Follow-up of women with epithelial ovarian cancer:

a systematic review

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See Appendix A for more information.

Executive summary

Follow-up has been defined as "a set of visits and examinations conducted in a systematic manner in the perspective of a pre-defined program".[1] Previous clinical practice guidelines from National Breast Cancer Centre (NBCC)* and Australian Cancer Network (ACN) on the management of epithelial ovarian cancer, published in 2004, included information on follow-up care after treatment of ovarian cancer. National Breast and Ovarian Cancer Centre (NBOCC) undertook a systematic review of literature published between January 2003 and January 2010 to update this information.

There was limited high level evidence available, with only one randomised controlled trial identified; the remaining studies were retrospective or observational. The systematic review found that symptoms and measurement of CA125 levels were the most common method of detection of recurrence, as part of follow-up. From the available evidence, it is unclear whether the method of detection of recurrence impacts on overall survival. The randomised controlled trial reported no differences in overall survival between early and delayed treatment with chemotherapy based on rising CA125 levels alone. No studies were identified which compared different follow-up intervals, sequence or duration. Common methods of follow-up included history and physical examination, CA125 and ultrasound, while common schedules included 3 monthly visits for years 1 and 2, 6 monthly visits for years 3 to 5, and annually for years 6 to 10.

While there were similarities in preferences and perceptions of follow-up between patients and health professionals in two studies identified, there were also some differences. Monitoring of disease progression was perceived as important by both patients and health professionals. Health professionals reported the most important part of the visit was the consultation and another reason for follow-up was for women to talk about their concerns. Patients and health professionals both acknowledged a potential role in follow-up for general practitioners (GPs) and/or nurses, however the extent of this potential involvement varied.

Ovarian cancer patients experience a range of psychological issues after treatment. Improvements in psychological issues were reported after participation in pilot follow-up studies.

While no trials comparing different models of follow-up care were identified, a pilot study of nurse-led telephone follow-up was identified.

* In February 2008 National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

1 Background

1.1 Ovarian cancer in Australia

In 2006, ovarian cancer was the ninth most commonly diagnosed cancer among Australian women (excluding non-reportable skin cancers) and the second most commonly diagnosed gynaecological cancer, with a total of 1,226 ovarian cancer cases diagnosed.[2] It is the sixth most common cause of cancer-related death for Australian women, and the most common cause of gynaecological cancer death, representing over half (55%) of such deaths.

Ovarian cancer is often diagnosed at an advanced stage, when treatment is less likely to be effective. While most women respond to treatment initially, the cancer often recurs. There has been some improvement in survival in the last twenty years, however the prognosis for women with ovarian cancer is relatively poor, with only 40% of women likely to survive five years post-diagnosis.[2]

1.2 Clinical practice guidelines

The need to review the evidence and revise existing information about follow-up for women with epithelial ovarian cancer was identified following consultation with a range of stakeholders and advisors.

National Breast Cancer Centre (NBCC) and Australian Cancer Network (ACN) released the *Clinical practice guidelines for the management of women with epithelial ovarian cancer* in 2004,[3] which included a chapter about follow-up.

There were no recommendations regarding follow-up. However, a common follow-up program/schedule was included:

- review every 2–3 months for 2 years then;
- review every 4 months for the next 2 years then;
- review 6 monthly for a year before moving to annual review.

The basic format for follow-up was stated as: an updated history, physical examination including pelvic examination, and blood taken for CA125. Radiological imaging should not be done routinely but should be performed if there is clinical or CA125 evidence of recurrence.

1.3 Follow-up of women with ovarian cancer

Follow-up has been defined as "a set of visits and examinations conducted in a systematic manner in the perspective of a pre-defined program".[1] While some common elements are included in most follow-up regimens, they have usually been developed by consensus or to reflect the approach of individual institutions, rather than on the basis of evidence.

While there is no evidence to show that follow-up of women with epithelial ovarian cancer has any impact on survival outcomes, follow-up for women who have completed active treatment, either first line or for subsequent recurrence, may be undertaken for a number of reasons. These include appropriate medical review, detection of recurrence, treatment of side effects and physical and emotional support for the woman.

A recent survey of Australian gynaecological oncologists investigated their current practice for the follow-up of asymptomatic women following treatment for invasive ovarian cancer. All respondents conducted a physical examination and most checked CA125 levels, but few routinely used computed tomography (CT) scans. Most indicated that the woman's preference determined the format of the follow-up. When asked about their usual practice for follow-up for an asymptomatic woman with a raised CA125 but negative clinical findings, more variation in practice was evident in areas such as the use of serial CA125 and imaging techniques (NBOCC/ASGO 2010, unpublished data).

Findings from a randomised controlled trial comparing early treatment of recurrence based on elevated CA125 levels alone to delaying treatment until clinical indications were present[4] has promoted discussion about follow-up practices amongst clinicians involved in the management of women with ovarian cancer.

The purpose of this review was to identify evidence published from January 2003 to January 2010 about follow-up of women with epithelial ovarian cancer.

2 Methods

The objective of the review was to investigate follow-up procedures for women who have completed active treatment for epithelial ovarian cancer.

Research questions addressed in this systematic review are:

- Does the method of detection of a recurrence influence outcomes?
- What is the optimal interval, sequence and duration of follow-up care?
- What are the patient's preferences for follow-up care?
- What are the health care providers' preferences for follow-up care?
- What evidence surrounds the role of follow-up care in psychosocial outcomes for women?
- Are there subsets of the defined population who have specific follow-up requirements?
- Do different models of conducting follow-up influence outcomes?

2.1 Inclusion criteria

2.1.1 Participants

Women who have completed active treatment (surgery, chemotherapy and/or radiotherapy) for epithelial ovarian cancer.

2.1.2 Intervention

Routine follow-up care for the purpose of detecting recurrence and/or new primary cancer, monitoring side effects of treatment and providing psychosocial care.

Standard follow-up procedures include medical history, physical examination including pelvic examination and rectal examination, and CA125 blood test. Intensive follow-up procedures include radiological imaging.

2.1.3 Comparison

Any comparisons of different types of follow-up care were recorded.

2.1.4 Outcome measures

Outcome measures of interest were:

- overall survival (OS)
- disease free survival (DFS)
- detection of recurrence/new primary cancer
- diagnostic accuracy
- quality of life (QoL)
- patient preferences
- provider preferences
- psychosocial outcomes
- information needs
- sexual health and sexuality
- anxiety reduction.

2.1.5 Additional issues of interest

The following additional areas of interest were not specifically searched for, however any information on these identified during the search was recorded:

- are there differences in access to follow-up for women with epithelial ovarian cancer in Australia?
- follow-up for other cancers arising from treatment
- high-risk mutation carriers
- effects of treatment on long term survivors.

2.2 Literature search

A systematic literature search was conducted in January 2010 to identify relevant trials which addressed the inclusion criteria. The search was conducted using several databases (see Appendix B), including:

- Medline (OVID)
- Embase (OVID)

- Pubmed
- Cochrane library.

Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy, developed with input from a multidisciplinary working group, used combined key terms which described epithelial ovarian cancer and follow-up (see Appendix C). The search was limited to trials conducted in humans which were published from January 2003 to January 2010 in the English language.

After the removal of duplicate citations and the addition of further citations sourced, a total of 626 unique citations remained. The titles and abstracts of these citations were assessed by two reviewers independently to determine eligibility for the current review based on the criteria described above. Ineligible studies were classified using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment, by the same two reviewers.

In addition to the above databases, guideline and clinical trial websites were searched for relevant information. Specific international guideline organisations were searched as well as the National Guidelines Clearinghouse and the Guidelines International Network (GIN) guideline database. Further information on sites searched can be found in Appendix D.

The following conference websites were searched from January 2006 to March 2010 to identify recently presented abstracts about follow-up for ovarian cancer:

- American Society of Clinical Oncology (ASCO) annual meeting
- International Gynecologic Cancer Society (IGCS) biennial meeting
- Society of Gynecologic Oncologists (SGO) annual meeting.

2.2.1 Exclusion criteria

Papers were excluded if they met any of the following criteria:

- not an original clinical study–publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- inappropriate population–studies conducted in a population other than patients treated for epithelial ovarian cancer. Studies that were conducted in a general cancer population were included only if data on ovarian cancer patients were reported separately
- inappropriate intervention–studies not investigating follow-up as defined in the inclusion criteria. Studies investigating diagnostic follow-up procedures (after clinical suspicion of recurrence) were not included
- inappropriate outcomes–studies not reporting on the effect of follow-up

- not published in the English language
- published prior to 2003.

Based on these criteria, 560 articles were excluded. The full texts of the remaining 66 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment, 14 citations were identified as eligible for the current review (see Appendix E). An additional paper reporting full results of a randomised controlled trial in one of the included abstracts was published after the search was completed. This has been incorporated into the relevant sections, bringing the number of citations included in the review to 15.

Full text citations for the review included:

- one guideline recommendation
- two systematic reviews – both on diagnostic accuracy for detection of recurrence
- one randomised controlled trial on early vs. delayed chemotherapy for recurrence
- five retrospective cohort studies on method of detection
- two pilot studies
- four qualitative/observational papers – one on patterns of care, three on patient preferences/satisfaction.

In addition to the peer-reviewed publications, two national guidelines were identified, along with two guidelines for individual Canadian provinces. The conference search identified eight abstracts of interest including one for the randomised controlled trial now published and included in this systematic review.

2.3 Data extraction

Data extraction was performed by one reviewer and verified by a second reviewer to ensure accuracy. Descriptive data extracted from the studies included characteristics such as population, interventions and primary outcomes. Schedules and procedures of follow-up care performed were also recorded.

Outcome data extracted from the studies included OS, DFS, QoL and detection of recurrence.

Qualitative data was also extracted on patient and/or health professional views of follow-up, with key themes and findings reported rather than specific outcome data.

3 Results

3.1 International guidelines

A limited number of international guidelines were identified regarding follow-up of ovarian cancer. National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) provide guidance for follow-up of ovarian cancer. However many of the statements made are based on consensus. Individual Canadian provinces have developed their own guidelines for follow-up. The main recommendations of the guidelines are summarised in Table 1 below. The recommendations relate to clinical visits and use of CA125, blood tests, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) and chest X-rays.

Table 1. International guidelines for follow-up of invasive epithelial ovarian cancer

Guideline	Clinical visit (history & physical examination)	CA125	Blood tests	Imaging studies (CT, MRI, PET)	Chest X-ray
ACN/NBCC 2004[†3]	Every 2-3 months for 2 years; then every 4 months for 2 years; then 6 monthly for year 5 and annually thereafter Including pelvic examination	May be done each visit if initially elevated		Only if clinically indicated	
NCCN 2009[5]	2-4 months for 2 years; then 3-6 months for 3 years; then annually after 5 years Physical examination including pelvic examination	CA125 or other tumour markers every visit if initially elevated	Complete blood count and chemistry profile as indicated	As clinically indicated	As clinically indicated
ESMO 2009[6]	History, physical examination including pelvic	May be performed		CT scans should be performed if	

[†] This is noted as a common program not a recommended program

Guideline	Clinical visit (history & physical examination)	CA125	Blood tests	Imaging studies (CT, MRI, PET)	Chest X-ray
	examination every 3 months for 2 years, every 4 months during the third year and every 6 months during years 4 and 5 or until progression is documented			there is clinical or CA125 evidence of progressive disease. FDG-PET-CT scans may be superior to CT scans in detecting small volume operable relapses	
Saskatchewan Cancer Agency 2009[7]	Patients to be followed by a gynaecologic oncologist every 3-4 months for two years, then every six months for a total of five years Follow-up examination includes physical examination, Pap smear and pelvic examination	A decision as to whether to routinely determine CA125 with each return visit should be individualised following a realistic discussion of the pros and cons of such monitoring between the patient and physician	Routine complete blood count or liver function tests are not recommended unless clinically indicated	Only if clinically indicated	Only if clinically indicated
BC Cancer Agency 2007[8]	Every 3 months for year 1; every 4 months year 2-3; every 6 months year 4-5; annually after 5 years General examination, pelvic examination and pelvic-rectal examination	Not required other than for the satisfaction of research protocol and for specific indications when they arise		Not required other than for the satisfaction of research protocol and for specific indications when they arise	
National Academy of Clinical Biochemistry 2008[9]		Every 2 to 4 months for 2 years and then less frequently			

ACN=Australian Cancer Network; BC=British Columbia; CT=computed tomography; ESMO=European Society for Medical Oncology; FDG=fluorodeoxyglucose; MRI=magnetic resonance imaging; NBCC=National Breast Cancer Centre; NCCN=National Comprehensive Cancer Network; PET=positron emission tomography

In addition, NCCN provides guidance for follow-up of borderline epithelial ovarian cancer (low malignant potential), as in Table 2.

Table 2. International guidelines for follow-up of borderline ovarian cancer

Guideline	Clinical visit (history & physical examination)	CA125	Blood tests	Imaging studies (CT, MRI, PET)	Other
NCCN 2009[5]	3-6 months for 5 years; then annually after 5 years Physical examination including pelvic examination	CA125 or other tumour markers every visit if initially elevated	Complete blood count and chemistry profile as indicated	Ultrasound as indicated for patients with fertility-sparing surgery	After completion of childbearing in patients who underwent unilateral salpingo-oophorectomy, consider completion surgery

CT=computed tomography; MRI=magnetic resonance imaging; NCCN=National Comprehensive Cancer Network; PET=positron emission tomography

3.2 Systematic reviews

A Cochrane protocol was identified on 'Evaluation of follow-up strategies for patients with epithelial ovarian cancer following completion of treatment'.[10] The protocol was registered in 2006 but was unpublished at the time of the systematic review.

Two systematic reviews were identified focusing on diagnostic accuracy of various methods used to detect ovarian cancer recurrence. Results are reported in the section about *Outcomes of method of detection*.

3.3 Included studies

Full text papers

Only one randomised controlled trial on follow-up for ovarian cancer was identified in the published literature. The remaining studies were retrospective or observational. However some subgroup analyses provided survival comparisons. Some studies were identified on diagnostic accuracy of methods of detection of recurrence. Qualitative studies reported on patient and/or health professional views of follow-up care.

Abstracts

Eight abstracts were identified, including one randomised controlled trial investigating early compared to delayed chemotherapy based on CA125 findings which has been superseded by the full text publication.[4,11] Four abstracts reported on various methods of detection, one reported on patterns of care, one reported on patient views of follow-up and one suggested follow-up guidelines for borderline tumours.

Table 3. Characteristics of included studies (full text papers)

Study	Design	Population and ovarian cancer stage (where available)	Question addressed	Outcomes
Amsterdam 2006[12]	Retrospective review/cohort	N=26 (27%) ovarian cancer patients Median age: 51yrs (range 25-76 years) 92% postmenopausal	Role of follow-up in psychosocial outcomes	Sexual symptomatology
Chan 2008[13]	Retrospective study	N=80 with ovarian cancer recurrence	Method of detection: CA125, symptoms and physical findings	First method of detection, survival
Cox 2008[14]	Retrospective study, before & after study	N=56 Mean 62 yrs (SD 10.89) . 49% had stage I/II and 51% had stage III/IV	Role of follow-up in psychosocial outcomes and other models of follow-up	Detection of recurrent disease and the identification and management of physical and psychological morbidity, quality of life
Fehm 2005[15]	Retrospective study	N=58 Median age was 58yrs (range 25-85 years). Majority of patients were stage III (56.9%)	Method of detection: symptoms, X-ray diagnostics, tumour markers (CA125), gynaecological examination and US	Diagnostic accuracy
Gadducci 2009[16]	Retrospective review of medical records	N=412 patients with recurrent ovarian cancer. 6.8% stage I, 6.6% stage II, 73% stage III (64.3% stage IIIC), 11.4% stage IV, 2.2% unknown. Median age at diagnosis 58 years (range 25-86 years)	Method of detection: clinical examination, CT scan, US, CA125	Overall survival, survival from recurrence, method of detection of recurrence
Garcia-Velloso 2007[17]	Retrospective study	N=86 (31 sub-group clinically disease free) 80% stage III/IV Median age 57 years (range 49-63 years)	Method of detection: PET, CA125, conventional radiological imaging	Diagnostic accuracy
Gu 2009[18]	Systematic review and meta-analysis	34 studies	Method of detection: CA125, PET alone, PET–CT, CT and MRI	Diagnostic accuracy
Havrilesky 2005[19]	Systematic review	10 ovarian cancer papers; 5 of which addressed use of surveillance PET in the	Method of detection: PET, conventional imaging,	Diagnostic accuracy

Study	Design	Population and ovarian cancer stage (where available)	Question addressed	Outcomes
		absence of clinical suspicion of which 3 were used to calculated pooled diagnostic accuracy	CA125	
Kew 2006[20]	Observational survey	24 responses. 23 out of 24 responses were from cancer centres. 75% networks had written guidelines	Optimal interval, sequence and duration of follow-up care	Patterns of follow-up care - provider of follow-up care, frequency & duration
Kew 2007[21]	Observational survey	96 patients (92% response rate), 32 health professionals (58% response rate) patients with gynaecological malignancy: 32% ovarian, 14% corpus, 24% cervix, 9% vulva, 1% vagina, 19% unknown Median age 58 years (29-88 years)	Patients' & health care provider's preferences and perceptions for follow-up care	Views on follow-up
Lydon 2009[22]	Observational focus groups	Patient focus group (n=6); health professionals focus group (n=7) Patients who had completed treatment for ovarian cancer: mean 64yrs, time since completion of first-line chemotherapy treatment mean 5yrs and 3mths. Health professionals responsible for follow-up care of ovarian cancer patients: a nurse clinician, two research registrars, two senior registrars, one junior registrar and a consultant oncologist	Patients' & health care provider's preferences and perceptions for follow-up care	Views on routine follow-up after treatment for ovarian cancer
Palmer 2006[23]	Observational survey	Patients on follow-up for epithelial ovarian cancer First survey n=90 (90% response rate), second survey n=26 out of 30 surviving patients (87% response rate)	Patient's & health provider preferences and perceptions for follow-up care	Questionnaire 1: assess patients in the follow-up clinic with their current CA125 result Questionnaire 2: assessment of change in practice & patient satisfaction
Rustin 2010[4]	Randomised controlled trial	N=529 patients in remission after first-line treatment for epithelial ovarian, fallopian tube, or serous primary peritoneal cancer, in whom CA125 concentration increased to twice the upper limit of normal during follow-up. ~8% stage I, 11% stage II, 68% stage III, 12% stage IV	Method of detection: CA125, symptoms	Overall survival, time to second-line chemotherapy, time to third-line treatment or death, quality of life

Study	Design	Population and ovarian cancer stage (where available)	Question addressed	Outcomes
		Median age 60-61 years (53-68 years)		
von Georgi 2004[24]	Retrospective review of medical records	N=704 with ovarian cancer:42.5% stage I, 23.7% stage II, 29.3% stage III, 4.5% stage IV; Mean age at time of diagnosis 56.9yrs N=186 cases with documented primary recurrence	Method of detection: CA125, symptoms, X-ray and physical findings	Efficiency of follow-up measures

CT=computed tomography; MRI=magnetic resonance imaging; PET=positron emission tomography; US=ultrasound

3.3.1 Impact of method of detection on patient outcomes

Five full text papers and two abstracts reported on the method by which ovarian cancer recurrence was first detected. Three full text papers and one abstract reported on overall survival based on method of detection of recurrence and two full text papers and one abstract provided survival information by time to treatment of recurrence. Four papers reported the diagnostic accuracy of methods to detect ovarian cancer recurrence, including two systematic reviews.

Method of detection of recurrences

Full text papers

Five full text papers reported on the method by which ovarian cancer recurrence was first detected.

Chan *et al* (2008) retrospectively reviewed records from 80 women with ovarian cancer recurrences to determine how the recurrences were first detected (method of detection).[13] At each follow-up visit, a history of any symptoms was obtained and a physical examination performed. Physical examination included routine palpation for enlarged lymph nodes and abdominal or pelvic masses and a pelvic examination including a speculum examination and a vaginal and recto-vaginal bimanual examination, as well as any symptom-directed examination. CA125 was checked at each visit. If recurrence was suspected, further investigations such as CT or PET scans or biopsy of the suspected recurrence were arranged.

Forty-nine patients first presented with a raised CA125 level. Twenty-eight patients first presented with symptoms and only three first presented with physical findings. Overall, 91% had raised CA125, 55% had symptoms and 52.5% had positive physical findings. Of the 9% without a raised CA125, all had symptoms with (6.3%) or without (2.5%) physical findings. No patient presented with physical findings alone.[13]

The distribution of patients with elevated CA125, symptoms and physical findings at tumour recurrence was as follows:[13]

- CA125 alone 26.3%
- symptoms alone 2.5%
- physical findings alone 0%
- CA125 + symptoms 20%
- CA125 + physical findings 18.8%
- symptoms + physical findings 6.3%
- CA125 + symptoms + physical findings 26.3%.

The most commonly reported symptoms were abdominal pain, abdominal discomfort/distension, nausea/vomiting and shortness of breath. Physical findings reported included a mass, ascites, enlarged lymph node and pleural effusion.[13]

A retrospective review conducted by von Georgi and colleagues (2004)[24] of 704 ovarian cancer patients with no evidence of disease post primary therapy and reported on the effect of follow-up, including method and time of detection on patients' overall survival. The study recorded if and where follow-up was provided, and what method led to the diagnosis of recurrence.[24] Of those attending follow-up (n=610): 47.2% attended follow-up visits at the university clinic, 7.5% at other clinics, 9.5% at gynaecologists, or a combination 35.7%. Ninety-four patients (13.4%) did not attend any follow-up. There were 186 cases with documented primary recurrence. The methods which led to the diagnosis of cancer recurrence were reported as follows: 28% by patients' complaints, 29% by X-ray diagnostic, 19.4% tumour marker serum levels, 15.1% gynaecological examination, 8.6% by ultrasound.[24]

A retrospective study by Fehm *et al* (2005) of 58 patients with recurrent ovarian cancer compared the sensitivity of tumour marker measurement and physical findings with radiological findings in detecting recurrence.[15] At the time of diagnosis of the recurrence, 60% of patients complained about symptoms which were mainly abdominal pain and constipation, 40% were symptom-free and reported well-being. The physical examination resulted in pathological findings in 78% of patients. Physical findings reported included pelvic tumour masses, ascites, enlarged lymph node and tumour infiltration of the rectum. CA125 serum levels were available from 54 of the 58 patients when recurrent disease was diagnosed. In 83% of patients, CA125 serum levels were elevated.[15] In 47 out of 54 patients, vaginal and abdominal ultrasound were performed when recurrent disease was diagnosed. Thirty-three of the 47 patients had pathological findings. Forty-two patients received CT scans of the pelvis and abdomen. Tumour recurrence was detected in 33 of these patients (80%). Combination of physical examination, gynaecological examination and CA125 determination was able to identify 98% of patients with ovarian cancer recurrence without any imaging techniques. CA125 had the highest sensitivity followed by CT scan and physical examination.[15] For patients with a pelvic recurrence, vaginal examination had the highest sensitivity, followed by vaginal ultrasound and CT scan. Note that none of these procedures provided false-positive results.[15]

Gadducci *et al* (2009) conducted a retrospective review of 412 patients with recurrent ovarian cancer.[16] Among the 331 asymptomatic ovarian cancer patients, the surveillance procedures which raised suspicion of recurrent disease were:

- clinical examination 14.8%
- CT scan 26.6%
- ultrasound 0.6%
- CA125 23.3%
- CA125 and imaging technique 34.7%.

In a retrospective study on the use of PET to detect recurrence reported by Garcia-Velloso *et al*[17] (2007), the findings on PET changed management in 11 (out of 31) patients considered clinically disease-free, with positive findings altering the plan from follow-up to treatment. In 55 patients with suspected recurrence, PET changed management in 27 patients: four were changed from surgery to follow-up, 23 were changed from follow-up to treatment.[17]

Abstracts

Results on detection of recurrence from a retrospective study of 79 stage IIIC or IV epithelial ovarian cancer patients who developed recurrence were presented at the SGO 2009 meeting.[25] The first evidence of recurrence was CA125 elevation (78.5%), positive clinical findings on physical examination (11.4%) and positive CT scan (8.9%). In addition, one patient was incidentally found to have recurrent cancer during hernia repair. The majority of patients with recurrence detected by physical examination presented with symptoms (7 out of 9, 77.7%). For those with asymptomatic recurrence, one had an elevated CA125 and the other had an abnormal CT scan.[25]

Taylor *et al* (2006) reported a prospective comparison of methods of surveillance at the SGO 2006 meeting.[26] One-hundred and forty-five patients were enrolled in a randomised controlled trial comparing consolidation treatment with placebo. The follow-up procedures used were intensive and included interval history, physical examination, and imaging (CT of abdomen and pelvic, chest X-ray and/or ultrasound). Imaging occurred every 3 months in the first year and every 6 months thereafter until relapse. CA125 levels were blinded and not used to determine relapse.[26] The median time to relapse from randomisation was 33 weeks. At relapse, of the 91 patients who relapsed:

- 72.5% had abnormal radiologic findings without clinical findings
- 23.1% had abnormal clinical findings
- 4.4% were diagnosed surgically
- 33% had normal CA125 (<35).

Outcomes by method of detection

Overall survival

Three full text papers and one abstract reported overall survival based on method of detection of recurrence. In all studies, CA125 was routinely measured, please refer to Table 3.

Chan *et al* (2008) reported the median survival from the time of recurrence for those who first presented with CA125, symptoms and physical findings were 25 months, 17 months and 11 months respectively.[13] There were no significant differences in survival between those who first presented with raised CA125 and those with symptoms. Patients who first presented with abnormal physical findings had significantly worse survival however the number in the group was too small to draw firm survival conclusions.[13] Those who had raised CA125 had significantly worse survival than those in whom CA125 remained normal (p=0.011). The median time to recurrence from completion of primary treatment was 12 months (range 2 – 62 months).[13]

von Georgi *et al* (2004) reported that 86.6% of patients attended follow-up, while 13.4% did not attend any follow-up visits. Patients who attended follow-up visits had an improved chance of survival compared to those who did not attend (p=0.004).[24] There was no difference in survival between those examined in the investigators' university clinic compared to those examined by generalist gynaecologists in their practices. The study found no significant difference in prognosis between patients whose recurrences were diagnosed by a general gynaecological examination and those by X-ray or CA125 determination. Also there was no significant difference for time between diagnosis and death by the way recurrence was diagnosed.[24] Neither early nor delayed therapy had a statistically significant influence on survival.

A retrospective review by Gadducci *et al* (2009) reported overall survival was equivalent for patients with or without symptoms at recurrence (no vs. yes, odds ratio: 0.90, 95% CI: 0.64 to 1.27, p=0.90).[16] Variables predictive of overall survival included stage of disease, residual disease after initial surgery >1cm, time to recurrence, site of recurrence and treatment at recurrence. Variables predictive of survival from recurrence included stage of disease, residual disease >1cm, time to recurrence and treatment at recurrence.[16]

The abstract presented by Taylor *et al* (2009) reported that overall survival and post-relapse survival were similar in patients diagnosed clinically or radiographically despite statistically significantly higher CA125 levels at time of relapse (p=0.0182) in those diagnosed clinically.[26] There were no differences in survival between those with normal vs. elevated CA125.[26]

A randomised controlled trial compared early chemotherapy for recurrence based on elevated CA125 levels alone (n=264) to delaying treatment until clinically indicated (n=263).[4] Second line chemotherapy started 4.8 months (95% CI: 3.6 to 5.3) earlier in the early treatment arm and 64% of women in this group received six or more cycles of chemotherapy compared to 51% in the delayed treatment group. After a median follow-up of 57 months from randomisation, the authors reported no difference in overall survival between the early (median survival 25.7 months) and delayed arms (median survival 27.1 months) (HR: 0.98, 95% CI: 0.80 to 1.20, p=0.85).[4] Seventy per cent of patients in both groups had died, of which approximately 96% were disease related. Two-year survival was 53.7% in the early treatment group and 54.7% in the delayed treatment group.[4]

von Georgi *et al* (2004) reported no difference in survival between patients who commenced therapy for cancer recurrence 0 – 10 days, 11 – 30 days, or more than 31 days after diagnosis of recurrence.[24]

A smaller US study was reported by Fleming *et al* as an abstract at SGO 2010 on a retrospective review of patients with recurrent epithelial ovarian cancer (n=74) who underwent secondary cytoreductive surgery.[27] In this selected group of patients, the authors report a correlation between a shorter length of time between 'study interval' (time between CA125 elevation and date of secondary surgery) and increased incidence of optimal cytoreduction (HR: 1.22, 95% CI: 1.00 to 1.49, p=0.05). Patients with optimal cytoreduction were reported to have significantly longer survival than those with suboptimal cytoreduction (47 vs. 23 months respectively, p<0.0001).[27]

Diagnostic accuracy

Studies were included if they investigated follow-up as defined in the inclusion criteria. Studies specifically investigating diagnostic follow-up procedures (after clinical suspicion of recurrence) were not included. Two systematic reviews were included, one separated results between patients undergoing PET after clinical suspicion and those undergoing PET without clinical suspicion.[19] The other review[18] investigated CA125, PET, CT and MRI but did not report separate results on whether tests were performed with or without clinical suspicion. In addition, one original study retrospectively evaluated the diagnostic yield of fluorodeoxyglucose-positron emission tomography (FDG-PET) for the diagnosis of recurrent ovarian cancer.[17] The study included a subgroup of 31 clinically disease-free patients who had 45 FDG-PET scans performed.

Diagnostic accuracy results from the two reviews (pooled results reported) and the retrospective study are provided in Table 4.

Table 4. Diagnostic accuracy of PET to detect ovarian cancer recurrence

Study	Test	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)	Accuracy (%)	FN	FP
Garcia-Velloso 2007[17]	CIM*	53	82	39	89	61	43/125	6/125
	CA125*	58	94	44	96	67	39/125	2/125
	PET*	87	79	68	92	85	12/125	7/125
	PET in clinically disease-free patients only	55	88	71	78	73%	9/45	3/45
Havrilesky 2005^[19]	PET in clinically disease-free patients	54	73					
	PET with rising CA125 and negative or equivocal CIM	96	80					
Gu 2009^[18]	CA125*	69	93					
	PET*	88	89					

	PET-CT*	91	88					
	CT*	79	84					
	MRI*	75	78					

CIM=conventional imaging modalities (CT scans/MRI); FN=false negative; FP=false positive; NPV=negative predictive value; PPV=positive predictive value

*Results for whole patient cohort which included patients both with and without clinical suspicion of recurrence; ^meta-analysis; pooled results

In a retrospective study by Garcia-Velloso *et al* (2007), recurrence was correctly identified in patients clinically considered disease-free by FDG-PET studies in 11 cases (24%), with a mean standardised uptake value (SUV) of 4.2±1.9 (median 4, range 0.8-6.5).[17] This study reported that the median relapse-free interval after a negative PET scan was 18 months compared with 2 months if the PET scan was positive.[17]

One systematic review assessed the diagnostic performance of FDG-PET in comparison to conventional imaging modalities in the assessment of patients with ovarian and cervical cancer, and results for each cancer were reported separately[19]. For the review, ten papers met the inclusion criteria for ovarian cancer. Five studies addressed use of surveillance PET to detect recurrent or persistent ovarian cancer in the absence of clinical suspicion. Three of these studies included at least 12 patients and required both negative CA125 and conventional imaging studies for classification as "no clinical suspicion" prior to PET imaging.[19] The pooled sensitivity and specificity of PET in these three studies was 0.54 and 0.73 respectively. Three studies addressed use of PET to detect recurrent ovarian cancer in the setting of rising CA125 and negative or equivocal conventional imaging studies. The pooled sensitivity and specificity were 0.96 and 0.80 respectively. Six studies addressed use of PET to detect recurrent ovarian cancer when clinical suspicion exists. Pooled sensitivity and specificity was 0.90 and 0.86 respectively.[19]

A systematic review and meta-analysis was published in 2009 evaluating the accuracy of CA125, PET alone, PET-CT, CT and MRI in diagnosing recurrent ovarian cancer.[18] Use in clinically disease-free patients and use in those in which recurrence was suspected was not distinguished in the review.[18] From the 34 included studies, CA125 had the highest pooled specificity (0.93) and PET-CT had the highest pooled sensitivity (0.91). PET, whether interpreted with or without the use of CT, had higher area under a curve (AUC) than that of CT or MR ($p<0.05$). No statistically significant difference was shown between PET alone and PET-CT.[18]

When comparing different methods of detection, specificity was highest for CA125[17-18] and sensitivity was highest for PET/PET-CT.[17-18] It should be noted that these comparisons used groups that include both clinically disease-free and those with suspicion of relapse. PET has lower sensitivity when performed in a clinically disease-free setting compared to under suspicion of recurrence.[17,19]

Taskiran *et al* presented an abstract at IGCS 2006 on the value of PET-CT in follow-up of ovarian cancer patients.[28] Nineteen patients were included in the analysis, four underwent PET-CT before second look laparotomy, and 15 were examined in the follow-up period to detect recurrence. In the follow-up group, PET-CT detected true recurrence in eight patients,

one patient had recurrence which was not detected by PET, the remaining six patients with negative PET findings had no recurrence in the follow-up period (mean 21 months).[28]

3.3.2 Optimal interval, sequence and duration of follow-up care

No trials were identified which compared different intervals, sequence or duration of follow-up care for ovarian cancer patients.

Most trials reported the follow-up schedule utilised in their individual setting and details on the different schedules reported in individual trials are provided in Table 5.

Table 5. Reported follow-up schedules

Study	Follow-up methods	Years after primary treatment		
		1st & 2nd year	3rd to 5th year	6th to 10th year
Chan 2008[13]	History and physical examination, CA125. If recurrences suspected further investigations such as CT or PET scans or biopsy of the suspected recurrence would be arranged	3 monthly	6 monthly	Annually≠
Fehm 2005[15]	Physical and gynaecological vaginal examination, CA125 and vaginal ultrasound examination. Abdominal ultrasound and CT scans were performed in patients considered to have a recurrence. Imaging techniques were also performed at regular intervals in patients who were enrolled in various clinical trials	3 monthly	6 monthly*	6 monthly≠*
Gadducci 2009[16]	6 centres with different surveillance protocols. CA125 regularly performed each visit; ultrasound, CT and/or chest X-ray were used at fixed times by some centres and only in the presence of suspicious symptoms or signs as well as rising CA125 levels by other centres	3–4 monthly	4–6 monthly	Annually
Gibb 2006^[29]	Pelvic examination and routine CA125 measurement mirrored follow-up visits, while diagnostic imaging was not a routine follow-up modality	3 monthly	6 monthly	Annually
Kew 2006^[20]	CA125 was routinely tested by 67% of cancer networks surveyed	3 monthly	6 monthly	
Lydon 2009[22]	Not reported	3 monthly	6 monthly	6 monthly. At 10 years, patients were discharged back to their GP
Palmer 2006[23]	CA125	2 monthly for first year, 3 monthly for the second year	4 monthly for third year, 6 monthly for further 2 years	Discharged or reviewed annually according to their wishes
Rustin 2010[4]	Physical and gynaecological examinations, ultrasound and	3 monthly		

	radiological examinations according to local practice, quality of life assessment, CA125 blood test			

≠follow-up continues beyond 10 years; *seen at outpatient department; ^most commonly reported schedule/suggested schedule

von Georgi *et al* (2004) have suggested the following treatment schedule (Table 6):[24]

Table 6. Follow-up schedule suggested by von Georgi 2004[24]

Method	Years after primary treatment		
	1st & 2nd year	3rd to 5th year	6th to 10th year
Medical history consultation	Every 3 months	Every 6 months	Every 12 months
Gynaecologic examination including transvaginal ultrasound	Every 3 months	Every 6 months	Every 12 months
Tumour markers CA125, CA72-4	Suspected relapse only	Every 6 months	Every 12 months
MRI, CT scans, X-ray diagnostic, ultrasound	In cases of suspected relapse only, especially for the development of treatment plans		
Mammography	Every 12 months		

CT=computed tomography; MRI=magnetic resonance imaging

Kew *et al* (2006) report on a survey of practice of 24 cancer networks in UK providing routine follow-up after treatment for a gynaecological cancer.[20] Seventy-five per cent of the networks had written guidelines on frequency and timing of follow-up for gynaecological cancer. Very few routine investigations were undertaken to detect recurrence. The exception was CA125 levels following treatment for ovarian cancer with 16 out of 24 networks (67%) routinely performed this test at each follow-up review.[20] The most common schedule for ovarian cancer follow-up was Year 1: 3 monthly (88%); Year 2: 3 monthly (46%); Year 3: 6 monthly (42%); Year 4: 6 monthly (50%); Year 5: 6 monthly (42%). The most commonly reported duration of follow-up was for 5 years (62.5%) followed by 10 years (29.2%), and lifelong (4.2%); data were missing for one network (4.2%). Twenty-five per cent of the networks reported using 'open access' as part of their follow-up service.[20]

Gibb *et al* (2006) reported an abstract on patterns of follow-up care for ovarian cancer patients at SGO 2006.[29] A questionnaire was completed by 323 SGO members (of 943 members, response rate 34%) to assess current follow-up care practice for stage I, II and III, optimally and suboptimally debulked patients who had not yet recurred.[29] After exclusion

due to incomplete responses or lack of long-term follow-up, responses from 283 members were used for analysis. Patients were seen, on average, every 3 months for years 1 and 2, every 6 months in years 3 to 5 and annually at year 10. Pelvic exams and CA125 measurement were routinely used, however diagnostic imaging was not.[29]

3.3.3 Patients' & health care provider's preferences and perceptions of follow-up care

Four full text papers and two abstracts provided information on patients' and/or health professionals' views on follow-up. In a small study from the UK, Lydon *et al*[22] (2009) reported views of follow-up care from two focus groups in the UK: an ovarian cancer patient focus group (6 participants); and a health professional's focus group (7 participants). Kew *et al*[21] (2007) report results from a survey of 96 gynaecological cancer patients and 34 health professionals in the UK. Cox *et al*[14] (2008) reported on women's experience after participating in nurse-led telephone follow-up and Palmer *et al*[23] (2006) assessed patients' satisfaction with follow-up, particularly with regards to CA125. The abstracts reported on a survey of health professionals[29] or of patients.[30]

Detection of disease

Patient perceptions

Lydon *et al* (2009) reported that patients viewed follow-up visits as 'reassuring' and saw the main purpose of their visits as being for medical staff to monitor their disease status and check for signs of further problems.[22] Patients accepted discomfort associated with internal examinations undertaken as part of routine care, with the perception of these examinations as necessary for the detection of progression. The discomfort experienced was outweighed by the reassurance of negative findings from clinical examinations. Opinions were divided on the necessity of physically attending clinics, one patient was 10 years from diagnosis and felt confident in her own ability to monitor for potential signs of progression, however those not as far from diagnosis were not as confident.[22]

Similarly, Kew *et al* (2007) reported that patients thought the most important part of the visit was the examination (70 out of 96, 73%), and the most important reason for follow-up was "to detect recurrence".[21] This finding was supported by the results of a large survey conducted in Germany of over 1000 patients with ovarian cancer presented at ASCO 2009 which found that patients thought the main objective for the follow-up is the early detection of relapse and a prolongation of overall survival (95.8%).[30]

Health professional perceptions

Kew *et al* (2007) reported that professionals thought the most important part of the visit was the consultation (27 out of 34, 79%), compared with 43% of patients ($p<0.001$), and the most important reason for follow-up was "to talk about concerns" with relation to their disease and treatment.[21]

The study by Lydon *et al* (2009) found that health professionals reported the primary reason for follow-up was related to the monitoring of symptoms of relapse following treatment.[22] It was also appreciated by the health professionals that it was uncommon to find evidence of relapse at consultations, based on physical examination alone.[22] Comments were also made

regarding usefulness of CA125 in confirming disease progression. It was reported the presence of symptoms, raised CA125 count, usually results in further investigations to confirm disease progression.

In an abstract at SGO 2006, Gibb *et al* (2006) reported on patterns of follow-up care for ovarian cancer patients.[29] Questionnaire responses from 283 SGO members found that most (66%) felt routine follow-up was unlikely to result in a recurrent cancer diagnosis that was potentially curative. However, 80% felt long-term follow-up resulted in a moderate to great impact on survival.[29]

Information and support needs

Patient preferences

Lydon *et al* (2009) reported patient views about the need for specialist information and support from health professionals.[22] Immediate access to information and support was considered essential. In the study, participants could telephone the oncology service for information if needed. Patients reported that the structure of appointments could inhibit reporting any concerns or seeking information as they didn't want to bother busy doctors and nurses when they had an upcoming appointment.

Patient participants reported feeling most 'vulnerable' in the time between the end of treatment and the first follow-up visit (usually 3 months) and reported they would like to have more contact with the hospital at the time but considered it inappropriate to contact the hospital with their concerns.[22] Patients discussed the need for support from health professionals, such as a telephone call between the end of treatment and first follow-up appointment from a nurse asking how they were, would have been appreciated. Participants commented on the relationship they had established with specialist oncology nurses.[22] Waiting times for appointments were often long (1-2 hours), although patients spoke about the informal contact with other patients whilst waiting for their appointment.[22]

In a questionnaire of 90 patients in the UK evaluating the use of CA125 in follow-up, an improvement in patient education and basic understanding was seen following the implementation of a fact sheet on CA125 monitoring.[23]

Health professionals preferences

The health professionals reported that patients in the follow-up stage of their disease trajectory, could self-manage their own care needs if given sufficient support and guidance.[22] Health professionals agreed they should be more proactive in helping patients to identify signs of progression and/or late onset side effects and that patients should be given guidelines and 'what to do' should they have concerns or problems. This information should be given towards the end of treatment, verbally and in writing.[22] Self-management and less frequent visits to hospital clinics were seen as having a positive impact on patient well being.

Provision of care

Patient preferences

Patients in a UK focus group did not consider that general practitioners (GPs) could take the place of the oncology team in managing their follow-up care.[22] GPs were perceived as having less time available to discuss concerns, lacking specialist knowledge, and therefore, the ability to effectively monitor post-treatment progress. Telephone follow-up was considered appropriate for some people, but some concerns were raised. Patients did not question the need for physical examinations, and were concerned how examinations would be organised if followed up by telephone.[22] Practical advantages to telephone follow-up were also reported, and including the need to rely less on family/friends to provide transport to hospital clinics, and the possible benefit of individually negotiated appointments.[22]

In a questionnaire of 96 gynaecological cancer patients in the UK by Kew *et al* (2007), most patients thought they should see a hospital doctor for follow-up (82 out of 96, 85%).[21] Patients were less likely to think that specialist nurses (22 out of 92, 24%) and/or GPs (6 out of 92, 6%) should be involved in providing follow-up care.[21]

Cox *et al* (2008) conducted a pilot study of nurse-led telephone follow-up for 52 women following treatment for ovarian cancer.[14] Follow-up consisted of a telephone call every 3 months over a 10 month period. The follow-up telephone call initially focused on the detection of recurrent disease. The nurse gave the patient their recent blood test results and discussed any implications of this result.[14] A discussion/assessment of current symptoms followed, protocols for care algorithms were consulted for any reported symptoms with an immediate referral back into medical care if necessary. The intervention then focussed on providing tailored information, practical advice and coping strategies in physical, psychological and social domains. Patients were asked to rate the support they had received during telephone follow-up. On a scale from 1 'dreadful' to 10 'excellent' the mean rating score was 8.24. Of the 44 women who answered the question on preference for method of follow-up, 73% preferred telephone appointments.[14] Advantages of telephone follow-up cited were: the relationship and discussions between the patient and the nurse, and the convenience of having follow-up appointments over the phone instead of having to attend clinic.[14] Palmer *et al* (2006)[23] conducted a questionnaire of 90 patients in the UK to evaluate the use of CA125 in follow-up. Only 50% of patients were satisfied with the original service, with 81% wanting their current CA125 result available in clinic. Eighty-two per cent were willing to attend their GP surgery in advance of their follow-up appointment to have the relevant blood sample taken. Following a change in CA125 follow-up procedure a second survey was conducted. From the second survey 92.3% of the 26 patients evaluated felt that the quality of their follow-up had been enhanced as a result of the change in practice and having their CA125 results available in the clinic.[23]

Results of the survey presented by Oskay-Oezcelik *et al* (2009) of ovarian cancer patients found that routine follow-up visits were mostly performed by gynaecologists in a gynaecological practice (56.9%) and in hospitals (49.5%).[30] Most patients (89%) were satisfied with their management of cancer care.[30]

Health professional preferences

Lydon *et al* (2009) found a consensus from their health professionals focus group on the need to modernise the current system and reduce frequency of clinic visits for asymptomatic

patients (given lack of evidence to support approach or of a survival benefit with early treatment).[22] Health professionals acknowledged the importance of follow-up in patients who were at risk of disease progression, but questioned the effectiveness of current follow-up procedures for asymptomatic patients. Local follow-up policy was perceived as excessive, generating unnecessary workload. The health professionals were in agreement that there should be a change in current follow-up procedures and were aware that there was little evidence for the current follow-up system. The benefits of nurse-led and telephone follow-up were discussed, especially for patients who were at low risk of relapse. Health professionals noted that telephone follow-up could be acceptable if CA125 tests were conducted at a local hospital or GP practice with a copy of results sent to hospital consultants. Shared care with GPs was seen to be a positive means of improving follow-up care. Improvements in service and more time for patients who needed to be seen would result from a reduced number of patients physically attending clinics, however this was tempered with an appreciation that patients may hold a different view. Health professionals thought nurses should play a pivotal role in follow-up.[22]

In a questionnaire of 34 healthcare professionals by Kew *et al* (2007), most professionals thought that the woman should see a hospital doctor (25 out of 34, 73%).[21] Professionals were more likely than patients to think that specialist nurses (19 out of 34, 56%) and/or GPs (8 out of 34, 24%) should be involved in providing follow-up care.[21]

Kew *et al* (2007)[21] found that both patients and professionals agreed that the specialist nurse had a potential role in follow-up by listening to concerns and answering questions. However both groups were uncertain about whether or not it was within the nurse's role to detect recurrence. Patients agreed that the nurse could take blood but professionals disagreed.[21]

Kew *et al* (2006) report on a survey of practice of 24 cancer networks in UK providing routine follow-up after treatment for a gynaecological cancer.[20] All routine follow-up reported took place in secondary care and was consultant based:

- 30% consultant only
- 62% consultant and specialist registrar
- 8% consultant and staff grade doctor
- 0% GP
- 4% senior house officer (present in addition to senior medical staff)
- 21% clinical nurse specialist (present in addition to senior medical staff).

Anxiety

In the questionnaire conducted by Kew *et al* (2007) of 89 women who responded to a question on how they feel before and after attending follow-up, 54% reported feeling more anxious before the visit (44% reported feeling the same as usual, 2% reported feeling less anxious) and 38% reported feeling less anxious after the visit (52% reported feeling the same as usual, 10% reported feeling more anxious).[21] Professionals put more emphasis on the anxiety that women suffered and relief obtained from follow-up visits than women.[21]

Results of the survey presented by Oskay-Oezcelik *et al* (2009) found more than 90% of the patients had CA125 measurements which was the procedure with the highest anxiety but was also regarded as the most important procedure for the patient.[30]

3.3.4 Role of follow-up care in psychosocial outcomes for women

Two papers were identified which included information on follow-up care and psychosocial outcomes.

A pilot study was conducted of nurse-led telephone follow-up in ovarian cancer from a psychosocial perspective.[14] Patients received a follow-up telephone call from a specialist nurse every 3 months over a 10-month period. The initial focus of the call was on detection of recurrent disease with the nurse providing recent blood test results and then the nurse discussed implications of this result, current symptoms and referred the patient back to medical care immediately if necessary. The second focus of the call was to provide tailored information, practical advice and coping strategies in physical, psychological and social domains. Aspects discussed in these domains are presented in Table 7 below.[14] Fifty-two women received telephone follow-up, of which 46 completed pre- and post-data collection.[14]

Table 7. Domains of information, advice and coping strategies for telephone follow-up[14]

Domain	Discussion points
Physical	Menopausal symptoms; altered body image; hair loss/growth; weight loss/gain; nutrition & fatigue
Psychological	Anxiety/depression; fear of recurrence; familial risk
Social	Sexual intimacy issues; family; work & finances; spirituality

Pre-intervention data showed that women had good QoL.[14] Scores between pre- and post-measures were relatively stable with few changes in physical wellbeing, social/family wellbeing and functional wellbeing.[14] Women reported significant improvement in emotional wellbeing ($p=0.016$). Thirty-three women were recorded as having discussed issues in the psychological domain, of which 10 (30%) were referred on for counselling. Thirty-nine women were recorded as having discussed issues in the social domain which led to 9 referrals (23%) for support to social services.[14]

Amsterdam and Krychman[12] reviewed 259 sequential charts of patients who attended the Sexual Health Program at Memorial Sloan Kettering Cancer Center from March 1 2003 to December 31 2004 and identified 96 patients with a history of gynaecologic neoplasm (27% ovarian). All patients were evaluated by a gynaecologist specialising in sexual medicine as part of routine, well-woman care.[12] The most frequent presenting sexual complaint encountered was dyspareunia (72%), followed by atrophic vaginitis (65%), hypoactive desire (43%), and orgasmic dysfunction (17%). Treatment recommendations included hormone therapy alternatives (89%), psychosexual counselling (46%), minimally absorbed vaginal

estrogens (34%) and vaginal dilations (25%). At a median of 6 months, 60 patients (63%) had received follow-up, and of them 42 (70%) self-reported improvement in their symptoms.[12]

3.3.5 Quality of life following initiation of treatment for recurrence

The RCT by Rustin *et al*[4] assessed quality of life measures such as duration of good quality of life in the global health score and time of first global health-related deterioration. Quality of life was assessed before each chemotherapy cycle until the end of third-line treatment with the EORTC QLQ-C30 questionnaire. The median time spent with good global health score was 7.2 months for women assigned to early treatment (based on elevated CA125 levels alone) and 9.2 months for those assigned to delayed treatment (when clinical symptoms were evident) (statistical significance was not reported). Time from randomisation to first deterioration in global health score or death was shorter (median 3.2 months) in the early group compared with delayed (median 5.8 months; HR: 0.71, 95% CI: 0.58 to 0.88, p=0.002). Subgroup analyses of individual components of the QLQ-C30 subscales showed evidence of significant disadvantages for role, emotional, social and fatigue subscales with early treatment.[4]

3.3.6 Subsets of the defined population with specific follow-up requirements

No particular subsets of the women with ovarian cancer with specific follow-up requirements were identified in full text papers.

A group from the US suggested follow-up guidelines for women with ovarian tumours of low malignant potential in an abstract at the SGO meeting in 2009.[31] The results of their literature review found that the reported mean times to first recurrence were from 22 to 90 months. The authors proposed the following follow-up strategy for low-malignant-potential tumours (Table 8):

Table 8. Follow-up schedule suggested by MacLaughlan 2009[31] for ovarian tumours of low malignant potential

Study	Methods	Years after primary treatment		
		1st & 2nd year	3rd to 10th year	After 10 years
MacLaughlan 2009[31]	Serum CA125 assessment; pelvic ultrasound for patients with intact adnexae; CT as indicated for symptoms	Annually	6 monthly	Annually

CT=computed tomography

3.3.7 Different models of conducting follow-up

No studies were identified which compared different models of conducting follow-up for ovarian cancer.

The previously described pilot study of nurse-led telephone follow-up suggested that this model offered an acceptable opportunity for psychosocial support for women with ovarian cancer.[14] Of 44 women who answered a question on preference of method, the majority of women (73%) expressed a preference for nurse-led telephone follow-up, 18% preferred doctor/consultant appointments and 9% were unsure. The main advantages of nurse-led telephone follow-up were reported as the relationship and discussions between the patient and the nurse, and the convenience of having follow-up appointments over the phone instead of attending clinic.[14] However, 21 women (30% of those approached) were unable to or refused to participate in this pilot study.[14]

Patient and health professional preferences reported in the literature for the conduct of follow-up differ; see section 3.3.3 under provision of care. Patients were unsure if GPs and/or nurses could manage their follow-up care.[21-22] However a potential role in follow-up for GPs and/or nurses was acknowledged by both patients and health care professionals.[21-22]

3.4 Additional papers of interest

The following retrospective case-control study which was published after the literature search was completed, was considered of interest.

Tanner *et al* (2010) reported results of a retrospective study of 121 patients with recurrent ovarian cancer which compared the survival impact of diagnosing recurrent disease by routine surveillance testing versus clinical symptomatology.[32]

Surveillance included physical examinations and serum CA125 levels at every visit and CT scans of the abdomen and pelvis at the physician's discretion.[32] Follow-up visits were 3 monthly for the first two to three years, and 6 monthly for an additional two to three years. The prevailing practice for performing CT scans was 6 monthly for first two years, then annually for an additional three years.[32]

Asymptomatic recurrences (82% of patients) were defined as those diagnosed with the use of a regularly scheduled physical examination, CA125 levels and/or radiographic study. Additionally, asymptomatic patients did not present with symptoms consistent with recurrence at the time of diagnosing the recurrence. Symptomatic patients were defined as those in which recurrent disease was diagnosed based on clinical symptomatology at an unscheduled office visit or hospitalisation. Asymptomatic recurrence had a median primary progression-free survival of 24.8 months compared with 22.6 months for symptomatic recurrences (p=0.36). Post-recurrence survival for asymptomatic and symptomatic recurrences was 45 months and 29.4 months respectively (p=0.006).[32] Patients with asymptomatic recurrence had a median overall survival of 71.9 months compared with 50.7 months for symptomatic recurrence (p=0.004).[32] A greater proportion of symptomatic patients presented with evidence of recurrent disease outside of the abdomen or pelvis (41% vs. 15% for asymptomatic patients).[32]

3.5 Ongoing trials

Two clinical trials registries (Clinical trials.gov: www.clinicaltrials.gov and Current Controlled Trials: www.controlled-trials.com) were searched to identify any additional follow-up studies which have not yet reported.

One ongoing trial was identified. This randomised study compares satisfaction with follow-up led by a trained cancer nurse compared to conventional medical follow-up after primary treatment for ovarian cancer (ISRCTN59149551[33]). The trial aimed to recruit 100 patients from the UK. Primary outcome measures of the study included patient satisfaction and QoL. The study has now been completed and published results are awaited.

4 Discussion

Limited international and national guidelines on follow-up after ovarian cancer were identified, with the majority based on consensus. Common elements include recommendations around clinical visits, CA125 and imaging.

Two systematic reviews were identified in the review, both of these focused on the diagnostic accuracy of different methods of follow-up in detecting ovarian cancer recurrence. A Cochrane protocol,[10] published in 2006, was also identified and publication of this Cochrane review is awaited with interest.

Limited high level evidence was available; only one randomised controlled trial on follow-up for ovarian cancer was identified. In addition, five cohort studies, two pilot studies and four qualitative/observational studies were identified. Another limitation of the evidence was that many studies had small patient numbers.

Does the method of detection of a recurrence influence outcomes?

Most ovarian cancer patients present with symptoms or raised CA125. The most common symptom reported is abdominal pain. It is unclear whether the method of detection of recurrence impacts on overall survival. Findings by Rustin *et al*[4] from a randomised controlled trial comparing early chemotherapy for recurrence based on elevated CA125 levels alone to delaying treatment until clinical indications were present, found there was no difference in overall survival between the early and delayed treatment arms. In assessing quality of life, the study by Rustin *et al*[4] found that women in the delayed treatment arm reported good global health scores for longer than those in the early treatment arm (for 9.2 months compared to 7.2 months). The findings of this study may be limited as the extent of initial surgery was not recorded and not used as a stratification factor,[4] contemporary therapies were not available to most trial participants[34] and patients had relatively short platinum-free intervals.[34] In addition, the Rustin trial investigated only early initiation of chemotherapy for recurrence, not surgical intervention.[4,34] Only 7% of the randomised patients received surgical intervention.[4,34]

Some papers reported on the diagnostic accuracy of different methods. PET appears to have high specificity and positive predictive value. Sensitivity is highest in patients with a clinical suspicion of recurrence prior to PET, such as elevated CA125. Specificity was highest for CA125. Results of the diagnostic accuracy study by Garcia-Velloso *et al* (2007)[17] are limited as verification of diagnosis was obtained by means of histology or cytology (gold standard) in only 54 cases, and based on clinical follow-up in the majority (71 cases).

Fehm *et al* (2005)[15] recommends that imaging procedures should not be included into standard follow-up examinations and be limited to patients in which a tumour recurrence is already suspected. The combination of physical and gynaecological examination in combination with serial CA125 analysis offers sufficient sensitivity to detect recurrence and should therefore be regarded as the standard procedure for follow-up.

Gu *et al* (2009)[18] concluded that PET-CT might be a useful supplement to current surveillance techniques, particularly for those patients with an increasing CA125 level and negative CT or

MR imaging. However, regarding diagnostic accuracy, interpreted CT images may have limited additional value to PET in detecting recurrent ovarian cancer. Similarly, the review by Havrilesky *et al* (2005)[19] also noted that while PET is less useful for detecting microscopic residual ovarian cancer, it does have fair sensitivity to detect recurrence in the setting of a rising CA125 and negative conventional imaging studies.

What is the optimal interval, sequence and duration of follow-up care?

No studies were identified which compared different intervals, sequences or durations of follow-up care for ovarian cancer patients, therefore an optimal regimen cannot be determined. Studies report either institutional programs or common regimens followed.

Methods of follow-up commonly reported included history and physical examination, CA125 and ultrasound. Commonly reported follow-up schedule included 3 monthly visits for year 1 and 2, 6 monthly visits for year 3 to 5 and the annually for year 6 to 10.

What are the patient's/health care provider's preferences for follow-up care?

Data on preferences vary in the literature. Patients were unsure if GPs and/or nurses could manage their follow-up care,[21-22] however a potential role in follow-up for GPs and/or nurses was acknowledged by both patients and health professionals.[21-22] Kew *et al* (2007)[21] postulate that a reason why the majority of women want to see a hospital doctor is because they see the main reason to attend follow-up is to detect recurrence whereas health professionals see the main reason to attend is to discuss concerns, therefore specialist nurses and/or GPs may be appropriate.[21]

What evidence surrounds the role of follow-up care in psychosocial outcomes for women?

Ovarian cancer patients experience a range of psychosocial issues following treatment. Women reported significant improvement in emotional wellbeing after participating in nurse-led telephone follow-up which provided psychosocial support.[14] In another pilot study, a majority of gynaecologic cancer patients attending a sexual health clinic reported improvements in symptoms.[12]

Are there subsets of the defined population who have specific follow-up requirements?

No trials were identified which addressed specific subsets of patients requiring specific follow-up care requirements. One abstract suggested a follow-up program for ovarian tumours of low malignant potential.[31]

Do different models of conducting follow-up influence outcomes?

No trials were identified which compare different models of conducting follow-up care for ovarian cancer patients. A pilot study of nurse-led telephone intervention suggests this may be an appropriate model for some patients.[14] Note 30% of those invited to participate were unable to or refused to be part of the study.

The use of alternate models of follow-up care for women with ovarian cancer, such as GP or nurse-led follow-up, telephone follow-up and patient initiated care is an area for future research.

5 Conclusions

This NBOCC review on follow-up for women with epithelial ovarian cancer included evidence published between January 2003 and January 2010, however there was limited high level evidence available.

One aim of follow-up is to detect recurrences. History and physical examination, CA125, ultrasound, and PET are methods used for the detection of recurrence. The most common methods of detection of recurrence were symptoms and raised CA125. There is some evidence that there are no differences in survival between patients in whom recurrence was detected by different methods. The results of the Rustin randomised controlled trial,[4] that there is no difference in overall survival between early and delayed chemotherapy treatment based on CA125 levels, have raised discussion about the utility of CA125 in follow-up.

No studies were identified that compared different follow-up intervals, sequence and duration, therefore no optimal regimen for follow-up was identified. However, studies reported institutional programs or commonly followed regimens.

While there were similarities in preferences and perceptions of follow-up between patients and health professionals in two studies identified, there were also some differences. Monitoring of disease progression was perceived as important by both patients and health professionals. Health professionals reported the most important part of the visit was the consultation and another reason for follow-up was to talk about concerns. Patients and health professionals both acknowledged a potential role in follow-up for GPs and/or nurses, however the extent of this potential involvement varied.

Ovarian cancer patients experience a range of psychological issues after treatment. The reported studies found improvements in psychological issues after participation in pilot follow-up studies.

While no trials comparing different models of follow-up care were identified, a pilot study of nurse-led telephone follow-up was identified[14] and this is also being investigated in an ongoing trial.[33]

Overall, due to a lack of high-quality evidence, it is unclear which method of detection of recurrence is most effective and what the optimal interval sequence and duration of follow-up may be. New models of follow-up care have been proposed, such as nurse-led telephone follow-up, however these have not been compared to other follow-up models.

Appendix A Contributors

Working group members

The follow-up of women with epithelial ovarian cancer systematic review was developed with input from an expert multidisciplinary Working Group with the following members:

- A/Prof Penny Blomfield (Chair) Gynaecological oncologist
- Dr Lynne Brothers Radiologist
- Ms Cecily DollmanSocial Worker
- Prof Michael Friedlander Medical oncologist
- Ms Tish Lancaster Clinical nurse consultant – Gynaecological oncology
- Ms Wanda Lawson Consumer representative
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- Ms Susanne Melia Consumer representative
- A/Prof Anthony Proietto Gynaecological oncologist

National Breast and Ovarian Cancer Centre staff

The following NBOCC staff were involved in the development of the systematic review

- Ms Katrina Anderson Project Officer – Research
- Ms Jane Francis Program Manager – Ovarian Cancer
- Ms Phillipa Hastings Project Officer
- Dr Karen Luxford General Manager
- Dr Anne Nelson Evidence Review & Research Leader
- Ms Rosemary Wade Senior Project Officer – Research

Appendix B Literature databases searched

Database	Results/Retrievals
Pubmed	213
Medline and Embase (Ovid)	516
Cochrane Library	1

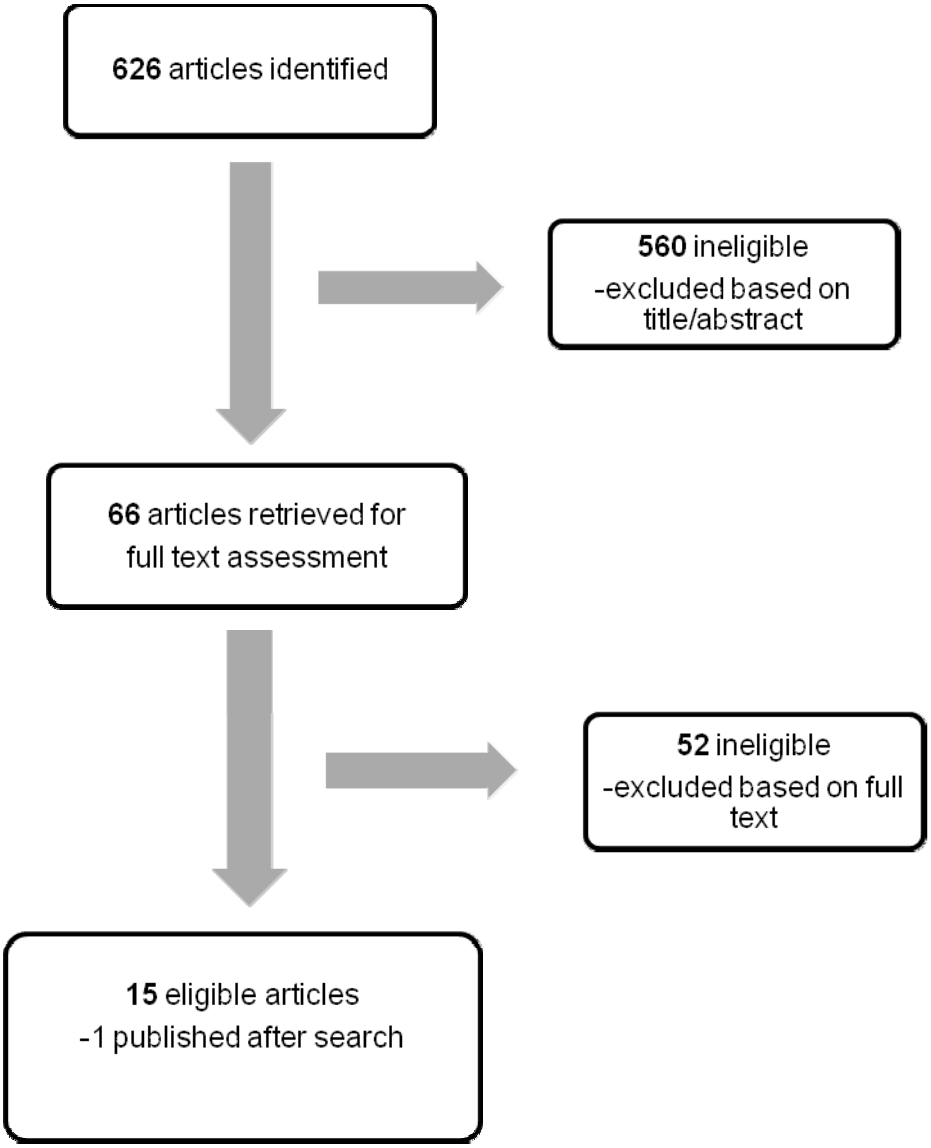
Appendix C Search strategy

Ovarian cancer	Ovarian Neoplasms/ Ovarian and (cancer or carcinoma or tumour)
Follow-up	"follow up care" or "follow up plan" or "follow up visit" or "follow up examination" or "clinical follow up" or "routine follow up" or "follow up model" or "follow up strategies" or "follow up methods" or "follow up program" or "routine test" or "postoperative surveillance" or "ovarian cancer surveillance" or (surveillance and survivors) aftercare/ postoperative care/

Appendix D Guideline and clinical trial sites searched

Acronym	Organisation	Website
CCO	Cancer Care Ontario (Canada)	http://www.cancercare.on.ca/
ESMO	European Society of Medical Oncology	http://www.esmo.org/
GIN	Guidelines International Network	http://www.g-i-n.net/
NCCN	National Comprehensive Cancer Network (US)	http://www.nccn.org/index.asp
NGC	National Guideline Clearinghouse (US)	http://www.guideline.gov/
NICE	National Institute for Health and Clinical Excellence (UK)	http://www.nice.org.uk/
SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
	ClinicalTrials.gov	http://www.clinicaltrials.gov/
	Current Controlled Trials	http:// www.controlled-trials.com/

Appendix E Flowchart of inclusion/exclusion



Abbreviations

ACN	Australian Cancer Network
ASCO	American Society Of Clinical Oncology
ASGO	Australian Society Of Gynaecologic Oncologists
AUC	area under curve
CI	confidence interval
CT	computed tomography
DFS	disease free survival
FDG	fluorodeoxyglucose
GIN	Guidelines International Network
GP	general practitioner
IGCS	International Gynecologic Cancer Society
MRI	magnetic resonance imaging
NBOCC	National Breast And Ovarian Cancer Centre
NCCN	National Comprehensive Cancer Network
OC	ovarian cancer
OS	overall survival
PET	positron emission tomography
QoL	quality of life
RCT	randomised controlled trial
SGO	Society Of Gynecologic Oncologists
SUV	standardised uptake value
US	ultrasound

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