

## SIGN 135 • Management of epithelial ovarian cancer

*A national clinical guideline*

November 2013 • Revised 2018

## KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

### LEVELS OF EVIDENCE

1 <sup>++</sup>	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1 <sup>+</sup>	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 <sup>-</sup>	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2 <sup>++</sup>	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2 <sup>+</sup>	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 <sup>-</sup>	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

### GRADES OF RECOMMENDATION

*Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.*

<b>A</b>	At least one meta-analysis, systematic review, or RCT rated as 1 <sup>++</sup> , and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1 <sup>+</sup> , directly applicable to the target population, and demonstrating overall consistency of results
<b>B</b>	A body of evidence including studies rated as 2 <sup>++</sup> , directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1 <sup>++</sup> or 1 <sup>+</sup>
<b>C</b>	A body of evidence including studies rated as 2 <sup>+</sup> , directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2 <sup>++</sup>
<b>D</b>	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2 <sup>+</sup>

### GOOD PRACTICE POINTS

✓	Recommended best practice based on the clinical experience of the guideline development group
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Scottish Intercollegiate Guidelines Network

# Management of epithelial ovarian cancer

A national clinical guideline



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# 1 Introduction

## 1.1 THE NEED FOR A GUIDELINE

Ovarian cancer was the sixth most frequently diagnosed cancer in women in Scotland in 2011, representing 3.7% of all newly diagnosed cancers, and 583 new cases in 2011. Overall incidence has, however, fallen by 10.1% during the 10 years to 2011 ( $p=0.0009$ ).<sup>1</sup> Ovarian cancer occurs as either an epithelial or a non-epithelial tumour. Epithelial tumours account for over 90% of all ovarian cancers and are the focus of this guideline.<sup>2</sup>

The disease is rare in girls and in women under the age of 30 years, with incidence increasing with age.<sup>3</sup> The aetiology of the disease is unknown. It is more common in nulliparous women, and epidemiological studies have shown a significant reduction in ovarian cancer risk in women who have used the oral contraceptive pill.<sup>4</sup> Most cases of epithelial ovarian cancer are sporadic, occurring in individuals with no family history of the disease. Among women in Scotland with no family history the lifetime risk of developing ovarian cancer is estimated to be 1 in 55.<sup>1</sup> In 5% to 10% of women with the disease, an inherited predisposition is a major contributory cause.<sup>5</sup>

For the majority of women with epithelial ovarian cancer standard therapy consists of a combination of surgery and chemotherapy. Survival is dependent on the stage of cancer at initial presentation (*see Annex 2*).

Although epithelial ovarian cancer has been described as a 'silent killer', because in over 60% of cases advanced disease is found at initial diagnosis,<sup>6</sup> recent evidence has shown that many women report abdominal symptoms to their general practitioner (GP) in the year preceding diagnosis (*see section 4.1.1*).

In Scotland the overall five year survival rate improved from 25.7% among patients diagnosed in 1983-87 to 37.8% among patients diagnosed in 2003-2007<sup>7</sup> and mortality fell by 13.6% in the 10 years to 2011 ( $p=0.007$ ).<sup>1</sup> In 2011, 363 women in Scotland died from the disease.<sup>1</sup>

Treatment is not usually curative. A typical patient will develop relapsed disease requiring repeated courses of chemotherapy. Relapsed disease is invariably fatal and its diagnosis has a huge impact on patients and their carers. The absence of a recognisable preventable cause and of any effective screening programme means that prospects for improving survival lie with earlier diagnosis and optimal management after initial presentation. The goal for healthcare professionals must be to ensure that where cure is not possible a woman can have a good quality of life with judicious use of surgery and chemotherapy.

### 1.1.1 UPDATING THE EVIDENCE

This guideline updates SIGN 75, published in October 2003, to reflect the most recent evidence. The key questions addressed in this update are listed in Annex 1.

Where no new evidence was identified to support an update, text and recommendations are reproduced verbatim from SIGN 75. The original supporting evidence was not re-appraised by the current guideline development group.

## 1.2 REMIT OF THE GUIDELINE

### 1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the management of epithelial ovarian cancer. It excludes the management of borderline tumours.

### 1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of interest to primary care staff, medical and clinical oncologists, gynaecologists, specialist nurses, community nurses, allied health professionals, geneticists, pathologists, specialists in laboratory medicine, pharmacists, radiologists, and palliative care specialists.

### 1.2.3 SUMMARY OF UPDATES TO THE GUIDELINE, BY SECTION

1	Introduction	Updated
2	Key recommendations	New
3	Screening and the role of prophylactic salpingo-oophorectomy	Completely revised
4	Diagnosis	Completely revised
5	Surgical management	Completely revised
6	Chemotherapy	Completely revised
7	Follow up	Completely revised
8	Management of malignant bowel obstruction in relapsed disease	Unchanged
9	Provision of information	Completely revised
10	Implementing the guideline	Completely revised
11	The evidence base	New
Annex 1	Key questions addressed in this update	New
Annex 2	Staging carcinoma of the ovary	Unchanged
Annex 3	Classification of ovarian cancer	Completely revised

Sections 7 (clinical trials) and 9 (specialist palliative care) in SIGN 75 have been removed from this version of the guideline because these are generic topics not specific to the management of epithelial ovarian cancer. Information on resource implications of recommendations, previously in Annex 3, is now in section 10.2.

## 1.3 DEFINITIONS

The International Federation of Gynaecology and Obstetrics (FIGO) staging system used throughout this guideline is given in Annex 2.<sup>8</sup> The histological classification of ovarian cancer is given in Annex 3.

## 1.4 STATEMENT OF INTENT

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.



#### 1.4.1 PRESCRIBING OF LICENSED MEDICINES OUTWITH THEIR MARKETING AUTHORISATION

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off label' use.

Medicines may be prescribed off label in the following circumstances:

- for an indication not specified within the marketing authorisation
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.

*"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability."<sup>9</sup>*

The General Medical Council (GMC) recommends that when prescribing a medicine off label, doctors should:

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists)
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the current version of the British National Formulary (BNF).<sup>9</sup> The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.<sup>10</sup>

#### 1.4.2 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

The Scottish Medicines Consortium (SMC) provides advice to NHS Boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 10.4.

## 2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

### 2.1 SCREENING AND THE ROLE OF PROPHYLACTIC SALPINGO-OOPHORECTOMY

- D** All women with non-mucinous ovarian or fallopian tube cancer should be offered *BRCA1* and *BRCA2* mutation testing.
- D** Screening for ovarian cancer in high risk groups should only be offered in the context of a research study.
- ✓ Women with a family history that appears to place them at high risk of developing ovarian cancer should be offered referral to a Clinical Genetics Service for assessment, confirmation of family history and consideration of genetic testing of an affected family member.

### 2.2 DIAGNOSIS

- C** In women presenting in general practice with one or more symptoms of abdominal distension or bloating with or without abdominal pain, feeling full quickly, difficulty eating, or urinary symptoms, of less than 12 months duration and occurring more than 12 times per month a diagnosis of ovarian cancer should be considered.
- D** CA125 blood serum level should be measured and urgent pelvic ultrasound carried out in women with persistent abdominal distension or feeling full and/or loss of appetite or pelvic or abdominal pain or increased urinary urgency and/or frequency (particularly if occurring more than 12 times per month and especially if she is over 50).  
If symptoms persist or worsen despite a normal CA125 blood serum level and a negative ultrasound scan, refer to secondary care.
- B** Computed tomography of the abdomen and pelvis should be performed in secondary care for all patients suspected of having ovarian cancer who have a Risk of Malignancy Index score greater than 200.
- D** Throughout their care pathway patients with ovarian cancer should have access to a clinical nurse specialist who should be an integral member of the gynaecological cancer team.

### 2.3 SURGICAL MANAGEMENT

- A** The use of neoadjuvant chemotherapy in women with stage IIIc or IV ovarian cancer may be considered as an alternative to primary debulking surgery.
- ✓ With regard to selecting who will benefit from neoadjuvant chemotherapy, treatment should be individualised to the patient taking into account resectability, age, histology, performance status and after ruling out the possibility of other primary tumours, and after full discussion at multidisciplinary team meetings.

## 2.4 CHEMOTHERAPY

**B** All women with high-grade early stage (Ia-Ib) ovarian cancer should be considered for adjuvant chemotherapy.

✓ Patients with low-grade serous, clear cell and mucinous histological subtypes should be considered for clinical trials.

## 2.5 FOLLOW UP

**A** In the absence of symptoms, routine measurement of CA125 during follow up is not mandatory.

## 3 Screening and the role of prophylactic salpingo-oophorectomy

### 3.1 SCREENING FOR OVARIAN CANCER IN THE GENERAL POPULATION

A large randomised controlled trial (RCT) of 78,216 women aged 55 to 74 in the United States demonstrated that testing for CA125 blood serum level combined with transvaginal ultrasound (TVUS) conferred no benefit in screening for ovarian cancer in the general population compared to usual care.<sup>11</sup> In this study, ovarian cancer was diagnosed in 212 women (5.7 per 10,000 person-years) in the intervention group and 176 (4.7 per 10,000 person-years) in the usual care group (rate ratio 1.21, 95% confidence interval (CI) 0.99 to 1.48). There were 118 deaths from ovarian cancer in the intervention group (3.1 per 10,000 person years) and 100 deaths (2.6 per 10,000 person-years) in the usual care group (mortality risk ratio (RR) 1.18, 95% CI 0.82 to 1.71).

1<sup>++</sup>

A current UK RCT (the UK Collaborative Trial of Ovarian Cancer Screening - UKCTOCS) designed to assess the effect of screening on mortality is expected to report in 2015. The results of the prevalence (initial) screen in UKCTOCS of 202,638 postmenopausal women aged 50-74 randomly assigned to no treatment, or annual CA125 screening with transvaginal ultrasound scan as a second line test, or transvaginal ultrasound alone, published in 2009, established that the screening strategies are feasible.<sup>12</sup> As yet, no clear benefit of such screening has been demonstrated.

Screening the high risk population is discussed in section 3.3.

A

**Screening for ovarian cancer in the general population should not be performed outwith the research setting.**

### 3.2 IDENTIFYING WOMEN AT HIGH RISK OF DEVELOPING OVARIAN CANCER

#### 3.2.1 DEFINING HIGH RISK GROUPS USING FAMILY HISTORY

Family history can be used to define women who are at increased risk of ovarian cancer.<sup>13</sup> A woman is defined as being at high risk of ovarian cancer if she meets one of the following criteria:

- she is a known carrier of relevant cancer gene mutations including *BRCA1*, *BRCA2*, mismatch repair genes
- she is an untested first degree relative of an individual with a mutation in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or mismatch repair genes
- she is an untested second degree relative, through an unaffected man, of an individual with a mutation in *BRCA1*, *BRCA2*, *RAD51C*, *RAD51D* or mismatch repair genes
- she has a first degree relative (mother, father, sister, brother, daughter or son) affected by cancer within a family that meets one of the following criteria:
  - two or more individuals with ovarian cancer, who are first degree relatives of each other
  - one individual with ovarian cancer at any age, and one with breast cancer diagnosed under age 50 years, who are first degree relatives of each other
  - one relative with ovarian cancer at any age, and two with breast cancer diagnosed under 60 years, who are connected by first degree relationships
  - three or more family members with colon cancer, or two with colon cancer and one with stomach, ovarian, endometrial, urinary tract or small bowel cancer in two generations. One of these cancers must be diagnosed under age 50 years and affected relatives should be first degree relatives of each other
  - one individual with both breast and ovarian cancer.

Individuals meeting the above criteria may be eligible for referral for prophylactic salpingo-oophorectomy by age 40 and breast screening or, in some, prophylactic mastectomy.<sup>14,15</sup>

- ✓ Women with a family history that appears to place them at high risk of developing ovarian cancer should be offered referral to a Clinical Genetics Service for assessment, confirmation of family history and consideration of genetic testing of an affected family member.

### 3.2.2 DEFINING HIGH RISK GROUPS USING GENETIC TESTING

A high risk of ovarian cancer is associated with mutation in the tumour suppressor genes *BRCA1* and *BRCA2*, in the mismatch repair genes associated with Hereditary Nonpolyposis Colorectal Cancer (HNCC) families, and rarely, in *RAD51C* and *RAD51D*.<sup>16,17</sup> Mutation in the *BRCA1* or *BRCA2* gene is estimated to confer a lifetime risk of ovarian cancer of 24-40% and 8-18%, respectively. *BRCA1* and *BRCA2* female mutation carriers also have an increased risk of fallopian tube and breast cancer. *BRCA1* and *BRCA2* male carriers have an increased risk of breast and prostate cancer. Other cancers associated with *BRCA2* mutations are pancreatic cancer, gall bladder/bile duct cancer, stomach cancer and melanoma.<sup>18-21</sup> The mismatch repair genes confer an increased lifetime risk of ovarian cancer of approximately 9-12% in addition to an increased risk of endometrial cancer.<sup>22</sup>

3

A systematic review has indicated that genetic testing is cost effective and should be performed in a clinical genetics setting in families with ovarian and/or breast cancer where the combined risk of *BRCA1* and *BRCA2* mutation exceeds 10%.<sup>23</sup> This is equivalent to a Manchester score of 15 or more.<sup>24</sup>

A number of studies have shown that women with non-mucinous ovarian cancer, unselected for family history, have an overall increased *BRCA1* or *BRCA2* mutation detection rate of between 6.2% and 17.5%.<sup>20,25-29</sup> The detection rate in women with non-mucinous ovarian cancer with no family history of ovarian or breast cancer is lower, ranging from 3.5% to 9%.<sup>27,28</sup> Only one study reviewed did not detect a mutation in women with no family history.<sup>26</sup> Overall, testing in cases of non-mucinous ovarian cancer is justified for the benefit of the family, even in women with no family history of breast or ovarian cancer.

2+

3

In the four studies that included women with mucinous tumours, no *BRCA1* or *BRCA2* mutations were identified.<sup>20,26-28</sup>

3

Molecular assessment for Lynch syndrome should be considered in the most appropriate affected individuals from families that meet the modified Amsterdam criteria.<sup>30</sup>

3

One study of 108 women with carcinoma of the fallopian tube in two centres in the USA and Canada showed that 30.6% of the women had *BRCA* mutations, 23 (21.3%) in *BRCA1* and 10 (9.3%) in *BRCA2*. The rate was higher in those diagnosed before age 60 (40.3%) than in those diagnosed at 60 years or older (17.4%).<sup>31</sup>

3

**D All women with non-mucinous ovarian or fallopian tube cancer should be offered *BRCA1* and *BRCA2* mutation testing.**

**D Women with ovarian cancer who have a family history of breast, ovarian or colon cancer should have a genetic risk assessment.**

**D *BRCA1* and *BRCA2* mutation analysis should be considered in a family where there is a 10% or greater risk of a mutation being present.**

### 3.2.3 REFERRAL TO CANCER GENETICS

General practitioners benefit from expert support from a specialist genetics service.<sup>32</sup> Highest demand and utilisation of familial cancer services relates to breast and/or ovarian cancer.<sup>33</sup>

4

Guidance from the Scottish Executive in 2001 provided information on risk stratification, counselling and management of patients with a family or personal history of cancer that might predispose them to breast, ovarian or colorectal cancer. The guidance included a referral pathway that indicated that those suspected as being at medium or high risk should be referred to genetic services for a detailed risk assessment.<sup>14</sup> Further guidance, issued in January 2009, confirmed that the 2001 guidance relating to ovarian cancer remained extant.<sup>15</sup>

4

- ✓ Close collaboration between primary care and specialist cancer genetics services is to be encouraged so that genetic cancer risk assessment in individuals who are at medium or high risk can be carried out efficiently.

### 3.3 SCREENING HIGH RISK GROUPS

One systematic review and three small cohort studies suggest that pre-symptomatic screening by grey scale ultrasound (with or without Doppler), CA125 blood serum level (*see section 4.1.2*), pelvic examination or combinations of these, are not effective in detecting tumours at an early stage (*see Annex 2*).<sup>34-37</sup> No clear evidence was identified as to whether screening in high risk groups has an impact on mortality from ovarian cancer. Two large scale studies addressing this issue (the UK Familial Ovarian Cancer Screening Study, and the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial in the USA) are still to report.

1+  
3

- D** Screening for ovarian cancer in high risk groups should only be offered in the context of a research study.

### 3.4 PROPHYLACTIC SALPINGO-OOPHORECTOMY

Women identified as being at high risk of ovarian cancer can be offered prophylactic salpingo-oophorectomy. The decision whether or not to proceed to prophylactic salpingo-oophorectomy is influenced by the fact that most women at increased risk of ovarian cancer are also at increased risk of breast cancer and there is evidence that oophorectomy reduces breast cancer risk in these cases.<sup>38</sup>

2++

Two large cohort studies confirm the benefits of prophylactic salpingo-oophorectomy for carriers of *BRCA1* or *BRCA2* mutations. Risk reduction for ovarian cancer is 96% and for breast cancer is 53% if surgery is carried out pre-menopausally.<sup>39</sup> The risk of primary peritoneal carcinoma is reduced to between 0.1%<sup>39</sup> and 0.5%<sup>38</sup> per year. This is considerably less than the lifetime risk of ovarian cancer for those who retain their ovaries. This benefit is not affected by giving hormone replacement therapy (HRT) to women whose ovaries are removed before the natural menopause.

Studies have shown that 2.3% of patients undergoing prophylactic salpingo-oophorectomy had previously unsuspected early stage ovarian cancer.<sup>37,38</sup>

2++  
3

Ovarian cancer is rare in *BRCA1* carriers under age 40 and *BRCA2* carriers under age 50, affecting 2-3% of women in these groups. However, 26-34% of female *BRCA2* carriers will develop breast cancer by age 50. As risk reducing bilateral salpingo-oophorectomy before age 40 provides the greatest reduction in breast cancer risk,<sup>40</sup> optimal timing is considered to be between the ages of 35-40 years and after childbearing is complete.

2+

- C** Women with genetic mutations of *BRCA1* or *BRCA2* genes should be offered prophylactic oophorectomy and removal of fallopian tubes at a relevant time in their life.

- ✓ Women at high risk in whom mutations have not been identified should have the opportunity to discuss the advantages and disadvantages of prophylactic salpingo-oophorectomy.

- ✓ Hormone replacement can be used after oophorectomy until the time of natural menopause without losing the benefits of breast cancer risk reduction.

#### 3.4.1 FERTILITY CONSERVATION

The possibility of preserving fertility in women at high risk of ovarian cancer, for example those who are *BRCA* mutation carriers, by undertaking bilateral salpingectomy (BS) followed by oophorectomy at a later stage has been considered.<sup>41,42</sup> However, no studies were identified that adequately assessed the impact of BS with retention of ovaries on the incidence of ovarian cancer. Therefore, BS alone cannot be recommended in a population at high risk of ovarian cancer (*see section 5.3.4 on fertility conserving surgery*).

## 3.4.2 QUALITY OF LIFE ISSUES

One qualitative study, one retrospective case control study and one cohort study looking at quality of life issues were identified.<sup>43-45</sup> Two of the studies report that women with *BRCA1* or *BRCA2* mutations regard prophylactic salpingo-oophorectomy as an acceptable option for ovarian cancer risk reduction.<sup>43,45</sup> The cohort study found that these patients do not expect prophylactic salpingo-oophorectomy to impair their quality of life.<sup>45</sup> The qualitative study found that women with *BRCA1* or *BRCA2* mutations have strong opinions regarding the costs and benefits of prophylactic salpingo-oophorectomy and that they would like more information about the physical and emotional after-effects of prophylactic salpingo-oophorectomy both before, and after, surgery.<sup>43</sup>

3  
4

The retrospective case control study investigated women who had chosen prophylactic salpingo-oophorectomy instead of prolonged screening and suggested that these women may have more physical and emotional symptoms than women who remain on an ovarian cancer screening programme but that they report equivalent levels of cancer worry.<sup>44</sup>

3

The studies identified highlight the importance of counselling, support and information for women making a decision about prophylactic salpingo-oophorectomy. There is insufficient evidence to make a recommendation.



Women who decide to have prophylactic salpingo-oophorectomy should be offered counselling, support and information before and after surgery.

## 4 Diagnosis

### 4.1 PRIMARY CARE

#### 4.1.1 SIGNS AND SYMPTOMS

Retrospective studies show that women with ovarian cancer present with non-specific symptoms including abdominal pain and bloating, changes in bowel habit, urinary and/or pelvic symptoms.<sup>46-48</sup> Cachexia is uncommon and women with advanced disease often look surprisingly well. Most women with ovarian cancer are diagnosed when they already have advanced disease. On average, a GP will see only one new case every five years.<sup>49</sup> Patients who present with non-specific gastrointestinal symptoms may be misdiagnosed as suffering from irritable bowel syndrome.

2+  
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A systematic review and six observational studies,<sup>50-56</sup> two of which were UK based,<sup>55,56</sup> looked at symptoms in women with ovarian cancer, the findings of which are generalisable to Scotland. The studies consistently reported that ovarian cancer is not an asymptomatic condition, with only 5-10% of women being asymptomatic. All studies identified abdominal distension/bloating as the most important symptom together with abdominal/pelvic pain, feeling full quickly or difficulty eating. Other symptoms found by some studies to be associated with ovarian cancer were postmenopausal bleeding, rectal bleeding, urinary symptoms and weight loss.

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The systematic review included 21 studies of varying quality, three of which were case control studies and the remainder cohort studies.<sup>50</sup> Fourteen studies took symptoms directly from patients (10 using symptom checklists) and seven took symptoms from medical records. Data collection was retrospective in 20 of the studies, varying from two weeks to 12 years after diagnosis. The most frequently reported symptoms (reported by at least 50% of respondents) were abdominal pain or discomfort, abdominal bloating and abdominal swelling.

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A case control study from the USA based on anonymous self reporting of symptoms by 128 ovarian cancer patients and 1,709 women seeking care in primary care clinics (control group) showed that women with ovarian cancer were significantly more likely than the control group to have increased abdominal size (odds ratio (OR) 7.4, 95% CI 3.8 to 14.2), bloating (OR 3.6, 95% CI 1.8 to 7.0), urinary urgency (OR 2.5, 95% CI 1.3 to 4.8), difficulty eating (OR 2.5, 95% CI 1.3 to 5.0), abdominal pain (OR 2.3, 95% CI 1.2 to 2.4) and pelvic pain (OR 2.2, 95% CI 1.2 to 3.9).<sup>54</sup> Women with malignant masses typically experienced symptoms 20-30 times per month and had significantly more symptoms of higher severity and more recent onset than women with benign masses or women in the control group. They also had a shorter median duration of symptoms (6 months or less compared with 12-24 months for the other two groups).

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A further case control study from the USA of 102 cases and 102 controls (matched for age, length of "membership of healthcare programme", and location of primary care facility) with a mean age of 58, undertook a structured review of medical records and symptoms recorded during the two years prior to diagnosis. However, the reviewer was not blinded to the status of each patient. The study looked at likelihood ratios (for symptoms with a statistically significant excess in cases) and found that none exceeded chance expectation in the 33 cases with stage Ia and Ib disease but that there was an excess among the 69 patients with stage Ic-IV disease, particularly for symptoms recorded in the six months prior to diagnosis. Symptoms reported by the cases were predominantly abdominal and gastrointestinal.<sup>52</sup>



Three studies were identified that attempted to predict the risk of ovarian cancer based on specific combinations of signs and symptoms.<sup>53,55,56</sup> In a case control study from the USA, 149 women with ovarian cancer and 488 women at high risk of having or developing ovarian cancer (referred for ultrasound or taking part in a screening programme) completed a symptom survey either preoperatively or pre-ultrasound, rating severity, frequency and duration of 23 symptoms. Logistic regression was used to find a model that predicted ovarian cancer, with the greatest sensitivity being for a model including pelvic/abdominal pain, increased abdominal size/bloating, feeling full/difficult eating for <12 months and >12 times per month. The sensitivity for identifying early stage disease was 56.7% and for advanced disease 79.5%, with specificities ranging from 86-90%.<sup>53</sup> This has become known as the Goff Index. There are, however, concerns about the comparability of the cases and controls and the fact that the controls were drawn from a high risk population.

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A retrospective cohort study comprising a derivation cohort of 1,158,723 women and a validation cohort of 608,862 women aged 30 to 84 and registered with GP practices in England and Wales was used to derive and validate an algorithm for identifying women with suspected ovarian cancer in primary care.<sup>56</sup> The outcome was diagnosis of ovarian cancer in the two years after study entry. The biggest independent predictors were abdominal distension, family history of ovarian cancer and abdominal pain (hazard ratios (HR), 23.1, 9.8 and 7.0, respectively). The algorithm showed that the 10% of women with the highest predicted risks contained 63% of all ovarian cancers diagnosed over the next two years.

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In a further UK based study of 212 women diagnosed with ovarian cancer in 2000-2007, and 1,060 controls (5 per case) comprising women aged 40 years and older from 39 GP practices in Devon, patient case notes were searched for symptoms recorded in the year before diagnosis. Symptoms were coded by three researchers blinded to diagnosis. Multivariate analysis showed that seven symptoms were independently associated with ovarian cancer: abdominal distension (positive predictive value (PPV) 2.5%, 95% CI 1.2 to 5.9; OR 240, 95% CI 46 to 1200), postmenopausal bleeding (PPV 0.5%, 95% CI 0.2 to 0.9; OR 24, 95% CI 9.3 to 64), loss of appetite (PPV 0.6%, 95% CI 0.3 to 1.0; OR 17, 95% CI 6.1 to 50), increased urinary frequency (PPV 0.2%, 95% CI 0.1 to 0.3; OR 16, 95% CI 5.6 to 48) abdominal pain (PPV 0.3%, 95% CI 0.2 to 0.3; OR 12, 95% CI 6.1 to 22), rectal bleeding (PPV 0.2, 95% CI 0.1 to 0.4; OR 7.6, 95% CI 2.5 to 23) and abdominal bloating (PPV 0.3, 95% CI 0.2 to 0.6; OR 5.3, 95% CI 1.8 to 16). In 181 (85%) of cases and 164 (15%) of controls, at least one of these seven symptoms was reported to primary care before diagnosis. After excluding symptoms reported in the 180 days before diagnosis, abdominal distension, urinary frequency and abdominal pain remained independently associated with a diagnosis of ovarian cancer.<sup>55</sup> Limitations of this study include its case control design, with its inherent potential for systematic differences between cases and controls, and the reliance on GP recording of symptoms which is often incomplete.

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A further large, population based study in the USA of 2,125 women (812 cases aged 35-74 with primary invasive or borderline epithelial ovarian cancer, and 1,313 population-based controls with at least one ovary and no history of ovarian cancer) assessed symptoms (pelvic or abdominal pain or bloating, feeling full, urinary urgency or frequency) using the Goff index (considered positive when symptoms were present at least daily for at least one week, with an onset of less than 12 months before diagnosis or reference date), or the American Cancer Society consensus recommendations (fulfilled when symptoms were present for at least one month, with onset of less than 12 months before diagnosis or reference date). The study concluded that the use of symptoms to trigger medical evaluation for ovarian cancer is likely to result in diagnosis of the disease in only one of 100 women in the general population with such symptoms.<sup>57</sup> Symptoms appeared in most cases within five months of diagnosis. Women with early-stage ovarian cancer were somewhat less likely to have symptoms (except nausea) than those with late-stage cancer. The estimated positive predictive value of the symptoms was 0.6-1.1% overall and less than 0.5% for early-stage disease. Recall bias was likely as patient interviews to determine symptoms took place nine months after diagnosis for cases and 10 months after reference date for controls.

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Identification of symptoms at an early stage could lead to earlier detection of ovarian cancer and avoid investigation of women who do not have the condition. It is possible that identification and dissemination of the specific symptoms could increase the number of urgent referrals putting pressure on tertiary investigative services and this would need to be addressed.

One descriptive study examined the impact of delayed referral from primary care on survival. Delay in referral was not found to be a frequent occurrence and did not impact on survival.<sup>58</sup>

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**C** In women presenting in general practice with one or more symptoms of abdominal distension or bloating with or without abdominal pain, feeling full quickly, difficulty eating, or urinary symptoms, of less than 12 months duration and occurring more than 12 times per month a diagnosis of ovarian cancer should be considered.

#### 4.1.2 INVESTIGATIONS IN PRIMARY CARE

Measurement of CA125 in blood serum is the test most widely used to detect ovarian cancer. CA125 is a glycoprotein and elevated concentrations of CA125 are associated with malignant tumours of the pancreas, breast, lung, colon and ovary.<sup>59</sup> Menstruation and benign conditions such as endometriosis, pelvic inflammatory disease and liver disease can also be associated with elevated concentrations of CA125.<sup>60</sup> CA125 may also be elevated in women with ascites, pleural or pericardial effusions and in women who have had a recent laparotomy.<sup>61</sup>

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Approximately 80% of patients with advanced ovarian cancer have elevated concentrations of CA125 in the blood serum. However, no more than 50% of patients with clinically detectable stage I disease have elevated CA125 levels.<sup>62</sup>

Recent guidance from NICE recommends that a woman who presents to her GP with symptoms of persistent abdominal distension or feeling full and/or loss of appetite or pelvic or abdominal pain or increased urinary urgency and/or frequency (particularly if occurring more than 12 times per month and especially if she is over 50) should have their CA125 level measured and if it is  $\geq 35$  IU/ml should have an ultrasound of the abdomen and pelvis. NICE also recommends that women over 50 with symptoms within the last 12 months suggestive of irritable bowel syndrome, and women with any of unexplained weight loss, fatigue or changes in bowel habit in whom ovarian cancer is suspected, should have their CA125 level measured.<sup>63</sup>

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**D** CA125 blood serum level should be measured and urgent pelvic ultrasound carried out in women with persistent abdominal distension or feeling full and/or loss of appetite or pelvic or abdominal pain or increased urinary urgency and/or frequency (particularly if occurring more than 12 times per month and especially if she is over 50).

If symptoms persist or worsen despite a normal CA125 blood serum level and a negative ultrasound scan, refer to secondary care.

## 4.2 SECONDARY CARE

### 4.2.1 RISK OF MALIGNANCY INDEX

There are two scoring systems for assessing malignancy risk, the Risk of Malignancy Index 1 (RMI 1) and the Risk of Malignancy Index 2 (RMI 2), each of which calculates scores using ultrasound features, menopausal status and preoperative CA125 level according to the equation:

$\text{RMI score} = \text{ultrasound score} \times \text{menopausal score} \times \text{CA125 level in U/ml}$ .

The original RMI 1 scoring system and the revised RMI 2 system are both outlined in Table 1.<sup>64,65</sup> The RMI 2 score gives greater weight to the ultrasound findings and menopausal status than the RMI 1 score.

Table 1: The risk of malignancy index (RMI) scoring system

Feature	RMI 1 Score	RMI 2 Score
Ultrasound features: <ul style="list-style-type: none"> <li>• multilocular cyst</li> <li>• solid areas</li> <li>• bilateral lesions</li> <li>• ascites</li> <li>• intra-abdominal metastases</li> </ul>	0 = none 1 = one abnormality 3 = two or more abnormalities	0 = none 1 = one abnormality 4 = two or more abnormalities
Premenopausal	1	1
Postmenopausal	3	4
CA125	U/ml	U/ml
RMI score = ultrasound score x menopausal score x CA125 level in U/ml		

A good quality systematic review showed that the RMI 1 was the most accurate scoring system studied with estimated pooled sensitivity and specificity using a threshold of >200, as originally proposed by Jacobs et al (1990),<sup>64</sup> to indicate malignancy of 78% (95% CI 71 to 85%) and 87% (95% CI 83 to 91%), respectively.<sup>66</sup> A more recent, good quality, systematic review including four meta-analyses and 53 primary diagnostic accuracy studies showed a similar pooled sensitivity and specificity of RMI 1 of 79.2% (95% CI 73.6 to 83.9) and 91.7% (95% CI 87.2 to 94.6), respectively, using the threshold score of 200.<sup>67</sup> This review also demonstrated that whilst RMI 2 has near identical pooled sensitivity of 79% (95% CI 71 to 87%) to RMI 1, it has a lower specificity of 81% (95% CI 72 to 90%), also using a threshold of 200, and has been validated in fewer studies.

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Several smaller diagnostic studies investigating which RMI scoring systems (including RMI 1, RMI 2 and the newer RMI 3 and RMI 4) perform best have shown mixed results,<sup>68-70</sup> supporting the view that explicit scoring systems are broadly similar in diagnostic competence.

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It has been suggested that RMI and other explicit scoring systems may be less sensitive than ultrasound morphological scores, but are more specific. Other morphological scoring systems are being developed that may supersede RMI 1, but these require more extensive external validation and may be more complicated to use in practice.<sup>67</sup>

A RMI 1 score can only be attained if the ultrasound report is explicit in describing the features used in its calculation. A locally agreed standardised report for the description of pelvic masses is therefore recommended.

**B Risk of Malignancy Index 1 score with threshold of 200 should be used to predict the likelihood of ovarian cancer. Patients with an RMI 1 score greater than 200 should be referred to a gynaecology-oncology multidisciplinary team.**

✓ In order to allow the calculation of RMI 1, ultrasound reports should list the presence or absence of the features that make up the ultrasound component of this scoring system.

✓ Although an RMI 1 threshold of 200 is recommended, benign conditions may cause elevation of the RMI score and early malignancy may not.

#### 4.2.2 FURTHER RADIOLOGICAL IMAGING

Although the FIGO staging system for gynaecological malignancies is a surgical-pathological staging system, the incorporation of radiological investigation is necessary in optimising patient management.

When ovarian malignancy is considered likely based on clinical assessment and an RMI 1 score greater than the threshold of 200, cross-sectional imaging in secondary care, in the form of a computed tomography (CT) scan of the abdomen and pelvis, is indicated to help assess the extent of disease and to help exclude alternative diagnoses.

Several recent systematic reviews on the diagnostic performance of magnetic resonance imaging (MRI) in characterising adnexal masses as malignant showed that CT and MRI are comparable.<sup>67,71-73</sup> No systematic reviews were identified that addressed the performance of MRI on staging of ovarian cancer, and although there is evidence that it performs as well as CT,<sup>74</sup> there is no evidence that it is superior. Since MRI takes longer to perform, is more prone to artefact, has difficulty in giving high resolution coverage of the entire abdomen and pelvis, and is less readily available, its routine use in diagnosis or staging for ovarian cancer is not advocated, and CT is considered the preferred option.

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MRI is, however, useful in diagnosing certain alternative benign pathologies (ie, fibroid disease, endometriosis, dermoid cysts) in women in whom ovarian malignancy is thought less likely, but who present with a pelvic mass. It should therefore be used for lesion characterisation if a pelvic mass is detected on physical examination or ultrasound, but the clinical likelihood of malignancy is thought to be low. MRI can also be used if there is a contraindication to contrast enhanced CT.

Evidence for the diagnostic ability and overall staging performance of positron emission tomography-computed tomography (PET-CT) in the initial evaluation of ovarian cancer is limited, and confined to non-systematic descriptive reviews.<sup>75-77</sup> Two primary studies describe PET-CT performance in both characterisation of the primary lesion and staging,<sup>78,79</sup> and one further primary study describes staging by PET-CT.<sup>80</sup>

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A meta-analysis of metastatic lymph node detection with CT, MRI, PET and PET-CT and a diagnostic accuracy study comparing CT and PET-CT for detection of supradiaphragmatic metastatic nodes were also found.<sup>81,82</sup> Taken together, this evidence suggests that PET-CT or PET Contrast Enhanced CT may be more accurate than CT alone at characterising an adnexal mass as malignant, and may be more accurate in metastatic lymph node detection and overall staging. There is currently, however, insufficient evidence that these techniques give significant additional benefit over CT alone. In combination with the lack of availability of readily accessible PET-CT, this modality, at present, cannot be recommended in the initial staging of ovarian cancer.

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There is a lack of evidence to advocate routine CT imaging of the entire thorax in all patients. Scanning of the abdomen and pelvis should, however, include the lung bases to allow assessment for the presence of pleural effusions and suspicious cardiophrenic lymph nodes. If intrathoracic disease is clinically suspected, however, CT of the thorax should be performed.

**B** Computed tomography of the abdomen and pelvis should be performed in secondary care for all patients suspected of having ovarian cancer who have a Risk of Malignancy Index score greater than 200.

**D** Magnetic resonance imaging is not recommended for routine staging of ovarian cancer.

**D** Positron emission tomography-computed tomography is not recommended in the diagnosis or initial staging of ovarian cancer.

✓ Magnetic resonance imaging should be considered for characterisation of indeterminate adnexal masses where an alternative diagnosis to ovarian cancer is thought more likely.

✓ Computed tomography of the entire thorax is not routinely recommended unless intrathoracic metastatic disease is clinically suspected. Imaging of the abdomen and pelvis should, however, include the lung bases.

### 4.3 THE ROLE OF THE CLINICAL NURSE SPECIALIST

An individual's cancer journey is complex, disjointed and involves interventions from various professionals who frequently are working in different hospitals. High quality and compassionate care that is properly planned and coordinated is needed. The clinical nurse specialist has a vital role in delivering this care. There is limited evidence on the role of the clinical nurse specialist (CNS) in the care of patients with ovarian cancer specifically, although evidence from studies relating to gynaecological and other cancers is considered relevant in this setting.<sup>83-87</sup>

The roles undertaken by the CNS are many and varied and include overseeing and coordinating services so that the cancer journey for individual patients is personalized, acting as the key advocate and accessible professional for the multidisciplinary team (MDT), and using their knowledge and experience to alleviate psychological suffering.<sup>83</sup> The provision of emotional support and coordination of care services that the CNS can provide helps to improve patients' awareness of clinical as well as practical issues which in turn helps to achieve positive patient outcomes.<sup>84</sup> The skills and expertise of the CNS are important to the MDT, and allow them to address complex and sensitive issues, such as sexual rehabilitation, with patients.<sup>86</sup>

Involving the CNS in patient care has been shown to reduce the number of emergency admissions, the length of hospital stay, the number of follow-up appointments and the number of medical consultations.<sup>84</sup> A study of 70 women with a first time diagnosis of gynaecological cancer showed that CNS involvement at the time the patient receives their diagnosis can lead to a clinically significant reduction in the level of psychological distress in patients six months after diagnosis and can therefore enhance psychological recovery.<sup>85</sup> In this study, the CNSs were well utilised as a source of information although by 6 months post-diagnosis, when contact with the hospital and hospital-linked professional sources of information had decreased, the use of lay sources of information (for example, television, magazines) generally increased. The role of the CNS as a source of professional information was, however, maintained if the CNS kept in contact with the patient.<sup>85</sup>

Research on the role of the CNS in prostate cancer care has demonstrated that patients who have been seen by a CNS have more positive experiences of receiving information about tests and treatment and about sources of advice and support and are more likely to say that they made their treatment decisions themselves.<sup>87</sup>

The important role played by the CNS is also recognised in the NHS Quality Improvement Scotland clinical standards on the management of ovarian cancer services which state that a clinical nurse specialist in gynaecological oncology is part of the "...minimum constitution of the gynaecological cancer MDT."<sup>88</sup>

**D** Patients should be given their diagnosis of ovarian cancer in the presence of a clinical nurse specialist who is a fully integrated member of the gynaecological cancer team.

**D** Throughout their care pathway patients with ovarian cancer should have access to a clinical nurse specialist who should be an integral member of the gynaecological cancer team.

## 5 Surgical management

### 5.1 PREPARATION FOR SURGERY

#### 5.1.1 VENOUS THROMBOEMBOLIC PROPHYLAXIS

Venous thromboembolic prophylaxis for patients undergoing gynaecological surgery is covered in SIGN 122: Prevention and management of venous thromboembolism.<sup>89</sup>

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#### 5.1.2 ANTIBIOTIC PROPHYLAXIS

The benefits, principles and administration of antibiotic prophylaxis in surgery is covered in SIGN 104: Antibiotic prophylaxis in surgery.<sup>90</sup>

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### 5.2 PATHOLOGY

Pathological examination of ovarian and other tissues defines the nature of the tumour and its stage. Staging is performed by examining histological sections of tissue samples and cytological assessment of fluid samples. It is important to adequately sample the ovary using, as a minimum, a block of tissue for each centimetre of the maximum diameter of the tumour, unless there is obvious macroscopic evidence of carcinoma reported according to Royal College of Pathologists guidelines.<sup>91</sup>

#### 5.2.1 INTRAOPERATIVE TECHNIQUES

Epithelial ovarian tumours display a spectrum of pathological changes. Tumours can be benign, borderline (low malignant potential or atypical proliferating lesions), or malignant (*see Annex 3*). Intraoperative frozen section histopathology can be used to confirm the presence of malignant disease but cannot precisely confirm borderline disease.<sup>92-95</sup> A recent, high-quality systematic review including 18 retrospective cohort studies concluded that frozen section histopathology reliably distinguishes between benign and invasive tumours, but is less accurate for the distinction between benign and borderline tumours, and borderline and invasive tumours, particularly for clear cell and mucinous lesions, as shown in Table 2.<sup>95</sup>

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Table 2: Comparison of sensitivity and specificity of frozen section for different tumour types

Tumour type comparison	Sensitivity (95% CI)	Specificity (95% CI)	Value* (95% CI)
Benign versus invasive	99.7 (99.4 to 99.9)	95.8 (94.6 to 96.8)	PPV: 97.9 (97.3 to 98.4) NPV: 99.5 (98.9 to 99.7) LR+: 23.99 (18.52 to 31.07) LR-: 0.003 (0.01 to 0.006)
Benign versus borderline	98.9 (98.5 to 99.3)	70.8 (66.5 to 74.7)	PPV: 94.9 (94.1 to 95.7) NPV: 92.3 (89.0 to 94.6) LR+: 3.384 (2.94 to 13.89) LR-: 0.015 (0.01 to 0.022)
Borderline versus invasive	93.6 (90.5 to 95.7)	93.1 (91.5 to 94.2)	PPV: 77.7 (73.5 to 87.4) NPV: 98.2 (97.3 to 98.8) LR+: 13.293 (10.94 to 16.15) LR-: 0.069 (0.047 to 0.103)

\*PPV: positive predictive value

LR+: positive likelihood ratio

NPV: negative predictive value

LR-: negative likelihood ratio

A large study in the UK based on 1,439 intraoperative frozen section analyses for suspected ovarian cancer performed between 2000 and 2010, concluded that, "...intraoperative frozen section analysis has excellent diagnostic test accuracy and assists gynaecological oncologists to perform the appropriate surgery in 95% of cases, thereby preventing the morbidity of surgical staging in benign cases and the morbidity of restaging procedures or chemotherapy in early-stage malignant tumours..." (overall sensitivity 91.2%, overall specificity 98.6%; positive and negative likelihood ratios 64.7% and 0.09%).<sup>96</sup>

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Two high-quality systematic reviews of the accuracy of frozen section histopathology in the diagnosis of the adnexal mass and in the diagnosis of ovarian tumours including 18 and 14 retrospective cohort studies, respectively,<sup>97,98</sup> (the latter including 3,659 women) showed acceptable sensitivities and high specificities although sensitivities were lower in borderline disease (65-97% for borderline-malignant and 71-100% for borderline-benign).<sup>97</sup>

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It is important that surgeons are aware of the limitations of this technique. There is no evidence that analysis of intraoperative frozen sections can define the grade of the cancer.

The clinical situations where the intraoperative, pathological assessment of an ovarian lesion is helpful are:

- to confirm malignancy where clinical assessment reveals a complex ovarian cyst with no apparent metastatic disease; and
- to exclude the presence of metastatic disease where suspicious looking extra ovarian lesions are present if fertility conserving surgery is planned for patients with malignant disease confined to an ovary.

**B**

**To minimise the need for a second operative staging procedure, intraoperative frozen section assessment can be used to diagnose malignancy and to exclude metastatic disease.**

### 5.3 MANAGEMENT OF EARLY DISEASE

Early disease refers to disease confined to the ovaries (*see Annex 2*). There are two clinical scenarios where early disease could be encountered:

- The gynaecologist is alerted to the possibility of malignancy being present prior to the laparotomy.
- The gynaecologist had no suspicion of cancer being present prior to surgery.

To minimise the risk of the gynaecologist encountering the second scenario, use should be made of the RMI scoring system if an isolated pelvic mass is discovered on preoperative imaging (*see section 4.2*). In young women the possibility of a non-epithelial ovarian tumour being present should also be considered.

#### 5.3.1 STAGING

The surgical dilemma in early disease is how comprehensively to stage a case and in particular whether to assess retroperitoneal pelvic and para-aortic nodes and take random peritoneal biopsies. The presence of positive retroperitoneal nodes or abdominal peritoneal implants upstages the case to stage III (*see Annex 2*).

Proponents of comprehensive staging argue that it is important to give accurate prognostic information to a patient and that the choice of chemotherapy regimen will be influenced by knowledge of the stage of disease (*see section 6*). In those patients with true early stage disease it may then obviate the need for chemotherapy. Descriptive studies have reported that at least 15% of patients thought to have disease confined to the ovaries are found to have positive lymph nodes.<sup>94,99,100</sup> The opponents of comprehensive staging argue that it cannot be recommended as routine practice due to the lack of RCT data demonstrating any survival benefit conferred to those who undergo full staging including systematic retroperitoneal nodal assessment and there is significant morbidity associated with the procedure. There is, however, evidence to support the usefulness of retroperitoneal pelvic and para-aortic lymph node sampling.<sup>101,102</sup>

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### 5.3.2 SYSTEMATIC RETROPERITONEAL LYMPHADENECTOMY

Systematic retroperitoneal lymphadenectomy (removal of pelvic and infra-renal para-aortic lymph nodes) for ovarian cancer is not standard management in the UK although it is routinely performed in many North American centres. Systematic lymphadenectomy is defined here as the removal of lymph nodes in specific areas including: the upper para-aortic region above the inferior mesenteric artery (IMA), the lower para-aortic region between the IMA and the bifurcation of the aorta, the inter-aortocaval area, the right paracaval area, the common and external iliac vessels, the obturator fossa and the internal iliac vessels.<sup>103</sup> Heterogeneity in the literature, however, means that it is often difficult to assess from studies the extent of lymphadenectomy undertaken.

A meta-analysis including two RCTs and seven observational studies looking at the effect of systematic lymphadenectomy on survival included a sub-analysis of studies (one RCT and two retrospective cohort studies) covering 7,158 patients with FIGO stage I-II disease.<sup>104</sup> Although this sub-analysis showed that systematic lymphadenectomy increased overall survival in FIGO stage I-II disease (HR=0.80, 95% CI 0.70 to 0.92), the RCT showed no effect of systematic lymphadenectomy compared with unsystematic lymphadenectomy on overall survival. However, the meta-analysis compared systematic lymphadenectomy with unsystematic lymphadenectomy rather than with no lymphadenectomy, and the observational studies had inherent biases.

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Three further cohort studies showed inconsistent results.<sup>105-107</sup> A Japanese study of 118 patients (62 with stage I-II and 56 with stage III-IV disease) with optimally debulked ovarian cancer (<2 cm residual disease) in two hospitals showed no improvement in 5-year overall survival but improved 5-year progression-free survival for those with stage I-II disease receiving lymphadenectomy (n=40) compared with those not receiving lymphadenectomy (n=22) (overall survival (OS) 100% v 80%, p=0.07; progression-free survival (PFS) 94% v 71%, p=0.04)<sup>105</sup> Among the 21/118 patients with stage I-II disease and clear cell carcinoma, 3-year OS and PFS were significantly improved in the lymphadenectomy group (P=0.01 and p=0.04, respectively). However, as patients receiving lymphadenectomy were all treated in one hospital and those not receiving it in another hospital, selection bias and/or surgical performance alone could explain the differences.

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A large scale retrospective cohort study from the USA including 49,783 women on the Surveillance, Epidemiology, and End Results (SEER) database showed improved 5-year cause-specific overall survival for those having limited lymphadenectomy or extensive lymphadenectomy compared to those having no lymph nodes examined (62%, 71% and 37%, respectively; p<0.001).<sup>106</sup> The authors concluded that cause-specific survival favoured lymphadenectomy in epithelial ovarian cancer whatever the stage of disease, however, "potential biases inherent in this retrospective methodology, such as staging migration, defining the extent of residual disease, and the possibility that thorough lymphadenectomy may reflect the quality of cytoreductive surgery, preclude any formal conclusions on the therapeutic role of lymphadenectomy."

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A further retrospective cohort study looking at surgical staging of stage I-II epithelial ovarian cancer covering 721 women (71% stage I) in the USA appeared to show limited improved 5-year survival in patients who had lymph node sampling compared with those who did not (84.2% v 69.6%; adjusted HR for risk of death for those with no lymph node sampling, 1.81, 95% CI 1.26 to 2.60).<sup>107</sup> Women who had node sampling had better survival than those who did not regardless of receipt of chemotherapy, possibly because of stage migration, although this may mean that adjuvant treatment may have been tailored to those at higher risk of lymph node involvement rather than that the procedure itself was beneficial. Lymph node sampling was also not defined and the study did not look specifically at systematic lymphadenectomy.

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The effect of undertaking systematic lymphadenectomy in all apparent early ovarian cancers would be upstaging of some stage I cancers, however it is not clear from the evidence whether this would imply any survival benefit although some additional patients may receive chemotherapy. There is the potential for some fully staged patients to be spared chemotherapy. There is a risk of causing harm to patients with benign or borderline disease if retroperitoneal lymphadenectomy were done routinely without using frozen section assessment in cases where disease is confined to the ovaries. On the basis of the studies reviewed, there is insufficient evidence to recommend systematic lymphadenectomy in all cases of apparent early stage ovarian cancer.

**C** Routine systematic lymphadenectomy in early stage epithelial ovarian cancer is not recommended.

### 5.3.3 THE ROLE OF RETROPERITONEAL LYMPH NODE SAMPLING

Knowledge of retroperitoneal lymph node status may influence adjuvant therapy decision making and provide prognostic information. The Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) study was an RCT designed to look at the impact of platinum based adjuvant chemotherapy following surgery in early stage ovarian cancer. It was not designed to demonstrate differences in survival due to surgical staging.<sup>108</sup>

The trial randomised 448 patients with early stage I-II ovarian cancer to observation only or chemotherapy following surgical staging. Surgical staging had to consist of at least careful inspection and palpation of all peritoneal surfaces, with biopsies of any suspect lesions. However, they did advise far more comprehensive staging recommending omentectomy; peritoneal washings; blind biopsies from the peritoneum in the pelvis (pouch of Douglas, bladder, pelvic sidewalls), the paracolic gutters, and the right hemidiaphragm; and iliac and peri-aortic lymph node sampling. The staging was considered to be optimal if this was performed. The median follow up was 5.5 years. The difference in overall survival between the two groups was not statistically significant (HR=0.69, 95% CI 0.44 to 1.08, p=0.10). Recurrence-free survival (RFS) was statistically significantly improved in the adjuvant chemotherapy group (76% v 65%, 95% CI 5% to 16%; HR=0.63, 95% CI 0.43 to 0.92, p=0.02). A subgroup analysis of the third of patients who were optimally surgically staged was performed. In the observation group (ie no adjuvant chemotherapy) comprehensive surgical staging significantly improved OS (HR=2.31, 95% CI 1.08 to 4.96, p=0.03) and RFS (HR=1.82, 95% CI 1.02 to 3.24, p=0.04). Comprehensive surgical staging did not confer any benefit in the chemotherapy group. In the non-optimally staged group, chemotherapy was associated with statistically significantly improved OS (HR=1.75, 95% CI 1.04 to 2.95, p=0.03) and RFS (HR=1.78, 95% CI 1.15 to 2.77, p=0.009). There was therefore no benefit from adjuvant chemotherapy in the optimally staged group.

A further study analysed the data with median follow up of 10.1 years. This supported all the conclusions from the original study and also found that OS after optimal surgical staging was improved, even among patients who had received adjuvant chemotherapy (HR=1.89, 95% CI 0.99 to 3.60, p=0.05). This supports the use of pelvic and para-aortic lymph node sampling in the management of those with early stage ovarian cancer.<sup>102</sup>

NICE clinical guideline 122 recommends that as part of optimal surgical staging in stage I ovarian cancer, retroperitoneal lymph node assessment should be done.<sup>63</sup> Optimal surgical staging is defined as:

- mid-line laparotomy to allow thorough assessment of abdomen and pelvis
- removal of ovarian cyst without causing capsular rupture followed by total abdominal hysterectomy and removal of contralateral ovary
- infracolic omentectomy
- biopsies of suspicious looking peritoneal nodules
- iliac and peri-aortic lymph node sampling.

**C** Retroperitoneal lymph node sampling should be considered as part of surgical staging for apparent early stage disease.

To minimise the need for a second operative staging procedure consideration should be given to using intraoperative frozen section assessment to diagnose a malignant ovarian cyst (*see section 5.2.1*).

### 5.3.4 FERTILITY CONSERVING SURGERY

In women who wish to conserve their fertility, adequate staging (excluding disease involving the liver, peritoneum, retroperitoneal nodes, appendix and diaphragm) is required and the risk of recurrent disease developing must be discussed.

Data from six descriptive studies from Europe,<sup>109,110</sup> the USA,<sup>111</sup> and Japan,<sup>112-114</sup> but applicable to the Scottish population, consistently reported that for stage I serous disease fertility conserving surgery is a valid option with no apparent reduction in overall survival,<sup>111-114</sup> disease-free survival,<sup>112,113</sup> recurrence-free survival,<sup>114</sup> or 5-year survival (91% for women undergoing oophorectomy, 95% CI 88% to 93%; 94% in women undergoing ovarian conservation, 95% CI 91% to 96%).<sup>111</sup> However, the studies reviewed all included more comprehensive surgical staging than is normal practice. The risk of recurrence in the remaining ovary ranged from 3.3% to 7%,<sup>109</sup> and the overall risk of developing relapsed disease ranged from 8.5%<sup>114</sup> to 13.8%.<sup>110</sup> Once relapsed disease develops, prognosis is very poor and further treatment is not curative. The risk of relapsed disease can be reduced by selecting patients for fertility conservation carefully, avoiding the procedure in high-grade disease, stage Ic or higher stage cases, and avoiding doing a cystectomy. When fertility conserving surgery is requested, use of frozen section assessment is important to minimise the risk of a second surgical procedure and more comprehensive surgical staging would be recommended to exclude the possibility of occult metastatic disease (*see section 5.3.1*).

Although the majority of studies looked at rates of relapse rather than pregnancy outcome, a total of 117 of the 422 women included in the studies became pregnant.

If fertility conservation is requested, it is an option in apparent stage Ia disease, but the benefits and drawbacks of this type of surgery must be discussed with the patient, particularly with regard to the need for a second procedure and the procedure being most appropriate if grade 1 (*see Annex 3*) disease is present.

**D** In women with stage Ia, grade 1 or grade 2 disease, fertility conserving surgery is an option as long as the contralateral ovary appears normal and there is no evidence of omental or peritoneal disease. Optimal surgical staging should be done and should include biopsies of suspicious looking peritoneal nodules, infracolic omentectomy, and iliac and peri-aortic lymph node sampling.

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## 5.4 OPTIMAL SURGERY FOR ADVANCED DISEASE

Most women with ovarian cancer present with advanced disease. The stage of disease at diagnosis is the most important factor affecting outcome. Advanced disease refers to cases where the disease has spread beyond the ovaries (FIGO stage Ic and above, *see Annex 2*). Treatment for these patients involves surgery and chemotherapy. This section addresses the issue of surgery before the initiation of chemotherapy.

### 5.4.1 CYTOREDUCTIVE SURGERY

The goal in the surgical management of advanced disease should be to remove all macroscopic disease. It is frequently not possible to do this with standard radical surgery. The goal instead is to remove all tumour deposits measuring more than 1 cm in diameter (optimal cytoreduction).

No RCTs have been conducted comparing chemotherapy and surgery alone, therefore the independent effect of surgery on the disease is difficult to establish. Retrospective studies have shown that the degree of cytoreduction achieved is associated with improved survival. These studies are subject to a number of biases. Randomised trials addressing the value of ultra-radical versus standard radical surgery have not been undertaken. It should be noted that the definition of optimal cytoreduction has changed over time as has management of ovarian cancer, with more women now having neoadjuvant chemotherapy (NACT).

A high quality systematic review of women with advanced stage ovarian cancer suggested improved overall survival for women with carcinomatosis receiving ultra-radical surgery compared with standard radical surgery (adjusted HR 0.64, 95% CI 0.41 to 0.98).<sup>115</sup> Another review showed improved survival for women receiving primary optimal cytoreductive surgery (defined in a sub analysis as <1 cm) compared with suboptimal primary surgery (defined as residual disease of >1 cm) (HR=1.36, 95% CI 1.10 to 1.68).<sup>116</sup> The latter review also showed improved progression-free survival in women receiving optimal cytoreductive surgery (HR=1.30, 95% CI 1.03 to 1.64). Residual disease of >2 cm did not show any beneficial effect of surgery.<sup>116</sup> Adverse events and quality of life were not reported adequately in either review.

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**C** In surgery for advanced ovarian cancer, the aim should be to achieve complete cytoreduction.

#### 5.4.2 NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGERY

Patients with extensive stage III and stage IV disease where resection of all macroscopic disease is unlikely to be feasible are increasingly being treated with chemotherapy prior to surgery when there is no doubt that the primary tumour is ovarian (*see section 6.2*). A multidisciplinary team should manage these patients and histology, rather than cytology, should be used to confirm the diagnosis.

A Cochrane review including one high quality RCT with 718 patients, relating to women with stage IIIc and stage IV disease, some of whom were from Scotland, reported significantly fewer surgically related serious adverse effects (SAE grade 3 and 4) in women receiving NACT compared to those receiving primary debulking surgery (PDS), for example, haemorrhage (12 NACT v 23 PDS; RR 0.50, 95% CI 0.25 to 0.99), venous thromboembolism (0 NACT v 8 PDS; RR 0.06, 95% CI 0 to 0.98), and infection (5 NACT v 25 PDS; RR 0.19, 95% CI 0.07 to 0.50). Women in the NACT group were also significantly more likely to be debulked to no residual disease or to residual disease measuring less than 1 cm in diameter than women receiving PDS (80.6% vs 41.6%).<sup>117</sup>

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The review showed no difference in progression-free (HR=1.01, 95% CI 0.86 to 1.17) or overall survival (HR=0.98, 95% CI 0.82 to 1.18) between the NACT and PDS groups despite the higher optimal cytoreduction rate in the NACT group. This result may, however, have been influenced by the fact that some centres enrolled the most serious cases into the RCT, ie patients with very large volume IIIc-IV disease where the surgeon felt it was impossible to significantly debulk without NACT. Complete resection of all macroscopic disease (at PDS or interval debulking after NACT) was the strongest independent variable in predicting overall survival. There was no difference in quality of life between the two groups.

As the majority (65%) of patients with ovarian cancer present with advanced disease and most of these will have stage III or IV disease, the adoption of NACT has the potential to reduce postoperative morbidity without any adverse effect on overall survival. NACT could also reduce delays in starting treatment as the main factor causing delay is getting a date for surgery within two weeks after the diagnosis has been made.

**A** The use of neoadjuvant chemotherapy in women with stage IIIc or IV ovarian cancer may be considered as an alternative to primary debulking surgery.

✓ With regard to selecting who will benefit from neoadjuvant chemotherapy, treatment should be individualised to the patient taking into account resectability, age, histology, performance status and after ruling out the possibility of other primary tumours, and after full discussion at multidisciplinary team meetings.

#### 5.5 RELAPSED DISEASE

Relapse in ovarian cancer is common, affecting approximately 75% of patients, and current practice is management with chemotherapy/hormonal agents (*see section 6.3*). Evidence of the possible survival benefit of secondary cancer surgery (SCS) in relapsed disease is lacking. A high-quality systematic review found no evidence from RCTs to inform decisions about secondary surgical cytoreduction plus chemotherapy compared to chemotherapy alone for recurrent epithelial ovarian cancer.<sup>118</sup> The results of the DESKTOP III RCT, comparing tumour debulking surgery versus chemotherapy alone in platinum-sensitive ovarian cancer, are awaited.

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A systematic review of 40 cohort studies of both prospective (n=12) and retrospective design (n=28) and including a total of 2,019 patients, found that the proportion of patients undergoing complete cytoreductive surgery was the only statistically significant clinical variable independently associated with post-recurrence survival time (p=0.019). After controlling for all other factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3-month increase in median cohort survival time (mean weighted median overall post-recurrence survival times was 30.3 months).<sup>119</sup>

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Three cohort studies indicated improved overall survival following SCS, compared with no SCS, especially if optimal (<1 cm) cytoreduction is achieved at SCS (35 months v 13 months, p<0.006, n=108;<sup>120</sup> 42 months v 26 months, p=0.718, n=54;<sup>121</sup> HR=0.76, 95% CI 0.66 to 0.87, n=1124).<sup>122</sup> These studies highlight the need for careful selection of patients for SCS and identify a number of possible prognostic factors including site of recurrence and PFS;<sup>121</sup> well planned surgery, a MDT approach and maximum cytoreduction;<sup>122</sup> and age, disease-free period, clinical presentation of relapse, completeness of SCS and response to second line chemotherapy.<sup>120</sup>

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Two further non-comparative studies, one from Italy involving 60 patients, and one from Germany involving 240 patients, looking at prognostic factors, identified a disease-free interval of >12 months, residual disease after primary surgery of <2 cm, the staging and grade at time of primary surgery;<sup>123</sup> and absence of ascites, platinum-sensitivity, initial FIGO stage <IV and complete resection<sup>124</sup> to be associated with better survival.

Overall, there is consistent evidence that in carefully selected patients with platinum-sensitive disease, SCS can improve overall survival. As with the primary surgical effort, the aim should be complete macroscopic resection. The DESKTOP II study suggests that patients should have PFS of greater than 6-12 months, good performance status, minimal or no ascites, and radiologically determined resectable disease.<sup>125</sup> The DESKTOP II study prospectively validated a scoring system (AGO score) to predict surgical outcome in recurrent ovarian cancer. This was based on a previous study (DESKTOP I) which had shown that complete resection at SCS was the strongest prognostic factor for survival. It also showed that three independent factors associated with complete resection were good performance status (ECOG score of 0), complete macroresection at first surgery, and absence of ascites (<500 ml). There was no PFS or OS data from the subsequent DESKTOP II as the aim of that study was to evaluate the AGO score. The RCT DESKTOP III is currently underway.

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Although the results of RCTs are awaited, improved overall survival with a tendency to less residual disease after SCS is a consistent result especially in those completely or 'optimally' cytoreduced at initial surgery. Morbidity and mortality were not, however, well reported, although one study reported a postoperative complication rate of 20.4% with no mortality,<sup>121</sup> and another reported a mortality rate of 7.8% within 30 days and 47.9% during follow up (median follow up duration 13.9 months, range 0.1 to 90.0, median OS 29 months, 95% CI 24.6 to 33.4).<sup>124</sup>

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**C** In selected patients with relapsed epithelial ovarian cancer which is platinum-sensitive, secondary cytoreductive surgery may be appropriate and may improve overall survival. The aim should be complete resection of all macroscopic disease. Where possible, this should be done in the context of a clinical trial.

## 6 Chemotherapy

### 6.1 EARLY DISEASE

#### 6.1.1 ADJUVANT CHEMOTHERAPY FOR STAGE IA AND STAGE IB DISEASE

In a recent high quality systematic review of adjuvant chemotherapy for early stage epithelial ovarian cancer that included five RCTs (1,277 participants), a meta-analysis of five-year data from three trials indicated that women who received adjuvant platinum based chemotherapy had better overall survival than those who did not (1,008 women; HR=0.71, 95% CI 0.53 to 0.93).<sup>126</sup> A second meta-analysis of four trials with broadly comparable patients and regimens indicated that women who received adjuvant chemotherapy had better PFS than those who did not (1,170 women; HR=0.67, 95% CI 0.53 to 0.84). The meta-analysis indicated that between nine and 100 women would have to be treated with adjuvant chemotherapy in order to prevent one death and between seven and 33 women would have to be treated with adjuvant chemotherapy in order to prevent one recurrence. The trials included in these meta-analyses gave consistent estimates of the effects of chemotherapy with a similar direction and magnitude of effect. In addition, these findings were robust over time (10-year PFS, two trials, 925 women; HR=0.67, 95% CI 0.54 to 0.84). There was, however, inconsistency in the extent to which individual trials analysed subgroups of patients according to level of risk or according to the extent of surgical staging. The authors concluded that adjuvant platinum based chemotherapy is effective in prolonging the survival of the majority of patients who are assessed as having early (FIGO stage I-IIa) epithelial ovarian cancer. However, it may be unnecessary for women in whom there is well differentiated encapsulated unilateral disease (stage Ia grade 1). A subgroup analysis suggested that women who had optimal surgical staging of their disease were unlikely to benefit from adjuvant chemotherapy (OS – HR=1.22; 95% CI 0.63 to 2.37; 2 trials, 234 women) whereas those who had suboptimal staging did (OS – HR=0.63; 95% CI 0.46 to 0.85; 2 trials, 772 women). However, the authors note that these subgroup findings could be due to chance and should be interpreted with caution.<sup>126</sup> The meta-analysis did not address the issue of histological subtype making it difficult to identify which women do not benefit from adjuvant chemotherapy.

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In the ACTION chemotherapy trial, one third of patients were optimally staged (*see section 5.3.3*). Adjuvant chemotherapy in this group of patients was not associated with a statistically significant improvement in overall and disease-free survival. The validity of a subgroup analysis in this study is questionable given the small number of patients involved. When the data from the ACTION trial were combined with that from the International Collaborative Ovarian Neoplasm (ICON) 1 trial (in which the majority of patients were not optimally staged) platinum based adjuvant chemotherapy resulted in an 8% improvement in overall survival at 5 years (82% in the chemotherapy arm v 74% in the observation arm; 95% CI 2% to 12%) and an 11% improvement in disease-free survival at 5 years (76% in the chemotherapy arm v 65% in the observation arm; 95% CI 5% to 16%).<sup>108</sup>

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**All women with high-grade early stage (Ia-Ib) ovarian cancer should be considered for adjuvant chemotherapy.**

### 6.1.2 MAINTENANCE THERAPY IN EARLY STAGE DISEASE

A high quality RCT of 542 women with stage I or II epithelial ovarian cancer compared the recurrence-free interval (RFI) and safety profile in patients with completely resected high-risk early-stage ovarian cancer treated with intravenous carboplatin and paclitaxel with or without maintenance low dose paclitaxel for 24 weeks (observation arm, n=268, 175 mg/m<sup>2</sup> q3 x3 followed by surveillance; maintenance arm, n=274, carboplatin AUC 6 plus paclitaxel 175 mg/m<sup>2</sup> q3 x3 followed by paclitaxel 40 mg/m<sup>2</sup> q1 week x24).<sup>127</sup> The median duration of follow up was 6.7 years for 445 patients still alive at last contact; there were 122 recurrences. The rate of recurrence within five years was 20.4% (95% CI 15.9 to 25.9) in the maintenance group versus 23.2% (95%CI 18.4 to 28.9) in the observation group. After adjusting for stage of disease and tumour grade, recurrence was 19.3% lower in the maintenance group (HR=0.807, 95% CI 0.56 to 1.15, p=0.24). The probability of surviving five years was 86.2% for the maintenance group and 85.4% for the surveillance group. The overall death rate was similar (HR=0.78, 95% CI 0.52 to 1.17, p=0.23).

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Toxicity was reported for 536 patients who received any study therapy and was worse for those in the maintenance group. The incidence of grade 2 or worse peripheral neuropathy (15.5% v 6.0%), infection or fever (19.9% v 8.7%), and dermatologic events (70.8% v 52.1%) was significantly higher among patients in the maintenance group (p<0.001). There was also a slightly greater incidence of grade 2 or worse cardiovascular events (8.1% v 3.8%, p=0.044) and the incidence of grade 3 or 4 peripheral neuropathy was 4.4% v 0.7% (p=0.012). In total, 21 patients (10 on maintenance and 11 on observation arm) developed a second primary cancer during follow up. There were no treatment-related deaths reported. The authors concluded that maintenance paclitaxel provides no significant increase in RFI.

**B For early stage disease, maintenance cytotoxic chemotherapy should not be given.**

## 6.2 ADVANCED DISEASE

Ovarian cancer is made up of different histological subtypes: high-grade serous, low-grade serous, endometrioid, mucinous, clear cell and carcinosarcoma. The most frequent subtype is high-grade serous carcinoma and hence these make up the vast majority of patients included in clinical trials. The applicability of the findings and conclusions of these trials to the rarer subtypes is difficult to establish as the numbers are generally too small for separate analysis. However, there is emerging evidence that the different subtypes are different diseases with different clinical behaviour and distinct molecular biology. As a result, they will require different treatment strategies but at present there are limited data and no completed phase III randomised control trials in the separate subtypes on which to base separate treatment recommendations. Where evidence exists from retrospective analyses or non-randomised studies, this will be discussed. Where possible, women should be included in ongoing histo-type specific trials.

### 6.2.1 ROLE OF PLATINUM AGENTS

Meta-analyses show significant benefit for use of platinum.<sup>128,129</sup>

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**A First line chemotherapy treatment of epithelial ovarian cancer should include a platinum agent either in combination or as a single agent, unless specifically contraindicated.**

### 6.2.2 CHOICE OF PLATINUM AGENTS

The platinum based drugs cisplatin and carboplatin are equally efficacious in the treatment of epithelial ovarian cancer.<sup>128</sup> Carboplatin has a more favourable toxicity profile. The combination of carboplatin and paclitaxel is as efficacious as cisplatin and paclitaxel combination therapy.<sup>130</sup>

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**A Carboplatin is the platinum drug of choice in both single and combination therapy.**

## 6.2.3 OTHER AGENTS

Two high-quality RCTs support the use of paclitaxel and cisplatin as an efficacious combination for advanced ovarian cancer.<sup>131,132</sup> A further study has suggested that carboplatin can be substituted for cisplatin.<sup>130</sup> | 1<sup>++</sup>

Although one RCT has shown that single agent cisplatin yielded both equivalent response rates and equivalent overall survival to cisplatin and paclitaxel, this trial is difficult to interpret due to treatment crossover issues.<sup>131</sup> The study recommends the taxane combination on the grounds of reduced toxicity compared to single agent cisplatin. The ICON 3 trial demonstrates equal effectiveness for carboplatin or CAP (cyclophosphamide, doxorubicin and cisplatin) compared with paclitaxel and carboplatin in ovarian cancer.<sup>133</sup> ICON 3 does not imply that paclitaxel has no role in the treatment of ovarian cancer, but it does suggest that the dramatic difference seen in the earlier studies was principally due to the inferiority of the cyclophosphamide and cisplatin control arm. An interpretation of a meta-analysis of all these studies does suggest a slight benefit for the taxane and platinum combination.<sup>133</sup> | 1<sup>++</sup>  
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Five good quality RCTs, including 6,873 patients, have investigated the addition of a third cytotoxic agent to standard therapy with carboplatin and paclitaxel for the first line treatment of advanced ovarian cancer (some studies included stage Ic to IV, but the majority included stage III and IV).<sup>134-138</sup> Agents investigated were doxorubicin, pegylated liposomal doxorubicin, gemcitabine, topotecan, and cisplatin in various schedules. The addition of a third cytotoxic agent to standard therapy with carboplatin and paclitaxel did not improve survival outcomes<sup>138</sup> but did increase toxicity, particularly haematological toxicity, for example, with gemcitabine,<sup>136,138</sup> pegylated liposomal doxorubicin,<sup>136</sup> and with topotecan.<sup>137</sup> | 1<sup>++</sup>  
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A further RCT comparing induction chemotherapy with carboplatin and gemcitabine (GC arm) to carboplatin and paclitaxel (TC arm) showed better overall survival in the carboplatin and paclitaxel arm, however, this difference was not maintained in a multivariate analysis (HR=1.22, 95% CI 0.99 to 1.52, p=0.067).<sup>139</sup> The incidence of grade 3-4 thrombocytopenia was significantly higher in the GC arm compared with the TC arm (n=279, 67.7% in GC arm; n=48, 11.8% in TC arm; p<0.001), and the incidence of grade ≥2 alopecia was significantly higher in the TC arm compared with the GC arm (n=208, 51.0% for TC; n=30, 7.3% for GC; p<0.001). In addition, the incidence of grade ≥2 neuropathy was also significantly higher in the TC arm compared with the GC arm (n=57, 14.0% for TC; n=9, 2.2% for GC; p<0.001). | 1<sup>++</sup>

An RCT comparing carboplatin (AUC 5) and paclitaxel (175 mg/m<sup>2</sup>) (standard therapy, TC arm) to carboplatin (AUC 5) and pegylated liposomal doxorubicin (30 mg/m<sup>2</sup>) (experimental, PLD/C arm) showed that the substitution of PLD for paclitaxel was not superior (OS 61.6 v 53.2, respectively, HR=0.89, 95% CI 0.72 to 1.12, p=0.32) but did show a different spectrum of toxicity with less neurotoxicity and alopecia but more haematologic adverse effects (grade 3/4 anaemia, 3% TC v 10% PLD/C; grade 3/4 thrombocytopenia, 8% TC v 16% PLD/C; ≥2 neuropathy, 19% TC v 3% PLD/C; grade 2 alopecia, 60% TC v 5% PLD/C). Including all grades, diarrhoea was more common with TC and stomatitis and skin toxicity with PLD/C.<sup>140</sup> | 1<sup>++</sup>

**A** Paclitaxel is recommended in combination therapy with platinum in the first line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, pegylated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative.

**A** Patients who are unfit for combination therapy should be offered single agent carboplatin.

**A** A third cytotoxic agent should not be added to carboplatin and paclitaxel.

## 6.2.4 SCHEDULING

Increasing the dose intensity by increasing the total dose or decreasing the interval between doses is a potential way of increasing the efficacy of chemotherapy. In recurrent, platinum-resistant, ovarian cancer, high response rates with dose-dense platinum containing regimens have been reported in non-randomised studies. Despite this, several studies have shown no benefit and increased toxicity from increasing the dose intensity of platinum therapy in the first line setting.<sup>141-143</sup>

However, one study in a Japanese population receiving first line therapy for advanced ovarian cancer has shown a significant and sustained improvement in progression-free and overall survival with weekly intravenous dose-dense paclitaxel (80 mg/m<sup>2</sup>, 1-h infusion, given on days 1, 8 and 15) plus carboplatin (AUC 6, given on day one of a 21 day cycle), compared with paclitaxel (180 mg/m<sup>2</sup>; 3-h infusion) plus carboplatin, given on day 1 of a 21 day cycle. Overall survival at three years was 72.1% in the dose-dense arm versus 65.1% in the control arm (HR=0.75, 95% CI 0.57 to 0.98, p=0.03). The difference is maintained at five years (58.6% v 51%, HR=0.79, p=0.0448). Median progression-free survival was 28 months versus 17.2 months (unadjusted HR=0.71, 95% CI 0.58 to 0.88, p=0.0015). Neutropenia (92% v 88%) and grade 3/4 anaemia (69% v 44%, p<0.001) were higher in the dose-dense arm.<sup>144</sup> It is possible that differences in pharmacogenomics will alter the tolerability of the regimen in a Caucasian population and studies are ongoing which will address this. This regimen also has implications for service delivery and for women undergoing treatment as they would need to attend weekly for 18 weeks instead of six visits but an economic analysis has demonstrated that it is a cost-effective treatment.<sup>145</sup>

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There are several ongoing studies that also assess the efficacy of dose-dense paclitaxel (ICON 8, GOG 262, MITO 7). The results of ongoing clinical trials are required in order to establish whether a regimen of carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m<sup>2</sup> (day 1, 8, 15 q21) should become the standard of care.

**B** Carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m<sup>2</sup> (day 1, 8, 15 q21) may be considered for the treatment of first line ovarian cancer. The increased toxicity and frequency of visits need to be discussed with the patient.

✓ Where possible, patients receiving treatment with carboplatin AUC 6 (day 1 q21) and paclitaxel 80 mg/m<sup>2</sup> (day 1, 8, 15 q21) for first line ovarian cancer should be enrolled in ongoing clinical trials in order to establish if this regime should become the standard of care.

## 6.2.5 BIOLOGICAL THERAPIES

Two RCTs have investigated the benefit of the addition of bevacizumab, a humanised monoclonal antibody, to vascular endothelial growth factor A (VEGF), to carboplatin and paclitaxel.<sup>146,147</sup> The GOG 218 study was a double-blind, placebo-controlled study of 1,873 patients with untreated stage III and IV disease (including 66% with stage IIIc and >1 cm residual disease or stage IV) and randomised between carboplatin (AUC 6) and paclitaxel (175 mg/m<sup>2</sup>) for six cycles plus bevacizumab 15 mg/kg during cycles 2–6 and placebo during cycles 7–22 or carboplatin and paclitaxel for six cycles plus bevacizumab during cycles 2–22.<sup>146</sup> A limitation of this study was the change of the primary end point from OS to PFS as maintenance of the blinding after progression was not considered acceptable. Therefore, postprogression therapy was not controlled, so many patients crossed over to receive bevacizumab, affecting the integrity of OS data. There was no difference in PFS between the control group and bevacizumab initiation group but there was a statistically significant improvement in PFS for the group who received bevacizumab throughout (median 10.3 v 14.1 months, HR=0.717, 95% CI 0.625 to 0.824, p<0.001).

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The ICON 7 study included 1,528 women with high-risk stage I-IIa and advanced stage IIb or IV epithelial ovarian cancer (9% had high risk early-stage disease, 70% had stage IIIc or IV ovarian cancer and 30% had stage IIIc >1 cm residual disease or stage IV). Patients were randomised between carboplatin (AUC, 5 or 6) and paclitaxel (175 mg/m<sup>2</sup>), given every three weeks for six cycles, or to this regimen plus bevacizumab (7.5 mg/kg), given concurrently every three weeks for five or six cycles and continued for 12 additional cycles or until progression of disease. There was a small but statistically significant improvement in PFS in the whole population (restricted mean at 42 months was 22.4 months without bevacizumab v 24.1 months

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with bevacizumab  $p=0.04$ ). In the women with stage IIIc and  $>1$  cm residual disease or stage IV, the benefit was greater (PFS, restricted mean, at 42 months of 14.5 months v 18.1 months with respective median overall survival of 28.8 and 36.6 months; HR for death in the bevacizumab group of 0.64, 95% CI 0.48 to 0.85,  $p=0.002$ ). Bevacizumab was associated with significantly higher rates of bleeding (mainly grade 1 mucocutaneous bleeding), hypertension of grade 2 or higher (18% with bevacizumab v 2% with standard therapy), thromboembolic events of grade 3 or higher (7% with bevacizumab v 3% with standard therapy), and gastrointestinal perforations (occurring in 10 patients in the bevacizumab group v three patients in the standard-therapy group). Quality of life scores did not differ between groups in either study.<sup>147</sup>

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The addition of bevacizumab during and after chemotherapy, at both 7.5 mg/kg and 15 mg/kg, prolongs PFS and the benefit is greater in women with incompletely resected ( $>1$  cm residual) stage III and IV disease. The benefit varies over time with maximal benefit in the ICON 7 trial at 12 months and in the GOG 218 trial at 15 months, disappearing by 24 months.<sup>146,147</sup> There was no difference in OS in the GOG 218 trial but these data are compromised by postprogression crossover. A 7.8 month median OS benefit was seen in the group of women with incompletely resected ( $>1$  cm residual) stage III and IV disease. The benefit seen in the ICON 7 trial with 7.5 mg/kg for the patients with stage IIIc and  $>1$  cm residual disease or stage IV disease was similar to the benefit seen in the GOG 218 trial with 15 mg/kg suggesting that 7.5 mg/kg is sufficient. The benefit for those with high-risk early disease and stage III disease with residual disease  $<1$  cm was very small.

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Further research is required to determine the optimal duration of therapy and to identify predictive markers of benefit from bevacizumab.

Bevacizumab 15mg/kg is accepted for restricted use by the SMC for combination with carboplatin and paclitaxel, for treatment of patients with stage IV disease (*see section 10.4*). Bevacizumab at the lower dose of 7.5mg/kg is not currently licensed due to concerns about increased toxicity.<sup>148</sup>

Several other biological agents have been assessed in randomised trials for the first-line treatment of ovarian cancer. These include the CA125-specific murine monoclonal antibody, oregovomab,<sup>150</sup> interferon gamma,<sup>151</sup> the farnesyltransferase inhibitor, lonafarnib,<sup>152</sup> and thalidomide,<sup>153</sup> but none has demonstrated a benefit with respect to PFS or OS. Trials of maintenance oral PARP inhibitors following first-line chemotherapy are ongoing (SOLO-1 and PRIMA).

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**Women with stage IV ovarian cancer should be offered bevacizumab in combination with carboplatin and paclitaxel.**

## 6.2.6 MAINTENANCE THERAPIES

Despite good initial responses to chemotherapy, most women with ovarian cancer will develop relapsed disease. This has led to an interest in maintenance therapy in order to try to delay relapse and/or increase survival.

A systematic review including six RCTs of 902 women included a meta-analysis of four RCTs ( $n=479$ ) of maintenance chemotherapy after complete response to first line platinum and paclitaxel which showed no benefit to overall survival from topotecan, anthracyclines or platinum.<sup>154</sup> An additional RCT including 296 women with advanced ovarian cancer who had achieved a complete response to first line platinum-paclitaxel chemotherapy, showed a statistically significant benefit to median PFS of eight months (22 compared with 14 months,  $p=0.006$ ) but no benefit to overall survival when 12 cycles of maintenance paclitaxel (135 mg/m<sup>2</sup>, q 21d) compared to three cycles were given following a complete response to primary platinum/paclitaxel (median OS 53 months v 48 months, respectively,  $p=0.34$ ). There was a higher incidence of grade 2 (23% v 15%) and 3 (6% v 1%) neuropathy, and grade 3 pain (4% v 1%) in the 12-cycle treatment arm.<sup>155</sup> In contrast another study of six cycles of paclitaxel (175mg/m<sup>2</sup>) after a complete response showed no difference in PFS or OS.<sup>156</sup>

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Continued maintenance therapy with bevacizumab following first line carboplatin, paclitaxel and bevacizumab has been shown to delay progression (*see section 6.2.5*) and the use of continued maintenance therapy with other biological agents is under investigation in clinical trials.

**A** For advanced ovarian cancer, maintenance cytotoxic chemotherapy should not be given following standard first line chemotherapy.

### 6.2.7 INTRAPERITONEAL CHEMOTHERAPY

A meta-analysis of nine RCTs, including six considered to be of high quality, concluded that women with a new diagnosis of epithelial ovarian cancer (stage II-IV) with residual disease of  $\leq 2$  cm, benefited from a chemotherapy regimen that included an intraperitoneal (IP) component compared to intravenous (IV) chemotherapy following primary cytoreductive surgery in terms of survival and progression-free interval (HR=0.81, 95% CI 0.72 to 0.90 and HR=0.78, 95% CI 0.70 to 0.86, respectively).<sup>157</sup> Intraperitoneal treatment was associated with greater serious toxicity (grade 3 and 4) with regards to gastrointestinal effects (RR 1.90, 95% CI 1.57 to 2.30), pain (RR 7.47, 95% CI 4.41 to 12.67), fever (RR 1.64, 95% CI 1.13 to 2.38) and infection (RR 3.34, 95% CI 2.06 to 5.43), but less ototoxicity (RR 0.67, 95% CI 0.46 to 0.99), although heterogeneity across trials, probably reflecting differing doses, makes comparison difficult.

1<sup>++</sup>

However, only three of the trials used an intravenous control regimen that would be considered comparable to current standard IV therapy. In addition only four studies used similar doses and schedule of chemotherapy in the IV and IP arms so results may be confounded by a higher dose intensity in the IP arm. One trial assessed the effects on quality of life (QoL) and found worse QoL in the IP arm during and immediately after treatment but no difference 12 months after treatment. In the GOG 172 study, women in the IP arm reported worse QoL and pain prior to the fourth chemotherapy cycle ( $p < 0.001$ ) and worse QoL three to six weeks post treatment ( $p = 0.009$ ). There were no significant QoL or pain score differences between arms one year post treatment. Trials are ongoing which aim to establish more tolerable IP regimens and which avoid confounding factors.

The population that is most likely to benefit from IP treatment has yet to be determined but bowel surgery may predispose to complications and the studies only included women with residual disease of  $\leq 2$  cm.

**B** Chemotherapy which includes an intraperitoneal element can be considered for women with a new diagnosis of epithelial ovarian cancer and residual disease of  $\leq 1$  cm after primary surgery provided a regimen of proven benefit in a clinical trial compared to intravenous therapy is used, it is delivered in a centre with appropriate expertise and the potential toxicities are fully explained.

✓ Where possible, women receiving intraperitoneal chemotherapy should be enrolled into ongoing clinical trials.

## 6.3 RELAPSED DISEASE

### 6.3.1 SYSTEMIC THERAPY IN RECURRENT OVARIAN CANCER

Relapse in ovarian cancer occurs in approximately 75% of patients and is therefore a significant problem, affecting approximately 375 patients a year in Scotland. Relapsed ovarian cancer is incurable but prolonged survival ( $> 1$  year) is possible in the majority of patients and improved treatment following relapse has resulted in incremental increases in the overall survival from ovarian cancer.

Three systematic reviews, one meta-analysis, and 14 good-quality RCTs of chemotherapy for relapsed ovarian cancer support the use of platinum-based combination chemotherapy (where likely to be tolerated) in platinum-sensitive relapsed disease.<sup>158-175</sup> For platinum-resistant ovarian cancer, the evidence is less clear, with data in some cases derived from small patient subgroups in studies of relapsed ovarian cancer rather than studies which were performed specifically in the platinum-resistant setting.

1<sup>++</sup>  
1<sup>+</sup>

The results from two systematic reviews including 13 and nine RCTs, respectively, provide good evidence that platinum based combination chemotherapy provides a survival benefit when compared to single agent platinum chemotherapy, although combination therapy was associated with higher rates of adverse events.<sup>158,160</sup> 1<sup>++</sup>

In the setting of platinum-sensitive relapsed ovarian cancer there is evidence from a large RCT with a low risk of bias that the combination of carboplatin and pegylated liposomal doxorubicin hydrochloride (PLDH) (CD arm) is more tolerable than carboplatin and paclitaxel (CP arm) and that it confers a progression-free survival benefit (median PFS 11.3 months for CD arm v 9.4 months for CP arm; HR=0.823, 95% CI 0.72 to 0.94, p=0.005).<sup>172</sup> 1<sup>++</sup>

Trabectedin combined with PLDH improved PFS compared to monotherapy, and increased overall survival compared to topotecan alone. However, this therapy was not as cost effective as paclitaxel or PLDH plus platinum.<sup>220</sup> Monotherapy with PLDH or paclitaxel is cost effective for the treatment of women with platinum-sensitive disease when platinum-based treatment is unsuitable.<sup>220</sup> 1<sup>++</sup>

Potential toxicities with combination therapy with either paclitaxel or PLDH include myelosuppression, fatigue, nausea, vomiting and palmoplantar erythrodysesthesiae. Treatment with paclitaxel is also associated with alopecia, neuropathy, and arthralgia. Stomatitis has been reported mainly with use of PLDH.<sup>220</sup> The use of platinum combination therapy compared to single-agent platinum depends on patient comorbidity and willingness to accept the additional toxicity, and the pros and cons of each approach should be discussed with the patient. 1<sup>++</sup>

In patients with platinum-resistant ovarian cancer, a network meta-analysis identified no significant difference in PFS or OS benefit between PLDH, three-weekly paclitaxel or topotecan monotherapy. This was in line with the findings from the individual trials.<sup>220</sup> NICE reported that paclitaxel or PLDH as monotherapy were cost effective and concluded that either could be recommended for treatment of women with platinum-resistant or refractory ovarian cancer.<sup>220</sup> 1<sup>++</sup>

The addition of bevacizumab to paclitaxel and carboplatin; gemcitabine and carboplatin; or bevacizumab with either PLDH, weekly paclitaxel or weekly topotecan, improved PFS (HR 0.53, 95% CI 0.45 to 0.63) and OS (HR 0.87, 95% CI 0.77 to 0.99).<sup>221</sup> Two of the trials included patients with platinum-sensitive ovarian cancer, and the other was in patients with platinum-resistant cancer. Common adverse events reported with bevacizumab use were hypertension, proteinuria, bleeding, wound healing disruption, gastrointestinal perforations, arterial thrombosis events and venous thrombosis events.<sup>221</sup> 1<sup>++</sup>

Bevacizumab is accepted by SMC for restricted use in combination with paclitaxel in patients with platinum-resistant recurrent ovarian cancer who have received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents (*see section 10.4*). However, SMC does not recommend it for use in combination with carboplatin and paclitaxel, or in combination with carboplatin and gemcitabine in patients with first-recurrence platinum-sensitive ovarian cancer.

**A** Women with platinum-sensitive relapsed ovarian cancer should be offered treatment with carboplatin combined with either paclitaxel or pegylated liposomal doxorubicin hydrochloride (depending on fitness, comorbidity and toxicity experienced with previous treatment).

**A** Women with platinum-resistant ovarian cancer should be considered for treatment with paclitaxel or single agent pegylated liposomal doxorubicin hydrochloride (depending on fitness, comorbidity and patient's wishes).

**A** Women with platinum-resistant relapsed ovarian cancer should be offered bevacizumab in combination with paclitaxel.

Trials of poly (ADP-ribose) polymerase (PARP) inhibitors have shown benefit in lengthening progression-free survival in patients with advanced, recurrent, platinum-sensitive ovarian cancer.<sup>222-224</sup>

A trial of olaparib reported improved PFS of 19.1 months compared to 5.5 months for placebo; HR 0.30 (95% CI 0.22 to 0.41).<sup>224</sup> Twelve-month PFS was 65% in the olaparib group versus 21% placebo, and 43% versus 15% for 24 month survival.<sup>224</sup> Overall survival data at five-year follow up from the Phase II trial showed improved survival compared to placebo, although it was not sufficient to be statistically significant (HR 0.73, 95% CI 0.55 to 0.96 across the patient groups. Median overall survival was 29.8 months with olaparib, compared to 27.8 in the placebo group.<sup>225</sup> 1++

Rucaparib also showed benefit with a PFS of 10.8 months versus 5.4 months with placebo, HR 0.36, 95% CI 0.30 to 0.45.<sup>222</sup> 1++

In the trial of niraparib PFS was longest in patients with a germline BRCA mutation (PFS 21 months v 5.5 months for placebo, HR 0.27 95% CI 0.17 to 0.41). Overall, for patients in the non-germline BRCA mutation cohort PFS was 9.3 months versus 3.9 months for placebo, HR 0.45 (95% CI 0.34 to 0.61). For patients who were non-germline BRCA with tumours with homologous recombination deficiency the PFS was 21.9 months versus 3.8 months placebo, HR 0.38, 95% CI 0.24 to 0.59.<sup>223</sup> 1++

Patients reported quality of life to be similar whether on PARP inhibitor or placebo.<sup>222-224</sup> All three trials reported anaemia as a common serious adverse event.<sup>222-224</sup> Thrombocytopenia and neutropenia were commonly reported with the use of niraparib, but could be managed with dose reduction.<sup>223</sup> The trials of olaparib and rucaparib resulted in the death of one patient due to the development of myeloid leukaemia.<sup>222,224</sup> Another patient in the rucaparib cohort died from treatment-related myelodysplastic syndrome.<sup>222</sup> In the long-term data from the phase II trial of olaparib, three patients developed myelodysplastic syndromes or acute myeloid leukaemia, one of whom was in the placebo group.<sup>225</sup> 1++

SMC has accepted olaparib for monotherapy for the maintenance treatment of patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy. Niraparib is accepted for monotherapy for maintenance treatment of patients with platinum-sensitive relapsed non germline BRCA mutation high grade serous epithelial ovarian cancer who are in response to platinum-based chemotherapy (*see section 10.4*).

**A** Olaparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive BRCA-mutated ovarian cancer.

**A** Niraparib monotherapy should be considered for maintenance treatment after response to platinum for patients with relapsed platinum-sensitive non-germline BRCA-mutated ovarian cancer.

### 6.3.2 THE ROLE OF HORMONAL THERAPY IN RELAPSED DISEASE

A Cochrane review of tamoxifen concluded that no evidence based recommendations could be made due to the lack of comparative studies assessing the effectiveness of tamoxifen in women with recurrent ovarian cancer.

Several small (n=27-60), single arm, phase II studies have investigated the use of various hormonal agents including tamoxifen, aromatase inhibitors, luteinizing hormone-releasing hormone (LHRH) agonists and antagonists in heavily pre-treated recurrent ovarian cancer.<sup>176-183</sup> All have shown low toxicity with modest response rates (from less than 10% to 18%) with additional patients achieving stable disease and some with prolonged disease control. In the four studies reporting toxicities (n=154), only three patients withdrew from studies because of toxicity (one each for nausea, rash and headache; all receiving letrozole).<sup>178-180,182</sup> There is evidence that higher levels of oestrogen receptor expression are associated with greater chance of response.<sup>178,181</sup> 3

Trials are needed to assess whether hormone receptor status is useful in selecting patients with recurrent ovarian cancer for tamoxifen therapy, whether certain histological subtypes of ovarian cancer are more likely to respond, and whether tamoxifen improves survival, symptom control and quality of life compared to chemotherapy or novel agents in platinum-resistant recurrent disease or to no therapy when used in the setting of asymptomatic progression to delay the onset of symptoms.<sup>184</sup>

**D** Hormonal therapy with tamoxifen or an aromatase inhibitor can be used for women with recurrent, platinum-resistant, ovarian cancer or in those wishing to avoid or delay further chemotherapy, particularly where their original tumour is expressing the oestrogen receptor.

#### 6.4 CHEMOTHERAPY FOR LOW-GRADE SEROUS, CLEAR CELL AND MUCINOUS HISTOLOGICAL SUBTYPES

Epithelial ovarian cancer is made up of at least five different histological subtypes: high-grade serous, low-grade serous, endometrioid, mucinous and clear cell carcinoma. In addition, carcinosarcomas, also known as mixed müllerian tumours, are also probably best classified as epithelial tumours. These different histological subtypes of ovarian cancer are now recognised as distinct diseases with different genetic factors, precursor lesions, molecular events during oncogenesis, patterns of spread and response to treatment.

In advanced disease, clear cell carcinomas and mucinous carcinomas have a poor prognosis when compared to high-grade serous and endometrioid tumours. They also respond less well to chemotherapy.<sup>185-190</sup>

Low-grade serous carcinoma has a relatively indolent natural history compared to high-grade disease but is also resistant to standard chemotherapy.<sup>191</sup>

In clear cell carcinoma, there has been one randomised phase II study comparing irinotecan plus cisplatin to carboplatin and paclitaxel for the first line treatment of stage I<sub>c</sub> to IV disease. This demonstrated that the combination was feasible and a subsequent phase III trial has completed recruitment. A retrospective review of population based outcomes in Canada suggested a potential advantage from pelvic radiotherapy over chemotherapy alone in stage I<sub>c</sub> and II clear cell carcinomas but this needs to be prospectively assessed in a clinical trial.<sup>192</sup> Early phase trials of angiogenesis inhibitors and motor inhibitors are in development.

A multinational randomised controlled phase III trial in mucinous ovarian cancer of oxaliplatin and capecitabine versus carboplatin and paclitaxel with a further randomisation to bevacizumab or no bevacizumab, is currently recruiting.

A single arm phase II study of the MEK 1/2 inhibitor, selumetinib, has shown activity in relapsed low-grade serous carcinoma with a response rate of 15% and stable disease in 65%.<sup>193</sup>

The rarer subtypes together make up a significant proportion of ovarian cancer. As understanding of the molecular biology of the different subtypes increases and new therapeutic opportunities emerge, it will no longer be appropriate to treat them as a single entity. Significant international collaboration and innovative trial design will be required in order to undertake subgroup specific trials because of the small patient numbers.

✓ Patients with low-grade serous, clear cell and mucinous histological subtypes should be considered for clinical trials.

## 7 Follow up

There are no RCTs specific to ovarian cancer that assess whether follow up at a multidisciplinary clinic reduces the risk of death. A descriptive study demonstrates that an independent prognostic factor for improved survival is follow up at a multidisciplinary clinic.<sup>194</sup> 3

A Cochrane systematic review of follow-up strategies for patients with epithelial ovarian cancer following completion of primary treatment identified one RCT (n=529) with a low risk of bias that suggested that routine surveillance of CA125 in blood serum in asymptomatic patients, with treatment at CA125 relapse, does not seem to offer survival advantage when compared to treatment at symptomatic relapse. Overall survival showed no significant difference between the immediate and delayed arms after a median follow up of 56.9 months (unadjusted HR=0.98, 95% CI 0.80 to 1.20, p<0.85).<sup>195</sup> It is important to note that the results of this RCT relate to the first relapse of ovarian cancer. 1++

Two further systematic reviews, one including 67 studies, five of which (one RCT and four observational studies) examined survival benefit,<sup>196</sup> and one including four studies (two reviews, two retrospective cohorts), three of which considered survival benefit,<sup>197</sup> concluded that there was no evidence of a positive effect on survival in women followed up after primary treatment of ovarian cancer. 2++  
2+

All three reviews concluded that further research is needed on the benefits of different types of routine follow up on, for example, outcomes, quality of life and psychological effects.

**A** Treatment of first relapse of ovarian cancer should be guided by the development of symptoms.

**A** In the absence of symptoms, routine measurement of CA125 during follow up is not mandatory.

## 8 Management of malignant bowel obstruction in relapsed disease

The true incidence of malignant intestinal obstruction due to progressive disease (not a primary diagnosis) is not known. Two autopsy studies of patients with ovarian cancer described cancer involvement in the bowel.<sup>198,199</sup> In one study 70% of patients had involvement of the small bowel and 78% involvement of the large bowel with an overall 51% incidence of intestinal obstruction.<sup>198</sup> In the other study there was small bowel involvement in 42% of cases and large bowel involvement in 49%.<sup>199</sup> Several pathophysiological mechanisms may be involved in intestinal obstruction due to progressive disease:<sup>200</sup>

- intraluminal obstruction
- intramural obstruction
- extramural obstruction
- motility disorders
- constipation.

### 8.1 SURGICAL MANAGEMENT

There is no clear evidence nor consensus on the surgical management of patients with advanced cancer. Surgery can only benefit selected patients with mechanical obstruction and should not be routine practice.<sup>200</sup> 1<sup>++</sup>

Prognostic criteria to help select patients who are likely to benefit from surgical intervention have been identified. They are given for guidance and may not cover the complexities of an individual situation.<sup>201-205</sup> 2<sup>+</sup>  
Each contraindication stands alone (*see Table 3*).

**C** **Surgery for malignant bowel obstruction in patients with advanced ovarian cancer must be justified on the basis of achieving a significant benefit.**

*Table 3: Contraindications to surgery for malignant bowel obstruction in patients with advanced ovarian cancer*

Absolute contraindications
Patient refusal
Previous abdominal surgery which showed diffuse metastatic cancer
Involvement of proximal stomach
Intra-abdominal carcinomatosis demonstrated radiologically with a contrast study revealing a severe motility problem
Diffuse palpable intra-abdominal masses (having excluded faecal masses)
Massive ascites which rapidly recurs after drainage
Relative contraindications
Non-symptomatic extensive extra-abdominal malignant disease (eg widespread metastases and pleural effusion)
Poor general performance status
Poor nutritional status (eg marked weight loss/cachexia, marked hypoalbuminaemia and low lymphocyte count)
Severe cachexia
Small bowel obstruction
Previous radiotherapy of the abdomen or pelvis

## 8.2 NON-SURGICAL MANAGEMENT

Symptoms of bowel obstruction (general abdominal pain, colic, nausea, vomiting, anorexia, dehydration) in women in whom surgery is not considered to be an option can be managed by pharmacological means.<sup>206</sup> Usually the onset of bowel obstruction is gradual over many weeks with symptoms becoming more continuous and severe. 2+

### 8.2.1 PAIN, NAUSEA AND VOMITING

The clinical aim is to control nausea, reduce the frequency and severity of vomiting to an acceptable level and to avoid a nasogastric tube (NGT), by using corticosteroids, antiemetic or antisecretory drugs. The route of drug delivery should be parenteral, normally by subcutaneous infusion.

A Cochrane review concluded that there was weak evidence that corticosteroids (dexamethasone 6-16 mg intravenously) may help the resolution of inoperable obstruction in some patients and the side effects of treatment were few.<sup>207</sup> 1+

Antiemetics are effective in controlling nausea.<sup>208</sup> Cyclizine is the first line antiemetic often used with a single bedtime dose of haloperidol. Levomepromazine in a single, low dose at bedtime is helpful when nausea receptor persists. There does not appear to be a routine role for 5-HT<sub>3</sub> antagonists (eg ondansetron) in managing nausea subsequent to obstruction. 4

Two trials have examined the antisecretory effects of octreotide and hyoscine butylbromide in patients with inoperable bowel obstruction. In one study all patients in the trial had an NGT<sup>209</sup> and in the other trial no patient had an NGT.<sup>210</sup> Octreotide was more effective and faster than hyoscine butylbromide in reducing the amount of gastrointestinal secretions in patients with NGTs. Octreotide was also more effective than hyoscine butylbromide in reducing the intensity of nausea and the number of vomiting episodes in patients without an NGT.<sup>210</sup> 1-

Nasogastric tubes are an ineffective means of controlling nausea and vomiting in malignant bowel obstruction.<sup>211,212</sup> NGTs are occasionally used in faeculant vomiting (the vomiting of small bowel contents infected by colonic bacteria), gastric outflow obstruction, or persistent vomiting whilst waiting for the delayed action of pharmacological agents. 3

Regular mouth care is the treatment of choice for dry mouth.<sup>213</sup> Parenteral hydration is sometimes indicated in patients who have nausea. 3

When laxatives are used in partial obstruction, the dose should be adjusted to maintain a comfortable stool without colic. Lactulose may add to the bowel volume. A combination of senna and docusate, or docusate alone should be used if colic is a problem.<sup>208</sup> In complete, inoperable obstruction, all laxatives should be stopped. 4

Pain (visceral and colic) can often be controlled using analgesic drugs most often given by syringe driver. Colic is a common problem. It is not relieved by strong opioids, but responds rapidly to parenteral hyoscine butylbromide. In complete, inoperable obstruction this can be given as a continuous subcutaneous infusion.<sup>208</sup> Involvement of the coeliac plexus can cause a severe visceral neuropathic pain that may partly respond to opioids or need an anti-neuropathic pain agent such as gabapentin.<sup>214</sup> For a more detailed discussion of pain assessment and management see SIGN guideline number 106 on the control of pain in patients with cancer.<sup>215</sup> 3  
4

**C** Symptoms of bowel obstruction can be relieved by using the following drug categories either alone or in combination:

- antiemetic
- antisecretory
- analgesic
- corticosteroids.



## 9 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing ovarian cancer with patients and carers and in guiding the production of locally produced information materials.

### 9.1 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive.

<b>Initial presentation</b>
<ul style="list-style-type: none"> <li>• After examination and assessment of the clinical picture, advise the patient of the need for referral to a specialist and how long they should expect to wait.</li> <li>• Explain what will happen at the appointment with a specialist.</li> <li>• When referring a patient with suspected cancer to a specialist service, primary healthcare professionals should assess the patient's need for continuing support while waiting for referral.</li> </ul>
<b>Referral</b>
<ul style="list-style-type: none"> <li>• Explain to the patient that a physical examination will be carried out and one or more diagnostic tests including:               <ul style="list-style-type: none"> <li>- serum CA125 level</li> <li>- ultrasound assessment</li> <li>- the Risk of Malignancy scoring system</li> <li>- computed tomography (CT scan).</li> </ul> </li> </ul>
<b>Diagnosis</b>
<ul style="list-style-type: none"> <li>• Inform the patient that they can bring a partner or family member or friend with them to their appointment if they wish.</li> <li>• Ensure the patient understands what ovarian cancer is, including genetic risk.</li> <li>• Explain to the patient that further tests may be done to 'stage' the cancer and that this helps to establish the stage to which the cancer has grown and perhaps spread.</li> <li>• Discuss treatment options with the patient, taking into account their individual needs and preferences. Offer written and verbal information outlining a clear pathway of how they will be treated and cared for. The amount of information given should be appropriate to their wishes, level of understanding, and delivered in a way which is sensitive, understandable to them, and accurate.</li> <li>• Allow sufficient time to discuss the following issues and ensure the patient is involved in discussions:               <ul style="list-style-type: none"> <li>- aims of treatments</li> <li>- prognosis (if the patient wishes)</li> <li>- depression and anxiety.</li> </ul> </li> <li>• Ensure the patient is aware that there may be a need for other surgery in addition to the planned surgery, for example, the need for colostomy.</li> <li>• Ensure the patient is aware of where to go to for further information and support including counselling services (<i>see section 9.2</i>).</li> <li>• Ensure the patient is aware of the support role of the clinical nurse specialist.</li> </ul>

<b>Treatment</b>
<ul style="list-style-type: none"> <li>• Inform the patient of their treatment plans and advise them of the time frame for treatment.</li> <li>• Advise the patient of the opportunity for family involvement if they wish them to be involved.</li> <li>• Discuss adjuvant chemotherapy/radiotherapy, its procedures and adverse side effects.</li> <li>• Discuss side effects of other treatments with the patient and how they can be managed.</li> <li>• Advise the patient how they will be prepared for surgery.</li> <li>• Inform the patient of activities they can and cannot do after surgery, for example housework, exercise, driving.</li> <li>• Discuss the following with the patient:               <ul style="list-style-type: none"> <li>- body image</li> <li>- sexual function</li> <li>- fertility and fertility conserving surgery (if this is an option for the patient)</li> <li>- hormone replacement.</li> </ul> </li> <li>• Ensure the patient understands the importance of attending ongoing follow-up appointments after discharge and inform them of how they are likely to be followed up, ie by whom, where and when.</li> </ul>
<b>Follow up</b>
<ul style="list-style-type: none"> <li>• Advise the patient that they will receive a physical examination and be asked about signs and symptoms.</li> <li>• Advise the patient that they should report any concerns they have following treatment.</li> <li>• Mention and discuss the fear of recurrence and advise the patient that recurrent symptoms should be reported.</li> <li>• The following issues should be discussed with the patient:               <ul style="list-style-type: none"> <li>- returning to work</li> <li>- financial issues</li> <li>- coping, depression, anxiety and fatigue.</li> </ul> </li> </ul>
<b>Palliative care</b>
<ul style="list-style-type: none"> <li>• The following should only be discussed with the patient if they require palliative care:               <ul style="list-style-type: none"> <li>- aim of palliative care</li> <li>- who is likely to be involved in their care</li> <li>- symptom management</li> <li>- management of side effects.</li> </ul> </li> <li>• Advise the patient of the availability of Macmillan nurses etc.</li> <li>• Advise the patient and carers about the availability of aids and equipment for the home and who to contact to arrange these.</li> </ul>

## 9.2 SOURCES OF FURTHER INFORMATION

### **Cancer Research UK**

Angel Building, 407 St John Street  
London EC1V 4AD  
Tel: 020 7242 0200  
[www.cancerresearchuk.org](http://www.cancerresearchuk.org)

Cancer Research UK funds research into cancer, campaigns on cancer issues and produces patient information leaflets.

### **Macmillan Cancer Support in Scotland**

132 Rose Street  
Edinburgh, EH2 3JD  
Tel: 0131 260 3720 or 0808 808 00 00  
[www.macmillan.org.uk](http://www.macmillan.org.uk)

Macmillan Cancer Support supports people with cancer (and their families) with practical, medical, emotional and financial advice.

### **Maggie's Centres Scotland**

[www.maggiescentres.org](http://www.maggiescentres.org) • Email: [enquiries@maggiescentres.org](mailto:enquiries@maggiescentres.org)

Maggie's provides practical, emotional and social support to people with cancer, their family and friends. Built alongside NHS cancer hospitals and staffed with professional experts, Maggie's Centres are warm and welcoming, full of light and open space, with a big kitchen table at their heart.

### **Maggie's Dundee**

Tom McDonald Avenue, Ninewells Hospital  
Dundee DD2 1NH  
Tel: 01382 632999  
Email: [dundee@maggiescentres.org](mailto:dundee@maggiescentres.org)

### **Maggie's Edinburgh**

The Stables, Western General Hospital, Crewe Road South  
Edinburgh EH4 2XU  
Tel: 0131 537 3131  
Email: [edinburgh@maggiescentres.org](mailto:edinburgh@maggiescentres.org)

### **Maggie's Fife**

Victoria Hospital, Hayfield Road  
Kirkcaldy KY2 5AH  
Tel: 01592 647997  
Email: [fife@maggiescentres.org](mailto:fife@maggiescentres.org)

### **Maggie's Glasgow**

Gartnavel General Hospital, 1053 Great Western Road  
Glasgow G12 0YN  
Tel: 0141 357 2269  
Email: [glasgow@maggiescentres.org](mailto:glasgow@maggiescentres.org)

### **Maggie's Highlands**

Raigmore Hospital, Old Perth Road  
Inverness IV2 3UJ  
Tel: 01463 706306  
Email: [highlands@maggiescentres.org](mailto:highlands@maggiescentres.org)

**Maggie's Lanarkshire**

Flat 78, Residential Accommodation, Wishaw General Hospital, 50 Netherton Road  
Wishaw ML2 0DP  
Tel: 01698 358392  
Email: [lanarkshire@maggiescentres.org](mailto:lanarkshire@maggiescentres.org)

**Marie Curie Cancer Care (Scotland)**

14 Links Place  
Edinburgh EH6 7EB  
Tel: 0131 561 3900  
[www.mariecurie.org.uk](http://www.mariecurie.org.uk)

Marie Curie Cancer Care provides practical nursing care at home and specialist care across ten Marie Curie centres

**NHS Inform**

[www.nhsinform.co.uk/](http://www.nhsinform.co.uk/)

The organisation provides quality-assured health information for the public.

**Ovacome**

Suite B5, City Cloisters, 196 Old Street  
London, EC1V 9FR  
Supportline: 0845 371 0054 or 0207 299 6650 • Tel: 0207 299 6654  
[www.ovacome.org.uk](http://www.ovacome.org.uk) • Email: [ovacome@ovacome.org.uk](mailto:ovacome@ovacome.org.uk)  
Email: [support@ovacome.org.uk](mailto:support@ovacome.org.uk)

Ovacome is a UK wide charity providing information and support for all those affected by ovarian cancer including patients, relatives, carers and health professionals. A newsletter is produced four times a year and fact sheets on many aspects of ovarian cancer are available on request.

**Ovarian Cancer Action**

8-12 Camden High Street  
London, NW1 0JP  
Help line: 0300 456 4700 • Tel: 0207 380 1730  
[www.ovarian.org.uk](http://www.ovarian.org.uk) • Email: [info@ovarian.org.uk](mailto:info@ovarian.org.uk)

Ovarian Cancer Action is a leading UK ovarian cancer charity. Their focus is on improving the prognosis of all women diagnosed with ovarian cancer. They fund the UK's first research centre dedicated solely to ovarian cancer at Imperial College, London.

**Ovarian Lets Shout for Linda**

3 Warwick, Calderwood  
East Kilbride G74 3PZ  
Tel: 01355 249007  
[www.ovarianletsshoutforlinda.co.uk](http://www.ovarianletsshoutforlinda.co.uk) • Email: [mail@ovarianletsshoutforlinda.co.uk](mailto:mail@ovarianletsshoutforlinda.co.uk)

This is a Scottish charity dedicated to ovarian cancer by raising awareness of it, by working with communities and disseminating information to actively advocate and champion prevention, screening and early diagnostic testing.

**Target Ovarian Cancer**

30 Angel Gate

London, EC1V 2PT

Tel: 020 7923 5470 • Fax: 020 7923 5471

[www.targetovariancancer.org.uk](http://www.targetovariancancer.org.uk) • Email: [info@targetovarian.org.uk](mailto:info@targetovarian.org.uk)

Target Ovarian Cancer is the national ovarian cancer charity providing help and support to women and their families. They offer a range of information for patients, carers and healthcare professionals.

**The Eve Appeal**

15B Berghem Mews, Blythe Road

London, W14 0HN

Tel: 020 7605 0100

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This charity promotes awareness of gynaecological cancers and produces a range of information for patients, their families and the public. They work in partnership with other organisations to improve the healthcare and support of women.

## 10 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

### 10.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

### 10.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations are considered likely to reach the £5 million threshold which warrants full cost impact analysis.

The recommendation in section 6.2.4 relating to treatment with carboplatin AUC 6 and paclitaxel 80mg/m<sup>2</sup> may have resource implications, particularly in terms of staffing, as women undergoing this treatment would need to attend weekly for 18 weeks instead of for six visits. The resource implications will be greater if the results of ongoing clinical trials identify this regimen as the standard of care.

### 10.3 AUDITING CURRENT PRACTICE

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

Following publication of the Quality Performance Indicators (QPIs) for Ovarian Cancer in Scotland, the guideline development group has identified that the eight published QPIs should form the basis for audit work in Scotland as these reflect key aspects of care identified in this guideline.<sup>216</sup>

#### 10.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

In October 2015 the SMC advised that bevacizumab (Avastin) is accepted for restricted use within NHSScotland in combination with carboplatin and paclitaxel, for the front-line treatment of patients with FIGO stage IV epithelial ovarian disease.

[www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-resubmission-80612/](http://www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-resubmission-80612/)

In August 2017 SMC accepted bevacizumab for restricted use within NHSScotland. Indication under review: in combination with paclitaxel, topotecan, or PLDH for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other vascular endothelial growth factor (VEGF) inhibitors or VEGF receptor-targeted agents. SMC restriction: to use in combination with paclitaxel.

[www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-fullsubmission-106315/](http://www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-fullsubmission-106315/)

In August 2017 SMC advised that bevacizumab is not recommended for use within NHSScotland in combination with carboplatin and paclitaxel for the treatment of adult patients with first recurrence of platinum-sensitive epithelial, ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents. This is due to the absence of a submission from the holder of the marketing authorisation.

[www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-nonsubmission-127517/](http://www.scottishmedicines.org.uk/medicines-advice/bevacizumab-avastin-nonsubmission-127517/)

In March 2013 SMC advised that bevacizumab is not recommended for use within NHSScotland in combination with carboplatin and gemcitabine, for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor-targeted agents.

[www.scottishmedicines.org.uk/media/1325/bevacizumab\\_avastin\\_final\\_february\\_2013\\_for\\_website.pdf](http://www.scottishmedicines.org.uk/media/1325/bevacizumab_avastin_final_february_2013_for_website.pdf)

In November 2016 SMC accepted olaparib for monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy. This SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of olaparib, and is contingent upon the continuing availability of the PAS in NHSScotland or a list price that is equivalent or lower. This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

[www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-resubmission-104715/](http://www.scottishmedicines.org.uk/medicines-advice/olaparib-lynparza-resubmission-104715/)

In August 2018 SMC accepted niraparib as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. Use is restricted to patients who do not have a germline BRCA mutation. This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of niraparib. This advice is contingent upon the continuing availability of the PAS in NHS Scotland or a list price that is equivalent or lower. This advice takes account of views from a Patient and Clinician Engagement (PACE) meeting.

[www.scottishmedicines.org.uk/media/3650/niraparib-tosylate-monohydrate-zejula-final-july-2018-amended-240718-for-website.pdf](http://www.scottishmedicines.org.uk/media/3650/niraparib-tosylate-monohydrate-zejula-final-july-2018-amended-240718-for-website.pdf)

# 11 The evidence base

## 11.1 SYSTEMATIC LITERATURE REVIEW

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2003-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

### 11.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to early management of patients with epithelial ovarian cancer. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

## 11.2 RECOMMENDATIONS FOR RESEARCH

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline (*see Annex 1*). The following areas for further research have been identified:

- What is the effect of ultra radical versus standard radical surgery on outcomes in patients with advanced ovarian cancer?
- What are the implications for training of gynaecological oncologists and cross-specialty working with surgeons skilled in bowel resection, diaphragmatic stripping, liver mobilisation and upper abdominal surgery if increasing numbers of women in Scotland receive ultra radical cytoreductive surgery and what are the implications for patients who would be expected to have higher morbidity rates and require additional high dependency or intensive care perioperatively?
- What is the best pathway for assessment and management of patients with a mildly elevated RMI 1 (below the original scoring development threshold of 200) who may have benign disease or early malignancy?
- Further validation of newer morphological scoring systems that may supersede RMI 1.
- Which women are most likely to benefit (in terms of survival and quality of life end points) from hormonal therapy and how does it compare to chemotherapy in platinum-resistant disease?
- What is the optimal duration of therapy with bevacizumab and are there predictive markers of benefit to bevacizumab?
- What is the optimal chemotherapy regimen for low-grade serous, clear cell and mucinous histological subtypes of ovarian cancer?

## 11.3 REVIEW AND UPDATING

This guideline was issued in 2013 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the review report, which is available in the supporting material section for this guideline on the SIGN website: [www.sign.ac.uk](http://www.sign.ac.uk)

Comments on new evidence that would update this guideline are welcome and should be sent to the SIGN Executive, Gyle Square, 1 South Gyle Crescent, Edinburgh, EH12 9EB (email: [sign@sign.ac.uk](mailto:sign@sign.ac.uk)).



## 12 Development of the guideline

### 12.1 INTRODUCTION

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising clinicians using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in SIGN 50: A Guideline Developer's Handbook, available at [www.sign.ac.uk](http://www.sign.ac.uk).

### 12.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Nadeem Siddiqui (Chair)	<i>Consultant Gynaecologist and Oncologist, Glasgow Royal Infirmary</i>
Ms Sandra Bredin	<i>Clinical Nurse Specialist, Glasgow Royal Infirmary</i>
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Dr Rosalind Glasspool	<i>Consultant Medical Oncologist and Honorary Senior Lecturer, Beatson Oncology Centre, Glasgow</i>
Professor Charlie Gourley	<i>Professor and Honorary Consultant in Medical Oncology, Western General Hospital, Edinburgh</i>
Dr Karen Gray	<i>Consultant Radiologist, Crosshouse Hospital, Kilmarnock</i>
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Ms Maureen Mackay	<i>Patient Representative</i>
Ms Dianna Manson	<i>Patient Representative</i>
Dr Zosia Miedzzybrodzka	<i>Reader in Medical Genetics, University of Aberdeen</i>
Dr David Millan	<i>Consultant Pathologist, Southern General Hospital, Glasgow</i>
Dr David Parkin	<i>Consultant Gynaecological Oncologist, Aberdeen Royal Infirmary</i>
Dr Nicholas Reed	<i>Clinical Oncologist, Gartnavel General Hospital, Glasgow</i>
Ms Diane Stirling	<i>Principal Genetic Counsellor, Western General Hospital, Edinburgh</i>
Mrs Lynne Smith	<i>Evidence and Information Scientist, SIGN</i>
Dr Valerie Wareham	<i>Consultant Gynaecologist, Raigmore Hospital, Inverness</i>
Professor David Weller	<i>Head, School of Clinical Sciences and Community Health, General Practice Section, University of Edinburgh</i>

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest and further details of these are available on request from the SIGN Executive.

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

Lesley Forsyth	<i>Events Coordinator</i>
Karen Graham	<i>Patient Involvement Officer</i>
Gemma Hardie	<i>Distribution and Office Coordinator</i>
Stuart Neville	<i>Publications Designer</i>
Gaynor Rattray	<i>Guideline Coordinator</i>

### 12.2.1 ACKNOWLEDGEMENTS

SIGN would like to acknowledge the guideline development group responsible for the development of SIGN 75: Epithelial ovarian cancer, on which this guideline is based and the following individual who contributed to the development of the guideline.

Mr Stephen Hay	<i>Lay Representative, Coatbridge</i>
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## 12.3 CONSULTATION AND PEER REVIEW

### 12.3.1 PUBLIC CONSULTATION

The draft guideline was available on the SIGN website for a month to allow all interested parties to comment. All contributors made declarations of interest and further details of these are available on request from the SIGN Executive.

### 12.3.2 SPECIALIST REVIEW

This guideline was also reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

Mr Desmond Barton	<i>Consultant Surgeon, Gynaecology Unit, The Royal Marsden, London</i>
Dr Patrick Cadigan	<i>Registrar, on behalf of the Royal College of Physicians, London</i>
Professor Stan Kaye	<i>Head of the Division of Clinical Studies, Institute of Cancer Research, and Consultant Medical Oncologist, The Royal Marsden, London</i>
Professor Sean Kehoe	<i>Lawson Tait Professor of Gynaecological Cancer, The University of Birmingham</i>
Mrs Kirsty MacFarlane	<i>Principal Pharmacist, on behalf of the Scottish Medicines Consortium, Glasgow</i>
Professor Iain McNeish	<i>Professor of Gynaecological Oncology, Institute of Cancer Sciences, University of Glasgow</i>
Dr Lindsey Pope	<i>Senior Clinical University Teacher, General Practice and Primary Care, University of Glasgow</i>
Dr Mary Porteous	<i>Consultant Clinical Geneticist, Western General Hospital, Edinburgh</i>

### 12.3.3 SIGN EDITORIAL GROUP

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows:

Professor Keith Brown	<i>Chair of SIGN; Co-Editor</i>
Dr Sara Twaddle	<i>Director of SIGN; Co-Editor</i>
Dr Roberta James	<i>Programme Lead, SIGN; Co-Editor</i>
Dr Tahir Mahmood	<i>Royal College of Obstetricians and Gynaecologists in Scotland</i>
Ms Fiona McMillan	<i>Royal Pharmaceutical Society</i>

All members of the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

## Abbreviations

<b>ACTION</b>	Adjuvant ChemoTherapy in Ovarian Neoplasm trial
<b>AFP</b>	alpha fetoprotein
<b>BNF</b>	British National Formulary
<b>BRCA1 or 2</b>	<i>BRCA1</i> , a gene on chromosome 17; <i>BRCA2</i> , a gene on chromosome 13. Mutations in <i>BRCA1</i> and <i>BRCA2</i> increase susceptibility to breast and ovarian cancer
<b>BS</b>	bilateral salpingectomy
<b>CA125</b>	A glycoprotein antigen. Measurement of CA125 is the blood test most widely used to detect ovarian cancer
<b>CEA</b>	carcinoembryonic antigen
<b>CI</b>	confidence interval
<b>CT</b>	computed tomography
<b>ECOG</b>	Eastern Cooperative Oncology Group
<b>FIGO</b>	International Federation of Gynecology and Obstetrics
<b>GMC</b>	General Medical Council
<b>GOG 262</b>	Paclitaxel and Carboplatin With or Without Bevacizumab in Treating Patients With Stage II, Stage III, or Stage IV Ovarian Epithelial Cancer, Primary Peritoneal Cancer, or Fallopian Tube Cancer Phase III Trial
<b>GP</b>	general practitioner
<b>hCG</b>	human chorionic gonadotropin
<b>HNCC</b>	Hereditary Nonpolyposis Colorectal Cancer
<b>HR</b>	hazard ratio
<b>HRT</b>	hormone replacement therapy
<b>IP</b>	intraperitoneal
<b>ICON</b>	International Collaborative Ovarian Neoplasm trial
<b>IV</b>	intravenous
<b>LHRH</b>	luteinizing hormone-releasing hormone
<b>LR+</b>	positive likelihood ratio
<b>LR-</b>	negative likelihood ratio
<b>MEK 1/2</b>	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
<b>MITO</b>	Multicentre Italian Trials in Ovarian Cancer
<b>MRI</b>	magnetic resonance imaging
<b>MDT</b>	multidisciplinary team
<b>NACT</b>	neoadjuvant chemotherapy
<b>NGT</b>	naso-gastric tube
<b>NICE</b>	National Institute for Health and Care Excellence
<b>NPV</b>	negative predictive value
<b>OR</b>	odds ratio

<b>OS</b>	overall survival
<b>PACE</b>	Patient and Clinical Engagement
<b>PARP</b>	poly (ADP-ribose) polymerase
<b>PAS</b>	Patient Access Scheme
<b>PDS</b>	primary debulking surgery
<b>PET</b>	positron emission tomography
<b>PET-CT</b>	positron emission tomography-computed tomography
<b>PFS</b>	progression-free survival
<b>PLDH</b>	pegylated liposomal doxorubicin hydrochloride
<b>PPV</b>	positive predictive value
<b>QoL</b>	quality of life
<b>QPI</b>	Quality Performance Indicator
<b><i>RAD51C or D</i></b>	genes essential for homologous recombination of DNA and DNA repair
<b>RCT</b>	randomised controlled trial
<b>RFI</b>	recurrence-free interval
<b>RFS</b>	recurrence-free survival
<b>RMI</b>	Risk of Malignancy Index
<b>RR</b>	risk ratio
<b>SAE</b>	serious adverse effects
<b>SCS</b>	secondary cancer surgery
<b>SMC</b>	Scottish Medicines Consortium
<b>UKCTOCS</b>	UK Collaborative Trial of Ovarian Cancer Screening
<b>US</b>	ultrasound
<b>VEGF</b>	vascular endothelial growth factor

# Annex 1

## Key questions addressed in this update

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Key question	See guideline section
1. Which patients with ovarian cancer should be considered for genetic testing?	3.2
2. In <i>BRCA</i> mutation carriers can salpingectomy be used to reduce the risk of ovarian cancer while preserving fertility?	3.4
3. What combination of symptoms should prompt a GP to consider a diagnosis of ovarian cancer?	4.1.1
4. In patients with suspected ovarian cancer, which scoring system is the most useful for predicting malignancy and aiding management?	4.2.1
5. Is there any evidence that MRI or PET-CT is better than CT for the diagnosis and staging of ovarian cancer?	4.2.2
6. In women with suspected ovarian cancer is frozen section a reliable technique for accurate diagnosis/staging?	5.2.1
7. In women with presumed early stage or stage I ovarian cancer is there any evidence that systematic lymphadenectomy improves survival?	5.3.2
8. In patients with early stage ovarian cancer, how does fertility conserving surgery affect survival compared to more conventional surgery?	5.3.4
9. In patients with advanced ovarian cancer how does complete cytoreduction compared with standard cytoreductive surgery affect survival?	5.4.1
10. In patients with advanced ovarian cancer how does neoadjuvant chemotherapy (NACT) followed by surgery compared with primary surgery affect survival, morbidity and quality of life?	5.4.2
11. In patients with relapsed ovarian cancer how does surgery in addition to chemotherapy compared with chemotherapy alone affect survival and quality of life?	5.5
12. Which patients with early stage ovarian cancer do not benefit from adjuvant chemotherapy? <i>Consider:</i> platinum (carboplatin), taxanes (paclitaxel), topotecan, bevacizumab, gemcitabine, trabectedin, pegylated liposomal doxorubicin; mono- and combination therapies (eg single agent carboplatin and combination of carboplatin and other drugs such as paclitaxel)	6.1
13. In patients with advanced ovarian cancer what is the optimal chemotherapy regimen? <i>Consider:</i> a) type of chemotherapy regimen (see list of drugs below) b) scheduling of chemotherapy (ie weekly or 3 weekly) c) maintenance chemotherapy Drugs: platinum (carboplatin), taxanes (paclitaxel), topotecan, bevacizumab, gemcitabine, trabectedin, pegylated liposomal doxorubicin; consider mono- and combination therapies (eg single agent carboplatin and combination of carboplatin and other drugs such as paclitaxel)	6.2.1-6.2.6

14. In patients with advanced ovarian cancer is there any evidence of benefit for intraperitoneal administration of chemotherapy?	6.2.7
15. In patients with relapsed ovarian cancer what is the optimal chemotherapy regimen? <i>Consider:</i> platinum (carboplatin), taxanes (paclitaxel), topotecan, bevacizumab, gemcitabine, trabectedin, pegylated liposomal doxorubicin; consider mono and combination therapies (eg single agent carboplatin and combination of carboplatin and other drugs such as paclitaxel)	6.3
16. In patients with relapsed ovarian cancer is there any role for hormonal therapies? <i>Consider:</i> tamoxifen, aromatase inhibitors, Megace, LHRH analogues, letrozole	6.3.2
17. In women who have been treated for ovarian cancer does early treatment based on follow-up measurements (eg CA125 marker concentration, routine imaging) compared with later treatment based on symptomatic relapse improve patient outcomes in first relapse of disease? <i>Consider:</i> frequency of follow up, different histological subgroups of patients and different stages	7

## Annex 2

### Staging carcinoma of the ovary

#### INTERNATIONAL FEDERATION OF GYNAECOLOGY AND OBSTETRICS (FIGO) NOMENCLATURE<sup>8</sup>

<b>Stage I - Growth limited to the ovaries</b>	
<b>Ia</b>	Growth limited to one ovary; no ascites containing malignant cells present. No tumour on the external surface; capsule intact.
<b>Ib</b>	Growth limited to both ovaries; no ascites containing malignant cells present. No tumour on the external surfaces; capsules intact.
<b>Ic*</b>	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.
<b>Stage II - Growth involving one or both ovaries with pelvic extension</b>	
<b>IIa</b>	Extension and/or metastases to the uterus and/or fallopian tubes
<b>IIb</b>	Extension to other pelvic tissues
<b>IIc *</b>	Tumour either Stage IIa or IIb, but with tumour on surface of one or both ovaries; or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
<b>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 II. Tumour is limited to the true pelvis, but with histologically proven malignant extension to small bowel or omentum.</b>	
<b>IIIa</b>	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
<b>IIIb</b>	Tumour of one or both ovaries with histologically confirmed implants, peritoneal metastasis of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
<b>IIIc</b>	Peritoneal metastasis beyond the pelvis >2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
<b>Stage IV</b>	
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 metastasis equals 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 malignant cells detected was peritoneal washings, or ascites.



## Annex 3

### Classification of ovarian cancer

Ovarian neoplasms are a heterogeneous group of tumours classified according to morphological and clinical features. The main subgroups are:

- epithelial tumours
- sex cord–stromal tumours
- germ cell tumours
- miscellaneous and metastatic tumours.

The majority of ovarian tumours (approximately 60% of all ovarian tumours and up to 90% of all primary ovarian malignancies) are epithelial. Epithelial tumours can be further classified as follows:

- serous
- mucinous
- endometrioid
- carcinosarcoma
- clear cell
- transitional cell
- mixed epithelial
- undifferentiated carcinomas.

The most common tumours are serous lesions.

Carcinosarcomas are now considered to be carcinomas with areas of metaplastic sarcomatous differentiation. The terms mixed mesodermal tumour and malignant mixed Müllerian tumour are no longer recommended.

A **benign** tumour has no abnormal cytological or proliferative features and no evidence of stromal invasion. There is no significant malignant potential.

A **borderline** (low malignant potential or atypically proliferating) tumour is a lesion which has abnormal cytological and proliferative features within its epithelium but which has no evidence of invasion into the stromal supporting tissues. Extra-ovarian disease can occur and these tumour deposits are referred to as implants. Non-invasive implants, including non-invasive desmoplastic implants, are associated with a good prognosis. Invasive implants are usually deposits of low-grade serous carcinoma and are associated with adverse outcome. Most borderline tumours present as stage I lesions and are cured by surgery. Stage by stage the overall survival of women with borderline tumours is superior to women with epithelial ovarian cancer.

A **malignant** tumour is present when there is evidence of invasion into the stromal tissues of the ovary. This is usually associated with cytological atypia and increased proliferative activity. Invasion is best defined as the presence of irregular speculated or ragged epithelial islands with individual cells extending into the stromal tissues. These stromal tissues can display reactive changes such as necrosis or an immature fibroblastic response. These cytological and proliferative changes can occur focally with the ovarian mass. An ovarian tumour must be adequately sampled for histological examination.

**Primary peritoneal cancer** is a tumour which shows similar morphological characteristics to ovarian cancer but which has no or minimal ovarian involvement.

## GRADING OF OVARIAN CANCER

There is no single universally accepted system for grading ovarian cancers. Many studies have used different systems proposed either by FIGO or WHO or the American Gynecologic Oncology Group (GOG). A proposed grading system, based on the Nottingham system of breast cancer grading, assesses the architectural pattern of the ovarian tumour, cytological atypia and the mitotic activity with the tumour.<sup>217-219</sup> This system has not been widely accepted and is of doubtful prognostic value. Current recommendations are that serous carcinomas are graded as low and high grade; endometrioid and mucinous tumours are graded using the FIGO system for endometrioid carcinomas of the endometrium; and that clear cell carcinomas, carcinosarcomas and undifferentiated carcinomas are considered by definition grade 3.<sup>91</sup> The FIGO staging system described in Annex 2 is a surgical staging system which does not incorporate the grade of the tumour.

## SEROUS CARCINOMAS

It has become apparent that there are two distinct biological types of ovarian serous carcinoma referred to by some as type 1 and type 2. However, rather confusingly, they are more commonly referred to as low-grade and high-grade despite being two different biological entities. They can be distinguished by differences in architecture, cytology, mitotic activity and pattern of necrosis. There are also significant molecular differences with high-grade serous carcinomas being associated almost universally with *TP53* mutation and low-grade serous carcinomas often containing *BRAF* or *KRAS* mutations. High-grade tumours are much more common, making up approximately 90% of serous carcinomas.<sup>91</sup>

## MUCINOUS CARCINOMAS

Primary mucinous carcinoma of the ovary is a rare tumour as many tumours are now recognised to represent metastatic tumours, often from the gastrointestinal tract. It is, in essence, a diagnosis by exclusion of a primary lesion elsewhere. Mucinous carcinomas are often found to have benign, borderline and malignant elements with the same tumour. This is not, however, proof of an origin at this site as metastatic mucinous tumours can exhibit a 'maturation phenomenon', producing a 'benign' or 'borderline' appearance.

## IMMUNOHISTOCHEMICAL ANALYSIS

The different types of epithelial ovarian cancer can be identified by their immunohistochemical profile. A potentially useful panel of antibodies includes CK7, CK20, WT-1, Pax8, Ca125, ER, PR, p53, p16 and possibly HNF-1beta. A suitable combination of these potentially helpful antibodies can be used at the discretion of the reporting pathologist.

## PSEUDOMYXOMA PERITONEI

*Pseudomyxoma peritonei* is a clinical condition characterised by the presence of mucinous material within the peritoneal cavity. This condition may originate from either the ovary or gastrointestinal tract. In gynaecological pathology it is more often seen in association with borderline mucinous ovarian tumours. In view of the debate about the primary site of origin of these tumours the appendix should be examined. Pathological examination of the mucinous material and associated tissues should specify whether epithelial cells are present or not. The cytological characteristics of the cells should also be described.

## BRCA1 AND BRCA2

Germline mutations in *BRCA1*, a gene on chromosome 17 and *BRCA2*, a gene on chromosome 13, increase susceptibility to breast and ovarian cancer.

# References

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