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Improving early detection of ovarian cancer

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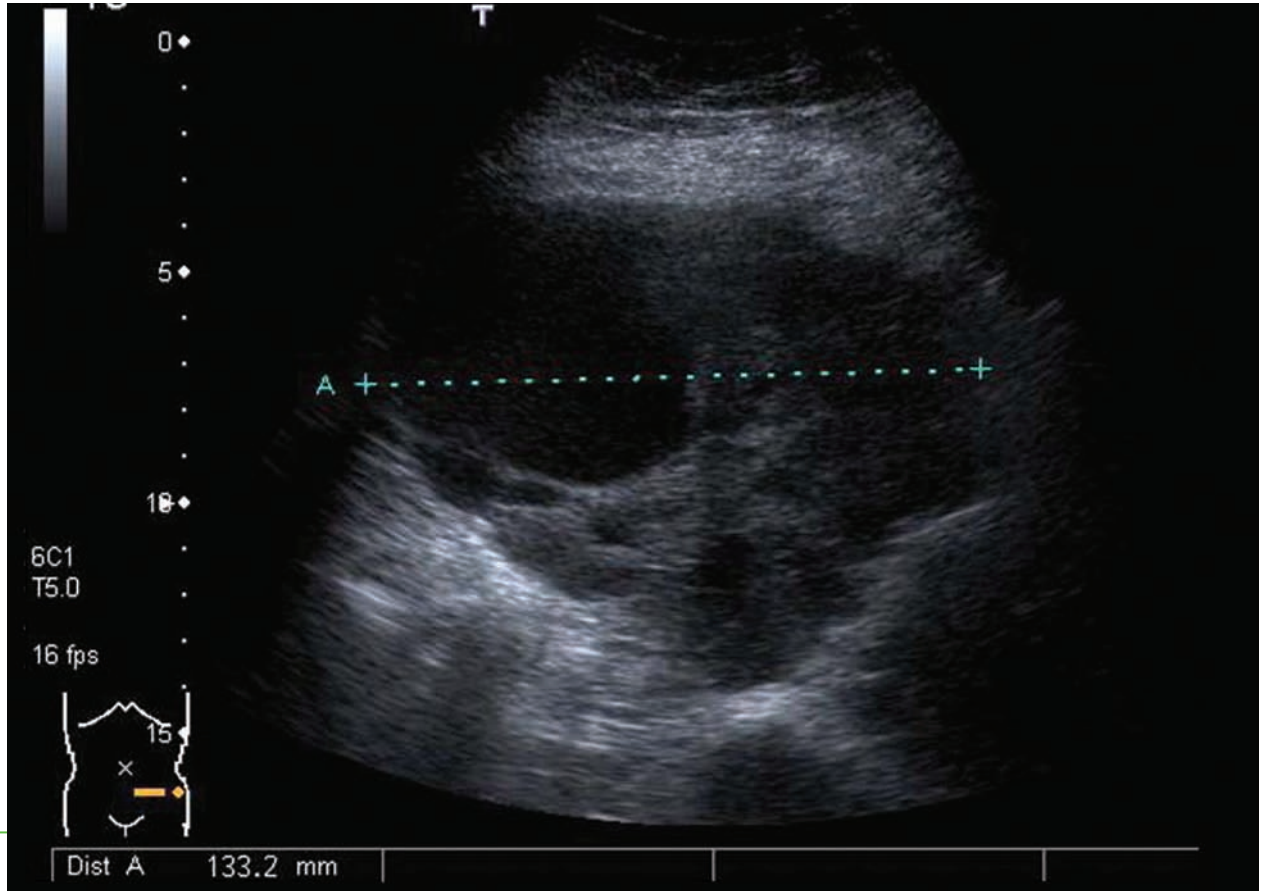
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Ultrasound scan showing ovarian cancer

What are the common symptoms?

OVARIAN CANCER IS THE FIFTH MOST COMMON CANCER IN WOMEN AND THE SECOND MOST

common gynaecological cancer, accounting for more than 6,700 new cases diagnosed each year in the UK. The incidence has increased over the past 20–25 years, particularly in the 65 and over age group.¹

The outcome for women with ovarian cancer is generally poor, with an overall five-year survival rate of less than 35%.² The survival rates for women with ovarian cancer in the UK are significantly lower than the European average³

What is the role of CA125 in diagnosis?

although the five-year survival rates increased dramatically from 20% in 1975 to 38.9% in 2006.² The improvement may have been due to early detection methods, improved treatment modalities, or inclusion of borderline tumours, which have a good prognosis.^{4,5}

Despite recommendations, published by NICE in 2005, on referral of patients with suspected cancer,⁶ the majority of women diagnosed with ovarian cancer are not electively referred via the ovarian cancer two-week pathway. They are often referred to the wrong specialty or present as emergencies. NICE has now published a clinical guideline on the

Which patients should be referred?

diagnosis and initial management of ovarian cancer.⁷

EARLY DIAGNOSIS

Ovarian cancer is the leading cause of gynaecological cancer-related mortality, accounting for 6% of all cancer-related deaths in women.⁸ 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.² However, when diagnosed at an early stage, the great majority of women can be cured.

It is therefore possible that earlier >>

Table 1

**Ovarian cancer symptoms and signs:
NICE recommendations**

- Refer urgently if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids)
- Carry out tests in primary care if a woman (especially aged 50 or over) reports having any of the following symptoms on a persistent or frequent basis, (particularly more than 12 times per month):
 - persistent abdominal distension (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 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 in any woman of 50 or over who has experienced symptoms within the past 12 months that suggest irritable bowel syndrome (IBS) because IBS rarely presents for the first time in women of this age

Table 2

Risk of Malignancy Index (RMI)

RMI combines three pre-surgical features: serum CA125, menopausal status (M) and ultrasound score (U).

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= premenopausal
 - 3= postmenopausal
- The classification of postmenopausal is women who have had no periods 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.

Refer to specialist multidisciplinary team if RMI > 250

diagnosis could improve survival outcome.⁹ However, the natural history of ovarian cancer is unknown and there is insufficient evidence to say whether the duration of symptoms before diagnosis affects overall survival, quality of life or disease specific survival.

Nonetheless, it is generally agreed that early symptom identification, with a high index of suspicion for ovarian cancer, has the potential to improve prognosis.

SYMPTOMS

Although ovarian cancer is often dubbed a silent killer, a systematic review¹⁰ estimated that 93% of women experienced symptoms before diagnosis.

The problem is that a GP with an average sized practice may only see one case of ovarian cancer every five years or so, which makes recognition of the symptoms and early diagnosis more difficult. Consequently, women may visit their GP with symptoms of ovarian cancer on several occasions before these symptoms are recognised as significant.

Evidence from case control studies has shown that combining a number of symptoms that occur on a persistent or frequent basis (particularly more than 12 times per month) can have a sensitivity of up to 85% and a positive predictive value of the order of 0.2% i.e. 1 in 500 women would have ovarian cancer.¹¹⁻¹³ These data form the basis of the recent

NICE guideline recommendations, see table 1, above.

This guidance also stresses that appropriate assessments for ovarian cancer should be initiated in any woman of 50 or over who develops symptoms that suggest irritable bowel syndrome (IBS) because IBS rarely presents for the first time in women of this age.¹⁴

‘Serum CA125 should be the initial test followed by pelvic and abdominal ultrasound if the CA125 is abnormal’

EXAMINATION AND INVESTIGATION

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. Delayed or missed diagnoses are the most common reason for medicolegal claims in general practice.¹⁵ The challenge facing GPs is to find the ovarian cancer needle in the symptomatic haystack without flooding the secondary care cancer pathways.

The majority of women with symptoms suggestive of ovarian cancer will not have the disease. The symptoms are non-specific and so are not sufficient to refer to secondary care on a cancer pathway alone.

Clinical examination, including pelvic examination, remains relevant, particularly if there is obvious abdominal distension or a palpable abdominal mass. However, in most cases further tests will be required.

The NICE guidance recommends that serum CA125 should be the initial test followed by pelvic and abdominal ultrasound if the serum CA125 is abnormal (i.e. ≥35 IU/ml).

If both tests are abnormal, then these women should be referred on the two-week urgent referral pathway to the local specialist unit. The guidance recommends that these tests should be requested by GPs prior to definitive referral. Successful implementation of this guidance is dependent on adequate access to these tests being made available.

Compared with referring women with either an abnormal serum CA125 or ultrasound alone, this sequential combination reduces the number of women referred but increases the incidence of ovarian cancer in the referred population from about 1 in 100 to 1 in 26.⁷ Even so, this should still ensure that most women with ovarian cancer would be put onto the right pathway in a timelier fashion.

key points

SELECTED BY

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Ovarian cancer is the fifth most common cancer in women and the second most common gynaecological cancer, accounting for more than 6,700 new cases diagnosed each year in the UK. The incidence has increased over the past 20-25 years, particularly in the 65 and over age group. The outcome for women with ovarian cancer is generally poor, with an overall five-year survival rate of less than 35%.

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. Earlier diagnosis could improve survival outcome. Although 93% of women experience symptoms before diagnosis, a GP with an average sized practice may only see one case of ovarian cancer every five years or so, which makes recognition of the symptoms and early diagnosis more difficult.

Evidence has shown that combining a number of symptoms that occur on a persistent or frequent basis (particularly more than 12 times per month) can have a sensitivity of up to 85% and a positive predictive value of the order of 0.2% i.e. 1 in 500 women would have ovarian cancer. These data form the basis of the recent NICE guideline recommendations.

The NICE guidance recommends that serum CA125 should be the initial test followed by pelvic and abdominal ultrasound if the serum CA125 is abnormal (i.e. ≥ 35 IU/ml). These tests should be requested by GPs prior to definitive referral. If both tests are abnormal, then these women should be referred on the two-week urgent referral pathway to the local specialist unit. Those with elevated serum CA125 but normal ultrasound scans may need a gynaecological referral whereas women with normal CA125 results may require appropriate gastrointestinal evaluation.

When ultrasound, CA125 and clinical status suggest ovarian cancer, a CT scan of the pelvis and abdomen should be performed to establish the extent of disease. Wherever possible the diagnosis should be histological as this is the only way of determining the cancer type and grade.

Surgery and chemotherapy, either in combination or individually, remain the therapeutic mainstays. Surgery is often performed at the outset of treatment, especially when assessment indicates that all macroscopic disease may be removed as in early disease. It allows staging and histological diagnosis, and is therapeutic, often curative, when all disease can be removed. In advanced disease chemotherapy has prime therapeutic importance.

REFERRAL

Women with suspected ovarian cancer should be referred on the two-week wait cancer pathway to the local gynaecological cancer unit. The criteria for referral are:

- physical examination identifies ascites and/or a pelvic or abdominal mass or
- elevated serum CA125 and abnormal ultrasound scan are suggestive of ovarian cancer

Women who have persistent symptoms but who do not meet the criteria for ovarian cancer pathway referral still need appropriate assessment and management. Ovulation and certain benign gynaecological conditions such as endometriosis, pelvic infection and fibroids may also result in raised CA125 levels. Those with elevated serum CA125 but normal ultrasound scans may need a gynaecological referral whereas women with normal CA125 results may require appropriate gastrointestinal evaluation.

Women who have ovarian cancer should be managed by a cancer centre multidisciplinary team¹⁶ so gynaecological cancer units need to be able to identify those who need to be referred on and which women with low or moderate risk of ovarian cancer can be managed locally in a cancer unit. The recent NICE guidance recommends that this triage be made using a risk of malignancy index (RMI) score, using a cut-off point of 250, see table 2, opposite.

CONFIRMING DIAGNOSIS

Once referred, the onus is on making the correct diagnosis as quickly as possible. Safety and cost-effectiveness are important considerations. When ultrasound, CA125 and clinical status suggest ovarian cancer, a CT scan of the pelvis and abdomen should be performed to establish the extent of disease and facilitate decisions concerning the appropriateness and timing of surgery. The NICE guidance does not advocate MRI as a routine test for assessing women with suspected ovarian cancer.

Wherever possible the diagnosis should be histological as this is the only way of determining the cancer type and grade and will also exclude diagnoses such as tuberculosis, inflammation, fibrosis and other infections.

Different histological types of ovarian cancer require different treatments. There are various methods of obtaining a tissue diagnosis including needle biopsy, laparoscopy or open laparotomy. All are invasive and

therefore carry risks.

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. Cytology 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 patient it may be concluded that a tissue diagnosis is not essential.

TREATMENT

Surgery and chemotherapy, either in combination or individually, remain the therapeutic mainstays. Surgery is often performed at the outset of treatment, especially when assessment indicates that all macroscopic disease may be removed as in early disease. It allows staging, and histological diagnosis and is therapeutic, often curative when all disease can be removed.

However, when dealing with advanced cancer that cannot be completely extirpated, the role, extent and timing of surgery are controversial. Surgery may be performed before or during chemotherapy; the best timing has yet to be established.

Whatever the value of surgery, in advanced disease chemotherapy has prime therapeutic importance. The current NICE guidance recommends systemic platinum-based combination therapy and although there is increasing evidence that intraperitoneal chemotherapy may be effective, albeit toxic, this is still under evaluation.

There is good evidence highlighting the need for the relevant information, tailored to the needs of the individual, to be offered to women at the time that most suits them. Immediately after diagnosis, this principally concerns information related to treatment, its side effects, the disease and prognosis.¹⁷⁻¹⁹

CONCLUSION

Ovarian cancer is the most common cause of gynaecological death in the UK. Given that most women will be diagnosed with advanced disease, earlier detection offers the potential for reducing mortality. Most women have had symptoms for months before diagnosis, and as these are frequently non-specific, delays often occur between presentation and referral to a specialist. Greater awareness of the >>

disease and appropriate initial investigations in primary and secondary care are needed to enable earlier referral to be made and optimum treatment given.

GPs have a vitally important role in this process. The recommendations and supporting evidence from the recent NICE guidance should give healthcare professionals the confidence to start the appropriate investigations, better direct referrals to the correct pathway, and raise awareness among women.

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Useful information

For healthcare professionals NICE

The following support tools have been created to help healthcare professionals in primary care implement CG122. *The recognition and initial management of ovarian cancer*

Clinical case scenarios: case studies that can be used as a basis for discussions on how the recommendations should be applied in practice, aimed at GPs (PDF and slide set versions)

Podcast: using clinical judgement and tests in primary care

Audit support for primary care
www.nice.org.uk/CG122

For patients NICE

NICE has produced a version of CG122 specifically written for patients

Macmillan Cancer Support
Macmillan Cancerline:
0808 808 00 00
(Mon-Fri 9am-8pm)
www.macmillan.org.uk

NHS Direct
Tel: 0845 4647
www.nhsdirect.nhs.uk

Ovacom
Tel: 0845 371 0554
www.ovacom.org.uk

Target Ovarian Cancer
Tel: 020 7923 5470
www.targetovarian.org.uk

Ovarian Cancer Action
Tel: 0300 456 4700
www.ovarian.org.uk

We welcome your feedback

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