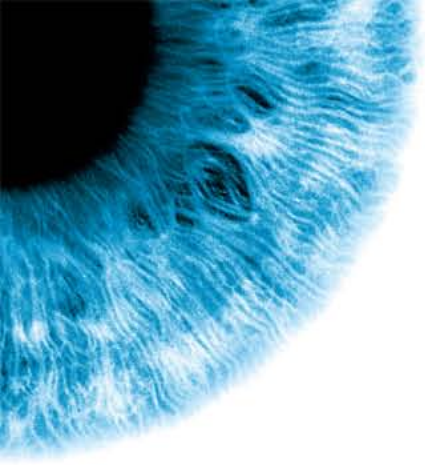

Ovarian Cancer:
Evidence Update January 2013

A summary of selected new evidence relevant to NICE clinical guideline 122 'The recognition and initial management of ovarian cancer' (2011)

Evidence Update 27

Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page for ovarian cancer.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.

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Contents

Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:

[1] **Ovarian cancer. NICE clinical guideline 122 (2011).**

A search was conducted for new evidence published between 1 January 2010 and 9 July 2012[2]. A total of 1388 pieces of evidence were identified and assessed, of which 14 were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprised of topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Other relevant accredited guidance

The focus of the Evidence Update is on the guidance stated above. However, overlap with other accredited guidance has been outlined as part of the Evidence Update process. Where relevant, this Evidence Update therefore makes reference to the following guidance:

- [3]Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal guidance 55 (2003).

Quality standards

- Ovarian cancer. NICE quality standard 18 (2012).

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

[1] NICE-accredited guidance is denoted by the Accreditation Mark
[2] Additionally, the Evidence Update Advisory Group was asked to highlight relevant evidence published between June 2009 and January 2010 to ensure that studies published since searches were performed for the NICE technology appraisal 55 review proposal were also considered.
[3] Guidance published prior to NHS Evidence accreditation

Key points

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG's opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

	Potential impact on guidance	
Key point	**Yes**	**No**
Management of suspected early (stage I) ovarian cancer		
• Evidence does not seem to support the use of adjuvant therapy for borderline ovarian cancer.		✓
• Maintenance paclitaxel does not seem to reduce recurrence-free intervals and may be linked with increasing levels of toxicity.		✓
Management of advanced (stage II–IV) ovarian cancer		
Chemotherapy		
• Evidence indicates that topotecan[4] plus paclitaxel plus carboplatin may not improve overall survival, progression-free survival or response rate and may have worse toxicity compared with paclitaxel plus carboplatin.		✓
• Pegylated liposomal doxorubicin[5] plus carboplatin may result in progression-free and overall survival similar to that of carboplatin plus paclitaxel.	✓*	
• Addition of gemcitabine[6] to paclitaxel and carboplatin as first-line treatment may not improve overall survival and may reduce progression-free survival compared with carboplatin plus paclitaxel.		✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

[4] Topotecan is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

[5] Pegylated liposomal doxorubicin is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

[6] Gemcitabine is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

Key point	Potential impact on guidance	
	Yes	No
• Weekly paclitaxel[7] plus carboplatin may result in longer progression-free and overall survival, but may increase toxicity compared with 3-weekly paclitaxel plus carboplatin for first-line treatment of advanced ovarian cancer. The weekly regimen may also be cost effective compared with 3-weekly dosing. Further research is needed to confirm these findings.	✓*	
• Maintenance chemotherapy may not be more effective than observation.		✓
• A NICE technology appraisal of bevacizumab, in combination with paclitaxel and carboplatin, for the first-line chemotherapy treatment of ovarian cancer is currently underway.		✓
Surgery		
• Complete cytoreduction of ovarian cancer seems to be associated with the best overall survival; however more research is needed to determine the best surgical treatment for women in whom complete cytoreduction cannot be achieved.		✓
Intraperitoneal Chemotherapy		
• Intraperitoneal chemotherapy may be more effective than intravenous chemotherapy in terms of overall survival and progression-free survival, but may have greater toxicity.		✓
Support needs of women with newly diagnosed ovarian cancer		
• Evidence suggests that receiving information and assistance from appropriate support teams is important to inform decision making.		✓

* Evidence Updates are intended to increase awareness of new evidence and do not change the recommended practice as set out in current guidance. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods. For further details of this evidence in the context of current guidance, please see the full commentary.

[7] Paclitaxel is licensed for first-line treatment of ovarian cancer in a 3-weekly dosing regimen. Weekly dosing of paclitaxel is not recommended by current guidance and at the time of publication of this Evidence Update did not have UK marketing authorisation for this regimen.

1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the 'key references' (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Detection in primary care

No new key evidence was found for this section.

1.2 Establishing the diagnosis in secondary care

No new key evidence was found for this section.

1.3 Management of suspected early (stage I) ovarian cancer

Borderline ovarian tumours

NICE CG122 did not include specific recommendations for women with borderline ovarian cancer; however, the introduction states 'the guideline recommendations are applicable to women with epithelial ovarian cancer (the most common type of ovarian cancer), as well as women with fallopian tube carcinoma, primary peritoneal carcinoma or borderline ovarian cancer.'

A Cochrane review by **Faluyi et al. (2010)** evaluated the overall survival (OS) of different treatments for borderline ovarian tumours. Secondary outcomes were recurrence-free survival, quality of life (QoL), fertility and adverse events. Seven randomised controlled trials (RCT, n=372) that compared different interventions for adult women with histologically confirmed borderline ovarian tumour of any variant were included. The authors were unable to pool the results in meta-analyses because they compared different interventions.

Six trials (n=340) included 87% of women who had International Federation of Obstetricians and Gynaecologists (FIGO) stage I tumours. These trials were conducted over 15 years ago and compared different forms of adjuvant therapy after radical surgery. They examined a range of interventions: chemotherapy (melphalan, thiotepa, cisplatin, and the addition of doxorubicin to a regimen of cisplatin and cyclophosphamide); intraperitoneal irradiation with gold or phosphorus; and external irradiation. Most participants were followed up over 10 years (median range 2.6 to 12.3 years).

One further trial included 32 patients with bilateral serous tumours who wanted to preserve their fertility and compared ultra-conservative surgery (bilateral cystectomy) with conservative surgery (oophorectomy of the most involved ovary and contralateral cystectomy). A significantly increased chance of pregnancy was noted (hazard ratio [HR]=3.3, 95% confidence interval [CI] 1.4 to 8.0), but earlier disease recurrence (HR=1.5, 95% CI 0.6 to 3.8) was not significantly different. This trial had the highest disease recurrence (19 of 32, 59%), but there was no significant difference between the 2 groups. This was the only trial that was considered to have a low risk of bias. The authors concluded that bilateral cystectomy may be offered to women with bilateral borderline ovarian tumours diagnosed intra-operatively who wish to preserve their fertility.

The overall death rate from all 7 studies was 4 out of 362 (1%) and recurrence-free survival was similar between different arms of these trials. One trial reported a significantly lower death rate in women who received thiotepa (24 out of 243, p=0.03). Recurrence rates were

1–2% for 5 of the 6 trials providing details. Because of the small numbers of participants, HRs could not be calculated.

Limitations of the 6 studies of adjuvant treatments were lack of reporting about adequate sequence generation, allocation concealment and whether they were free from selective reporting. Both QoL and adverse events were incompletely reported and all 6 trials were at high risk of bias. No study reported blinding of the outcome assessor or provided insufficient information to ascertain whether any additional risk factor for bias existed. The trials mostly studied early stage tumours, evaluated different interventions and may not have had sufficient power to detect differences in survival.

The results of this review are unlikely to have an impact on NICE CG122 because it does not contain specific recommendations for managing borderline ovarian cancer. The lack of evidence to support the use of adjuvant therapy in this Cochrane review led the authors to suggest that further RCTs evaluating the benefits of adjuvant therapy with optimally dosed chemotherapy and newer targeted drugs are needed, particularly for advanced borderline ovarian tumours.

Key reference

Faluyi O, Mackean M, Gourley C et al. (2010) Interventions for the treatment of borderline ovarian tumours (review). Cochrane Database of Systematic Reviews issue 9: CD007696

Adjuvant systemic chemotherapy for stage I disease

NICE CG122 recommends that women with high-risk FIGO stage I disease (grade 3 or stage Ic) should be offered adjuvant chemotherapy consisting of 6 cycles of carboplatin.

An open-label phase III RCT reported by **Mannel et al. (2011)** compared low-dose paclitaxel maintenance treatment with observation in people with histologically confirmed FIGO stage IA/B (grade 3 or clear cell), IC or II epithelial ovarian cancer who received 3 cycles of carboplatin plus paclitaxel. The primary outcome was recurrence rate confirmed by clinical or radiographic evidence of a new tumour. All patients received carboplatin area under the curve (AUC) 6 and paclitaxel 175 mg/m^2 every 21 days for 3 cycles. Participants were randomly assigned to observation (n=268) or paclitaxel 40 mg/m^2 weekly for 24 weeks (n=274). Of the 542 patients 72% had stage I and 28% had stage II disease.

Recurrence rates within 5 years were 20.4% (95% CI 15.9% to 25.9%) for those assigned to paclitaxel and 23.2% (95% CI 18.4% to 28.9%) for those assigned to observation. Adjusting for stage of disease and tumour grade, the recurrence rate did not differ significantly between the paclitaxel and observation groups (HR=0.81, 95% CI 0.57 to 1.15, p=0.24). The overall death rate for the 2 groups was similar (HR=0.78, 95% CI 0.52 to 1.17, p=0.23). The incidence of grade 2 or worse peripheral neuropathy (15.5% vs 6.0%), infection or fever (19.9% vs 8.7%) and dermatological events (70.8% vs 52.1%) was higher for the maintenance paclitaxel regimen (p=0.001). Cardiovascular events (grade 2 or worse) were higher in the maintenance group (8.1% vs 3.8%, p=0.044).

The authors did not discuss potential limitations of the study. The types of cancer treated appeared to be well balanced between treatment groups, but there was no discussion on whether some forms may have responded better to treatment than others.

NICE CG122 recommends a 6 cycle regimen of carboplatin as standard treatment compared with the 3 cycles in this US study. Also, 28% of women in this study had stage II disease and the guidance recommendation is specific to stage I disease so the results of this study are unlikely to have an impact on guidance. In addition, maintenance paclitaxel did not seem to reduce recurrence and appeared to increase toxicity.

Key reference

Mannel RS, Brady MF, Kohn EC et al. (2011) A randomized phase III trial of IV carboplatin and paclitaxel x 3 courses followed by observation versus weekly maintenance low-dose paclitaxel in patients with early-stage ovarian carcinoma: A Gynecologic Oncology Group Study. Gynecologic Oncology 122: 89–94

1.4 Management of advanced (stage II–IV) ovarian cancer

Chemotherapy

NICE CG122 refers to recommendations in NICE technology appraisal (TA) 55 on first-line chemotherapy in the management of advanced ovarian cancer. NICE TA55 recommends that paclitaxel in combination with a platinum-based compound or platinum-based therapy alone (cisplatin or carboplatin) are offered as alternatives for first-line chemotherapy (usually following surgery) in the treatment of ovarian cancer. NICE CG122 also discusses the option of neoadjuvant chemotherapy prior to surgery in the recommendation for the management of primary surgery.

Topotecan

Topotecan is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

An Italian, prospective phase III multicentre RCT by **Bolis et al. (2010)** evaluated first-line topotecan plus paclitaxel plus carboplatin (TPC, n=156) versus paclitaxel plus carboplatin (PC, n=170) in women with histologically or cytologically confirmed FIGO stage III–IV epithelial ovarian cancer. The primary outcome was OS; secondary outcomes were progression-free survival (PFS) and response rate.

Complete response was defined as complete disappearance of all known disease for at least 4 weeks. Partial response was defined as 50% or greater decrease in the length and width of the largest measurable lesion for at least 4 weeks with no simultaneous increase in a known lesion or appearance of new lesions. In the PC arm, patients received paclitaxel 175 mg/m^2 plus carboplatin AUC 5 on day 1 and every 21 days for 6 cycles. In the TPC arm, patients received topotecan 1.0 mg/m^2 daily for 3 days and on the third day patients received paclitaxel plus carboplatin as in the PC arm. The chemotherapy regimen was repeated every 3 weeks for 6 cycles.

In the TPC arm, life table estimates of survival probabilities were 0.92 at 1 year (95% CI 0.86 to 0.95), 0.52 at 3 years (95% CI 0.42 to 0.61) and 0.32 at 5 years (95% CI 0.22 to 0.43) and for PC were 0.94 at 1 year (95% CI 0.88 to 0.97), 0.53 at 3 years (95% CI 0.44 to 0.62) and 0.32 at 5 years (95% CI 0.23 to 0.42). The difference between the 2 groups was not statistically significant at 5 years. There were also no statistically significant differences between the 2 groups in terms of PFS, complete response (p=0.62) and partial response (p=0.67).

One hundred and thirty nine women (89.1%) in the TPC arm and 151 women (88.8%) in the PC arm had at least 1 event possibly related to the study drugs. However, 86 women (24%) in the TPC arm and 79 women (23.6%) in the PC arm had at least 1 severe adverse event. Thirty seven women (10.3%) in the TPC arm and 16 women (4.8%) in the PC arm had at least 1 life-threatening adverse event. Fatigue (p=0.05), anaemia (<0.01), leukopenia (p=0.004) and neutropenia (p=0.0004) were significantly more frequent in the TPC arm.

The authors did not discuss limitations of the study, although they stated that delivery of the third chemotherapeutic drug at an adequate dosage was difficult to achieve.

Another phase III multinational RCT by **Hoskins et al. (2010)** evaluated the effects of topotecan plus cisplatin plus paclitaxel plus carboplatin (TCPC, n=409) compared with paclitaxel plus carboplatin (PC, n=410). The primary outcome was PFS, measured by Response Evaluation Criteria in Solid Tumours (RECIST) and CA125 values. Secondary outcomes included OS, toxicity and QoL. QoL was assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire. Women with newly diagnosed, advanced FIGO stage IIb–IV ovarian, fallopian tube or primary peritoneal cancer who had completed all primary surgery were included.

Women in the TCPC arm received cisplatin 50 mg/m^2 on day 1 followed by topotecan 0.75 mg/m^2 on days 1 to 5 for 4 cycles at 3 week intervals. Patients then received 4 cycles of carboplatin AUC 5 and paclitaxel 175 mg/m^2 at 3 week intervals. Women in the PC arm received carboplatin AUC 5 plus paclitaxel 175 mg/m^2 every 3 weeks for 8 cycles.

Median PFS was 14.6 months in the TCPC group and 16.2 months in the PC group (HR=1.10, 95% CI 0.94 to 1.28, p=0.25). A total of 406 deaths were reported at the time of data cut-off for the study with a median OS of 42.3 months in the TCPC arm and 42.1 months in the PC arm. A final analysis of the data was planned when 631 deaths had occurred.

Toxicity was greater in the TCPC arm. More than 85% of women in the TCPC arm had at least 1 cycle delayed compared with 50% in the PC arm. Most (77%) delays were due to myelosuppression in the TCPC arm. Myelotoxicity was substantially greater in the TCPC arm with an 85% rate of grade 4 granulocytopenia compared with 58% in the PC arm (p<0.001). Febrile neutropenia or infection with grade 3 or 4 neutropenia was 22% in the TCPC arm and 6% in the PC arm (p<0.001). Hospitalisation during treatment was also more common in the TCPC arm (11.3% cycles) than the PC arm (7.1% cycles). Thromboembolic events (p<0.001), nausea (p=0.01) and vomiting (p<0.001) were also more common in the TCPC arm. There were substantially more neurosensory effects (p<0.001) and allergic reactions (p<0.001) in the PC arm. No statistically significant differences in QoL between groups were seen.

The authors stated that their study had few limitations, and that it was adequately powered to detect a difference in the primary endpoint. The survival data were described as “immature” and the final results need more follow-up. However, the method of randomisation was not adequately described.

The results of both of these studies indicate that the addition of topotecan or topotecan plus cisplatin to PC in first-line treatment for advanced (stage IIb-IV) ovarian cancer does not significantly increase OS, PFS or response rate, and has a worse toxicity profile than PC alone. These results are consistent with the guidance recommendations in NICE TA55.

Key references

Bolis G, Scarfone G, Raspagliesi F et al. (2010) Paclitaxel/carboplatin (PC) versus topotecan/paclitaxel/carboplatin (TPC) in patients with FIGO suboptimally resected stage III-IV epithelial ovarian cancer a multicentre, randomized study. European Journal of Cancer 46: 2905–12

Hoskins P, Vergote I, Cervantes A et al. (2010) Advanced ovarian cancer: phase III randomized study of sequential cisplatin-topotecan and carboplatin-paclitaxel vs carboplatin-paclitaxel Journal of the National Cancer Institute 102: 1547–56

Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

A multicentre, Italian, phase III RCT (MITO-2) by **Pignata et al. (2011)** evaluated carboplatin plus pegylated liposomal doxorubicin (CPLD, n=410) compared with paclitaxel plus carboplatin (PC, n=410). Women with newly diagnosed, histologically or cytologically confirmed FIGO stage Ic to IV epithelial ovarian cancer who were receiving first-line treatment were included.

Women assigned to the CPLD arm received carboplatin AUC 5 and PLD (30 mg/m^2), while women in the PC arm received carboplatin AUC 5 and paclitaxel 175 mg/m^2. In both arms chemotherapy was given on day 1 every 3 weeks, initially for 3 cycles and then patients with stable or responding disease continued treatment for a further 3 cycles.

The primary outcome was PFS measured by RECIST, and the first among the following events defined progression: increase of more than 20% in the sum of the largest diameters of known lesions; appearance of a new lesion; confirmed increase of more than 25% in CA125; or death without clinical or instrumental signs of disease progression.

Median PFS times were 19.0 months in the CPLD group and 16.8 months in the PC group (HR=0.95, 95%CI 0.81 to 1.13; p=0.58). In multivariate analysis adjusted by stage, performance, residual disease, age and size of the institution, the difference between treatments remained non-significant (HR=0.97 95% CI 0.82 to 1.14, p=0.70). With 313 deaths recorded (38.2%), the median OS was 61.6 months in the CPLD arm compared with 53.2 months in the PC arm (HR=0.89, 95% CI 0.72 to 1.12, p=0.32).

A total of 297 women (36.2%) were eligible for analysis according to RECIST criteria, 33.4% in the CPLD arm and 39% from the PC arm. The overall response rate was 57% in the CPLD arm (23 complete and 55 partial responses; p=0.76) and 59% in the PC arm (24 complete and 71 partial responses). In 173 patients with elevated CA125 only, CA125 became normal in 86% and 82% of patients in the CPLD and PC arms respectively (p=0.70).

Six deaths were potentially treatment related: 2 in the CPLD arm and 4 in the PC arm. Thrombocytopenia and anaemia were significantly more frequent and severe in the CPLD arm (both p<0.001); red blood cell transfusions were more frequently needed in the CPLD arm than the PC arm (6% vs 2%; p=0.001). Leukopenia, infections, platelet transfusions and bleeding were not significantly different. Skin toxicity and stomatitis were significantly worse in the CPLD arm (p<0.001) while hair loss, neuropathy and diarrhoea were significantly worse in the PC arm (all p<0.001). There were no significant differences in QoL scores.

The study was stopped early due to event occurrence slowing before the planned number of events being attained (556 instead of 632), which reduced the statistical power to 75%, but there was still 80% power to detect an HR of 0.79 for PFS. The QoL assessment was limited to the treatment period so residual issues were not assessed. The authors also noted the cost of CPLD and its lack of regulatory approval, which may affect treatment choice.

CPLD was not superior to PC, which remains the standard first-line chemotherapy in line with NICE TA55. However, CPLD may be an alternative to PC for people at high risk of neuropathy or who wish to avoid hair loss. Therefore, this evidence may have a potential impact on NICE CG122, although the details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

Key reference

Pignata S, Scambia G, Ferrandina G et al. (2011) Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. Journal of Clinical Oncology 29: 3628–35

Gemcitabine

Gemcitabine is not recommended by current guidance for first-line treatment of ovarian cancer and at the time of publication of this Evidence Update did not have UK marketing authorisation for this indication.

A phase III RCT by **du Bois et al. (2010)** evaluated paclitaxel 175 mg/m^2 plus carboplatin AUC 5 every 3 weeks (PC, n=882) compared with PC plus gemcitabine 800 mg/m^2 on days 1 and 8 (PCG, n=860) in women receiving first-line therapy with histologically confirmed stage I–IV ovarian cancer.

The primary endpoint was OS. Secondary endpoints included QoL, PFS, response to treatment and toxicity. Most patients received at least 6 treatment cycles: 87.2% in the PC arm and 86.2% in the PCG arm.

Median OS was 49.5 months for PCG and 51.5 months for PC arm (p=0.51). Objective response was greater in the PCG arm and was observed in 86.2% of 174 patients compared with 77.5% of 182 patients in the PC arm (p=0.03). However, this result was not replicated for PFS which was 17.8 months in the PCG arm compared with 19.3 months in the PC group (p<0.01). Investigation of subgroups by stage of cancer or histological type did not show any evidence of a benefit in the PCG group. No significant differences were observed in QoL after chemotherapy was completed.

Fatigue (p=0.0125) and grade 3 to 4 haematological toxicities (all p<0.001) occurred significantly more frequently in the PCG arm. Furthermore, grade 3 to 4 febrile neutropenia occurred more frequently in the PCG arm and PCG-treated patients received more packed red blood cells, antibiotics and supportive care with erythropoietin, granulocyte-colony stimulating factor, or granulocyte-macrophage-colony stimulating factor.

The authors concluded that addition of gemcitabine to PC reduced PFS and did not improve OS, therefore its use was not advised for first-line treatment of ovarian cancer. Consequently, the evidence is consistent with NICE TA55, as referred to in NICE CG122, in recommending that PC remains the standard first-line treatment.

Key reference

Du Bois A, Herrstedt J, Hardy-Bessard A-C et al. (2010) Phase III trial of carboplatin plus paclitaxel with or without gemcitabine in first-line treatment of epithelial ovarian cancer. Journal of Clinical Oncology 28: 4162–9

Weekly paclitaxel

The section of NICE CG122 discussing the management of advanced ovarian cancer makes a cross-reference to NICE TA55, which recommends that paclitaxel and carboplatin are options for first-line treatment of ovarian cancer; however dosing regimens are not discussed. Paclitaxel is licensed for first-line treatment of ovarian cancer in a 3-weekly dosing regimen. Weekly dosing of paclitaxel is not recommended by current guidance and at the time of publication of this Evidence Update did not have UK marketing authorisation for this regimen.

A Japanese phase III RCT by **Katsumata et al. (2009)** compared dose-dense (weekly) paclitaxel plus carboplatin (ddPC, n=312) with 3-weekly paclitaxel plus carboplatin (PC, n=319) in patients with newly diagnosed advanced (stage II–IV) epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer. People in the ddPC arm were given paclitaxel 80 mg/m^2 on days 1, 8 and 15 plus carboplatin AUC 6 mg/ml/minute on day 1 of a 21 day cycle, whereas the PC arm received the standard dose of paclitaxel 180 mg/m^2 plus carboplatin AUC 6 mg/ml/minute on day 1 of a 21 day cycle. Both groups were randomised to

receive 6 cycles of treatment. The primary endpoint was PFS and secondary endpoints were OS, response rate and adverse events. Complete response was defined as complete disappearance of all measurable and assessable lesions; partial response was defined as 50% or greater decrease in the lesions.

Women in the ddPC group had a 29% lower risk of disease progression and a 25% lower risk of death than the PC group. By the time of last follow-up (median duration=29 months) there were 160 disease progression events in the ddPC group versus 200 in the PC group. Median PFS was 28.0 months (95% CI 22.3–35.4) in the ddPC group and 17.2 months (15.7–21.1) in the PC group (HR=0.71, 95% CI 0.58–0.88, p=0.0015).

The OS at 2 years was 83.6% in the ddPC group and 77.7% in the PC group (p=0.049). By 3 years the OS for ddPC was 72.1% and with PC was 65.1% (p=0.03). Clinical response was assessed in 282 patients who had measurable disease at study entry. Overall response rate was similar between groups (PC group=72 [53%] of 135 patients, ddPC group=82 [56%] of 147 patients, p=0.72).

Withdrawal because of toxicity was higher in the ddPC group (n=113, 36%) compared with the PC arm (n=69, 22%). Haematological toxicity was the most common reason for withdrawal (68 withdrawals from ddPC versus 30 from PC, p=0.03). Anaemia was the only adverse event (grade 3 and 4) that was significantly different between the 2 groups (ddPC=69% versus PC=44%, p=0.0001). The incidence of neutropenic sepsis was not reported. Levels of withdrawal because of neurotoxicity were low with both ddPC (n=3) and PC (n=5). The most common adverse event was neutropenia, effecting 92% of the ddPC arm and 88% of the PC arm, but other adverse events were similar between groups. Granulocyte-colony stimulating factor was used in 60% of the ddPC group and 67% of the PC group.

The authors stated some limitations with their study. Even though the rates of neurotoxicity were similar between groups this may be because more patients in the ddPC group withdrew from treatment than in the PC group. Fewer than half of the ddPC group completed the study according to protocol mostly because of frequent delays with treatment cycles in this group, mainly due to neutropenia. However, 62% patients receiving ddPC eventually received six (or more) cycles in total. The authors noted that benefits of this magnitude have been rare in women with advanced ovarian cancer treated with paclitaxel and the optimum dose and schedule of ddPC have not yet been established.

A subsequent cost-effectiveness analysis based on the RCT by Katsumata et al. (2009) was reported by **Dalton et al. (2012)**. The analysis used a Markov model with a 48-month time horizon based on the treatments and outcomes from the results of the RCT. The structure of the model was based on 4 states: treatment, discontinuation of treatment or follow-up, progression, and death. The economic analysis included the costs of the 2 regimens (medical evaluation, chemotherapy administration, drugs and laboratory work), granulocyte-colony stimulating factor and blood transfusions for treatment of neutropenia and discontinuation (additional physician evaluation, laboratory work and wasted drugs).

Most resource data were taken from published clinical trials and costs were based on Medicare reimbursement figures and the pharmacy at the University of California. One-way sensitivity analyses were used to calculate PFS, OS and HRs between arms, complication rates and utility and cost parameters. A lump sum cost of hospitalisation due to adverse events was included in the sensitivity analysis. The primary measurement was the incremental cost-effectiveness ratio (ICER) expressed as the cost per progression-free life year saved (PFLYS).

The cost of chemotherapy administration for ddPC was $128 per cycle compared with $43 per cycle for PC. The estimated total costs of treatment per cycle of combination chemotherapy were $873 for ddPC compared with $535 for PC. These figures included the

costs associated with physician evaluation, laboratory testing and pre-treatment drugs, such as antiemetics and steroids. With a median PFS of 28 months with ddPC versus 17.2 months with PC, the ICER was $5809 per PFLYS for ddPC compared with PC.

Limitations of the study recognised by the authors were that it was based largely on the results of 1 study and as such does not account for all clinical scenarios. Katsumata et al. (2009) lacked details of the management of neutropenia and other non-haematological complications, such as use of drugs, treatment delay, and dose reduction.

Dalton et al. (2012) did not include costs of progressive or recurrent disease, the year of price calculations was not stated explicitly and US Medicare reimbursement figures are different from UK NHS costs, which may limit the applicability of these results. The model also assumed that the HR is constant over time, which may not be appropriate for advanced ovarian cancer. The authors concluded that these results need to be confirmed in a larger and more diverse cohort. Future trials could show a lower magnitude of benefit, which may result in a higher ICER than was demonstrated in this model.

The study by Katsumata et al. (2009) showed a lower risk of disease progression and death from ddPC compared with PC, but withdrawals were significantly higher in the ddPC group and further research is needed to confirm the findings. An efficacy trial by the Medical Research Council (ICON 8) is currently recruiting participants to determine if weekly paclitaxel or carboplatin is more effective and safe than standard 3-weekly paclitaxel or carboplatin in treating ovarian cancer. The economic analysis by Dalton et al. (2012) seems to show cost-effectiveness of ddPC in a US population; however this would need confirming in a UK NHS population. The findings appear to be consistent with the recommendations in NICE TA55, as referred to in NICE CG122, that paclitaxel and carboplatin are options for first-line treatment of advanced ovarian cancer.

However, there is no discussion of treatment regimens in the guidance recommendations and NICE TA55 is unable to recommend any unlicensed dosing regimen. Weekly paclitaxel differs from the standard 3-weekly administration so there may be a potential impact on NICE CG122. The details of any impact are outside the scope of the Evidence Update. Decisions on how the new evidence may impact guidance will not be possible until the guidance is reviewed by NICE following its published processes and methods.

A critical abstract of the study by Dalton et al. (2012) was produced for the Centre for Reviews and Dissemination's NHS Economic Evaluation Database.

Key references

Katsumata N, Yasuda M, Takahashi F et al. (2009) Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 374: 1331–8

Dalton HJ, YU X, Hu L et al. (2012) An economic analysis of dose dense weekly paclitaxel plus carboplatin versus every 3 week paclitaxel plus carboplatin in the treatment of advanced ovarian cancer. Gynecologic Oncology 124: 199–204

Supporting references

Centre for Reviews and Dissemination (2012) An economic analysis of dose dense weekly paclitaxel plus carboplatin versus every 3 week paclitaxel plus carboplatin in the treatment of advanced ovarian cancer. NHS Economic Evaluation Database.

Medical Research Council. An international phase III randomised trial of dose fractionated chemotherapy compared to standard three weekly chemotherapy, following immediate primary surgery or as part of delayed primary surgery, for women with newly diagnosed epithelial ovarian, fallopian tube or primary peritoneal cancer (NCT01654146).

Maintenance chemotherapy

NICE CG122 does not contain any recommendations about maintenance chemotherapy.

A Cochrane review by **Mei et al. (2010)** evaluated 6 RCTs (n=902) assessing the effectiveness, toxicity and QoL of maintenance chemotherapy compared with observation, maintenance radiotherapy or other maintenance therapy. Maintenance chemotherapy refers to chemotherapy given after complete clinical remission or pathological complete remission, after initial surgery and induction chemotherapy. The treatment group consisted of women with newly diagnosed tumours, most of whom had advanced epithelial ovarian cancer.

Four trials comparing maintenance chemotherapy with observation were suitable for meta-analysis. The intended number of cycles ranged from 3 to 6. There were no significant differences in 3, 5 or 10 year PFS or OS. For 5 year OS the combined relative risk (RR) was 1.07 (95% CI 0.91 to 1.27) and for the 5 year PFS the RR was 1.18 (95% CI 0.88 to 1.58).

One of these studies was a 3-arm study comparing maintenance chemotherapy, maintenance radiotherapy and no further treatment. Ten-year PFS in the pathological complete remission group was in favour of whole abdominal radiotherapy (RR=0.51, 95% CI 0.27 to 1.00); however the confidence intervals suggest that this result was not significant. No trials comparing different maintenance therapies were identified.

Five trials described the toxicities of maintenance treatments, but none made comparisons between intervention and control groups. When comparing chemotherapy with radiotherapy more side effects were noted in the radiotherapy group, notably gastrointestinal effects.

Limitations reported by the authors were that only 2 studies described the method of randomisation, only 1 had adequate allocation concealment. None of the studies used blinding, but this was unlikely to have affected outcomes of OS and PFS. QoL could not be addressed because trials lacked QoL data.

When all chemotherapy regimens were combined, meta-analysis indicated no significant difference in OS or PFS between observation or maintenance radiotherapy and maintenance chemotherapy. Consequently, the evidence is unlikely to have an impact on NICE CG122.

Key reference

Mei L, Chen H, Wei DM et al. (2010) Maintenance chemotherapy for ovarian cancer. Cochrane Database of Systematic Reviews issue 9: CD007414

Bevacizumab

A NICE technology appraisal of bevacizumab in combination with paclitaxel and carboplatin for the first-line chemotherapy treatment of ovarian cancer, is currently underway. Although the Evidence Update found new evidence in this area (see Burger RA et al. 2011 and Perren TJ et al. 2011 in the key references below), commentary is not provided because a technology appraisal is in progress, which should be referred to as the latest guidance once it is published.

Key references

Burger RA, Brady MF, Bookman MA et al. (2011) Incorporation of bevacizumab in the primary treatment of ovarian cancer. New England Journal of Medicine 365: 2473–83

Perren TJ, Swart AM, Pfisterer J et al. (2011) A phase 3 trial of bevacizumab in ovarian cancer. New England Journal of Medicine 365: 2484–96

Primary surgery

NICE CG122 recommends that 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.

A Cochrane review by **Elattar et al. (2011)** evaluated the effectiveness, safety and cost-effectiveness of optimal primary cytoreductive surgery for women with surgically staged advanced stage III and IV epithelial ovarian cancer confirmed by histological diagnosis with no other concurrent malignancy. The secondary objective was to assess the impact on OS of various residual tumours over a range between 0 and 2 cm. Included studies defined optimal cytoreduction as surgery leading to residual tumours with a maximum diameter of any threshold up to 2 cm. All patients received adjuvant platinum-based chemotherapy following surgery.

Eleven retrospective studies consisting of a total of 4735 women were included. When suboptimal (margins >1 cm) was compared with optimal (margins <1 cm) cytoreduction the survival estimates were reduced but remained statistically significant in favour of the lower volume disease group.

There was no significant difference in OS and only a slight difference in PFS when residual disease of greater than 2 cm and less than 2 cm were compared (OS HR=1.65, 95% CI 0.82 to 3.31; PFS HR=1.27, 95% CI 1.00 to 1.61, p=0.05). All analyses showed an OS benefit in women whose surgery was optimal when defined as residual disease less than 1 cm (>1 cm vs <1 cm HR=1.36, 95% CI 1.10 to 1.68; 1–2 cm vs <1 cm HR=1.70, 95% CI 1.11 to 2.60; and > 2 cm vs <1 cm HR=2.00 95% CI 1.36 to 2.94), but there was no significant difference in OS for residual disease of greater than and less than 2 cm (HR=1.65, 95% CI 0.82 to 3.31).

The effect of treatment for time to event (OS or PFS) was measured by HR to limit the effect of censoring in all studies. The included studies were a combination of RCTs, prospective studies and retrospective studies, which meant that the comparison of residual disease was retrospective in nature and consequently all studies were at a high risk of bias. Methods of sequence generation, allocation concealment and blinding of the outcome assessor were not reported in any of the studies. Selection bias may have led to biologically less aggressive tumours being selected because they were more amenable to surgery.

The results indicated that all attempts should be made to achieve complete cytoreduction. This evidence is consistent with the recommendation of complete resection in NICE CG122. The authors' conclusion that prospective RCTs are needed to determine whether the surgical intervention or patient related and disease factors are associated with the improved survival concurs with the research recommendation in NICE CG122 for research to determine the effectiveness of primary surgery in women with advanced ovarian cancer whose tumour cannot be fully excised.

Key reference

Elattar A, Bryant A, Winter-Roach BA et al. (2011) Optimal primary surgical treatment for advanced epithelial ovarian cancer. Cochrane Database of Systematic Reviews issue 8: CD007565

Intraperitoneal chemotherapy

NICE CG122 recommends that intraperitoneal chemotherapy should not be offered to women except as part of a clinical trial.

In a Cochrane review by **Jaaback et al. (2011)** the authors sought to determine whether adding a component of chemotherapy into the peritoneal cavity affects OS or PFS in the primary treatment of epithelial ovarian cancer compared with intravenous chemotherapy. Secondary objectives included the effect on QoL and toxicity. Only women with a new diagnosis who had undergone primary surgery were assessed.

Nine RCTs consisting of 2119 women were included with 6 of those deemed to be high quality. Eight trials (2026 women) were included in the meta-analysis for OS. The intraperitoneal group had a significant improvement in OS (HR for time to death=0.81, 95% CI 0.72 to 0.90). There was no evidence of heterogeneity and there was no significant difference between subgroups. Five trials (1311 women) were included in the meta-analysis of time to recurrence, with a significant improvement in PFS in the intraperitoneal intervention group (HR for time to death=0.78, 95% CI 0.70 to 0.86).

Severe adverse events (grade 3–4) more likely to occur in the intraperitoneal group were: fever (RR=1.64, 95% CI 1.13 to 2.38); fatigue (RR=2.32, 95% CI 1.06 to 5.07); gastrointestinal (RR=1.70, 95% CI 1.28 to 2.26); infection (RR=3.34, 95%CI 2.06 to 5.43); metabolic (RR=4.45, 95%CI 2.72 to 7.26); pain (RR=7.47, 95% CI 4.41 to 12.67). Hearing loss was more common in the intravenous chemotherapy group (RR=0.67, 95% CI 0.46 to 0.99). There was no significant difference between interventions for haematological, renal, neurological and pulmonary adverse events, although these meta-analyses had substantial heterogeneity. QoL was only assessed in 1 trial in which more disruption was noted in the intraperitoneal arm during and up to 6 weeks after treatment but there were no significant differences between arms 1 year after treatment.

Limitations of the review were lack of blinding after allocation to treatment and that a variety of different regimens were used. Three of the trials were considered to be of lower quality because of inadequate or absence of information on randomisation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Catheter-related complications of intraperitoneal drug administration were discussed in all trials but the data retrieved were insufficient to produce a meta-analysis.

The evidence indicates that intraperitoneal chemotherapy may be more effective than intravenous chemotherapy in terms of OS and PFS, but with greater toxicity. Jaaback et al. (2011) is an updated version of a Cochrane review by Jaaback and Johnson (2006), including 1 additional study. The original review was considered by NICE CG122 and the updated review does not include substantially more evidence or different conclusions to Jaaback and Johnson (2006) so is unlikely to have an impact on guidance. The need remains for further, more conclusive evidence to establish efficacy and toxicity levels of modern treatments.

Key reference

Jaaback K, Johnson N, Lawrie TA (2011) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database of Systematic Reviews, issue 11: CD005340

Supporting reference

Jaaback K, Johnson N. (2006) Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database of Systematic Reviews issue 1: CD005340

1.5 Support needs of women with newly diagnosed ovarian cancer

Healthcare use

NICE CG122 recommends offering all women with newly diagnosed ovarian cancer information about their disease. This information includes: the stage of the disease, treatment options and prognosis; how to manage the side effects of the disease and its treatments in order to maximise wellbeing; symptoms and signs of disease recurrence.

An RCT from the USA by **McCorkle et al. (2011)** evaluated the effectiveness of an intervention provided by oncology advanced practice nurses (APNs) and a psychiatric consultation-liaison nurse (PCLN) on patients' self-reported use of healthcare compared with an attention control intervention in women undergoing surgery for suspected ovarian cancer.

Women were randomised to the intervention group (n=67) or the attention control group (where people in the control group receive the same amount of attention as those in the treatment group, n=70). They were assigned at baseline within 48 hours after surgery and 1, 3 and 6 months after surgery. All patients had a suspected primary diagnosis of ovarian cancer after abdominal surgery, a prognosis of surviving at least 6 months, and had been discharged from hospital before planned chemotherapy.

The intervention consisted of 18 contacts by an oncology APN during the first 6 months after discharge from hospital. Their primary objective was to assist patients in developing and maintaining self-management skills, to facilitate active participation in decisions affecting their treatment and to monitor and manage their physical and psychological health. Screening for emotional distress was also completed at baseline using the distress thermometer scale. Those women in the intervention arm who scored 4 or more, indicating significant distress, had a collaborative plan of care agreed by the PCLN and APN. Women who scored 4 or more in the attention control had usual care from the medical social worker.

All patients received a health education manual with information about intervention strategies addressing symptoms commonly experienced after surgery or with chemotherapy. Healthcare use was measured by the number of admissions to hospital and the number of outpatient visits. Four standardised scales were used to measure QoL outcomes: depressive symptoms, uncertainty, symptom distress, and physical and mental health. Patient characteristics were similar in the 2 groups: 58% had a primary diagnosis of ovarian cancer, and 32% had early stage disease.

Within a month of hospital discharge, no significant difference in healthcare use was seen between the groups. Almost 63% of women in both groups were not hospitalised and more than 76% were not admitted to the emergency department more than 6 months after surgery. For the subsample of women who used healthcare services there were no differences in hospitalisations or oncology outpatient visits between the 2 groups. Patients who received the PCLN and APN intervention reported fewer primary care visits ($\beta=-0.59 \pm 0.16$, $p=0.0003$).

The authors concluded that the interventions provided by the APNs assisted those women with depressive symptoms, whereas the attention-control group sought additional help through their primary care providers.

Limitations of the study included that the study was not designed to focus on healthcare use however the authors did not describe the intended primary outcome of the study. The authors admitted that there was a lack of a pre-specified sample size estimate because of the lack of previous studies testing the APN intervention effect on healthcare use. This study also relied only on self-reporting, which may affect the validity of the results.

The results of the study are consistent with NICE CG122, reinforcing the importance of receiving information and assistance from appropriate support teams to inform patients' decision making.

Key reference

McCorkle R, Jeon S, Ercolano E et al. (2011) Healthcare utilization in women after abdominal surgery for ovarian cancer Nursing Research 60: 47–57

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Management of suspected early (stage I) ovarian cancer

- Adjuvant therapy for the treatment of advanced borderline ovarian tumours

Management of advanced (stage II-IV) ovarian cancer

- Paclitaxel for maintenance chemotherapy for ovarian cancer
- Complete cytoreduction for advanced epithelial ovarian cancer
- Intraperitoneal carboplatin versus cisplatin for primary epithelial ovarian cancer

Further evidence uncertainties for ovarian cancer can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.

Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:

- Ovarian cancer. NICE clinical guideline 122 (2011).

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 1 January 2010 (the end of the search period of NICE clinical guideline 122) to 9 July 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- DARE (Database of Abstracts of Reviews of Effects)
- EMBASE (Excerpta Medica database)
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)
- HTA (Health Technology Assessment) database

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. It was also modified from that of the baseline guideline by adding in additional MeSH terms, with advice from the Chair, which has increased the sensitivity of the search. The search strategy was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews .

Subsequent to these searches we also asked the EUAG to highlight any significant evidence published between June 2009 (when the NICE TA55 review proposal searches were conducted) and January 2010 to ensure that studies published in this period were also considered.

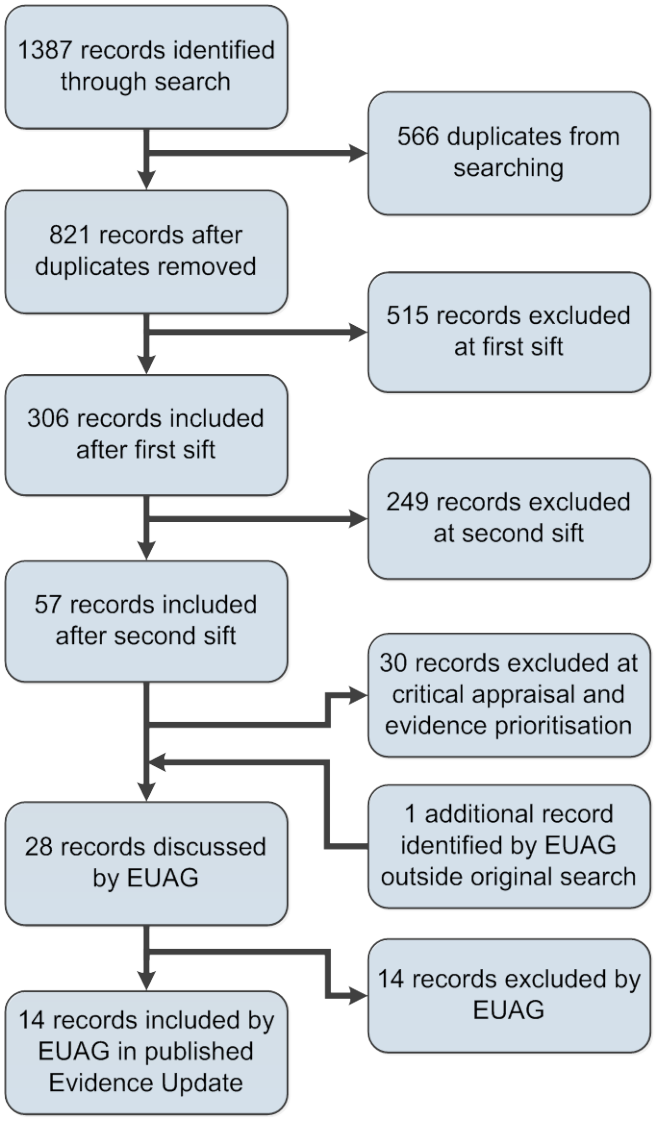
Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

1	Ovarian Neoplasms/
2	Adnexal Diseases/
3	"Hereditary Breast and Ovarian Cancer Syndrome"/
4	Peritoneal Neoplasms/
5	Fallopian Tube Neoplasms/
6	Pseudomyxoma Peritonei/
7	Mesonephroma/
8	Choriocarcinoma, Non-gestational/
9	Granulosa Cell Tumor/
10	Struma Ovarii/
11	Brenner Tumor/
12	Adenocarcinoma, Papillary/
13	exp Cystadenocarcinoma/
14	Krukenberg Tumor/
15	((ovar$ or fallopian or peritoneal$) adj5 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumo?r$ or adenocarcin$ or adeno-carcin$ or sarcoma$ or chorio?carcinoma$ or dysgerminoma$ or seminoma$ or teratoma$ or teratocarcinoma$ or terato-carcinoma$ or cystadenocarcin$ or fibrosarcoma$ or fibro-sarcoma$ or rhabdo???sarcoma$ or rhabdo-myosarcoma$ or rhabdo-sarcoma$ or leiomyosarcoma$ or leio-myosarcoma$ or carcinosarcoma$ or carcino-sarcoma$ or granulosa$)).tw.
16	((borderline or border line) adj4 ovar$).tw.
17	(ovar$ adj5 (mesonephroma? or non-gestational choriocarcinoma? or cystadenocarcinoma? or papillary adenocarcinoma?)).tw.
18	(pseudomyxoma peritonei or struma ovarii).tw.
19	((granulosa cell or Brenner or Krukenberg) adj3 (cancer? or tumo?r?)).tw.
20	or/1-19

Figure 1 Flow chart of the evidence selection process



EUAG – Evidence Update Advisory Group

Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

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