate protocols for training are developed and maintained by the College, as part of the ongoing reaccreditation process, both of individual surgeons and Units.

APPENDIX 5 – PRACTICAL GUIDELINES FOR THE MANAGEMENT OF SYMPTOMS IN PATIENTS WITH RECURRENT DISEASE

GASTROENTEROLOGICAL PROBLEMS

Nausea and vomiting

Causes:

- Obstruction
 - Pseudo obstruction (See Constipation)
 - In small and large bowel by cancer, usually multiple sites
 - Gastroparesis
- Constipation
- Chemotherapy
- Inanition

Constipation

Causes:

- Analgesic use
- Poor diet
- Dehydration
- Lack of exercise

FLUID ACCUMULATION

Pleural

Pleural effusion is often from transudation and may be managed in a variety of ways:

- Pleural tap - relieves symptoms only. May be necessary to make a diagnosis
- Pleuradhesion - using talc, antibiotic or chemotherapy. May be indicated if this is the only sign of disease, or reaccumulation cannot be controlled by any other means
- Concomitant chemotherapy offers the best chance of controlling effusion, if the disease is chemosensitive

Peritoneal (ascites)

Ascites are often a sign of miliary spread of tumour and may be managed in a variety of ways:

- Paracentesis
- Chemotherapeutic control
- Peritoneo-venous shunt - if there is a high output with low particulate matter, and a reasonable prognosis i.e. 2-3 months.

Metastasis to 'difficult' sites

- Brain
Often associated with reasonable long term survival if this is the only site. Is usually only seen after successful chemotherapy. It is worth using active or aggressive therapy, including surgery and radiation therapy.
- Vaginal disease
Usually penetration from intraperitoneal sites, with or without fistulation. The major problem is discharge, which is both malodorous and bloody.

Thrombo-embolic phenomena

Malignancy per se is associated with hypercoagulation.

- overt deep venous thrombosis.

The question is at what stage anticoagulation is used and also what type, as monitoring may be an impediment to good quality of life in someone who is dying.

- Heparin - with full scale Warfarin?
- Clexane without monitoring
- No further treatment.

Mental trauma

Psychosocial issues are particularly relevant to women with ovarian cancer.

- Social isolation
- Anxiety
- Depression
- Coping problems

Quality of dying

Two separate scenarios need attention.

- Remission, relapse and then death.

Here, the chemotherapy gives a breather with a response to therapy, but then comes the relapse. The dilemma is how to manage this, where retreatment often produces a second response, and the traumas associated with the reprieve but ultimate failure down the track.

- Chemoresistant disease where the initial chemotherapy does not produce a response.

Second, and often several, lines of chemotherapy are tried and may produce transient but not continues remissions. Hope needs to be tempered with reality and the preparation for death, even during good quality of life periods

Preparation for death

Each of the above scenarios will require a reasonable preparation for death.

APPENDIX 6 - GUIDELINE DEVELOPMENT PROCESS

In November 2000, the Australian Cancer Network (ACN) established a multidisciplinary working party to develop clinical practice guidelines for the management of women with epithelial ovarian cancer. With the establishment of the National Ovarian Cancer Program in 2001, the National Breast Cancer Centre (NBCC) worked collaboratively with the Australian Cancer Network to develop, revise and complete the guidelines (*see Appendix 8*) in a manner consistent with that prescribed by the National Health and Medical Research Council (NHMRC), and according to the standards indicated by the Quality of Care in Health Outcomes Committee (QCHOC).

Members of the Working Party were representative of the broad organisations from which they came. Three face-to-face meetings were held in the course of developing the guidelines, with a number of executive meetings to monitor progress.

PURPOSE AND SCOPE OF THE GUIDELINES

Need for clinical practice guidelines for epithelial ovarian cancer

There are currently no clinical practice guidelines available for clinicians or health professionals who care for women suspected of having, or who are diagnosed with, epithelial ovarian cancer.

Target audience

These guidelines were developed to assist clinicians, including gynaecological oncologists, gynaecologists, general surgeons, gastroenterologists, urologists and medical and radiation oncologists and other health professionals, provide appropriate care and management for women with epithelial ovarian cancer. The guidelines may also be of interest to consumers and consumer groups, although it is planned to develop a consumer guide, based on the clinical practice guidelines.

Scope of the guidelines

The guidelines cover aspects of epithelial ovarian cancer from its aetiology, pathology and risk factors for developing the disease to management of women with ovarian cancer and the psychosocial issues for the woman, her family and the clinicians and health professionals caring for her.

Focus of the guidelines

The primary focus of the *Clinical practice guidelines for the management of women with epithelial ovarian cancer* is to close the gap on information both for medical providers and women, so that awareness of ovarian cancer is raised and the possibility of earlier diagnosis and optimal treatment is realised.

Best available evidence

Literature searches for evidence to support guideline recommendations were undertaken in PubMed, Medline (1966-2003) and other relevant databases. Search terms used to gather information included; 'ovarian cancer'; 'ovarian neoplasm'; 'ovarian carcinoma'; 'epithelial ovarian cancer'; 'borderline ovarian tumours' and 'tumours of low malignant potential'. Within specific areas, for example surgery, the search terms were expanded to cover 'surgical management'; 'treatment'; 'cytoreduction'; 'secondary cytoreduction'; 'interval cytoreduction' ; 'second look surgery'; and so on. From the available abstracts the studies were assessed for their quality, based on aspects such as study type, sample size and inclusion of significance levels and p values. The bibliographies of the initial relevant papers were also used to provide other relevant articles missed in the original search. Members of the Working Party prepared chapters on their topic, summarising the evidence and submitted them for review. Each chapter was submitted for review by an appropriate member of the Working Party or an external invitee.

Dissemination and implementation of clinical practice guidelines for epithelial ovarian cancer

The National Breast Cancer Centre will coordinate the dissemination and implementation of the guidelines. The guidelines for epithelial ovarian cancer will be relevant to gynaecological oncologists, gynaecologists, general surgeons, gastroenterologists, urologists, medical and radiation oncologists and general practitioners.

Strategies for the dissemination and implementation of the guidelines will be drawn from the experience and expertise of the National Breast Cancer Centre, gained through the involvement in the development of a number of clinical practice guidelines.

Approval

The guidelines were approved by the National Health and Medical Research Council (NHMRC) and will be circulated to relevant stakeholders as a critical step to aid dissemination and implementation.

Dissemination

The guidelines will be made widely available through the Internet on the National Breast Cancer Centre's Ovarian Cancer Program web site and Australian Cancer Network's web site. The guidelines can be formatted to allow for downloading and printing. A direct link to the NHMRC website will be included on the websites of the NBCC and the ACN to facilitate access.

Funding is available to initially disseminate copies to gynaecological oncologists, gynaecological clinics, general surgeons, gastroenterologists, urologists and medical and radiation oncologists. Subject to additional funding, copies of the guidelines will be made available to other relevant clinical groups, allied health organisations, State and Territory authorities, cancer treatment centres, consumer groups, professional college and associations and policy makers.

The availability of the guidelines will be widely advertised through a variety of means. This will include notification to relevant:

- professional groups and associations
- cancer council/societies
- state and Territory health authorities
- consumer groups and organisations
- hospitals and cancer treatment centres
- university medical schools
- public policy makers

The guidelines will be advertised through newsletters published by the NBCC, the ACN, other cancer organisations and professional colleges and promoted through presentations at professional meetings and conferences

Consultation and feedback

These guidelines have undergone an extensive consultation process that included both a public consultation process and additional consultation in which the guidelines were sent to professional colleges and other interested parties, such as relevant expert groups, Cancer Council/societies, consumer groups etc, for review. (*A list of submissions received is provided in Appendix 7*)

Consideration of local conditions and resources

The opportunity to implement some of the recommendations may be limited by the availability of, or access to, resources such as provided by multidisciplinary teams. For some situations the guidelines present both the optimal situation and recommendations for what can be realistically achieved given limited resources.

Evaluation

A strategy for evaluating the guidelines will be drafted at the implementation stage and will include collection of data to determine the impact of the guidelines on the care of women with epithelial ovarian cancer. This may include repetition of studies which investigated care patterns for women prior to the implementation of the guidelines.

Revision of guidelines

It is anticipated that the *Clinical practice guidelines for the management of women with epithelial ovarian cancer* will be revised in 2009.

Future research needs

- Centres for education and research in histopathology of rare and variant ovarian tumours. Such centres would have unusual or otherwise difficult or interesting cases referred to them for further diagnosis
- A laboratory centre at which specialised histologic functions such as uncommon immunohistochemistry and DNA analysis can be performed
- A randomised, prospective study to clarify the role of secondary cytoreduction with randomisation between chemotherapy alone and surgery followed by chemotherapy for patients with a disease-free interval of at least 2 years and no evidence of ascites
- Randomised controlled trial to compare the efficacy and toxicity of Whole Abdominal Radiation Therapy (WART) alone versus chemotherapy alone as adjuvant therapy for ovarian cancer
- A randomised study to develop a template for appropriate follow up for women with ovarian cancer

APPENDIX 7 - RESPONDENTS TO PUBLIC CONSULTATION

Associate Professor Judy Kirk
Director
Familial Cancer Service
Westmead Hospital
WESTMEAD NSW 2145

Ms Marlene Watson
Chief Executive Officer
Australasian Society of Plastic Surgeons
Level 1, 33-35 Atchison Street
ST LEONARDS NSW 2065

Ms Helen Hopkins
Executive Director
Consumers' Health Forum of Australia
PO Box 170
CURTIN ACT 2605

Ms Rosemary Bryant
Executive Director
Royal College of Nursing Australia
PO Box 219
DEAKIN WEST ACT 2600

Associate Professor Brenda Wilson
Chief Executive Officer
The Cancer Council South Australia
PO Box 929
UNLEY SA 5061

Professor David Scott
Executive Director for Surgical Affairs
Royal Australasian College of Surgeons
College of Surgeons' Gardens
Spring Street
MELBOURNE VIC 3000

Associate Professor Michael Millward
Head, Clinical Research
Department of Medical Oncology
Royal Prince Alfred Hospital
Missenden Road
CAMPERDOWN NSW 2050

John Harding
Head, Health Registers and Cancer
Monitoring Unit
Australian Institute of Health and Welfare
GPO Box 570
CANBERRA ACT 2601

Dr Kaye Birks
General practitioner
Member, Royal Australian College of
General Practitioners
C/o Moe Medical Centre
MOE VIC 3825

Professor Peter Russell
Department of Anatomical Pathology
Royal Prince Alfred Hospital
Missenden Road
CAMPERDOWN NSW 2050

Dr Anne Hamilton
Medical Oncologist
Sydney Cancer Centre
Royal Prince Alfred Hospital
Missenden Road
CAMPERDOWN NSW 2050

Ms Eugenia Koussidis
10 Fuller Street
PARKSIDE SA 5063

Professor Judy Lumby
Executive Director
NSW College of Nursing
Locked Bag 3030
BURWOOD NSW 1805

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Chief Executive Officer
Royal Australian and New Zealand
College of Obstetricians and
Gynaecologists
College House
254-260 Albert Street
EAST MELBOURNE VIC 3002

Ms Susan Rooney
Chief Executive Officer
Cancer Council Western Australia
46 Ventnor Avenue
PERTH WA 6005

Dr Gerard Wain
Director
Department of Gynaecological Oncology
Westmead Hospital
WESTMEAD NSW 2145

Dr Margaret Davy
Director
Department of Gynaecological Oncology
Royal Adelaide Hospital
North Terrace
ADELAIDE SA 5000

Professor Lester Peters
Dean
Faculty of Radiation Oncology
The Royal Australian and New Zealand
College of Radiologists
Level 9, 51 Drutt Street
SYDNEY NSW 2000

Dr Christopher Milross
Radiation Oncologist
Senior Lecturer (Conjoint)
Prince of Wales Clinical School
RANDWICK NSW 2031

Dr David Bernshaw
Radiation Oncologist
Peter MacCallum Cancer Institute
St Andrew's Place
EAST MELBOURNE VIC 3002

Professor Michael Friedlander
Director, Department of Radiation
Oncology
Prince of Wales Hospital
Randwick on behalf of the Medical
Oncology Group of Australia Inc
Level 6, 52 Phillip Street
SYDNEY NSW 2000

Dr Helen Zorbas
Clinical Director
National Breast Cancer Centre
Locked Bag 16
CAMPERDOWN NSW 1450

Verbal comments received from:

Associate Professor Don Marsden
Gynaecological Oncologist
Royal Hospital for Women
RANDWICK NSW 2031

Dr Sally Baron-Hay
Medical Oncologist
Mater Medical Centre
ST LEONARDS NSW 2065

APPENDIX 8 - AUSTRALIAN CANCER NETWORK MANAGEMENT OF WOMEN WITH EPITHELIAL OVARIAN CANCER WORKING PARTY

The Australian Cancer Network (ACN) Management of Women with Epithelial Ovarian Cancer Working Party was established in 2000 to guide the development of the *Clinical practice guidelines for the management of women with epithelial ovarian cancer*. The Working Party is a multidisciplinary working group comprising representatives from a range of specialities. With the establishment of the National Ovarian Cancer Program in 2001, the National Breast Cancer Centre (NBCC) joined the Working Party.

TERMS OF REFERENCE

- i. To develop evidence-based guidelines to provide optimal management for malignancies of the ovary.
- ii. To address the magnitude of the problem of ovarian malignancy and optimise management and cost factors to achieve control.
- iii. To promote optimal care of malignancies of the ovary and achieve NHMRC accreditation of the guidelines produced, to provide evidence-based best practice care for malignancies of the ovary.
- iv. To present guidelines in a range of formats, to meet requirements of specialists, general practitioners, associated health professionals and consumers.

MEMBERSHIP OF THE ACN MANAGEMENT OF WOMEN WITH EPITHELIAL OVARIAN CANCER WORKING PARTY

Dr Margaret Davy AM (Chair)	Gynaecological Oncologist
Dr Kaye Birks	General Practitioner
Dr Colin Bull	Radiation Oncologist
Dr Jennifer Doust	Epidemiologist
Dr David Grimes	Medical Oncologist
Professor Neville Hacker	Gynaecological Oncologist
A/Professor Paul Harnett	Medical Oncologist
A/Professor Judy Kirk	Medical Geneticist
Ms Eugenia Koussidis	Consumer
Ms Letitia Lancaster	Oncology Nurse
A/Professor Andrew Ostor#	Pathologist
A/Professor Michael Quinn	Gynaecological Oncologist
Dr Melissa Robbie	Histopathologist
Dr Alison Venn	Epidemiologist
Emeritus Professor Tom Reeve AC CBE**	Convenor
Ms Jane Francis*	Manager
Dr Karen Luxford*	Program Director

Corresponding members:

Mr Robert Rome

Gynaecological Oncologist

Dr Gerard Wain

Gynaecological Oncologist

* Ovarian Cancer Program, National Breast Cancer Centre ** Senior Medical Advisor, Australian Cancer Network

Deceased January 2003

REVIEW PANEL FOR PUBLIC SUBMISSIONS - 29 APRIL 2003

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Honorary Senior Clinical Advisor, National
Cancer Control Initiative

Dr Margaret Davy AM

Gynaecological Oncologist. Chair, ACN
Working Party

Dr Gerard Wain

Gynaecological Oncologist

Professor Peter Russell

Pathologist

Dr Penelope Webb

Epidemiologist

A/Professor Kate White

Public Health and Nursing

Ms Eugenia Koussidis

Consumer Representative

A/Professor Paul Harnett

Medical Oncologist

Dr Greg Robertson

Gynaecological Oncologist

Emeritus Professor Tom Reeve AC CBE

Convenor

Dr Karen Luxford

Program Director, NBCC

Ms Jane Francis

Manager, Ovarian Cancer Program, NBCC

ACKNOWLEDGMENTS:

The following are also gratefully acknowledged for their contribution to these guidelines:

Dr Mary Brooksbank - Palliative Care

Professor Alan Coates AM - Medical Oncology

Professor Michael Friedlander - Medical Oncology

Professor John Hopper - Medical Genetics

Dr Anne Kricke - Epidemiology

Professor Helen Lapsley - Health Economics

Dr Jennifer Leary - Molecular biology

Professor Norelle Lickiss - Palliative Care

Professor Ian Maddocks - Palliative Care

Professor Lester Peters - Radiation Oncology

Associate Professor Kelly-Anne Phillips - Medical Oncology/Medical Genetics

Associate Professor David Roder AM - for contributing sections on the aims of cancer registries and clinical cancer registry data from South Australia

Staff of the National Cancer Statistics Clearing House, AIHW, particularly Dr Paul Jelfs,

Ms Edith Christensen and Mr Krystian Sadkovsky

Dr Christopher Steer - Medical Oncology

Dr Martin Stockler - Medical Oncology

Professor Martin Tattersall - Medical Oncology

Ms Vicky Thursfield of the Cancer Epidemiology Unit, Anti-Cancer Council of Victoria

Dr Jane Turner - Psychiatry

APPENDIX 9 - RESOURCES AND CONTACTS FOR PATIENTS AND HEALTH PROFESSIONALS

RESOURCES

The following guides and reports are available from the National Breast Cancer Centre (NBCC).

- Advice about familial aspects of breast cancer and ovarian cancer: a guide for health professionals (card). (*Currently being reviewed*)
- Ovarian Cancer in Australian Women
- Priority actions for ovarian cancer control: a framework for a national approach
- Report of the Ovarian Cancer Workshop. Improving outcomes for Australian women with ovarian cancer

RESOURCES FOR HEALTH PROFESSIONALS

Communication skills training

Information on Communication Skills Training for clinicians may be obtained from:

National Communication Skills Training Strategy

National Breast Cancer Centre

Ph: (02) 9036 3030

Fax: (02) 9036 3077

Email: director@nbcc.org.au

Website: www.nbcc.org.au/bestpractice/communication

Pam McLean Cancer Communications Centre

Block 4 Level 5 Royal North Shore Hospital

St Leonards NSW 2065

Ph: (02) 9926 8494

Fax: (02) 9926 7730

Email: pam.mclean@med.usyd.edu.au

Website: www.mcleancentre.org

Resources for health professionals, women and their families

Detailed information about available resources for specific cancers can be obtained from the Cancer Helpline or State and Territory cancer organisations (see contact details listed later in this section).

The Internet also has a considerable amount of information about cancer. A good place to start searching the Internet is through the Home Page of reputable cancer organisations/associations or support networks. A list of recommended Internet sites is also available in Appendix 13.

CONTACTS

To learn more about cancer and the services and support available to a woman and her family, the following contacts may be helpful.

Nationally

Cancer Helpline

The Cancer Helpline provides general information as well as information on local resources. This service can be accessed from anywhere in Australia for the cost of a local call, connecting to local cancer organisations.

Ph: 13 11 20

Ovarian Cancer Program - National Breast Cancer Centre (NBCC)

In September 2001, the Commonwealth Government announced the establishment of The Ovarian Cancer Program, to be implemented by the National Breast Cancer Centre. The Program aims to improve outcomes for women with ovarian cancer by providing the most accurate, evidence-based information available to both women and health professionals.

Contact details are:

Locked Bag 16

Camperdown NSW 1450

Ph: (02) 9036 3030

Fax: (02) 9036 3077

Email: director@nbcc.org.au

Website: www.ovariancancerprogram.org.au

The National Cancer Control Initiative (NCCI)

The NCCI is a partnership between the Cancer Council Australia and the Australian Government Department of Health and Ageing. It provides advice on all issues related to cancer control and manages a range of cancer related projects. The Initiative works closely with other bodies and takes account of the National Health Priorities of the Commonwealth Government. The Initiative can also provide information and access to

Australian Cancer Organisations and other Australian Health Links including Australian Government and State and Territory Health Departments.

Contact details are:

1 Rathdowne St

Carlton VIC 3053

Ph: (03) 9635 5108

Fax: (03) 9635 5320

Email: enquiries@ncci.org.au

Internet: www.ncci.org.au

The Cancer Council Australia

Australia's national non-government cancer control organisation. Its members are the eight State and Territory cancer organisations. They work together to undertake and fund cancer research, prevent and control cancer and provide information and support for people affected by cancer.

Contact details are:

Level 5 92-94 Parramatta Road Camperdown NSW 2050

Ph: (02) 9036 3100

Fax: (02) 9036 3101

Email: info@cancer.org.au

Website: www.cancer.org.au

Australian Cancer Network (ACN)

Established by The Cancer Council Australia and the Clinical Oncological Society of Australia to improve cancer management and promote collaboration between and with professional bodies across Australia. It extends the outreach of the Cancer Council Australia to a large number of professional colleges and societies. The ACN has developed and disseminated evidence-based clinical practice guidelines for several areas of cancer management.

Contact details are:

Mail: GPO Box 4708

Sydney NSW 2001

Ph: (02) 9036 3120

Fax: (02) 9036 3121

Email: acn@cancer.org.au

National Health and Medical Research Council (NHMRC)

Government body that brings together and draws upon the resources of all components of the Australian health system. It funds health and medical research, provides ethical guidance on health and medical research issues, and provides health advice. It publishes guidelines, information papers and pamphlets on a range of health issues, drawing on the best expert advice and ensuring that the published advice is both current and relevant for the Australian community.

Contact details are:

GPO Box 9848

Canberra ACT 2601

Ph: 02 6289 9148

Fax: 02 6289 9197

Website: www.nhmrc.gov.au

Australian Council of Stoma Associations (ACSA)

The ACSA represents all stoma associations throughout Australia. It provides liaison with the Australian government and appliance suppliers and coordinates the Stoma Appliance Scheme. The ACSA also coordinates support services for ostomates throughout Australia and publishes a national journal. The ACSA can provide patients who have undergone stomal surgery access to local associations and support groups, and information and advice about locally available resources.

Contact details are:

Website: www.australianstoma.org.au

Palliative Care Australia

The national peak body for palliative care in Australia with member groups in each of the States and Territories. Their goal is to work toward the relief of pain and suffering of dying people and the provision of the care they, and their families, need. Contact details are listed below. State and Territory contact details can be obtained from the national body.

Contact details are:

PO Box 24

Deakin West ACT 2600

Ph: (02) 6232 4433

Fax: (02) 6232 4434

Email: pcainc@pallcare.org.au

STATE AND TERRITORY CANCER ORGANISATIONS AND ASSOCIATED NUMBERS

State and Territory Cancer Councils provide information and educational resources on all types of cancers. Some have lending libraries. Many cancer organisations have also developed their own publications about cancer and treatments. To find out about cancer support groups and other local services, State or Territory cancer organisations and the Cancer Helpline should be contacted.

The Cancer Council ACT

159 Maribyrnong Avenue

Kaleen ACT 2617

Ph: (02) 6262 2222

Fax: (02) 6262 2223

Email: reception@actcancer.org

Website: www.cancer.org.au/act/

The Cancer Council New South Wales

153 Dowling St

Woolloomooloo NSW 2011

Ph: (02) 9334 1900

Fax: (02) 9358 1452

Email: feedback@nswcc.org.au

Website: www.cancercouncil.com.au

The Cancer Council Northern Territory

Casi House

Unit 1-3

25 Vanderlin Dr

Casuarina NT 0810

Ph: (08) 8927 4888

Fax : (08) 8927 4990

Email: admin@cancernt.org.au

Website: www.cancercouncilnt.com.au

The Cancer Council Tasmania

140 Bathurst St

Hobart TAS 7000

Ph: (03) 6233 2030

(03) 6233 2088

Fax: (03) 6233 2123

Email: infotas@cancer.org.au

Website: www.cancer.org.au/tas

The Cancer Council Victoria

1 Rathdowne St
Carlton South VIC 3053
Ph: (03) 9635 5000
Fax: (03) 9635 5270
Email: enquiries@cancervic.org.au
Website: www.accv.org.au

The Cancer Council South Australia

202 Greenhill Rd
Eastwood SA 5063
Ph: (08) 8291 4111
Fax: (08) 8291 4122
Email: tcc@cancersa.org.au
Website: www.cancersa.org.au

The Cancer Council Western Australia

46 Ventnor Ave
West Perth WA 6005
Ph: (08) 9212 4333
Fax: (08) 9212 4334
Email: inquiries@cancerwa.asn.au
Website: www.cancerwa.asn.au

Queensland Cancer Fund

553 Gregory Terrace
Fortitude Valley QLD 4006
Ph: (07) 3258 2200
Fax: (07) 3257 1306
Email: qldcf@qldcancer.com.au
Website: www.qldcancer.com.au

ACTION AND SUPPORT GROUPS

OvCa Australia (National Ovarian Cancer Network)

A 'not-for-profit' organisation that aims to increase awareness of ovarian cancer, to promote the need for effective early detection and to provide support to women and families. OvCa has implemented a 'Buddy Support' program through which women with ovarian cancer can access one-to-one support from a volunteer who is themselves either a patient with ovarian cancer or a supporter or carer.

Contact details are:
PO Box 2365
Fitzroy VIC 3065
Ph: 1300 660 334
Email: info@ovca.org
Website: www.ovca.org

Other

For information about local action and/or support groups not listed above, or teleconference support, patients can contact local State and Territory organisations or the Cancer Helpline on 13 11 20.

SUPPORT GROUPS FOR SPECIFIC DIFFICULTIES

Lymphoedema Associations & Support Groups

These groups provide information on lymphoedema, local services and resources and support. Some states and territories also have regional and special interest support groups. Contact numbers are available from the state or territory lymphoedema organisations.

The Lymphoedema Association of Australia

Dr Judith Casley-Smith (Chair)

94 Cambridge Terrace

Malvern SA 5061

Ph: (08) 8271 2198

Fax: (08) 8271 8776

Email: casley@internode.on.net

Website: www.lymphoedema.org.au

Lymphoedema Support Group, ACT

Jenny Moore

Peter Sack

19 Bardsley Place

5 Hobbs Street

Holt ACT 2615

O'Connor ACT 2602

Ph: (02) 6254 4753

Ph: (02) 6249 8672

NT Lymphoedema Support Group

PO Box 42719

Casuarina NT 0811

Ph: (08) 8927 4888

Fax: (08) 8927 4990

Lymphoedema Support Group, NSW

204/5-9 Everton St

Pymble NSW 2073

Ph: (02) 9402 5625

Fax: (02) 9402 5774

Lymphoedema Association of QLD

Ms Jean Lowe (Secretary)

PO Box 68

Brackenridge QLD 4017

Ph: (07) 3833 4376

Fax: (07) 3269 7305

Branches at Brisbane, Bundaberg, Mackay & Torquay

Lymphoedema Support Group of SA

Ms Maureen Bartel (Chairperson)

26 Sandford St

Kensington Gardens SA 5068

Ph: (08) 8431 4190

Email: bartel.maureen@saugov.sa.gov.au

Tasmania Lymphoedema Support Group

Ms Jill Wood

42 Stanley St

Bellerive Hobart TAS 7018

Ph: (03) 6244 4632

Lymphoedema Association of Victoria Inc

Ms Mary D'Elia

PO Box 2412

North Ringwood VIC 3134

Ph: 1300 852 850

Email: info@lav.org.au

Website: www.lav.org.au

Lymphoedema Association of Western Australia

Joan Shepherd (Secretary)

PO Box 2037

Claremont North WA 6010

Ph: 0500 576 000

CONTINENCE SUPPORT GROUPS

Continence Foundation of Australia

The Continence Foundation of Australia exists to serve the interests of incontinent people throughout Australia by improving access to and availability of services, providing information and advice and promoting education, support and research.

The Foundation can be contacted at:

AMA House 293 Royal Parade

Parkville VIC 3052

Ph: (03) 9347 2522

Fax: (03) 9347 2533

Website: www.contfound.org.au

National Continence Helpline

The National Continence Helpline is a joint project of the Commonwealth Government and the Continence Foundation of Australia. It provides free, professional and confidential advice about any continence issue to people with incontinence, their families and carers. The Helpline also provides supplementary information for medical and allied health professionals

Ph: 1800 330 066

In addition to the National Office the Foundation also has State and Territory branches as follows:

CFA Victoria

C/- St George Health Service

283 Cotham Rd

Kew VIC 3101

Ph: (03) 9816 8266

Fax: (03) 9816 8366

Email: cfavic@continencevictoria.org

Website: www.continencevictoria.org

CFA ACT

Community Care, Continence Clinic

PO Box 825

Canberra City ACT 2601

Ph: (02) 6205 3308

Fax: (02) 6206 1162

CFA Western Australia

C/- Hollywood Private Hospital

GPO Box 591

Claremont WA 6910

Ph: (08) 9386 9777

Fax: (08) 9389 8001

Email: continencewa@optusnet.com.au

CFA South Australia

Contact National Office

Ph: (03) 9347 2522

Fax: (03) 9347 2533

CFA New South Wales

C/0 Cumberland Hospital

PO Box 2522

North Parramatta NSW 1750

Ph: (02) 9890 4165

Fax: (02) 9840 4163

Email: contfoundnsw@ozemail.com

CFA Tasmania

Contact National Office

Ph: (03) 9347 2522

Fax: (03) 9347 2533

CFA Northern Territory

Specialist Health Service

Territory Health Services

Ph: (08) 8922 7283

Fax: (08) 8922 7399

Email: gail.mcbean@nt.gov.au

CFA Queensland

Contact National Office

Ph: (07) 9347 2522

Fax: (03) 9347 2533

Alice Springs (CFA NT)

C/- Adolescent & Adult Health Services,

Community Health Services Centre

PO Box 721

Alice Springs NT 0871

Email: sandra.clyne@nt.gov.au

Look Good...Feel Better

A community service for women undergoing cancer treatment, sponsored by the Cosmetic, Toiletry and Fragrance Association of Australia Inc., dedicated to teaching women beauty techniques to help restore their appearance and self-image during chemotherapy and radiotherapy. Workshops are held every 6-8 weeks at selected cancer treatment centres. For further information, contact:

National Helpline: 1800 650 960

Services for lesbian women

Peer-based counselling about sexual health/health-related issues is available over the telephone through the Gay and Lesbian Community Services of Australia.

NSW, QLD, VIC and WA	1800 184 527.
SA	1800 182 233.
Tasmania	1800 633 900
NT	1800 184 527 (call will be re-directed to SA contact)

APPENDIX 10 - FINANCIAL ASSISTANCE FOR TRAVEL AND ACCOMMODATION

Patients travelling to the city for treatment may be eligible for a government scheme to provide financial assistance for travel and accommodation expenses. However, many patients are unaware of their eligibility for this support. This scheme has a different name in each State and Territory:

ACT	Interstate Patient Travel Assistance Scheme (IPTAS)
NSW	Isolated Patients' Travel and Accommodation Assistance Scheme (IPTAAS)
NT	Patient Assistance Travel Scheme (PATS)
QLD	Patient Travel Subsidy Scheme (PTSC)
SA	Patient Assistance Transport Scheme (PATS)
TAS	Patient Travel Assistance Program (PTAP)
VIC	Victorian Patient Transport Assistance Scheme (VPTAS)
WA	Patient Assisted Travel Scheme (PATS)

Patients should be advised that they may need to claim in advance in some states. In some states, support is available for family members, and some states also have patient accommodation available through the cancer organisations or hospitals at reduced costs. A list of available resources can be obtained from each State and Territory cancer organisation or local hospital.

APPENDIX II - SERVICES FOR PATIENTS FROM CULTURALLY AND LINGUISTICALLY DIVERSE BACKGROUNDS

The Translating and Interpreting Service (TIS) is a national service with offices in each State and Territory. The service offers both telephone and face-to-face interpreting. If an interpreter is needed to attend an appointment, this will need to be booked a few days in advance. TIS is available 24 hours a day, 7 days a week. The TIS can be contacted from anywhere in Australia, for the cost of a local telephone call, on 13 14 50.

Some states and territories also have other interpreter services available in a range of community languages. Some have health interpreters who are specially trained to interpret medical terms and procedures. The service is usually free of charge in public hospitals (some services do charge a fee). In addition to the interpreter services listed below, the patient's GP or local Departments of Social Security may be able to provide information on additional services in their area.

National (Australia Wide)

Translating and Interpreting Service (TIS) 13 14 50 (local call cost, 24 hour).
To book an on-site interpreter call 1300 655 081

ACT

ACT Health Care Interpreters (02) 6205 3333

NSW

Health Care Interpreter Service

Central & South Eastern Sydney	(02) 9515 3222
Northern Sydney	(02) 9926 7560 (02) 9962 5772 (A/H)
South Western Sydney	(02) 9828 6088 (02) 9616 8111 (A/H)
Western Sydney & Wentworth	(02) 9840 3456 (02) 9840 3456 (A/H)
Hunter	(02) 4924 6285 (02) 4921 3000 (A/H)
Illawarra	(02) 4274 4211
Greater Murray and Southern	1800 247 272
All other country areas	1800 674 994

NT

Northern Territory Interpreter and Translator Service

Darwin 1800 676 254

Alice Springs (08) 8951 5389

Aboriginal Translator services

Darwin (08) 8924 4300

(08) 8924 4223

Alice Springs (08) 8951 5576

(09) 8924 3400

QLD

No other accredited interpreter services. Call TIS: 13 14 50

SA

Interpreting and Translating Centre (ITC), Multicultural and Ethnic Affairs Commission (08) 8226 1990

TAS

AMIGOS Translate (03) 6288 5480

VIC

Central Health Interpreting Service (CHIS) (03) 9370 1222

Victorian Interpreting and Translating service (03) 9280 1955

WA

Multicultural Access Unit - Translation Service (08) 9400 9512

APPENDIX 12 - MULTICULTURAL CANCER INFORMATION SERVICE

This is a telephone service in Arabic, Cantonese, Mandarin, Greek and Italian for those diagnosed with cancer and their families.

What does the service provide?

- information about cancer in Arabic, Cantonese, Mandarin, Greek and Italian to those diagnosed with cancer and their families
- a confidential telephone service
- information workers who speak Arabic, Cantonese, Mandarin, Greek and Italian. Each information worker also speaks English
- emotional support for people diagnosed with cancer and their families and friends
- information about referral to other services related to cancer
- information about cancer including investigations and treatment options
- information on attitudes and beliefs related to cancer in people from non-English speaking backgrounds for health care providers and community workers
- feedback to doctors and other health care providers about the person's concerns (at the person's request)
- information for the media about cancer
- information sessions to language specific community groups
- some assistance to bilingual cancer support groups
- bi-lingual brochures on cancer.

About the Information Workers

The information workers are trained in the clinical, cultural and psychosocial aspects of cancer. They have a background in nursing, social work and counselling. The information workers receive regular debriefing sessions by a psychologist or counsellor.

For further details, contact the Service on (02) 9334 1758.

Contact details for the Bilingual Information Workers:

These numbers may be called from NSW and anywhere in Australia for the cost of a local call. The days listed are the 'usual' days of operation, but they may vary.

Arabic	Monday, Tuesday & Thursday	1300 301 625
Cantonese and Mandarin	Monday to Friday	1300 300 935
Greek	Tuesday, Thursday & Friday	1300 301 449
Italian	Monday, Thursday & Friday	1300 301 431

APPENDIX 13 - RECOMMENDED INTERNET SITES

This is not an exhaustive list but gives some indication as to what is available.

Australian

The Ovarian Cancer Program

www.ovariancancerprogram.org.au

The Cancer Council Australia

www.cancer.org.au

Australia's national non-government cancer control organisation.

The Cancer Council Victoria

www.accv.org.au

Victoria Cancer Council information and educational resources for all types of cancers.

The Cancer Council of South Australia

www.cancersa.org.au

South Australia Cancer Council information and educational resources for all types of cancers.

The Cancer Council New South Wales

www.cancercouncil.com.au

NSW Cancer Council information and educational resources for all types of cancers.

HealthInsite

www.healthinsite.gov.au

A wide range of up-to-date and quality assessed information on important health topics including cancer is available on this site.

OvCa Australia (National Ovarian Cancer Network)

www.ovca.org

Information on the OvCa Australia website is oriented for patients and others personally affected by ovarian cancer. Information is provided on symptoms, statistics, news and other links.

OvCare

<http://128.250.188/ovcare/>

OvCare is a national initiative focusing on ovarian cancer research and education. Website has general information on ovarian cancer, research projects and links to other cancer sites.

Ovarian Cancer Research Foundation

www.ocrf.com.au

The Ovarian Cancer Research Foundation (OCRF) has been established to foster research into ovarian cancer. The website provides general information on ovarian cancer, research projects, news and fund raising events.

Peter MacCallum Cancer Institute

www.petermac.org

Peter MacCallum Cancer Institute is a comprehensive specialist oncology centre providing cancer services in Melbourne and throughout Victoria, Australia. Website includes information about the institute's services and cancer library.

National Cancer Control Initiative

www.ncci.org.au

The NCCI is a partnership between the Cancer Council Australia and the Australian Government Department of Health and Ageing. It provides advice on all issues related to cancer control as well as manages a range of cancer related projects.

Australian Society of Gynaecologic Oncologists (ASGO)

www.users.bigpond.com.asgo

Provides a list of current practising Gynaecological Oncologists and has a list of Gynaecological Oncology Departments.

Gynaecological Cancer Society

www.gcsau.org

Information on website is for patients, carers & families, professionals and students. The information is holistic, authoritative and cancer specific, covering the full range of gynaecological cancers.

Clinical Trials Centre (NHMRC)

www.ctc.usyd.edu.au

Details of clinical trials and other research conducted in Australia.

International

National Cancer Institute

www.cancer.gov

Information developed by the US National Cancer Institute for health professionals, the general public, and cancer researchers from a variety of sources. Also offers links to Cancer Trials.

University of Pittsburgh Cancer Institute

www.upci.upmc.edu

A National Cancer Institute-designated Comprehensive Cancer Centre

American Cancer Society

www.cancer.org

Useful site providing information about cancer including information about the American Cancer Society, its publications, programs and local offices

CancerBACUP

www.cancerbacup.org.uk / www.cancerbacup.org.uk/ovary

The UK's leading cancer information service

<http://cancer.med.upenn.edu>

Sponsored by the University of Pennsylvania Cancer Centre. Directed towards physicians, health professionals, social workers, and cancer patients including their family and friends.

Institute of Cancer Research

www.icr.ac.uk

Information about the Institute plus information for patients and families.

International Agency for Research on Cancer

www.iarc.fr

Part of the World Health Organisation and responsible for coordinating and conducting research on the causes of human cancer.

*National Comprehensive Cancer Network (NCCN) and American Cancer Society (ACS)
Cancer Treatment Guidelines for patients*

www.nccn.org

The NCCN and ACS have translated the NCCN Oncology Practice Guidelines into easy-to-understand information that can assist patients and families in making medical decisions. While some guidelines provide information about breast, colon and rectal, lung, and prostate cancer, the others provide information about cancer related physical symptoms such as fatigue, pain, and nausea and vomiting. Access is available by clicking on the 'NCCN/ACN treatment guidelines' link in the above website.

PubMed

www.ncbi.nlm.nih.gov/entrez/query.fcgi

US National Library of Medicine's search service. Provides access to citations in MEDLINE and other databases.