Guidelines for CA-125 Requesting

The purpose of this protocol is to provide guidance for the appropriate requesting of the tumour marker CA-125, referencing NICE guidelines CG122 (Ovarian cancer: recognition and initial management).

Definitions

αFP	Alpha-fetoprotein
βHCG	Beta-human chorionic gonadotropin
CEA	Carcinoembryonic antigen
HE4	Human epididymis protein 4
HNPCC	Hereditary Nonpolyposis Colorectal Cancer
RMI	Risk of Malignancy Index

Background

The best available marker for epithelial ovarian cancer is still considered to be CA-125 due to a combination of reliability and general availability. HE4 is more sensitive than specific than CA-125, however the former is not in routine use. NICE still therefore recommends CA-125 rather than HE4. CA-125 is used for the diagnosis of ***epithelial*** ovarian cancer. αFP and βHCG are useful for identifying those who have tumours of ***germ cell*** origin.

Evidence base for using CA-125 in detection of ovarian cancer

For use in diagnosis of ***epithelial*** ovarian cancer, the most frequently quoted reference range for CA-125 is 0-35 U/L. The care pathway for patients is shown in Appendix 2. The justification given in CG122 for this triage pathway (i.e. measurement of CA-125 before referral for ultrasound) is as follows. Assuming a prevalence of ovarian cancer in women with symptoms presenting to primary care of 0.23%:

- If all women with symptoms were referred to secondary care, around 1 in every 500 women referred would turn out to have ovarian cancer.
- The positive predictive values of the ***individual*** tests mean that around 1 in every 100 women referred to secondary care with positive serum CA-125 ***or*** ultrasound would have ovarian cancer. Negative predictive values mean that 1 in every 2,000 women with negative tests would turn out to have ovarian cancer.
- 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).
- When using ***combined*** tests, if women were only referred if they had a positive serum CA-125 test ***or*** ultrasound scan, then 1 in every 157 referred would have ovarian cancer (assuming conditional independence between serum CA-125 and ultrasound). 3% of women with ovarian cancer and symptoms would not be referred.
- If women were only referred when both CA-125 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.

Clinical specificity of CA-125

CA-125 is elevated in multiple benign diseases, some of which are shown in the table below (on page 2). Other conditions associated with raised CA-125 levels are pregnancy, menstruation, ascites, heart failure and pleural effusion. CA-125 may also be raised in endometrial and cervical cancer.

Disorder	Approx. % with CA-125 >35 U/L
Endometriosis	24
Benign ovarian tumours	10
Acute salpingitis	40
Chronic salpingitis	8
Uterine myoma	10
Cirrhosis	67
Cirrhosis with ascites	100
Chronic active hepatitis	10
Acute pancreatitis	32
Chronic pancreatitis	2
Renal failure	15

Screening for ovarian carcinoma

Problems with CA-125 as a screening test for ovarian cancer:

- lack of sensitivity for early stage disease (50% stage 1)
- lack of specificity

Screening is a symptomatic decision. Symptoms are non-specific and widely experienced by the general population, but they have greater significance in women over 50 years old, or women with a significant family history (2 or more cases of ovarian or breast cancer diagnosed at an early age in first degree relatives.) CA-125 cannot be recommended for general population screening to detect sporadic forms of the disease.

Targeting a high risk population

CA-125 may have a role in combination with transvaginal ultrasound and pelvic examination in the early detection of ovarian cancer in women with a hereditary ovarian cancer syndrome. Although there is no data showing that screening these high-risk women can reduce their mortality from ovarian cancer a NIH consensus statement has recommended that these women undergo at least annual testing.

Diagnosis

Serum CA-125 measurement and an abdominal and pelvic ultrasound, along with the woman's menopausal status, are used to calculate a risk of malignancy index. An RMI ≥ 250 necessitates referral to a specialist multidisciplinary team. Appendix 3 provides the definition of RMI. Confirmation of diagnosis is by histology or cytology.

Prognosis

CA-125 levels after chemotherapy is one of the strongest available indicators of disease outcome. A prolonged half-life for CA-125 or a less than 7-fold decrease during the early months of treatment has also been shown to predict poor outcome.

Monitoring

The most important application of CA-125 is the monitoring of patients with epithelial ovarian cancer. Serial levels can pre-clinically detect recurrent disease earlier and more cost-effectively than radiological procedures. This may lead to altered patient management, but no study has yet shown this leads to enhanced survival.

Women with a family history of ovarian cancer

For women who either are HNPCC positive or have two or more 1st or 2nd degree relatives with ovarian cancer or young age breast cancer, screening is offered at St Michael's. If queries are received suggest that the doctor contacts Mr John Murdoch (Consultant Oncologist/ Gynaecologist) at St Michael's Hospital.

Main CG122 recommendations

CA-125 should be measured in the following situations:

Primary Care
Women (especially if 50 or over) presenting with one or more of the following symptoms on a persistent (at least 1 month) or frequent (12 times per month) basis:

- 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
- unexplained weight loss
- unexplained fatigue
- unexplained changes in bowel habit (for example, constipation or diarrhoea)
- symptoms that suggest irritable bowel syndrome - if the woman is 50 years or over

If serum CA-125 is 35 U/ml or greater, an ultrasound scan of the abdomen and pelvis should be arranged.

Note: Patients should be referred to a gynaecological cancer service within 2 weeks if physical examination identifies ascites and/or a pelvic or abdominal mass (which is not obviously uterine fibroids). ***CA-125 measurement is not a prerequisite for referral; therefore referral should not be delayed whilst waiting for CA-125 result.***

If the woman has a normal serum CA-125, or a raised CA-125 but a normal ultrasound, then the GP should assess her carefully for other clinical causes of her symptoms and investigate if appropriate.

Secondary care

- Measure serum CA-125 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 αFP and βhCG as well as serum CA-125, to identify women who may not have epithelial ovarian cancer.

Reporting results

All raised CA-125 results will come to clinical validation. Raised results *on a first request* should have the following coded comment where appropriate (mainly primary care samples):

C125 Increased CA-125, an ultrasound scan should be arranged, as per NICE guidelines CG122. CA-125 is not specific for ovarian cancer and is raised in other malignancies and benign conditions including; menstruation, pregnancy, endometriosis, benign ovarian cysts, inflammatory pelvic disease, liver cirrhosis and ascites.

Related documents

- **NICE support tools to help you put CG122 guidance into practice**
- Care pathways for ovarian cancer in primary and secondary care (from NICE CG122)

References

1. The recognition and initial management of ovarian cancer. NICE Clinical guidelines, CG122. 2011

2. Screening for ovarian cancer: a systematic review. Health technology assessment. (**Note:** CG122 doesn't deal with population screening.)

Appendix 1: Support tools to help you put this guidance into practice

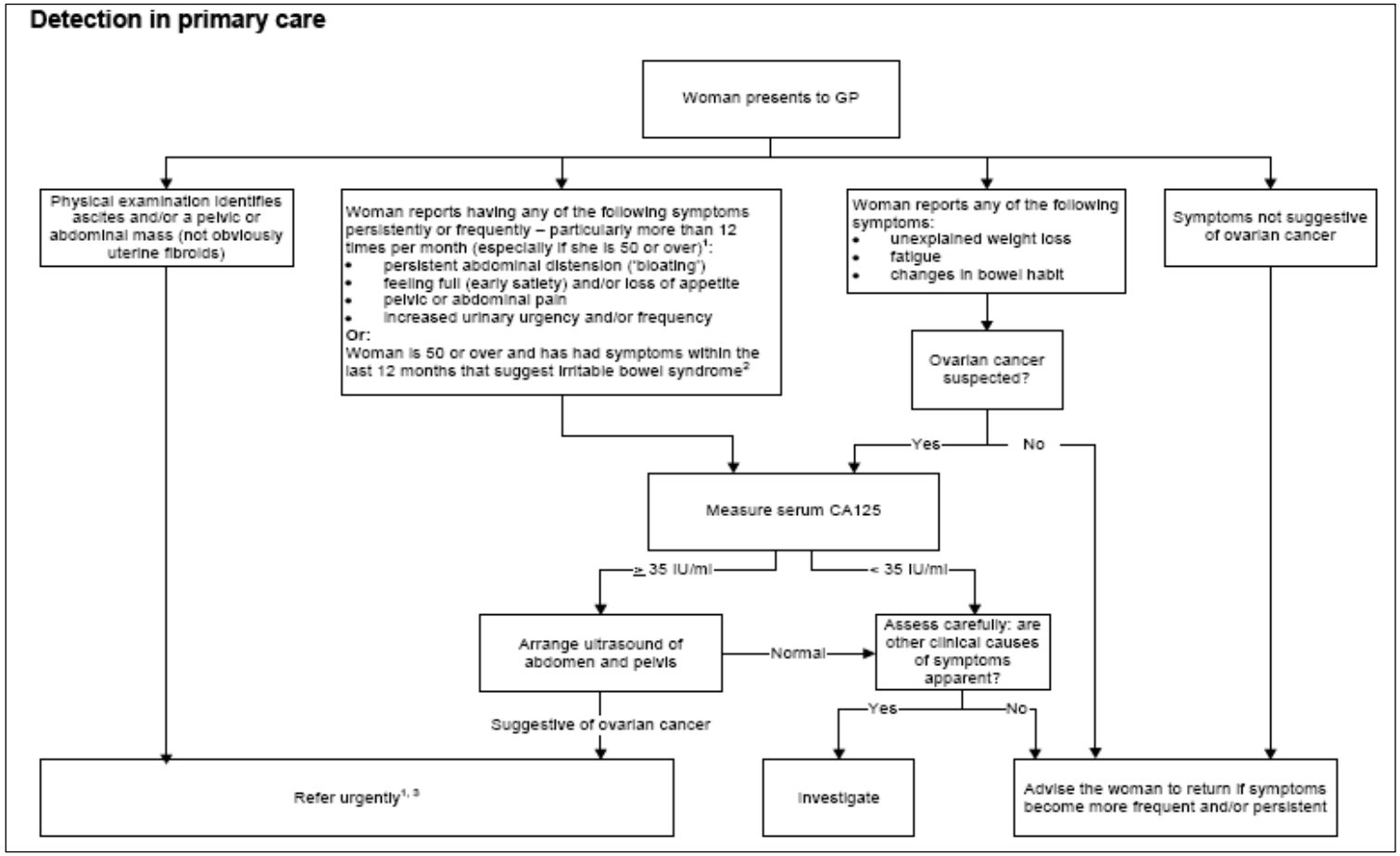
This NICE slide set might be helpful when discussing this guideline in a practice meeting; the baseline assessment tool can help to identify where you might need to change your clinical practice, and there is online learning available.

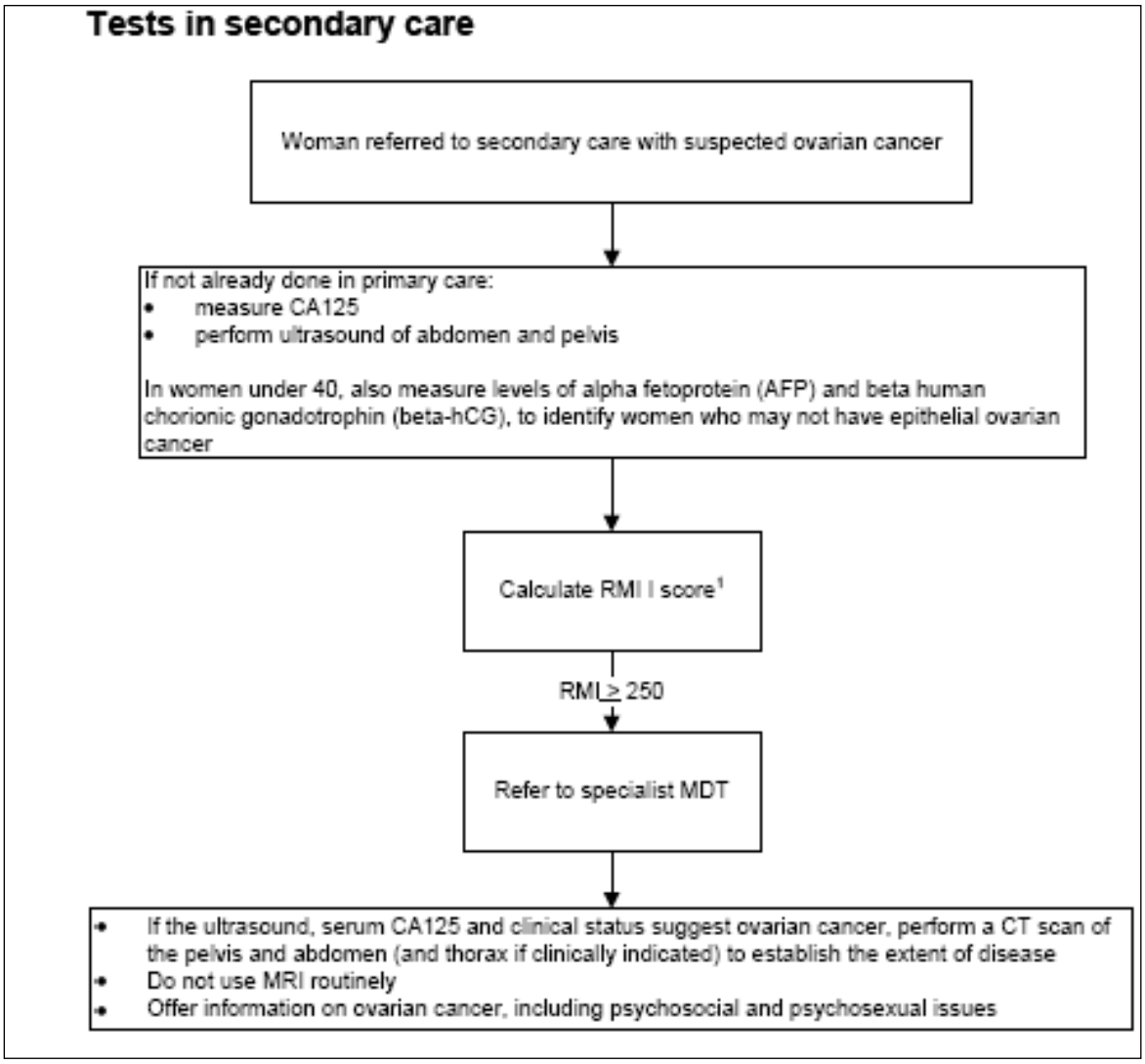
You can also find a podcast about this guidance, on the NICE website, featuring Dr Craig Dobson, a GP and Senior Lecturer in Medical Education and General Practice at Hull/York Medical School and a member of the guideline development group for the Ovarian Cancer guideline.

This podcast focuses specifically the use of CA-125 tests and how to manage patients who have negative results.

For full information about this guidance, and support from NICE for putting the guidance into practice, see NICE guidance CG122 for ovarian cancer.

Appendix 2: Care pathways for ovarian cancer in primary and secondary care (adapted from NICE CG122 interactive pathways)




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

Appendix 3: Risk of Malignancy Index Calculation

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.