NICE National Institute for Health and Care Excellence

Surveillance report 2016 – Ovarian Cancer (2011) NICE guideline CG122

Surveillance report

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Surveillance decision

We will plan an update of these sections of the guideline:

- Establishing a diagnosis in secondary care
  - For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?
- Detection in primary care
  - For women with suspected ovarian cancer, what are the most effective first tests in primary care?
  - What are the risk factors for ovarian cancer that should be identified in primary care?

Reason for the decision

We found 91 new studies relevant to the guideline through the surveillance process. This included evidence identified for detection in primary care, management of stage I and II–IV ovarian cancer, establishing a diagnosis in secondary care and support needs of women with newly diagnosed ovarian cancer. Topic expert feedback noted that there may be new studies on human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) for the diagnosis of ovarian cancer, although no specific studies were highlighted.

New evidence and stakeholder consultation feedback that could affect recommendations was identified. Topic experts, including those who helped to develop the guideline, advised us about whether the following sections of the guideline should be updated:

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?

CG122 did not include substantial evidence on HE4 and recommended CA125 as the serum tumour marker for the diagnosis of ovarian cancer. New evidence at the 4-year surveillance of CG122 provides further comparative data on the diagnostic accuracy of

HE4. The newly identified systematic reviews and diagnostic studies indicate that HE4 has a higher specificity than CA125 but similar sensitivities for the diagnosis of ovarian cancer. Topic experts noted that an increased specificity may be useful in the pre-menopausal population as it may prevent unnecessary referrals.

The topic experts advised that HE4 is not widely used or available in the NHS or a primary care setting. However stakeholders highlighted at consultation that there may be role for HE4 in the clinical pathway for the diagnosis of ovarian cancer. The consultation identified a number of diagnostic accuracy studies relating to the serum tumour marker tests, indicating that HE4 has a higher specificity than CA125, which is the tumour marker recommended by CG122 for the diagnosis of ovarian cancer.

New evidence was found on the Risk for Ovarian Malignancy Algorithm (ROMA). The topic experts noted that ROMA takes into account menopausal status and in pre-menopausal women the ROMA score may reduce the number of patients going to tertiary care.

Comments received from stakeholders at consultation expressed a need for NICE to review the recommendations on serum tumour markers for the diagnosis of ovarian cancer, in particular the role of HE4 and ROMA.

Decision: This review question should be updated.

Detection in primary care

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

New evidence comes from two prospective cohort studies and one prognostic study. Two new prospective cohort studies were non-comparative to CA125 or ultrasound alone and only investigates use in combination. The guideline recommends CA125 as the tumour marker to be used in primary care. Although the new evidence does not indicate a need for update, the question may be impacted as the question above, on serum tumour markers, is to be updated.

Decision: This review question should be updated.

- What are the risk factors for ovarian cancer that should be identified in primary care?

Feedback from stakeholder consultation indicated that there is a gap in the

recommendations in CG122 on risk factors for ovarian cancer in primary care. This is also not covered by any NICE guidance. This new question will be added to the guideline. This would align with the recently published referral for suspected cancer NICE guideline.

Decision: This new review question should be added to the guideline.

See how we made the decision for further information.

Commentary on selected new evidence

With advice from topic experts we selected 2 studies for further commentary.

Establishing the diagnosis in secondary care – Tumour markers: which to use?

We selected a systematic review by Zhen et al. (2014) for a full commentary because this study was identified during the surveillance review as new comparative evidence for human epididymis protein 4 (HE4) and cancer antigen 125 (CA125) that may impact on the recommendations.

What the guideline recommends

CG122 recommends CA125 as the tumour marker to be used in the diagnosis of ovarian cancer (1.2.1.1). The guideline developers searched for evidence on CA125, HE4 and a number of other tumour markers for the diagnosis of ovarian cancer in secondary care. Five studies were included that compared HE4 to CA125. The committee noted that at the time of publication of the guideline there was a lack of substantial evidence on HE4 that would warrant recommending it over CA125.

Methods

The systematic review searched Medline, Embase, Cochrane database and checked the reference lists of included papers. The search dates for included papers was between 2008 and 2010.

Inclusion criteria were papers with a population that included women 50 years or older and had ovarian cancer confirmed by pathological examination of a biopsy, compared the diagnostic accuracy of HE4 to CA125 for the diagnosis of ovarian cancer, reported sensitivity and specificity and clearly reported cut-off thresholds. Exclusion criteria included case reports and non-comparative data.

Two authors independently extracted the data from the studies. The studies were quality assessed using a modified quality assessment of diagnostic accuracy studies (QUADAS-2)

tool. If information was missing then authors of studies were contacted.

Meta-analysis was performed using the program Meta-Analysis of Diagnostic and Screening Test (Meta-disc) and Review Manager. This was performed on the pooled sensitivity, pooled specificity and pooled diagnostic odds ratios. Heterogeneity was considered as an I^2 value greater than 50%. When heterogeneity was found a random effects model was used.

Results

The search identified 270 studies and after exclusions 25 studies were included. A total of 4729 women were included.

The included studies varied in setting with 60% in a gynaecological oncology setting and 40% in a gynaecological setting. The proportion of women pre and post-menopause and stage of ovarian cancer also differed.

Meta-analysis was performed and all related outcomes were pooled, including those from different populations, settings and HE4 cut-off thresholds.

The study reported the results of the meta-analysis:

- Sensitivity for HE4 was 0.74 with a 95% confidence interval (CI) of 0.72–0.76. CA125 was 0.74 with a 95% CI of 0.72–0.76.
- Specificity for HE4 was 0.90 with a 95% CI of 0.89–0.91. CA125 was 0.83 with a 95% CI of 0.81–0.84.
- Summary diagnostic odds ratio (DOR) for HE4 was 43.35 with a 95% CI of 29.13–64.51. CA125 was 17.06 with a 95% CI of 10.97–26.51.
- Positive likelihood ratios for HE4 was 10.59 with a 95% CI of 7.20–15.58. CA125 was 4.84 with a 95% CI of 3.59–6.54.
- Negative likelihood ratios for HE4 was 0.27 with a 95% CI of 0.24–0.31. CA125 was 0.31 with a 95% CI of 0.26–0.38.
- Area under the curve for HE4 was 0.8915 and for CA125 was 0.8538.

Nine studies compared the combination of CA125 and HE4 to HE4 or CA125 alone.

Meta-analysis sub-group results were reported for these studies:

- Sensitivity for HE4 was 0.71 with a 95% CI of 0.67–0.75. CA125 was 0.74 with a 95% CI of 0.69–0.78. The combination of CA125 and HE4 was 0.90 with a 95% CI of 0.87–0.92.
- Specificity for HE4 was 0.92 with a 95% CI of 0.90–0.94. CA125 was 0.73 with a 95% CI of 0.69–0.76. The combination of CA125 and HE4 was 0.85 with a 95% CI of 0.82–0.87.
- DOR for HE4 was 31.83 with a 95% CI of 19.77–51.26. CA125 was 10.31 with a 95% CI of 6.18–17.21. The combination of CA125 and HE4 was 53.92 with a 95% CI of 26.07–111.54.

The meta-analysis reported similar sensitivities of HE4 and CA125 but that HE4 had a higher specificity, diagnostic odds ratio and AUC than CA125. The combination of CA125 and HE4 reported a higher sensitivity than both HE4 or CA125 alone but not a higher specificity than HE4 alone.

Strengths and limitations

Strengths

The systematic review included a number of strengths:

- It had clear inclusion and exclusion criteria.
- Quality assessment of the included papers using a modified QUADAS-2. The included studies were rated as high quality using this tool.
- It searched a number of databases and checked the references of papers for any further papers.
- Publication bias was assessed through the use of funnel plots.

Limitations

Overall, the systematic review is at high risk of bias due to:

- Included studies were meta-analysed although they had different cut-off thresholds for HE4, took place in different settings, included women at different stages of ovarian cancer and had different criteria for inclusion.
- The meta-analysis of the pooled specificity for HE4 and HE4+CA125 has high heterogeneity and inconsistency.
- The search terms were not extensive.
- None of the included studies took place in the UK and therefore the applicability to the UK NHS setting is unclear.

The authors noted the limited available evidence on HE4, compared with the larger amount of evidence available on CA125. The authors also noted that the review did not take into account menopause in the population for meta-analysis and this may be a potential limitation. Publication bias was detected by the authors.

Impact on guideline

CG122 did not include substantial evidence on HE4 and recommended CA125 as the serum tumour marker for the diagnosis of ovarian cancer. This systematic review identifies a number of studies comparing HE4 to CA125 for the diagnosis of ovarian cancer that were published after 16 July 2010, the cut-off date for the evidence searches for the original guideline. The evidence indicates that HE4 may have a higher specificity than CA125. There is a need to review the recommendations on serum tumour markers for the diagnosis of ovarian cancer to include new published evidence on HE4.

Management of advanced (stage II–IV) ovarian cancer – The value of primary surgery

We selected the RCT by Kehoe et al. (2015) for a full commentary because topic expert feedback identified this as an important paper that provides further evidence in an area that a research recommendation was made, however would not affect the recommendations at this time.

What the guideline recommends

CG122 recommends '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.' (1.4.1.1) The committee made a recommendation for further research on 'the effectiveness of primary surgery for women with advanced ovarian cancer whose tumour cannot be fully excised.'

Methods

Kehoe et al. (2015) conducted a multi-centre randomised controlled trial (RCT) on primary debulking surgery followed by platinum based chemotherapy compared to primary platinum based chemotherapy followed by delayed surgery.

The RCT took place between March 2004 and August 2010 in 2 centres in New Zealand and 74 in the UK. The study included 13 women from New Zealand and 539 from the UK. Two women were excluded due to lack of consent or administrative errors, leaving 550 women included.

The RCT included women with imaging identifying a pelvic mass consistent with suspected advanced (FIGO stage III or IV) ovarian cancer and either a ratio of cancer antigen 125 (CA125) to carbinoembryonic antigen (CEA) greater than 25 or less than 25 and investigations confirming the pelvic mass was not gastrointestinal cancer.

In a 1:1 ratio 276 women were randomised to primary surgery and 274 to primary chemotherapy. Randomisation was stratified by International Federation of Gynecology and Obstetrics (FIGO) stage, chemotherapy treatment, tumour size and randomising centre. The RCT was a non-inferiority, open-labelled trial.

The primary surgery group received debulking surgery and then 6 chemotherapy cycles. The primary chemotherapy group received chemotherapy for 3 cycles, then debulking surgery, then a further 3 cycles of chemotherapy. The chemotherapy regimen differed depending on the person and local practice but the chemotherapy was carboplatin or a combination with carboplatin, such as carboplatin and paclitaxel. Surgery was conducted by specialist gynaecological oncologists who were accredited by the Royal College of Obstetricians and Gynaecologists.

The primary outcome was overall survival (OS). Secondary outcomes included quality of life (QoL), progression-free-survival (PFS) and adverse events at each chemotherapy cycle.

Results

Baseline characteristics for FIGO stages, ratio of CA125/CEA, tumour size, age, chemotherapy treatment and WHO performance status were similar in each group.

The study concluded that primary surgery was non-inferior to primary chemotherapy. The RCT pre-defined a 90% upper confidence interval of less than 1.18 for non-inferiority. The 90% upper CI for death was 0.98. In an intention to treat analysis it was reported that primary chemotherapy was favoured with a hazard ratio of 0.87 and a 95% CI of 0.72–1.05 for the outcome of death as at 31 May 2014. For survivors the median follow-up was 4.4 years. In the primary surgery group 231 women out of 276 had died compared to 220 out of 274 in the primary chemotherapy group. 88% of all deaths were from ovarian cancer.

Progression-free-survival also favoured the primary chemotherapy group with a hazard ratio of 0.91 and a 95% CI of 0.76–1.09.

Quality of life in survivors at 6 months was significantly higher than at baseline in the primary chemotherapy group (n=114) compared to the primary surgery group (n=103) (p=0.0438). At 12 months quality of life was higher than at baseline in the primary chemotherapy group (n=64) compared to the primary surgery group (n=69) but this difference was not significant (p=0.0515).

The RCT reported adverse events after each chemotherapy cycle. Toxicity was not significant between the two groups (p=0.654). Neutropenia rates were similar in the two groups. Neutropenic sepsis caused one death in the primary chemotherapy group.

The trial also reported post-operative adverse event rates. Death within 28 days of surgery was significantly higher in the primary surgery group than in the primary chemotherapy group (p=0.001). Other reported adverse events were significantly different between the two groups (p=0.007), with the primary surgery group reporting more adverse events.

Strengths and limitations

Strengths

The study had a number of strengths. It reported similar rates of discontinuation in each group and missing data are adequately reported. All of the pre-specified (primary and

secondary) outcomes were reported.

Limitations

There were a number of limitations:

- Treatments in the primary chemotherapy group differed and therefore the results of the comparisons may need to be interpreted with caution.
- There is no blinding and insufficient information about the sequence generation process.

The authors also noted that is uncertain whether radical or aggressive surgery would have been of benefit as there is no previous research on this compared with standard surgery.

Impact on guideline

This trial reported that primary surgery is non-inferior to primary chemotherapy. Therefore the new evidence may provide support for the current guideline recommendation, which did not recommend either primary surgery or primary chemotherapy but that the aim should be complete resection of all macroscopic disease.

How we made the decision

We check our guidelines regularly to ensure they remain up to date. We based the decision on surveillance 4 years after the publication of ovarian cancer (2011) NICE guideline CG122.

For details of the process and update decisions that are available, see ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual'.

An evidence update was previously published and is available on our website.

New evidence

We found 51 new studies in a search for randomised control trials and RCTs published between 09 July 2012 and 01 June 2015. We also considered 8 additional studies identified by members of the Guideline Committee who originally worked on this guideline. We also considered 19 additional studies identified through stakeholder consultation.

Evidence identified in the previous evidence update (January 2013) was also considered. This included 14 studies identified by search.

From all sources, 91 studies were considered to be relevant to the guideline.

We also checked for relevant ongoing research, which will be evaluated again at the next surveillance review of the guideline.

See appendix A: decision matrix for summaries and references for all new evidence considered in surveillance of this guideline.

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline.

Views of stakeholders

Stakeholders commented on the decision not to update the guideline. Comments received from stakeholders at consultation expressed a need for NICE to review the recommendations on serum tumour markers for the diagnosis of ovarian cancer, in particular the role of HE4 and ROMA. Following stakeholder consultation it was agreed to update the guideline. See appendix 2 for stakeholders' comments and our responses.

See ensuring that published guidelines are current and accurate in 'Developing NICE guidelines: the manual' for more details on our consultation processes.

Date of next surveillance

Our next surveillance to decide whether the guideline should be updated is scheduled for 2017.

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The NICE project team would like to thank the topic experts who participated in the surveillance process.