Ovarian carcinoma

Nation-wide guideline, Version: 1.0

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Method: Evidence based

Justification: CRGO

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General

Literature review:

Purpose

Eleven national consensus-based guidelines for gynaecological (pre)malignancies became available via the website oncoline in 2004. These guidelines were formulated by a multidisciplinary Committee for Guidelines in Gynaecological Oncology (Commissie Richtlijnen Gynaecologische Oncologie, CRGO), established on the initiative of the Dutch Gynaecologic Oncology Group (Werkgroep Oncologische Gynaecologie, WOG) of the Dutch Society of Obstetrics and Gynaecology (Nederlandse Vereniging van Obstetrie en Gynaecologie, NVOG). The CRGO consists of representatives from the specialties gynaecology, medical oncology, radiotherapy and pathology, taking into account that members come from the various IKC regions (see appendix 1). It was the explicit wish of the CRGO not only to ensure existing guidelines remain current, but to convert these into an evidence-based guideline. The components of the guideline that have been made evidence-based, can be recognised by the following tabs: conclusions, considerations and recommendations. For various reasons (incidence, multidisciplinary therapeutic approach, poor prognosis), it has been decided that the guideline epithelial ovarian cancer is to be the first to be translated to an evidence-based structure. To formulate the guideline ovarian carcinoma, a committee was established that consisted of a number of members of the CRGO, supplemented with representatives from the Dutch Federation of Cancer Patient Associations (Nederlandse Federatie Kankerpatiëntenverenigingen, NFK), the oncology department of the Dutch Nurses' Association (Verpleegkundigen en Verzorgenden Nederland, V&VN), Dutch Society for Psychosocial Oncology (Nederlandse Vereniging Psychosociale Oncologie, NVPO) and the Dutch Professional Association of Psychologists (Nederlands Instituut voor Psychologen, NIP).

Objective

This guideline is a document with recommendations to support daily practice. The guideline is based on results, scientific research and opinions on these results, and focuses on determining good medical practice. It indicates the best possible care for patients with ovarian carcinoma, in general, given current standards and accepted medical practice in the Netherlands. The guideline provides recommendations regarding identification, diagnostics, medication-based treatment, non-medication based treatment, patient education and guidance of adult patients with an ovarian carcinoma.
Specific objectives of this guideline are creating uniformity in relation to identification, diagnostics, treatment and guidance of patients. Frameworks within which the multidisciplinary care of these patients can take place are required. This guideline can also contribute to improved communication between treating physicians, and between patients and their families.

Target group

This guideline is intended for all professionals involved in the diagnostics, treatment and guidance of patients with an ovarian carcinoma. This guideline is also used to create patient information material in collaboration with the Dutch Cancer Society (KWF Kankerbestrijding).

Clinical questions

This guideline is based on an earlier published consensus-based guideline. Nine clinical questions were formulated in the development of this guideline. These questions followed from a bottleneck inventory collected in the field from professionals and patients (representatives). The bottleneck inventory and clinical questions can be found in the appendix (see appendix 2 and 3 respectively).

Methods of the working group

A subgroup with representatives from relevant disciplines was formed for every clinical question. An editorial team, consisting of the chairperson of the CRGO, the process advisor and project secretary of the VIKC, took care of coordination and alignment between subgroups. The working group worked on the text for the concept guideline for approximately a year. The members of the working group formulated the text individually or in subgroups, which was discussed during plenary meetings and approved after the comments were processed. The full working group met six times to discuss the results of the subgroups. The texts of the subgroups have been merged and aligned by the editorial team to form one document: the concept guideline.
The concept was sent to all associations and organisations represented within this working group as well as to all regional tumour working groups for comment. After the comments were processed, the guideline was established by the full working group and the CRGO and sent to the relevant professional associations

for authorisation.
The framework used in development of the guidelines for oncological and palliative care is the AGREE instrument. This instrument was created for evaluation of existing, new and revised guidelines (see appendix 14).
The AGREE Instrument evaluates both the quality of the reports and the quality of particular aspects of the recommendations. It evaluates the likelihood that a guideline will achieve its objective, but not the actual impact on patient outcomes.

For background information in relation to
Members of the working group (see appendix 1)
Clinical questions (see appendix 3)
Composition of the working group (see appendix 4)
Independence of working group members (see appendix 5)
Scientific argumentation (see appendix 6)
Mandating associations (see appendix 7)
Validity (see appendix 8)
Implementation (see appendix 9)
Ownership (see appendix 11)
Legal significance of the guideline (see appendix 12)
AGREE (see appendix 14)

Epidemiology and Aetiology

Literature review:
Epidemiology
The incidence of ovarian carcinoma in the Netherlands is 1,100 per year. The number of deaths per year is 900. As a result, ovarian carcinoma is the most frequent cause of gynaecological cancer death.

Aetiology
Studies on the biological reason for development of ovarian carcinoma can be subdivided into research on:

- Reproductive factors: these studies show that having no or a low number of children increases the chance of ovarian carcinoma. The chance of ovarian carcinoma is reduced by 30 to 50% by the use of ovulation inhibitors for more than 3 years or by multiple pregnancies.
- Genetic factors: genetic research has shown that gene mutations (BRCA-1, BRCA-2, Lynch syndrome: MLH1, PMS2, MSH2, MSH6) can occur in familial occurrence of ovarian cancer. It is assumed that approximately 10% of ovarian carcinomas have a hereditary character; two syndromes are distinguished: the combination of hereditary ovarian and breast cancer and Lynch syndrome in which particularly colon and endometrial carcinoma occur, as well as other non-colorectal tumours such as ovarian carcinoma.

Pathology

Literature review:
The (malignant) ovarian tumours can be subdivided into:

1. borderline tumours
2. ovarian carcinomas
3. non-epithelial malignant tumours

This guideline concerns itself exclusively with ovarian carcinoma.

Ovarian carcinoma metastasises by intraperitoneal implantation in an early phase. This is linked with intraperitoneal localisation of the ovaries, exfoliative growth of the ovarian carcinoma and spread of tumour

cells by the constant circulation of peritoneal fluid along the ovaries. Due to this early (micro)metastasis in the peritoneal cavity, an early-stage of ovarian carcinoma and a subclinical stage III can only be distinguished using extensive surgical staging that is performed in a consequent manner. In doing so, it appears that in 25% of patients with a clinically early-stage of ovarian carcinoma, the tumour has spread outside the ovaries. Performing a staging operation in an optimal manner is essential in determining which patients need to be treated with adjuvant chemotherapy.

Metastasis of other tumours to the ovaries

Both breast cancer and tumours of the digestive tract (Krukenberg tumour) and the thyroid gland can metastasise to the ovaries (sometimes as sole metastasis). These tumours are generally less sensitive to chemotherapy for ovarian carcinoma. A good pathologic evaluation of the tumour in the ovary is therefore essential. Surgery is preferable in the case of solitary metastasis in the ovary.

Screening

Literature review:
Due to the inability to detect the ovarian cancer in an early-stage, it has so far not been worthwhile to screen the general population. Only women with a high risk of hereditary ovarian cancer are currently being screened annually using gynaecological examination, vaginal ultrasonography and serum CA 125. However, in nine cohort studies (three prospective and six retrospective) on the efficacy of ovarian screening in women with a BRCA1/2 mutation, screening was not found to be effective. A large retrospective Dutch study also does not show a reduction in mortality, putting screening up for discussion.

Prognosis

Literature review:
The most important prognostic factor for ovarian carcinoma is the FIGO stage. Patients with a early-stage, FIGO I-IIa, have a 5-year survival of 75% - 100%. The 5-year survival for patients with a advanced-stage, FIGO IIb-IV, is 20% - 60%.

With a early-stage, stage Ia, Ib, Ic and IIa, the differentiation grade and completeness of staging are the most important prognostic factors for survival and recurrence-free survival. The histological tumour type is only of prognostic significance for survival.

- Low risk group: well-differentiated tumours (G1) and complete staging: five-year survival 90 -100%.
- High risk group: moderately and poorly-differentiated tumours (G2 - 3) and complete staging: five-year survival 78 - 85%.

With a advanced-stage, stage IIb, IIc, III and IV, the most important prognostic factors are:

- The FIGO stage
- The differentiation grade of the tumour
- The Karnofsky index
- The diameter of the largest lesion after primary debulking surgery

The prognosis and course of tubal carcinoma and extra-ovarian carcinoma are comparable to that of ovarian carcinoma. Classification and treatment are therefore the same.

Diagnostics

Literature review:
General
Ovarian cancer often does not cause symptoms until a later stage of the disease. As a result, 70% of women with ovarian carcinoma have a high-stage (stage II b, c, III or IV) at the time of diagnosis. Complaints are usual non-specific and consist of:

- Vague gastrointestinal complaints
- An increase in size of the abdomen
- Micturation or defecation problems

Sometimes an ovarian carcinoma is found because the tumour causes an acute abdomal pain after rupture of a cyst or torsion.

Physical examination

Literature review:
Important findings during a physical examination can be:

- A space-occupying mass in the lesser pelvis
- A palpable mass in the pleural abdomen
- Ascites and/or pleura fluid
- An (increase in) prolapse of uterus and/or vagina as a result of a space-occupying mass
- An enlarged supraclavicular lymph node

Laboratory testing

Literature review:

- Routine blood examination
- Tumour markers:
    - CA 125
    - Optionally (dependent on pre-operative findings) CEA

In 80% of women with ovarian cancer, the tumour marker CA 125 in serum is raised. This applies to a lesser degree to mucinous tumours. In patients with a early-stage, the CA 125 value in serum is only raised in 45% of cases.

Imaging research

Literature review:
Different types of imaging research

Ultrasound
Abdominal and/or transvaginal ultrasonography: the size and aspect of the tumour can be determined using ultrasound. Ultrasonographic characteristics of a malignant ovarian tumour are:

- Multilocularity
- Septum thickness of more than 3 mm. No sharp boundary line

- Echodense areas
- Papillary masses in the cyst cavity
- Ascites

The RMI (Risk of Malignancy Index) is increasingly being used for preoperative differential diagnostics of an adnex tumour. At a cut-off value of 200, the diagnosis ovarian carcinoma (including borderline tumours) can be made with a sensitivity of 70 - 75% and a specificity of 85 - 90%.

Echo - criteria (U)				**Menopause status (M)**		
- multilocular		1		*premenopausal*		***1***
- echodense areas		1		*postmenopausal*		***3***
- bilateral		1				
- ascites		1		**Serum CA 125 (E/ml)**		
- intra-abdominal meta's		1				
total		..				
				RMI = U x M x CA 125		
Score	0	▶	1			
	1	▶	1			
	≥2	▶	3			

Table by Tingulstadt

X-Thorax / CT Thorax
These can be used to detect pleural fluid, lung metastases and/or mediastinal lymph nodes.

CT scan abdomen
The CT scan can be used to detect further metastases in the abdomen; particularly metastases in omentum, liver, spleen and retroperitoneum. It has not been demonstrated that preoperative imaging enables a good estimation of surgical resectability to be made. In the next paragraph "Predicting operability", a literature search has been performed focussing on the additional value of imaging techniques to estimate the chance of obtaining at least an optimal debulking (residual tumour < 1 cm) in patients with advanced stage of ovarian cancer.

See the evidence table: Appendix 15

Conclusions:
It has not been shown that preoperative imaging enables a good estimation of surgical resectability. However, a number of scoring systems have been designed on the basis of retrospective data and selected populations. Each of these scoring systems has a moderate predictive value and, aside from one (Axtell 2007[82]), have not been tested prospectively. As a result, preference for one of these scoring systems cannot be made on the basis of these studies.
Level 3 C Axtell 2007[82]

Considerations:
Six articles (see Appendix 15) have been found to satisfy the selection criteria. All these studies are retrospective, and are therefore subject to a number of limitations.
Firstly, there is the danger of selection bias: it is noticeable that from the large number of available patients per article, only a small number is included for analysis, namely only those patients that have undergone surgery and of whom a CT scan was made beforehand. Therefore analysis is always based on a small section of the advanced ovarian cancer patients. In doing so, it is plausible that a selection bias has occurred. After all, all the patients incorporated in the analyses have had surgery; the group who, for whatever reason, has not obtained surgery are not incorporated in the analysis. The same is true for those in whom no CT scan has been made.
None of the studies uses a format to indicate the completeness of surgery. Most studies do not provide

information about the surgical expertise of the gynaecologists.
The most important problem with the studies mentioned here is that the scoring systems that have been developed have not been validated in a prospective series, with the exception of the study by Axtell (Axtell 2007[82]). However, Axtell has shown that a model that has been developed on the basis of one series and that appears usable, has a much lower predictive value than when it is applied prospectively.

Predicting operability

Recommendations:
There are no objective imaging criteria available to predict surgical resectability, with the following side-note: imaging techniques such as ultrasound or CT scan can be used to gain preoperative information regarding the extent of the disease at the start of treatment, so that the treatment strategy and role of surgery can potentially be adjusted.

Literature review:
Can imaging diagnostics be helpful to estimate pre-operatively the chance of obtaining an optimal debulking (residual tumour < 1 cm) in patients with an advanced stage ovarian cancer? If yes, under which conditions (echo, CT, MRI)?
Introduction
The standard treatment for patients with ovarian carcinoma consists of a combination of surgery and chemotherapy. In principle, primary debulking is performed and followed by at least six courses of chemotherapy (paclitaxel carboplatin). The objective of primary debulking must be: a complete debulking in which no macroscopic disease is left behind, if this is not possible at least an optimal debulking should be obtained (visible residual tumour <1 cm). Various imaging techniques have been described for preoperative prediction of the resectability in patients with an advanced stage ovarian carcinoma. The term resectability refers to successful cytoreductive surgery, in which preferably a complete debulking is achieved, or at least an optimal debulking (residual tumour remains <1 cm).
It is uncertain whether the standard treatment (primary debulking) is the best treatment for patients with advanced ovarian carcinoma, in which the disease is very extensive and where it is unlikely that complete debulking can be performed. These patients may benefit from induction chemotherapy, followed by interval debulking after three courses, after which the remaining three courses of chemotherapy can be administered. It is questionable if this group of patients can be selected using imaging diagnostics, to prevent patients undergoing (primary) surgery unnecessarily.

Summary of the literature
In a retrospective study amongst 65 patients with FIGO stage II/IV, CT scans were reviewed and 14 radiological criteria used that could have a predictive value for resectability. The presence of diaphragm lesions and metastases on the mesenterium of the colon appeared to be strong predictors for irresectability. The combination of these two predictors had a sensitivity of 79% and a specificity of 75% in relation to irresectability. However, when these two predictors were prospectively applied during validation of two other series, the sensitivity and specificity decreased significantly (Axtell 2007[82]).
In a retrospective study (Bristow 2000[8]) incorporating 41 patients with a FIGO stage III/IV ovarian carcinoma, all preoperative CT scans were evaluated for 25 items, blinded for the outcome of the operation. Nine topics were selected, each receiving two points, and five topics that each received one point (on the basis of specificity, positive predictive value (PPV) and negative predictive value (NPV)).
A Predictive Index Score was formulated for; a score of ≥ 4 the model provided a good prediction of irresectability (accuracy 92.7%, sensitivity of 100% and a specificity of 85%). PPV ≥ 4 is 87.5% (which means that 12.5% of patients are considered irresectable but can still be optimally debulked), NPV was 100%.
Drawbacks: the model is based on a (too) small, selected group of patients (selection bias), the model has not been prospectively validated on another series.
Dowdy (2004[18]) analysed CT scans of 87/321 patients in a retrospective study. Of the 17 tumour localisations by CT scan in a univariate analysis, only diffuse peritoneal thickening provided a predictive value for irresectability (P=0001). However, in a multimodality model with ascites, the PPV without ascites was 57%, with ascites only 68% and with concurrent diaphragm lesions 79% (with a sensitivity of 64%, 52% and 44% respectively). Drawbacks: selection of patients who obtained surgery; moderate efficacy; the model has not been prospectively validated on another series.

In a retrospective series of 56 patients (out of 252), Everett (2004) outlined that 3 localisations of disease (omentum, peritoneum and ascites) occurred significantly more often in patients with suboptimal debulking. Drawbacks of this study: only 20% of all treated patients have been included in the study (selection bias), and the model has not been prospectively validated on another series.
Byrom (2002[84]) outlined a retrospective series of 77 patients undergoing laparotomy due to ovarian tumour in which a CT scan was performed prior to surgery. Fifty one of these patients were diagnosed as having ovarian cancer and of these 25 patients had residual tumour after surgery. Parameters associated with residual tumour after surgery were: ascites, omental cake, mesenteric, paracolic and diaphragm tumour deposits, as well as pleural fluid (sens 88%, spc 98%). Drawbacks of the study: selected group of patients who obtained a CT scan (selection bias), parameters have not been prospectively tested, no information about surgery. CT and MRI are equivalent in the prediction of disease (Quayyum 2005[43]).

Evidence table (see appendix 15)

Pathology

Literature review:
The diagnosis ovarian carcinoma can only be made on the basis of histological examination. Invasive growth is a prerequisite for the diagnosis ovarian carcinoma.

The group of epithelial tumours include serous, mucinous, endometrioid, clear cell tumours, Brenner tumours, mixed forms of the aforementioned tumours and undifferentiated carcinomas. Each of these tumour types has a characteristic histological profile. Invasive growth is an essential criterion for each type of carcinoma to differentiate these tumours. Invasion is defined differently for the serous and mucinous tumours. Most cases show extensive invasive growth; it is not uncommon that the lack of differentiation characteristics makes it difficult or even to impossible determine the type of ovarian carcinoma involved.

The first step in diagnostics is always to determine what type of tumour is involved; the most frequent are the serous and mucinous tumours.

Stage classification follows the FIGO guidelines. The stage is generally determined by surgical means, excluding stage IV, in which a CT scan usually provides additional information about the extraperitoneal metastases. Stage IV diagnosis needs to be confirmed either cytologically or histologically. Stage classification is, amongst other things, also necessary to determine the right treatment and to estimate prognosis.

Frozen section diagnostics

Literature review:
Performing frozen section research is only worthwhile if this affects the policy in relation to the surgery to be performed. If frozen section is requested, it is good to realise that it often is difficult to determine the tumour type or infiltration. The difference between a grade 1 tumour and a borderline tumour, and between a non-epithelial tumour and a poorly differentiated epithelial tumour is often difficult to determine. In young patients, the result of this evaluation may determine whether fertility is retained. It is therefore recommended to make these types of important decisions for this specific group of patients on the basis of definitive pathological diagnosis; the risk that a second laparotomy is required is more acceptable than an unnecessary castration afterwards.

In women who desire to have children and have a stage I ovarian carcinoma that has been fully staged, the uterus and non-affected adnex may be retained. The chance that both ovaries are involved, amounts approximately 25% for serous carcinoma and 10% for mucinous carcinoma, but occult localisations are rarely involved. If the other ovary appears normal, the chance of bilateral carcinoma is less than 5%. If the contralateral ovary does not appear normal, a wedge-shaped excision is taken from the abnormal area.

Grading

Literature review:
Grading ovarian carcinoma
Despite the fact that there is no generally accepted grading system for epithelial ovarian tumours, grading is of importance in determining treatment policy with stage I tumours. The National Working Group Gynaecopathology (Landelijke Werkgroep Gynaecopathologie, LWGP) is a strong supporter of the grading system according to Silverberg. Points are given on the basis of the following characteristics: growth pattern, nuclear polymorphy and mitotic activity.

Grading according to Silverberg is based on the classic histological classification and the following architectural characteristics (predominant pattern):

Growth pattern (predominant pattern):
Glandular = 1, papillary = 2, solid = 3

Nuclear polymorphy:
weak = 1, moderate = 2, strong = 3

Mitosis activity per 0.345 mm2:
0-9=1, 10-24=2, > 24=3

The tumour is graded based on the total points given: grade 1 = 3 - 5, grade 2 = 6 or 7 and grade 3 = 8 or 9.

Note: when grading, squamous differentiation with solid fields ("morula") are not considered solid growth DNA flow cytometry and morphometry are applied by some as a supplement to the determination of the grade of differentiation of an ovarian carcinoma.

Reporting

Literature review:
Histopathological reporting of ovarian tumours:
Macroscopy

- Diameter of the tumour, unilocular or bilateral
- Other tumour localisations, size
- Capsule status (intact, rupture or tumour growth through capsule)
- Cross-sectional aspect (unilocular, multicystic, solid parties)

Microscopy:

- Classification
- Grade
- Microscopic growth through capsule
- Tumour localisation in biopsies
- Lymph node metastases (specify number of lymph nodes per localisation)

Given the large variation within a tumour, it is obligatory that enough biopsies are taken; at least one biopsy per cm diameter. It is recommended that biopsies form the capsule are separately marked as such.

WHO classification

Literature review:
WHO (World Health organisation) classification of epithelial ovarian tumours.

Serous tumours

- Benign
- Borderline
- Malignant

Mucinous tumours (endocervical and intestinal type)

- Benign
- Borderline
- Malignant

Endometrioid tumours (with or without squamous differentiation)

- Benign
- Borderline
- Malignant

Epithelial-stromal and stromal

- Adenosarcoma (homologous and heterologous)
- Mixed mesodermal malignant tumour (homologous and heterologous)
- Stromal sarcoma

Clear cell tumours

- Benign
- Borderline
- Malignant

Transitional epithelial tumours

- Brenner tumour
- Proliferating Brenner tumour
- Malignant Brenner tumour
- Transitional epithelial carcinoma that is not Brenner related

Squamous cell carcinoma
Multiple differentiations within a tumour

- Benign
- Borderline
- Malignant

Undifferentiated carcinoma

Metastasis

Treatment

Literature review:
Prognosis per stage of ovarian carcinoma
With a early-stage, stage Ia, Ib, Ic and IIa, the differentiation grade and completeness of staging are the most important prognostic factors for survival and recurrence-free survival. The histological tumour type is only of prognostic significance for survival.

- Low risk group: well-differentiated tumours (G1) and complete staging: 5-year survival 90 - 100%.
- High risk group: moderate and poorly-differentiated tumours (G2 - 3) and complete staging: 5-year survival 78 - 85%.

With a advanced-stage, stage IIb, IIc, III and IV, the most important prognostic factors are:

- The differentiation grade of the tumour.
- The FIGO stage
- The Karnofsky index.
- The diameter of the largest lesion after primary debulking surgery.

The prognosis and course of tubal carcinoma and extra-ovarian carcinoma are comparable to ovarian carcinoma. Classification and treatment are therefore the same.

In the following chapters, the treatment for early-stage and advanced stage are outlined separately.

Treatment of early-stage carcinoma (I - IIa)

Literature review:
Early-stage (I - IIa)
With a early-stage (FIGO, Ia, Ib, Ic and IIa, the differentiation grade and completeness of staging are the most important prognostic factors for survival and recurrence-free survival. The histological tumour type is only of prognostic significance for survival.

- Low risk group: well-differentiated tumours (G1) and complete staging: five-year survival 90 - 100%.
- High risk group: moderate and poorly-differentiated tumours (G2 - 3) and complete staging: five-year survival 78 - 85%.

The prognosis and course of tubal carcinoma and extra-ovarian carcinoma are comparable to ovarian carcinoma. The classification and treatment are therefore the same.

The treatment of early-stage ovarian carcinoma consists of surgery, sometimes in combination with chemotherapy.

- fully staged:
    - ♦ follow-up

The committee could not reach full agreement in case of fully staged early-stage grade III tumour. A number of members were supporters of providing additional chemotherapy in this situation.

- incompletely staged:
    - ♦ restaging
    - ♦ if restaging cannot be performed however, it seems reasonable to treat these patients as a stage III tumour with six courses of paclitaxel carboplatin, given the substantial chance of micrometastases.

In well-executed staging surgery, 20 - 25% of patients will be found to already have occult metastases outside the uterus and adnexa. These patients therefore have an advanced-stage ovarian carcinoma. In women with a desire to have children and a stage I ovarian carcinoma that has been fully staged, the uterus and non-affected adnex may be retained. The chance that both sides are involved amounts approximately 25% for serous carcinoma and 10% for mucinous carcinoma, but occult localisations are rarely involved. If the other ovary does not appear normal, a wedge-shaped excision is taken from the abnormal area.

Surgery

Literature review:
Guidelines for staging surgery:

- Median lower and upper abdominal laparotomy.
- Aspiration ascites for cytological research. In the absence of ascites, the abdomen needs to be flushed with physiological saline and the flushing liquid submitted for cytological research.
- Inspection and palpation of all serous surfaces in the abdominal cavity.
- Hysterectomy with bilateral salpino-oophorectomy (see frozen section diagnostics).
- Infracolic omentectomy.
- Staging biopsies of:
    - ♦ all locations to which the ovarian tumour has adhered to or grown into.
    - ♦ all macroscopic locations and adhesions that are suspect.
    - ♦ biopsies of the peritoneum of:
        - ◊ the pouch of Douglas.
        - ◊ the bladder peritoneum.

- ◊ the peritoneum of the pelvic walls.
- ◊ the left and right paracolic gutters.
- ◊ the right diaphragm.

- Lymph node sampling: (Information about lymph node sampling is outlined in an evidence-based manner in the following paragraph). Lymph node sampling should consist of resection of at least 10 nodes from the following node regions:
  - ♦ Paraaortic and paracaval lymph nodes (under the renal vein and above the origin of the inferior mesenteric artery), and lymph nodes around the common, internal and external iliac vessels on both sides and from the obturator fossa.
  - ♦ There are no indications that a radical lymphadenectomy results in better survival than adequate lymph node sampling.

Lymph nodes

Recommendations:
The committee has determined that finding lymph node metastases in a clinically early-stage of ovarian cancer increases with the number of lymph nodes removed. Extensive, radical lymphadenectomy has not been shown to provide better survival than adequate, more limited lymph node sampling. A radical lymphadenectomy is correlated with more late morbidity.
For this reason, the committee recommends adequate lymph node sampling and not a radical lymphadenectomy. The minimum number of lymph nodes to be removed is 10, with the side-note that a greater number of nodes increases the chance of finding metastases. The number 10 is an absolute minimum; it is recommended that these lymph nodes are sampled from different lymph node regions, of which the most important are: paraaortic and paracaval between the renal vain and inferior mesenteric artery, the common, internal and external iliac vessels and nodes from the obturator fossa. Unilateral sampling in the case of a unilateral tumour is discouraged due to the (too high) risk of contralateral lymph node metastases.

Literature review:
What is adequate lymph node sampling in the case of a clinically early-stage ovarian carcinoma;

- what number of lymph nodes should be removed?
- from which locations should lymph nodes be sampled?

Does a complete pelvic and paraaortic lymphadenectomy lead to an improved prognosis in comparison with an adequate lymph node sampling?

- Lymph node sampling should consist of resection of at least 10 nodes of different node regions, of which the following are the most important: paraaortic and paracaval above the level of the inferior mesenteric artery, the internal and external iliac nodes, the common nodes and obturator nodes.
- There are no indications that a radical lymphadenectomy leads to better survival.

Summary of the literature
There is only one RCT that compared lymphadenectomy for early-stage ovarian carcinoma with lymph node sampling (Maggioni 2006[34]). A lymphadenectomy was performed in 138 patients (median number of lymph nodes removed was 47) and lymph node sampling in 130 patients (median number of lymph nodes removed was 5.5). In patients undergoing a lymphadenectomy, the median length of surgery was longer and the number of blood transfusions required higher compared to patients with lymph node sampling (240 and 150 min respectively, P<0.001; and 36 versus 22%, P=0.012). Perioperative complications did not significantly differ between both procedures. The largest difference was seen in late complications. Patients in the lymphadenectomy group often experienced lymphocele and lymphoedema, compared to none of the patients in the lymph node sampling group. Tumour-positive lymph nodes were found more often in the lymphadenectomy group (in 22% of the lymphadenectomy group versus 9% of the lymph node sampling group, P=0.007). The percentage of positive nodes correlated with the tumour grade (31% of the grade 3 versus 11% of the grade 1 and 2 tumours) and histology (33% of the serous/undifferentiated versus 10% of the other histological tumours).

The hazard ratio of disease progression (HR 0.72 (95% CI 0.46 - 1.21, P=0.16) and death (HR 0.85 (95% CI 0.49 - 1.47), P=0.56) were reduced after lymphadenectomy in relation to lymph node sampling, but this was not statistically significant. Patients found to have a lymph node metastases, remained in the study and were not excluded due to the stage (III).
A side-note must be made here: the study was too small to show a small but clinically important difference. Furthermore, a substantial percentage of patients received adjuvant chemotherapy and there was an imbalance in adjuvant chemotherapy between patients in both arms of the study. Patients from the lymph node sampling group received adjuvant chemotherapy more frequently, although not statistically significant (66% and 56%, p=0.11); however in patients with negative lymph nodes on the other hand, the difference was significant between both groups (66% in the lymph node sampling group and 51% in the lymphadenectomy group; p=0,03).

Several retrospective cohort studies have been performed in which the effect of lymphadenectomy and lymph node sampling has been examined. Skirnisdottir (2005[50]) saw a significantly longer survival (p=0.004) and disease-free survival (p=0.005) in patients that had undergone extensive lymph node sampling or lymphadenectomy (N=20) in comparison to patients without extensive lymph node sampling (N= 93) (5-year disease-free survival lymph node sampling: 95.0%, without lymph node sampling: 62.4% (p<0.005); HR 0.09 (95% CI 0.013 - 0.617). All patients in this study were treated with adjuvant chemotherapy. Patients with lymph nodes metastases were staged as stage IIIc and excluded from the study. In the Cox proportional hazard regression analysis, tumour grade and extensive lymph node sampling were the only statistically significant and independent prognostic factors.
Carnino (1997[12]) found lymph node metastases in FIGO stage I - III tumours 3.9 times more frequently after removal of more than 10 lymph nodes than after removal of 1 - 5 lymph nodes (95%CI 1.0 - 15.4).
Chan (2007[14]) studied a cohort of 6,686 patients with a FIGO stage I (only patients with negative lymph nodes were included). They found a significantly higher 5-year survival in patients that had undergone a lymphadenectomy, compared to patients without a lymphadenectomy (92.6% and 87.0% respectively, (p<0.001)). In addition, patients with a FIGO stage Ic in whom more than 10 lymph nodes were removed had a significantly higher 5-year survival than patients with less than 10 lymph nodes removed (90.1% and 86.7% respectively; p<0.001). A drawback of this study is the lack of data whatsoever on adjuvant chemotherapy.
Different studies found contralateral lymph node metastases in the case of unilateral ovarian tumours: in 44% (N=9; Onda 1996[41]); 40% (N=5; Suzuki 2000[51]); 50% (N=10; Cass 2001[13]); 37% (N=19; Negishi 2004[40]); and in 45% (N=11) of patients (Ayhan 2005[4]).

On the basis of a cohort of 110 patients with a complete lymphadenectomy, Onda calculated that the sensitivity and the negative predictive value of lymphadenectomy were the highest with a combination of paraaortic paracaval lymphadenectomy (under the renal vein and above the origin of the inferior mesenteric artery opens out), around the internal iliac vessels, around the external iliac vessels and around the obturator fossa (sensitivity of 94% and negative predictive value of 95%). Half the lymph nodes with metastases were not clinically suspect (60% (N=5)(Suzuki 2000[51]), 46% (N=13) (Onda 1996[41])).

See the evidence table (appendix 16).

Conclusions:
There is no exact limit value above which the removal of more lymph nodes provides added value. There are however, indications that at least 10 lymph nodes must be removed, because positive lymph nodes with metastasis are found significantly less frequently and survival of patients is poorer when less than 10 lymph nodes are sampled.
Level 3 C Carmino 1997[12], Chan 2007[14]

The sensitivity and negative predictive value of lymph node resection appears to be highest with a combination of resection of paraaortic and paracaval lymph nodes (under the renal artery and above the orgin of inferior mesenteric artery opens out), lymph nodes around the common, internal and external iliac vessels and from the obturator fossa. It has been proven that contralateral lymph node metastasis also occur with unilateral ovarian tumours.
Level 3 C Onda 1996[41], Suzuki 2000[51], Cass 2001[13], Negishi 2004[40], Ayhan 2005[4].

There is no evidence that an extensive, radical lymphadenectomy results in better survival than more limited lymph node sampling. The only randomised study about this topic is too small however, to show a

limited but clinically important difference; furthermore, there is an imbalance in favour of the lymph sampling group between the number of patients with negative lymph nodes that nonetheless received adjuvant chemotherapy.
Level 3 C Maggioni 2006[34].

Considerations:
It is impossible to answer the above mentioned questions on the basis of randomised studies and therefore with sufficient evidence. This is an implicit problem, given that an adequate experimental design for randomised trials in this context is impossible. It does appear important however, given the large clinical need and the fact that this is a continuously recurring question, to formulate the answer that the evidence available might provide.

A number of conclusions can be obtained from available literature that, for an important part, should be considered indirect evidence:

- The committee has realised that a seeming contradiction is hidden in the fact that, on the one hand, the conclusion is drawn that an adequate lymph node sampling contains at least 10 nodes (sub-question a1) and, on the other hand, the citation of a RCT is cited in which the medium number of nodes removed in the lymph node sampling arm was only 5.5. In that context, the lymph node sampling in the study by Maggioni cannot be called adequate. Nonetheless, this study has been used by the committee because it is the only RCT in which lymph node sampling and radical lymphadenectomy have been compared. Furthermore, the lack of difference in survival between the two arms only becomes greater as the lymph node sampling is performed less adequately.
- It is plausible that survival and disease-free survival improve when lymph nodes are removed, compared to when no lymph nodes are removed (Trimbos 2003[55]; Skirmisdottir 2005[50]; Chan 2007[14]).
- The chance of finding lymph node metastases is higher when a greater number of lymph nodes are removed (Carmino 1997[12]; Maggioni 2006[34]; Chan 2007[14]).
- In combined series positive lymph nodes are found paraaortic and paracaval in approximately 50%, in the pelvis in 25% and in both locations 25%. This illustrates the importance of the paraaortic and paracaval route as the first metastatic pathway.
- There is a positive correlation between the number of positive lymph nodes and the FIGO stage (stage II), tumour grade (grade 3) and histology (serous and undifferentiated tumour (Maggioni 2006[34]; Chan 2007[14]; Ayhan 2005[4]; Cass 2001[13]).
- Also the occurrence of micrometastasis in lymph nodes (ultrastaging) may be correlated with a more unfavourable prognosis in relation to overall survival (Suzuki 2001[52]).
- Complete, radical lymphadenectomy is associated with more late morbidity than selective lymph node sampling (Maggioni 2006[34]).
- Bilateral lymph node sampling is also advised in case of an unilateral tumour, given the occurrence of contralateral lymph node metastasis in approximately 40% of cases (Onda 1996[41]; Suzuki 2000[51]; Cass 2001[13]; Negishi 2004[40]; Ayhan 2005[4]).
- Not only the number of lymph nodes removed but also the removal of lymph nodes from different lymph node regions is important. The most important lymph node stations in this respect are: paraaortic and paracaval between the level of the renal vein and inferior mesenteric artery (79%), paraaortic and paracaval below the level of the inferior mesenteric artery (71%), around the internal iliac vessels, around the external iliac vessels and from the obturator fossa (79%)(Onda 1996[41]).
- Removal of at least 10 lymph nodes appears to be the minimal threshold number for an adequate lymph node sampling. Lymph node sampling with at least 10 lymph nodes is associated with a higher incidence of lymph node metastasis (Carmino 1997[12]) as well as better survival (Chan 2007[14]) compared to less than 10 nodes. The number of lymph nodes being 10, (from different regions) is supported by studies in the area of endometrial cancer (Killgore 1995[87]; Chuang 1995[86]; Burke 1996[83]).
- Removal of only enlarged lymph nodes appears insufficient because positive lymph nodes with metastasis were not clinically suspect in 50% of cases (Suzuki 2000[51]; Onda 1996[41]).
- Both paraaortic and pelvic lymph node sampling can be performed adequately using laparoscopy.
- Because well-differentiated, mucinous tumours, have the best prognosis. Retrospective studies have suggested that lymph node sampling could be left out in such cases (Morice 2003[88]; Cho 2006[85]) but these contain too few patients to be able to draw a reliable conclusion. In the study by Maggioni (2006[34]), positive lymph nodes are still found in 10% of grade 1 and 2 tumours and in

10% of the non-serous or not poorly differentiated tumours. It therefore appears that insufficient data are available to be able to consider the well-differentiated, mucinous tumours as a separate subgroup in relation to the requirement for lymph node sampling.

- Lymph nodes are generally removed with a varying amount of surrounding fat tissue; sometimes large nodes are separately removed. There are no studies that have evaluated the manner in which these lymph node resection samples have been processed. For this reason, the following recommendation is only based on general practical considerations in relation to processing of these samples. The lymph nodes must be separated from the fat. Lymph nodes smaller than 5 mm should be included in their entirety. Lymph nodes between 5 and 10 mm are halved and included in their entirety. Lymph nodes greater than 10 mm are lamellated in 5 mm thick slices and included in their entirety.

Chemotherapy

Recommendations:
On the basis of the aforementioned, the committee advises that a complete surgical (re)staging is performed in patients with a clinical early-stage ovarian carcinoma. When a complete (re)staging cannot be performed, the committee advises adjuvant chemotherapy. Because of a substantial chance of micrometastasis in the case of incomplete staging (NCS), it is advised to treat these patients as a stage III tumour with six courses of Paclitaxel Carboplatin. (http://www.ikcnet.nl/sib/)
After complete staging (CS), the committee recommends an expectative policy (surgery only). Specifically in relation to grade 3 tumours, the committee could not reach an agreement. A number of members were supporters of providing additional chemotherapy in this situation, but there is no scientific data to support this statement.

Literature review:
What is the optimal treatment schedule for early-stage ovarian carcinoma?

- **Does adjuvant chemotherapy after incomplete staging lead to an improved prognosis?**
- **If yes, what is the optimal chemotherapy schedule (paclitaxel/carboplatin)**

Approximately one third of patients with ovarian carcinoma has a early-stage FIGO stage I - IIa (tumour limited to ovaries, tubes and uterus). The prognosis of these patients is much better than that of patients with an advanced stage. The 5-year survival amounts to approximately 85% and varies dependent on the FIGO-age, grade of differentiation and degree of surgical staging.
The biggest problem is determining the right stage because of the presence of occult metastases in clinically so-called earlier stages, and therefore actually concerns advanced stage tumours. After incomplete staging (NCS) this chance is 33%, varying from 15% (with a well-differentiated tumour) to 46% (with a poorly differentiated tumour). After complete staging (CS) this chance lies between the 0 and 15% for a completely staged (CS) ovarian carcinoma. It is therefore essential to distinguish between CS and NCS patients for a correct interpretation of literature information.
One could state that there are in fact two types of patients with early-stage ovarian carcinoma with entirely different prognosis: completely and incompletely staged patients. In other words, one can actually only speak of an early-stage ovarian carcinoma after a CS.

Summary of the literature
ICON1 and ACTION
The role of adjuvant chemotherapy (AC) is still controversial worldwide. Two large randomised studies have evaluated the effect of AC versus no chemo after surgery. The ICON1 trial randomised 477 patients with ovarian carcinoma without macroscopic residual tumours after surgery, with the only inclusion criterion: "uncertainty of the treating physician or where adjuvant chemotherapy is indicated". Different platinum-containing chemotherapy schedules were allowed, with a minimum of four courses. The ICON1 study found a significant reduction in death of 9% and an improvement in the recurrence-free survival of 11% in favour of the AC group (Colombo 2003[15]). The long-term results of ICON1 with a follow-up of nine years were recently presented which showed no significant difference any longer in survival between the two groups in the study (Trope 2007[57]). The difference only continued to exist for the subgroup of poorly

differentiated tumours.

The ACTION study included 448 patients with FIGO stage I-IIA ovarian carcinoma. This study also randomised between AC and no AC, but in contrast to ICON1, the level of staging was extensively analysed and involved in the non-planned subgroup analysis. No survival benefit associated with AC was found in the ACTION study (P=0.1) but the recurrence-free survival was significantly better in the AC arm (8%)(Trimbos 2003[55]). A third of the patients in the ACTION study were completely staged (N=151) and two thirds not (N=297). The patients in the control arm that had undergone complete staging, had a significantly better survival (p=0.03) and recurrence-free survival (p=0.04) than patients in the arm with incomplete staging. This difference was not seen in the AC arm. In contrast, a significantly better survival (p=0.009) was found in favour of the AC arm in the incompletely staged patients. AC did not provide a benefit in the completely staged patients, neither in terms of survival nor disease-free survival (Trimbos 2003[55]). In the combined analysis of ICON1 and ACTION, in which the majority of patients were not completely staged, a significantly better survival (8%) and disease-free survival (11%) was seen after AC (Trimbos 2003a[56]).

Complete staging and prognosis
Complete staging in itself has been shown to favourably influence the prognosis of early-stage ovarian carcinoma (Trope 2007[57]). A retrospective study (Zanetta 1998[61]) and a randomised clinical study (Trimbos 2003[55]) showed that the level of staging was a significant independent prognostic factor for survival and progression-free survival. Patients with a NCS had significantly poorer survival (Hazard Ratio (HR) 2.31, p=0.03) and disease-free survival (HR 1.82, p=0.04) compared to patients with CS (Trimbos 2003[55]).
The phenomenon of better survival after staging is probably due to the effect of stage migration.

AC or no AC
In the meta-analysis of five randomised studies in which adjuvant chemotherapy (AC) was compared to no adjuvant chemotherapy (no AC), a significant difference in mortality (RR 0.74, p=0.01) and recurrence (RR 0.70, p=0004) was found in favour of AC (Elit 2004[20], Winter 2003[60], Trope 2007[57]).
In the ACTION study, in which part of the patients had undergone a CS, no difference in survival was found (HR 0.69, p= 0.10).
In the two largest randomised studies, AC improved the 5-year absolute and disease-free survival of patients from the ICON1 and NCS patients of the ACTION study (Colombo 2003[15]; Trimbos 2003[55]), which indicates that patients without CS benefit from AC.
In the recently presented nine-year follow-up data from the ICON1 study however, survival is no longer significantly better in the AC group (Trope 2007[57]). A significant difference in survival in favour of the AC group was only found in the group of poorly differentiated tumours.

Complete staging and AC
It has never been shown that AC improves the prognosis for patients with CS. Subgroup analysis of the ACTION trial showed that AC does not provide any improvement in survival or progression-free survival after CS in relation to no AC (Trimbos 2003[55]). Furthermore, the response in patients with a recurrence from the control group is higher than in patients from the AC group. The five-year survival after recurrence in the control group was 40% and in the AC group 18% (Trimbos 2003). In a systematic review of all RCT's in this area, those studies that had randomised completely staged patients between AC and no AC were studied in a meta-analysis (Trope 2007[57]). It appeared from this meta-analysis that AC did not make a difference in survival: HR=0.91; 95% CI 0.51 - 1.61. With respect to this area, the authors concluded: "We do not believe that AC is indicated in the majority of stage I tumours that are adequately staged. In small and selective groups of very high risk patients, we consider the use of adjuvant CP" (Trope 2007[57]).
It should be pointed out that so-called AC in a large proportion of patients is not adjuvant but therapeutic because some of the micrometastases have been missed (Winter 2003[60]).

Number of courses
There is no conclusive data regarding optimal chemotherapy and number of courses of AC in the case of NCS. In the two largest randomised studies (AC versus no AC), an average of five courses of Carboplatin or Cisplatin, either in combination with Cyclophosphamide and Adriamycine or not, were administered in the AC group according to the standard therapy relevant at that time for advanced-stage ovarian carcinoma (Colombo 2003[15]; Trimbos 2003[55]; Trimbos 2003a[56]). Given the rationale of AC is to treat an occult stage III, the same therapy as for advanced-stage ovarian carcinoma, i.e., six courses of Paclitaxel Carboplatin, would seem the right course of action.
In a randomised GOG study, patients with a CS ovarian carcinoma were randomised between three and

six courses of Paclitaxel Carboplatin (Bell 2006[5]). No difference was found in this study in survival (five-year survival of 81% and 83% respectively for the three and six courses and the same as for the CS patients in the ACTION study). In terms of death, the figures were the same for both groups (HR 1.02 p=0.94). In relation to recurrence, the figures are also the same for the three and six courses (p=0.18). The conclusion that three courses are as good as six courses AC cannot be drawn from this study, because these patients had had a CS.

Late effects of AC
Patients with an early-stage ovarian carcinoma have a relatively good prognosis with a long survival. In that context, it is a population that is sensitive to late side-effects of chemotherapy, such as neurotoxicity and especially the development of a second primary tumour such as leukaemia. After 15 years, the risk is estimated at 20% (Travis 1999[54]). In patients with a early-stage ovarian carcinoma with a good prognosis, AC therefore needs to be based on a good indication.

See the evidence table (appendix 17).

Conclusions:
It is plausible that complete surgical staging in early-stage ovarian carcinoma is important and of favourable prognostic significance
Level 3 B Trimbos 2003[55], Trope 2007[57], Zanetta 1998[61]

AC has been shown to result in an improved five-year and disease-free survival if the level of staging is unknown.
Level 1 A Trimbos 2003[55], Trope 2007[57], Zanetta 1998[61]

AC has not been shown to provide significantly better survival after 10 years in an unselected patient group where the level of staging is unknown. In that case, the improved survival only applies to the group of patients with poorly differentiated carcinomas
Level 3 B Trope 2007[57]

There is no chemotherapy schedule available that has been sufficiently examined in early-stage ovarian carcinoma. The committee therefore advises standard schedule for stage III ovarian carcinoma, i.e., 6 courses of Paclitaxel Carboplatin
Level 4 D Committee

It has not been demonstrated that AC is of benefit in completely staged, early ovarian carcinoma, and there is no proof that AC makes a contribution to a better (disease-free) survival in this category of patients has not been shown to be plausible
Level 3 C Trope 2007[57]

Treatment of advanced-stage carcinoma (IIb IV)

Literature review:
The treatment of advanced-stage ovarian carcinoma consists of the combination of surgery and chemotherapy. Standard treatment is currently primary debulking, followed by chemotherapy.
A randomised phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with stage IIIc of IV epithelial ovarian carcinoma is accomplished. Soon data will become available.

In advance stage ovarian cancer (FIGO stage IIb, IIc, III and IV, the most important prognostic factors are:

- The differentiation grade of the tumour.
- The Karnofsky index.
- The diameter of the largest residual tumour lesion after primary debulking surgery.

The prognosis and progression of tubal carcinoma and extra-ovarian carcinoma are comparable to ovarian carcinoma. Classification and treatment are therefore the same.

This chapter is subdivided into subchapters and/or paragraphs. Click in the left column on the subchapter and/or paragraph title in order to view the contents.

Surgery

Literature review:
Surgery
Primary debulking surgery is the standard treatment in advanced-stage ovarian carcinoma; this means removal of the adnexa, uterus, at least the infracolic part of the omentum, as well as resection of all visible tumour localisations. If a complete (no residual tumour visible) or optimal debulking surgery (all lesions ≤ 1cm) is not possible, as much of the tumour as possible is removed. In doing so, the morbidity of the intervention should always be kept in mind.

- complete debulking = no residual tumour visible
- optimal debulking = all residual tumour lesions ≤ 1cm
- incomplete debulking = residual tumour > 1 cm

Definition of residual lesion
The size of the residual tumour, defined as the maximum diameter (length, width or depth) of the individual tumour depositions after debulking surgery and performance status, are the most important prognostic factors for survival and progression-free survival. While eighty percent of the ovarian tumours respond to paclitaxel/platinum chemotherapy, the chance of complete remission in patients with large tumour residues and in a poor condition is only 20%. The chance of (pathologically) complete remission in patients with macroscopic resection of all tumour lesions however, is 80%. The overall five-year survival of all patients that were treated with both surgery and chemotherapy is only 30%. Patients with a macroscopic complete debulking have a five-year survival of more than 60%. This last piece of information underlines the responsibility for practitioners performing a debulking operation. Surgery should therefore be performed by, or in collaboration with, an experienced gynaecological oncologist.

Patients in whom primary tumour debulking surgery is contra-indicated, can start with induction chemotherapy, followed by interval debulking surgery after three courses of chemotherapy.

If primary debulking has not lead to an optimal result, interval debulking should be considered after three courses of chemotherapy and a good response. Interval debulking is outlined in the next paragraph.

Interval debulking surgery

Literature review:
Van de Burg showed that interval debulking after suboptimal primary cytoreductive surgery lead to extension of the (disease-free) survival (Van de Burg 1995[11]). However, this was not confirmed by Rose (2004[89]), who also researched the effect of interval debulking after suboptimal primary surgery. In this study, maximum efforts by the gynaecological oncologist was already required during the primary debulking procedure, which was not always the case in the study by Van de Burg. The degree of residual tumour after primary cytoreductive surgery was therefore smaller than in the study by Rose, while in addition, a more effective, paclitaxel-containing chemotherapy schedule was given.

Chemotherapy

Literature review:
Chemotherapy
Current standard chemotherapy for stage FIGO IIb-IV consists of combination therapy with:

- Taxol 175 mg/m2 (in a 3-hour infusion)
- Carboplatin with a AUC of 6 (creatinin clearance calculated using the Cockcroft-Gault formula and the dosage carboplatin via the Calvert formula),

or

1. Taxol 175 mg/m2 (in a 3-hour infusion)
2. Cisplatin 75 mg/m2.

A minimum of six three-weekly courses are administered (more extensive information on this can be found on ‘SIB op maat' SIB op maat is a website with patient information on adverse events related to drugs used in the treatment of cancer).

Intraperitoneal chemotherapy (IP)
It has been shown that IP chemotherapy for patients with FIGO stage III ovarian carcinoma (Armstrong schedule) that have obtained a complete or optimal debulking (intraperitoneal residual lesions < 1 cm) leads to a better disease-free and overall survival compared to the standard intravenous cisplatin combination therapy (relevant at the time of the study). However, treatment is associated with substantial toxicity.

Chemotherapy in platinum-resistant tumours.
Platinum-resistant tumours can be treated with topotecan, liposomal doxorubicine, gemcitabine, oral etoposide or weekly platinum combination therapy. Approximately 12% to 15% of patients will respond to these agents, while around 30% of patients will have stable disease with a time to progression period between 12 to 22 weeks.

Induction chemotherapy with intervention surgery

Recommendations:
Await the outcome of EORTC 55971. Until such time, continue using standard policy: primary cytoreductive surgery followed by multichemotherapy.

Literature review:
Which treatment is preferred in the case of advanced disease: induction chemotherapy with intervention surgery or primary debulking followed by chemotherapy?

Introduction

Soon the data of the randomised phase III study comparing upfront debulking surgery versus neoadjuvant chemotherapy in patients with stage IIIc or IV epithelial ovarian carcinoma (EORTC 55971) will become available. Therefore the search is limited to randomised trials, meta-analyses and systematic reviews.
The standard treatment for women with ovarian carcinoma is cytoreductive surgery, followed by multichemotherapy. Interval cytoreductive surgery after neoadjuvant chemotherapy can be indicated in case of poor general condition or other contra-indications for primary surgery. This applies even more, when, in patients with advanced stage disease, parameters are present that predict poor resectability (e.g. pleural thickening, ascites, omental cake etc.).
Prelimanary data with respect to such predictors have recently been presented, but the definitive evaluation still needs to be published. In select cases however, induction chemotherapy with interval debulking has been shown to give comparable survival percentages to that of women obtaining a primary cytoreductive operation, followed by chemotherapy (Schwartz 1999[49]). Van de Burg showed that interval debulking after suboptimal primary cytoreductive surgery lead to extension of the (disease-free) survival (Van de Burg 1995[11]). However, this was not confirmed by Rose (2004[89]), who also examined the effect of interval debulking after suboptimal primary surgery. In the latter study, maximum exertion by a gynaecological oncologist was already required in first instance to arrive at optimal debulking, which was not always the case in the study by Van de Burg. Tumour residues after primary cytoreductive surgery were therefore also smaller than in the study by Rose, while in addition, a more effective, paclitaxel-containing chemotherapy schedule was given.
The available literature was evaluated with the question if there are indications that neoadjuvant chemotherapy provides a comparable or better survival than standard treatment.

Summary of the literature

There is one Cochrane review (Morrison J 2007[37]) incorporating 48 articles, containing just one randomised study, but with too small a number to be able to answer the research question. In a systematic review by Bristow (Gynecol Oncol 2007[10]), 26 studies between 1989 and 2006 were included; however, the selection again did not contain any randomised studies. The conclusion of the authors is that "maximum cytoreductive surgery is the standard treatment for the majority of patients with primary ovarian carcinoma, even when an advanced stage of disease is suspected. Neoadjuvant chemotherapy remains a good alternative for a limited number of patients in the case irresectability is suspected". Thus far however, available data suggests a better survival of patients that are operated on upfront, compared to patients that initially receive chemotherapy.
An analysis by the same author performed the year before (Bristow 2006[9]), and including nearly the same studies, had a different research question: what is the overall survival in case of neoadjuvant chemotherapy and what are the prognostic variables for survival in case of neoadjuvant chemotherapy? In was concluded that in more recent studies a higher chance of survival was obtained in patients with an optimal interval debulking. The chance of survival was lower in studies with more stage IV patients and decreased with increasing number of preoperative courses given (that is a longer delay in cytoreductive surgery).

See the evidence table (appendix 19).

Conclusions:

So far, no randomised studies have been published and therefore the clinical question cannot be answered. On the basis of available data, no pronouncement can be made in relation to whether a different treatment policy other than the standard treatment (primary cytoreductive surgery, followed by combination chemotherapy) leads to better survival, a better disease-free survival and/or less morbidity. The first preliminary results of the large randomised study (EORTC 55971; A randomised phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with stage IIIc or IV epithelial ovarian carcinoma) have recently been presented. Until the definitive evaluation is published, there is no reason to deviate from the standard policy unless there is a contraindication for primary surgery.

There are no indications that a treatment policy other than the standard policy leads to a better (disease-free) survival.
Level 4 D Committee

Considerations:

The first large randomised study (including more than 700 patients) on this research question (EORTC 55971; A randomised phase III study comparing upfront debulking surgery versus neo-adjuvant chemotherapy in patients with stage IIIc or IV epithelial ovarian carcinoma) has been accomplished of which the first data have been resented during the world congress of the International Gynecologic Cancer Society (IGCS Bangkok 2008). There was no difference in survival and disease-free survival between the two groups. In patients who obtained induction chemotherapy followed by interval debulking the length of operation was shorter and postoperative complications less than in patients that first received chemotherapy. The complete resection of all macroscopic tumour tissue was the most important prognostic factor for survival in the multivariate analysis.

However, before deciding to elevate neoadjuvant chemotherapy as standard treatment of stage IIIc and IV ovarian carcinoma, the peer-reviewed publication must be evaluated.

Intraperitoneal chemotherapy

Recommendations:
It has been shown that the addition of intraperitoneal (IP) chemotherapy to intravenous chemotherapy for patients with a FIGO stage III ovarian carcinoma that have had a complete or optimal debulking (residula intraperitoneal residual lesions, <1 cm) leads to a better disease-free and overall survival. However, treatment is associated with substantial toxicity.

Restraint should be exercised with IP chemotherapy if there is an increased risk of anastomotic leakage, such as after colon surgery.

It is plausible to advise the schedule used by Armstrong (2006[2]), on the basis of the greatest advantage in survival.

There are indications that less catheter obstructions are seen with a single lumen bard, a non-fenestrated 9.6 F catheter.

It is the opinion of the committee that this treatment requires a particular expertise; as a result, it is advised that this treatment is performed in a centre that has gained experience in this area. All patients treated with IP chemotherapy should Information relating to any patients treated with IP chemotherapy should also be registered, for a clear picture of complications.

See 'SIB op maat' for background information regarding the schedule and side effects of carboplatin/taxol.

Literature review:
Does intraperitoneal chemotherapy in the treatment of advanced ovarian carcinoma lead to an improved prognosis?Introduction
The standard treatment for stage II-IV ovarian carcinoma consists of a combination of surgery in which as much of the disease is removed and at least six courses of chemotherapy in which a combination of carboplatin and taxol is administered. According tot the current standard chemotherapy is administered intravenously (IV). A number of randomised studies examined the value of a combination of IV and intraperitoneal (IP) chemotherapy after primary debulking surgery. It is open to question whether this provides an improvement in disease-free survival and whether the side-effects weigh up against the benefits.

Summary of the literature
Four meta-analyses of sufficient quality were published in 2007, which studied the effect of IP chemotherapy on disease-free survival and survival (Elit 2007[21], Jaaback 2007[30], Hess 2007, Fung Kee 2007[23]). In each one of these meta-analyses, between six and eight randomised controlled studies were evaluated, with a total of patients between 1716 and 1826 patients. The analyses were performed at the level of studies and not at an individual patient level. In most of the randomised studies, only patients with FIGO stage III were included, a few studies also reported inclusion of patients with FIGO stage II and IV. The degree of residual tumour after primary debulking also varied, from ≤1 cm ≥2 cm, in which most patients tumour residues smaller or equal to 1 cm. Each of these meta-analyses showed a significant

improvement in disease-free survival and overall survival as a result of IP administration of chemotherapy. In the largest randomised studies, IP administration lead to an improvement in survival with 8, 11 and 16 months (Alberts 1996[81], Markman 2001[35], Armstrong 2006[2]),
IP chemotherapy resulted in more complications and side-effects of treatment, in particular, bone marrow toxicity, gastrointestinal complaints, abdominal pain and catheter-related complications occurred (Jaaback 2007[30]).
One study also measured the Quality of Life. This was reduced during IP chemotherapy in relation to IV chemotherapy only, and remained for one year after completing chemotherapy (Armstrong 2006[2]).

See the evidence table (appendix 18).

Conclusions:
It has been shown that the combination of IV and IP chemotherapy leads to a better disease-free survival and overall survival in patients with a high-stage ovarian carcinoma.
This applies at least for patients with a FIGO stage III ovarian carcinoma who obtained a complete or optimal (residues ≤ 1cm) primary debulking, in which the treatment commenced immediately after surgery.
The extent to which patients with a FIGO stage II or IV and patients with residual tumours > 1cm benefit from this treatment is less clear, given less patients with this stage were treated. However, treatment is associated with substantial toxicity.
The IP schedules in which survival benefit was most pronounced, contained both cisplatin and paclitaxel. It is not clear what the optimal number of courses and optimal schedule is, given the individual IP schedules have not been compared to each other.
Level 1 A Elit 2007[21], Jaaback 2007[30], Hess 2007[29], Fung Kee 2007[23], Alberts 1996[81], Markman 2001[35], Amstrong 2006[2]

Considerations:
Whether the above questions that have not yet been answered, are sufficient reason to arrive at negative advice in relation to IP chemotherapy, is controversial. An alternative is to define a subgroup of patients in which the administration of IP chemotherapy seems justified.

Follow-up

Literature review:
Follow-up frequency:

- First and second year: follow-up every three months.
- Third year: follow-up every four months.
- Fourth and fifth year: follow-up every six months.
- More than five years: follow-up once per year.

Patients treated with chemotherapy have been checked frequently. Therefore it can be difficult for them psychologically to obtain abruptly a follow-up scheme of three months directly, after the therapy ends. For them scheduling the first follow-up within the first six weeks is worth considering.

The follow-up will generally alternate between visits to the gynaecologist and medical oncologist. This offers a certain continuity with a multidisciplinary approach.

There is no reason to withhold HRT (hormonal replacement therapy) from patients. This can already be started during treatment.

During follow-up, a general physical and gynaecological examination can be performed and serum CA 125 can be determined. On indication (increase in CA 125, or complaints), the examination is supplemented with imaging diagnostics such as CT scan and/or ultrasonography. If the localisation of recurrencce cannot be detected, the international consensus is to wait and only treat patients if the increase in CA 125 is accompanied by clinical detection of the recurrence. So far, it has not been shown that treatment solely based on an increase in CA 125 offers benefits, and therefore practitioners can choose to determine CA 125 in patients with a clinically complete response only in case of complaints or where a recurrence is suspected.
The value of a CA 125 determination in the follow-up is currently the primary objective in an international randomised study. This study is discussed further in the next subchapter. Click in the left column on the subchapter to view the contents.

Determining CA 125

Recommendations:
It is not recommended to treat a patient on the basis of an increasing serum CA 125 value if the patient is asymptomatic.

Literature review:
Does early (and asymptomatic) detection of recurrent ovarian carcinoma using CA 125 determination lead to an eventual extension in survival and what is the influence of this on the well-being (quality of life) of a patient?

Literature selection criteria
The research question led to 16 articles (see appendix 21), none of which contained data providing an answer to the abovementioned question. A number of articles do make a pronouncement about the treatment of asymptomatic patients with an increase in CA 125 that is based on ‘circumstantial evidence'.

In conclusion, there is currently no evidence in the literature that commencing treatment of an asymptomatic patient with an increasing CA 125 serum value after prior primary treatment for epithelial ovarian carcinoma (EOC) positively influences the prognosis and/or quality of life. In addition, not a single trial has been described in literature that researches this scientific question. Recently the inclusion for a large multicentred study by the EORTC and UK Medical Research Council (OVO5/5595) as been completed with the abovementioned question as study topic. Preliminary results of this study are expected in 2009.

Introduction

The CA 125 serum value is initially increased in 80 to 90% of all patients with EOC. This value is dependent on the FIGO stage, in which patients with a stage I only show an increase in value in 50% of cases (Jacobs, Human Repr 1989). On the basis of this low sensitivity, CA 125 is not used to screen asymptomatic women unless for the purpose of scientific research. CA 125 has proven its value as monitor of primary treatment; many studies have shown that the CA 125 serum value is a good reflection of disease progression. (tuxen 2002[90])

In most centres worldwide, CA 125 is therefore used within the framework of the follow-up. The aim of this application is the preclinical detection of progression of disease or of its recurrence. In multiple publications, CA 125 was able to detect the recurrence one to 15 months earlier, with an average lead-time of three to four months. An increase in the CA 125 serum value to more than twice the upper limit of normal was predictive for recurrence with a sensitivity of 84% and a false positive value less than 2% (Rustin Ann Oncol 1996).

In the primary treatment of cancer it is emphasized that early diagnosis and intervention are important with respect to prognosis. In the case of recurrent ovarian carcinoma however, we are dealing with a different situation in which treatment is generally no longer seen to be curative. In this situation, treatment is seen as a form of palliation, in which the reduction of complaints plays a central role alongside potential extension of survival.

Aside from an unfounded reassurance of the patient, treatment of asymptomatic patients on the basis of an increasing CA 125 value also has the potential benefit of a better prognosis. However, the latter has never been proven. This treatment does certainly have a number of disadvantages, such as a shortening of the disease-free interval and induction of the toxicity associated with the treatment.

Summary of the literature

There is no study available in literature that answers the abovementioned question.

See the evidence table (appendix 21).

Conclusions:

The committee has the opinion that awaiting the final result OVO5/5595-study, the management of an asymptomatic patient with an increasing serum CA 125 value should be expectative until the patient develops complaints or a clinical recurrence is detected and there is an expectation that these complaints will be reduced or the prognosis will be improved if treatment is commenced.

Level 4 D Committee

Recurrence

Literature review:
The standard treatment of recurrent ovarian carcinoma consists of chemotherapy. In individual cases, surgery and/or radiotherapy can be part of the treatment process.

It should be discussed with the patient that it concerns a palliative treatment but with the possibility of response, extension of survival and progression-free and symptom-free survival. The chance of response in relation to side-effects expected should be discussed as well as the option of intervention surgery where appropriate in the case of platinum-sensitive tumours.

Chemotherapy
Patients with a therapy-free interval of more than one year (platinum-sensitive patients), respond well to repeated treatment with a platinum-containing combination chemotherapy. In these patients, repeated treatment with a taxol and platinum combination is the first choice.

Patients with a platinum-free interval of 6 - 12 months are also considered platinum-sensitive. They can also respond anew to taxol/platinum-containing chemotherapy.

Patients with a tumour recurrence within 6 months after the last platinum-containing chemotherapy (platinum-resistance) or progression during treatment with platinum (platinum-refractory patients), have a poor prognosis. An alternative is monotherapy treatment, including liposomal doxorubicine, topotecan, gemcitabine, oral etoposide or weekly platinum combination therapy.

Surgery
Surgery as part of the treatment recurring ovarian carcinoma has been a point of discussion for some time. Although there are no randomised studies, based on retrospective data, maximum cytoreductive surgery prior to chemotherapy in these patients only leads to a significant extension in survival when the procedure results in an optimal, and preferably complete (no macroscopic residue) debulking.
The percentage of patients with a recurrent ovarian carcinoma in which an optimal or complete debulking can be performed again varies from 13 to 86%.
Renewed surgery should only be considered if the criteria below are fulfilled:

- clinically complete remission after initial therapy
- disease-free interval ≥ 6 months
- the estimation that an optimal debulking can be achieved (again).

Click in the left column on the subchapter cytoreductive surgery for evidence-based information about this topic.

Radiotherapy

Radiotherapy has a limited role in the treatment of ovarian carcinoma. However, radiotherapy can be important in the palliative phase in reducing complaints of the primary tumour or metastases.
Indications for radiotherapy:

- Symptomatic metastasis, for example:
    - Bone metastasis
    - Supraclavicular or inguinal node metastasis
    - Brain metastasis
    - Pelvic localisations, such as complaints of nerve plexus compression, bleeding, pain, or stasis.

Cytoreductive surgery

Recommendations:
Debulking surgery prior to chemotherapy in patients with recurrent ovarian carcinoma shouild only be considerd if the below criteria are fullfilled:

- clinically complete remission after initial therapy
- disease-free interval > 6 months
- it is estimated that a renewed optimal debulking can be achieved (good performance status, initial complete debulking or early-stage ovarian carcinoma, <500 mL ascites or no indications for a peritonitis carcinomatosa, limited number of tumour localisations).

Literature review:
Does cytoreductive surgery for recurrent ovarian carcinoma lead to an improved prognosis? If yes, under what conditions?

Literature selection criteria
A selection was made of relevant articles on the basis of the abstract or entire article. Those selected were the systematic reviews (SR) and original studies on recurrent epithelial ovarian carcinoma (EOC) patients that were published later than the inclusion period date of the SR's.
Articles not included, were articles that specifically studied one particular intervention (e.g. milt extirpation), in which the combination with intraperitoneal hyperthermia was studied, or in which the surgical intention was other than achieving maximum cytoreduction.

Summary of the literature
Many studies have been conducted on the value of cytoreductive surgery in recurrent EOC however, there are no randomised controlled trial (RCT) or otherwise well-controlled studies of sufficient size that have been performed. Only two studies contain prospectively gathered data. Selection bias therefore plays a role in all studies. The duration of the disease-free interval varies in the studies from 0 to > 12 months. Except for FIGO stage III, the majority of studies also include patients with FIGO I - II as well as FIGO IV. All studies compare, within the group of operated patients, the patients in whom an optimal debulking is achieved with the patients in whom the debulking is not optimal. The definition of an optimal debulking used in the studies varies from complete (no macroscopic tumour residues) to residual tumours < 2 cm. Three studies also report a patient group in which only chemotherapy was applied as therapy, but the numbers are small and the study does not outline how the patients were selected (Vaccarello 1995[99]; Jin 2006[31]; Matsumoto 2006[36]). Information about second-line chemotherapy is lacking in most studies, as well as performing an intervention debulking after second-line induction chemotherapy.
In literature, three systematic reviews have been published (Bristow 1996[7]; Munkarah 2004[39], Harter 2005[27]). These reviews are based on the abovementioned retrospective or prospective cohort studies. As a result, the "level of evidence" remains limited to level C.

All articles are summarised in the evidence table (see appendix 20). Table 2 (see appendix 22) shows the "adequate debulking" percentage reported in the various studies with the associated result (survival). Nearly all studies find a significant increase in duration in survival when a complete debulking can be performed on patients with a recurrent EOC in comparison to the group of patients in whom a complete debulking cannot be achieved; however, the median survival duration varies strongly per study (for complete debulking: 19 - 100 months). Most studies in which optimal debulking is defined as criterium (residual tumours varying from <0.5 cm - <2 cm), also report a significant increase in survival when this result is achieved, but the benefit is less convincing and less unanimous.
A few studies describe parameters available preoperatively that are associated with a complete debulking. Table 3 (see appendix 23) shows the significant parameters per study, obtained on the basis of an eventual multivariable analysis. Only the study by Harter (2006[28]) has processed the significant parameters (good performance status, and initial complete debulking or early-stage ovarian carcinoma, <500 mL ascites) in a predictive score. This led to a positive predictive value of 79% in this study if patients fullfilled all three criteria; however, the negative predictive value however was only 58% (sensitivity 35%, specificity 91%).

Conclusions:
For a selected group of patients with recurrent ovarian carcinoma, renewed maximum cytoreductive

surgery prior to chemotherapy may result in a significantly extended survival.
Level 3 C Vaccarello 1995[99]; Jin 2006; Matsumoto 2006[36]; Bristow 1996[7]; Munkarah 2004[39], Harter 2005[27]

Preoperative parameters that appear to be associated with a complete debulking are:

- good performance status
- initial complete debulking or early-stage ovarian carcinoma
- <500 mL ascites or no indications for a peritonitis carcinomatosa
- Limited number of tumour localisations

Level 3 C Cho 2006[85], Eisenkop 1995[98], Gronlund 2005[25], Harter 2005[27], Harter 2006[28], Pfisterer 2005[42], Zang 2000[62]

Considerations:
While only based on retrospective data, it can be postulated that renewed maximum cytoreductive surgery in the case of a recurrent ovarian carcinoma leads to a significant extension in survival when the procedure results in an optimal, and preferably complete (no macroscopic residue) debulking in comparison to patients in whom optimal debulking is not achievable. As a comparison to patients with only chemotherapy is lacking in most studies, no pronouncement can be made about the potential effect of a non-optimal debulking.
The percentage of patients with a recurrent ovarian carcinoma in which an optimal or complete debulking can be performed (again) varies in publications from 13 to 86% and is partly dependent on the inclusion criteria used in these studies. In addition, the expertise of the surgeons also plays a role.

Nursing and supporting care

Literature review:
Involving a psychosocial care provider (oncological or social nurse, social worker, sexologist or psychologist) can be of benefit or even required. Structural guidance may lead to an improvement in quality of life. However, the literature is not univocal on this topic, as outlined in the evidence-based section of the guideline: the value of structural guidance. Click in the left column on the subchapter to view the contents.

Nutritional behaviours in general and adequate perioperative nutrition in particular, can also provide a contribution to quality of life.
Inform patients on the possibility of contact with fellow patients and the patient association Olijf foundation ('Stichting Olijf").

The value of structural guidance

Recommendations:
The committee is of opinion that care and treatment aimed at psychosocial complaints such as fear, depression, nausea and vomiting can contribute to the quality of life of patients.
During treatment of ovarian carcinoma, it is recommended that patients are informed regarding the possibility of psychosocial care.
The committee also advises that the psychosocial guidance in these patients is performed by a nurse specialist in oncology, a psychologist or spiritual care provider.
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Literature review:
Does structural guidance by a specialised psychosocial care provider (sexologist, social worker, psychologist, nurse specialist in oncology, nutritionist, and spiritual care provider) lead to an improved quality of life with patients during and after treatment?

Introduction
Cancer diagnosis and treatment have consequences beyond physical functioning. Psychological problems can occur to a greater or lesser degree at different moments during the disease. Ovarian carcinoma, most patients present with an advanced stage of the disease. At the time the diagnosis has just become known, feelings of fear, depression and intense emotions can arise. Physical problems, mostly, develop during treatment, such as chemotherapy and in the terminal phase of the disease (Haes de 2001[91]). It seems that cancer is associated with a reduced quality of life at the time the diagnosis as well as during treatment, but that worsening after this point in time is not common (Edlinger 1998[92]). An explanation can be the "response shift" phenomenon, i.e. patients adjust their reference framework of a 'good' quality of life. Research on the quality of life of women with ovarian carcinoma shows that 33% of patients suffers from fear and depression (Kornblith 1995[93]); while a reduced physical condition often influences psychological well-being.
Many studies on cancer make use of disease-specific measuring questionnaires as instrument for measuring quality of life. EORTC-QLQ-C30 has been developed by the European Organisation for Research and Treatment of Cancer (EORTC). Aside from this generally quality-of-life questionnaire, other modules have been developed for different types of cancer, such as the EORTC OV28 (EORTC 2007), which is specifically aimed at ovarian carcinoma. These questionnaires however are incidently mentioned in the literature studied.
No studies have analysed the effect of interventions for ovarian carcinoma patients alone. Several studies have been conducted as to the effects of psychosocial interventions in breast cancer patients and with heterogeneous groups of cancer patients. These studies largely involved interventions aimed at symptom management.

The outcome measures vary per study and concern:

- Quality of Life
- Fear

- Depression
- Mood
- Nausea and vomiting
- Pain
- Coping
- Knowledge

Summary of the literature

Arving (2007[94]) conducted a randomised controlled trial with breast cancer patients. Clinical questions: are there differences in quality of life, fear, depression and posttraumatic stress between patients guided by a nurse or psychologist and patients receiving standard care and are there differences in relation to the use of generally available psychosocial care?
Results: Especially the intervention groups showed improvement with respect to sleeping and financial worries. Patients in the intervention groups suffered less from intrusive thoughts. The intervention groups used other psychosocial care services less often. Breast cancer patients appear to have a need for psychosocial support. Guidance by a trained oncology nurse or psychologist could offer this need. The effects of guidance are generally limited.
Study limitations: no screening of psychological problems for inclusion, insufficient power, not well randomised. Patients from the control group also partly received supporting care and this causes confusion about the results.
Study qualification B
Conclusion: Limited effects of the intervention.

Devine (1995[95]) conducted a meta-analysis with the aim of collecting accurate predictions of effects of psychosocial care in cancer patients. The studies (n=116) outline the effects of psychosocial care of adult patients with cancer. The interventions are aimed at psychological and physical well-being and knowledge. Dependent variables are: fear, depression, mood, nausea, vomiting, pain and knowledge.
The studies compared diifferent interventions with standard care, either as monotherapy or in combination: (psycho) education, counselling, (cognitive) behaviour therapy, relaxation exercises, hypnotherapy, and imaginary stimulation. The effects of different forms of psychoeducation appear to have a positive effect on fear and depression. Nausea and vomiting during chemotherapy were reduced as a result of relaxation exercises either in combination with imaginary stimulation and systematic desensitisation or alone. Positive effects were seen more frequently with the 4th or 5th course than the first cycle. Quality of life was generally not studied.
Study qualification A2
Conclusion: psychosocial care may have a positive effect on fear, depression, mood, nausea and vomiting, pain and knowledge.

Maughan (2001[96]) outlines a randomised controlled trial. The research population: women (n=36) that are on the waiting list for radical pelvic surgery for gynaecological cancer. The objective of the study is:

- To gain insight in the adaptation of patients after a large pelvic operation relation to psychological, social and sexual aspects.
- To examine the influence of an intervention by a nurse specialist on the psychological, social and sexual "recovery" after gynaecological cancer.
- To understand how gynaecological cancer is perceived by women confronted by the disease.

Women in the intervention group were guided by a nurse specialist; the form in which guidance is provided is not outlined further.
Results: there is a positive effect in relation to emotional, cognitive and social functioning and better sexual functioning in the intervention group. However, the differences are not statistically significant. The global health status did improve significantly, as well as a faster recovery in sexual activities and less sleep disorders. Limitations of the study: sample size is small, the study largely looked at the consequences for sexual functioning. The researcher performed the intervention.
Study qualification B
Conclusion: There are no significant differences between the two groups but guidance by a specialised nurse may be effective, in relation to emotional, cognitive and sexual functioning.

Uitterhoeve (2004[97]) conducted a review on ‘The efficacy of psychosocial interventions in patients with an advanced stage of cancer on the quality of life (‘De effectiviteit van psychosociale interventies bij patiënten

met een gevorderd stadium van kanker op de kwaliteit van leven'). In this review, thirteen randomised clinical trials are outlined; eight studies only incorporated women.
Analysis of results of the trials showed that in almost all cases (n=12) there was a positive effect of psychosocial interventions on one or multiple aspects of the quality of life. This concerned in particular fear, depression and feelings of sadness.
Study qualification A2
Conclusion: cognitive behavioural therapy may have a positive effect on the quality of life of patients with advanced-stage cancer, particularly in the area of emotional functioning.

See the evidence table in appendix 24.

Conclusions:
Structural guidance by a specialised psychosocial care provider has not been examined for ovarian patients.
Therefore a clear answer to the question whether structural guidance by a specialised psychosocial care provider (sexologist, social worker, psychologist, nurse specialist in oncology, and spiritual care provider) leads to an improved quality of life for patients during and after treatment cannot be given.
Structural guidance may lead to an improved quality of life in patients with cancer. This applies in particular to the role of the psychologist, nurse specialist and spiritual care provider. No studies have been found in which the role of the sexologist and social worker are outlined.

In relation to generalisability of the research results in cancer patients in general. It can be that the effects of interventions that concern side-effects of chemotherapy will also be positive in patients with ovarian carcinoma. The results in relation to fear and depression that have been shown to occur in particular with breast cancer patients and cancer patients with an advanced stage of cancer, as far as they are effective, are possibly also effective with ovarian carcinoma patients.
Given the fact that the research results used are not specifically related to the target group, the level of evidential value must be estimated at level 4.

Effects of interventions:

Fear and depression
The committee is of opinion that fear can be reduced by relaxation exercises as monotherapy or in combination with guided fantasy exercises.
Psychoeducation aimed at the reduction of depression can be worthwhile
Level 4 D Committee A2 Devine 1995[95], B Arving 2007[94], A2 Uitterhoeve 2004[97]

Nausea and vomiting
The committee is of opinion that nausea and vomiting, as side-effects of chemotherapy treatment, can be reduced by different forms of treatment such as relaxation exercises, systematic desensitisation and guided fantasy exercises (Devine 1995) as a supplement to the application of standard antiemetics. These interventions appear to be more effective in later course cycles. Particularly in relation to nausea, better effects of interventions are seen in the 4th and 5th course. It cannot be determined which of the different interventions are the most effective. It has not become clear which discipline is best in applying these interventions.
Level 4 D Committee; Devine 1995[95]

Mood
The committee is of opinion that psychoeducation and/or cognitive therapy can be considered to reduce feelings of depression in patients in both an advanced stage of cancer and in the diagnostic phase.
Level 4 D Committee; Arving 2007[94], Devine 1995[95], Uitterhoeve 2004[97]

Coping
The committee is of opinion that interventions aimed at learning a different coping style, such as psychoeducation, systematic desensitisation, guided fantasy exercises, and learning of relaxation exercises could lead to a better quality of life. There are indications that counselling aimed at coping by terminal patients can contribute to a better quality of life.
Level 4 D Committee; Arving 2007[94], Devine 1995[95], Uitterhoeve 2004[97]

Sexuality
The committee is of opinion that cognitive therapy by a psychologist and psychoeducation by a nurse specialist could lead to an improvement in sexual function. There are indications that insufficient light has been shed on this specific problem and that it requires much more attention.
Level 4 D Committee; Maughan 2001[96]

Communication and patient information

Literature review:
Communication
With the patient:

- has the patient understood the information
- does the patient have a sufficient amount of time to think between diagnostics and therapy
- is the patient actively involved in the decision-making

With the general practitioner:

- feedback to the general practitioner regarding findings, intended treatment and treatment result.

Patient information
The patient is informed about the nature and objective of the proposed diagnostic tests. If available, provide patient with written information regarding these tests and the proposed treatment. A brochure from the Dutch Cancer Society (KWF kankerbestrijding) is available specifically for ovarian carcinoma.

If ovarian carcinoma is suspected, the patient needs to be informed about the possibility of a malignant disorder. If malignancy is determined during surgery, the ovaries/fallopian tubes, uterus, omentum, lymph nodes (where required), a number of peritoneum biopsies and potentially tumour lesions found elsewhere will be removed (intestinal surgery where required, with a chance of stoma).

The consequences of treatment, psychological aspects, potential infertility as well as sexuality, processing, needs to receive sufficient attention. Preferably, written information will also be provided. However, it is not always easy for the complex situation to be summarised in simple words. Good verbal information will be able to fill in any gaps.

Brochures from the Dutch Cancer Society (KWF kankerbestrijding): ovarian carcinoma, chemotherapy, living with cancer, scientific research, cancer and tiredness, cancer and nutrition, and heredity (where applicable).

Before treatment is started, a (legally prescribed) conversation in which patient information is outlined, will need to take place with the patient (preferably in the presence of family) in order to discuss the diagnosis, treatment, expected results and consequences (including the risks and potential side-effects). In doing so, the wishes of the patient are taking into account. Any information required about possible trials will be provided. Planning and possible waiting time also need to be discussed. If an hereditary form of ovarian carcinoma is suspected, the patient is pointed to the guideline hereditary ovarian carcinoma, as well as the possibility of contact with fellow patients and the patient association Olijf Foundation (‘Stichting Olijf").

Organisation of care

Literature review:
Every staging, interval and debulking operation takes place in collaboration with a gynaecological oncologist and preferably only in hospitals with sufficient expertise and intensive care possibilities. Another option is to refer the patient to a tertiary centre of care. On the basis of literature, it is plausible that both the volume of patients with advanced ovarian carcinoma and the expertise of the gynaecologist influences survival. There is limited evidence that the number of medical oncologists per hospital influences the prognosis.

While it has not been demonstrated that structural regional consultation leads to an improved prognosis for the patient, the committee is of opinion that every hospital should function within a regional collaboration with a regular multidisciplinary oncological consultation.

Dissimilation and concentration

Recommendations:
If a patient is suspected of having an ovarian carcinoma, the operation should be performed by a gynaecological oncologist and/or in a specialised hospital.

Literature review:
Do concentration and/or specialisation lead to improved care in the treatment of patients with ovarian carcinoma?

- **Do the surgeon and location (nature of the hospital) contribute to the prognosis of a patient with an early and/or advanced stage ovarian carcinoma?**
- **Do the experience of the medical oncologist and location (nature of the hospital) contribute to the prognosis of a patient with an ovarian carcinoma?**
- **Does structural regional consultation lead to an improved prognosis for the patient?**

Introduction
Achieving an optimal surgical debulking remains an important prognostic factor for survival in the treatment of ovarian carcinoma. In the Netherlands, women suspected of having a malignancy originating from the ovary are generally operated in the same hospital the diagnosis is made and are optionally referred to a centre for surgical treatment. This is in contrast to the treatment of several other solid tumours, in which the positive relationship between volume and outcome has lead to centralisation of treatment.
Is has been the topic of many studies to examine a relationship between volume and subspecialisation of the treating physician and outcome during treatment of the ovarian carcinoma. In the Netherlands there are three branches of gynaecology specialisation. General gynaecologists working in peripheral (non-academic) hospitals, gynaecologists with oncological specialisation (gynaecologen met oncologisch aandachtsgebied, GOA) working in peripheral hospitals, while gynaecological oncologists work in oncological/academic centres.

The Dutch situation distinguishes itself also in other specific aspects, such as the consultant function, having a second specialist assisting during surgery (achievable due to short distances), as well as the presence of medical oncologists in all hospitals.
The above elements need to be taken into consideration when evaluating data from literature.

Summary of the literature
Within a cohort of patients with EOC (epithelial ovarian carcinoma), the studies compare the effect of the specialisation of the gynaecologist and/or hospital on the prognosis of EOC. No studies have been found that specifically look at the influence of the specialisation of the medical oncologist or the effect of regional multidisciplinary consultation in relation to patients. Virtually all studies are retrospective cohort studies. There is one case-control study (Tingulstad 2003[76]). Two systematic reviews have been published (Giede

2005[64] en Vernooij 2007[65]), which are therefore only based on the abovementioned retrospective cohort studies. Therefore evidence level B is the maximum achievable classification.

There is a difference in definitions used in the studies in relation to the specialisation of the gynaecologist, and nature and volume of the hospital, making comparison of studies difficult.
Three studies only mention the involvement of a gynaecological oncologist (Carney 2002[71], Chan 2007[14], Earle 2006[66]), and the actual surgeon is therefore not included in evaluation of the effect of the specialisation of the gynaecologist on the prognosis. Because the local organisation of health care plays a role in the answer to this question, studies with Dutch data are seen as more important in answering the abovementioned questions. In relation to published data, this applies to two cohort studies (Vernooij 2008[79] en Engelen 2006[68]). The first study is a large Dutch cohort that examined the effect of the hospital on total survival, while the second study studied the effect on total survival for both the specialisation of the gynaecologist and the type of hospital but in only one region. Recent data for the entire Dutch situation, both for the type of hospital and the specialisation of the gynaecologist, are available but have not yet been published and are therefore not yet incorporated in the results tables.

All articles are summarised in evidence tables.

Appendix 25 shows the effect of the gynaecologist on total survival. This effect was evaluated in two different ways: whether the gynaecologist was recognised as subspecialist and/or the number of interventions per year per gynaecologist.
In relation to recognition as subspecialist, two studies found a positive effect on survival (Engelen 2006[68] en Chan 2007[14]). In three studies, a positive effect was only seen with advanced disease (Junor 1999[70], Carney 2002[71] en Paulsen 2006[73]). In three studies, no positive effect was seen in any subanalyses (Shylasree 2006[74], Vernooij 2008[79]; Grossi 2002[69]). A note must be made for the study by Grossi (2002[69]) however: this study corrects for outcome of the surgery while this is actually a plausible reason that differences in survival exist between treating physicians. Adding this factor to the multivariable analysis leads to an unjust overcorrection.
In terms of the influence of the number of interventions per gynaecologist, it is noticeable that a significant difference is found in the Dutch study (Vernooij 2008[79]) that therefore did not appear to be related to the recognition as subspecialist. Another study (Woodman 1997[80]) did not find a significant difference.
Appendix 27 shows the effect of the gynaecologist on the overall survival, in which the effect is measured in relation to a general surgeon. Both studies find a significant difference in survival in favour of the gynaecologist. However, this situation almost never occurs in the Netherlands. Appendix 28 shows the effect of the hospital on survival; however, different definitions of a specialised hospital were used. While not always explicitly mentioned, the effect of the medical oncologist has also been researched in these analyses.
No effect was observed in two studies in relation to volume (Stockton 2000[75] en Elit 2002[67]). However, in one of these studies a positive effect was seen for hospitals with a radiotherapy and oncology unit in comparison to hospitals without these departments. In the three remaining studies in which a positive effect was seen, two studies only used advanced disease as inclusion criterion (Tingulstad 2003[77] en Paulsen 2006[73]) and one study included all stages (Oberaigner 2006[72], Vernooij 2008[79]). In the Dutch study on the effect of hospital specialisation on survival of ovarian carcinoma patients, the greatest effect was found in the group of patients with stage I-IIb disease (Vernooij 2008[79]).

Conclusions:
It is plausible that patients with an advanced ovarian carcinoma who are treated in a specialised hospital have a better survival.
Level 2 B Wolfe 1997[78], Tingulstad 2003[77], Paulsen 2006[73], Oberaigner 2006[72], Vernooij 2008[79]

It is plausible that patients with an advanced EOC who are operated on by a gynaecological oncologist have a better chance of survival than when they are operated on by a general gynaecologist.
Level 2 B Junor 1999[70], Paulsen 2006[73], Engelen 2006[68], Chan 2007[14]

There are indications that the number of medical oncologists per hospital influences the prognosis of patients with an advanced EOC.
Level 3 C Vernooij 2008[79]

The committee is of the opinion that every hospital should function within a regional collaboration with a

regular multidisciplinary oncological consultation.
Level 4 D Committee

Considerations:
A direct relationship has not been found between survival and specialisation of the gynaecologist and/or hospital in early-stage EOC. In saying this, it must be noted that patients have had adjuvant chemotherapy in most studies. In the Netherlands, in accordance with the guideline, adequate staging will not be followed by adjuvant chemotherapy. In this situation, complete staging is of vital importance because it will result in the detection of occult metastasis in a large percentage of patients which by means of stage migration will result in adjuvant chemotherapy and associated improvement in prognosis.
A conclusion cannot yet be drawn from available data in relation to the influence of specialisation and/or remaining treatments and diagnostics, such as the (additional) treatment with chemotherapy and the pathologic evaluation. However, if referral to a centre takes place, it is possible that these aspects will be of influence.

TNM/FIGO classification

Literature review:
FIGO classification of ovarian carcinoma

TNM	Stage	FIGO
Tx		staging not possible
T0		no primary tumour
T1	stage I	tumour is confined to the ovaries
T1a	stage IA	only one ovary is affected by the tumour, the ovary capsule is intact, malignant cells are not detected in ascites[1] or peritoneal washings, no tumour is detected on the surface of the ovary
T1b	stage IB	both ovaries are affected by the tumour, the ovary capsule is intact, malignant cells are not detected in ascites[1] or peritoneal washings, no tumour is detected on the surface of the ovaries
T1c	stage IC	the tumour is limited to one or both ovaries, with the ovary capsule ruptured, and/or the tumour is detected on the ovary surface, and/or positive malignant cells are detected in the ascites or peritoneal washings
T2a	stage IIA	the tumour has extended into the uterus or the fallopian tubes, malignant cells are not detected in ascites[1] or peritoneal washings
T2b	stage IIB	the tumour has extended to another organ in the lesser pelvis, malignant cells are not detected in ascites[1] or peritoneal washings
T2c	stage IIC	stage IIA or IIB and malignant cells are detected in the ascites or peritoneal washings
T3	stage III	histologically confirmed peritoneal metastasis outside the lesser pelvis and/or regional lymph node metastasis
T3a	stage IIIA	microscopic peritoneal metastasis beyond the pelvis
T3b	stage IIIB	macroscopic peritoneal metastasis beyond the lesser pelvis 2 cm or less in greatest dimension (diameter of separate tumour nodules)
T3c	stage IIIC	peritoneal metastasis beyond the lesser pelvis >2 cm in greatest dimension (diameter of separate tumour nodules) and/or regional lymph nodes metastasis
T4	stage IV	distant metastasis beyond the peritoneal cavity and regional lymph nodes

[1] FIGO defines ascites as the accumulation of excess peritoneal fluid containing malignant cells.
Liver capsule metastasis is a peritoneal metastasis, a T3/FIGO stage III.
Liver parenchymal metastasis is an M1, FIGO stage IV.
Pleural fluid must contain positive tumour cells for an M1/FIGO IV.

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Appendices

1. Working group members
Working group members

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3. Clinical questions

Diagnosis	
1.	Can imaging diagnostics be helpful to estimate pre-operatively the chance of obtaining an optimal debulking (residual tumour < 1 cm)? In patients with an advanced stage ovarian cancer? If yes, under which conditions (echo, CT, MRI)?
2.	What is the definition of lymph node sampling in the case of a clinically early-stage ovarian carcinoma and does a complete pelvic and paraaortic lymphadenectomy, in comparison with an adequate lymph node sampling lead to an improved prognosis?
treatment	
3.	What is the optimal treatment schedule for early-stage ovarian carcinoma? • Does adjuvant chemotherapy after incomplete staging lead to an improved prognosis? • If yes, what is the optimal chemotherapy schedule (paclitaxel/carboplatin)
advanced ovarian carcinoma	
4.	Does intraperitoneal chemotherapy in the treatment of advanced ovarian carcinoma lead to an improved prognosis?
5.	Which treatment is preferred in the case of advanced disease: induction chemotherapy with intervention surgery or primary debulking followed by chemotherapy?
recurrent ovarian carcinoma	
6.	Does cytoreductive surgery for recurrent ovarian carcinoma lead to an improved prognosis? If yes, under what conditions?
Follow Up	
7.	Does early (and asymptomatic) detection of recurrent ovarian carcinoma using CA 125 determination lead to an eventual extension in survival and what is the influence of this on the well-being (quality of life) of a patient?
psychosocial care	
8.	Does structural guidance by a specialised psychosocial care provider (sexologist, social worker, psychologist, nurse specialist in oncology, nutritionist, and spiritual care provider) lead to an improved quality of life with patients during and after treatment?
Organisation	
9.	Does concentration and/or specialisation lead to improved care in the treatment of patients with ovarian carcinoma? • Does the surgeon and location (nature of the hospital) contribute to the prognosis of a patient with an early and/or advanced stage ovarian carcinoma? • Does the experience of the medical oncologist and location (nature of the hospital) contribute to the prognosis of a patient with an ovarian carcinoma? • Does structural regional consultation lead to an improved prognosis for the patient?

4. Composition of the working group

Composition of the working group

A big part of the working group members are representatives from medical professionals and were authorised for there input. In composing the working group, consideration was given whenever possible to the geographic distribution of working group members and a balanced representation of various disciplines. A delegation of the V&VN (Verpleegkundigen en Verzorgenden Nederland) and Stichting Olijf (patiënten vereniging gynaecologische kanker) where also part of the working group.

5. Conflict of interest

Conflict of interest

All working group members have declared they have acted independently during the guideline process.

6. Wetenschappelijke onderbouwing
The recommendations in this guideline are based on evidence from published scientific research, where possible. Relevant articles were located by conducting systematic search actions by an information specialist in Cochrane Library, Medline, Embase and Cinahl and f nessecary in Psychinfo. The articles were selected on the basis of the following criteria: English, German, French or Dutch publications. There was searched from 1996 until juni 2008.

Terms used for patientpopulation where: neoplasms / cancer,/ tumor/ tumour/ carcinoma/ malignancy, combined with ovar*.

Vraag 1. radiography/ MRI / CT/ ultrasonography/ pre-operative, in combinatie met een van de volgende termen: surgery/ debulking/ treatment outcome/ sensitivity/ specificity/ prognosis/ prediction/ staging

Vraag 2. lymph-nodes/ lymph-node-excision/ lymphadenectomy/ lymph node palpation/ lymph node examination/ lymphatic-metastasis

Vraag 3. stage or FIGO in combinatie met I or II or IA or I-A or IB or I-B or IC or I-C or IIA or II-A or early or local or regional/ neoplasm-Staging Deze termen werden gecombineerd met chemotherapy-adjuvant/ antineoplastic-agents/ antineoplastic-combined-chemotherapy-protocols/ carboplatin/ paclitaxel/ taxoids/ drug-administration-schedule/ cycle* or dos* or course* or schedule gecombineerd met de volgende termen : survival-rate/ mortality/ cause-of-death/ survival-analysis/ disease-free-survival/ prognosis-/ recurrence/ follow up/ prediction

Vraag 4. antineoplastic-combined-chemotherapy-protocols/ antineoplastic-protocols/ chemotherapy-adjuvant/ combined-modality-therapy/ neoadjuvant-therapy/ paclitaxel/ cisplatin/ cyclophosphamide/ carboplatin/ injections-intraperitoneal/ intracavitar*/ intraperitonea* /infusions-parenteral

Vraag 5. antineoplastic/ combined-modality-therapy/ neoadjuvant / cisplatin/ taxo*/ carboplatin/ neoadjuvant/ primary chemotherapy/ induction chemotherapy, in combinatie met surgery / debulk* / cytoreduct*

Vraag 6 neoplasm-recurrence-local/ neoplasm-residual/ recurren*/ residual/ relaps/ ovarian-neoplasms surgery/ secondary operation/ secondary surg*/ secondary treatm*/ secondary reoperation/ secondary cytoreduct/ secondary debulking. Studies waarbij de combinatie met intraperitoneale hyperthermie werd bestudeerd of waarbij geen therapeutische maar palliatieve chirurgische ingreep plaatsvond werden uitgesloten.

Vraag 7 CA-125-Antigen / tumor-markers-biological / CA?125/ ca 125/ cancer antigen/ tumo(u)r marker/ serial monitoring/ assessing follow up/ follow-up studies / follow-up / re-evaluated/ monitoring recurr* Deze termen werden gecombineerd met: neoplasm-residual/ recurren* / residual / relaps/ longitudinal-studies physician's-practice-pattern/ quality-of-life / time-factors / patient-satisfaction

Vraag 8. psychosocial-Care/ Rehabilitation-Psychosocial/ Community-Reintegration/ Support-Psychosocial/ Nursing-Care-Plans/ Social-Skills/ Psychology-Social/ psychosocial intervention/ Psychosocial-Factors/ Advanced-Nursing-Practice/ psychiatry/ psychology/ social-psychology/ mental-health-care/ psychiatric-nursing/ mental-health-service/ empathy/ doctor-nurse-relation/ doctor-patient-relation/ mental-compliance/ nurse-patient-relationship/ social-network/ trust/ patient-attitude/ community-health-nursing/ nursing-care/ Nursing-Process/ Adaptation-Psychological/ Social-Support/ nursing/ psychology/ Health-Personnel/ Community-Health-Aides/ Nurses'-Aides/ Health-Educators/ Nursing-Staff/ Empathy-, Needs-Assessment/ Motivation-/ Intention-, Power-Psychology, Models-Nursing/ social worker/ spiritual worker/ imam/ pastor/ Religion/ Spirituality-/ Sexuality/ Women's-Health, gecombineerd met de term quality of life.

Vraag 9. Medical-Oncology/ Internal-Medicine/ Specialties/ Physicians/ Hospitalists/ Hospitals/ Academic-Medical-Centers/ Interdisciplinary-Communication/ Patient-Centered-Care/ Patient-Care-Team/ Health-Care-Reform/ Physician's-Practice-Patterns/ gynaecologist/ gynaecologist/ oncologist / specialist/ hospital/ clinic/ center/ multidisciplinary team/ multidiscplinary care/ joint clinic/ joint hospital/ joint centre/ Professional-Competence/ caseload/ workload/ volume/ expert*, gecombineerd met de termen Survival/ Mortality/ Survival-Rate/ Treatment-Outcome

Belangrijke selectiecriteria hierbij waren: vergelijkend onderzoek met hoge bewijskracht zoals meta-analyses, systematische reviews, randomized controlled trials (RCT's) en controlled trials (CT's). Waar deze niet voorhanden waren werd verder gezocht naar vergelijkend cohort onderzoek, vergelijkende patiëntcontrole studies of niet vergelijkend onderzoek.
De kwaliteit van deze artikelen werd door de werkgroepleden beoordeeld aan de hand van ‘evidencebased richtlijnontwikkeling' (EBRO) -beoordelingsformulieren. Artikelen van matige of slechte kwaliteit werden uitgesloten. Na deze selectie bleven de artikelen over die als onderbouwing bij de verschillende conclusies in de richtlijn staan vermeld in de evidencetabellen. De geselecteerde artikelen zijn vervolgens gegradeerd naar de mate van bewijs, waarbij onderstaande indeling is gebruikt. De mate van bewijskracht en niveau van bewijs zijn in de conclusies van de verschillende hoofdstukken weergegeven. De belangrijkste literatuur waarop de conclusies zijn gebaseerd is daarbij vermeld.

Indeling van methodologische kwaliteit van individuele studies

	Interventie	**Diagnostisch accuratesse onderzoek**	**Schade of bijwerkingen, etiologie, prognose***
A1	Systematische review van tenminste twee onafhankelijk van elkaar uitgevoerde onderzoeken van A2-niveau		
A2	Gerandomiseerd dubbelblind ver−gelijkend klinisch onderzoek van goede kwaliteit van voldoende omvang	Onderzoek ten opzichte van een referentietest (een ‘gouden standaard') met tevoren gedefinieerde afkapwaarden en onafhankelijke beoordeling van de resultaten van test en gouden standaard, betreffende een voldoende grote serie van opeenvolgende patiënten die allen de index- en referentietest hebben gehad	Prospectief cohort onderzoek van voldoende omvang en follow-up, waarbij adequaat gecontroleerd is voor ‘confounding' en selectieve follow-up voldoende is uitgesloten.
B	Vergelijkend onderzoek, maar niet met alle kenmerken als genoemd onder A2 (hieronder valt ook patiëntcontrole onderzoek, cohort-onderzoek)	Onderzoek ten opzichte van een referentietest, maar niet met alle kenmerken die onder A2 zijn genoemd	Prospectief cohort onderzoek, maar niet met alle kenmerken als genoemd onder A2 of retrospectief cohort onderzoek of patiëntcontrole onderzoek
C	Niet-vergelijkend onderzoek		
D	Mening van deskundigen		

* Deze classificatie is alleen van toepassing in situaties waarin om ethische of andere redenen gecontroleerde trials niet mogelijk zijn. Zijn die wel mogelijk dan geldt de classificatie voor interventies.

Niveau van conclusies

	Conclusie gebaseerd op
1	Onderzoek van niveau A1 of tenminste 2 onafhankelijk van elkaar uitgevoerde onderzoeken van niveau A2, met consistent resultaat
2	1 onderzoek van niveau A2 of tenminste 2 onafhankelijk van elkaar uitgevoerde onderzoeken van niveau B
3	1 onderzoek van niveau B of C
4	Mening van deskundigen

7. Authorisation
Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG)
Dutch association for obstetrics and gynaecology

Nederlands Instituut van Psychologen (NIP)

Dutch professional association of psychologists

Nederlandse Internisten Vereniging (NIV)
Dutch association of specialists for internal diseases

Nederlandse Vereniging voor Medische Oncologie (NVMO)
Dutch association for medical oncology

Nederlandse Vereniging voor Psychosociale Oncologie (NVPO)
Dutch Society for Psychosocial Oncology

Verpleegkundigen en Verzorgenden Nederland (V&VN), afdeling oncologie
Dutch Nurses' Association

8. Validity
The period of validity of the guideline (maximum of 5 years) is being monitored by the VIKC programme office. For various reasons, it may be necessary to revise the guideline earlier than intended. Sections of the guideline will be amended in the interim, when required.

11. Ownership
The owner of the guideline must be able to show that the guideline has been realised in a careful manner and using the required expertise. By owner, we are referring to the professional associations authorising the guideline. The VIKC s financialy responsable and takes care of managing and releasing the guideline.

12. Legal implications

The guideline contains recommendations of a general nature. It is possible that these recommendations are not applicable to an individual case. Facts or circumstances may in fact arise that require deviation from the guideline in the interest of the patient. When there is deviation from this guideline however, this must be substantiated in document format. The applicability and application of the guideline in the field is the responsibility of the treating physician.

14. AGREE
The AGREE Instrument consists of 23 items organised in six domains. Each domain covers a separate dimension of guideline quality, namely:

- **Scope and goal** is concerned with the overall aim of the guideline, the specific clinical questions answered by the guideline and the target patient population.
- **Stakeholder involvement** focuses on the extent to which the guideline represents the views of its intended users.
- **Methodology** relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations and to update them.
- **Clarity and presentation** deals with the language and format of the guideline.
- **Applicability** pertains to the likely organisational, behavioural and financial implications of applying the guideline.
- **Editorial independence** is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline working group.

22. tabel 2

Tabel 2 : Percentage "adequate debulking" met bijbehorend resultaat (overleving)

click here .

23. tabel 3

Predictieve parameters voor wat betreft kans op complete debulking

click here for tabel.

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Legal implications
The guideline consists of general recommendations. It is possible that these recommendations are not applicable to an individual patient. Additional facts or circumstances may arise making it desirable to deviate from the guideline. Deviation from the guideline should be justified and documented. In practice, the treating physician is responsible for determining the applicability of the guideline and the application of the guideline itself.

Holdership of the guideline
The holder of the guideline must be able to demonstrate that the guideline has been developed carefully and with necessary expertise. By the holder is meant the associations of professionals who authorized the guideline.

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