

PRACTICE

GUIDELINES

Recognition and initial management of ovarian cancer: summary of NICE guidance

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This is one of a series of *BMJ* summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Ovarian cancer is the leading cause of death from gynaecological cancer in the United Kingdom, and its incidence is rising. It is the fifth most common cancer in women, with a lifetime risk of about 2% in England and Wales.¹ The outcome for women with ovarian cancer is generally poor, with an overall five year survival rate of less than 35%.² Most women have had symptoms for months before presentation, and as these are frequently non-specific, delays often occur between presentation and referral to a specialist.³ Greater awareness of the disease and appropriate initial investigations in primary and secondary care are needed to enable earlier referral and optimum treatment. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the recognition and initial management of women with ovarian cancer.⁴

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in *italic* in square brackets.

Detection in primary care

Awareness of symptoms and signs

- Refer the woman urgently to a gynaecological cancer service if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not caused by known uterine fibroids). Urgent referral for suspected cancer should be within the national target in England and Wales, which is currently two weeks. For recommendations on the support and information needs of people with suspected cancer, see NICE's guidelines.⁵

- Carry out tests in primary care if a woman (especially if aged 50 years or over) reports having any of the following symptoms on a persistent or frequent basis—particularly more than 12 times a month:
 - Persistent abdominal distension (women often refer to this as bloating)
 - Feeling full (early satiety) or loss of appetite, or both
 - Pelvic or abdominal pain
 - Increased urinary urgency or frequency, or both.
- Consider carrying out tests in primary care if a woman reports unexplained weight loss, fatigue, or changes in bowel habit.
- Carry out appropriate tests for ovarian cancer in any woman aged 50 years or over who has had symptoms within the past 12 months that suggest irritable bowel syndrome,⁶ because IBS rarely presents for the first time in women of this age.
- Advise any woman who is not suspected of having ovarian cancer to return to her general practitioner if her symptoms become more frequent or persistent.

[All the above are based on moderate quality retrospective case-control studies]

First tests

- Measure serum CA125 concentration in primary care in women with symptoms that suggest ovarian cancer.
- If serum CA125 concentration 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 for further investigation.⁵
- For any woman who has normal serum CA125 concentration (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 general practitioner if her symptoms become more frequent and/or persistent.

[All the above are based on indirect evidence from systematic reviews of these tests in secondary care or screening studies]

Establishing the diagnosis in secondary care

Tumour markers

- Measure the serum CA125 concentration in secondary care in all women with suspected ovarian cancer, if this has not already been done in primary care.
- In women aged under 40 years with suspected ovarian cancer, measure serum concentrations of α fetoprotein, β human chorionic gonadotrophin, and CA125, to identify women who may not have epithelial ovarian cancer.

[Both the above are based on low to moderate quality case series]

Malignancy indices

Calculate a score on the risk of malignancy index I (RMI I) (box 1) after ultrasonography, and refer all women with a score of 250 or greater to a specialist multidisciplinary team. [Based on a good quality systematic review]

Imaging

- Perform ultrasonography 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 scan, the serum CA125 concentration, and the clinical status suggest ovarian cancer, perform computed tomography of the pelvis and abdomen to establish the extent of disease. Include the thorax if clinically indicated.
- Do not use magnetic resonance imaging routinely for assessing women with suspected ovarian cancer.

[All the above are based on good quality diagnostic systematic reviews and meta-analysis]

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.

[Both the above recommendations are based on moderate quality retrospective studies with small numbers of patients]

Methods of tissue diagnosis other than laparotomy:

- 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.

[Both the above recommendations are based on low quality evidence from case series for the risks and accuracy of each technique individually]

Management of suspected early (stage I) ovarian cancer

Role of systematic retroperitoneal lymphadenectomy

Conduct an assessment of the retroperitoneal lymph nodes as part of optimal surgical staging in women with suspected ovarian cancer whose disease seems to be confined to the ovaries (that is, seems to be stage I disease). Optimal surgical staging consists of 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 assessment of the retroperitoneal lymph nodes.⁸ [Based on low quality evidence from two retrospective observational studies, one non-randomised comparative study, and a small randomised controlled trial]

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 seems to be confined to the ovaries (that is, seems to be stage I disease). [Based on low quality evidence from two retrospective observational studies, one non-randomised comparative study, and a small randomised controlled trial]

Adjuvant systemic chemotherapy for stage I disease

- Do not offer adjuvant chemotherapy to women who have had optimal surgical staging and have low risk stage I disease (grade 1 or 2, stage Ia or 1b) (box 2).
- 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 and seem to have stage I disease.

[All the above are based on a high quality Cochrane review and a lower quality randomised controlled trial]

Management of advanced (stage II to IV) ovarian cancer

Primary surgery

When performing surgery in women with ovarian cancer, whether before chemotherapy or after neoadjuvant chemotherapy, the objective should be complete resection of all macroscopic disease. [Based on limited, contradictory evidence from two Cochrane systematic reviews and two small randomised controlled trials]

Intraperitoneal chemotherapy

Do not offer intraperitoneal chemotherapy to women with ovarian cancer, except as part of a clinical trial. [Based on two

Box 1 Risk of malignancy index I⁷

The risk of malignancy index I (RMI I) combines three presurgical features: serum CA125 concentration, menopausal status, and ultrasound score. The RMI is a product of the score for the ultrasound scan (U), the score for menopausal status (M), and the serum CA125 concentration (IU/mL), thus: $RMI I = U \times M \times CA125$

Scoring system

- 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 follows: 1 = premenopausal and 3 = post-menopausal. The classification of post-menopausal is for 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 concentration can vary from 0 to hundreds or even thousands of units.

Box 2 FIGO staging* for ovarian cancer*Stage I: Limited to one or both ovaries*

- 1a—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 is limited to ovaries with any of the following: ruptured capsule, tumour on ovarian surface, positive washings

Stage II: Pelvic extension or implants

- IIa—Extension or implants on to uterus or fallopian tube; negative washings
- IIb—Extension or implants on to other pelvic structures; negative washings
- IIc—Pelvic extension of implants with positive peritoneal washings

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

- IIIa—Microscopic peritoneal metastases beyond pelvis
- IIIb—Macroscopic peritoneal metastases (<2 cm in size) beyond pelvis
- IIIc—Peritoneal metastases (>2 cm) beyond pelvis, or lymph node metastases

Stage IV: Distant metastases to liver or outside peritoneal cavity

*Staging classifications according to the International Federation of Gynecology and Obstetrics

high quality systematic reviews and one randomised controlled trial]

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 matters) 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 available information covers:
 - The stage of the disease, treatment options, and prognosis
 - How to manage the side effects of both the disease and its treatments 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.

[Both the above recommendations are based on moderate quality qualitative studies]

Overcoming barriers

Primary care doctors have understandably been concerned that they should not needlessly subject women with non-specific symptoms to the distress and unpleasantness of investigations to detect this relatively rare disease. However, their caution is likely to have contributed to delays in diagnosing ovarian cancer, with women often presenting as emergencies or to inappropriate management pathways. The recommendations and supporting evidence should give healthcare professionals the confidence to start the appropriate investigations, better direct referrals to the correct pathway, and raise awareness among women. The recommended tests and necessary clinical resources will need to be made available and accessible.

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Further information on the guidance

This guidance was developed by the National Collaborating Centre for Cancer (NCC-C) in accordance with NICE guideline development methods.⁹ A Guideline Development Group (GDG) was established by the NCC-C that incorporated healthcare professionals, patient and carer members, and NCC-C staff. The GDG identified relevant clinical questions, collected and appraised clinical evidence, and evaluated the cost effectiveness of proposed interventions where possible. The draft guideline underwent a rigorous reviewing process during which stakeholder organisations were invited to comment; all comments were taken into consideration when producing the final version of the guideline.

NICE has produced four different versions of the guideline: a full version containing all the evidence, the process used for developing the recommendations, and all the recommendations; a quick reference guide; a version containing a list of all the recommendations, known as the "NICE guideline"; and a version for patients and the public. All these versions are available from the NICE website (www.nice.org.uk/CG122). Further updates of the guidance will be produced as part of the NICE guideline development programme.

Future research

- What is the relationship between the duration and frequency of symptoms in women with ovarian cancer before diagnosis, and the stage of disease at diagnosis and subsequent survival?
- What is the optimum threshold on the risk of malignancy index I (RMI I) that should be applied in secondary care to guide the management of women with suspected ovarian cancer?
- How does computed tomography compare with magnetic resonance imaging in accuracy of staging and prediction of optimal cytoreduction? Answering this will require large, multicentre case-control studies.
- What are the cost effectiveness and risks of systematic retroperitoneal lymphadenectomy in women whose ovarian cancer seems to be confined to the ovaries? Answering this will require a prospective randomised trial.
- What is the effectiveness of primary surgery in women with advanced ovarian cancer that cannot be fully excised?

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