GUIDELINES

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

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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 in the full version of this article on bmj.com.

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.

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.

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.

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.

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. The supporting evidence statements and further information about the guidance are in the full version on bmj.com.

Box 1 | Risk of malignancy index I[7]

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 x M x 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.

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.

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 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.

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]

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).

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 Ib) (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.

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.

Intraperitoneal chemotherapy

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

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Previous articles in this series

- Inpatient management of diabetic foot problems (*BMJ* 2011;342:d1280)
- Assessment and management of psychosis with coexisting substance misuse (*BMJ* 2011;342:d1351)
- Diagnosis, assessment, and management of harmful drinking and alcohol dependence (*BMJ* 2011;342:d700)
- Diagnosis and assessment of food allergy in children and young people (*BMJ* 2011;342:d747)

Box 2 | 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 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

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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10-MINUTE CONSULTATION

Gilbert's syndrome

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This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

A 22 year old man presents with a resolving episode of mild jaundice after an influenza-like illness. He reports a previous episode after an appendicectomy, which also resolved spontaneously, but he is worried about the implications of this recurrence. Biochemical records from his surgical admission show a slightly raised bilirubin concentration of 48 µmol/L (normal < 22 µmol/L), but alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase and albumin were all within normal limits.

What you should cover

The history and biochemistry in this patient strongly suggest Gilbert's syndrome, a hereditary (usually autosomal recessive) condition caused by impaired hepatic bilirubin clearance.[1] Gilbert's syndrome is present in 5-10% of Western European populations with 1 in 3 of those affected unaware that they have it.[2 3] Diagnosis of the disorder is often made after an incidental finding of isolated hyperbilirubinaemia on routine liver biochemistry testing.

Bilirubin is the normal by-product of the breakdown of red blood cells (haemoglobin). Patients with Gilbert's syndrome have a defect in the gene that encodes for glucuronyltransferase, which results in a 60-70% reduction in the liver's ability to conjugate bilirubin. This subsequent increase in serum concentrations of unconjugated bilirubin can lead to intermittent episodes of non-pruritic jaundice, which can be precipitated by fasting, infections, dehydration, surgery, physical exertion, and lack of sleep. Symptoms, including tiredness, that occur during episodes of jaundice are caused by the precipitating factor and do not result directly from Gilbert's syndrome.

Drugs that inhibit glucuronyltransferase activity such as gemfibrozil, and the protease inhibitors atazanavir and indinavir, can also trigger episodes of jaundice.[4] Altered metabolism of paracetamol has been shown in a subgroup

USEFUL READING

For patients

British Liver Trust (www.britishlivertrust.org.uk/home/the-liver/liver-diseases/gilberts-syndrome/aspx)

Patient UK (www.patient.co.uk/health/Gilbert's-Syndrome.htm)

For healthcare professionals

NHS Clinical Knowledge Summaries (www.cks.nhs.uk/gilberts_syndrome)

of patients with Gilbert's syndrome,[5] but no cases of toxicity have been reported after therapeutic doses. There is also a theoretical increased risk of myositis when statins are used in combination with gemfibrozil.[6]

What you should do

History and examination

Inquire about symptoms suggestive of hepatobiliary disease, such as abdominal pain and features of cholestasis (pruritus, pale stools, and dark urine), and examine the patient to exclude hepatosplenomegaly and stigmata of liver disease.

Investigations

Confirm the diagnosis by requesting liver biochemistry with conjugated (direct) and unconjugated (indirect) bilirubin concentrations, and full blood count with reticulocyte count and blood film to exclude haemolysis. There should be no bilirubinuria on urine dipstick because unconjugated bilirubin is not water soluble.

Diagnosis

- Gilbert's syndrome can be confidently diagnosed in the primary care setting when the patient has:
  - -Unconjugated hyperbilirubinaemia (conjugated bilirubin is within the normal range and/or <20% of total bilirubin—this is an important distinction because sometimes conjugated bilirubin will be slightly raised but in those circumstances it should be <20% of the total bilirubin) [7]
  - -Normal liver enzymes and albumin
  - -No additional symptoms or signs which suggest hepatobiliary disease
  - - A negative haemolysis screen (normal haemoglobin and reticulocyte count, and no fragmented or abnormal red cells on blood film).

Rarer causes of unconjugated hyperbilirubinaemia

Haemolysis
- Autoimmune haemolytic anaemia
- Glucose-6-phosphate dehydrogenase deficiency
- Sickle cell disease
- Thalassaemia
- Hereditary spherocytosis
- Sepsis
- Prosthetic heart valve

Other genetic disorders of bilirubin clearance
- Crigler-Najjar syndrome type I, a rare disorder in which bilirubin conjugation is absent, leading to severe jaundice in first few days of life
- Crigler-Najjar syndrome type II, in which conjugating enzyme activity is less than 10%; this syndrome usually presents with persistent jaundice in childhood

Drugs
- Rifampicin
- Methyldopa
- Sulfasalazine

Other
- Reabsorption of a large haematoma (excessive haemoglobin breakdown increases bilirubin production)
- Thyrotoxicosis (can sometimes lead to decreased glucuronyltransferase activity)

- Provocation tests, such as looking for a rise in unconjugated bilirubin after a 48 hour fast are impractical and non-specific for Gilbert's syndrome.[8]
- In cases where diagnostic doubt remains or patients are particularly anxious, genetic testing can be done for confirmation, but this should rarely be necessary.
- Liver or biliary imaging and referral to secondary care are not needed.
- Rarer causes of unconjugated hyperbilirubinaemia (see box) can be excluded with a comprehensive history and the simple investigations listed.
- Over-investigation is the greatest danger to patients with this benign condition.

Patient advice and education

- Explain to him that the disorder has occurred as a result of a genetic variation in the way he metabolises the pigment bilirubin, which results in him having slightly higher circulating levels than the average person.
- Reassure him that he does not have a disease and that episodes of jaundice are not contagious and will resolve spontaneously within a few days.
- Jaundice does not indicate or result in liver damage, and the condition does not reduce life expectancy or affect life insurance.[9]
- Dietary restrictions are not necessary and alcohol is safe within recommended limits.
- Recommend that he informs medical staff of his disorder if admitted to hospital and when prescribed new medication.
- Tell him to consult you if he has an episode of jaundice that is more severe or persistent than usual because this may indicate a separate condition.

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