Ovarian cancer:

the recognition and initial management of ovarian cancer

This guidance updates and replaces recommendation 1.7.4 in 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; published June 2005).

Full Guideline

April 2011

Contents

Foreword

These clinical guidelines review a number of clinical questions that involve the detection, diagnosis and initial management of ovarian cancer and which focus on areas of uncertainty or where there is a wide variation in clinical practice.

The clinical questions were chosen using a consultative process that involved an array of stakeholders that included patient groups, representatives from relevant professional organisations and the pharmaceutical industry.

For each chapter of the guideline, the Guideline Development Group (GDG) have made evidence-based recommendations concerning clinical practice and, where applicable, some recommendations on future research.

The GDG are pleased that the focus of many of the clinical issues relate to an early stage in the patient pathway with particular relevance to patients and their families. In particular, identifying the first tests in primary care should help ensure women are directed onto the right clinical pathway in a timely fashion.

The chair and lead clinician were aided and supported by a diverse and engaged GDG membership whose complementary skills and perspectives have been instilled in this guideline.

Mr Sean Duffy   Mr Charles Redman
GDG Chair   GDG Lead clinician

Key priorities

Awareness of symptoms and signs

1. Carry out tests in primary care (see section 2.2 on page 21) if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month[1]:
   - persistent abdominal distension (women often refer to this as 'bloating')
   - feeling full (early satiety) and/or loss of appetite
   - pelvic or abdominal pain
   - increased urinary urgency and/or frequency.
2. Carry out appropriate tests for ovarian cancer (see section 2.2. on page 21) in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[2], because IBS rarely presents for the first time in women of this age.

Asking the right question – first tests

3. Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer (see section 2.1 on page 16).
4. If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
5. For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
   - assess her carefully for other clinical causes of her symptoms and investigate if appropriate
   - if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent.

Malignancy indices

6. Calculate a risk of malignancy index I (RMI I) score[3] (after performing an ultrasound; see section 3.3 on page 32) and refer all women with an RMI I score of 250 or greater to a specialist multidisciplinary team.

Tissue diagnosis

7. If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer, first obtain a confirmed tissue diagnosis by histology (or by cytology if histology is not appropriate) in all but exceptional cases.

---

[1] See also 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; available at www.nice.org.uk/guidance/CG27) for recommendations about the support and information needs of people with suspected cancer.

[2] See 'Irritable bowel syndrome in adults' (NICE clinical guideline 61; available at www.nice.org.uk/guidance/CG61).

[3] See Box 3.1 for details of how to calculate an RMI I score.

The role of systematic retroperitoneal lymphadenectomy

8. Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

Adjuvant systemic chemotherapy for stage I disease

9. Do not offer adjuvant chemotherapy to women who have had optimal surgical staging[4] and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib).

Support needs of women with newly diagnosed ovarian cancer

10. Offer all women with newly diagnosed ovarian cancer information about their disease, including psychosocial and psychosexual issues, that:
    *   is available at the time they want it
    *   includes the amount of detail that they want and are able to deal with
    *   is in a suitable format, including written information.

---

[4] Optimal surgical staging constitutes midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment [Winter Roach BA, Kitchener HC, Dickinson HO (2009) Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews, Issue 3: CD004706]

Key research recommendations

1. **Further research should be undertaken on the relationship between the duration and frequency of symptoms in women with ovarian cancer before diagnosis, the stage of disease at diagnosis and subsequent survival.**

   Most women presenting with ovarian cancer have advanced disease and have had symptoms for months. Greater awareness among both women and healthcare professionals might result in women presenting earlier with less advanced disease, leading to better outcomes. There is insufficient understanding of the factors that influence earlier diagnosis in women with ovarian cancer, especially the relationship between duration of symptoms and stage at diagnosis. Data demonstrating benefits from earlier presentation will justify investment in raising awareness among women and healthcare professionals. This is likely to be a population-based study that records both the duration and frequency of symptoms.

2. **Further research should be undertaken to determine the optimum RMI I threshold that should be applied in secondary care to guide the management of women with suspected ovarian cancer.**

   Variation exists in the current evidence base with regard to the optimum RMI I threshold that should be applied in secondary care. The cut-off levels used will have implications for both the management options considered and the number of women who will be referred for specialist treatment. Therefore it is important to establish the relative sensitivities and specificities at the different levels. The research should be a prospective observational cohort study evaluating women referred with suspected ovarian cancer. Diagnostic accuracy, sensitivity, specificity and cost effectiveness should be examined at the different RMI I thresholds.

3. **Large multicentre case–control studies should be conducted to compare the accuracy of CT versus MRI for staging and for predicting optimal cytoreduction in women with ovarian cancer.**

   Currently most women with ovarian cancer will undergo a CT scan before surgery to assess the extent and resectability of disease. CT and MRI are complementary in their abilities to detect disease, but no adequate studies have been performed that compare their effectiveness in women with suspected ovarian cancer. No comparative studies have been undertaken evaluating surgical outcome. A prospective study in women undergoing primary surgery would be feasible.

4. **A prospective randomised trial should be undertaken to evaluate the therapeutic effect, associated risks and cost effectiveness of systematic retroperitoneal lymphadenectomy in women with ovarian cancer whose disease appears to be confined to the ovaries.**

Systematic retroperitoneal lymphadenectomy is an untested procedure but is likely to be more accurate than lymph node sampling, with a potential benefit for the woman of avoiding chemotherapy. However, increased risks are associated with it. Although there may be no overall survival advantage of this procedure, avoidance of chemotherapy and impact on quality of life may make it attractive to some women as a treatment option. In order to counsel women appropriately it is essential to understand fully the risks associated with this surgery as well as the benefits. Researchers should be encouraged to develop a prospective randomised trial with international collaboration to answer this question in a timely manner.

5. Research should be undertaken to determine the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised.

Most women with advanced ovarian cancer undergo surgery at some point. Previous studies have shown that surgery after the completion of chemotherapy has no therapeutic value. Studies are being performed to investigate whether the timing of surgery during primary chemotherapy influences outcome. No studies have evaluated whether primary surgery itself has any therapeutic value when compared with chemotherapy alone. The potential advantages of surgery have to be offset against the morbidity, occasional mortality and undoubted costs associated with it. This would be a prospective randomised clinical trial recruiting women who have biopsy-proven advanced ovarian cancer and who are fit enough to receive surgery and chemotherapy. Women would be randomised to either chemotherapy and surgery (conventional arm) or chemotherapy alone (experimental arm). Primary outcome measures would be survival at 1 and 5 years.

List of all recommendations

Chapter 2: Detection in primary care

Awareness of symptoms and signs

- Refer the woman urgently[1] if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids)[2].
- Carry out tests in primary care (see section 2.2 on page 21) if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month[2]:
  - persistent abdominal distension (women often refer to this as 'bloating')
  - feeling full (early satiety) and/or loss of appetite
  - pelvic or abdominal pain
  - increased urinary urgency and/or frequency.
- Consider carrying out tests in primary care (see section 2.2 on page 21) if a woman reports unexplained weight loss, fatigue or changes in bowel habit.
- Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent.
- Carry out appropriate tests for ovarian cancer (see section 2.2 on page 21) in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[3], because IBS rarely presents for the first time in women of this age.

Asking the right question – first tests

- Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer (see section 2.1 on page 16).
- If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
- If the ultrasound suggests ovarian cancer, refer the woman urgently[1] for further investigation[2].
- For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
  - assess her carefully for other clinical causes of her symptoms and investigate if appropriate
  - if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent.

---

[1] An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

[2] See also 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; available at www.nice.org.uk/guidance/CG27) for recommendations about the support and information needs of people with suspected cancer.

[3] See 'Irritable bowel syndrome in adults' (NICE clinical guideline 61; available at www.nice.org.uk/guidance/CG61).

Chapter 3: Establishing the diagnosis in secondary care

Tumour markers: which to use?

- Measure serum CA125 in secondary care in all women with suspected ovarian cancer, if this has not already been done in primary care.
- In women under 40 with suspected ovarian cancer, measure levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG) as well as serum CA125, to identify women who may not have epithelial ovarian cancer.

Malignancy indices

- Calculate a risk of malignancy index I (RMI I) score[4] (after performing an ultrasound; see section 3.3 on page 32) and refer all women with an RMI I score of 250 or greater to a specialist multidisciplinary team.

Imaging in the diagnostic pathway: which procedures?

- Perform an ultrasound of the abdomen and pelvis as the first imaging test in secondary care for women with suspected ovarian cancer, if this has not already been done in primary care.
- If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, perform a CT scan of the pelvis and abdomen to establish the extent of disease. Include the thorax if clinically indicated.
- Do not use MRI routinely for assessing women with suspected ovarian cancer.

Tissue diagnosis

Requirement for tissue diagnosis

- If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer, first obtain a confirmed tissue diagnosis by histology (or by cytology if histology is not appropriate) in all but exceptional cases.
- Offer cytotoxic chemotherapy for suspected advanced ovarian cancer without a tissue diagnosis (histology or cytology) only:
  - in exceptional cases, after discussion at the multidisciplinary team **and**
  - after discussing with the woman the possible benefits and risks of starting chemotherapy without a tissue diagnosis.

Methods of tissue diagnosis other than laparotomy

- If surgery has not been performed, use histology rather than cytology to obtain a diagnosis. To obtain tissue for histology:
  - use percutaneous image-guided biopsy if this is feasible
  - consider laparoscopic biopsy if percutaneous image-guided biopsy is not feasible or has not produced an adequate sample.
    Use cytology if histology is not appropriate.

---

[4] See Box 3.1 for details of how to calculate an RMI I score.

Chapter 4: Management of suspected early (stage I) ovarian cancer

The role of systematic retroperitoneal lymphadenectomy

- Perform retroperitoneal lymph node assessment[5] as part of optimal surgical staging[6] in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).
- Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

Adjuvant systemic chemotherapy for stage I disease

- Do not offer adjuvant chemotherapy to women who have had optimal surgical staging[6] and have low-risk stage I disease (grade 1 or 2, stage Ia or Ib).
- Offer women with high-risk stage I disease (grade 3 or stage Ic) adjuvant chemotherapy consisting of six cycles of carboplatin.
- Discuss the possible benefits and side effects of adjuvant chemotherapy with women who have had suboptimal surgical staging[6] and appear to have stage I disease.

Chapter 5: Management of advanced (stage II–IV) ovarian cancer

Primary surgery

- If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.

Intraperitoneal chemotherapy

- Do not offer intraperitoneal chemotherapy to women with ovarian cancer, except as part of a clinical trial.

Chapter 6: Support needs of women with newly diagnosed ovarian cancer

- Offer all women with newly diagnosed ovarian cancer information about their disease, including psychosocial and psychosexual issues, that:
  - is available at the time they want it
  - includes the amount of detail that they want and are able to deal with
  - is in a suitable format, including written information.

---

[5] Lymph node assessment involves sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls if there is a palpable abnormality, or random sampling if there is no palpable abnormality.

[6] Optimal surgical staging constitutes: midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum; and retroperitoneal lymph node assessment [Winter Roach BA, Kitchener HC, Dickinson HO (2009) Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews issue 3: CD004706].

- Ensure that information is available about:
  - the stage of the disease, treatment options and prognosis
  - how to manage the side effects of both the disease and its treatments in order to maximise wellbeing
  - sexuality and sexual activity
  - fertility and hormone treatment
  - symptoms and signs of disease recurrence
  - genetics, including the chances of family members developing ovarian cancer
  - self-help strategies to optimise independence and coping
  - where to go for support, including support groups
  - how to deal with emotions such as sadness, depression, anxiety and a feeling of a lack of control over the outcome of the disease and treatment.

Methodology

Introduction

What is a clinical guideline?

Guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances – from prevention and self-care through to primary and secondary care and on to more specialised services. NICE clinical guidelines are based on the best available evidence of clinical and cost effectiveness, and are produced to help healthcare professionals and patients make informed choices about appropriate healthcare. While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

Clinical guidelines for the NHS in England, Wales and Northern Ireland are produced as a response to a request from the Department of Health (DH). They approve topics for guideline development. Before deciding whether to refer a particular topic to the National Institute for Health and Clinical Excellence (NICE) they consult with the relevant patient bodies, professional organisations and companies. Once a topic is referred, NICE then commissions one of four National Collaborating Centres (NCCs) to produce a guideline. The Collaborating Centres are independent of government and comprise partnerships between a variety of academic institutions, health profession bodies and patient groups. The National Collaborating Centre for Cancer (NCC-C) was referred the topic of the recognition and initial management of ovarian cancer in October 2007 as part of NICE's seventeenth wave work programme. However, the guideline development process began officially in February 2009 when sufficient capacity became available at the NCC-C.

Who is the guideline intended For?

This guideline does not include recommendations covering every detail of the recognition and initial management of ovarian cancer. Instead this guideline has tried to focus on those areas of clinical practice (i) that are known to be controversial or uncertain; (ii) where there is identifiable practice variation; (iii) where there is a lack of high quality evidence; or (iv) where NICE guidelines are likely to have most impact. More detail on how this was achieved is presented later in the section on 'Developing Clinical Evidence Based Questions'.

This guideline is relevant to all healthcare professionals who come into contact with patients with ovarian cancer or suspected of having ovarian cancer, as well as to the patients themselves and their carers. It is also expected that the guideline will be of value to those involved in clinical governance in both primary and secondary care to help ensure that arrangements are in place to deliver appropriate care for the population covered by this guideline.

The remit of the guideline

Guideline topics selected by the DH identify the main areas to be covered by the guideline in a specific remit. The following remit for this guideline was received as part of NICE's seventeenth wave programme of work:
- 'To prepare a clinical guideline on the recognition and initial management of ovarian cancer, to include both surgery and chemotherapy.'

Involvement of stakeholders

Key to the development of all NICE guidance is the involvement of relevant professional and patient/carer organisations that register as stakeholders. Details of this process can be found on the NICE website or in the 'NICE guidelines manual' (NICE 2009). In brief, their contribution involves commenting on the draft scope, submitting relevant evidence and commenting on the draft version of the guideline during the end consultation period. A full list of all stakeholder organisations who registered for the recognition and initial management of ovarian cancer guideline can be found in Appendix 6.2.

The process of guideline development – who develops the guideline?

Overview

The development of this guideline was based upon methods outlined in the 'NICE guidelines manual' (NICE 2009). A team of health professionals, lay representatives and technical experts known as the Guideline Development Group (GDG) (see Appendix 6.1), with support from the NCC-C staff, undertook the development of this clinical guideline. The basic steps in the process of developing a guideline are listed and discussed below:

- using the remit, define the scope which sets the inclusion/exclusion critera of the guideline
- forming the GDG
- developing clinical questions
- developing the review protocol
- systematically searching for the evidence
- critically appraising the evidence
- incorporating health economic evidence
- distilling and synthesising the evidence and writing recommendations
- agreeing the recommendations
- structuring and writing the guideline
- updating the guideline.

The scope

The remit was translated into a scope document by the Guideline Development Group (GDG) Chair and Lead Clinician and staff at the NCC-C in accordance with processes established by NICE (NICE 2009). The purpose of the scope was to:

- set the boundaries of the development work and provide a clear framework to enable work to stay within the priorities agreed by NICE and the NCC-C and the remit set by the DH
- inform professionals and the public about the expected content of the guideline.
- provide an overview of the population and healthcare settings the guideline would include and exclude
- specify the key clinical issues that will be covered by the guideline
- inform the development of the clinical questions and search strategy

Before the guideline development process started, the draft scope was presented and discussed at a stakeholder workshop. The list of key clinical issues were discussed and revised before the formal consultation process. Further details of the discussion at the stakeholder workshop can be found on the NICE website (http://www.nice.org.uk/guidance/index.jsp?action=folder&o=46933).

The scope was subject to a four week stakeholder consultation in accordance with processes established by NICE in the 'NICE guidelines manual' (NICE 2009). The full scope is shown in Appendix 4. During the consultation period, the scope was posted on the NICE website (www.nice.org.uk). Comments were invited from registered stakeholder

organisations and the NICE Guideline Review Panel (GRP). Further information about the GRP can also be found on the NICE website. The NCC-C and NICE reviewed the scope in light of comments received, and the revised scope was reviewed by the GRP, signed off by NICE and posted on the NICE website.

The guideline development group (GDG)

The ovarian cancer GDG was recruited in line with the 'NICE guidelines manual' (NICE 2009). The first step was to appoint a Chair and a Lead Clinician. Advertisements were placed for both posts and candidates were interviewed before being offered the role. The NCC-C Director, GDG Chair and Lead Clinician identified a list of specialties that needed to be represented on the GDG. Requests for applications were sent to the main stakeholder organisations, cancer networks and patient organisations/charities (see Appendix 6.2). Individual GDG members were selected by the NCC-C Director, GDG Chair and Lead Clinician, based on their application forms. The guideline development process was supported by staff from the NCC-C, who undertook the clinical and health economics literature searches, reviewed and presented the evidence to the GDG, managed the process and contributed to drafting the guideline. At the start of the guideline development process all GDG members' interests were recorded on a standard declaration form that covered consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared new, arising conflicts of interest which were always recorded (see Appendix 6.1).

Guideline Development Group meetings

Eleven GDG meetings were held between 27 April 2009 and 20 July 2010. During each GDG meeting (either held over one or two days) clinical questions and clinical and economic evidence were reviewed, assessed and recommendations formulated. At each meeting patient/carer and service-user concerns were routinely discussed as part of a standing agenda item.

NCC-C project managers divided the GDG workload by allocating specific clinical questions, relevant to their area of clinical practice, to small sub-groups of the GDG in order to simplify and speed up the guideline development process. These groups considered the evidence, as reviewed by the researcher, and synthesised it into draft recommendations before presenting it to the GDG as a whole. Each clinical question was led by a GDG member with expert knowledge of the clinical area (usually one of the healthcare professionals). The GDG subgroups often helped refine the clinical questions and the clinical definitions of treatments. They also assisted the NCC-C team in drafting the section of the guideline relevant to their specific topic.

Patient/carer members

Individuals with direct experience of ovarian cancer gave an important user focus to the GDG and the guideline development process. The GDG included three patient/carer members. They contributed as full GDG members to writing the clinical questions, helping to ensure that the evidence addressed their views and preferences, highlighting sensitive issues and terminology relevant to the guideline and bringing service-user research to the attention of the GDG.

Developing Clinical Evidence-Based Questions

Background

Clinical guidelines should be aimed at improving clinical practice and should avoid ending up as 'evidence-based textbooks' or making recommendations on topics where there is already agreed clinical practice. Therefore the list of key clinical issues listed in the scope were developed in areas that were known to be controversial or uncertain, where there was identifiable practice variation, or where NICE guidelines were likely to have most impact.

Method

From each of the key clinical issues identified in the scope the GDG formulated a clinical question. For clinical questions about interventions, the PICO framework was used. This structured approach divides each question into four components: the population (the population under study – P), the interventions (what is being done - I), the comparisons (other main treatment options – C) and the outcomes (the measures of how effective the interventions have been – O). Where appropriate, the clinical questions were refined once the evidence had been searched and, where necessary, sub-questions were generated.

The final list of clinical questions can be found in Appendix 5.

Review of Clinical Literature

Scoping search

An initial scoping search for published guidelines, systematic reviews, economic evaluations and ongoing research was carried out on the following databases or websites: National Library for Health (NLH) Guidelines Finder (now NHS Evidence), National Guidelines Clearinghouse, Cochrane Database of Systematic Reviews (CDSR), Heath Technology Assessment Database (HTA), NHS Economic Evaluations Database (NHSEED), DH Data, Medline and Embase.

At the beginning of the development phase, initial scoping searches were carried out to identify any relevant guidelines (local, national or international) produced by other groups or institutions.

Developing the review protocol

For each clinical question, the information specialist and researcher (with input from other technical team and GDG members) prepared a review protocol. This protocol explains how the review was to be carried out (see Table A) in order to develop a plan of how to review the evidence, limit the introduction of bias and for the purposes of reproducibility. All review protocols can be in the full evidence review.

Table A Components of the review protocol

Component	Description
Clinical question	The clinical question as agreed by the GDG.
Objectives	Short description; for example 'To estimate the effects and cost effectiveness of…' or 'To estimate the diagnostic accuracy of…'.
Criteria for considering studies for the review	Using the PICO (population, intervention, comparison and outcome) framework. Including the study designs selected.
How the information will be searched	The sources to be searched and any limits that will be applied to the search strategies; for example, publication date, study design, language. (Searches should not necessarily be restricted to RCTs.)
The review strategy	The methods that will be used to review the evidence, outlining exceptions and subgroups. Indicate if meta-analysis will be used.

Searching for the evidence

In order to answer each question the NCC-C information specialist developed a search strategy to identify relevant published evidence for both clinical and cost effectiveness. Key words and terms for the search were agreed in collaboration with the GDG. When required, the health economist searched for supplementary papers to inform detailed health economic work (see section on 'Incorporating Health Economic Evidence').

Search filters, such as those to identify systematic reviews (SRs) and randomised controlled trials (RCTs) were applied to the search strategies when there was a wealth of these types of studies. No language restrictions were applied to the search; however, foreign language papers were not requested or reviewed (unless of particular importance to that question).

The following databases were included in the literature search:
- The Cochrane Library
- Medline and Premedline 1950 onwards
- Excerpta Medica (Embase) 1980 onwards
- Cumulative Index to Nursing and Allied Health Literature (Cinahl) 1982 onwards
- Allied & Complementary Medicine (AMED) 1985 onwards
- British Nursing Index (BNI) 1985 onwards
- Psychinfo 1806 onwards
- Web of Science [specifically Science Citation Index Expanded]
- (SCI-EXPANDED) 1899 onwards and Social Sciences Citation Index (SSCI) 1956 onwards
- Biomed Central 1997 onwards

From this list the information specialist sifted and removed any irrelevant material based on the title or abstract before passing to the researcher. All the remaining articles were then stored in a Reference Manager electronic library.

Searches were updated and re-run 6–8 weeks before the stakeholder consultation, thereby ensuring that the latest relevant published evidence was included in the database. Any evidence published after this date was not included. For the purposes of updating this guideline, 16 July 2010 should be considered the starting point for searching for new evidence.

Further details of the search strategies, including the methodological filters used, are provided in the evidence review (and appear on the CD-ROM accompanying this guideline).

Critical Appraisal

From the literature search results database, one researcher scanned the titles and abstracts of every article for each question and full publications were ordered for any studies considered relevant or if there was insufficient information from the title and abstract to inform a decision. When the papers were obtained the researcher applied inclusion/exclusion criteria to select appropriate studies which were then critically appraised. For each question, data on the type of population, intervention, comparator and outcomes (PICO) were extracted and recorded in evidence tables and an accompanying evidence summary prepared for the GDG (see evidence review). All evidence was considered carefully by the GDG for accuracy and completeness.

GRADE (Grading of Recommendations, Assessment, Development and Evaluation)

For interventional questions, studies which matched the inclusion criteria were evaluated and presented using a modification of GRADE (NICE 2009; http://gradeworking group.org/). Where possible this included meta-analysis and synthesis of data into a GRADE 'evidence profile'. The evidence profile shows, for each outcome, an overall assessment of both the quality of the evidence as a whole (low, moderate or high) as well as an estimate of the size of effect. A narrative summary (evidence statement) was also prepared.

Each topic outcome was examined for the quality elements defined in table B and subsequently graded using the quality levels listed in table C. The reasons for downgrading or upgrading specific outcomes were explained in footnotes.

Table B Descriptions of quality elements of GRADE

Quality element	Description
Limitations	Limitations in the study design and implementation may bias the estimates of the treatment effect. Major limitations in studies decrease the confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator or outcomes between the available evidence and the clinical question.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect relative to the minimal important difference.
Publication bias	Publication bias is a systematic underestimate or overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table C Overall quality of outcome evidence in GRADE

Quality element	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

All procedures were fully compliant with NICE methodology as detailed in the 'NICE guidelines manual' (NICE 2009). In general, no formal contact was made with authors; however, there were ad hoc occasions when this was required in order to clarify specific details.

Needs assessment

As part of the guideline development process the NCC-C invited a specialist registrar, with the support of the GDG, to undertake a needs assessment (see Appendix 6.3). The needs assessment aims to describe the burden of disease and current service provision for patients with ovarian cancer in England and Wales, which informed the development of the guideline.

Assessment of the effectiveness of interventions is not included in the needs assessment, and was undertaken separately by researchers in the NCC-C as part of the guideline development process.

The information included in the needs assessment document was presented to the GDG. Most of the information was presented in the early stages of guideline development, and other information was included to meet the evolving information needs of the GDG during the course of guideline development.

Incorporating Health Economics Evidence

The aim of providing economic input into the development of the guideline was to inform the GDG of potential economic issues relating to the recognition and initial management of ovarian cancer. It is important to investigate whether health services are both clinically effective and cost effective, i.e. are they 'value for money'.

Prioritising topics for economic analysis

In addition to the review of the relevant clinical evidence, the GDG were required to determine whether or not the cost-effectiveness of each of the individual clinical questions should or could be investigated. After the clinical questions were decided, and with the help of the health economist, the GDG agreed which of the clinical questions were an economic priority for analysis. Further details of the economic prioritisation are provided in the evidence review (and appear on the CD-ROM accompanying this guideline). These 'economic priorities' were chosen on the basis of the following criteria, in broad accordance with the NICE guidelines manual (NICE 2009):

Overall relevance of the topic:
- *The number of patients affected*: interventions affecting relatively large numbers of patients were given a higher economic priority than those affecting fewer patients
- *The health benefits to the patient*: interventions that were considered to have a potentially significant impact on both survival and quality of life were given a higher economic priority
- *The per patient cost*: interventions with potentially high financial (cost/savings) implications were given high priority compared to interventions expected to have lower financial implications
- *Likelihood of changing clinical practice*: priority was given to topics that were considered likely to represent a significant change to existing clinical practice.

Uncertainty:
- *High level of existing uncertainty*: higher economic priority was given to clinical questions in which further economic analysis was considered likely to reduce current uncertainty over cost-effectiveness. Low priority was given to clinical questions when the current literature implied a clearly 'attractive' or 'unattractive' incremental cost-effectiveness ratio, which was regarded as generalisable to a UK healthcare setting
- *Likelihood of reducing uncertainty with further analyses (feasibility issues)*: when there was poor evidence for the clinical effectiveness of an intervention, there was considered to be less justification for an economic analysis to be undertaken.

For each topic that was prioritised for economic analysis a comprehensive systematic review of the economic literature was conducted. Where published economic evaluation studies were identified that addressed the economic issues for a clinical question, these are presented alongside the clinical evidence wherever possible. For those clinical areas reviewed, the information specialists used a similar search strategy as used for the review of clinical evidence but with the inclusion of a health economics filter. Each search strategy was designed to find any applied study estimating the cost or cost effectiveness of the topic under consideration. A health economist reviewed abstracts and relevant papers were ordered for appraisal.

Published economic evidence was obtained from a variety of sources:
- Cochrane HTA
- NHS Economic Evaluations Database (NHS EED)
- Medline
- Embase.

Economic analysis

Once the priority topics for economic analysis had been agreed by the GDG, the health economist investigated whether or not a cost-effectiveness analysis of each topic could be

carried out. Cost-effectiveness evaluations require evidence on numerous parameters, including treatment effects, health-related preferences (utilities), healthcare resource use and costs. However, high quality evidence on all relevant parameters within an economic analysis is not always available. If the evidence base used to inform a cost-effectiveness analysis is poor, decisions based upon such an analysis may be subject to a high degree of uncertainty and therefore cost effectiveness analysis would not be appropriate.

For those clinical questions where an economic model was required, cost-utility analysis was undertaken using a decision tree approach. Decision tree is an analytical method of evaluating all options and consequences relevant to a specific decision problem. Assumptions and designs of the decision models were explained to and agreed by the GDG members during meetings, and they commented on subsequent revisions.

The details of the model are presented in the evidence review and Appendix 1. During the analysis the following general principles were adhered to:
- the GDG Chair and Clinical Lead were consulted during the construction and interpretation of the analysis
- the analysis was based on the best evidence from the systematic review
- assumptions were reported fully and transparently
- the results were subject to thorough sensitivity analysis and limitations discussed
- costs were calculated from a health services perspective.

Linking to NICE technology appraisals

When this guideline was commissioned there was one published technology appraisal (TA) which was relevant to the guideline (TA55: Paclitaxel for the treatment of ovarian cancer; http://guidance.nice.org.uk/TA55). Published TAs are periodically reviewed to determine if they need to be updated particularly if any new evidence becomes available since the publication of the appraisal which means the original recommendations needed to be changed. In October 2009, NICE consulted with stakeholders to assess whether TA55 should be updated within the guideline. The outcome was that TA55 should remain on the 'static list' and therefore its recommendations were reproduced unchanged in the most appropriate section of the guideline

Agreeing the Recommendations

For each clinical question the GDG were presented with a summary of the clinical evidence, and where appropriate economic evidence, derived from the studies reviewed and appraised. From this information the GDG were able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying LETR statement.

LETR (Linking Evidence to Recommendations) statements

As clinical guidelines were previously formatted, there was limited scope for expressing how and why a GDG made a particular recommendation from the evidence of clinical and cost effectiveness. To make this process more transparent to the reader, NICE have introduced an explicit, easily understood and consistent way of expressing the reasons for making each recommendation. This is known as the 'LETR statement' and will usually cover the following key points:
- the relative value placed on the outcomes considered
- the strength of evidence about benefits and harms for the intervention being considered
- the costs and cost-effectiveness of an intervention (if formally assessed by the health economics team)
- the quality of the evidence (see GRADE)
- the degree of consensus within the GDG
- other considerations – for example equalities issues

Where evidence was weak or lacking the GDG agreed the final recommendations through informal consensus. Shortly before the consultation period, ten key priorities and five key research recommendations were selected by the GDG for implementation and the patient algorithms were agreed. To avoid giving the impression that higher grade recommendations are of higher priority for implementation, NICE no longer assigns grades to recommendations.

Consultation and Validation of the Guideline

The draft of the guideline was prepared by NCC-C staff in partnership with the GDG Chair and Lead Clinician. This was then discussed and agreed with the GDG and subsequently forwarded to NICE for consultation with stakeholders.

Registered stakeholders (see Appendix 6.2) had one opportunity to comment on the draft guideline which was posted on the NICE website between 24 September 2010 and 19 November 2010 in line with NICE methodology (NICE 2009). The Guideline Review Panel also reviewed the guideline and checked that stakeholder comments had been addressed.

The pre-publication check process

Following stakeholder consultation and subsequent revision, the draft guideline was then subject to a pre-publication check (NICE 2009). The pre-publication check provides registered stakeholders with the opportunity to raise any concerns about factual errors and inaccuracies that may exist in the revised guideline after consultation.

During the pre-publication check the full guideline was posted on the NICE website for 15 working days, together with the guideline consultation table that listed comments received during consultation from stakeholders and responses from the NCC-C and GDG.

All stakeholders were invited to report factual errors using a standard proforma. NICE, the NCC and the GDG Chair and Lead Clinician considered the reported errors and responded only to those related to factual errors. A list of all corrected errors and the revised guideline were submitted to NICE, and the revised guideline was then signed off by Guidance Executive. The list of reported errors from the pre-publication check and the responses from the NCC-C were subsequently published on the NICE website.

The final document was then submitted to NICE for publication on their website. The other versions of the guideline (see below) were also discussed and approved by the GDG and published at the same time.

Other Versions of the Guideline

This full version of the guideline is available to download free of charge from the NICE website (www.nice.org.uk) and the NCC-C website (www.wales.nhs.uk/nccc).

NICE also produces three other versions of the ovarian cancer guideline which are available from the NICE website:
- the NICE guideline, which is a shorter version of this guideline, containing the key priorities, key research recommendations and all other recommendations
- the Quick Reference Guide (QRG), which is a summary of the main recommendations in the NICE guideline. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk
- 'Understanding NICE Guidance' ('UNG'), which describes the guideline using non-technical language. It is written chiefly for people suspected of, or diagnosed with, ovarian cancer but may also be useful for family members, advocates or those who care for patients with cancer of unknown primary. For printed copies, phone NICE publications on 0845 003 7783 or email publications@nice.org.uk

Updating the Guideline

Literature searches were repeated for all of the clinical questions at the end of the GDG development process, allowing any relevant papers published before 16 July 2010 to be considered. Future guideline updates will consider evidence published after this cut-off date.

Three years after publication of the guideline, NICE will commission a National Collaborating Centre to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an early update.

Funding

The National Collaborating Centre for Cancer was commissioned by NICE to develop this guideline. Health economic analysis for this guideline was provided by the London School of Hygiene and Tropical Medicine and funded by the National Collaborating Centre for Cancer.

Disclaimer

The GDG assumes that healthcare professionals will use clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply these guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by the practitioner in light of individual patient circumstances, the wishes of the patient and clinical expertise.

The NCC-C disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

References

Briggs, A., Claxton K, Sculpher M, Decision Modelling for Health Economic Evaluation. 2006, Oxford: Oxford University Press.

National Institute for Health and Clinical Excellence (2009) The guidelines manual. London: National Institute for Health and Clinical Excellence.

Algorithms

Overview of pathway

```
                    ┌──────────────────────────────┐
                    │      Woman presents to GP     │
                    └──────────────────────────────┘
                                   │
                                   ▼
                    ┌──────────────────────────────┐
                    │      GP assesses symptoms     │
                    └──────────────────────────────┘
                                   │
                                   ▼
                    ┌──────────────────────────────┐
                    │      Tests in primary care    │
                    └──────────────────────────────┘
                                   │
                        Suspicion of ovarian cancer
                                   ▼
                    ┌──────────────────────────────┐
                    │ Urgent referral: assessment   │
                    │       in secondary care       │
                    └──────────────────────────────┘
                                   │
                        Suspicion of ovarian cancer
                                   ▼
                    ┌──────────────────────────────┐
                    │ Review by specialist          │
                    │ multidisciplinary team (MDT)  │
                    └──────────────────────────────┘
                                   │
                                   ▼
                    ┌──────────────────────────────┐
                    │ Confirmation of diagnosis:    │
                    │ • surgical staging or         │
                    │ • tissue diagnosis by         │
                    │   histology (preferably)      │
                    │   or cytology if considering  │
                    │   chemotherapy before or      │
                    │   instead of surgery for      │
                    │   advanced ovarian cancer     │
                    └──────────────────────────────┘
```

Ascites and/or pelvic or abdominal mass

Management of suspected early ovarian cancer

Management of advanced ovarian cancer

Support and information

Detection in primary care

Woman presents to GP

Physical examination identifies ascites and/or a pelvic or abdominal mass (not obviously uterine fibroids)

Woman reports having any of the following symptoms persistently or frequently – particularly more than 12 times per month (especially if she is 50 or over)[1]:

- persistent abdominal distension ('bloating')
- feeling full (early satiety) and/or loss of appetite
- pelvic or abdominal pain
- increased urinary urgency and/or frequency

Or:

Woman is 50 or over and has had symptoms within the last 12 months that suggest irritable bowel syndrome[2]

Woman reports any of the following symptoms:

- unexplained weight loss
- fatigue
- changes in bowel habit

Symptoms not suggestive of ovarian cancer

Ovarian cancer suspected?

Yes

No

Measure serum CA125

≥ 35 IU/ml

< 35 IU/ml

Arrange ultrasound of abdomen and pelvis

Assess carefully: are other clinical causes of symptoms apparent?

Normal

Yes

No

Suggestive of ovarian cancer

Investigate

Advise the woman to return if symptoms become more frequent and/or persistent

Refer urgently[1,3]

[1] See also 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; available at www.nice.org.uk/guidance/CG27) for recommendations about the support and information needs of people with suspected cancer.

[2] See 'Irritable bowel syndrome in adults' (NICE clinical guideline 61; available at www.nice.org.uk/guidance/CG61). Irritable bowel syndrome rarely presents for the first time in women of this age

[3] An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

Tests in secondary care

Woman referred to secondary care with suspected ovarian cancer

If not already done in primary care:
- measure CA125
- perform ultrasound of abdomen and pelvis

In women under 40, also measure levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG), to identify women who may not have epithelial ovarian cancer

Calculate RMI I score[1]

RMI ≥ 250

Refer to specialist MDT

- If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, perform a CT scan of the pelvis and abdomen (and thorax if clinically indicated) to establish the extent of disease
- Do not use MRI routinely
- Offer information on ovarian cancer, including psychosocial and psychosexual issues

---

[1] See Box 3.1 for details of how to calculate an RMI I (risk of malignancy index I) score

1 Epidemiology

1.1 Introduction

This chapter provides a summary of the needs assessment that was carried out to inform development of this guideline and includes current information regarding the epidemiology of ovarian cancer.

1.2 Data collection

Office of National Statistics (ONS) and cancer registries

The data on incidence, mortality and survival of ovarian cancer for the United Kingdom is published by the ONS (2007). It is based on the data collated by 11 cancer registries covering England, Wales, Scotland and Northern Ireland (Department of Health, 2008).

Sources for this data include general hospitals, cancer centres, hospices, private hospitals, cancer screening programmes, primary care, nursing homes and death certificates. The minimum dataset of information includes:

- Patient details (name, date of birth, NHS number, address, ethnicity and sex)
- Hospital details (hospital, consultant and patient unit number)
- Diagnostic, tumour and treatment details (site and type of primary tumour, laterality, stage and grade of the tumour, and some treatment information)
- Death details (date of death, cause and place of death and post mortem information).

There is approximately a two year gap between the event time and the publication of the summary statistics. There is a high degree of completeness in terms of diagnosis and deaths. However, the completeness and quality of data collected on a specific individual and their cancer can be variable.

Registries record information about cancers apparent at the time of diagnosis of the primary neoplasm. However, they do not always record information about management and treatment received. Consequently national data on the management of ovarian cancer is sparse

Some international data are available from GLOBOCAN and EUROCARE and are valuable for the purpose of comparison. The GLOBOCAN project provides contemporary estimates of the incidence of, and mortality from the major types of cancer at a national level, for all countries of the world. The GLOBOCAN estimates are presented for 2008 separately by sex and for all ages. These are calculated from the recent data provided by the International Agency of Research for Cancer (IARC)[1]. The EUROCARE project seeks to standardise the cancer survival data across Europe in order to provide meaningful comparisons between countries (Berrino, 2003). An important point to remember when looking at the results is that cancer registration in several European countries only covers a small proportion of the total national population. Summary results for these countries may not therefore represent the situation in the country as a whole and hence might not be a true comparison (Berrino et al., 2009).

---

[1]http://globocan.iarc.fr/

Hospital inpatient care

In England, the Hospital Episode Statistics (HES) record information on all NHS admissions. These include all day case and inpatient admissions to NHS hospitals (including private patients and non-UK residents) and admissions to independent providers commissioned by the NHS. The information recorded includes patient demographic information, diagnosis for each admission and date and length of admission. A similar system, Patient Episode Database Wales (PEDW) operates in Wales.

The data is processed nationally to remove duplicates and any obvious errors in order to provide the most robust data possible. The quality of the data is only as good as the quality of data entry and this may vary between providers. Systematic misclassification will occur but it is not possible to quantify and its effect is unknown. The Welsh Cancer Intelligence and Surveillance Unit (WCISU) has combined their registry and HES/PEDW data to obtain information on the treatment received by ovarian cancer patients in their locality. There is a similar project being carried out in England by the Trent Cancer Registry and the results are expected later this year.

Hospital outpatient care

Outpatient data have also been collected through the HES and PEDW dataset since 2003. These data record the speciality associated with the appointment but does not record the particular investigation carried out or the results of the appointment and so have not been examined as part of this needs assessment.

1.3 Incidence

Ovarian cancer is the fifth commonest cancer in women in the UK after breast, colorectal, lung and uterus. Approximately 6,700 new cases of ovarian cancer were diagnosed every year in United Kingdom between 2004 and 2007 accounting for approximately 1 in 20 cases of cancer in women (Walsh and Cooper, 2005).

Incidence in the UK, constituent countries and cancer networks

Data in Table 1.1 show that in 2007 6,719 new cases of ovarian cancer were diagnosed in the UK which equates to a crude rate of 21.6 per 100,000 population. The European age standardised incidence rate (EASR) is 17.0 per 100,000 population. There are slight variations in the incidence rate across the constituent countries of the UK. Wales has a higher incidence rate compared to the national rates and Northern Ireland the lowest (14.2 per 100,000 population).

Table 1.1 Number of new cases and rates registered for ovarian cancer in 2007.

	England	Wales	Scotland	N.Ireland	United Kingdom
Cases	5,566	381	625	147	6,719
Crude rate per 100,000 population	21.4	25.0	23.5	16.4	21.6
Age-standardised rate (European) per 100,000 population	17.0	18.4	17.8	14.2	17.0
95% CI	*16.6–17.4*	*16.6–20.3*	*16.4–19.2*	*11.9–16.5*	*16.6–17.5*

Data source: Reproduced from Cancer Research UK.

The latest data of incidence rate by cancer network is from 2005 (Figure 1.1). Comparing networks within England, the incidence rate was highest in the North London Cancer Network with a rate of 24.3 per 100,000 population. The lowest incidence rate was noted in the North of Scotland with an incidence rate of 12.0. All cancer networks in Wales had

rates higher than the UK average. These differences in the incidence rates across the UK may have arisen from differences in diagnostic criteria or cancer registration or both.

Figure 1.1 Age-standardised incidence rates of ovarian cancer by Welsh and English Cancer Network, Scotland and Northern Ireland (2005).

Data sources: ISD Scotland, Northern Ireland Cancer Registry, UK Association of Cancer Registries, Welsh Cancer Intelligence and Surveillance.

These data include borderline malignancies. A further confounding issue is that primary peritoneal cancer and metastatic malignant disease of unknown primary origin may also be included.

European and Worldwide comparison

Figure 1.2 shows the incidence rates of ovarian cancer across the world in 2008. The United Kingdom has a relatively high incidence rate of up to 14.6 per 100,000 population. The incidence rates are highest in Central America and Northern Europe and lowest in some parts of Africa and Asia.

Figure 1.2 Worldwide estimated age-standardised incidence rate of ovarian cancer per 100,000 population; all ages (2008).

Data source: GLOBOCAN 2008 (IARC).

In comparison with other European countries, the UK is among those with the highest incidence rates of ovarian cancer (Figure 1.3). Generally the highest rates are in the Northern and Eastern European countries of Lithuania, Latvia, Ireland, Slovakia and Czech Republic. The lowest rates are in Southern European countries of Portugal and Cyprus.

Figure 1.3 Age-standardised incidence rates of ovarian cancer in the European Union (2008).
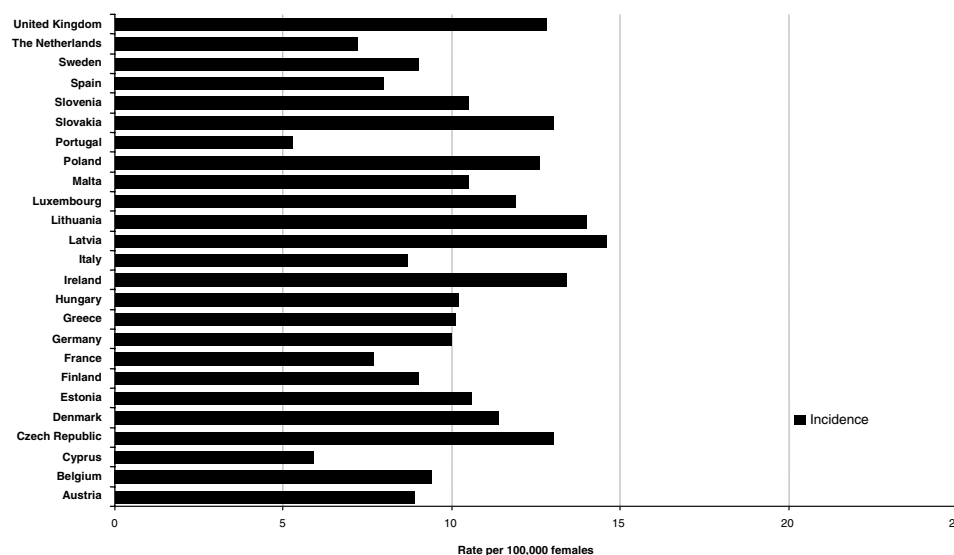

Data source: Globocan 2008 (IARC).

Incidence rates of ovarian cancer by age

The lifetime risk of women being diagnosed with ovarian cancer is 1 in 48 (Walsh and Cooper, 2005). The data in Figure 1.4 show that overall 90% of the ovarian cancer recorded in the UK in 2007 were in women aged 45 years and above. The incidence rates are higher in postmenopausal women, with the highest in the age group of 60–64 years of age.

Figure 1.4 Number of new cases diagnosed and incidence rate of ovarian cancer by age in the United Kingdom (2007).
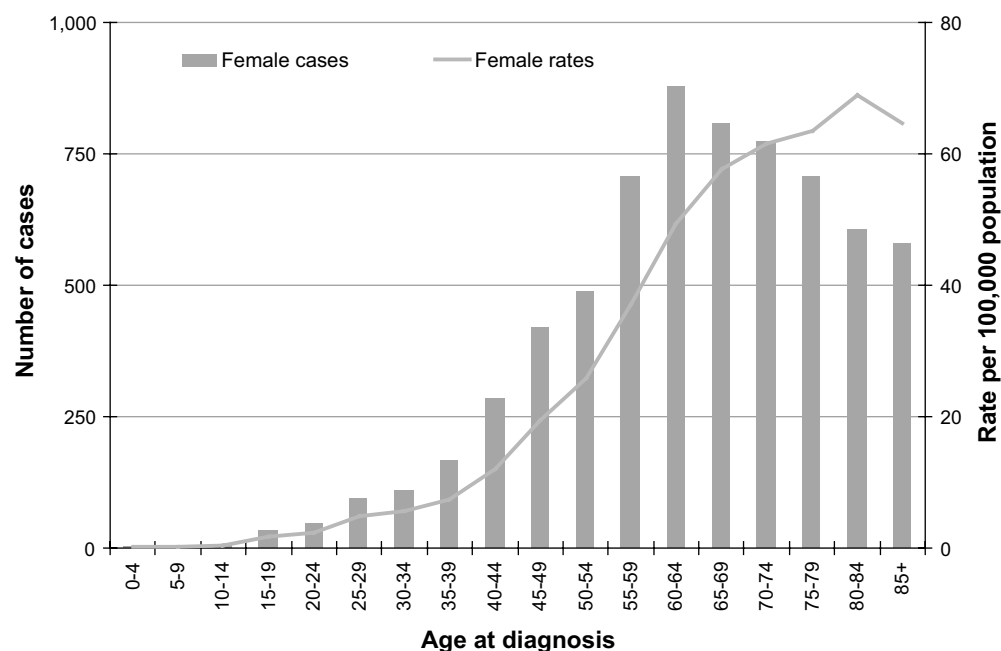

Data source: Office for National Statistics.

Trends in incidence rates of ovarian cancer

The age standardised incidence rates of ovarian cancer have increased in the UK from 14.7 in 1975 to 16.4 in 2007 (Figure 1.5). Incidence rates peaked around 1995–1999 and this may be associated with the inclusion of 'cancer of borderline malignancy' within the category of 'malignant cancer' according to International Classification of Disease for Oncology (ICDO2). The ICDO2 was introduced in England and Wales in 1995, Scotland in 1997 and Northern Ireland in 1996. This could also explain the rising trend of incidence rates after 1996.

**Figure 1.5** Trends in age standardised incidence rates of ovarian cancer (1975–2007).
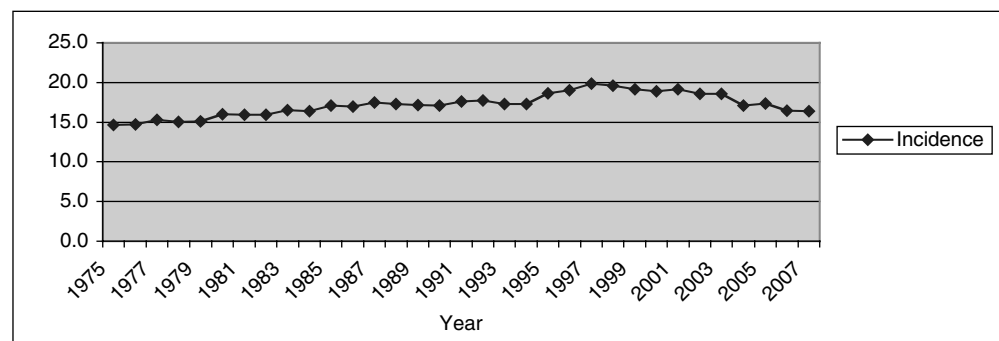
Data Source: Cancer Research UK.

Socioeconomic status and ethnicity

Socioeconomic status has no affect on incidence of ovarian cancer (Figure 1.6).

The National Cancer Intelligence Network (NCIN) recently published a report analysing the relationship between cancer incidence and ethnicity in those diagnosed with cancer in England (2002-2006) (NCIN, 2009). It showed Asian and Black ethnic groups have lower incidence rates of ovarian cancer compared to the White ethnic group. The analysis was presented only on Asian, Black and White ethnic group due to the small number of Chinese and Mixed ethnic groups in the study.

Figure 1.6 Ovarian cancer incidence by deprivation quintile, England (2000-2004).
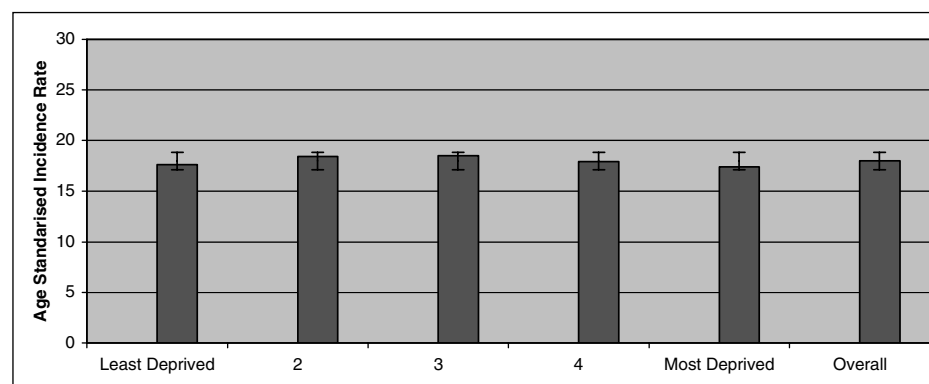
Data source: NCIN 2009.

1.4   Mortality

Approximately 4,300 women die from ovarian cancer each year in the UK which makes it the leading cause of death in gynaecological cancers (Cancer Research UK[2]). It accounts for 6% of all cancer deaths in women. The reason for the high mortality rate in ovarian cancer

---

[2] http://info.cancerresearchuk.org/cancerstats/index.htm

may be because most women are diagnosed with advanced ovarian cancer at the time of detection.

Mortality rates in the United Kingdom

The age-standardised mortality rates are similar across all countries within the UK with an overall average of 9.7 (Table 1.2). The highest mortality rate is seen in Northern Ireland (11.0) compared to the UK average. Wales has the lowest mortality rate in spite of a high incidence rate (see Table 1.1).

Table 1.2 Number of deaths and European age-standardised mortality rates of ovarian cancer per 100,000 population in the UK (2008).

	England	**Wales**	**Scotland**	**N. Ireland**	**United Kingdom**
Deaths	3,609	215	423	126	4,373
Crude rate per 100,000 population	13.8	14.0	15.9	13.9	14.0
Age-standardised rate (European) per 100,000 population	9.6	9.3	10.4	11.0	9.7
95% CI	*9.3-9.9*	*8.1-10.5*	*9.4-11.4*	*9.1-12.9*	*9.4-10.0*

Data sources: Office of National Statistics, reproduced from Cancer Research UK

Mortality rates by cancer network

The mortality rate of ovarian cancer by cancer network in 2005 was highest in the Peninsula and Mid Trent Cancer Network and lowest in the North London, West London and North East London Cancer Networks (Figure 1.7).

Figure 1.7 Age-standardised mortality rates of ovarian cancer by cancer network in the UK (2005).
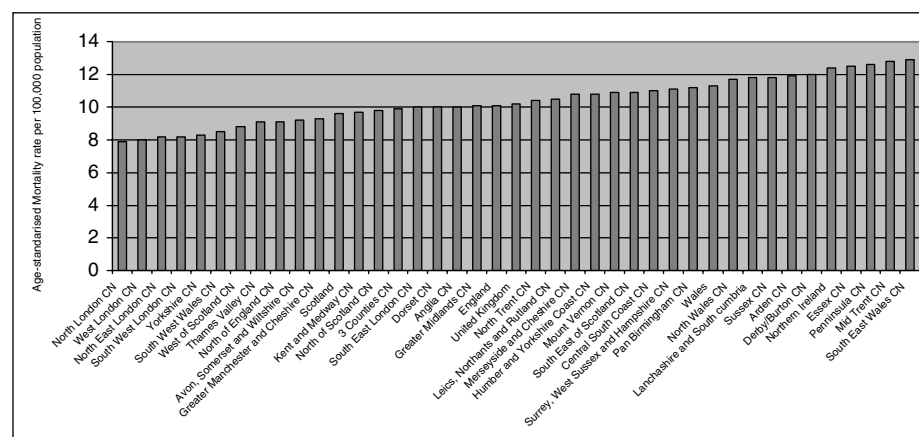
Data sources: ISD Scotland; Northern Ireland Cancer Registry; UK Association of Cancer Registries; Welsh Cancer Intelligence and Surveillance Unit; NCIN 2008

Mortality rates and number of deaths by age

Data in Figure 1.8 show the number of deaths and mortality rate by age in the UK in 2008. The number of deaths is highest in 70-74 years age group, but the highest mortality rates are in the 80-84 years age group.

Figure 1.8 Number of deaths and mortality rate of ovarian cancer in the UK by age (2008).
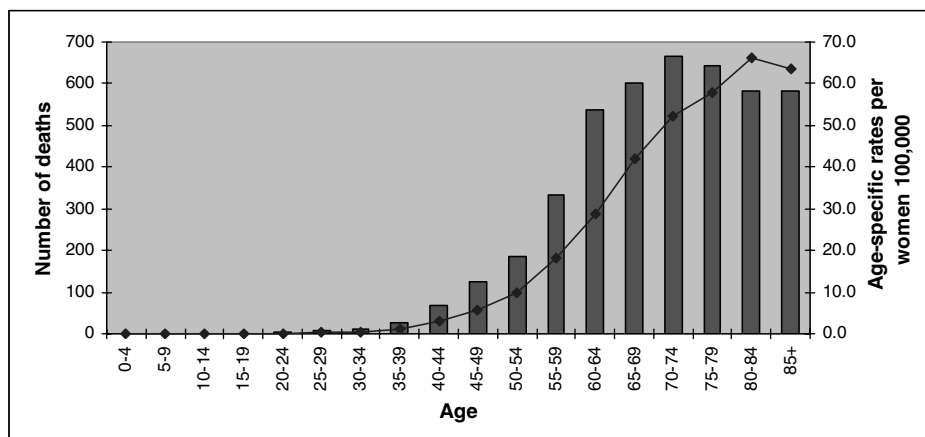
Data source: Reproduced from Cancer Research UK.

Worldwide and European comparisons

The global and European data in this section for ovarian cancer are contemporary estimates from the GLOBOCAN project (Figure 1.9). The advantage of global data is national coverage and long-term availability. However, the data quality varies considerably. These data indicate that the United Kingdom and Ireland have comparatively high mortality rates even when compared to other European countries.

Figure 1.9 Worldwide estimated age-standardised mortality rate of ovarian cancer per 100,000 population, all ages (2008).
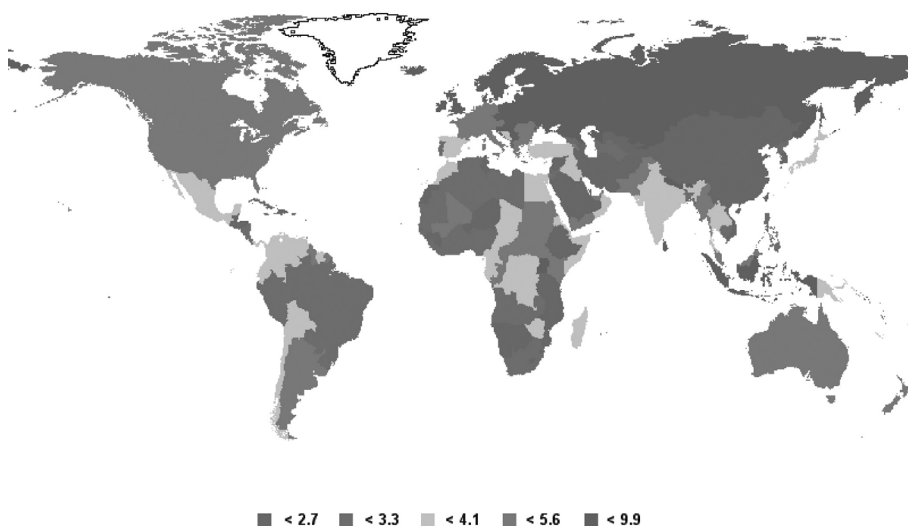
Data source: GLOBOCAN 2008 (IARC).

Across Europe, the highest mortality rates are seen in Northern Europe and Ireland (Figure 1.10). This is similar to the high incidence rates seen in these regions.

Figure 1.10 Estimated age-standardised mortality rate of ovarian cancer, European Union (2008).
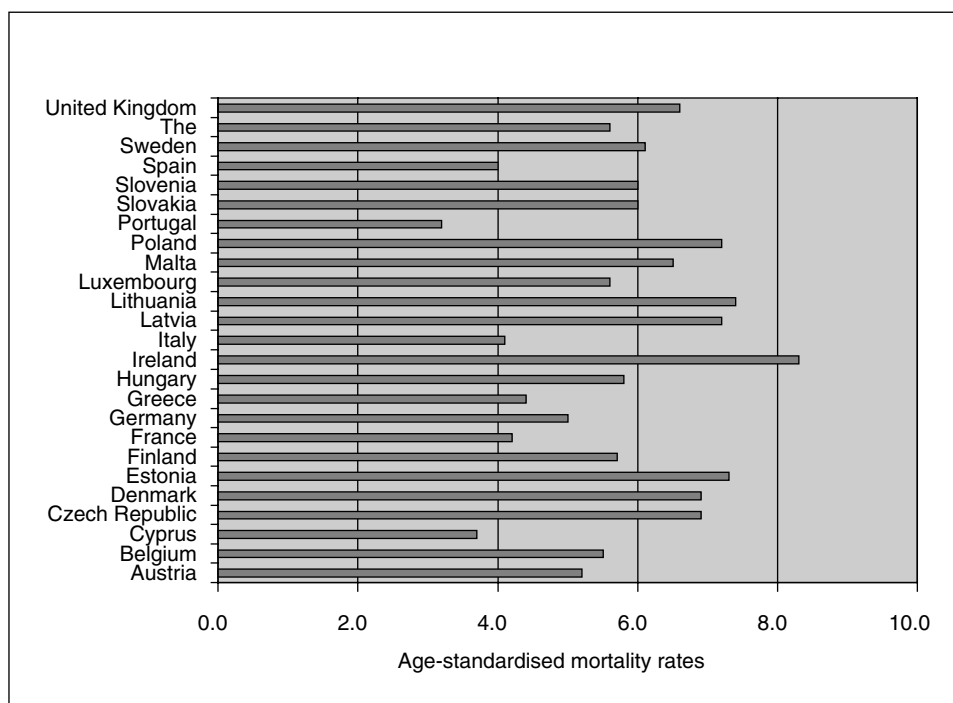
Data source: GLOBOCAN 2008 (IARC).

Trends in mortality rates and numbers of deaths from ovarian cancer

Data in Figure 1.11 show the trends in the age-specific mortality rate of ovarian cancer from 1971 to 2008. The trends vary across the different age groups. The mortality rate shows a gradual increase in women over 65 years of age with some decline in younger women. It is evident from the graph that the mortality rate has been fairly stable over the last 10 years in women under 49 years of age compared to the age group of 50-64 years where there has been a steady decline. Overall mortality rate of ovarian cancer remains relatively stable in spite of the increasing incidence.

Figure 1.11 Trends in age specific mortality rate of ovarian cancer by age in United Kingdom (1971-2008).
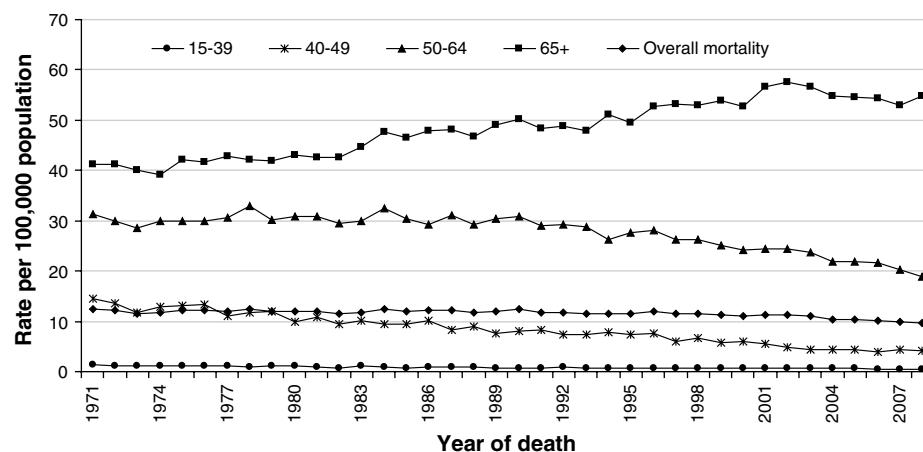
Data source: Reproduced from Cancer Research UK.

1.5 Survival

Most women are diagnosed with advanced stage disease and this contributes to ovarian cancer having the lowest relative five year survival rate of all gynaecological cancers (ONS 2007).

Trends in survival rates from ovarian cancer

The five year survival rates for patients with ovarian cancer have increased dramatically from 20% in 1975 to 38.9% in 2006 (Figure 1.12). A similar trend has been observed in ten year survival rate from 20% between 1971-1975 to 33.3% between 1996-2000 (Figure 1.13). The two fold increase in the survival rate may be due to early detection methods, improved treatment modalities, or inclusion of borderline tumours which have a good prognosis (ONS 2007; Richard 2008; Rachet et al., 2009).

Figure 1.12 Trends in the age-standardised one year, five year and ten year (1971-2000) survival rate of ovarian cancer in England and Wales (1971-2006).
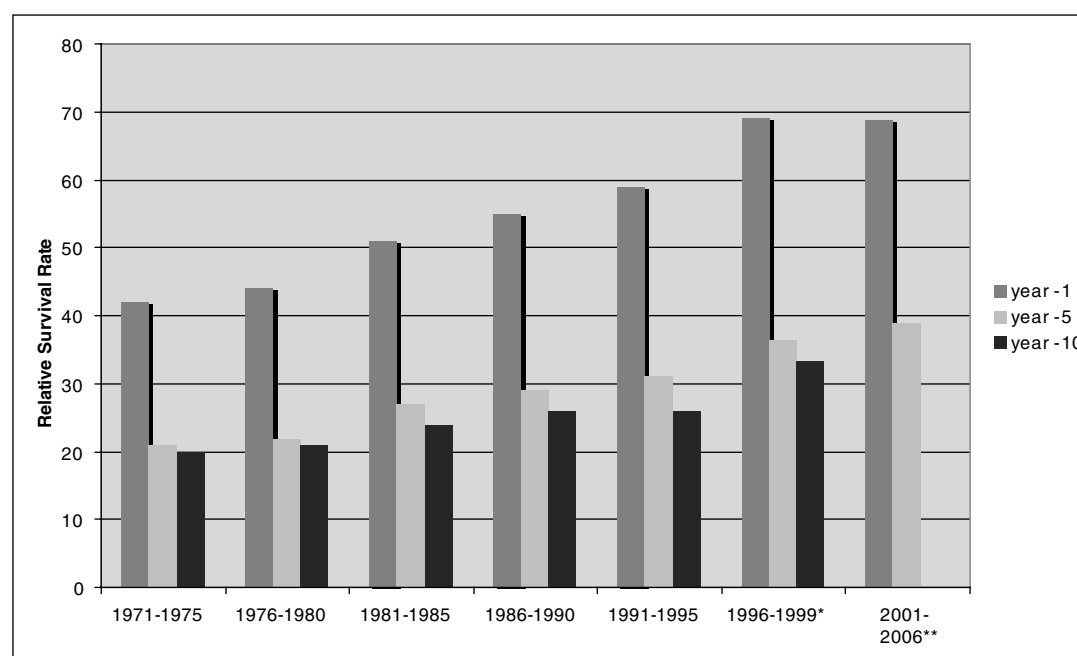
(* England only data, ** shows one year survival between 2001-2003 and five year survival between 2001-2006)
Data source: Office of National Statistics and Cancer Research UK

Survival rate by age at diagnosis

The survival rate based on age at diagnosis is shown in Figure 1.13. Both the one-year and five year survival are higher in young women (15-39) compared to older women (>40). In women aged 15-39 years the one year and five year survival are 93% and 84% respectively compared to 31% and 14% in the 80-89 age group.

Figure 1.13 Age-standardised five year relative survival of ovarian cancer by age in England (2001-2006).
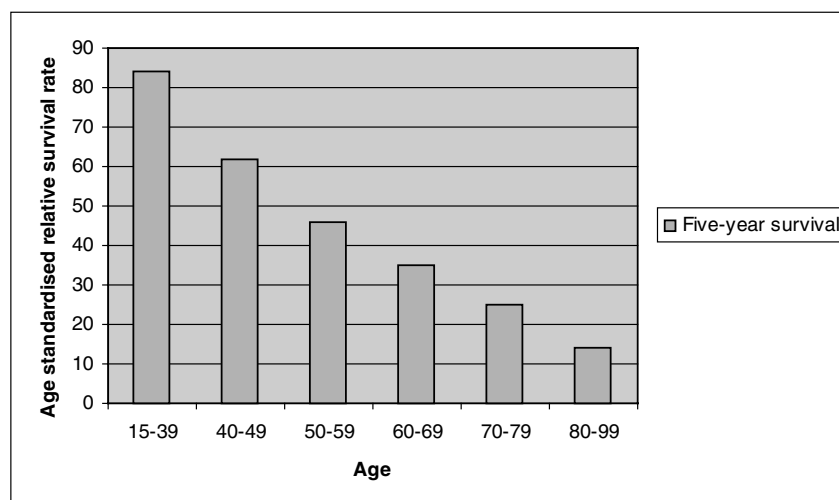
Data source: Office of National Statistics-Statistical Bulletin Cancer survival in England (Berrino 2003; Berrino et al., 2009)

International comparison

In this section international data are presented from EUROCARE and the International Cancer Benchmarking Partnership (ICBP) and are valuable for the purpose of comparison. The EUROCARE project seeks to standardise the cancer survival data across Europe in order to provide meaningful comparisons between countries (Berrino, 2003). The ICBP compares 12 jurisdictions in six countries with comprehensive cancer registration, and broadly similar healthcare systems. The ICBP is also the most up to date international survival comparison providing data from 1995 to 2007, whereas the main EUROCARE studies completed in 1999.

In an international comparison of women diagnosed with ovarian cancer in 1995–1999, the survival rates in England, Wales, Scotland and Northern Ireland were significantly lower than the European average (Figure 1.14). A more up to date study from 1995–2007 reported an increase in survival in England, Wales and Northern Ireland, but a persistent gap in five year survival between the UK nations and Norway, Australia and Canada (Figure 1.15) (ICBP, 2011). It has been estimated that the 5 year ovarian cancer survival gap compared to the best in Europe accounts for 500 avoidable deaths a year (Abdel-Rahman et al., 2009).

Figure 1.14 Relative five year survival rate, cumulative of ovarian cancer for women aged 15-99 years diagnosed 1995-1999 across Europe.
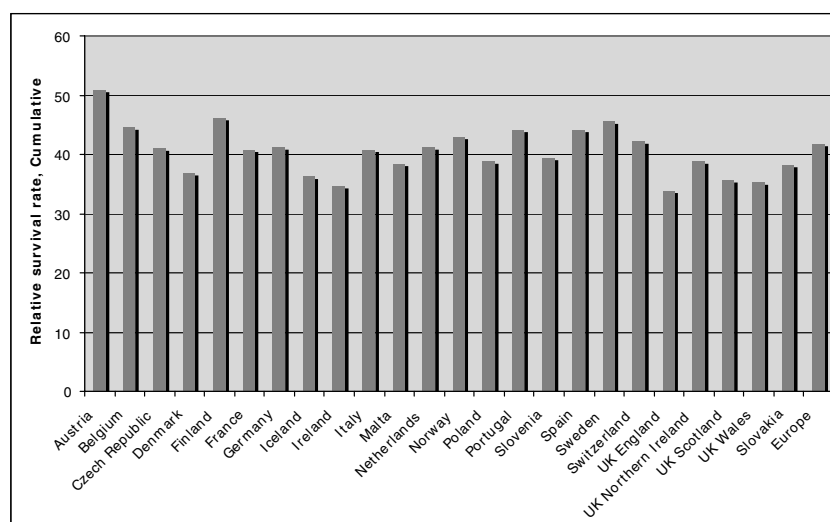
Data source: Eurocare 4 Database

Figure 1.15. Relative five year age standardized survival rate (Australia = New South Wales, Victoria, Canada = Alberta, British Columbia, Ontario, Manitoba, UK = England, Wales, Northern Ireland).
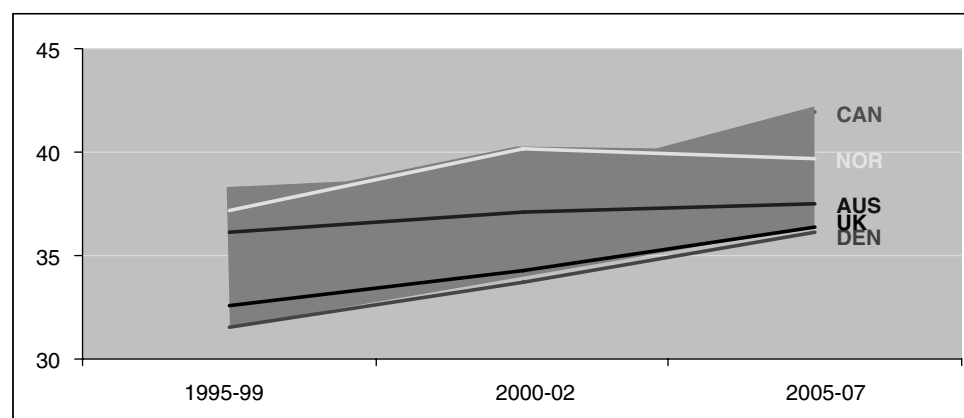
Data source: ICBP, 2011

Survival by stage

Ovarian cancer is staged using the FIGO classification (Box 1.1), based on the information obtained from surgery, supplemented by imaging information where appropriate. Optimum surgical staging comprises midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter-Roach et al., 2009). Cancer registries use TNM classification similar to FIGO staging.

Box 1.1 FIGO staging for ovarian cancer

Stage I: limited to one or both ovaries

Ia   involves one ovary; capsule intact; no tumour on ovarian surface; no malignant cells in ascites or peritoneal washings
1b   involves both ovaries; capsule intact; no tumour on ovarian surface; negative washings
1c   tumour limited to ovaries with any of the following: capsule ruptured, tumour on ovarian surface, positive washings

Stage II: pelvic extension or implants

IIa   extension or implants onto uterus or fallopian tube; negative washings
IIb   extension or implants onto other pelvic structures; negative washings
IIc   pelvic extension of implants with positive peritoneal washings

Stage III: microscopic peritoneal implants outside of the pelvis; or limited to the pelvis with extension to the small bowel or omentum

IIIa   microscopic peritoneal metastases beyond pelvis
IIIb   macroscopic peritoneal metastases beyond pelvis less than 2 cm in size
IIIc   peritoneal metastases beyond pelvis >2 cm or lymph node metastases

Stage IV: distant metastases to the liver or outside the peritoneal cavity

---

Currently there is only data available in Wales on the stage at presentation for women with ovarian cancer. Data from WCISU showed that only 10-20% of staging data are recorded on their Cancer registry database for patients with ovarian cancer (Figure 1.16). This makes statistical analysis based on staging difficult. Data from England is expected and has yet to be published.

Figure 1.16 Ovarian cancer by stage, Wales (2000-2007).
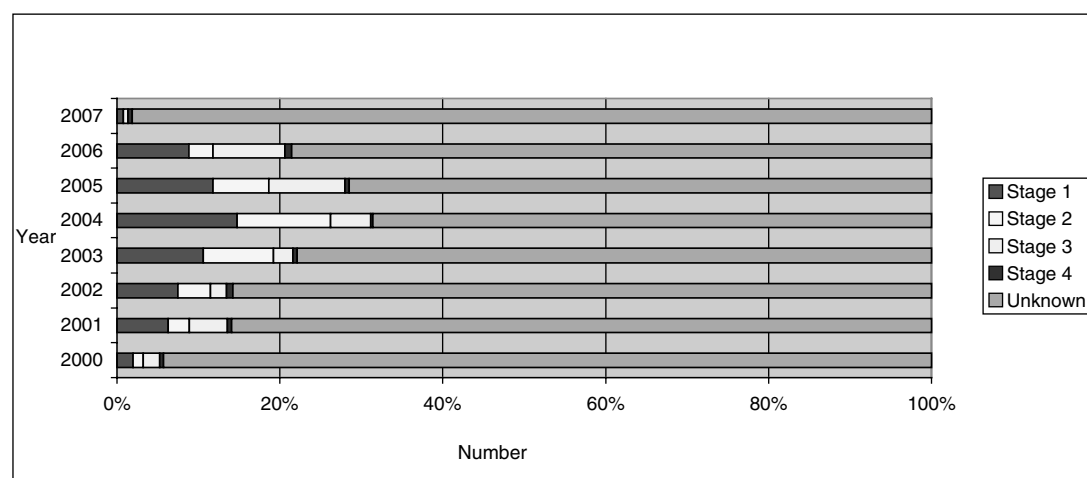
Data source: WCISU

Socioeconomic status and ethnicity

Among adults living in the most deprived areas who were diagnosed cancer between 1981 and 1990, 5-year survival was significantly lower than for those in the most affluent areas for 44 of 47 different cancers (Coleman et al., 1999). More recent data would suggest that whilst there still remains a gap in survival at one year in women living in deprived areas, this has largely disappeared in terms of five year survival. The gap at one year may well relate to presentation with advanced disease combined with poor access to appropriate treatment. Improvement in the latter (Cooper et al., 2008) may be reflective of improved access to specialist treatment.

1.6   Routes to diagnosis

For all patients diagnosed with cancer in England in 2007, the National Cancer Intelligence Network (NCIN) has published data on the different routes taken by patients to their cancer diagnosis (NCIN, 2010). Data in Table 1.3 highlights a wide variation in routes to diagnosis for ovarian cancer patients and shows that the majority of patients attend electively, however a significant proportion attend as emergencies. A large proportion of elective admissions present outside the urgent (two week) referral pathway.

Table 1.3 Routes to diagnosis for ovarian cancer, England (2007).

Cancer type	Two Week Wait	GP referral	Other outpatient	Inpatient elective	Emergency presentation	Death Certificate Only	Unknown	Total	Number of patients
Ovary	26%	22%	15%	1%	29%	1%	6%	100%	5012

Courtesy: Route to Diagnosis, NCIN data briefing, November 2010.

1.7   Treatment

Ovarian cancer is managed using a number of treatments which usually comprise chemotherapy or surgery often in combination. As there was no available comparative national data on treatment modalities, a questionnaire was developed by the GDG and sent to all cancer networks. Only two cancer networks were able to provide data on treatments used. In one region it appeared that up to 40% of patients are managed with chemotherapy alone (this had an association with age). In the other region there was marked variation between hospitals and within hospitals over time in the proportion of patients receiving chemotherapy. The reason for this variation is not understood.

Surgery

Currently there is only data available in Wales on the surgical management of women with ovarian cancer. Data from England is expected and yet to be published.

WCISU recently combined PEDW data on the surgical management of women with ovarian cancer using data from the financial years 2004 to 2009. There were a total of 1919 women diagnosed with ovarian cancer during that time.

Figure 1.17 illustrates the different procedures carried out in the three cancer networks in Wales. The most frequent procedure undertaken involves total abdominal hysterectomy, bilateral salphingo-oopherectomy and omentectomy as this involves the staging laparotomy.

Figure 1.17 Number of different surgical procedures performed for ovarian cancer by cancer network, Wales (2004-2008).
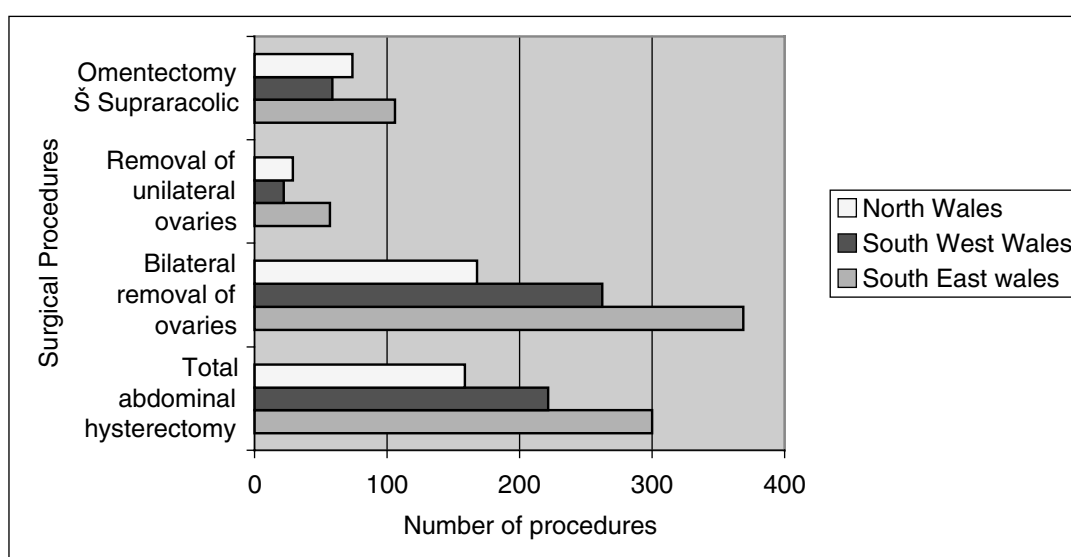
Data source: WCISU

1.8 The findings of cancer peer review of gynaecology cancer teams in England 2004-2007

The Calman-Hine report on a 'Policy Framework for Commissioning Cancer Services' published in 1995 and the series of NICE 'Improving Outcome Guidance' formed the basis of establishing national standards for cancer care in England. This led to the establishment of a National Cancer Peer Review (NCPR) process which is a national quality assurance programme for NHS cancer services in England. It aims to improve the care of the patients with cancer and their families. This is done through self-assessment by cancer service teams and external review by professional peers against nationally agreed quality peer review measures.

The first programme of review focussed on services in four tumour site areas; breast, lung, colorectal, gynaecology and was coordinated on a regional rather than national basis. The programme was independently evaluated, the results of which informed the development of the 2004-08 National Cancer Peer Review Programme.

Currently the NCPR programme consists of the three key stages illustrated in the Figure 1.18.

Figure 1.18 Stages of the National Cancer Peer Review Programme on gynaecology cancer teams (2004-2008).

All cancer networks in England and all their designated local and specialist Gynaecology cancer teams were reviewed against the national standards by a team of clinical peers between 2004 and 2008. The reports of these reviews are available publicly via the 'CQuiNS' website[3].. The review was for all gynaecological cancers and not for ovarian cancer alone. During the targeted visit, the peer group reviewed whether each measure is achieved or not and whether overall progress is being made toward the achievement of the standards. Following the outcome of the review, the cancer networks should agree actions in order to meet those standards not currently being met achieved within defined timescales.

The results of the most recent peer review process in England (2009-2010) were published by the National Cancer Action Team (NCAT) in October 2010 and included a separate report for gynaecology MDTs. They reported that MDTs have improved their overall compliance against the measures since the 2004/2008 peer review round by 11%. A summary of all the findings can be found in the full report (NCAT, 2010).

1.9   Summary

Ovarian cancer is the second most common gynaecological cancer in the UK accounting for over 6,700 new cases diagnosed each year. The rates have been steadily increasing over the past 20-25 years, with a notable increase in the 65 years and above age group. There is some geographic variation in the incidence rate across the UK. This may be due to variation in diagnostic criteria, cancer registration or population.

Ovarian cancer is the leading cause of death in women with gynaecological cancer and accounts for 6% of all deaths in women. The mortality rate remains almost the same in all regions of the UK. There has been a two fold increase in the survival rate over the last two decades which might reflect better diagnostic and treatment methods.

The process of producing this report has highlighted the lack of data available to assess the burden of the disease based on the stage and the type of ovarian cancer. It is clear that there are difficulties in the collection and definitions in the minimum dataset for ovarian cancer. This deficiency makes the interpretation of effectiveness of treatments highly uncertain and is an important obstacle to improving cancer care for women with ovarian cancer.

---

[3] www.cquins.nhs.uk

References

Abdel-Rahman M., Stockton D., Rachet B., Hakulinen T., and Coleman MP (2009) What if cancer survival in Britain were the same as in Europe: how many deaths are avoidable? British Journal of Cancer 101 (Suppl 2): S115–24.

Berrino F (2003) The EUROCARE study: strengths, limitation and perspectives of population bases, comparative survival studies. Annals of Oncology 14: 9–13

Berrino F., Verdecchia A., Lutz J.M., et al.,: the EUROCARE working group (2009) Comparative cancer survival information in Europe. European Journal of Cancer 45: 901–908.

Coleman MP., Babb P., Damiecki P., et al., (1999) Cancer Survival Trends in England and Wales 1971–1995: Deprivation and NHS Region. London: The Stationery Office; Series SMPS No. 61.

Coleman MP., Forman D., Bryant H., Butler J., Rachet B., Maringe C., Nur U., Tracey E., Coory M., Hatcher J., McGahan CE., Turner D., Marrett L., Gjerstorff ML., Johannesen TB., Adolfsson J., Lambe M., Lawrence G., Meechan D., Morris EJ., Middleton R., Steward J., Richards MA,. ICBP Module 1 Working Group (2010) Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995–2007. The International Cancer Benchmarking Partnership: an analysis of population-based cancer registry data. Lancet. 377(9760):127–38

Cooper N., Quinn MJ., Rachet B., et al., (2008) Survival from cancer of the ovary in England and Wales up to 2001. British Journal of Cancer 99: S70–S72

Department of Health (2008) The national cancer registration system 2008.

Elliss-Brookes L. (2010) Routes to Diagnosis results: presentation at UKACR and NCIN joint conference. Available at http://www.library.ncin.org.uk/docs/RtD_NCIN_18thJune10_LEB.pdf

NCAT (2010) National cancer peer review programme. Report 2009/2010. An overview of the findings from the 2009/2010 National Cancer Peer review of Cancer Services in England. Available at: http://ncat.nhs.uk/sites/default/files/_resources_reports_NCAT_NCPR_National_Report_2009_10.pdf

NCIN (2009) Cancer incidence and survival by major ethnic group, England, 2002-2006: incidence rate ratios and estimated ASRs.

NCIN (2008) Cancer incidence and mortality by cancer network, UK, 2005. http://library.ncin.org.uk/docs/081007-NCIN-UK_Incidence_Mortality_05-Report.pdf

NCIN (2010) Routes to diagnosis – NCIN data briefing. Available at http://www.ncin.org.uk/publications/data_briefings/routes_to_diagnosis.aspx

Office for National Statistics (ONS) (2007) Survival Rates in England, patients diagnosed 2001–2006 followed up to 2007. Available at http://www.statistics.gov.uk/statbase/product.asp?vlnk=14007

ONS (2007) Cancer statistics registrations: registrations of cancer diagnosed in 2007. England. Series MB1 no.38.

Rachet B., Maringe C., Nur U. et al., 2009. Population-based cancer survival trends in England and Wales up to 2007:an assessment of the NHS cancer plan for England. The Lancet Oncology. 10(4): 351–369.

Richard MA. (2008) Trends and inequalities in survival for 20 cancers in England and Wales 1986–2001: population-based analyses and clinical commentaries . British Journal Cancer. 99 (Supp 1): S1.

Walsh P. and Cooper N. (2005) Ovary, Cancer Atlas of the United Kingdom and Ireland 1991–2000. p: 193–201

Winter-Roach BA., Kitchener HC and Dickinson HO (2009). Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane DB Sys Rev 2009, Issue 3. Art. No: CD004706. DOI: 10.1002/14651858.CD004706.pub3.

2 Detection in primary care

The challenge presented by ovarian cancer is to make the correct diagnosis as early as possible despite the non-specific nature of symptoms and signs. It is therefore important to establish those symptoms and signs which initiate the first best test that will ensure the woman is directed to the most appropriate clinical pathway.

The two objectives of this chapter were:

1. to identify which symptoms and signs are associated with ovarian cancer to potentially allow earlier recognition of ovarian cancer in primary care
2. to assess the relationship between the duration of symptoms and ovarian cancer outcome.

2.1 Awareness of symptoms and signs

Early recognition of ovarian cancer symptoms

Ovarian cancer has been termed 'the silent killer' but it is increasingly recognised that the majority of women with ovarian cancer have symptoms. These symptoms are non-specific and widely experienced among the general population. However, they have greater significance in older women (over 50 years of age) and in those with a significant family history (two or more cases of ovarian or breast cancer diagnosed at an early age in first degree relatives).

Two important pieces of work have been published on the signs and symptoms of ovarian cancer which should be considered alongside the recommendations in this guideline. In 2005 NICE published a set of recommendations for GPs for the urgent referral of woman suspected of having gynaecological cancer, including ovarian cancer (NICE, 2005). This guideline updates and will replace recommendation 1.7.4 in 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; published June 2005). NICE are currently reviewing whether the entire guideline should be updated and a decision is expected in November 2010.

A more recent programme has been the Department of Health-led National Awareness and Early Diagnosis Initiative (NAEDI) project in England which coordinates and provides support to activities and research that promote the earlier diagnosis of cancer. Part of this initiative has led to the development of 'Key messages for ovarian cancer for health professionals'[1] which aim to raise awareness of signs and symptoms of the disease and were published in February 2009.

Most women are diagnosed with advanced (stage II-IV) disease that is associated with poor survival rates. On the other hand a great majority of women with early stage (stage I) ovarian cancer can be cured.

---

[1] Available at: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110534

Women with ovarian cancer are often suspected of having gastrointestinal disease such as irritable bowel syndrome and therefore not investigated, with resulting delays to diagnosis. However it is now known that women with ovarian cancer experience some symptoms more frequently, more severely and more persistently than women who do not have the disease.

Clinical question: What are the symptoms and signs of ovarian cancer?

Clinical evidence

Evidence about symptoms and signs of ovarian cancer came from case control studies. For practical reasons these studies were retrospective and prone to recall bias. For example if women with ovarian cancer can recall their symptom history better than controls, the predictive value of symptoms would be inflated.

A systematic review by Bankhead *et al.*, (2005) estimated that 93% [95%CI: 92% to 94%] of women experienced symptoms before diagnosis. Evidence from case control studies shows that abdominal pain, abdominal distension, urinary symptoms, abdominal mass and postmenopausal/abnormal bleeding are more likely to be reported by women before a diagnosis of ovarian cancer than in women without ovarian cancer (Table 2.1).

Table 2.1 Individual symptoms for ovarian cancer

Symptom	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*	References
Abdominal pain	17% to 64%	70% to 95%	0.07% to 0.33%	99.97% to 99.99%	Friedman *et al.*, 2005; Goff *et al.*, 2004; Hamilton *et al.*, 2009; Kim *et al.*, 2009; Lurie *et al.*, 2009; Olson *et al.*, 2001; Rossing *et al.*, 2010; Vine *et al.*, 2001
Abdominal bloating	5% to 68%	62% to 98%	0.01% to 0.30%	99.95% to 99.98%	Bankhead *et al.*, 2008; Goff *et al.*, 2004; Friedman *et al.*, 2005; Hamilton *et al.,* 2009
Abdominal distension	22% to 86%	53% to 99%	0.07% to 2.26%	99.97% to 99.99%	Bankhead *et al.*, 2008; Goff *et al.*, 2004; Friedman *et al.*, 2005; Hamilton *et al.*, 2009; Lurie *et al.*, 2009
Abdominal mass/swelling	16% to 33%	99% to 100%	0.48% to 11%	99.97% to 99.98%	Hamilton *et al.*, 2009; Lurie *et al.*, 2009
Urinary frequency or urgency	11% to 43%	78% to 97%	0.05% to 0.17%	99.97% to 99.98%	Friedman *et al.*, 2005; Hamilton *et al.*, 2009; Lurie *et al.,* 2009; Olson *et al.,* 2001; Rossing *et al.*, 2010; Vine *et al.*, 2001
Abnormal or postmenopausal bleeding	13% to 20%	96% to 99%	0.13% to 0.42%	99.97%	Bankhead *et al.*, 2008; Friedman *et al.*, 2005; Hamilton *et al.*, 2009; Lurie *et al.*, 2009; Vine 2001
Loss of appetite	14% to 39%	70% to 98%	0.05% to 0.49%	99.97%	Bankhead *et al.*, 2008; Lurie *et al.*, 2009; Olson *et al.*, 2001; Friedman *et al.*, 2005; Hamilton *et al.*, 2009

*Assuming a prior probability of undiagnosed ovarian cancer of 0.04% (Hamilton et al., 2009)

Box 2.1 Definitions of terms used in this section

Sensitivity is the proportion of women with ovarian cancer who experienced the symptom in the year prior to diagnosis.

Specificity is the proportion of women without ovarian cancer who did not experience the symptom within the last year.

The ***prior probability*** or pre-test probability is the background risk that a woman has undiagnosed ovarian cancer, regardless of her symptoms. Hamilton *et al*., (2009) estimated the prior probability of undiagnosed ovarian cancer in women presenting to primary care (for symptoms experienced within the previous year) at 0.036%, using UK national incidence data for ovarian cancer. However, as Hamilton *et al*., (2009) point out, not all women will present to primary care in a given year. In Hamilton's study, 10.8% of the control group had not consulted in primary care over the one year period of the study. For women consulting in primary care the prior probability of ovarian cancer was estimated at 0.04%.

The ***positive predictive value*** (PPV) of a given symptom for ovarian cancer is the proportion of women with that symptom who have ovarian cancer. For example if a symptom had a PPV of 0.2% for ovarian cancer, 1 in 500 women with that symptom would have ovarian cancer. The PPV of a symptom for ovarian cancer in those presenting to primary care depends both on the sensitivity/specificity of the symptom and the background risk of ovarian cancer in this population.

The ***negative predictive value*** (NPV) of a given symptom for ovarian cancer is the proportion of women without that symptom who do not have ovarian cancer.

The positive predictive value of bloating as a symptom of ovarian cancer showed great variability, probably due to various definitions of bloating used in the studies (from intermittent temporary bloating to permanent or continued abdominal distension).

While the sensitivity of individual symptoms for ovarian cancer is low (see Table 2.1) it can be improved by combining the symptoms (Table 2.2). Hamilton *et al.,* (2009) and Rossing *et al.,* (2010) noted that 85% of women with ovarian cancer reported at least one symptom during the year before diagnosis.

The Goff symptom index (Goff *et al*., 2007) uses a more restrictive definition of symptoms which incorporates symptom frequency and onset. This improves specificity at the expense of sensitivity.

Table 2.2 Combining symptoms to improve sensitivity

Symptom	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*	References
Any symptom[†]	85%	74% to 85%	0.13% to 0.21%	More than 99.99%	Hamilton *et al.,* (2009); Rossing *et al.,* (2010)
Goff symptom index[‡]	64% to 69%	88% to 97%	0.20% to 0.94%	99.99%	Rossing *et al.,* (2010); Goff *et al.,* (2007); Andersen *et al.,* (2010); Kim *et al.,* (2009)

* Assuming a prior probability of undiagnosed ovarian cancer of 0.04% (Hamilton *et al.*, 2009).
[†] Any of the following symptoms for at least a week during the previous year: urinary frequency/urgency, abdominal distension, abdominal bloating, pelvic/abdominal pain or loss of appetite. Hamilton *et al.,* (2009) also included postmenopausal or rectal bleeding. Rossing *et al.*, (2010) also included nausea and diarrhoea/constipation.
[‡] Any of the following symptoms at least 12 times a month (but present for less than one year): pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating, and difficulty eating/feeling full (Goff *et al.*, 2007).

[2] An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

[3] See also 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; available at www.nice.org.uk/guidance/CG27) for recommendations about the support and information needs of people with suspected cancer.

[4] National Institute for Health and Clinical Excellence (2008) Irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. NICE clinical guideline 61. London: National Institute for Health and Clinical Excellence.

Recommendations

- Refer the woman urgently[2] if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids)[3].
- Carry out tests in primary care (see section 2.2 on page 21) if a woman (especially if 50 or over) reports having any of the following symptoms on a persistent or frequent basis – particularly more than 12 times per month[3]:
  - – persistent abdominal distension (women often refer to this as 'bloating')
  - – feeling full (early satiety) and/or loss of appetite
  - – pelvic or abdominal pain
  - – increased urinary urgency and/or frequency.
- Consider carrying out tests in primary care (see section 2.2 on page 21) if a woman reports unexplained weight loss, fatigue or changes in bowel habit.
- Advise any woman who is not suspected of having ovarian cancer to return to her GP if her symptoms become more frequent and/or persistent.
- Carry out appropriate tests for ovarian cancer (see section 2.2 on page 21) in any woman of 50 or over who has experienced symptoms within the last 12 months that suggest irritable bowel syndrome (IBS)[4], because IBS rarely presents for the first time in women of this age.

Linking evidence to recommendations

The GDG placed a high value on obtaining a definitive diagnosis of ovarian cancer. It considered increasing patient and primary care awareness of the symptoms of ovariancancer to be important. The GDG was aware of the need to achieve a balance between the increased numbers of women undergoing investigation to achieve this and the impact on patient morbidity and finite healthcare resources.

The GDG considered that there was reasonable quality, retrospective evidence that certain symptoms and signs, when experienced frequently and persistently, are suggestive of a woman having ovarian cancer. It was agreed that identifying those symptoms and signs which should prompt healthcare professionals to consider ovarian cancer, could lead to earlier diagnosis. The GDG believed that the potential benefits of earlier diagnosis could outweigh the potentially increased demand for investigation of women, and associated anxiety.

The GDG noted that none of the existing scoring systems for symptoms were sufficiently accurate on their own to initiate an immediate urgent referral. Therefore the GDG took elements of these scoring systems to identify which symptoms warrant further investigation in primary care.

The GDG recognised that women who are 50 or over represent a higher risk group for ovarian cancer on the basis of age alone, but they did not want to use age as a cut point as this could disadvantage the 20% of women who have ovarian cancer but are younger than 50. Therefore the GDG highlighted the 50 or over age group in the recommendation without excluding those who were younger.

Despite the fact that abnormal vaginal bleeding was linked with the existence of ovarian cancer (Hamilton *et al*. 2009, Goff *et al*. 2007) the GDG felt that the urgent clinical pathway already established for abnormal vaginal bleeding (NICE, 2005) was likely to detect ovarian cancer as part of that investigation. Therefore they did not include this symptom in the recommendations.

In the absence of comparative analysis data of cost and outcomes. health economic evaluation was not feasible.

Duration of symptoms and the effect on stage at presentation

It has been suggested that earlier diagnosis in a number of cancers could improve survival outcome (Thomson and Forman, 2009). However, the natural history of ovarian cancer is unknown.

Ovarian cancer is the fifth most common cancer in women. A GP with an average size practice may only see one case of ovarian cancer every five years which makes recognition of the symptoms and early diagnosis more difficult. This may mean that women visit their GPs with symptoms of ovarian cancer on several occasions before these are recognised as significant.

It is not known if earlier recognition and referral will translate into earlier stage at diagnosis. However, there is general agreement that early symptom identification, with a high index of suspicion for ovarian cancer, has the potential to improve prognosis.

The GDG explored the evidence to assess the relationship between the duration of symptoms prior to diagnosis and the survival rates in ovarian cancer.

Clinical question: What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?

Clinical evidence

Duration of symptoms and stage at diagnosis

Low quality evidence, from retrospective observational studies, suggests women presenting with advanced ovarian cancer experience a similar duration of symptoms to those presenting with early stage disease.

Six studies compared the duration of symptoms according to disease stage at diagnosis (Fruchter et al. 1981; Menczer et al., 2009; Goff et al., 2000; Olsen et al., 2007; Robinson et al. 1984; Webb et al., 2004). None of these studies found a statistically significant difference between the duration of symptoms of women presenting with early and advanced disease.

Olson et al. (2001) found the duration of symptoms before diagnosis was shorter in women with advanced stage (III to IV) than for early stage (I to II) ovarian cancer for all their symptom categories, except constipation. This difference was not statistically significant, however, except for diarrhoea.

Goff et al. (2000) reported that women with early stage disease at diagnosis were less likely to report ignoring their symptoms than women with advanced stage disease at diagnosis (74% versus 85%, P=0.002), although there was no significant difference in the time from symptom onset to diagnosis in early versus advanced stage in their study (P=0.56).

Neal et al. (2007) analysed the stage at diagnosis of patients with ovarian cancer according to their referral pathway. There was no significant difference between the stage at diagnosis of urgent guideline referrals and patients diagnosed through other routes (P=0.52).

Duration of symptoms, quality of life and survival

Notwithstanding the particular importance of this clinical question to patients and healthcare professionals, there was insufficient evidence to say whether the duration of symptoms before diagnosis affects overall survival, quality of life or disease specific survival.

> **Research recommendation**
>
> - Further research should be undertaken on the relationship between the duration and frequency of symptoms in women with ovarian cancer before diagnosis, the stage of disease at diagnosis and subsequent survival.

Linking evidence to recommendations

The GDG acknowledged the lack of available evidence on the outcomes of interest. However, the GDG placed a high value on the potential benefits to be derived from an improved understanding of the relationship between the duration of symptoms and subsequent outcomes.

Examination of all the evidence found no association, one way or the other, between the duration of symptoms on the outcomes studied. However, the GDG felt strongly that this lack of evidence should not preclude timely and appropriate referral.

As this clinical question addressed an epidemiological issue it was felt unlikely to lend itself to health economic evaluation.

2.2 Asking the right question – first tests

The majority of women with symptoms suggestive of ovarian cancer will not have ovarian cancer, so symptoms alone are not sufficient to refer to secondary care. Given the increased emphasis on symptom recognition this has to be combined with effective assessment to enable timely and appropriate referral onto the ovarian cancer pathway. There is con`siderable variation in practice across the UK as to what tests are currently performed in primary care. In addition many women are referred to other specialists in error.

The GDG sought to identify the next steps in primary care, given the resources available to GPs.

Further test options included pelvic examination, serum CA125 or pelvic ultrasound either individually or in combination.

Clinical examination is an integral part of the assessment of any woman with symptoms. Whilst this is the case it is also recognised that pelvic examination has limitations in its ability in detecting adnexal pathology.

A raised serum CA125 in younger women is less likely to be related to a diagnosis of ovarian cancer and when elevated in this group, can raise considerable worry for patient and GP alike. A serum CA125 of, for example, >1000 IU/ml in an older postmenopausal woman is a highly significant finding that points to some sort of malignancy, the most likely being ovarian or primary peritoneal cancer, although other cancers such as lung or pancreatic cancer cannot be excluded on this one test alone. In addition serum CA125 levels of several hundred may occur as a consequence of non-malignant conditions such as heart failure.

Abdomino-pelvic ultrasound is useful for characterising pelvic disease, however, its unselected use in primary care may place an unsustainable burden on diagnostic resources and is operator dependent. Because of this, good practice would dictate that ultrasound scans are performed by a practitioner that is trained and accredited in transabdominal and transvaginal ultrasound of the pelvis.

Clinical question: For women with suspected ovarian cancer, what are the most effective first tests in primary care?

Clinical evidence

There was no direct evidence comparing serum CA125, morphological ultrasound and pelvic examination in women with symptoms in primary care. Indirect evidence comes from systematic reviews of these tests in secondary care or in screening studies. Due to the differences in case mix between these settings it is likely that the tests will perform differently in each place.

Assuming a prevalence of ovarian cancer in women with symptoms presenting to primary care of 0.23%, the positive predictive values of the individual tests were 0.81% for serum CA125 (Myers *et al.*, 2006) and 1.14% for morphological ultrasound (Liu *et al.*, 2007). This means that around 1 in every 100 women referred to secondary care with positive serum CA125 or ultrasound would have ovarian cancer. Negative predictive values were 99.94% for serum CA125 (Myers *et al.*, 2006) and 99.96% for morphological ultrasound (Liu *et al.*, 2007), suggesting around 1 in every 2,000 women with negative tests would turn out to have ovarian cancer.

The evidence suggested pelvic examination is relatively insensitive for the detection of adnexal masses. Myers *et al.* (2006) estimated that only 45% of adnexal masses would be detected on pelvic examination. In women with palpable masses (assuming an ovarian cancer prevalence of 0.23%), pelvic examination had a positive predictive value of 2.03% for ovarian cancer and a negative predictive value of 99.93% (Myers *et al.*, 2006).

If there is disagreement between the individual tests, there is value in combining them. Tests can be combined to improve the overall sensitivity at the cost of specificity (by referring women who are positive on any of the tests). Tests can also be combined to improve specificity at the cost of sensitivity (by only referring women who are positive on all the tests).

There was no direct evidence about the performance of combined serum CA125, ultrasound and pelvic examination in primary care. The accuracy of combined tests was therefore estimated using the values from the meta-analyses of individual tests and assuming conditional independence between tests. Combining tests to improve sensitivity meant a reduced positive predictive value of 0.5% to 0.8% but an improved negative predictive value of 99.96 to 99.99% (depending on which combination was used).

Using figures from Hamilton *et al.* (2009) and Bankhead *et al.* (2005), approximately 0.23% of women with symptoms consistent with ovarian cancer in primary care actually have ovarian cancer. If all women with symptoms were referred to secondary care, around 1 in every 500 women referred would turn out to have ovarian cancer.

If women were only referred if they had a positive serum CA125 test *or* ultrasound scan (Table 2.3 below), then 1 in every 157 referred would have ovarian cancer (assuming conditional independence between serum CA125 and ultrasound). 3% of women with ovarian cancer and symptoms would not be referred.

If women were only referred when both CA125 test *and* ultrasound were positive, then 1 in every 26 referred would have ovarian cancer. 34% of women with ovarian cancer and symptoms would not be referred at initial presentation.

Table 2.3 Distribution of cases according to test results in a theoretical cohort of 100,000 women with symptoms consistent with ovarian cancer presenting to primary care. Assumed prevalence of undiagnosed ovarian cancer is 0.23% in women with such symptoms.

Referral strategy	Test result	Ovarian cancer		Proportion with ovarian cancer
		Yes	No	
Refer if CA125 is positive	CA125 positive	179	21,949	0.81%
Don't refer if CA125 is negative	CA125 negative	51	77,821	0.07%
Refer if ultrasound is positive	ultrasound positive	196	16,961	1.14%
Don't refer if ultrasound is negative	ultrasound negative	34	82,809	0.04%
Refer if CA125 or ultrasound is positive	CA125 or ultrasound positive*	223	34,920	0.63%
Don't refer if CA125 and ultrasound are negative	CA125 and ultrasound negative*	7	64,850	0.01%
Refer if CA125 and ultrasound are positive	CA125 and ultrasound positive*	152	3,991	3.67%
Don't refer if CA125 or ultrasound is negative	CA125 or ultrasound negative*	78	95,779	0.08%

* assuming conditional independence

Health economic evaluation (see Appendix 1)

This clinical question was highlighted as a priority for economic analysis because of the large number of patients with symptoms suggestive of ovarian cancer. In addition there are significant differences in costs and health outcomes associated with the diagnostic pathway as well as the considerable economic burden of treating ovarian cancer.

Economic evaluations of a diagnostic investigation require evidence on a number of issues, including disease prevalence and test accuracy. Furthermore, the accurate estimation of cost-effectiveness of one diagnostic strategy over another requires consideration of downstream treatment effects, health-related preferences (utilities), healthcare resource use and costs. High quality evidence on all relevant parameters is essential, but not always available. When published evidence is sparse, expert opinion can be used to estimate relevant parameters. To test the robustness of the results of the cost-effectiveness analysis, a sensitivity analysis is undertaken.

A decision tree was constructed outlining seven strategies of interest: three of the strategies consisted of a single test (pelvic examination, ultrasound and serum CA125) and the remaining four strategies were comprised of a combination of tests (pelvic examination + serum CA125; pelvic examination + ultrasound; serum CA125 + ultrasound and pelvic examination + serum CA125 + ultrasound). A Markov process was embedded in the decision tree to model the recurrence of disease and survival based on the results of the diagnostic tests and the subsequent management of women presenting with symptom(s) of ovarian cancer in a primary care setting.

The clinical evidence required to populate the model was obtained from a number of different sources. Prevalence of the disease in primary care was assumed to comprise of linear summation of the prevalence of ovarian and colorectal malignancies and benign gynaecological problems. The estimates of the prevalence of ovarian and colorectal malignancies were obtained from published literature (CancerResearchUK, 2007; Hamilton et al., 2009).

The accuracy of the diagnostic procedures, in terms of the corresponding sensitivity and specificity values, were obtained from the systematic reviews of the clinical evidence conducted for this guideline (see clinical evidence in sections 2.2 and 2.3) (Hunink and Glasziou 2001; Bell et al., 1998). There was no consistent reporting of the proportion of patients in each treatment arm, as defined by the model structure, in the published literature. Therefore, the estimates of proportion were elicited from the GDG.

Effectiveness of treatment in terms of survival and morbidity rates were obtained from published literature (Kosary 1994; Chien et al., 2005; Gerestein et al., 2009; Loft et al., 1991; Venesmaa and Ylikorkala 1992; International Collaborative Ovarian Neoplasm Group 2002). In addition, healthcare resource use associated with providing supportive care and follow-up monitoring were also obtained via GDG consensus.

Utility weights were required to estimate quality adjusted life years (QALYs). Estimates of health state utilities specific to ovarian cancer patients were obtained from published studies (Swart et al., 2007; Tappenden et al., 2007; Drummond et al., 2005).

The costs considered in the analysis were those relevant to the UK NHS, and included costs of diagnostic investigations (both in primary and secondary care); costs of therapy (surgery, drug acquisition costs and administration costs) and costs associated with healthcare resource use for provision of supportive care and follow-up monitoring. Unit costs were based on NHS Reference Costs 2008-09 or the Unit Costs of Health and Social Care (PSSRU, 2009).

Within health economic evaluation, discounting of costs and health outcomes is standard practice – where costs and benefits that accrue in the future are given less weight to those which occur in the present. Following methodological guidance published by NICE, all costs and health outcomes are discounted at 3.5% per year (PSSRU, 2009).

A summary of expected cost and expected effectiveness estimates associated with each diagnostic strategy in the model is presented in Table 2.4. The cost of the strategies varies widely, ranging from the least expensive strategy (serum CA125) at just over £1,500 to the most expensive (combination of pelvic examination plus serum CA125 plus ultrasound) at £3,160 per patient. Health outcomes, measured in terms of QALYs, ranged from 20.391 for the serum CA125 strategy to 19.524 for the pelvic examination plus serum CA125 plus ultrasound combination strategy. Serum CA125 (single test) strategy on average generates 20.391 QALYs and ultrasound (single test) generates 20.387 – a difference of 0.004 QALYs is an equivalent (on average) of an additional 1.5 days of perfect health.

Table 2.4 Base case total expected cost and QALYs

Strategy	Cost (£)	Effectiveness (QALY)	ICER[†]
Serum CA125	1,532.32	20.391	
Ultrasound	1,604.24	20.387	(Dominated)
Pelvic examination + serum CA125	1,809.06	20.316	(Dominated)
Pelvic examination + ultrasound	1,864.16	20.298	(Dominated)
Pelvic examination	2,112.49	20.177	(Dominated)
Serum CA125 + ultrasound	2,850.49	19.681	(Dominated)
Pelvic examination + ultrasound + serum CA125	3,160.73	19.524	(Dominated)

[†]ICER – incremental cost-effectiveness ratio

All strategies in this analysis are dominated by the serum CA125 strategy. A strategy is said to be dominated if it is both more costly and less effective than its comparator.

A series of one-way sensitivity analyses were conducted to assess the robustness of the study results. One-way sensitivity analysis describes the process of changing one parameter in the model and re-running the model to see how a change in this parameter influences overall results.

Five scenarios were considered and are detailed below:

- nationally-agreed drug discounts
- a decrease in prevalence of ovarian malignancy in primary care
- the prevalence of benign gynaecological problem varied over an agreed range (20% - 30%)
- a decrease in the proportion of patients who are not fit for further treatment following diagnostic investigation
- an increase in age at the start of the model.

The results of the base case analysis were not sensitive to any of the five scenarios outlined above. The effect of applying nationally agreed price discounts did alter the overall expected costs but did not alter the ranking of the most cost-effective strategy. Specifying the parameters as distributions and performing a probabilistic sensitivity analysis showed that the CA125 strategy did little to alter this conclusion. Similarly, the results of the one-way sensitivity analysis in the other scenarios showed changes in the overall expected costs and health benefits but did not alter the ranking of the cost-effective diagnostic strategy.

Recommendations

- Measure serum CA125 in primary care in women with symptoms that suggest ovarian cancer (see section 2.1 on page 16).
- If serum CA125 is 35 IU/ml or greater, arrange an ultrasound scan of the abdomen and pelvis.
- If the ultrasound suggests ovarian cancer, refer the woman urgently[5] for further investigation[6].
- For any woman who has normal serum CA125 (less than 35 IU/ml), or CA125 of 35 IU/ml or greater but a normal ultrasound:
  - assess her carefully for other clinical causes of her symptoms and investigate if appropriate
  - if no other clinical cause is apparent, advise her to return to her GP if her symptoms become more frequent and/or persistent.

Linking evidence to recommendations

The recommendations were based on evidence of test performance and a health economic evaluation of the most cost-effective first test.

The GDG recognised the need for an initial test using an objective and standardised assessment in symptomatic women because this would reduce observer variability. Serum tumour markers fulfil these criteria. High value was placed on serum CA125 as it is currently the most widely used and reliable serum tumour marker for ovarian cancer. The GDG acknowledged that the clinical evidence was of limited applicability because it did not come from symptomatic women in primary care. This evidence was based on data in a secondary care setting. The main difference between the two populations is that the prevalence of ovarian cancer is lower in primary care than in secondary care. However, the sensitivity analysis conducted as part of the health economic analysis showed that changing the prevalence of ovarian cancer in the economic model did not affect the results. The GDG therefore felt it was appropriate to apply this data in primary care.

---

[5] An urgent referral means that the woman is referred to a gynaecological cancer service within the national target in England and Wales for referral for suspected cancer, which is currently 2 weeks.

[6] See also 'Referral guidelines for suspected cancer' (NICE clinical guideline 27; available at www.nice.org.uk/guidance/CG27) for recommendations about the support and information needs of people with suspected cancer.

> The clinical evidence demonstrated that no single test on its own adequately selected a manageable number of women for referral to secondary care. The combination of raised serum CA125 and sequential ultrasound of the abdomen and pelvis reduced significantly the number of women who would be referred, though a greater proportion of symptomatic women would be directed to the right pathway in a more timely fashion. Although the trade off in adopting a sequential strategy as recommended means that some women with ovarian cancer would be missed in the first instance, the view of the GDG was that this was a sensible and pragmatic decision as those women whose symptoms persist would subsequently re-attend and be referred.
>
> Having identified a sequential testing strategy on clinical evidence, the health economic modelling unequivocally identified that serum CA125 was the most cost-effective first test as opposed to ultrasound or ultrasound and serum CA125 in combination.
>
> It was recognised that there would be an impact on health service resources and women tested due to the low prevalence of ovarian cancer in the symptomatic patient group. Equally, it was felt that in order to ensure symptomatic women were placed along the correct pathway as soon as possible it could only be achieved using such a sequential testing strategy.

References

Andersen MR (2010). Use of a Symptom Index, CA125, and HE4 to predict ovarian cancer. Gynecol.Oncol. 116: 378-383.

Bankhead CR, Kehoe ST and Austoker J (2005). Symptoms associated with diagnosis of ovarian cancer: a systematic review. BJOG. 112: 857-865.

Bankhead CR, Collins C, Stokes-Lampard H, Rose P, Wilson S, Clements A, Mant D, Kehoe ST and Austoker J (2008). Identifying symptoms of ovarian cancer: a qualitative and quantitative study. BJOG. 115: 1008-1014.

Bell R., Petticrew M., Luengo S., Sheldon TA. (1998) Screening for ovarian cancer: a systematic review. Health Technology Assessment, 1998. 2(2): 2

CancerResearchUK (2007) Cancer Stats: Incidence [cited; Available from: www. cancerresearchuk.org

Chien P., Khan K. and Mol BW. (2005) How to interpret the findings of the eVALuate study. BJOG: An International Journal Of Obstetrics And Gynaecology. 112(4): 391-393.

Drummond M F. Sculpher MJ., Torrance GW., O'Brien BJ. and Stoddart GL. (2005). Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, England.

Friedman GD, Skilling JS, Udaltsova NV and Smith LH (2005). Early symptoms of ovarian cancer: a case-control study without recall bias. Fam.Pract. 22: 548-553.

Fruchter RG and Boyce J. (1981) Delays in diagnosis and stage of disease in gynecologic cancer. Cancer Detection & Prevention 4(1-4): 481-6

Gerestein CG., Damhuis RA., Burger CW. and Kooi GS. (2009) Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. Gynecologic Oncology. 114(3): 523-527.

Goff BA, Mandel L, Muntz HG and Melancon CH. (2000) Ovarian carcinoma diagnosis. Cancer 89(10): 2068-75

Goff BA, Mandel LS, Melancon CH and Muntz HG (2004). Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. JAMA. 291: 2705-2712.

Goff BA, Mandel LS, Drescher CW, Urban N, Gough S, Schurman KM, Patras J, Mahony BS and Andersen MR (2007). Development of an ovarian cancer symptom index: possibilities for earlier detection.[see comment]. Cancer. 109: 221-227.

Hamilton W, Peters TJ, Bankhead C and Sharp D (2009). Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. BMJ. 339: b2998-

Hunink M. and Glasziou P. (2001) Decision making in health and medicine. Cambridge University Press: Cambridge, UK.

International Collaborative Ovarian Neoplasm Group (2002) Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 360(9332): 505.

Kim MK, Kim K, Kim SM, Kim JW, Park NH, Song YS and Kang SB (2009). A hospital-based case-control study of identifying ovarian cancer using symptom index. J Gynecol Oncol. 20: 238-242.

Kosary CL. (1994) FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Seminars In Surgical Oncology. 10(1): 31-46.

Liu JZ, Xu YF and Wang JC.(2007) Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma. Eur Journal Radiol 62(3): 328-34.

Loft A., Andersen TF., Brønnum-Hansen H,, Roepstorff C. and Madsen M. (1991) Early post operative mortality following hysterectomy. A Danish population based study 1977-1981. British Journal of Obstetrics and Gynaecology. 98(2): 147-54.

Lurie G, Thompson PJ, McDuffie KE, Carney ME and Goodman MT (2009). Prediagnostic symptoms of ovarian carcinoma: a case-control study. Gynecol.Oncol. 114: 231-236.

Menczer J, Chetrit A, Sadetzki S and the National Israel Ovarian Cancer Group. (2009) The effect of symptom duration in epithelial ovarian cancer on prognostic factors. Arch Gynecol & Obstet 279(6): 797-801

Myers ER, Bastian LA, Havrilesky LJ, Kulasingam SL and Terplan MS, Cline KE, et al. (2006) Management of adnexal mass. Evidence Report/Technology Assessment (130): 1-145

National Institute for Health and Clinical Excellence (2005) Referral guidelines for suspected cancer. NICE clinical guideline 27. London: National institute for Health and Clinical Excellence.

Neal RD, Allgar VL, Ali N, Leese B, Heywood P, Proctor G, et al. (2007) Stage, survival and delays in lung, colorectal, prostate and ovarian cancer: comparison between diagnostic routes. Br J Gen Practice 57(536): 212-9

Olsen CM, Cnossen J, Green AC and Webb PM. (2007) Comparison of symptoms and presentation of women with benign, low malignant potential and invasive ovarian tumors. Eur J Gynaecol Oncol 28(5): 376-80

Olson SH, Mignone L, Nakraseive C, Caputo TA, Barakat RR and Harlap S. (2001) Symptoms of ovarian cancer. Obstet & Gynecol 98(2): 212-7

PSSRU (2009) Unit Costs of Health and Social Care 2009. www.pssru.ac.uk/uc/uc2009contents.htm

Robinson E, Mohilever J, Zidan J and Sapir D. (1984) Delay in diagnosis of cancer. Possible effects on the stage of disease and survival. Cancer 54 (0008-543X (Print), 0008-543X (Linking), 7): 1454-60

Rossing MA, Wicklund KG, Cushing-Haugen KL and Weiss NS (2010). Predictive value of symptoms for early detection of ovarian cancer. J.Natl.Cancer Inst. 102: 222-229.

Swart AC. et al., on behalf of ICON collaborators. (2007) Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON1). Journal of Clinical Oncology (Meeting Abstracts). 25(18_suppl): 5509

Tappenden P., Chilcott J., Eggington S., Patnick J., Sakai H., and Karnon J. (2007) Option appraisal of population-based colorectal cancer screening programmes in England. Gut 56(5): 677-684.

Thomson CS and Forman D (2009) Cancer survival in England and the influence of early diagnosis: what can we learn from recent EUROCARE results? British Journal of Cancer, 101: S102–S109.

Venesmaa, P. and Ylikorkala O. (1992) Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstetrics And Gynecology. 79(2):168-172.

Vine MF., Ness RB., Calingaert B., Schildkraut JM and Berchuck A (2001) Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. Gynecol Oncol 83: 466-471.

Webb PM. (2004) Symptoms and diagnosis of borderline, early and advanced epithelial ovarian cancer. Gynecol Oncol 92(1): 232-9.

3 Establishing the diagnosis in secondary care

The objectives of this chapter were:

1. to estimate the sensitivity, specificity and positive/negative predictive values of serum tumour markers (other than serum CA125) in women with suspected ovarian cancer
2. to determine which malignancy index is the more accurate in assessing the probability of malignant pathology in women with suspected ovarian cancer
3. to determine which imaging tests should be done in women with suspected ovarian cancer
4. to determine when it is appropriate for women with suspected advanced ovarian cancer not to have a tissue diagnosis before starting chemotherapy
5. to determine whether samples from image-guided biopsy or laparoscopic biopsy are the best method of tissue diagnosis before chemotherapy.

3.1   Tumour markers: which to use?

Tumour markers are a group of proteins, hormones, enzymes, receptors, and other cellular products that are over-expressed by malignant cells. The evidence supporting the use of serum CA125 as a useful predictive tumour marker in suspected ovarian cancer is strong (see clinical evidence in section 2.2). It is raised in 90% of such women but can also be significantly elevated in other benign and malignant conditions.

This review of clinical evidence sought to look at individual tumour markers in addition to serum CA125, especially ones which had been developed more recently, to see if any of these might facilitate the diagnosis in women with suspected ovarian cancer, if routinely carried out. These included CEA, CDX2, CA 72-4, CA 19-9, AFP, beta-hCG and HE4.

> **Clinical question: For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?**

Clinical evidence

The evidence review considered the diagnostic accuracy of the following serum tumour markers CEA, CDX2, CA 72-4, CA 19-9, AFP, beta-hCG and HE4 in comparison to serum CA125 in women with suspected ovarian cancer. The evidence came from 39 studies of women who had surgery for pelvic tumours with histopathology to confirm their diagnosis. This means that the evidence is not directly applicable to women with symptoms of ovarian cancer in primary care.

The overall methodological quality of these studies was moderate to low – most were case series and not designed as prospective diagnostic studies. The reference standard diagnosis (histopathology) was consistently applied but the timing of the serum tumour marker tests and the use of blinding in the interpretation of tests were rarely reported.

HE4

There was consistent evidence, from five studies comparing HE4 and serum CA125 in women with pelvic masses, that HE4 is more sensitive and specific than serum CA125 for the diagnosis of ovarian cancer (Abdel-Azeez *et al.,* 2010; Huhtinen *et al.,* 2009; Moore *et al.,* 2008; Nolen *et al.,* 2010; Shah *et al.,* 2009). These five studies included a total of 434 women with ovarian cancer and 583 with benign disease.

Summary ROC curves suggested peak sensitivity/specificity of 77% for serum CA125 compared with 83% for HE4. From these figures, for every 1,000 women referred for diagnosis of a pelvic tumour, using HE4 instead of serum CA125 would identify an additional seven patients with cancer with 81 fewer false positives (assuming a 10% prevalence of undiagnosed ovarian cancer in this population (Myers *et al.*, 2006)).

Five studies looked at the combination of HE4 and serum CA125 (Abdel-Azeez *et al.,* 2010; Huhtinen *et al.,* 2009; Moore *et al.,* 2008; Moore *et al.,* 2009; Nolen *et al.,* 2010). The evidence suggests that the combination of HE4 and serum CA125 is more specific, but less sensitive than either marker in isolation.

CA 72.4

Ten studies, including 933 women with ovarian cancer and 1,300 with benign disease, compared CA 72.4 to serum CA125. The pooled results suggested CA 72.4 and serum CA125 have similar peak sensitivity/specificity, 78% and 77% respectively. It is clear from the ROC curves, however, that (at least at the diagnostic thresholds used in the studies) CA 72.4 has a lower sensitivity and higher specificity than serum CA125. Evidence from a further six studies suggests that combining the two markers could increase their specificity, but at the cost of sensitivity.

CA 19.9

Eight studies including 576 women with malignant tumours and 1,432 with benign disease, compared the diagnostic accuracy of CA 19-9 and serum CA125 in women with pelvic masses.The summary ROC curve suggests CA 19.9 has relatively low sensitivity for the diagnosis of ovarian cancer, at the diagnostic thresholds used in the studies.

CEA, CDX2, AFP and beta-hCG

Eight studies including 1,172 women, reported the diagnostic accuracy of CEA for the diagnosis of ovarian cancer in women with suspected ovarian cancer. Serum CEA was raised in approximately 26% of women with ovarian cancer (sensitivity 26%), but specificity varied widely between studies.

The literature searches found no studies about the use of the marker CDX2. There was a single study each about the use of serum beta-hCG and serum AFP in the diagnosis of ovarian cancer, suggesting low sensitivity for these markers. AFP and hCG are important markers for triage.

Multiple tumour marker panels

Three of the studies (Nolen *et al.,* 2010; Moore *et al.*, 2008; Abel-Azeez *et al.,* 2010) investigated panels combining three or more serum tumour markers. There was no evidence to suggest that multiple tumour markers were much better than the two marker combination of serum CA125 and HE4.

Recommendations

- Measure serum CA125 in secondary care in all women with suspected ovarian cancer, if this has not already been done in primary care.
- In women under 40 with suspected ovarian cancer, measure levels of alpha fetoprotein (AFP) and beta human chorionic gonadotrophin (beta-hCG) as well as serum CA125, to identify women who may not have epithelial ovarian cancer.

Linking evidence to recommendations

The GDG placed a high value on the outcomes of sensitivity and specificity of the different tumour marker tests for facilitating a diagnosis of ovarian cancer. At this time there is ample evidence supporting the clinical utility of serum CA125 in diagnosing ovarian cancer. The GDG acknowledged that the methodological quality of the evidence was low, with most studies being case series and not designed as prospective diagnostic or prognostic studies.

The GDG noted that although the preliminary data on HE4 showed it to have a relatively high sensitivity and specificity, it was not in routine clinical use and studies about its diagnostic performance had only recently been published. The GDG therefore did not feel the data on HE4 was substantial enough to enable it to be recommended instead of serum CA125 – the only serum tumour marker with widely accepted clinical utility in women with ovarian cancer. They therefore recommended the routine use of serum CA125.

This clinical question was agreed as a medium priority for health economic evaluation because although there are potential cost differences between the different combinations of serum tumour markers used, other clinical questions were considered higher priority for investigation.

3.2 Malignancy indices

In women with an adnexal mass it is important to distinguish between benign and malignant pathology before surgical treatment. 'Improving outcomes in gynaecological cancers guidance' (Department of Health, 1999) recommends that women with ovarian cancer be discussed at a multidisciplinary team meeting and be offered, where appropriate, a laparotomy, a full staging procedure and optimal debulking in a cancer centre by a trained gynaecological oncologist. In contrast, women with low or moderate risk of ovarian cancer can be managed by gynaecological cancer leads in a cancer unit. At present, several parameters are available to help distinguish between benign and malignant masses. These include menopausal status or age, ultrasound characteristics with or without Doppler flow assessment and tumour markers such as serum CA125. These parameters can be combined to provide risk of malignancy indices that can help to predict the probability of malignancy. At present, none of the currently available tests can provide 100% sensitivity or specificity; however, most of the available prediction models are useful in the pre-operative assessment of the adnexal mass.

Clinical question: For women with suspected ovarian cancer, which malignancy index is the most effective?

Clinical evidence

The evidence for this topic comprised one good quality systematic review of diagnostic studies (Geomini *et al.*, 2009) in which the reviewers appraised 109 studies of eighty-three validated risk of malignancy models. By pooling data appropriately the authors concluded that the RMI I proposed by Jacobs *et al.*, (1990) was superior in terms of sensitivity and specificity to the other comparators. With a cut-off score of 200, sensitivity = 78% [95%CI: 71-85%] and specificity = 87% [95%CI: 83-91%] and with a cut-off score of 50, sensitivity = 91% [95%CI: 85-97%] and specificity = 74% [95%CI: 69-80%].

Raza *et al.*, (2010) published a rapid communication reporting the results of a prospective observational study that had been conducted in a UK hospital. Using Jacob's RMI I, as modified by Tingulstad *et al.*, (1996) they referred all women with a suspicious mass and a score of ≥450 directly to the cancer clinic. All patients were first discussed at a MDT meeting and those with a lower RMI score may still have been referred if there were clinical indications of malignancy. Of 104 women in the study, 27 were directly referred, of which one had benign disease. One woman with a low RMI was referred to the clinic on the basis of having had a suspicious CT scan. With a cut-off score in this very limited population, the RMI I index had sensitivity = 96.2% [95%CI: 80.4-99%] and specificity 98.7% [95%CI: 93.1-100%].

Recommendation

- Calculate a risk of malignancy index I (RMI I) score[1] (after performing an ultrasound; see section 3.3 on page 32) and refer all women with an RMI I score of 250 or greater to a specialist multidisciplinary team.

Linking evidence to recommendations

The GDG noted that there was high-quality evidence that RMI I was the most useful index at identifying women with ovarian cancer compared to other malignancy indices, but only in the secondary care setting. However the GDG recognised that although the evidence showed RMI I to be the more useful index, it did not indicate the optimum cut-off score to use for guiding management.

The GDG felt that an RMI I cut-off of 250 should be used because this would ensure access to specialist centres whilst not overburdening them with benign disease (and the additional costs associated with this).

It was also noted that the value of the cut-off score used, affected the sensitivity of RMI I relative to the specificity. For example, a low cut-off score could mean that some women who did not have ovarian cancer would be wrongly identified as positive and referred for specialist treatment. Conversely, a high cut-off score could mean that some women who did have ovarian cancer would not be identified or referred for specialist treatment.

The GDG agreed that this clinical question was not relevant for health economic evaluation because it is unlikely that the different malignancy indices would have a direct impact on patient outcomes.

---

[1] See Box 3.1 for details of how to calculate an RMI I score.

Box 3.1 Risk of malignancy index RMI I[2]

RMI I combines three pre-surgical features: serum CA125 (CA125), menopausal status (M) and ultrasound score (U). The RMI is a product of the ultrasound scan score, the menopausal status and the serum CA125 level (IU/ml).

RMI = U x M x CA125

- The ultrasound result is scored 1 point for each of the following characteristics: multilocular cysts, solid areas, metastases, ascites and bilateral lesions. U=0 (for an ultrasound score of 0), U=1 (for an ultrasound score of 1), U=3 (for an ultrasound score of 2-5).
- The menopausal status is scored as 1= pre-menopausal and 3 = post-menopausal
- The classification of 'post-menopausal' is women who have had no period for more than one year or women over the age of 50 who have had a hysterectomy.
- Serum CA125 is measured in IU/ml and can vary between 0 to hundreds or even thousands of units.

Research recommendation

- Further research should be undertaken to determine the optimum RMI I threshold that should be applied in secondary care to guide the management of women with suspected ovarian cancer.

3.3 Imaging in the diagnostic pathway: which procedures?

Imaging is used to characterise the extent and spread of ovarian cancer. This information can be used for staging and influencing management decisions. In addition it may facilitate image-guided biopsy to enable histological confirmation of diagnosis. Appropriate imaging will also allow a baseline to be established in order that later imaging can assess response to chemotherapy, or assess disease relapse.

The principal imaging modalities comprise ultrasound, computerised tomography (CT) scans and magnetic resonance imaging (MRI), all of which have the capacity to characterise adnexal masses and to assess extent of spread and operability. In addition to how well a test functions one should consider other issues such as availability, cost, and safety.

Ultrasound has the advantage of being more available, cheaper and safer. Grey-scale ultrasound performs well in identifying simple cystic masses that have a high negative predictive value. It is therefore well placed as an initial test and enables adnexal masses to be triaged into low (not ovarian cancer) and higher risk (suspected ovarian cancer) categories.

Women with ovarian cancer can often have associated pleural effusions, which if malignant, have significant staging and possible management implications. CT is the investigation of choice for detection of disease in the thorax.

MRI is established as a tool for characterisation of pelvic masses because of its ability to discriminate masses that contain both fat and blood, neither of which are features of malignancy. However, MRI is less available, scan times are much longer, and imaging of the abdomen can be degraded by movement caused by breathing which may affect the sensitivity of detection of omental and peritoneal disease.

---

[2] Jacobs I, Oram D, Fairbanks J, Turner J, Frost C and Grudzinskas JG (1990) A risk of malignancy index incorporating CA125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. *Br J Obstet Gynaecol,* 97**:** 922-929.

In higher risk women, further assessment of extent of spread is required to aid management in terms of identifying sites for biopsy and consideration for surgery. A CT scan has the advantage of enabling a more comprehensive assessment of the body, and is superior to MRI and ultrasound for assessment of the sub-diaphragmatic regions, gastro-splenic ligament, lesser sac and retroperitoneal nodal disease; sites of likely spread of ovarian cancer. CT is less operator dependent than ultrasound, and more available than MRI. Finally CT also provides optimal baseline information in order to assess response to chemotherapy and disease relapse.

Clinical question: For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management?

Clinical evidence

Differentiation of benign from malignant ovarian tumours

Evidence from good quality diagnostic systematic reviews and meta-analysis (Liu *et al.,* 2007, Kinkel *et al.,* 2000; Kinkel *et al.,* 2005; Medeiros *et al.,* 2009; Myers *et al.,* 2006) suggests the accuracy of combined grey-scale/colour Doppler ultrasound, CT and MRI for the differentiation of benign and malignant ovarian masses, are broadly similar, with sensitivity approaching 90% and specificity exceeding 85%.

Li *et al.,* (2007) note that ultrasound is most accurate in identifying simple cystic masses, and the ultrasound studies in their meta-analysis had a lower prevalence of complex ovarian lesions than the CT and MRI studies. It is possible that the diagnostic utility of MRI and CT is underestimated in the meta-analyses. Kinkel *et al.,* (2005) reviewed evidence for imaging in women with indeterminate masses at grey-scale ultrasound, presumably excluding those women with simple cystic masses. In this group of patients MRI had a higher positive predictive value (post-test probability), than CT and combined grey-scale/colour Doppler ultrasound.

Staging

There was limited evidence about the optimal imaging modality for staging. A prospective multicentre study including 280 women (Tempany *et al.*, 2000) concluded that CT and MRI were more accurate than ultrasound for staging ovarian cancer.

Prediction of optimal cytoreduction

Most of the evidence about the prediction of optimal cytoreduction came from studies using CT (Bristow *et al.,* 2000; Byrom *et al.,* 2002 Dowdy *et al.,* 2004; Ferrandina *et al.,* 2009; Forstner *et al.,* 1995; Gemer *et al.,* 2009; Meyer *et al.,* 1995; Nelson *et al.,* 1993; Kebapci *et al.,* 2010; Jung *et al.,* 2010; Qayyum *et al.,* 2004) with only one ultrasound study (Testa *et al.*, 2006) and two MRI studies (Forstner *et al.,* 1995; Qayyum *et al.,* 2005).

Five studies (Nelson *et al.*, 1993; Bristow *et al.*, 2000; Dowdy *et al.*, 2004; Quayyum *et al.*, 2004; Meyer *et al.*, 1995) reported models to predict suboptimal cytoreduction on the basis of CT features.

Although the authors of these models report reasonable sensitivity and specificity for their models, two independent studies (Axtell *et al.,* 2007; Gemer *et al.,* 2009) did not validate these findings. The low positive predictive values reported by Axtell *et al.,* (2007) and Gemer *et al.,* (2009) suggest that most patients predicted to have sub-optimal cytoreduction will in fact be optimally cytoreduced at operation.

Recommendations

- Perform an ultrasound of the abdomen and pelvis as the first imaging test in secondary care for women with suspected ovarian cancer, if this has not already been done in primary care.
- If the ultrasound, serum CA125 and clinical status suggest ovarian cancer, perform a CT scan of the pelvis and abdomen to establish the extent of disease. Include the thorax if clinically indicated.
- Do not use MRI routinely for assessing women with suspected ovarian cancer.

Linking evidence to recommendations

The GDG placed a high value on the need to establish a diagnosis of ovarian cancer and to determine the extent of disease to inform multidisciplinary team discussions.

There was good quality evidence from systematic reviews on which to base the recommendations on diagnosis. The GDG agreed that the sensitivity and specificity of ultrasound and CT for establishing a diagnosis, were shown to be broadly equivalent, but that the evidence did not specify which of these imaging modalities was the most effective. Given that ultrasound and CT had been shown to have equivalent sensitivity and specificity, and that ultrasound is more readily available, less costly and involves no radiation unlike CT, the GDG felt it was appropriate to recommend ultrasound as the initial imaging test for women with suspected ovarian cancer.

The GDG noted that the evidence for the staging of ovarian cancer was sparse. The GDG recognised that ultrasound is subjective and operator dependent and has limitations in detecting peritoneal disease, whereas multi-slice CT has high spatial resolution and is more sensitive for assessment of omental and peritoneal disease, and abdominal and pelvic lymph nodes. CT is the investigation of choice for staging thoracic disease. For these reasons the GDG chose CT to be the investigation of choice for staging.

MRI is less specific for establishing the extent of disease, it is less available and takes longer than CT or ultrasound. For these reasons the GDG were unable to recommend MRI for routine use.

This clinical question was considered as a medium priority for health economic evaluation because the population involved was relatively small and the cost difference between the competing alternatives was minimal.

Recommendations

- Large multicentre case–control studies should be conducted to compare the accuracy of CT versus MRI for staging and for predicting optimal cytoreduction in women with ovarian cancer.

3.4 Tissue diagnosis

Requirement for tissue diagnosis

Without a tissue diagnosis there is always a degree of diagnostic uncertainty. In most instances, histology is the only way of determining the cancer type and grade and will also exclude other diagnoses such as tuberculosis, inflammation, fibrosis and other infections. Different histological types of ovarian cancer require different treatments, and so confirmed histological diagnosis is considered important.

Histological diagnosis is usually made following surgery. In some cases, for example where surgery is not feasible or where chemotherapy is the initial treatment, other options for obtaining a histological diagnosis may be considered.

There are a range of methods of obtaining a tissue diagnosis including needle biopsy, laparoscopy or open laparotomy. All are invasive and therefore carry risks. In addition, attempts at tissue diagnosis are not always successful and this may delay the start of treatment. Another method of obtaining a tissue diagnosis is the use of frozen section at the time of surgery. However, this suffers from sampling error and is not widely practised in the UK.

Cytology (examination of individual cells aspirated from intra-abdominal fluid or rarely from a tumour) is generally safer than tissue biopsy but has a lower diagnostic accuracy.

When it is hazardous or difficult to obtain a tissue diagnosis, the risks of such procedures need to be weighed against the potential benefits of greater diagnostic accuracy. After discussion with the woman it may be concluded that a tissue diagnosis is not essential.

Clinical question: For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy?

Clinical evidence

There were no studies comparing the outcomes of women with suspected versus confirmed advanced ovarian cancer treated with chemotherapy. Evidence from case series suggests a minority of women (4–5%) with presumed advanced ovarian cancer on the basis of clinical and imaging findings will not have ovarian cancer (Griffin *et al.,* 2009; Freedman *et al.*, 2010). Thus if tissue diagnosis were omitted some women might receive inappropriate treatment.

Cytomorphology combined with immunocytochemistry had a rate of definitive diagnosis of primary tumour site in malignant effusions ranging from 57% to 87% (Mottolese *et al.*, 1988; Pomjanski *et al.*, 2005; Longatto-Filho *et al.*, 1997; DiBonito *et al,.* 1993). In comparison, histopathology plus immunohistochemistry had a diagnostic rate between 87% and 97% in women with peritoneal carcinomatosis of unknown origin (Hewitt *et al.*, 2006; Spencer *et al.*, 2001) or presumed advanced ovarian cancer (Griffin *et al.,* 2009).

There were no data about complications of effusion cytology. Percutaneous core biopsy was associated with minor local bruising and discomfort (Fisherova *et al.,* 2008; Griffin *et al.,* 2009; Hewitt *et al.,* 2006; Pombo *et al.,* 1997; Spencer *et al.,* 2001). There was no direct evidence about the harms of diagnostic laparoscopy or laparotomy in women with suspected advanced ovarian cancer due to receive chemotherapy. Indirect evidence comes from studies reporting diagnostic laparoscopy in patients with ascites of unknown origin (Bedioui *et al.,* 2007; Chu *et al.*, 1994; Yoon *et al.*, 2007). Minor complications were reported in less than two percent of laparoscopies. Major complications occurred at a rate of less than one percent.

Recommendations

- If offering cytotoxic chemotherapy to women with suspected advanced ovarian cancer, first obtain a confirmed tissue diagnosis by histology (or by cytology if histology is not appropriate) in all but exceptional cases.
- Offer cytotoxic chemotherapy for suspected advanced ovarian cancer without a tissue diagnosis (histology or cytology) only:
  – in exceptional cases, after discussion at the multidisciplinary team **and**
  – after discussing with the woman the possible benefits and risks of starting chemotherapy without a tissue diagnosis.

Linking evidence to recommendations

The GDG noted that the evidence for this clinical question consisted of small retrospective studies of moderate quality.

The GDG felt that having a tissue diagnosis was essential to guiding future treatment, but recognised that on occasions the risks of obtaining a histological diagnosis might not be justified. In these circumstances, the use of cytological diagnosis alone will suffice but the risk of giving chemotherapy when the diagnosis might be uncertain has to be weighed against the potential risks of obtaining histological confirmation.

This clinical question was agreed as a low priority for health economic evaluation because of the lack of good quality prospective clinical studies in this area.

Methods of tissue diagnosis other than laparotomy

Image-guided biopsy is usually performed under local anaesthetic in the radiology department using ultrasound or CT to sample an accessible area of abnormality such as a peritoneal deposit or omental disease. The biopsy needle is inserted percutaneously and several passes are usually made to obtain thin tissue cores. This technique is not suitable for all women, for example if the disease is not in an accessible location. It is associated with minor complications, such as local bruising and discomfort. Targeting of the abnormality for biopsy is limited by the imaging technique used and the samples are much smaller, reducing the diagnostic yield. This potentially results in a lower success rate requiring a repeat procedure or surgical biopsy.

When image-guided biopsy is not appropriate or if the procedure has failed to obtain an adequate sample, a secondary intervention may be required to obtain tissue for diagnosis. Laparoscopy is a surgical technique that uses an endoscope that gives a complete view but full visualisation of the peritoneal cavity and allows a biopsy to be performed. It requires a general anaesthetic and is more complex to perform. Laparoscopy is associated with both major and minor complications, with higher associated major complication rates than image-guided biopsy.

Both techniques have the potential to damage the abdomino-pelvic organs which may be displaced or tethered to abnormal positions by tumour, fibrosis or inflammation. There is also a potential risk of tumour being deposited along the biopsy needle track or implanted into the laparoscopic surgery sites.

Clinical question: What is the best method of tissue diagnosis before chemotherapy, samples from image-guided biopsy or laparoscopic biopsy?

Clinical evidence

The literature search found no studies directly comparing image-guided with laparoscopic biopsy. Evidence from case series indicates a definitive diagnostic rate between 87% and 97% for image-guided biopsy (Griffin *et al.*, 2009; Hewitt *et al.*, 2006; Spencer *et al.*, 2001), but our searches found no studies reporting the diagnostic yield of laparoscopic biopsy.

Percutaneous core biopsy was associated with minor local bruising and discomfort (Griffin *et al.*, 2009; Hewitt *et al.*, 2006; Spencer *et al.*, 2001). Minor complications were reported in less than two percent of laparoscopies from three series (Dedioui *et al.,* 2007, Chu *et al.*, 1994; Yoon *et al.*, 2007) with 1,284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent.

Recommendations

- If surgery has not been performed, use histology rather than cytology to obtain a tissue diagnosis. To obtain tissue for histology:
  – use percutaneous image-guided biopsy if this is feasible
  – consider laparoscopic biopsy if percutaneous image-guided biopsy is not feasible or has not produced an adequate sample.
    Use cytology if histology is not appropriate.

Linking evidence to recommendations

There was low quality evidence, with no studies directly comparing image-guided biopsy with laparoscopic biopsy, and so case series evidence for the risks and accuracy of each technique in isolation was reviewed.

The GDG acknowledged that although there was evidence for the diagnostic yield of image-guided biopsy there was none reporting the diagnostic yield of laparoscopic biopsy. They also noted that higher associated major complication rates were reported with laparoscopic biopsy than image-guided biopsy. The GDG therefore put a high value on the outcomes of morbidity and adverse events associated with the two techniques, and agreed that the simplest and least invasive technique was image-guided biopsy.

This clinical question was originally agreed a high priority for health economic evaluation because the number of patients involved could potentially be large and there could be significant cost implications. Due to the lack of comparative clinical evidence, which would hinder the development of a robust economic analysis it was reconsidered as a low priority. Economic evaluation based on poor quality data would carry a high level of uncertainty and potentially limit its usefulness in informing recommendations.

References

Abdel-Azeez HA, Labib HA, Sharaf SM and Refai AN (2010). HE4 and mesothelin: novel biomarkers of ovarian carcinoma in patients with pelvic masses. Asian Pacific Journal of Cancer Prevention: Apjcp. 11: 111-116.

Axtell AE, Lee MH, Bristow RE, Dowdy SC, Cliby WA, Raman S, Weaver JP, Gabbay M, Ngo M, Lentz S, Cass I, Li AJ, Karlan BY and Holschneider CH (2007) Multi-institutional reciprocal validation study of computed tomography predictors of suboptimal primary cytoreduction in patients with advanced ovarian cancer J.Clin.Oncol. 25: 384-389.

Bedioui, H., Ksantini R., , N. K., Mekni, A., & Chebbi, F. (2007). Role of laparoscopic surgery in the etiologic diagnosis of exudative ascites: a prospective study of 90 cases. Gastroenterol Clin Biol 31[12], 1146-1149.

Bristow RE, Duska LR, Lambrou NC, Fishman EK, O'Neill MJ, Trimble EL and Montz FJ (2000) A model for predicting surgical outcome in patients with advanced ovarian carcinoma using computed tomography Cancer 89: 1532-1540.

Byrom J, Widjaja E, Redman CW, Jones PW and Tebby S (2002) Can pre-operative computed tomography predict resectability of ovarian carcinoma at primary laparotomy?[see comment] BJOG: Int J Obstet Gynaecol 109: 369-375.

Chu CM, Lin SM, Peng SM, Wu CS, Liaw YF.(1994) The role of laparoscopy in the evaluation of ascites of unknown origin. Gastrointestinal Endoscopy 40(3): 285-9

Department of Health (1999) Improving outcomes in gynaecological cancers. Service guidance. Available from www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005385

DiBonito, L., Falconieri, G., Colautti, I., Bonifacio, D., & Dudine, S. (1993). The positive peritoneal effusion. A retrospective study of cytopathologic diagnoses with autopsy confirmation. Acta Cytologica, 37, 483-488.

Dowdy SC, Mullany SA, Brandt KR, Huppert BJ and Cliby WA (2004) The utility of computed tomography scans in predicting suboptimal cytoreductive surgery in women with advanced ovarian carcinoma Cancer 101: 346-352.

Ferrandina G, Sallustio G, Fagotti A, Vizzielli G, Paglia A, Cucci E, Margariti A, Aquilani L, Garganese G and Scambia G (2009) Role of CT scan-based and clinical evaluation in the preoperative prediction of optimal cytoreduction in advanced ovarian cancer: a prospective trial Br.J.Cancer 101: 1066-1073.

Fischerova D, Cibula D, Dundr P, Zikan M, Calda P, Freitag P and Slama J (2008) Ultrasound-guided tru-cut biopsy in the management of advanced abdomino-pelvic tumors International Journal of Gynecological Cancer 18: 833-837.

Forstner R, Hricak H, Occhipinti KA, Powell CB, Frankel SD and Stern JL (1995) Ovarian cancer: staging with CT and MR imaging Radiology 197: 619-626.

Freedman OC, Dodge J, Shaw P, Oza, AM., Bernadini M and Klachook S (2010). Diagnosis of epithelial ovarian carcinoma prior to neoadjuvant chemotherapy. Gynecologic Oncology. – in press

Geomini P, Kruitwagen R, Bremer GL, Cnossen J and Mol BW. (2009) The accuracy of risk scores in predicting ovarian malignancy: a systematic review. Obstet Gynecol 113 (2 Pt 1): 384-94

Gemer O, Gdalevich M, Ravid M, Piura B, Rabinovich A, Gasper T, Khashper A, Voldarsky M, Linov L, Ben S, I, Anteby EY and Lavie O (2009) A multicenter validation of computerized tomography models as predictors of non- optimal primary cytoreduction of advanced epithelial ovarian cancer Eur.J.Surg.Oncol. 35: 1109-1112.

Griffin N, Grant LA, Freeman SJ, Jimenez-Linan M, Berman LH, Earl H, Ahmed A, Crawford R, Brenton J and Sala E (2009) Image-guided biopsy in patients with suspected ovarian carcinoma: a safe and effective technique? Eur.Radiol. 19: 230-235.

Hewitt MJ, Hall GD, Wilkinson N, Perren TJ, Lane G and Spencer JA (2006) Image-guided biopsy in women with breast cancer presenting with peritoneal carcinomatosis International Journal of Gynecological Cancer 16: 108-110.

Huhtinen K, Suvitie P, Hiissa J, Junnila J, Huvila J, Kujari H, et al.(2009) Serum HE4 concentration differentiates malignant ovarian tumours from ovarian endometriotic cysts. Br J Cancer 100(8): 1315-9

Jacobs I., Oram D., Fairbanks J., Turner J., Frost C and Grudzinskas JG (1990) A risk of malignancy index incorporating CA 125, ultrasound and menopausal status for the accurate preoperative diagnosis of ovarian cancer. Br J Obstet Gynaecol 97: 922-929.

Jung DC, Kang S, Kim MJ, Park SY and Kim HB (2010). Multidetector CT predictors of incomplete resection in primary cytoreduction of patients with advanced ovarian cancer. Eur.Radiol. 20: 100-107.

Kebapci M, Akca AK, Yalcin OT, Ozalp SS, Calisir C and Mutlu F (2010). Prediction of suboptimal cytoreduction of epithelial ovarian carcinoma by preoperative computed tomography. Eur.J.Gynaecol.Oncol. 31: 44-49.

Kinkel K, Hricak H, Lu Y, Tsuda K and Filly RA (2000) US characterization of ovarian masses: a meta-analysis. DARE Structured Abstract available Radiology 217: 803-811.

Kinkel K, Lu Y, Mehdizade A, Pelte MF and Hricak H (2005) Indeterminate ovarian mass at US: incremental value of second imaging test for characterization--meta-analysis and Bayesian analysis Radiology 236: 85-94.

Liu J, Xu Y and Wang J (2007) Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma Eur.J.Radiol. 62: 328-334.

Longatto FA, Bisi H, Alves VA, Kanamura CT, Oyafuso MS, Bortolan J and Lombardo V (1997). Adenocarcinoma in females detected in serous effusions. Cytomorphologic aspects and immunocytochemical reactivity to cytokeratins 7 and 20. Acta Cytol. 41: 961-971.

Medeiros LR, Rosa DD, da Rosa MI and Bozzetti MC (2009) Accuracy of ultrasonography with color Doppler in ovarian tumor: a systematic quantitative review International Journal of Gynecological Cancer 19: 1214-1220.

Meyer JI, Kennedy AW, Friedman R, Ayoub A and Zepp RC (1995) Ovarian carcinoma: value of CT in predicting success of debulking surgery AJR 165: 875-878.

Mottolese M, Venturo I, Donnorso RP, Curcio CG, Rinaldi M, Natali PG. (1988) Use of selected combinations of monoclonal antibodies to tumor associated antigens in the diagnosis of neoplastic effusions of unknown origin. Eur J Cancer Clin Oncol. 24(8): 1277-84.

Moore RG, Brown AK, Miller MC, Skates S, Allard WJ, Verch T, *et al*. (2008) The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. Gynecol Oncol 108(2): 402-8.

Moore RG, McMeekin DS, Brown AK, DiSilvestro P, Miller MC, Allard WJ, *et al*. (2009) A novel multiple marker bioassay utilizing HE4 and CA125 for the prediction of ovarian cancer in patients with a pelvic mass. Gynecol Oncol 112(1): 40-6.

Myers ER, Bastian LA, Havrilesky LJ, Kulasingam SL, Terplan MS, Cline KE, Gray RN and McCrory DC (2006). Management of adnexal mass. Evid.Rep.Technol.Assess.(Full.Rep.). 1-145.

Nelson BE, Rosenfield AT and Schwartz PE (1993) Preoperative abdominopelvic computed tomographic prediction of optimal cytoreduction in epithelial ovarian carcinoma J.Clin.Oncol. 11: 166-172.

Nolen B, Velikokhatnaya L, Marrangoni A, De GK, Lomakin A, Bast RC, Jr. and Lokshin A (2010). Serum biomarker panels for the discrimination of benign from malignant cases in patients with an adnexal mass. Gynecol.Oncol. 117: 440-445.

Pombo F, Rodriguez E, Martin R and Lago M (1997) CT-guided core-needle biopsy in omental pathology Acta Radiol. 38: 978-981.

Pomjanski N, Grote HJ, Doganay P, Schmiemann V, Buckstegge B, Bocking A. (2005) Immunocytochemical identification of carcinomas of unknown primary in serous effusions. Diagnostic Cytopathology. 33(5): 309-15.

Qayyum A, Coakley FV, Westphalen AC, Hricak H, Okuno WT and Powell B (2005) Role of CT and MR imaging in predicting optimal cytoreduction of newly diagnosed primary epithelial ovarian cancer Gynecol.Oncol. 96: 301-306.

Raza A, Mould T, Wilson M, Burnell M, Bernhardt L. (2010) Increasing the effectiveness of referral of ovarian masses from cancer unit to cancer center by using a higher referral value of the risk of malignancy index. Int J Gynecol Cancer 20(4): 552-554.

Shah CA, Lowe KA, Paley P, Wallace E, Anderson GL, McIntosh MW, et al. (2009) Influence of ovarian cancer risk status on the diagnostic performance of the serum biomarkers mesothelin, HE4, and CA125. Cancer Epidemiology, Biomarkers & Prevention 18(5): 1365-72.

Spencer JA, Swift SE, Wilkinson N, Boon AP, Lane G and Perren TJ (2001) Peritoneal carcinomatosis: Image-guided peritoneal core biopsy for tumor type and patient care Radiology 221: 173-177.

Sturgeon CM, Duffy MJ, Stenman UH, Lilja H, Brunner N, Chan DW, *et al*. (2008) National Academy of Clinical Biochemistry laboratory medicine practice guidelines for use of tumor markers in testicular, prostate, colorectal, breast, and ovarian cancers. Clin Chem 54(12): e11-79.

Tempany CM, Zou KH, Silverman SG, Brown DL, Kurtz AB and McNeil BJ (2000) Staging of advanced ovarian cancer: comparison of imaging modalities–report from the Radiological Diagnostic Oncology Group Radiology 215: 761-767.

Testa AC, Ludovisi M, Savelli L, Fruscella E, Ghi T, Fagotti A, Scambia G and Ferrandina G (2006) Ultrasound and color power Doppler in the detection of metastatic omentum: a prospective study Ultrasound in Obstetrics & Gynecology 27: 65-70.

Tingulstad S., Hagen B., Skjeldestad FE., Onsrud M., Kiserud T., Halvorsen T and Nustad K (1996) Evaluation of a risk of malignancy index based on serum CA125, ultrasound findings and menopausal status in the pre-operative diagnosis of pelvic masses. Br J Obstet Gynaecol 103: 826-831.

Yoon YJ, Ahn SH, Park JY, Chon CY, Kim do Y, Park YN, *et al*. (2007) What is the role of diagnostic laparoscopy in a gastroenterology unit? J Gastroenterol 42(11): 881-6.

4 Management of suspected early (stage I) ovarian cancer

The two objectives of this chapter were:

1. to determine whether the systematic removal of the retroperitoneal lymph nodes during surgical treatment for suspected early stage ovarian cancer confers any added benefit as opposed to conventional surgical staging which includes lymph node sampling.

2. to determine the clinical benefits and toxicity of first-line adjuvant chemotherapy for women with stage I ovarian cancer.

4.1 The role of systematic retroperitoneal lymphadenectomy

In women whose disease is thought to be confined to the ovary(s), optimum surgical staging comprises midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter-Roach *et al.*, 2009). In women where the disease appears to be confined to one ovary and who wish to conserve fertility, then conservative surgery can be considered where the uterus and contra-lateral ovary are conserved.

It is recognised that around 22% of women considered to have stage I ovarian cancer, will in fact have occult retroperitoneal lymph node metastases which can only be identified by removing affected nodes (Maggioni *et al.*, 2006). Current surgical staging guidelines advocate only sampling a number of pelvic and/or para-aortic nodes but inevitably less will be sampled than in a systematic retroperitoneal lymphadenectomy, which aims to remove all pelvic and para-aortic lymph nodes up to the renal vessels as a block dissection on both sides. Removing all affected nodes will improve staging and might be therapeutic.

Systematic retroperitoneal lymphadenectomy is a major surgical procedure which carries the potential risks of prolonged anaesthesia and surgical complications such as increased blood loss and transfusion, ureteric injury, lymphoedema, lymphocysts, damage to nerves and major vessels. In addition to concerns about morbidity, there are resource implications. The use of peri-operative frozen section to confirm malignancy has been proposed. This might be a way of selecting only those patients with ovarian cancer for systematic retroperitoneal lymphadenectomy, thereby reducing the risks and costs of this strategy.

There is, however, no international agreement on whether the potential survival benefits of systematic retroperitoneal lymphadenectomy outweigh the risks.

Clinical question: For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management?

Clinical evidence

The evidence for this topic was generally of low quality, comprising two retrospective observational studies, one non-randomised comparative study and a small randomised controlled trial (RCT) (Table 4.1). Across all studies, the majority of women had stage I ovarian cancer. Only the RCT reported the incidence of post-surgical morbidity and none of the papers reported on patient quality of life. The results of survival outcomes were inconsistent between studies.

Maggioni *et al.*, (2006) presented results from a small, underpowered study that was unable to demonstrate a difference in short or long term survival between patients having surgery alone or surgery with systematic lymphadenectomy (SL). But the more extensive operation was associated with increased morbidity. Conversely, Yokoyama *et al.*, (1999) found a significant difference in the rates of 5 and 10 year survival for women with stage I/II disease who had received SL compared with those who had not (100% vs. 71.4% (P<0.05) and 83.9% vs. 61.1% (P<0.05) respectively). These results may have been confounded by the addition of different chemotherapy regimens to the study arms.

The retrospective studies also reported conflicting results for survival. The largest study (Chan *et al.*, 2007; N=6,686) found a significant improvement in the rate of 5 year disease-specific survival for women who underwent SL as part of staging compared with women who did not (92.6% ± 0.6 vs. 87% ± 0.6 P<0.001). However, during the study period participants had unrecorded treatments including surgery and/or chemotherapy which could have confounded these results. The smaller study (Yang *et al.*, 2007) found no significant differences in survival after 1, 3, 5 or 10 years between women that had undergone SL after primary surgery and those who had not. Again, some participants had subsequently received chemotherapy which could have confounded the results.

Kim *et al.*, (2010) conducted a thorough systematic review and meta-analysis of RCTs and observational studies to determine the possible benefit of systematic retroperitoneal lymphadenectomy to women with all stages of ovarian cancer. A sub-set of patients had stage I-II disease and these data showed a survival advantage with SL (HR: 0.80 [95%CI: 0.70-0.92] (P=0.001) with no between studies heterogeneity. However, the included studies were not of high evidential quality consisting of Chan *et al.*, 2007; Maggioni *et al.*, 2006 and a small retrospective observational study (Suzuki *et al.*, 2008).

Table 4.1 GRADE profile: For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management?

No of studies	Quality						Summary of findings				Quality
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Patients with SL	Patients with no SL	% survived SL	% survived no SL	Quality
5 year disease-specific survival. All study participants (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,862	3,824	92.6 ± 0.6	87 ± 0.6	VERY LOW
5 year disease-specific survival. Age >50 years (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	1,562	2,360	92 ± 0.9	82.3 ± 0.9	VERY LOW
5 year disease-specific survival. Non-clear cell epithelial carcinoma (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,136	2,900	93.3 ± 0.7	85.9 ± 0.9	VERY LOW
5 year disease-specific survival. No hysterectomy (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	603	1,240	96.5 ± 0.9	92.0 ± 0.9	VERY LOW
5 year disease-specific survival. Hysterectomy (P=0.01) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,253	2,342	91.5 ± 0.5	88.3 ± 0.7	VERY LOW
5 year disease-specific survival. No surgery (P=0.02) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	6	242	100 ± 0.0	32.9 ± 4.2	VERY LOW
5 year disease-specific survival. Stage I disease (P<0.001) Chan et al. (2006).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	845	995	88.1 ± 1.4	72.8 ± 1.6	VERY LOW
5 year disease-specific survival. Grade 3 disease (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	631	633	88.8 ± 1.6	74.4 ± 2.0	VERY LOW

Table 4.1 (Cont.)

No of studies	Design	Quality					Summary of findings				Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Other	Patients with SL	Patients with no SL	% survived SL	% survived no SL	
5 year disease-specific survival. No radiation therapy (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,758	3,722	92.9 ± 0.6	87.1 ± 0.6	VERY LOW
5 year disease-specific survival. Caucasian race (P<0.001) Chan et al. (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,166	2,906	92.9 ± 0.7	86.1 ± 0.7	VERY LOW
1 year survival stage I (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	99.4	97.5	VERY LOW
3 year survival stage I (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	92.3	91.9	VERY LOW
5 year survival stage I (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	83.5	82.7	VERY LOW
10 year survival stage I (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	82.1	81.0	VERY LOW
1 year survival stage II (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	87.2	86.3	VERY LOW
3 year survival stage II (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	76.5	74.6	VERY LOW

Table 4.1 (Cont.)

No of studies	Quality						Summary of findings				
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Patients with SL	Patients with no SL	% survived SL	% survived no SL	Quality
5 year survival stage II (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	68.9	65.4	VERY LOW
10 year survival stage II (% only) Yang et al. (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	54.3	50.6	VERY LOW
Estimated 5 year survival for stages I and II (% only) Yokoyama et al. (1999)											
1	non-randomised comparative study	N/A	N/A	N/A	N/A	nil	80	75	100	71.4	VERY LOW
Estimated 10 year survival for stages I and II (% only) Yokoyama et al. (1999)											
1	non-randomised comparative study	N/A	N/A	N/A	N/A	nil	80	75	83.9	61.1	VERY LOW
Risk of death. All participants (P>0.05) Maggioni et al. (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	138	130	HR=0.85 (0.49-1.47)	-	LOW
Risk of progression All participants (P>0.05) Maggioni et al. (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	138	130	HR=0.72 (0.46-1.14)	-	LOW
5 year overall survival Maggioni et al. (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	84%	81.6%	MD=2.4 (-8.3-8.9)		LOW

Table 4.1 (Cont.)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Patients with SL	Patients with no SL	% survived SL	% survived no SL	Quality
5 year progression-free survival Maggioni et al. (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	78.3%	73.4%	MD=4.9 (-5.9-12.5)	-	LOW
Overall survival. Kim et al., (2010)[1]											
3	randomised trial and observational studies	serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	-	-	HR=0.80 (0.70-0.92)	-	MODERATE

[1] This study combined one small RCT and two observational studies which showed no between studies heterogeneity (0%) and gave a significant result. Nonetheless, the included studies were themselves between 'low' and 'moderate' quality.

Recommendation

- Perform retroperitoneal lymph node assessment[1] as part of optimal surgical staging[2] in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease)
- Do not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment in women with suspected ovarian cancer whose disease appears to be confined to the ovaries (that is, who appear to have stage I disease).

Linking evidence to recommendations

The GDG acknowledged that evidence on the basis of study quality assessed according to GRADE was limited and of poor quality. There was no demonstrable survival benefit from systematic retroperitoneal lymphadenectomy compared to lymph node sampling. They also noted that no studies reported on quality of life.

The GDG reaffirm the need for accurate staging, particularly in women with suspected early ovarian cancer, but were not convinced that the greater risks and costs of systematic retroperitoneal lymphadenectomy compared to conventional lymph node sampling were justifiable. Therefore they were unable to recommend its use in women whose disease appears to be confined to the ovaries.

This clinical question was agreed as a low priority for health economic evaluation because of the lack of good quality RCT data in this area. Also, given that an economic evaluation would be unlikely to clarify the uncertain health benefits associated with these interventions, the added value of such an analysis was lower than for other clinical questions.

Research recommendation

- A prospective randomised trial should be undertaken to evaluate the therapeutic effect, associated risks and cost effectiveness of systematic retroperitoneal lymphadenectomy in women with ovarian cancer whose disease appears to be confined to the ovaries.

4.2 Adjuvant systemic chemotherapy for stage I disease

No surgical staging procedure is perfect and in a proportion of women in whom the disease is thought to be confined to the ovaries and completely removed at operation there may, in fact, be occult residual disease.

In women with apparent stage I disease, chemotherapy can be given in certain circumstances, such as poorly differentiated tumours and in certain histological sub-types (for example, clear cell carcinomas). This is done to treat residual disease that is suspected but may not, in fact, exist. Therefore some women without residual disease will receive chemotherapy with its associated risks.

---

[1] Lymph node assessment involves sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls if there is a palpable abnormality, or random sampling if there is no palpable abnormality.

[2] Optimal surgical staging constitutes: midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum; and retroperitoneal lymph node assessment [Winter Roach BA, Kitchener HC, Dickinson HO (2009) Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews issue 3: CD004706].

Given that women with stage I ovarian cancer have significantly less disease it is possible that less chemotherapy will be required for cure. Currently NICE technology appraisal guidance 55 (NICE, 2003) recommends a choice of either platinum based compound on its own or in combination with paclitaxel (see section 5.3) but does not stipulate the number of cycles to be given. It is logical that reducing the number of cycles of chemotherapy is likely to reduce toxicity but could compromise effectiveness. The GDG felt that establishing the evidence base for reducing chemotherapy cycles should be investigated in order to quantify any risk-benefit assessment.

Clinical question: For women with stage I ovarian cancer, what is the most effective first line chemotherapy?

Clinical evidence

The evidence for this topic consisted of one high quality Cochrane review and a lower quality randomised controlled trial (RCT) (Table 4.2). Across these studies, women had undergone primary surgery and had stage I or II ovarian cancer.

Winter-Roach *et al.*, (2009) conducted a review which investigated whether adjuvant therapy with mainly platinum-containing regimens was associated with a survival advantage compared to withholding chemotherapy until disease progression, and whether certain sub-groups of patients gained more or less from this approach. After an average follow-up of nearly ten years it was found that women receiving adjuvant therapy had a considerable advantage in overall survival (HR=0.71 [95%CI: 0.53 to 0.93] P=0.015) and progression-free survival (HR=0.67 [95%CI: 0.53-0.84] P=0.00046). In particular, those women who had been adequately staged gained no survival advantage from immediate adjuvant chemotherapy (HR=1.22 [95%CI: 0.63-2.37] P=0.56) whereas women who had been inadequately staged did (HR=0.63 [95%CI: 0.46 to 0.85] P=0.0031).

Bell *et al.*, (2006) compared six vs. three cycles of adjuvant carboplatin and paclitaxel in women with early stage ovarian cancer (N=457). Across all patients and after an average follow-up of 6.8 years, there were no statistically significant differences in the risk of death (HR=1.02 [95%CI: 0.66-1.57] P=0.94) or the rate of disease recurrence (HR=0.76 [95%CI: 0.51-1.13] P=0.18). The higher number of treatment cycles was associated with significantly increased morbidity.

The systematic review (Winter-Roach *et al.*, 2009) included evidence from the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial which has now been updated by Trimbos *et al.*, (2010). The results showed that, even with observation, optimally surgically staged patients had a significantly better prognosis compared with patients who had been non-optimally staged: cancer-specific survival (risk of death: HR 3.28 [95%CI: 1.47-7.33] (P=0.002); recurrence-free survival (risk of death: HR 1.91 [95%CI: 1.17-3.11] P=0.009). In non-optimally staged patients only, adjuvant chemotherapy provided significantly improved cancer-specific survival (risk of death: HR 0.58 [95%CI: 0.35-0.95] P=0.029) and recurrence-free survival (risk of death: HR 0.60 [95%CI: 0.41-0.87] P=0.007) when compared with observation. The authors concluded, therefore, that the benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging who, perhaps, had a greater risk of unidentified residual disease.

The results of Bell *et al.*, 2006 were re-analysed in a more recent report (Chan *et al.*, 2010) after a median follow-up of 91 months. The authors grouped data by tumour type (i.e. serous or non-serous) and showed that only women with serous cancer derived a significant benefit from six cycles compared with three cycles of adjuvant carboplatin and paclitaxel chemotherapy (HR=0.33 [95%CI: 0.14-0.77] P=0.007). Although interesting, the original study was underpowered for sub-group analyses which, in any event, have been performed post hoc.

Table 4.2 GRADE profile: For women with stage I ovarian cancer, what is the most effective first line chemotherapy

No of studies	Quality assessment						No of patients		Summary of findings		Quality
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other			Effect		
							Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
OS 5 years. Follow-up 46-110 months. Winter-Roach et al (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	506	502	HR 0.71 (0.53 to 0.93) P=0.015	-	HIGH
OS 5 years (sub-grouped by staging - all data). Follow-up 46-110 months. Winter-Roach et al (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	506	500	HR 0.72 (0.53 to 0.97) P=0.033	-	HIGH
OS 5 years (sub-grouped by staging - optimal staging). Follow-up 46-110 months. Winter-Roach et al (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[1]	N/A	117	117	HR 1.22 (0.63 to 2.37) P= 0.56	-	MODERATE
OS 5 years (sub-grouped by staging - sub-optimal staging. Follow-up 46-110 months. Winter-Roach et al (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	389	383	HR 0.63 (0.46 to 0.85) P=0.0031	-	HIGH
OS 10 years (sub-grouped by risk - all). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	totals not selected	-	N/A
OS 10 years (sub-grouped by risk - low/medium risk). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
OS 10 years (sub-grouped by risk - high risk). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A

Table 4.2 (Cont.)

No of studies	Quality assessment						No of patients		Summary of findings		
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Effect		Quality
									Relative (95% CI)	Absolute	
PFS 5 years. Follow-up 46-110 months. Winter-Roach et al (2009)											
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	587	583	HR 0.67 (0.53 to 0.84) P=0.00046	-	HIGH
PFS 5 years (data sub-grouped by staging - all). Follow-up 46-110 months. Winter-Roach et al (2009)											
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	587	581	HR 0.64 (0.52 to 0.78) P=0.000012	-	HIGH
PFS 5 years (data sub-grouped by staging - optimal staging). Follow-up 46-110 months. Winter-Roach et al (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[2]	N/A	117	117	HR 0.67 (0.36 to 1.22) P=0.19	-	MODERATE
PFS 5 years (data sub-grouped by staging - sub-optimal staging). Follow-up 46-110 months. Winter-Roach et al (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	470	464	HR 0.64 (0.50 to 0.82) P=0.00041	-	HIGH
PFS 10 years (sub-grouped by risk). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	totals not selected	-	N/A
PFS 10 years (sub-grouped by risk - low/medium risk). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A

49

Table 4.2 (Cont.)

No of studies	Quality assessment						No of patients		Summary of findings		
									Effect		
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	Quality
PFS 10 years (sub-grouped by risk - high risk). Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
DSS. Follow-up 46-110 months. Winter-Roach et al (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[3]	N/A	81	81	HR 0.94 (0.37 to 2.37) P=0.90	-	MODERATE
Death from ovarian cancer. Follow-up 46-110 months. Winter-Roach et al (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	41/346	54/347	RR 0.76 (0.52 to 1.11) P=0.16	-	HIGH
10 year cancer-specific survival, all patients. Follow-up 10.1 years. Trimbos et al (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	82% (75-87%)	76% (69-82%)	HR 0.73 (0.48 to 1.13) P=0.16	-	HIGH
10 year cancer-specific survival, optimally staged patients. Follow-up 10.1 years. Trimbos et al (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	85% (73-92%)	89% (79-95%)	HR 1.58 (0.61 to 4.08) P=0.34	-	HIGH
10 year cancer-specific survival, non-optimally staged patients. Follow-up 10.1 years. Trimbos et al (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	80% (71-86%)	69% (60-77%)	HR 0.58 (0.35 to 0.95) P=0.029	-	HIGH
10 year recurrence-free survival, all patients. Follow-up 10.1 years. Trimbos et al (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	70% (62-76%)	62% (54-66%)	HR 0.64 (0.46 to 0.89) P=0.007	-	HIGH

Table 4.2 (Cont.)

No of studies	Design	\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ Quality assessment					No of patients		Summary of findings		
---	---	---	---	---	---	---	---	---	Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
10 year recurrence-free survival, optimally staged patients. Follow-up 10.1 years. Trimbos et al (2010)										
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	78% (66-86%)	72% (59-81%)	HR 0.73 (0.38-1.42) P=0.351	-	HIGH
10 year recurrence-free survival, non-optimally staged patients. Follow-up 10.1 years. Trimbos et al (2010)										
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	65% (56-73%)	56% (47-64%)	HR 0.60 (0.41 to 0.87) P=0.007	-	HIGH
10 year cancer-specific survival, patients with grade 3 disease. Follow-up 10.1 years. Trimbos et al (2010)										
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	75% (62-84%)	66% (51-74%)	HR 0.62 (0.34-1.12) P=0.108	-	HIGH

No of studies	Design	Quality assessment					No of patients		Summary of findings		
---	---	---	---	---	---	---	---	---	Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Other	3 cycles	6 cycles	Relative (95% CI)	Absolute	
Overall death rate 5 years. 6 cycles vs. 3 cycles. Follow-up 6.8 years. Bell et al (2006)										
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[5]	N/A	213	214	HR 1.02 (0.66 to 1.57) P=0.94		LOW
Rate of recurrence 5 years. 6 cycles vs. 3 cycles. Follow-up 6.8 years. Bell et al (2006)										
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	213	214	HR 0.76 (0.51 to 1.13) P=0.18		LOW

Table 4.2 (Cont.)

No of studies	Quality assessment						No of patients		Summary of findings		Quality
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other			Effect		
							3 cycles	6 cycles	Relative (95% CI)	Absolute	
Rate of recurrence. 6 cycles vs. 3 cycles. Follow-up 91 months. Serous tumours. Chan et al. (2010)											
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	60.4%	82.7%	HR 0.33 (0.14 to 0.77) P=0.007		LOW
Rate of recurrence. 6 cycles vs. 3 cycles. Follow-up 91 months. Non-serous tumours. Chan et al. (2010)											
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	78.6%	78.7%	HR 0.94 (0.60 to 1.49) P=0.806		LOW

[1] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.92) and >1.25 x the effect size (1.53). The result suggests no significant difference between comparators.

[2] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.50) and >1.25 x the effect size (0.84). The result suggests no significant difference between comparators.

[3] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.71) and >1.25 x the effect size (1.20). This may due to low sample number. The result suggests no significant difference between comparators.

[4] There were few details of the randomisation allocation or assessment blinding methodology given.

[5] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.76) and >1.25 x the effect size (1.28). The result suggests no significant difference between comparators.

[6] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.57) and >1.25 x the effect size (0.95). The result suggests no significant difference between comparators.

Recommendations

- Do not offer adjuvant chemotherapy to women who have had optimal surgical staging[3] and have low-risk stage I disease (grade 1 or 2, stage Ia or 1b).
- Offer women with high-risk stage I disease (grade 3 or stage Ic) adjuvant chemotherapy consisting of six cycles of carboplatin.
- Discuss the possible benefits and side effects of adjuvant chemotherapy with women who have had suboptimal surgical staging[3] and appear to have stage I disease.

Linking evidence to recommendations

Interventions that improve the likelihood of disease free survival are very important, but that benefit needs to be weighed against the morbidity and effects on overall quality of life. The GDG noted that there was some evidence suggesting adjuvant chemotherapy in stage I disease could reduce the risk of relapse and death from ovarian cancer. This evidence was limited and of varying quality on the basis of study quality assessed according to GRADE. The GDG was aware that there was a lack of data on both the toxicity associated with adjuvant chemotherapy and on how this affected quality of life.

In women whose risk of relapse was small the GDG felt the adverse effects and costs of adjuvant treatment would significantly outweigh any benefit from treatment and therefore did not recommend adjuvant chemotherapy.

The GDG was also aware that different women might place different personal value on the short-term adverse effects of treatment as well as on the possible long-term benefits. Therefore discussion of treatment options, as well as the option of no treatment was important.

The GDG noted that single agent platinum-based therapy, using 6 cycles of carboplatin, had demonstrated a survival benefit in women with early stage ovarian cancer. They were also aware that combination therapy had been shown to be more toxic than monotherapy and has not been evaluated in this setting. The GDG therefore decided to recommend 6 cycles of adjuvant carboplatin for most women.

This clinical question was considered a low priority for health economic evaluation because of the small patient numbers involved.

References

Bell, J., M. F. Brady, R. C. Young, J. Lage, J. L. Walker, K. Y. Look, G. S. Rose, N. M. Spirtos, and Gynaecologic Oncology Group (2006). Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynaecologic Oncology Group study. Gynaecol Oncol 102: 432-439.

Chan JK., Munro EG., Cheung MK., Husain A., Teng NN., Berek JS and Osann K (2007) Association of lymphadenectomy and survival in stage I ovarian cancer patients. Obstetrics and Gynecology 109: 12-19.

Chan JK, Tian C, Fleming GF, Monk BJ, Herzog TJ, Kapp DS et al. (2010). The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. Gynecol Oncol 116(3): 301-306.

Kim HS, Ju W, Jee BC, Kim YB, Park NH, Song YS et al. (2010) Systematic lymphadenectomy for survival in epithelial ovarian cancer a meta-analysis. Int J Gynecol Cancer 20(4):520-528.

---

[3] Optimal surgical staging constitutes midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment [Winter Roach et al. (2009) Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 3: CD004706]

Maggioni A., Benedetti PP., Dell'Anna T., Landoni F., Lissoni A., Pellegrino A., Rossi RS., Chiari S., Campagnutta E., Greggi S., Angioli R., Manci N., Calcagno M., Scambia G., Fossati R., Floriani I., Torri V., Grassi R and Mangioni C (2006) Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer 95: 699-704

National Institute for Health and Clinical Excellence (2003) Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal guidance 55. London: National Institute for Health and Clinical Excellence.

Suzuki S, Kajiyama H, Shibata K, Ino K, Nawa A, Sakakibara K, Matsuzawa K, Takeda A, Kinoshita Y, Kawai M, Nagasaka T and Kikkawa F (2008). Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? Ann.Oncol. 19: 1284-1287.

Trimbos B, Timmers P, Pecorelli S, Coens C, Ven K, van der Burg M et al.. (2010). Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial. J Natl Cancer Inst 102(13): 982-987.

Winter-Roach BA., Kitchener HC and Dickinson HO (2009). Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. Cochrane DB Sys Rev 2009, Issue 3. Art. No: CD004706. DOI: 10.1002/14651858.CD004706.pub3.

Yang X., Hou M., Yang K., Wang H., Peng., Cao Z and Mingrong X. (2007) Prognosis in epithelial ovarian cancer: clinical analysis of 287 pelvic and para-aortic lymphadenectomy. Chinese-German Journal of Clinical Oncology 6 (5): 492-496.

Yokoyama Y., Sakamoto T., Sato S and Saito Y (1999). Evaluation of cytoreductive surgery with pelvic and para-aortic lymphadenectomy and intermittent cisplatin-based combination chemotherapy for improvement of long-term survival in ovarian cancer. Eur J Gynaecol Oncol 20: 361-366.

5 Management of advanced (stage II-IV) ovarian cancer

The two objectives of this chapter were:

1. to assess the role of surgery in the treatment of women with advanced stage (II-IV) ovarian cancer and to determine the optimal timing of surgery within the treatment pathway

2. to determine the clinical benefits and toxicity of intraperitoneal chemotherapy given as part of the first-line management of advanced stage (II-IV) ovarian cancer.

5.1 The value of primary surgery

Surgery can be either primary (performed for the first time, either before or after chemotherapy) or secondary (performed after primary surgery). Secondary surgery can be sub-classified into either being early, when performed during chemotherapy (usually termed interval debulking surgery or IDS) or late when performed after primary chemotherapy (also called second-look laparotomy).

Historically, surgery has been an integral part of treating ovarian cancer, and before the advent of radiotherapy and chemotherapy, the only treatment. This historical fact accounts for why surgery came to occupy the position it does without formal scrutiny. Surgery alone can be curative when cancer is confined to the ovaries but this is not the case for the majority of women with ovarian cancer. It is in this group of patients that the value of surgery, its optimal timing and extent are currently debated.

With the advent of active chemotherapy (in particular cisplatin) and its associated survival benefit, primary cytoreductive surgery became part of standard active treatment for advanced ovarian cancer, even in cases when all disease could not be removed. The rationale for early cytoreductive surgery as part of primary management was to improve tumour chemo-sensitivity and avoid chemo-resistance (Goldie & Coleman 1979: Skipper 1974). The improvement in survival seen with the advent of platinum-based therapy has occurred despite a disparity in surgical success rates. The beneficial effects of cytoreductive surgery in advanced disease are only seen in conjunction with active chemotherapy and the independent contribution of surgery in this context remains to be established.

Many studies show an association between survival and the amount of postoperative residual disease but these studies are retrospective. Although the disease remaining at the end of the operation is a powerful adverse prognostic factor, it cannot be assumed that this association is one of 'cause and effect'. Consequently, debate ensues as to whether the benefit accrued is a function of the surgery (and surgeon) or of the biological nature of the disease. There are studies that show an association between the type of surgeon and surgical outcome, both in terms of achieving optimal cytoreduction rates (however defined) and survival (Bristow et al 2002; Chen et al 1985; Eisenkop et al 1992; Junor et al 1994;

Junor et al 1999; Kehoe et al 1994; Woodman et al 1997). This may be because some gynaecological oncologists achieve higher optimal cytoreductive rates than other surgeons but it might also reflect other patient factors (for example, patients with intestinal obstruction are more likely to present to general surgeons, require emergency surgery and have poorer prognostic factors such as ascites and poor performance scores). It is recognised that optimal resection rates between centres can vary considerably, ranging from 25 – 75% and that gynaecological oncologists can achieve high rates of cytoreduction in cases deemed to be unresectable by less experienced surgeons (Bristow et al 2002). This was the rationale behind the recommendation in 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) that "surgery for ovarian cancer should be carried out by specialised gynaecological oncologists at Cancer Centres"

Two approaches have developed to optimise cytoreduction rates, namely the development of more extensive surgery and neoadjuvant chemotherapy. In the last 10-20 years, there has been an increasing adoption of complex upper abdominal procedures, such as peritoneal stripping, splenectomy and distal pancreatectomy to accomplish optimal cytoreduction with acceptable morbidity. Retrospective studies, with the attendant problems of selection bias, have shown improved optimal cytoreduction rates and suggest an associated survival benefit in selected patients (Aletti et al 2006; Bristow et al 1999; Eisenhauer et al 2006; Wimberger 2007). Differences in survival rates noted between institutions might be attributable to differences in surgery but could also be due to other variables.

The move towards extensive surgery has been coupled with a greater stringency as to what constitutes optimal cytoreduction; this is increasingly being defined as removal of all macroscopic disease (Chi *et al.*, 2006; DuBois & Harter 2006; Wimberger *et al.*, 2007). Such extensive surgery can be complicated and carry a significant risk of morbidity. Furthermore, the patient's medical condition might preclude extensive primary surgery. Consequently induction or neoadjuvant chemotherapy have been used to reduce tumour burden and facilitate surgery, possibly optimising cytoreduction and reducing morbidity.

This approach has been used in the primary management of ovarian cancer in two situations; either as induction chemotherapy after initial primary surgery and before a second operation (termed interval debulking surgery) or as neoadjuvant chemotherapy prior to primary surgery. Interval debulking surgery (IDS) is usually performed after 2 to 4 cycles of chemotherapy so as to prevent the development of chemo-resistance.

A number of studies have reported optimal cytoreduction rates comparable to best results achieved at primary surgery (Chan et al 2003; Giannopoulos et al 2006; Jacob et al 1991; Lawton et al 1989) and that these results can be achieved with less associated morbidity.

These data, from primary surgery prior to chemotherapy, or from primary surgery after neoadjuvant chemotherapy or after IDS, all confirm the prognostic value of post-operative residual disease status. But fundamental questions remain: is primary surgery prior to chemotherapy more beneficial than after neoadjuvant chemotherapy; and does primary surgery in women with advanced ovarian cancer have a therapeutic value in terms of overall survival, especially when all macroscopic disease cannot be removed?

Clinical question: What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?

Clinical evidence

The evidence for this topic was limited and consisted of two Cochrane systematic reviews and two small randomised controlled trials (RCTs) which dealt with different aspects of surgery (Table 5.1). The total number of women across studies was 1,206 and all but stage I disease was represented. None of the studies addressed patient quality of life.

Morrison *et al.*, (2007) conducted a Cochrane review of chemotherapy versus surgery for the initial treatment of advanced ovarian cancer. Despite an extensive search of the literature, the authors identified only one small RCT which had randomised 85 women to receive either one cycle of chemotherapy followed by embolisation of the ovarian artery, debulking surgery and adjuvant chemotherapy or debulking surgery and adjuvant chemotherapy only. There was no statistically significant difference in median overall survival (26 months [95%CI: 19.2-32.8 months] versus 25 months [95%CI: 22.8-27.2 month]) (P>0.05)) between treatments. The chemo-embolisation arm did experience less surgery related morbidity but no other adverse events were reported.

Tangitjamol *et al.*, (2009) reviewed three RCTs in which women with ovarian cancer who had undergone sub-optimal primary surgery were randomised to chemotherapy with interval debulking surgery (IDS) or chemotherapy without IDS. There was significant between studies heterogeneity and so the authors performed sub-group analyses. They concluded that if women had received their primary surgery from a general surgeon, as opposed to a gynaecological oncologist, or had received less extensive surgery, then IDS showed a marginal survival benefit (RR=0.68 [95%CI: 0.53-0.87] P=0.003). There was no statistically significant difference between study arms in terms of either adverse events or quality of life.

Nicoletto *et al.*, (1997) randomised 102 women with ovarian cancer, who had an apparently complete clinical response to primary surgery and adjuvant chemotherapy, to either second-look surgery or a watch and wait policy. After a mean follow-up of 70 months the authors could demonstrate no significant difference in overall survival (HR=0.68 [95%CI: 0.28-1.64] P=0.39) even though patients with a positive second-look surgery were subsequently treated with non cross-reactive chemotherapy. Luesley *et al.*, (1988) recruited women with ovarian cancer who had received primary surgery (but were left with residual disease) and adjuvant cisplatin, randomising them to receive either second-look surgery followed by chemotherapy with chlorambucil or pelvic irradiation. A third group received chemotherapy only. With an average follow-up of 46 months, there was no significant difference in median overall survival between the two surgical groups (21 months [95%CI: 11-31 months] versus 15 months [95%CI: 11-19 months)] P=0.75)) or between the surgery plus chemotherapy group versus the chemotherapy only group (21 months [95%CI: 11-31 months] versus 17 months [95%CI: 13-21 months] P=0.75)).

Vergote *et al.*, (2010) reported the results from a multi-centre randomised controlled trial for which women with stage IIIC-IV ovarian cancer were recruited from 1998 to 2006. The study compared interval debulking surgery (three cycles of platinum-based chemotherapy before and after surgery) versus primary surgery followed by six cycles of platinum based chemotherapy. The groups showed significant equivalent overall survival (HR of death: 0.98 (90%CI: 0.84-1.13) (P<0.01 for non-inferiority) but equivalence could not be demonstrated for progression-free survival (HR 1.01 (90%CI: 0.89-1.15). There were little comparative data reported on adverse events or quality of life. This study may have been underpowered (only 89% of the intended numbers were recruited and went on to treatment) which may make it difficult to confidently interpret the outcomes.

Table 5.1 GRADE profile: What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?

| | Quality assessment | | | | | | Summary of findings | | | | |
| | | | | | | | Time in months | | Effect | | |
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemotherapy before surgery	Chemotherapy after surgery	Relative (95% CI)	Absolute	Quality
Mean OS (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	33.7 (95%CI: 24.7-42.6)	32.4 (95%CI: 24.9-39.8)	-	-	LOW
Median OS (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	26 (95%CI: 19.2-32.8)	25 (95%CI: 22.8-27.2)	-	-	LOW
Median DFI (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	18.2 (no 95%CI)	14.2 (no 95%CI)	-	-	LOW
Overall survival (^{2}= 6.48; P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	-	-	-	-	LOW

[1] This was a non-English language study that had not apparently been translated by the Cochrane reviewers. Although the original study authors stated that they had randomised patients, there were no details of randomisation or allocation and blinding of outcome assessors was not mentioned. Intention to treat (ITT) analysis was used but treatment withdrawals were no discussed.

[2] The Kaplan Meier plot and tables accompanying the text of Liu *et al.*, (2004) were not accessible and may have included more data with regard to survival. However this was a low patient number trial. Patients: women with stage III (actually II) or IV EOC; Intervention: neoadjuvant intra-arterial chemo (1 cycle), ovarian artery embolisation then primary surgery followed by adjuvant i.v. chemo (7 cycles) (n=42); Control: primary surgery followed by adjuvant i.v. chemo (8 cycles) (n=43).

Table 5.1 (Cont.)

		Quality assessment					Summary of findings				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Patients		Effect		Quality
							Interval debulking surgery	No interval debulking surgery	Relative (95% CI)	Absolute	
Risk of death (P=0.04) (if surgery was performed by general surgeons). Follow-up 42-48 months. Tangjitgamol et al., 2009											
2	RCT	no serious limitations[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	N/A	177	180	RR=0.68 (0.53-0.87)	-	HIGH
Risk of death (P=0.9) (if surgery was less extensive or performed by gynaecological surgeons). Follow-up 42-48 months. Tangjitgamol et al., 2009											
1	RCT	no serious limitations[1]	N/A	no serious indirectness	no serious imprecision	N/A	216	208	RR=0.99 (0.79-1.24)	-	HIGH
Toxic reactions to chemotherapy (P=0.7). Follow-up 42-48 months. Tangjitgamol et al., 2009											
2	RCT	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	N/A	7/177	6/180	RR=1.23 (0.42-3.56)	1 fewer per 100	MODERATE

[1] The three included studies in this systematic review were described by the authors as having given sufficient details of randomisation and allocation but blinding of treatment assessors was not described. All studies used intention to treat (ITT) analysis.

[2] The original pooled data for survival from the three included studies showed significant heterogeneity (I^2=58%) and the authors addressed this by stratifying data by surgical speciality, as shown in the table.

[3] The confidence interval around the estimate of effect spans '1' (the line of no effect) and the limits for 'appreciable harm' and 'appreciable benefit'.

Table 5.1 (Cont.)

	Quality assessment						Summary of findings				
							Patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	2nd look surgery	Watchful waiting	Relative (95% CI)	Absolute	
Overall survival (x^2=0.74; P=0.39). Follow-up ~70 months. Nicoletto et al., 1997											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	54	48	HR=0.68 (0.28-1.64)	-	LOW

[1] This study did not demonstrate adequate details of randomisation, allocation or blinding of treatment assessors. The study used intention to treat (ITT) analyses.
[2] The confidence interval is wide and crosses the line of no effect as well as exceeding limits for 'appreciable harm' and 'appreciable benefit'. This is probably due to the low patient number

	Quality assessment						Summary of findings			
							Patients			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	[A] 2nd look surgery then chemotherapy	[B] 2nd look surgery then radiotherapy	[C] Chemotherapy	
Median survival (A vs. B: x^2=0.11; P=0.75; A vs. C: x^2=0.11; P=0.75). Follow-up 46 months (range: 21-64 months). Luesley et al., 1988										
1	RCT	very serious limitations[1]	N/A	no serious indirectness	very serious imprecision[2]	N/A	21 months (95%CI: 11-31 months) N=42/53	15 months (95%CI: 11-19 months) N=49/56	17 months (95%CI: 13-21 months) N=44/57	VERY LOW

[1] This study did not demonstrate adequate details of randomisation, allocation, blinding of treatment assessors or intention to treat (ITT) analysis.
[2] The comparison of Group A vs. Group C may be unsafe since, on the Kaplan Meier plot shown, the lines representing each population cross several times. The statistics (chi square and P value) from Groups A vs. B and A vs. C are identical which may be accurate or not. The study is probably underpowered to detect a significant difference between study arms.

Recommendation

- If performing surgery for women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease.

Linking evidence to recommendations

The GDG placed a high value on the outcomes of survival and morbidity. They noted that the evidence, using the GRADE quality assessment tool, concerning surgery was limited, of poor quality, contradictory and open to interpretation. Therefore the GDG made recommendations for further research into the effectiveness of surgery.

The GDG noted that in one RCT (Rose et al., 2004), the primary surgery had been performed by gynaecological oncologists, and interval debulking surgery conferred no significant overall survival benefit. In the two other RCTs (Redman 1994 et al., and Van der Burg et al., 1995) the primary operations were predominantly performed by general surgeons or gynaecologists in various hospitals and the sub-group met-analysis interval debulking surgery performed in this group of patients appeared to confer a survival benefit. This might suggest a value for cytoreductive surgery when done properly but the authors of the analysis emphasised that these results have to be interpreted with caution.

This clinical question was considered a low priority for economic analysis because although the number of patients involved could potentially be large, there was considerable uncertainty over the health benefits of performing surgery, due to a lack of RCT data.

Research recommendation

- Research should be undertaken to determine the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised.

5.2 Intraperitoneal chemotherapy

Ovarian cancer commonly involves the peritoneal surfaces of the intra-abdominal cavity without distant metastatic spread. Efforts to directly target small volume tumour deposits have included the use of intra-peritoneal stripping, monoclonal antibodies, radionuclides and intraperitoneal chemotherapy. The most promising of these strategies is intraperitoneal chemotherapy and several studies have shown a moderate improvement in disease free and overall survival. Most of these trials are dated, being carried out in the early 1990s, involving agents such as cisplatin and cyclophosphamide, now considered inferior to the current agents of carboplatin with or without paclitaxel.

Two more recent trials have reignited the interest in intraperitoneal chemotherapy and confirmed the feasibility of administering paclitaxel by this route. Both trials reported significant immediate toxicities and further research is urgently needed.

Clinical question: For women with ovarian cancer, is intraperitoneal chemotherapy effective in primary management?

Clinical evidence

The evidence for this topic comprises two high quality systematic reviews (Jaaback and Johnson, 2006; Elit *et al.*, 2007) and one randomised controlled trial (RCT) (Wenzel *et al.*, 2007) (Table 5.2). Between them, these studies reported on all the outcomes of interest. The two systematic reviews included meta-analyses of data from the same RCTs but both reviews were appraised because the authors reported different survival outcomes. The majority of trial data derived from the United States of America and all the studies compared the use of standard intravenous chemotherapy with chemotherapy regimens incorporating a component of intra-peritoneal drug delivery for the first line adjuvant treatment of primary ovarian cancer.

High quality evidence from pooled data from up to eight trials suggested that chemotherapy given directly into the peritoneal cavity as part of adjuvant treatment, may significantly reduce the risk of death (HR: 0.80 [95%CI: 0.71-0.90] P=0.0003) and disease recurrence (HR: 0.79 [95%CI: 0.69-0.90] P=0.0004) an effect also seen after five years of follow-up (RR of death: 0.88 [95%CI: 0.81-0.95] P=0.002; RR of disease progression: 0.91 [95%CI: 0.85] P=0.02). However, incidences of pain, fever, fatigue, hearing loss, infection and gastrointestinal and metabolic effects occurred up to eight times more frequently in women receiving intra-peritoneal chemotherapy. The one exception to this observation was the incidence of cardiovascular effects which were not significantly different between study arms. The evidence about haematological, pulmonary, renal and neurological adverse effects was too poor in quality to allow conclusions to be drawn about the relative contribution of the drug delivery route. Health-related quality of life was measured in one trial and found to be significantly worse for women receiving intra-peritoneal chemotherapy in the early days of treatment and shortly (3 to 6 weeks) after all study treatment, but a difference between study arms was not apparent after one year of follow-up.

Table 5.2 GRADE profile: For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management

No of studies	Quality assessment						No of patients		Summary of findings		Quality
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Effect		
									Relative (95% CI)	Absolute	
Time to death (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	895	924	HR 0.80 (0.71 to 0.9) P=0.000333		MODERATE
Time to death (high quality studies only) (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
5	randomised trials	no serious limitations[2,4]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	808	833	HR 0.79 (0.7 to 0.89) P=0.00021		HIGH
Time to recurrence (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	no serious limitations[2,5]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	519	526	HR 0.79 (0.69 to 0.9) P=0.00044		HIGH
Time to recurrence (high quality studies only) (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
3	randomised trials	no serious limitations[2,6]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	486	491	HR 0.78 (0.68 to 0.89) P=0.00025		HIGH
Survival (risk of death) 5 years (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Elit et al. (2007).											
6	randomised trials	no serious limitations[7]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	439/851 (51.6%)	531/886 (59.9%)	RR 0.88 (0.81 to 0.95) P=0.002	7 fewer per 100 (from 30 fewer to 114 fewer)	HIGH
Progression-free survival (risk of progression) at 5 years (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Elit et al. (2007).											
3	randomised trials	no serious limitations[6]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	352/496 (71%)	384/494 (77.7%)	RR 0.91 (0.85 to 0.98) P=0.02	7 fewer per 100 (from 16 fewer to 117 fewer)	HIGH

Table 5.2 (Cont.)

No of studies	Design	Quality assessment					No of patients		Summary of findings Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95 % CI)	Absolute	
Adverse effects anaemia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[20]	N/A	79/383 (20.6%)	91/429 (21.2%)	RR 0.97 (74 to 1.26) P=0.80	1 fewer per 100 (from 6 more to 1548 more)	LOW
Adverse effects thrombocytopenia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[3]	very serious[13,14]	no serious indirectness	serious[20]	N/A	169/867 (19.5%)	65/912 (1.1%)	RR 1.16 (0.33 to 4.06) P=0.81	1 more per 100 (from 5 fewer to 22 more)	VERY LOW
Adverse effects leukopenia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[3]	very serious[13,15]	no serious indirectness	no serious imprecision[19]	N/A	477/867 (55%)	482/912 (52.9%)	RR 0.94 (0.75 to 1.19) P=0.63	3 fewer per 100 (from 13 fewer to 10 more)	VERY LOW
Adverse effects renal. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[5]	serious[13,16]	no serious indirectness	no serious imprecision[19]	N/A	22/518 (4.2%)	8/527 (1.5%)	RR 2.55 (0.8 to 8.1) P=0.11	2 more per 100 (from 0 fewer to 11 more)	LOW
Adverse effects pulmonary. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	serious[13,17]	no serious indirectness	no serious imprecision[19]	N/A	10/455 (2.2%)	6/486 (1.2%)	RR 2.9 (0.49 to 17.36) P=0.24	2 more per 100 (from 1 fewer to 20 more)	MODERATE
Adverse effects cardiovascular. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision[19]	N/A	27/440 (6.1%)	16/437 (3.7%)	RR 1.69 (0.93 to 3.09) P=0.085	3 more per 100 (from 0 fewer to 8 more)	HIGH

Table 5.2 (Cont.)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	No of patients		Effect		Quality
							IP chemo-therapy	IV chemo-therapy	Relative (95 % CI)	Absolute	
Adverse effects fever. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	47/736 (6.4%)	26/767 (3.4%)	RR 1.92 (1.2 to 3.06) P=0.0063	3 more per 100 (from 1 more to 7 more)	HIGH
Adverse effects fatigue. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	43/440 (9.8%)	12/437 (2.7%)	RR 3.63 (1.95 to 6.74) P=0.00046	7 more per 100 (from 3 more to 16 more)	HIGH
Adverse effects gastrointestinal. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[5]	serious[17]	no serious indirectness	no serious imprecision	N/A	202/518 (39%)	117/527 (22.2%)	RR 1.60 (1.13 to 2.25) P=0.0079	13 more per 100 (from 3 more to 28 more)	LOW
Adverse effects infection. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	44/440 (10%)	16/437 (3.7%)	RR 2.78 (1.6 to 4.82) P=0.00029	7 more per 100 (from 2 more to 14 more)	HIGH
Adverse effects metabolic. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	andomized trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	78/440 (17.7%)	18/227 (7.9%)	RR 4.38 (2.68 to 7.15) P<0.00001	27 more per 100 (from 13 more to 49 more)	HIGH
Adverse effects neurological. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
5	andomized trials	no serious limitations[11]	serious[13,18]	no serious indirectness	serious[20]	N/A	108/768 (14.1%)	99/803 (12.3%)	RR 1.18 (0.66 to 2.05) P=0.58	2 more per 100 (from 4 fewer to 13 more)	LOW

Summary of findings

Table 5.2 (Cont.)

No of studies	Quality assessment						No of patients		Summary of findings		Quality
	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Effect		
									Relative (95% CI)	Absolute	
Adverse effects pain. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	68/455 (14.9%)	9/486 (1.9%)	RR 8.13 (4.11 to 16.1) P<0.00001	13 more per 100 (from 6 more to 28 more)	HIGH
Adverse effects hearing loss. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
3	randomised trials	no serious limitations[12]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	36/487 (7.4%)	59/522 (11.3%)	RR 0.67 (0.46 to 0.99) P=0.044	4 fewer per 100 (from 0 fewer to 6 fewer)	HIGH
QOL at baseline (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	198	201	-	MD 3.6 higher (0.61 to 6.59 higher)[21] P=0.018	HIGH
QOL at baseline (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	198	201	-	MD 1.8 higher (0.43 to 2.97 higher)[21] P=0.007	HIGH
QOL before cycle 4 (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	148	172	-	MD 6.6 higher (4.95 to 11.45 higher) P<0.001	HIGH

Table 5.2 (Cont.)

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	No of patients		Effect		Quality
			Quality assessment				IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute (Summary of findings)	
QOL before cycle 4 (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	148	172	-	MD 2.9 higher (2.27 to 4.73 higher) P<0.001	HIGH
QOL 3-6 weeks after treatment (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	159	171	-	MD 4.6 higher (2.89 to 9.51 higher) P=0.002	HIGH
QOL 3-6 weeks after treatment (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	159	171	-	MD 1.3 higher (0.4 to 2.1 higher) P=0.041	HIGH
QOL 1 year after treatment (FACT-G) (measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	139	140	-	MD 0.3 higher (1.47 lower to 5.47 higher) P=0.85	HIGH
QOL 1 year after treatment (FACT-O subscale) (measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel et al. (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	139	140	-	MD 0.2 higher (1.15 lower to 1.55 higher) P=0.71	HIGH

[1] 7/8 trials reported duration of follow-up which in 3 trials was stated to be >60 months.
[2] The review authors reported and assessed the allocation method, concealment, assessor blinding and intention-to-treat for all studies. On this basis they judged 3 studies to be 'good', 2 studies as 'fair' and 3 studies as 'poor' in quality. Details of loss to follow-up are not reported for individual studies or overall.
[3] For this outcome, 3 papers have been graded 'good', 2 as 'fair' and 2 as 'poor'.

4 For this outcome, 3 papers have been graded 'good' and 2 as 'fair'.

5 For this outcome, 2 papers have been graded 'good', 1 as 'fair' and 1 as 'poor'.

6 For this outcome, 2 papers have been graded 'good' and 1 as 'fair'.

7 For this outcome, 1 paper has been graded 'good', 2 as 'fair' and 1 as 'poor'.

8 For this outcome, 3 papers have been graded 'good', 2 as 'fair' and 1 as 'poor'.

9 For this outcome, 2 papers have been graded 'good'.

10 For this outcome, 3 papers have been graded 'good' and 1 as 'fair'.

11 For this outcome, 3 papers have been graded 'good', 1 as 'fair' and 1 as 'poor'.

12 For this outcome, 2 papers have been graded 'good' and 1 as 'poor'.

13 High levels of between studies heterogeneity in adverse effects outcomes are explained adequately in the review discussion highlighting the fact that different drugs, doses and regimes were used across studies. Also, 2/8 of the studies used extremely high doses of chemotherapy in the intraperitoneal chemotherapy which increased the likelihood of adverse events. The authors conclude that for leukopenia, thrombocytopenia, renal, neurological and pulmonary outcomes, data pooling (although undertaken) could be considered inappropriate.

14 Between studies heterogeneity was measured at 90%.

15 Between studies heterogeneity was measured at 80%.

16 Between studies heterogeneity was measured at 36%.

17 Between studies heterogeneity was measured at 59%.

18 Between studies heterogeneity was measured at 76%.

19 The 95% confidence interval crosses the line of no effect plus the lower value of the interval is <0.75 and/or upper value >1.25. But the event rate is <5% so study quality is not downgraded.

20 The 95% confidence interval crosses the line of no effect plus the lower value of the interval is <0.75 and/or upper value >1.25. But the event rate is >5% so study quality is downgraded

21 Calculated as a raw difference for data before randomisation and adjusted mean difference for all time points thereafter. NB. FACT-O score = scores of FACT-O subscale & FACT-G combined.

> **Recommendation**
>
> Do not offer intraperitoneal chemotherapy to women with ovarian cancer except as part of a clinical trial.

Linking evidence to recommendations

The GDG placed a high value on improving the outcomes of disease-free and overall survival, both of which were shown to benefit from the use of intra-peritoneal chemotherapy compared to standard intravenous chemotherapy.

However, the GDG recognised that intra-peritoneal chemotherapy was associated with more toxicity/adverse events than standard intravenous chemotherapy and that one study had shown health-related quality of life to be adversely affected by intra-peritoneal chemotherapy in the short term. The GDG also recognised that the administration of intra-peritoneal chemotherapy was more complex and more expensive than that for standard intravenous chemotherapy.

Although there was high-quality evidence (assessed according to GRADE analysis) on the use of intra-peritoneal chemotherapy, the GDG noted that the studies investigated historical drug regimens and did not investigate intra-peritoneal administration of drugs given intravenously in current standard UK regimens. There was also a lot of heterogeneity in the studies making it difficult to draw robust conclusions from the evidence. In addition, only one study presented quality of life data and so it was difficult to know if these data were representative. Based on this the GDG did not feel able to recommend the use of intra-peritoneal chemotherapy outside of clinical trials.

This clinical question was not considered to be a high priority for health economic evaluation due to a relatively small patient group and a lack of evidence related to current chemotherapy agents.

5.3 Chemotherapy regimens

Recommendations on first-line chemotherapy for ovarian cancer can be found in 'Guidance on the use of paclitaxel in the treatment of ovarian cancer', NICE technology appraisal guidance 55[1]. The recommendations which relate to first-line treatment are 1.1 and 1.2.

These recommendations refer to both early and advanced disease and should be read in conjunction with chapter 4.

References

Aletti GD, Dowdy SC, Gostout BS, et al. (2006) Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstet Gynecol 107: 77-75.

Bristow RE, Montz FJ, Lagasse LD, et al. (1999) Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol 72: 278-87.

Bristow RE, Tomacruz RS, Armstrong DK et al. (2002) Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 20: 1248-59.

Chan YM, Ng TY, Ngan HY et al. (2003) Quality of life in women treated with neoadjuvant chemotherapy for advanced ovarian cancer: a prospective longitudinal study. Gynecol Oncol 88: 9-16.

Chen SS, Bochner R. (1985) Assessment of morbidity and mortality in primary cytoreductive surgery fro advanced ovarian carcinoma. Gynecol Oncol 20: 190-5.

Chi DS, Eisenhauer EL, Lang J, et al. (2006) What is the primary goal of cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol 103: 559-64.

---

[1] http://guidance.nice.org.uk/TA55

Du Bois A, Harter P. (2006) The role of surgery in advanced and recurrent ovarian cancer. Ann Oncol 17: x235-40.

Eisenkop SM, Spirtos NM, Montag TW, et al. (1992) The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol 47: 203-09.

Eisenhauer EL, Abu-Rustum NR, Sonoda Y, et al. (2006) The addition of extensive upper abdominal surgery to achieve optimal cytoreduction improves survival in patients with stage IIIC-IV epithelial ovarian cancer. Gynecol Oncol 103: 1083-90.

Elit L., Oliver TK., Covens A., Kwon J., Fung MF., Hirte HW and Oza AM. (2007) Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. Cancer 109(4): 692-702.

Giannopoulos T, Butler-Manuel S, Taylor A, et al. (2006) Clinical outcomes of neoadjuvant chemotherapy and primary debulking surgery in advanced ovarian carcinoma. J Gynecol Oncol 27: 25-8.

Goldie JH, Coldman AJ. (1979) A mathematic model for relating drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 63: 1727-33.

Griffiths CT (1975) Surgical resection of tumour bulk in the primary treatment of ovarian carcinoma. Natl Cancer Inst Mono 42: 101–104.

Hacker NF, Berek JS, Lagasse LJ, Neilburg RK, Elasoff RM (1983) Primary cytoreductive surgery for epithelial ovarian cancer. Obstetrics and Gynecology Apr; 61(4): 413-20.

Jaaback K and Johnson N (2006). Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2006 Issue 1. Art. No. CD005340.

Jacob JH, Gerhenson DM, Morris M, et al. (1991) Neoadjuvant chemotherapy and interval debulking for advanced epithelial ovarian cancer. Gynecol Oncol 42: 146-50.

Junor EJ, Hole DJ, Gillis CR (1994) Management of ovarian cancer: referral to a multidisciplinary team matters. Br J Cancer 70:363–370.

Junor EJ, Hole DJ, McNulty L, et al. (1999) Specialist gynaecologists and survival outcome in ovarian cancer: A Scottish national study 1866 patients. Br J Obstet Gynaecol 106: 1130-36.

Kehoe S, Powell J, Wilson S, et al. (1994) The influence of the operating surgeon's specialisation on patient survival in ovarian cancer. Br J Cancer 70: 1014-17.

Lawton FG, Redman CW, Luesley DM, et al. (1989) Neoadjuvant (cytoreductive) chemotherapy combined with intervention debulking surgery in advanced, unresected epithelial ovarian cancer. Obstet Gynecol 73: 61-5.

Liu EL and Mi RR. (2004) Neoadjuvant intraarterial chemotherapy and embolization in treatment of advanced ovarian epithelial carcinoma. Chinese Medical Journal (Engl) 117(10):1547–51.

Luesley D, Blackledge G, Kelly K, Wade-Evans T, Fielding J, Lawton F, Hilton C, Rollason T, Jordan J, Latief T, Chan KK. (1988) Failure of second-look laparotomy to influence survival in epithelial ovarian cancer. Lancet 332 (8611): 599-603

Lyngstadaas A, Ekanger R, Hagen B, et al. (2005) Primary treatment of ovarian cancer. Tidsskr Nor Laegeforen 125:278–281.

Morrison J, Swanton A, Collins S, Kehoe S. (2007) Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. Cochrane Database of Systematic Reviews 2007, Issue 4. Art. No.: CD005343. DOI: 10.1002/14651858.CD005343.pub2.

National Institute for Health and Clinical Excellence (2003) Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal guidance 55. London: National Institute for Health and Clinical Excellence.

Nicoletto MO, Tumolo S, Talamini R, Salvagno L, Franceschi S, Visona E, Marin G, Angelini F, Brigato G, Scarabelli C, Carbone A, Cecchetto A, Prosperi A, Rosabian A, Giusto M, Cima GP, Morassut S, Nascimben O, Vinante O, Fiorentino MV. (1997) Surgical second look in ovarian cancer: a randomized study in patients with laparoscopic complete remission--a Northeastern Oncology Cooperative Group-Ovarian Cancer Cooperative Group Study. J Clin Oncol. 15(3): 994-9.

Parker RT, Parker CH, Willbanks GD (1980) Cancer of the ovary: survival studies based upon operative therapy, chemotherapy and radiotherapy. Am J Obstet Gynecol 108;878-888.

Redman CW, Warwick J, Luesley DM et al., (1994). In Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. (2009) Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub4.

Rose PG. et al., (2004). In Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. (2009) Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub4.

Skipper HE. (1974) Thoughts on cancer chemotherapy and combination modality treatment. JAMA 230:1033-5.

Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. (2009) Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub4.

Van der Burg ME et al., (1995) In Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. (2009) Interval debulking surgery for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews 2009, Issue 2. Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub4.

Vergote CG, Trope F, Amant GB, Kristensen T, Ehlen N, Johnson RH, Verheijen ME, van der Burg AJ, Lacave PB, Panici GG, Kenter A, Casado C, Mendiola C, Coens L, Verleye GC Stuart, Pecorelli S and Reed NS. (2010). Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N.Engl.J.Med. 363(10): 943-953.

Wenzel LB., Huang HQ., Armstrong DK., Walker JL and Cella D. (2007) Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: A Gynecologic Oncology Group Study. J Clin Oncol 25 (4): 437-443.

Wharton JT, Edwards CL, Rutledge FN (1984) Long term survival after chemotherapy for advanced ovarian epithelial carcinoma. Am J Obstet Gynecol 148;997-1005.

Wimberger P, Lehmann N, Kimmig R, et al. (2007) Prognostic factors for complete debulking in advanced ovarian cancer and its impact on survival. An exploratory analysis of a prospectively randomized phase III study of the Arbeitsgemeinshaft Gynaekologische Onkologie Ovarian Caner Study Group (AGO-OVAR). Gynecol Oncol 106: 69-74.

Woodman C, Baghdady A, Collins S, et al. (1997) What changes in the organisation of cancer services will improve the outcome for women with ovarian cancer? Br J Obstet Gynaecol 104: 135-39.

6 Support needs of women with newly diagnosed ovarian cancer

Previous guidance on 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) made recommendations on a number of patient perspectives related to gynaecological cancer. These included the need for effective communication, delivery of relevant and timely information, and psychosocial and psychosexual support and counselling.

In addition NICE service guidance 'Improving palliative and supportive care for adults with cancer' (NICE, 2004) has set standards to ensure that patients with cancer, along with their families and carers, receive the support and care to help them cope with cancer and its treatment at all stages.

Healthcare professionals involved in the care of women with ovarian cancer are expected to implement the recommendations made in 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) and 'Improving supportive and palliative care for adults with cancer' (NICE, 2004). Implementation of these recommendations is monitored by the National Cancer Peer Review Programme in England. This programme involves self assessment by MDTs and external reviews of teams conducted by professional peers against nationally agreed peer review measures[1]. In Wales there is a similar process of self assessment against national minimum standards for gynaecological cancers[2].

This section of the guideline specifically focuses on the support needs of women newly diagnosed with ovarian cancer, and the psychosocial and psychosexual issues that are particular to them.

Women diagnosed with ovarian cancer have a range of information and support needs, whose types and timing are as varied as the people reporting them. These needs tend to be connected with treatment, its side effects, the disease and its prognosis, as well as issues regarding sexuality.

The Department of Health guidance 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) included recommendations about psychosocial support and psychosexual counselling and stated that "psychosocial support should be available at every stage to help patients and their families to cope with the effects of the disease and its treatment". In addition, "specialist interventions should be available for women and their partners to help them to understand and cope with the effects of treatment on sexual relationships". The guidance recommends that each patient should have access to a named oncology clinical nurse specialist with counselling expertise.

---

[1] http://www.cquins.nhs.uk/?menu=resources

[2] http://wales.gov.uk/topics/health/publications/health/guidance/nationalstandardscancer?lang=en

Clinical question: For women newly diagnosed with ovarian cancer, what support should be offered?

Clinical evidence

Evidence from qualitative studies suggests that most women with ovarian cancer need emotional support. 'Improving outcomes in gynaecological cancers (Department of Health, 1999), made a series of recommendations to improve supportive care in this group. However, there is evidence from the Pathfinder study (Target Ovarian Cancer, 2009) that emotional support needs still go unmet in a minority of patients.

Clinical nurse specialists play an important role in emotional support for women with ovarian cancer (Jefferies, 2002; Target Ovarian Cancer, 2009), but there is evidence that there is variation in the workloads of nurse specialists and the resources available to them (Target Ovarian Cancer, 2009). In the Pathfinder study only 55% of the women who responded were given contact details for a clinical nurse specialist at the time of diagnosis. Over a third of the women who responded (36%) were not given any contact details at all and 25% of women who responded stated that support needs go unmet. Most women who responded (84%) had access to a clinical nurse specialist at some point during their cancer journey.

Women reported a range of information and support needs, reflecting different values, preferences and circumstances. However certain types of information and support needs were more commonly reported than others. Women were most likely to report information and support needs connected with their treatment and its side effects and their disease and prognosis (Beesley *et al.,* 2008; Browall *et al.,* 2004; Steele and Fitch 2008; Fitch and Steele, 2010).

Power *et al.,* (2008) reported that many patients expressed a desire not to find out all the information they could about their condition, and they purposefully avoided dealing with it whenever possible as a "coping strategy".

Recommendations

- Offer all women with newly diagnosed ovarian cancer information about their disease, including psychosocial and psychosexual issues, that:
  - is available at the time they want it
  - includes the amount of detail that they want and are able to deal with
  - is in a suitable format, including written information.
- Ensure that information is available about:
  - the stage of the disease, treatment options and prognosis
  - how to manage the side effects of both the disease and its treatments in order to maximise well being
  - sexuality and sexual activity
  - fertility and hormone treatment
  - symptoms and signs of disease recurrence
  - genetics, including the chances of family members developing ovarian cancer
  - self-help strategies to optimise independence and coping
  - where to go for support, including support groups
  - how to deal with emotions such as sadness, depression, anxiety and a feeling of a lack of control over the outcome of the disease and treatment.

Linking evidence to recommendations

The GDG placed a high value on patient support but recognised there were continuing variation and gaps in service support and delivery. The GDG felt this variation led to unmet needs which need to be overcome.

There was good quality evidence highlighting the need for the relevant information, tailored to the needs of the individual women, to be offered to women at the time that most suits their individual practical and psychological needs. The GDG noted that immediately after diagnosis, a woman's most pressing information needs related to treatment, its side effects, the disease and her prognosis. Other information including psychosocial and psychosexual issues, although important was not ranked as highly at this time. The GDG therefore felt it was important to make recommendations on both of these areas.

This clinical question was not considered amenable to health economic evaluation as there was no comparative analysis.

References

Beesley V, Eakin E, Steginga S, Aitken J, Dunn J and Battistutta D. (2008) Unmet needs of gynaecological cancer survivors: implications for developing community support services. Psycho-Oncology 17(4): 392-400

Browall M, Carlsson M and Horvath GG. (2004) Information needs of women with recently diagnosed ovarian cancer--a longitudinal study. Eur J Oncol Nursing 8(3): 200-7

Department of Health (1999) Improving outcomes in gynaecological cancers. Service guidance. Available from www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005385

Fitch M and Steele R (2010). Identifying supportive care needs of women with ovarian cancer. Canadian Oncology Nursing Journal, 20, 66-74.

Jefferies H. (2002) Ovarian cancer patients: are their informational and emotional needs being met? J Clin Nursing 11(1): 41-7

National Institute for Clinical Excellence (2004) Improving supportive and palliative care for adults with cancer. NICE cancer service guidance. London: National Institute for Clinical Excellence

Power J, Brown L and Ritvo P. (2008) A qualitative study examining psychosocial distress, coping, and social support across the stages and phases of epithelial ovarian cancer. Health Care for Women International 29(4): 366-83

Steele R and Fitch MI. (2008) Supportive care needs of women with gynecologic cancer. Cancer Nursing 31(4): 284-91

Target Ovarian Cancer. (2009) Mapping the experiences of those living or working with ovarian cancer in the UK. The Target Ovarian Cancer Pathfinder Study.

Appendix 1

A cost-utility analysis of diagnostic investigations in primary care for women with symptoms of ovarian cancer

Introduction

Around 6,700 new cases of ovarian cancer are diagnosed each year in the UK (CancerResearch UK, 2007) with an overall five-year survival of about 80% in women diagnosed with early disease (stage I-II) and 25% in women with advanced disease (stage III-IV) (Hamilton *et al.*, 2009). For women presenting with symptoms in primary care, accurate diagnostic information at this stage enables timely referral which subsequently plays a vital role in the choice of treatment and achievable survival.

This clinical question was highlighted as a priority for economic analysis because of the large number of patients with symptoms suggestive of ovarian cancer. In addition, there are significant differences in costs and health outcomes associated with the different diagnostic pathways, as well as the considerable economic burden of treating ovarian cancer.

Objective

To assess the cost-effectiveness of diagnostic strategies in primary care for women presenting with symptoms suggestive of ovarian cancer.

Methods

Economic evaluations of a diagnostic investigation require evidence on a number of issues, including disease prevalence and test accuracy. Furthermore, the accurate estimation of cost-effectiveness of one diagnostic strategy over another requires the consideration of downstream treatment effects, health-related preferences (utilities), healthcare resource use and unit costs. Therefore, the evaluation was undertaken by synthesizing evidence from a number of different sources using decision analytic techniques.

Study population

The population considered within the analysis consisted of women presenting in primary care with symptoms consistent with suspected ovarian cancer.

Perspective

This analysis was carried out from the perspective of the UKs National Health Service (NHS), in line with NICEs methodological recommendations. Health outcomes were expressed in terms of quality-adjusted life-years (QALYs).

Interventions

Given the large number of different diagnostic tests and potential combinations, a decision was made at the outset to limit the number of interventions to those that were listed by the Guideline Development Group (GDG) in the PICO tables for this clinical question. In all, seven core strategies were evaluated. To capture downstream consequences following the initial referral,

the members of the GDG were asked to identify clinical pathways that were reflective of current UK clinical practice (Table A1.1).

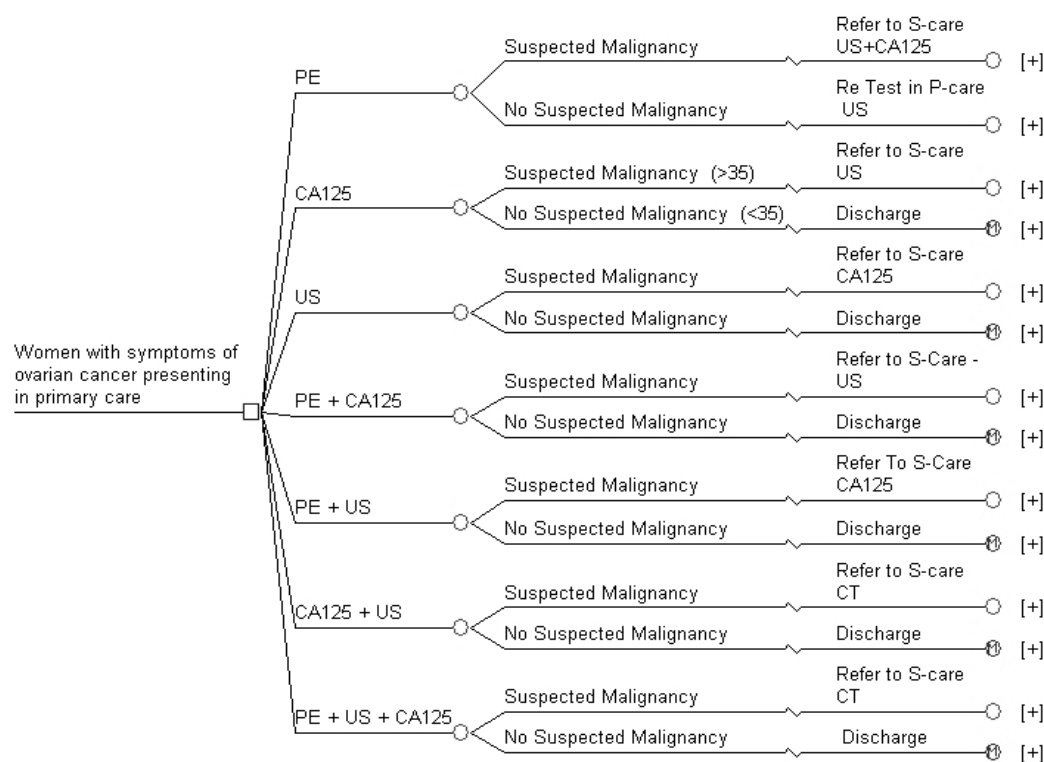**Table A1.1** Summary of diagnostic strategies

Strategy	Primary care diagnostic investigation(s)	Secondary care diagnostic investigation(s) (following referral)
1	Pelvic examination	Serum CA125 and ultrasound
	Ultrasound*	CT scan
2	Serum CA125	Ultrasound
		CT scan
3	Pelvic examination and serum CA125	Ultrasound
		CT scan
4	Ultrasound	Serum CA125
		CT scan
5	Pelvic examination and ultrasound	Serum CA125
		CT scan
6	Serum CA125 and ultrasound	CT scan
7	Pelvic examination, serum CA125 and ultrasound	CT scan

* Only done where pelvic examination did not detect a suspicious mass.

Structure of the model

A decision tree (Figure A1.1) was constructed outlining the seven strategies of interest: three of the strategies included a single first test and the remaining four strategies were combination tests. The model was constructed using TreeAge Pro (2009) software. A Markov process was embedded in the decision tree to model recurrence of the disease and survival based on the results of the diagnostic tests and the subsequent management of women presenting with symptom(s) of ovarian cancer.

A hypothetical cohort of women presenting with symptom(s) of ovarian cancer in the primary care setting was considered for the analysis. In the base case, it was considered that the starting age of the patient population in the model was 40 years of age, while further analyses considered a starting age of 50 years.

Figure A1.1 Diagnostic strategies in primary care

Decision tree for accuracy of staging procedures and related complications

The square node at the beginning of the decision tree shows graphically the seven diagnostic strategies (see Table A1.1) that have been defined as relevant to the decision problem (Figure A1.1).

Independent of which diagnostic strategy is undertaken; patients may or may not have a suspicious mass. This way of structuring the model allows information about the prevalence of a suspicious mass and accuracy of the diagnostic procedures as reported in the systematic reviews of the clinical evidence related to diagnostic investigation in primary care (in terms of their sensitivity and specificity values (Hunink and Glasziou, 2001)) to be used.

Patients in whom the results of primary care investigation did not identify a suspicious mass were assumed to be discharged, with the exception of those undergoing pelvic examination as their primary care test. Patients in whom malignancy has been suspected are referred to secondary care for further investigation. Patients who have undergone pelvic examination (strategy 1) as part of their initial investigation in primary care are referred to secondary care if the test outcome identifies a suspicious mass. Patients in whom pelvic examination did not identify an abnormality undergo ultrasound in primary care. The result of the ultrasound is used to decide whether to refer the patient to secondary care.

The pathway of diagnostic investigations in secondary care depends in part on the type of diagnostic test performed in primary care. The diagnostic pathway for each strategy following referral was outlined by the GDG. In order to maintain consistency within the guideline, imaging procedures reflect the current guideline recommendations.

Pelvic examination

Patients following strategy 1 (see Table A1.1) as part of their investigation pathway and where the initial test (pelvic examination) identified a suspicious mass, are referred to secondary care and undergo combination serum CA125 plus ultrasound as the next diagnostic tests. At this stage, patients in whom a suspicious mass was not detected following investigation in

secondary care (i.e. combination of serum CA125 plus ultrasound), undergo a repeat of the same test within a month and are either referred for a computerised tomography (CT) scan (to confirmed ovarian cancer) or are discharged. Patients in whom a suspicious mass was detected undergo further investigation (in secondary care) with a CT scan, which may confirm the presence and extent of suspected ovarian malignancy.

Serum CA125; pelvic examination plus serum CA125; ultrasound; pelvic examination plus ultrasound

In the case of strategies 2, 3, 4 and 5 (see Table 1), those referred to secondary care with a suspicious mass either undergo ultrasound (strategies 2 and 3) or serum CA125 (strategies 4 and 5). If the result of the ultrasound further identifies a suspicious mass, the patient undergoes a CT scan to confirm the presence of ovarian malignancy. Similarly, patients in whom a suspicious mass was not detected following ultrasound or serum CA125 undergo a repeat of the same test within a month and are either referred to undergo a CT scan (to confirmed ovarian cancer) or are discharged.

Serum CA125 plus ultrasound; pelvic examination plus CA125 plus ultrasound

Lastly, patients following strategies 6 and 7 (see Table A1.1)) where a suspicious mass was detected, are referred to secondary care and undergo a CT scan to assess the extent of the ovarian cancer or an alternate diagnosis.

To capture the downstream consequences of each diagnostic strategy, a clinical pathway was outlined encompassing treatment options following confirmation of ovarian malignancy. As such, it was agreed that following a CT scan, a proportion of patients with confirmed ovarian malignancy, will undergo either a surgical procedure, pathological investigation (biopsy) or will receive supportive care (where the patient is not fit for further treatment/investigation). For the purpose of this model it was agreed that following surgical and pathological procedures patients would be classified as either having disease confined to the ovaries (FIGO stage Ia – Ic) or disease which is not confined to the ovaries (FIGO stages II-IV). Furthermore, patients in whom the CT scan did not confirm ovarian malignancy, undergo further investigation to differentiate the nature of the suspicious mass. One particular issue that the model needed to deal with was that referral and testing might correctly identify a suspicious mass that was unrelated to ovarian cancer. It was therefore agreed that for the purposes of this model two subgroups of patients without confirmed ovarian malignancy (but with a confirmed suspicious mass) would be included: patients with a benign gynaecological problem (for example a simple cyst) and patients with colorectal malignancy. Treatment options were defined for each subgroup of patients. A summary of the key structural assumptions are listed in Box A1.1.

Box A1.1 Key Structural Assumptions

In primary care
- With the exception of those undergoing pelvic examination, patients in whom no malignancy was suspected from initial tests are discharged with no further follow up
- Patients who undergo pelvic examination in primary care and have no suspicious malignancy are re-tested using ultrasound

In secondary care
- Patients in whom further investigation showed no suspicion of malignancy are re-tested within a month
- Computerised tomography scan is able to differentiate between ovarian and non-ovarian masses
- Histopathological tests are assumed to be 100% accurate

Markov process to model prognosis of patients in the long term

A Markov process was embedded in the decision tree to reflect the prognosis of patients according to the management received following the test results. In a Markov process a patients' possible prognosis is divided into a series of discrete health states. Costs and benefits are assigned to each health state and transition probabilities are defined to model the movement of an individual between these health states over a particular time frame (cycle length). The costs and benefits of comparative treatments are then estimated on the basis of the length of time individuals spend in each health state.

The aim of introducing a Markov process at the end of the decision tree was to reflect the pattern of recurrences and survival of patients in a simplified way, depending on whether the diagnostic investigation had been accurate in identifying a suspected mass and, consequently, whether patients were appropriately managed according to their true condition.

Three health states were considered for patients in whom malignancy is confined to the ovaries and who have completed treatment: remission, recurrence and death (all causes). For patients with advanced disease only two health states were considered: remaining in the advanced (recurrence) disease state or death. On each given cycle, patients with confined disease could remain in the disease-free state (remission), have a recurrence and progress to advanced disease or die. Patients with advanced disease could either remain in the advanced stage or die.

Patients in whom colorectal malignancy was identified could either remain in that disease stage (Dukes stage A-D), progress or die. Two health states were considered for patients who have undergone treatment for a benign gynaecological problem, who require no further treatment or were discharged following a negative test outcome: patients could either remain alive or die. A one-year cycle length was used in all instances.

The different probabilities of moving from one health state to another depend on the associated risk of recurrence, disease progression and death. Death can result from ovarian cancer (if the patient had progressed), colorectal malignancy, or from all other causes.

Clinical evidence

Economic modelling is a useful tool to synthesise data derived from multiple sources, given the fact that all the relevant costs and benefits of an intervention are rarely accurately captured by one single study. Although randomised controlled trials are usually the most reliable sources of evidence, they are not always available. Data is often used from non-randomised studies or from expert opinion in which case transparency and consistency is essential. Conducting a sensitivity analysis examines the robustness of the results obtained and the variables most likely to influence the results.

Data inputs

Prevalence and test accuracy

The clinical evidence required to populate the model was obtained from the systematic reviews conducted within the ovarian cancer guideline. The prevalence of the disease in primary care was assumed to be a linear summation of the prevalence of ovarian and colorectal malignancies and benign gynaecological problems. The estimates of prevalence of ovarian and colorectal malignancies are obtained from published literature (CancerResearch UK, 2007; Hamilton *et al.*, 2009). GDG consensus was used to estimate the prevalence of benign gynaecological problems. The accuracy of the diagnostic procedures, in terms of the corresponding sensitivity and specificity values, was obtained from the systematic reviews of the clinical evidence conducted for this guideline (see clinical evidence in sections 2.2 and 2.3). The accuracy of combination strategies were calculated assuming conditional independence. A summary of the estimates of disease prevalence and test accuracy used to populate the model are reported in Table A1.2.

Table A1.2 Disease prevalence and test accuracy

Parameter description	Parameter estimate		Data source
Disease	**Disease prevalence**		
Ovarian cancer	0.23%		Hamilton et al., 2009
Benign gynaecological problem	25% Range (20% - 30%)		GDG consensus
Colorectal cancer	0.06%		CancerResearchUK, 2007
Test accuracy	**Sensitivity**	**Specificity**	
Pelvic examination	0.45	0.90	Myers et al., 2006
Serum CA125	0.78	0.78	Myers et al., 2006
Ultrasound	0.85	0.83	Liu et al., 2007
Combination tests			
Pelvic examination + CA125	0.88	0.70	Derived from single test estimates assuming test independence (see section 2.2 of the Evidence Review)
Pelvic examination + ultrasound	0.92	0.75	
CA125 + ultrasound	0.97	0.65	
Pelvic examination + CA125 + ultrasound	0.98	0.58	
Secondary care test			
CT scan	0.85	0.86	Liu et al., 2007

Proportion estimates

The proportion of patients in each treatment arm, as defined by the model structure, was not consistently reported in the published literature. Therefore, proportions were estimated by the GDG. The estimates of the proportions are shown in Table A1.3.

Table A1.3 Estimates of proportions

Parameter description	Estimate (%)
Patients in whom *no cancer of the ovaries* was detected following secondary care test†:	
Proportion of patients who are diagnosed with a benign gynaecological problem (for example a simple cyst)	85
Proportion of patient who are diagnosed with 'other' cancer (colorectal)	15
Patients in whom *cancer of the ovaries* was detected following secondary care test[1]†:	
Proportion of patients undergoing percutaneous biopsy (or any other histopathological investigation)	35
Proportion of patients undergoing surgery	60
Proportion of patients who are not fit to undergo any further investigation and receive supportive care	5

---

[1] Estimation is based on an assumption that of all patients in whom cancer of the ovaries is detected: 75% will have advanced stage disease and 25% will have early stage disease (Kosary 1994; Bell et al., 1998). Of those with advanced stage disease 50% will undergo surgery and 50% biopsy.

Table A1.3 (cont.)

Parameter description	Estimate (%)
Patients who have *undergone surgery*†:	
Proportion of patients in whom disease is confined to the ovaries (stage I)[2]	40
Proportion of patients in whom disease is not confined to the ovaries (stage II-IV)	60
Patients with disease *confined* to the ovaries‡ :	
Proportion of patients undergoing chemotherapy (carboplatin)	50
Proportion of patients who do not require further treatment (following surgery) and receive follow-up care	50
Patients with disease *not confined* to the ovaries†:	
Proportion of patients undergoing chemotherapy (paclitaxel/carboplatin)	85
Proportion of patients undergoing chemotherapy (paclitaxel/carboplatin) and further surgery	10
Proportion of patients who are not fit for further treatment (following staging surgery) and are receiving supportive care	5

Source: † GDG Consensus; ‡ Warwick *et al.* 2009

Treatment

Surgery

Historically, the mainstay of treatment for ovarian cancer was surgical excision. It has been estimated that the majority of patients with early and about half with advanced stage disease will require some form of surgery (Bell et al., 1998; Kosary 1994). For the purpose of this model, the GDG agreed that the majority of patients, in both groups, will undergo laparotomy with intent to perform total abdominal hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO)/omentectomy/peritoneal washings. In patients where no malignancy was suspected (for example, a simple cyst) it was agreed to assume the same procedures would be carried out. Mortality and morbidity rates associated with these surgical procedures were obtained from the published literature (Chien et al., 2005; Gerestein et al., 2009; Loft et al., 1991; Venesmaa and Ylikorkala 1992) or through GDG consensus and are shown Table A1.4.

Table A1.4 Mortality and morbidity associated with laparotomy

	Confined to the ovaries (stages 1a-1c)	Not confined to the ovaries (stages II-IV)	Benign gynecological problem
Mortality	1%†	3%††	0.16%‡
Morbidity	5%*	10-15%*	5%**

Source: † Venesmaa *et al.*, (1992); †† Gerestein *et al.*, (2009) (stage II-IV); ‡ Loft *et al.*, (1991) (benign problem); * GDG consensus; ** Chien *et al.*, (2005)

Chemotherapy

Within the guideline, a review of the clinical evidence was conducted to ascertain the most effective chemotherapy regimen in patients with early disease. To assure consistency between the guideline as a whole and the economic model, it was agreed that for the purposes of economic analysis, patients in whom cancer is confined to the ovaries receive a carboplatin-based chemotherapy regimen. Dosage, duration of treatment, estimates of overall survival and progression free survival were obtained from the ICON 1 trial (Swart et al., 2007)) (Table A1.5).

---

[2] stage I includes stages Ia- Ic.

The study did not report major toxicities associated with carboplatin. Patients with advanced disease (i.e. where cancer is not confined to the ovaries) followed the treatment pathway outlined by 'Guidance on the use of paclitaxel in the treatment of ovarian cancer' (NICE, 2003). Similarly, estimates of overall survival, progression free survival, duration of treatment and dosages of a combination of agents were taken from Bagnall et al., (2002) (see Table A1.5 below).

Table A1.5 Dosage, duration of treatment and survival estimates assumed by the model

	Confined to the ovaries	**Not confined to the ovaries**
Agent (s)	Carboplatin	Paclitaxel/carboplatin
Dosage	AUC6	175 mg/m^2 AUC6
Number of cycles	6	6
Progression free survival (PFS)	67% (10 years PFS)	17.1 months (median)
Overall survival (OS)	72% (10 years OS)	37.1 months (median)
Data source	ICON 1 Trial (Swart *et al.*, 2007)	ICON 3 Trial (Bagnall *et al.*, 2002)

Supportive care and follow-up monitoring

Supportive care

No studies were found to provide estimates of healthcare resource use for the provision of supportive care specifically in this group of patients. Given the advanced stage of the disease, it was agreed that a patient will spend a third of their time at home, a third in a hospital and the latter stage in a hospice. For the purpose of this analysis, we obtained estimates of unit costs of resource use by GDG consensus.

Follow-up monitoring

Similarly, no studies were found quantifying healthcare resource use associated with the follow-up monitoring of women who had undergone treatment (surgery and chemotherapy). Other guidelines were used to identify relevant components of care and a likely schedule of follow-up monitoring for women who have undergone active treatment. The GDG agreed that follow-up monitoring should include a history and physical examination (including pelvic examination) every three months for three years and once a year for the following five years. Estimates of resource use were obtained by GDG consensus and are summarised in Table A1.6.

Table A1.6 Resource use associated with provision of supportive care and follow-up monitoring

	Number of units
Supportive care (per patient)	
Hospital stay (in days)	14
Hospice stay (in days)	14
Home stay	
GP visits (0.5/week)	1
District nurse	4
Nurse specialist	2
Follow-up monitoring (per year)	
Years 1-3	
Physical examination (including pelvic examination)	4
Years 4 – onwards	
Physical examination (including pelvic examination)	1

Other cancer – colorectal

It was agreed that for the purposes of this economic model estimates of survival associated with treatment for colorectal cancer would also be used as proxy for the subgroup of patients in whom a non-gynaecological cancer was identified following diagnostic investigation. A summary of average survival (by stage) is reported in Table A1.7.

Table A1.7 Distribution and survival by stage (at diagnosis)

Disease stage	Proportion (NCIN, 2009)	Average Survival (Tappenden et al., 2007)
Dukes A	13.2%	11years
Dukes B	36.9%	11 years
Dukes C	35.9%	8.7 years
Dukes D	14.0%	1.4 years

Health benefits

The health benefits derived from using the alternative diagnostic strategies compared in the analysis were estimated in terms of the number of quality-adjusted life years (QALYs) gained. The base case analysis considered a lifetime horizon, although a shorter time horizon was considered in the sensitivity analysis.

Markov processes were used to estimate life expectancy and QALYs gained by four different patient subgroups:
- Patients who were considered to have a suspicious mass at the beginning of the model (following initial test) and have undergone an appropriate treatment (true positive)
- Patients who did not have a suspicious mass at the beginning of the model (following initial test) but have undergone treatment after being wrongly diagnosed (false positive)
- Patients who did not have a suspicious mass at the start of the model (following initial test) and were discharged (true negative)
- Patients who have a suspicious mass at the start of the model (following initial test) but were wrongly discharged following diagnostic investigation (false negative).

Estimates of life expectancy

Estimates of life-expectancy were generated using a series of Markov models. The transition probabilities of moving across the various health states (Figures A1.2-A1.4) were estimated from published studies (International Collaborative Ovarian Neoplasm Group, 2002; Swart et al., 2007), which reported rates of remission, recurrence and death following chemotherapy treatment in patients with localised and advanced disease. An appropriate adjustment was conducted to obtain yearly transition probabilities of recurrence and death in this subgroup of patients (Hunink and Glasziou, 2001). Moreover, the transition probabilities were assumed to be constant throughout the time horizon of the model

.

Figure A1.2 Markov process for prognosis of patient with early ovarian disease
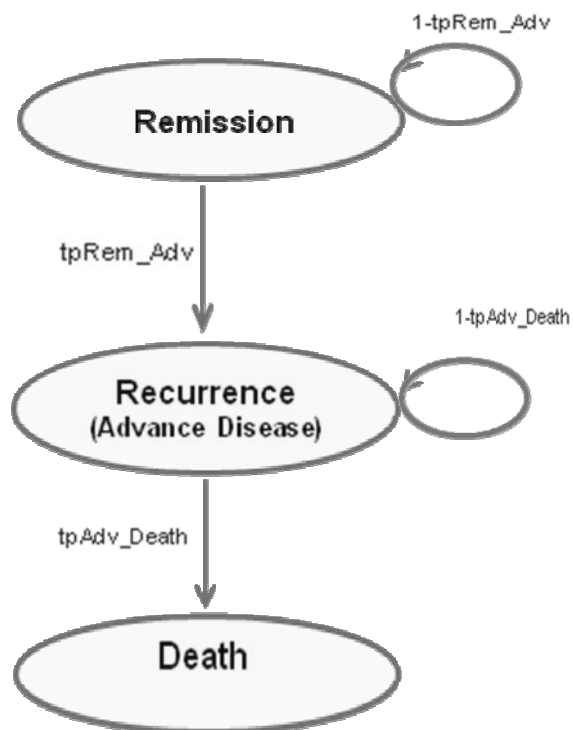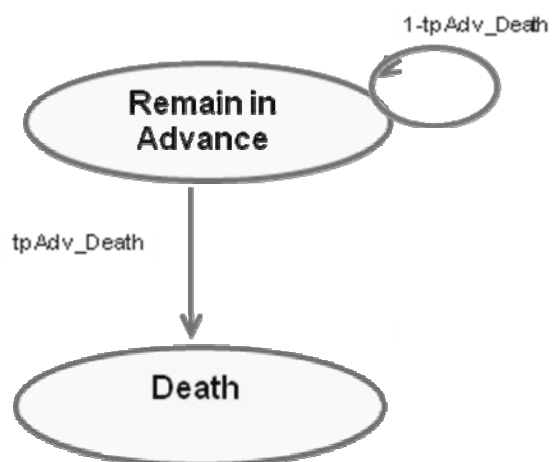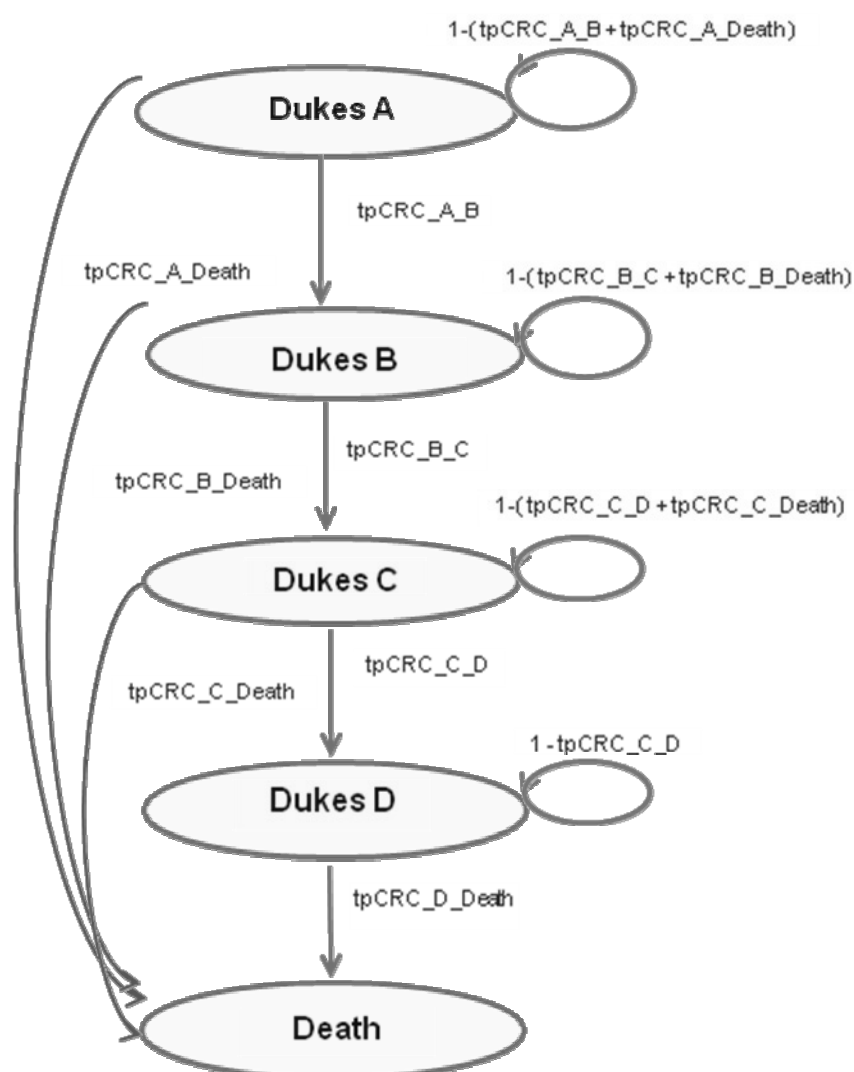

Figure A1.3 Markov process for prognosis of patient with advanced ovarian disease

Note: the formulae relate to the various transition probabilities and are described in more detail below (Table A1.8)

Figure A1.4 Markov process for prognosis of a patient with colorectal cancer

For patients who did not have the disease, had a benign condition or required follow-up monitoring after undergoing chemotherapy, transition probabilities of moving from "alive" to "dead" from all causes were estimated using the age-related mortality rates (as reported by the Office of National Statistics, 2009).

For patients who are diagnosed with colorectal malignancy, progression from initial stage to the next or to death was captured by the transition probabilities reported in Tappenden et al., (2007).

A summary of all transition probabilities used to populate the model is reported in Table A1.8.

Table A1.8 Transition probability between health states

Transition probability	Mean	Description
Ovarian cancer		
tpRem_Adv	0.105	Probability of recurrence (early disease)
1-tpRem_Adv	0.895	Probability of remaining in remission
1- tpAdv_Death	0.797	Probability of remaining in the advanced disease state
tpAdv_Death	0.203	Probability of dying (advanced disease)

Table A1.8 (cont.)

Transition probability	Mean	Description
Colorectal cancer		
tpCRC_A_B	0.5829	Probability of moving from Dukes A to Dukes B
tpCRC_A_Death	0	Probability of dying (Dukes A)
tpCRC_B_C	0.6555	Probability of moving from Dukes B to Dukes C
tpCRC_B_Death	0.01	Probability of dying (Dukes B)
tpCRC_C_D	0.8668	Probability of moving from Dukes C to Dukes D
tpCRC_C_Death	0.0602	Probability of dying (Dukes C)
tpCRC_D_Death	0.3867	Probability of dying (Dukes D)

Utility estimates

The value of estimating the number of QALYs gained is that this single measure combines the gains from mortality (quantity gains) and from morbidity (quality gains) (Drummond et al., 2005). An index based on an individual's preference for a specific health state in relation to alternative health states (utility weights) were required in the model to estimate quality-adjusted life years (QALYs), which are calculated by weighting life expectancy by a measure of associated health-related quality of life. Estimates of health state utilities specific to ovarian cancer patients were obtained from published studies. There are a number of studies that report utility weights associated with diagnostic investigations and treatments of ovarian cancer. Havrilesky et al., (2009) reported utility estimates related to various heath states following false positive/negative test results and treatment with toxicities. Utility estimates obtained using the time trade-off method (TTO) tended to be slightly higher compared to those obtained using a visual analogue score (VAS). Drummond et al., (2005) noted that visual scales for comparing health state preferences are subject to inherent biases and are generally less accurate. For this reason we used utility estimates derived using the TTO method. Utility estimates associated with undergoing surgery and colorectal cancers were obtained from Grann et al., (1998) and Tappenden, et al. (2007) respectively. The utility values used in the model are summarised in Table A1.9.

Table A1.9 Utility values

Health state	Mean	Data Source
Diagnostic test false positive/negative result	0.88	Havrilesky *et al.*, 2009
Chemotherapy (carboplatin)	0.81	Havrilesky *et al.*, 2009
Chemotherapy (paclitaxel)	0.55	Havrilesky *et al.*, 2009
Toxicity grade 3-4 (paclitaxel)	0.49	Havrilesky *et al.*, 2009
Surgery	0.68	Grann *et al.*, 1998
Recurrence	0.47	Havrilesky *et al.*, 2009
Remission (early)	0.83	Havrilesky *et al.*, 2009
Stable - advanced disease	0.63	Grann *et al.*, 1998
Colorectal cancer (by stage)		
Dukes A	0.74	Tappenden *et al.*, 2007
Dukes B	0.70	Tappenden *et al.*, 2007
Dukes C	0.50	Tappenden *et al.*, 2007
Dukes D	0.25	Tappenden *et al.*, 2007
Supportive care	0.16	Havrilesky *et al.*, 2009
Follow-up	0.99	Assumed

Cost estimates

The costs considered in this analysis were only those relevant to the UK NHS, in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated based on 2008-9 prices. When costs have been taken from other sources and are applicable to a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2009). The categories of costs included:

- Cost of diagnostic tests (in primary and secondary care)
- Cost of therapy (surgery, drug acquisition costs, administration costs)
- Cost of major treatment related to morbidity
- Cost of healthcare resource use associated with supportive care and follow-up monitoring

Costs of diagnostic tests

The cost estimates of diagnostic tests relevant to this analysis were obtained from various sources. Unit costs of ultrasound, CT and MRI were obtained from the NHS Reference Costs and estimated at £69, £143 and £178 respectively (HRG codes: RA24Z, RA13Z and RA01Z). The cost of pelvic examination was estimated using unit cost reported in the Personal Social Services Research Unit (PSSRU 2009) and included the cost of GP's and nurses' time. Unit costs of tumour marker test (serum CA125) was estimated at £23 and obtained using GDG consensus. Unit costs of combination tests were estimated as a sum of the unit costs of the individual tests.

The cost estimates of pathological investigation were assumed to consist of the cost of percutaneous biopsy and aspiration cytology. These costs were obtained from NHS Reference costs and from GDG consensus, and were estimated to be £1,124 and £42 respectively. A summary of unit costs of diagnostic tests are presented in Table A1.10.

Table A1.10 Cost estimates of diagnostic tests

	Mean (£)	Data source
Ultrasound	69	NHS Reference Cost: HRG code RA24Z
Pelvic examination		
GP practitioner (per procedure)	52	PSSRU 2009
GP nurse (per procedure)	10	PSSRU 2009
Total	62	
Serum CA125	23	GDG consensus
Cost estimation of combination diagnostic tests		
Pelvic examination + ultrasound	115	
Pelvic examination + serum CA125	85	
Serum CA125 + ultrasound	76	
Pelvic examination + ultrasound + serum CA125	138	
CT scan	143	NHS Reference Cost: HRG code RA13Z
Biopsy		
Percutaneous biopsy	1124	NHS Reference Cost: HRG code FZ12C
Aspiration cytology	42	GDG consensus
Total	1166	
MRI	178	NHS reference Cost: HRG code RA01Z

Cost of Treatment

Chemotherapy

The drug costs were calculated for chemotherapy regimens for patients with localised and advanced disease, assuming that a patient received one dose per 3-week cycle for single or combination therapy (Table A1.11). In addition to the drug acquisition costs, the cost of administering the drug was estimated from the NHS Reference Costs. Administration of carboplatin and the carboplatin/paclitaxel combination regimens was assumed to be performed on an outpatient basis. The cost of administering these regimens was estimated using outpatient tariffs of £272 (HRG SB12Z) and £335 (HRG SB13Z) respectively. This cost includes hospital overheads, the administration costs of chemotherapy and clinical time. These assumptions were verified with the GDG.

The base case analysis used list prices for drugs obtained from the British National Formulary (BMG Group and Pharmaceutical Press, 2010). The effect of the drug discounts were explored through sensitivity analysis.

Table A1.11 Drug acquisition costs

Strategy	Carboplatin	Carboplatin/paclitaxel	
	Carboplatin	Carboplatin	Paclitaxel
List prices, £ (BNF 59, 2010)			
5 ml vial			66.85
15 ml vial	56.29	56.29	
50 ml vial			601.03
60 ml vial	260	260	
i.v. concentrate (mg/ml)	10	10	6
Recommended dose (mg/m^2)	696	660	175
Average cost per vial (£)	316.29	316.29	667.88
Number of vials	1	1	1
Average drug cost per cycle (£)	316.29	316.29	667.88

Surgery

Patients identified as having ovarian cancer or a benign gynaecological problem undergo a surgical procedure. The unit costs considered in this analysis were estimated by mapping the Classification of Surgical Operations and Procedures from the Office of Population, Censuses and Survey (OPCS – 4) into Health Related Groups (HRGs) and by identifying the relevant unit cost as reported in the NHS Reference Costs for the specific HRGs. OPCS – 4 codes for laparotomy for malignant and benign conditions were obtained via GDG consensus. Costs of surgical procedures for malignant and benign gynaecological problems are reported in Table A1.12.

Table A1.12 Costs of surgical procedures

	Mean (£)	Data source
Laparotomy **with malignancy** *(no complications)*	3,561	NHS Reference Cost: HRG code MA06Z
Laparotomy **with malignancy** *(with complications)*	3,705	NHS Reference Cost: HRG code MA06Z*
Laparotomy **without malignancy** *(no complications)*	2,967	NHS Reference Cost: HRG code MA07B
Laparotomy **without malignancy** *(with complications)*	3,101	NHS Reference Cost: HRG code MA07A

* Extra cost associated with complication was obtained using percentage change between HRG MA07A and MA07B as a proxy.

Treatment of colorectal cancer

Lifetime costs estimates of the treatment of colorectal cancer were obtained from a published study by Tappenden *et al.*, (2007) and are reported in the Table A1.13 below.

Table A1.13 Lifetime costs of treatment of colorectal cancer

Disease stage	Mean cost (£)
Dukes A	8,299
Dukes B	12,441
Dukes C	19,077
Dukes D	11,946

Source: Tappenden *et al.*, 2007

Cost of supportive care and follow-up monitoring

No published data was found that quantified healthcare resource use associated with the provision of supportive care and follow up monitoring specifically in patient subgroups identified in the model. Categories and number of units of relevant resource use items were obtained via GDG consensus. The total number of units for each category of resource use was multiplied by the cost of providing it (PSSRU, 2009). A summary of unit costs for each category of resource use are shown in Table A1.14.

Table A1.14 Unit cost of supportive care resource use

Resource	Unit cost (£)	Data source
Hospital specialist palliative care support	133	NHS Reference costs: HRG code SD03A
Hospice specialist palliative care	418	NHS Reference costs: HRG code SD01A
GP visits	58	PSSRU, 2009
District nurse	114	PSSRU, 2009
Nurse specialist	82	PSSRU, 2009
Annual follow-up monitoring		
Years 1-3	248	PSSRU, 2009
Year 4 (onwards)	62	PSSRU, 2009

Discounting

Within health economic evaluation, the discounting of costs and health outcomes is standard practice – since costs and benefits that accrue in the future are given less weight to those which occur in the present. Following NICE methodological guidance (NICE, 2008), all costs and health outcomes are discounted at 3.5% per year.

Sensitivity analysis

A series of one-way sensitivity analyses were conducted to assess the robustness of the study results. One-way sensitivity analysis describes the process of changing one parameter in the model and re-running the model to see how a change in this parameter influences overall results.

Five scenarios were considered and are detailed below:
- Nationally-agreed drug discounts in England were as follows: the cost per dose of paclitaxel is £63.15 compared to a list price of £668 per dose (NHS Purchasing and Supplies Agency, August 2009). The price of carboplatin is £23.93 compared to a list price of £316 per dose. In Wales, nationally-agreed discounts were: 97% per dose for paclitaxel and 92% for carboplatin (personal communication from the Welsh Health Supplies, August 2009). Based on these rates, the discounted cost of each regimen was calculated for England and for Wales. Whilst it is acknowledged that regional pharmacies and/or commissioners may negotiate other discounts separately, only nationally agreed discounts are considered (NICE, 2008). The average discounted cost across both regions is also reported in Table A1.15.
- The prevalence of ovarian malignancy in primary care was decreased to 0.14%.
- The prevalence of benign gynaecological problem was varied over an agreed range (20% - 30%).
- The proportion of patients who are not fit for further treatment following diagnostic investigation was decreased to 2%.
- The age at the start of the model was increased from 40 to 50 years of age.

Table A1.15 Discounted drug acquisition costs in England and Wales

Regimen	Carboplatin	Carboplatin/paclitaxel
Average cost of regimen per cycle (£)		
List price	316	984
Discount price (England)	26	89
Discount price (Wales)	25	45

However these scenarios are unlikely to happen independently; they are more likely to occur concurrently. To fully characterise this uncertainty and to estimate the effects of the parameter uncertainty on the results, a probabilistic sensitivity analysis (PSA) was undertaken.

Firstly, the stochastic parameters in the model were identified (presented in the first column of Table A1.16). These are parameters which are (arguably) measureable, but are associated with sampling uncertainty.

Secondly, these parameters were specified as distributions rather than point estimates (see fourth column of Table A1.16). Distributions associated with each of these parameters were selected according to a well developed body of methodological literature. The data required to inform these distributions was taken from the same sources as was used for the point estimates.

Parameters not chosen for PSA:
- unit costs of health professionals and drug acquisition
- estimates of test accuracy

Thirdly, the analysis was run 10,000 times. For each simulation, different values were picked from the various distributions for each stochastic parameter in the model.

Table A1.16 Parameters varied in the probabilistic sensitivity analysis

Parameter	Deterministic value	Distribution assigned	Source
Utilities			
Diagnostic test false positive/negative result	0.88		Havrilesky. *et al.*, 2009
Stable – advanced disease	0.63	Beta	Grann *et al.*, 1998
Advanced (undergoing chemotherapy)	0.55	Beta	Havrilesky. *et al.*, 2009
Advanced (undergoing chemotherapy with toxicity)	0.49	Beta	Havrilesky. *et al.*, 2009
Early (chemotherapy)	0.81	Beta	Havrilesky. *et al.*, 2009
Early (recurrence)	0.47	Beta	Havrilesky. *et al.*, 2009)
Early (remission)	0.83	Beta	Havrilesky. *et al.*, 2009
Surgery	0.68	Beta	Grann *et al.*, 1998
Colorectal cancer – Dukes A	0.74	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes B	0.70	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes C	0.50	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes D	0.25	Beta	Tappenden *et al.*, 2007
Supportive care	0.16	Beta	Havrilesky. *et al.*, 2009
Follow-up	0.99	Beta	Assumed
Transition probability			
tpAdv_Dead	0.203	Beta	Bagnall *et al.*, 2002
tpRem_RecAdv	0.11	Beta	Swart *et al.*, 2007
tpCRC_A_B	0.58	Dirichlet	Tappenden *et al.*, 2007
tpCRC_A_Death	0	Dirichlet	Tappenden *et al.*, 2007
tpCRC_B_C	0.66	Dirichlet	Tappenden *et al.*, 2007
tpCRC_B_Death	0.01	Dirichlet	Tappenden *et al.*, 2007
tpCRC_C_D	0.87	Dirichlet	Tappenden *et al.*, 2007
tpCRC_C_Death	0.06	Dirichlet	Tappenden *et al.*, 2007
tpCRC_D_Death	0.39	Dirichlet	Tappenden *et al.*, 2007
Proportions and rates			
Prior – disease prevalence	0.2529	Beta	Hamilton *et al.*, 2009
Rate of toxicity (alopecia in advanced stage)	0.73	Beta	Bagnall *et al.*, 2002
Rate of mortality (early) – post surgery	0.01	Beta	Venesmaa *et al.* 1992

Table A1.16 (Cont.)

Parameter	Deterministic value	Distribution assigned	Source
Rate of mortality (advanced) - post surgery	0.03	Beta	Gerestein *et al.*, 2009
Rate of mortality (benign) – post surgery	0.0016	Beta	Loft *et al.*, 1991
Rate of morbidity (early) – post surgery	0.05	Beta	GDG consensus
Rate of morbidity (advanced) - post surgery	0.13	Beta	GDG consensus
Rate of morbidity (benign) – post surgery	0.05	Beta	Chien *et al.*, 1991
Proportion of patients with disease confined to the ovaries (undergoing treatment)	0.5	Beta	GDG consensus
Proportion of patients in whom ovarian cancer is detected (following secondary care test)	(0.35; 0.60; 0.05)	Dirichlet	GDG consensus
Proportion of patients with disease not confined to the ovaries (undergoing treatment)	(0.85; 0.1; 0.05)	Dirichlet	GDG consensus
Proportion of patients with benign gynaecological problem	0.85	Beta	GDG consensus
Proportion of patients with colorectal cancer	0.15	Beta	GDG consensus
Proportion of Dukes A-D	(0.13; 0.37; 0.36; 0.14)	Dirichlet	Tappenden *et al.*, 2007

Results

A summary of expected costs and effects associated with each diagnostic strategy in the model are presented in Table A1.17. The expected cost of the strategies varies widely, ranging from the least expensive (serum CA125) at just over £1,500 to the most expensive (combination strategy of pelvic examination plus serum CA125 plus ultrasound) at £,3160 per patient. Health outcomes, measured in terms of QALYs, ranged from 20.391 for the serum CA125 strategy to 19.524 for pelvic examination plus serum CA125 plus ultrasound combination strategy. Serum CA125 (single test) strategy on average generates 20.391 QALYs and ultrasound (single test) generates 20.387 – a difference of 0.004 QALYs is an equivalent (on average) of an additional 1.5 days of perfect health.

Table A1.17 Base case total expected cost and QALYs

Strategy	Cost (£)	Effectiveness (QALY)	ICER[†]
Serum CA125	1,532.32	20.391	
Ultrasound	1,604.24	20.387	(Dominated)
Pelvic examination + serum CA125	1,809.06	20.316	(Dominated)
Pelvic examination + ultrasound	1,864.16	20.298	(Dominated)
Pelvic examination	2,112.49	20.177	(Dominated)
Serum CA125 + ultrasound	2,850.49	19.681	(Dominated)
Pelvic examination + ultrasound + serum CA125	3,160.73	19.524	(Dominated)

†ICER – incremental cost-effectiveness ratio

All strategies in this analysis are dominated by the serum CA125 strategy. A strategy is said to be dominated if it is both more costly and less effective than its comparator. Graphical representation of the base case shown on Figure A1.5.

Figure A1.5 Cost-effectiveness plane for base-case results
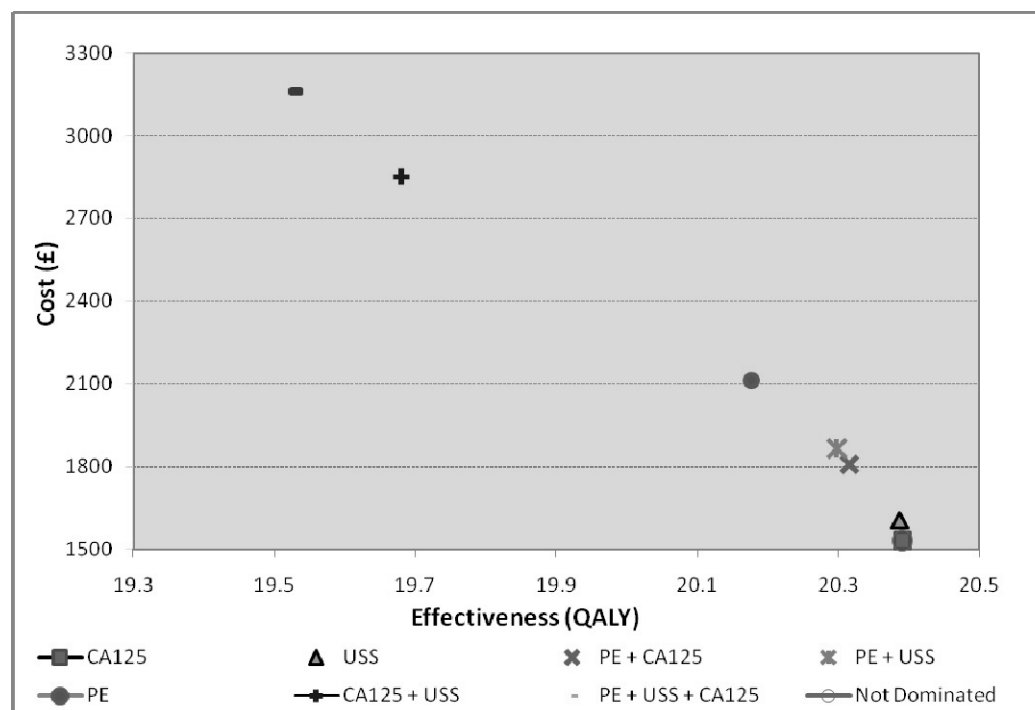
Sensitivity analysis

The results of base case analysis were not sensitive to any of the five scenarios outlined above in section 3.8.

The discount on paclitaxel and carboplatin available in England and Wales is considerable; the price is about 10% of the list price. This drastically reduced the costs attributed to marginal reduction in the overall expected costs for each of the strategies, but did not alter the ranking of the cost-effective diagnostic strategies (Table A1.18).

Table A1.18 One-way sensitivity analysis – drug discounts (the cost of paclitaxel and carboplatin is assumed to be £89 in England and £45 in Wales instead of the base case estimates)

Strategy	Costs (£) England	Costs (£) Wales	Effectiveness (QALY)
Serum CA125	1,525.1	1,524.8	20.3909
Ultrasound	1,596.5	1,596.2	20.3867
Pelvic examination + serum CA125	1,800.9	1,800.5	20.3155
Pelvic examination + ultrasound	1,855.8	1,855.5	20.2979
Pelvic examination	2,103.8	2,103.4	20.1765
Serum CA125 + ultrasound	2,841.3	2,840.9	19.6802
Pelvic examination + ultrasound + serum CA125	3,151.4	3,151.0	19.5241

Similarly, the results of the one-way sensitivity analysis of the other scenarios (for example, changes in the prevalence, proportion of patients undergoing supportive care and starting age of the patients in the model) showed changes in the overall expected costs and health benefits but did not alter the ranking of the cost-effective diagnostic strategy. The results of deterministic sensitivity analysis are presented in Tables A1.19 and A1.20.

Table A1.19 One-way sensitivity analysis – change in the (prior) prevalence of the ovarian cancer and benign non-gynaecological cancer

Strategy	Prevalence of ovarian cancer 0.14%		Prevalence of benign condition 20%		Prevalence of benign condition 30%	
	Costs (£)	QALYs	Costs (£)	QALYs	Costs (£)	QALYs
Serum CA125	1,525.6	20.4024	1,362.1	20.5313	1,702.6	20.2504
Ultrasound	1,597.1	20.3989	1,423.1	20.5289	1,785.4	20.2446
Pelvic examination + serum CA125	1,801.6	20.3283	1,621.7	20.4551	1,996.5	20.1760
Pelvic examination + ultrasound	1,856.6	20.3108	1,675.8	20.4368	2,052.6	20.1590
Pelvic examination	2,104.8	20.1898	1,924.9	20.3092	2,300.1	20.0438
Serum CA125 + ultrasound	2,843.2	19.6935	2,701.3	19.7818	2,999.7	19.5786
Pelvic examination + ultrasound + serum CA125	3,153.6	19.5374	3,023.9	19.6159	3,297.6	19.4323

Note: setting the prevalence of colorectal cancer to 0% instead of 0.06% in a one way sensitivity analysis had a negligible effect on the results.

Table A1.20 One-way sensitivity analysis – proportions of patients receiving supportive care estimates and starting age at time of testing

Strategy	Prop. Supportive Care 2%		Starting age 50 years	
	Costs (£)	QALYs	Costs (£)	QALYs
Serum CA125	1,532.7	20.3909	1,531.2	17.9052
Ultrasound	1,604.6	20.3868	1,603.2	17.9019
Pelvic examination + serum CA125	1,809.5	20.3156	1,808.0	17.8403
Pelvic examination + ultrasound	1,864.6	20.298	1,863.1	17.825
Pelvic examination	2,112.9	20.1766	2,111.5	17.7197
Serum CA125 + ultrasound	2,851.0	19.6803	2,849.7	17.2885
Pelvic examination + ultrasound + serum CA125	3,161.2	19.5242	3,160.0	17.153

To fully assess the effects of the parameter uncertainty on the results, the base case model was estimated using probabilistic sensitivity analysis. As with the deterministic results, the results of PSA showed serum CA125 as the dominant strategy. The corresponding cost-effectiveness acceptability curve (CEAC) shows that, at a threshold of £20,000 per QALY, the probability that the serum CA125 strategy is the most cost effective option is almost 73%. Moreover, the serum CA125 strategy had the highest probability of being the most cost-effective when compared to other strategies, at any level of willingness-to-pay per additional QALY gained (Figure A1.6).

Figure A1.6 Cost-effectiveness acceptability curve for base case results
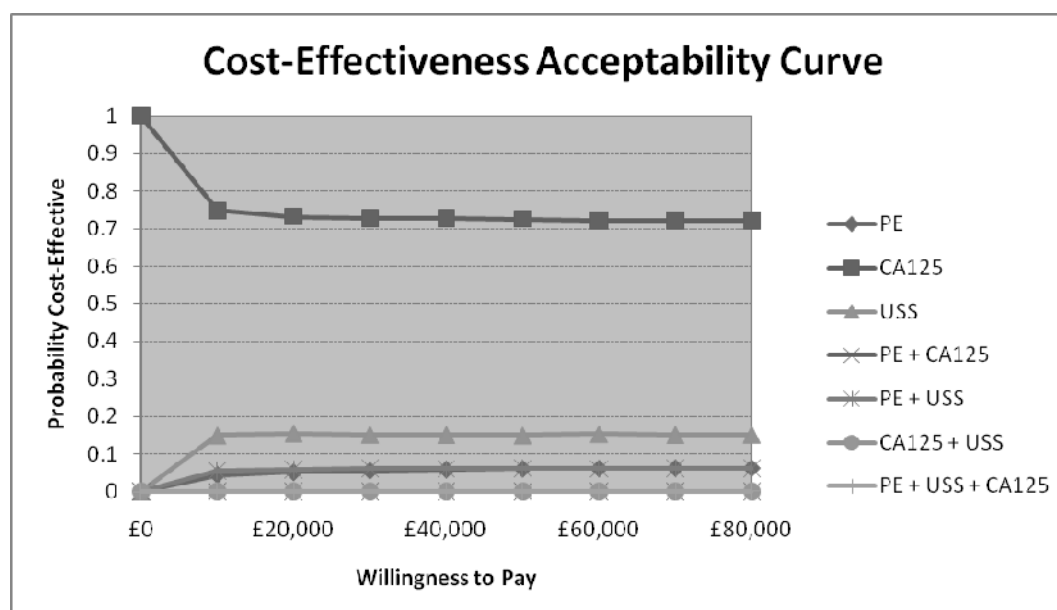
PE = pelvic examination; CA125 = serum CA125; USS = ultrasound

Discussion

The aim of this study was to assess the cost-effectiveness of diagnostic strategies for women presenting with symptoms suggestive of ovarian cancer in primary care. A cost-utility analysis was undertaken to estimate the incremental cost per QALY of seven diagnostic strategies, which included the downstream costs and consequences of subsequent treatments considered likely to reflect current UK clinical practice and to be consistent with recommendations made within this guideline.

Given the various structural and parameter-related assumptions, the base-case results suggest that serum CA125 is the most cost effective test. Indeed the results indicate that the serum CA125 diagnostic strategy dominates all other strategies, that is, it is less costly and more effective than at least one other option. The robustness of the model was tested using one-way sensitivity analysis. The results of the deterministic sensitivity analysis showed that although expected costs and health outcomes varied across strategies, the overall ranking of the cost-effective strategy did not change. Moreover, probabilistic sensitivity analysis was undertaken to fully assess the effects of the parameter uncertainty on the results. The results of the PSA showed serum CA125 as the dominating strategy and the corresponding cost-effectiveness acceptability curve (CEAC) shows that, at a threshold of £20,000 per QALY, the probability that the serum CA125 strategy is the most cost effective option is almost 73%.

There are a number of limitations to this analysis. The sensitivity analyses conducted were aimed at assessing only parameter uncertainty; however given the complexity of the downstream consequences associated with each strategy further analysis of the later structural assumptions would be beneficial. The costs used were often proxies for costs that were hard to capture and may not fully capture the differences between the different diagnostic strategies, for instance the costs of pelvic examination. Moreover, in the absence of suitable data, the individual test results were assumed to be independent of each other, when in reality this is unlikely. However, the implication of this in terms of the relative cost effectiveness of each of the (combination) tests is unclear.

> Despite these acknowledged limitations, this analysis does provide some useful information which the guideline development group can use in its deliberations over the recommendations to be made on this clinical question. Serum CA125 is the most cost-effective (dominating) strategy and as shown above is more likely to be cost-effective compared to other strategies in the model.

References

Bell R., Petticrew M., Luengo S., Sheldon TA. (1998) Screening for ovarian cancer: a systematic review. Health Technology Assessment, 1998. 2(2): 2

BMJ Group and Pharmaceutical Press (2010) British National Formulary 59. BMJ Group and Pharmaceutical Press: London

CancerResearchUK (2007) Cancer Stats: Incidence [cited; Available from: www. cancerresearchuk.org

Chien P., Khan K. and Mol BW. (2005) How to interpret the findings of the eVALuate study. BJOG: An International Journal Of Obstetrics And Gynaecology. 112(4): 391-393.

Drummond M F. Sculpher MJ., Torrance GW., O'Brien BJ. and Stoddart GL. (2005). Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, England.

Gerestein CG., Damhuis RA., Burger CW. and Kooi GS. (2009) Postoperative mortality after primary cytoreductive surgery for advanced stage epithelial ovarian cancer: A systematic review. Gynecologic Oncology. 114(3): 523-527.

Grann VR., Panageas KS., Whang W., et al. (1998) Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. Journal Of Clinical Oncology 16(3): 979-985.

Hamilton W., Peters TJ.,, Bankhead C and Sharp D. (2009) Risk of ovarian cancer in women with symptoms in primary care: population based case-control study. British Medical Journal. 339(7721): 616-616.

Havrilesky LJ., Broadwater G., Davis DM., et al., Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. Gynecologic Oncology, 2009. 113(2): 216-220

Hunink M. and Glasziou P. (2001) Decision making in health and medicine. Cambridge University Press: Cambridge, UK.

International Collaborative Ovarian Neoplasm Group (2002) Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet 360(9332): 505.

Kosary CL. (1994) FIGO stage, histology, histologic grade, age and race as prognostic factors in determining survival for cancers of the female gynecological system: an analysis of 1973-87 SEER cases of cancers of the endometrium, cervix, ovary, vulva, and vagina. Seminars In Surgical Oncology. 10(1): 31-46.

Liu J., Xu Y. and Wang J. (2007) Ultrasonography, computed tomography and magnetic resonance imaging for diagnosis of ovarian carcinoma. European Journal of Radiology 62(3): 328-334.

Loft A., Andersen TF., Brønnum-Hansen H,, Roepstorff C. and Madsen M. (1991) Early post operative mortality following hysterectomy. A Danish population based study 1977-1981. British Journal of Obstetrics and Gynaecology. 98(2): 147-54.

Myers E,R., Bastian LA., Havrilesky LJ., et al. (2006). Management of adnexal mass. Evidence Report/Technology Assessment(130): 1-145.

National Cancer Intelligence Network (2009) Colorectal Cancer Survival by Stage National Cancer Intelligence Briefing. Data Briefing. Northern and Yorkshire Cancer Registry and Information Service

National Institute for Health and Clinical Excellence (2003) Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal guidance 55. London: National Institute for Health and Clinical Excellence.

National Institute for Health and Clinical Excellence (2008). Guide to the methods of technology appraisal. National Institute for Health and Clinical Excellence: London

Office of National Statistics (2009) Interim Life Tables, England & Wales 2006-2008. www.statistics.gov.uk

PSSRU (2009) Unit Costs of Health and Social Care 2009. www.pssru.ac.uk/uc/uc2009contents.htm

Swart AC. et al., on behalf of ICON collaborators. (2007) Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON1). Journal of Clinical Oncology (Meeting Abstracts). 25(18_suppl): 5509.

Tappenden P., Chilcott J., Eggington S., Patnick J., Sakai H., and Karnon J. (2007) Option appraisal of population-based colorectal cancer screening programmes in England. Gut 56(5): 677-684.

Treeage Pro (2009) Treeage Pro User's Manual. Williamstown, USA.

Venesmaa ,P. and Ylikorkala O. (1992) Morbidity and mortality associated with primary and repeat operations for ovarian cancer. Obstetrics And Gynecology. 79(2):168-172.

Warwick J,. Vardaki E., Fattizzi N., et al. (2009). Defining the surgical management of suspected early-stage ovarian cancer by estimating patient numbers through alternative management strategies. BJOG:116(9): 1225-1241.

Appendix 2

Abbreviations

AFP	alpha fetoprotein
Beta-hCG	beta human chorionic gonadotrophin
CA125	cancer antigen 125
CT	computerised tomography
FIGO	International Federation of Gynecology and Obstetrics
GP	general practitioner
HE4	human epididymis protein 4
IBS	irritable bowel syndrome
IDS	interval debulking surgery
IP	intra-peritoneal
MDT	multidisciplinary team
MRI	magnetic resonance imaging
PET-CT	positron emission tomography fused with computed tomography
RCT	randomised controlled trial
RMI I	risk of malignancy index I

Appendix 3

Glossary

Abdomen
The region of the body and its contents between the chest and the pelvis.

Adjuvant treatment
Treatment as a follow-up to surgery designed to remove any traces of tumour which may have been left behind.

Adnexal mass
A mass in the pelvis close to one or other side of the womb.

Ascites
An abnormal accumulation of fluid in the abdominal cavity.

Benign
Something that is not cancer and treatment or removal is curative.

Bilateral lesion
Tumours that occur in both paired organs, such as the ovaries.

Bilateral salpingo-ophporectomy
Surgical removal of both fallopian tubes and ovaries.

Biopsy
Removal of a sample of tissue from the body to allow diagnosis.

Cancer Centre
Usually situated in larger hospitals, it provides a high degree of specialisation and a comprehensive range of cancer services and treatments that encompass all facets of cancer care necessary in modern cancer management.

Carcinoma
Cancer.

Case series
A series of case reports involving patients who were given similar treatment. Reports of case series usually contain information about individual patients including demographic information, information on diagnosis, treatment, response to treatment and follow-up.

Cellular product
Something produced by a cell.

Chemotherapy

Drug(s) that kill cells dividing faster than normal. These drugs are usually used in the treatment of cancer.

Colour Doppler ultrasound

A diagnostic imaging technique that uses ultrasound methods (sound waves) to measure the flow of blood through a blood vessel indicated by different colours.

Computed tomography (CT)

A diagnostic imaging technique that uses X-rays and a computer to produce detailed pictures of cross sections of the body.

Cytology

The study of cells, their origin, structure, function and pathology.

Cytoreduction

To surgically remove cancer as much as possible but perhaps not totally.

Debulking

To surgically reduce the amount cancer.

Disease free survival

Length of time after treatment during which no disease is found/seen/identified.

Disease relapse

The return of signs and symptoms of the disease after a patient has had a period of time without any signs and symptoms.

Disease specific survival

The proportion of people in a study who have survived a particular disease since diagnosis or treatment. Deaths from other causes are not counted.

Doppler flow

A diagnostic imaging technique that uses sound waves (ultrasound) to measure the flow of blood through a blood vessel.

Enzyme

A protein produced by certain cells that enables biochemical reactions.

False negative

A result that appears negative but should have been positive, i.e. a test failure.

False positive

A result that appears positive but should have been negative, i.e. a test failure.

Fibrosis

An increase in fibrous tissue, e.g. scarring, which may make an area seem abnormal on imaging or at surgery.

Frozen section diagnosis

A pathological laboratory procedure which rapidly freezes and slices tissue during surgery for immediate microscopic analysis and diagnosis.

Gastro-splenic ligament

A structure connecting the stomach to the spleen.

General anaesthetic

A type of anaesthesia used for pain relief during surgical procedures, which makes you completely lose consciousness so that the surgery can be performed without causing pain or distress.

Grey-scale doppler

A diagnostic imaging technique that uses sound waves (ultrasound) to measure the flow of blood through a blood vessel, indicated by proportional shades of grey.

Gynaecological oncologist

A surgeon who is an expert in the treatment of cancer affecting the female reproductive system.

Gynaecological cancer lead

The clinician, usually a gynaecological oncologist, who leads and is responsible for the gynaecological cancer services.

Heart failure

The inability of the heart to supply sufficient blood flow to meet the body's needs.

Heterogeneity

More variation than would be expected.

Histology or histopathology

An examination of tissue using a microscope.

Hormone

A chemical released by a cell that sends out messages that affect cells in other parts of the body.

Hysterectomy

Surgical removal of the womb.

Imaging

The production of a clinical image using radiology, for example an x-ray, or ultrasound/CT/MRI/PET-CT.

Image guided biopsy

A technique which uses an ultrasound or CT scanner to guide the positioning of a needle for an accurate biopsy.

Infracolic omentectomy

Surgical excision of the pad of fat attached to the large bowel.

Interval debulking surgery

Surgery performed during primary chemotherapy with further chemotherapy to follow.

Intra-abdominal cavity

Space within the abdomen.

Intra-abdominal fluid

More fluid found in the abdomen than expected.

Intraperitoneal chemotherapy

Chemotherapy drugs infused into the abdomen through a tube.

Intraperitoneal stripping

Operative removal of the peritoneal lining of the abdominal cavity.

Intravenous

Infusion or injection into a vein.

Irritable bowel syndrome

A condition that affects the colon and small intestine.

Laparotomy

General term for abdominal surgery requiring an incision in the abdominal wall.

Laparoscopy

Examination of the abdominal cavity using a laparoscope (telescope).

Lesion

Term for an abnormal finding in the body.

Lesser sac

An anatomical name for the potential space in the abdomen behind the stomach.

Local anaesthetic

A type of localised anaesthesia which numbs an area of the body.

Lymphadenectomy

A surgical procedure in which lymph nodes are removed for analysis.

Lymph nodes

Small structures (glands) which act as filters of the lymphatic system. Lymph nodes close to a primary tumour are often one of the first sites to which cancer spreads.

Lymph node assessment

This involves sampling of retroperitoneal lymphatic tissue from the para-aortic area and pelvic side walls wherever there is a palpable abnormality;or random sampling when this is not the case.

Lymphocysts

A localised collection of lymph fluid from injured lymph vessels.

Lymphoedema

Distant swelling often of a limb because of obstruction or impaired circulation of lymphatic fluid.

Magnetic resonance imaging (MRI)

A diagnostic imaging technique that uses powerful electromagnets and a computer to produce well-defined images of the body's internal structures.

Malignant

Cancerous.

Markers

Substances found in increased amounts in the blood, other body fluids or tissues which may be associated with the presence of a certain type of cancer in the body

Mass

A lump.

Median

The middle value of an ordered set of measurements.

Menopause

The permanent cessation of ovarian function.

Meta-analysis

A method of summarising previous research by reviewing and combining the results of a number of different clinical trials.

Metastases/Metastatic

Spread of cancer away from the original site to somewhere else in the body, usually via the bloodstream or the lymphatic system.

Midline laparotomy

A surgical procedure involving a vertical incision through the abdominal wall to gain access into the abdominal cavity

Monoclonal antibodies

Drugs that recognise, target, and stick to particular chemicals on the surface of cells, stimulating the body's immune system to destroy the cells. These are artificially made in the laboratory in pure form from a single clone of cells.

Morbidity

A diseased condition or state.

Multidisciplinary team (MDT)

A team with members from different healthcare disciplines (including for example, oncology, pathology, radiology, nursing).

Multilocular cyst

A cyst containing internal partitions.

Multi-slice

The use of imaging techniques, such as CT or MRI scans, that can image the body in multiple sections. These images are reconstructed by a computer.

Observational study

A non-randomised study that observes the characteristics and outcomes over time of subjects who do and do not take a particular therapy.

Occult

Hidden or difficult to observe.

Omentum

A fold of fat attached to the stomach.

Optimal surgical staging

This comprises midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy; biopsies of any peritoneal deposits; random biopsies of the pelvic and abdominal peritoneum and retroperitoneal lymph node assessment (Winter-Roach et al., 2009).

Oncologist

A doctor who specialises in managing cancer.

Organ

A structure in the body e.g. liver.

Ovary/ovaries

One or a pair of reproductive organs found in women which produce eggs and hormones.

Overall survival

The time one lives after a diagnosis of cancer. Often quoted as a percentage chance of living a number of years (e.g. 5 or 10).

Over-expressed

An increase in the amount (and activity) of a molecule in a cell, for example of a gene or growth factor receptor.

Para-aortic lymph node

Lymph nodes which sit in front of the lower spine either side of the aorta.

Pathology

A branch of medicine concerned with the study of disease.

Pelvis

Part of the body below the abdomen, encircled by bones.

Percutaneous core biopsy

Biopsy technique where tissue is obtained by needle puncture of a tumour through the skin, obtaining a core of tissue for histological examination.

Peritoneum

A transparent membrane that lines the abdominal cavity.

Peritoneal deposits

Lumps of cancer that has spread to the peritoneum.

Peritoneal surfaces

Surfaces of the peritoneum lining the abdominal and pelvic cavity.

Pleural effusions

Abnormal accumulation of fluid between the lung and chest wall.

Positron emission tomography

A diagnostic imaging technique using a radio-active tracer which shows increased tissue metabolism.

Post-menopausal

The time from one year after her last menstrual period.

Prediction model

A model which assesses the risk and susceptibility to cancer, used in clinical decision making.

Predictive value

The chances of something happening.

Pre-menopausal

The phase in a woman's life before the onset of menopause.

Pre-operative assessment

The assessment and management of the patient before surgery, e.g. imaging, diagnosis and preparation for surgery.

Primary care

Services provided in a community setting, outside secondary care, where patients are usually first seen.

Primary treatment

Initial treatment used.

Prognostic study

A study that examines selected predictive variables, or risk factors, and assesses their influence on the outcome of a disease.

Prospective diagnostic study

A study that looks at a new diagnostic method to see if it is as good as the current 'gold standard' method of diagnosing a disease.

Proteins

Molecules that are made up of amino acids and are needed for the body to function properly.

Quality of life

An overall appraisal of well being.

Radiation

Energy released in the form of particle or electromagnetic waves, which can damage living cells.

Radiology department

A department providing a wide range of diagnostic imaging services.

Radionuclides

An unstable form of a chemical element that releases radiation as it breaks down to become more stable.

Radiotherapy

A treatment for cancer that uses high energy ionising radiation (usually X-rays) to kill cells.

Randomised controlled trials (RCTs)

A clinical trial in which subjects are randomised to different groups for the purpose of studying the effect of a new intervention, for example a drug or other therapy.

Receptor

A molecule inside or on the surface of a cell that binds to a specific substance, resulting in a specific physiologic effect.

Residual disease

Cancer cells that remain after attempts to remove the cancer have been made e.g. by surgery, chemotherapy or radiation.

Retroperitoneal

The area outside or behind the peritoneum.

Secondary care

Services provided by the hospital, as opposed to the General Practitioner and the primary care team.

Sensitivity

The proportion of individuals who have disease correctly identified by the study test.

Serum

The clear liquid part of the blood that remains after blood cells and clotting proteins have been removed.

Serum tumour marker

Substances sometimes found in increased amounts in the blood, other body fluids or tissues which suggests that a certain type of cancer may be in the body.

Spatial resolution

Ability to tell two things apart.

Specificity

The proportion of individuals who do not have a disease and who are correctly identified by the study test.

Staging

Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.

Sub-diaphragmatic region

Area directly under the diaphragm.

Supportive care

Support for the patient and their family to cope with cancer and any treatment given throughout the cancer pathway.

Systematic retroperitoneal lymphadenectomy

A systematic stripping of all lymph nodes from the pelvic and para-aortic region to the level of the renal veins.

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Tissue diagnosis

Diagnosis based on the microscopic examination of biopsies from tissues in the body.

Toxicity

Refers to the undesirable and harmful side effects of a drug.

Tuberculosis

Disease due to infection with M. tuberculosis bacteria.

Tumour marker

Substances sometimes found in increased amounts in the blood, other body fluids or tissues which suggests that a certain type of cancer may be in the body.

Triage

A process in which patients are sorted according to their need for care.

Ultrasound

An imaging method in which high-frequency sound waves are used to outline a part of the body.

Ureter

The tubes that carry urine from the kidneys to the bladder.

Appendix 4

Guideline scope

Guideline title

Ovarian cancer: the recognition and initial management of ovarian cancer

Short title

Ovarian cancer

The remit

The Department of Health has asked NICE: 'To prepare a clinical guideline on the recognition and initial management of ovarian cancer, to include both surgery and chemotherapy.'

Clinical need for the guideline

Ovarian cancer is the leading cause of gynaecological cancer death in the UK and its incidence is rising. It is the fourth most common malignancy in women, with a lifetime risk of about 2% in England and Wales.

The overall outcome for women with ovarian cancer is poor, with an overall 5-year survival rate of less than 30%. This is because most women who develop ovarian cancer present with advanced disease.

The stage of the disease is the most important factor with regard to outcome. The woman's general health at the time of presentation is also important because it affects what treatments can be used. Most women have had symptoms for months prior to initial presentation, and there are often delays between initial presentation and specialist referral. There is a need for greater awareness of the disease and also initial investigations enabling earlier referral and maximising of treatment options.

Current practice

There are variations in:
- modalities used for early detection and diagnosis of ovarian cancer
- the number of drugs used and duration of treatment in women with ovarian cancer
- the timing, extent and effectiveness of surgery in women with ovarian cancer in whom complete removal of the disease is not possible.

A clinical guideline will help to address these issues and offer guidance on best practice.

The guideline

The guideline development process is described in detail on the NICE website (see 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

If we are to produce a high-quality guideline within the allotted time it will not be possible to cover the entire care pathway described by the remit.

Therefore we intend to focus on clinical issues:
- for which there is uncertainty or disagreement on best practice
- that will have the most significant impact on the clinical service and on the management of patients with ovarian cancer
- that could improve health outcomes and/or make better use of health resources
- that could help to avoid unlawful discrimination and reduce health inequalities.

A list of the key clinical issues (section 4.4) has been developed using advice from the Guideline Development Group chair and clinical lead, attendees at the NICE ovarian cancer stakeholder workshop and registered stakeholders. We acknowledge that there will be some important topics that are not part of the final prioritised list.

The areas that will be addressed by the guideline are described in the following sections.

Population

Groups that will be covered

- Adult women (18 years and older) with epithelial ovarian cancer.
- Adult women with fallopian tube carcinoma.
- Adult women with primary peritoneal carcinoma.
- Adult women with suspected ovarian or primary peritoneal carcinoma.
- Adult women with borderline ovarian cancer.
- No patient subgroups needing special consideration have been identified.

Groups that will not be covered

- Children (younger than 18 years) with ovarian malignancy.
- Women with pseudomyxoma peritonei.
- Women with relapsed ovarian, fallopian tube or peritoneal cancer.
- Women with germ cell tumours of the ovary.
- Women with sex cord stromal tumours of the ovary.
- Women with secondary cancers metastasising to the ovary or peritoneum.

Healthcare setting

- Primary care.
- Secondary care, including diagnosis, surgery and chemotherapy.
- Tertiary care in cancer centres, and regional centres with specialties such as intraperitoneal chemotherapy.
- NHS hospice care.

Main outcomes

- Sensitivity of diagnostic tests
- Specificity of diagnostic tests
- Overall survival
- 5 year survival
- Median survival
- Disease free survival
- Morbidity
- Mortality
- Number and severity of adverse events
- Quality of life

Clinical management

Key clinical issues that will be covered

- The signs and symptoms of ovarian cancer.
- The relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival.
- For women with suspected ovarian cancer, the most effective first test in primary care.
- For women with suspected ovarian cancer, the most effective malignancy index.
- For women with suspected ovarian cancer, the serum tumour marker tests that should be routinely carried out to determine future management.
- For women with suspected ovarian cancer, the most appropriate imaging to be done to determine future management.
- For women with suspected ovarian cancer, when it is appropriate not to have a tissue diagnosis before starting chemotherapy.
- The best method of tissue diagnosis before chemotherapy: samples from image guided biopsy or laparoscopic biopsy.
- The effectiveness of surgery in the primary management of women with ovarian cancer, who will receive chemotherapy.
- For women with ovarian cancer whose disease appears to be confined to the ovaries, the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management.
- For women with ovarian cancer, the effectiveness of intra-peritoneal chemotherapy in primary management.
- For women diagnosed with ovarian cancer, the support that should be offered.
- What is the most clinically effective primary chemotherapy for women with ovarian cancer

Clinical issues that will not be covered

- Population-based screening.
- Surveillance of high-risk groups, including women with a family history of ovarian cancer.

Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually only be from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

Status

Scope

This is the final scope.

Guideline

The development of the guideline recommendations will begin in May 2009.

Related NICE guidance

- Referral guidelines for suspected cancer. NICE clinical guideline 27 (2005). Available from www.nice.org.uk/CG27
- Improving supportive and palliative care for adults with cancer. Cancer service guidance (2004). Available from www.nice.org.uk/csgsp
- Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal guidance 55 (2003). Available from www.nice.org.uk/TA55
- Improving outcomes in gynaecological cancers. Cancer service guidance (1999). Department of Health, National Cancer Guidance Steering Group. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005385

Further information

Information on the guideline development process is provided in:
- 'How NICE clinical guidelines are developed: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'.
- These are available from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the NICE website (www. nice.org.uk).

Appendix 5

List of topics covered by each chapter

Chapter 2 – Detection in primary care

- What are the symptoms and signs of ovarian cancer?
- What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?
- For women with suspected ovarian cancer, what are the most effective first tests in primary care?

Chapter 3 – Establishing the diagnosis in secondary care

- For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?
- For women with suspected ovarian cancer, which malignancy index is the most effective?
- For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management?
- For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy?
- What is the best method of tissue diagnosis before chemotherapy, samples from image guided biopsy or laparoscopic biopsy?

Chapter 4 – Management of suspected early stage ovarian cancer

- For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management?
- For women with stage I ovarian cancer, what is the most effective first line chemotherapy?

Chapter 5 – Management of advanced stage (II-IV) ovarian cancer

- What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?
- For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management?

Chapter 6 – Support needs for women with newly diagnosed ovarian cancer

- For women newly diagnosed with ovarian cancer, what support should be offered?

Appendix 6

People and organisations involved in production of the guideline

Appendix 6.1

Members of the Guideline Development Group (GDG)

GDG Chair

Mr Sean Duffy — Medical Director of the Yorkshire Cancer Network

GDG Lead Clinician

Mr Charles Redman — Consultant Gynaecological Oncologist, University Hospital of North Staffordshire, Stoke-on-Trent

Group Members

Dr Susan Barter — Consultant Radiologist, Addenbrooke's Hospital, Cambridge University Hospitals Foundation

Audrey Bradford — Network Director, Anglia Cancer Network

Dr Laurence Brown — Consultant Histopathologist, Leicester Royal Infirmary, Leicester

Mr Derek Cruickshank — Consultant Gynaecological Oncologist, The James Cook University Hospital, Middlesbrough

Dr Craig Dobson — Senior Lecturer in Medical Education and General Practice, Hull/York Medical School

Linda Facey — Patient/carer member

Dr Marcia Hall — Consultant in Medical Oncology, Mount Vernon Cancer Centre, Middlesex

Mr Jed Hawe — Consultant Obstetrician and Gynaecologist and Local Gynaecological Cancer Lead, Countess of Chester NHS Foundation Trust

Dr Cathy Hughes — Clinical Nurse Specialist and Cancer Lead, National Patient Safety Agency, London

Frances Reid — Patient/carer member, Target Ovarian Cancer

Michael Scanes — Patient/carer member

Professor Nicholas SA Stuart — Medical Oncologist and Professor of Cancer Studies, University of Bangor

Declarations of interest

The Guideline Development Group were asked to declare any possible conflicts of interest which could interfere with their work on the guideline. The interests that were declared are as follows:

GDG Member	Interest Declared	Type of Interest	Decisions Taken
Mr Sean Duffy	Chief investigator for a trial of a nutritional supplement in patients with ovarian cancer, that is receiving support from Nutricia	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as interventions included in the trial or made by Nutricia are not being investigated by the guideline
Mr Charles Redman	Received travel and subsistence expenses from Schering Plough Oncology to take part in a debate on the role of lymphadenectomy with a group of gynae-oncologists in March 2010	Personal pecuniary, specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
Professor Nicholas S A Stuart	Chief investigator for a trial investigating the mechanisms of fatigue induced by sunitinib in patients with advanced/metastatic renal cancer, which received funding from Pfizer	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as interventions included in the trial or made by Pfizer are not being investigated by the guideline
	Received travel and subsistence expenses from Novartis to attended the American Society of Clinical Oncology meeting in May 2009	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
Michael Scanes	Member of the group that recently published 'Key Messages on Ovarian Cancer'	Personal non-pecuniary	Declare and can participate in discussions on all topics
Frances Reid	Involved in advocating for the role of symptoms in ovarian cancer to be acknowledged, based on research emerging from the USA	Personal non-pecuniary	Declare and can participate in discussions on all topics
Dr Marcia Hall	Received travel and subsistence expenses from Boehringer Ingelheim to attend the American Society of Clinical Oncology meeting in June 2010	Personal pecuniary, non-specific	Declare and can participate in discussions on all topics as the expenses were not beyond reasonable amounts
Mr Derek Cruickshank	Asked to provide expert advice, by The HTA, on the value of research into hyperthermic intra-peritoneal chemotherapy in ovarian cancer	Personal non-pecuniary	Declare and can participate in discussions on all topics

Appendix 6.2

Organisations invited to comment on guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

A Little Wish

Abbott Laboratories Limited

Aberdeen Royal Infirmary

Airedale NHS Foundation Trust

Almac Diagnostics

Anglia Cancer Network

Arden Cancer Network

Association for Clinical Biochemistry

Association for Palliative Medicine of Great Britain and Ireland

Association of British Insurers (ABI)

Association of Chartered Physiotherapists in Oncology and Palliative Care

Association of Clinical Biochemists, The

Association of clinical pathologists

Association of the British Pharmaceuticals Industry (ABPI)

AstraZeneca UK Ltd

Barnsley Hospital NHS Foundation Trust

Beckman Coulter UK Ltd

Belfast Health and Social Care Trust

Birmingham Cancer Network

Birmingham Women's NHS Trust

BMJ

Boehringer Ingelheim Ltd

Brighton and Sussex University Hospitals Trust

British Dietetic Association

British Gynaecological Cancer Society

British National Formulary (BNF)

British Nuclear Medicine Society

British Society for Cancer Genetics

British Society for Human Genetics

British Society of Urogynaecological Radiology

BUPA

Cambridge University Hospitals NHS Foundation Trust (Addenbrookes)

Cancer Care Cymru

Cancer Research UK

Care Quality Commission (CQC)

Central South Coast Cancer Network

Cheshire PCT

College of Emergency Medicine

College of Occupational Therapists

Commission for Social Care Inspection

Connecting for Health

Daiichi Sankyo UK

Department for Communities and Local Government

Department of Health

Department of Health Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI)

Department of Health, Social Services & Public Safety, Northern Ireland (DHSSPSNI)

Derby-Burton Cancer Network

Derbyshire Mental Health Services NHS Trust

Dorset Cancer Network

East Lancashire Hospitals NHS Trust

East Midlands Cancer Network

Essex Cancer Network

Eusapharma (Europe) Ltd

Eve Appeal, The

GE Healthcare

GlaxoSmithKline UK

Greater Manchester and Cheshire Cardiac and Stroke Network

Greater Midlands Cancer Network

Guerbet Laboratories Ltd

Guys and St Thomas NHS Trust

Harrogate and District NHS Foundation Trust

Hospira UK Limited

Human Fertilisation and Embryology Authority

Humber and Yorkshire Coast Cancer Network

Imaging Equipment Limited

Institute of Biomedical Science

James Cook University Hospital

Leeds PCT

Leeds Teaching Hospitals NHS Trust

Leicestershire Northamptonshire and Rutland Cancer Network

Luton & Dunstable Hospital NHS Foundation Trust

Lymphoedema Support Network, The

Macmillan Cancer Support

Medical Research Council Clinical Trials Unit

Medicines and Healthcare Products Regulatory Agency (MHRA)

Ministry of Defence (MoD)

MRC-CTU

National Council for Palliative Care

National Patient Safety Agency (NPSA)

National Public Health Service for Wales

National Treatment Agency for Substance Misuse

NCC - Cancer

NCC - Mental Health

NCC - National Clinical Guidance Centre (NCGC)

NCC - Women & Children

NETSCC, Health Technology Assessment

NHS Clinical Knowledge Summaries Service (SCHIN)

NHS Direct

NHS Improvement

NHS Kirklees

NHS Knowsley

NHS Plus

NHS Quality Improvement Scotland

NHS Sefton

NHS Sheffield

NHS Western Cheshire

NICE - CPHE

NICE - CPHE Methodology - Simon for info

NICE - Guidelines Coordinator - for info

NICE - Guidelines HE for info

NICE – Implementation consultant - Region East

NICE - Implementation consultant - Region SW

NICE - Implementation consultant - SE/London

NICE - Implementation consultant - Region NW/NE

NICE - Implementation consultant - Region West Midlands

NICE - Implementation co-ordination - for info

NICE - PPIP

NICE - Technical Appraisals (Interventional Procedures) - for info

North East London Cancer Network

North East London Cancer Network

North Tees and Hartlepool Acute Trust

North Trent Cancer Network

North West London Cancer Network

North Yorkshire and York PCT

Northern Ireland Cancer Network

Nottingham University Hospitals NHS Trust

Novartis Pharmaceuticals UK Ltd

Novo Nordisk

Ovacome

Ovarian Cancer Action

Patients Council

Pelvic Pain Support Network

PERIGON Healthcare Ltd

Pfizer Limited

Poole and Bournemouth PCT

Randox Laboratories Ltd

Roche Diagnostics

Roche Products Limited

Royal College of General Practitioners

Royal College of General Practitioners Wales

Royal College of Nursing

Royal College of Obstetricians and Gynaecologists

Royal College of Pathologists

Royal College of Physicians London

Royal College of Radiologists

Royal Cornwall Hospitals Trust

Royal Society of Medicine

Sandwell PCT

Sanofi-Aventis

Schering-Plough Ltd

Scottish Intercollegiate Guidelines Network (SIGN)

Sedgefield PCT

Sheffield PCT

Sheffield Teaching Hospitals NHS Foundation Trust

Social Care Institute for Excellence (SCIE)

Society and College of Radiographers

South East Wales Cancer Network

South Tees Hospitals NHS Trust

Southend University Hospitals NHS Trust

Sussex Cancer Network

Target Ovarian Cancer

Teenage Cancer Trust, The

Teenagers and Young Adults with Cancer (TYAC)

Thames Valley Cancer Network

The Roy Castle Lung Cancer Foundation

The Royal College of Radiologists

The Society and College of Radiographers

UK Clinical Pharmacy Association

University Hospital Birmingham NHS Foundation Trust

Welsh Assembly Government

Welsh Scientific Advisory Committee (WSAC)

West Hertfordshire PCT & East and North Hertfordshire PCT

Western Cheshire Primary Care Trust

Western Health and Social Care Trust

York NHS Foundation Trust

Appendix 6.3

Individuals carrying out literature reviews and complementary work

Overall Co-ordinators

Dr John Graham   Director, National Collaborating Centre for Cancer, Cardiff

Dr Andrew Champion   Centre Manager, National Collaborating Centre for Cancer, Cardiff

Project Managers

Angela Bennett   Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff

Victoria Titshall[1]   National Collaborating Centre for Cancer, Cardiff

Helen Pearson[2]   National Collaborating Centre for Cancer, Cardiff

Researchers

Dr Nathan Bromham   National Collaborating Centre for Cancer, Cardiff

Dr Karen Francis   Senior Researcher, National Collaborating Centre for Cancer, Cardiff

Angela Melder[3]   Senior Researcher, National Collaborating Centre for Cancer, Cardiff

Dr Lakshmi Sandu Aana   Registrar in Obstetrics and Gynaecology, Northwest Deanery

Information Specialists

Elise Collins   National Collaborating Centre for Cancer, Cardiff

Sabine Berendse   National Collaborating Centre for Cancer, Cardiff

Stephanie Arnold[4]   National Collaborating Centre for Cancer, Cardiff

---

[1] From March 2010 – August 2010

[2] From August 2009 – February 2010

[3] From October 2008 – November 2009

[4] From October 2008 – October 2009

Health Economists

Eugenia Priedane   Research Assistant, London School of Hygiene and Tropical Medicine

Dr Alec Miners   Lecturer in Health Economics, London School of Hygiene and Tropical Medicine

Needs Assessment

Dr Lakshmi Sandu Aana   Registrar in Obstetrics and Gynaecology, Northwest Deanery

Appendix 6.4

Members of the Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The members of the Guideline Review Panel were as follows:

Dr John Hyslop – Chair

Consultant Radiologist, Royal Cornwall Hospital NHS Trust

Dr Ash Paul

Deputy Medical Director, Health Commission Wales

Professor Liam Smeeth

Professor of Clinical Epidemiology, London School of Hygiene and Tropical Medicine

Kieran Murphy

Health Economics & Reimbursement Manager, Johnson & Johnson Medical Devices & Diagnostics (UK)

Sarah Fishburn

Lay member

Members of the NICE project team

Fergus Macbeth

Centre for Clinical Practice Director

Nicole Elliott[1]

Guideline Commissioning Manager

Claire Turner[2]

Guideline Commissioning Manager

Emma Banks[3]

Guidelines Coordinator

Anthony Gildea[4]

Guidelines Coordinator

---

[1] From October 2008 – July 2009
[2] October 2009 – present
[3] From October 2008 – June 2010
[4] June 2010 – present

Amanda Killoran

Technical Lead

Stefanie Reken

Health Economist

Lynn Knott

Editor

Barbara Meredith

Patient Involvement Lead