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This document is available on the website of the Belgian Health Care Knowledge Centre.

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
ADNEX	Assessment of Different NEoplasias in the adneXa
AUC	Area under the curve
BMI	Body mass index
BRAF	v-Raf murine sarcoma viral oncogene homolog B
cq	*Casu quo*
CT	Computed tomography
DTA	Diagnostic test accuracy
DW-MRI	Diffusion-Weighted Magnetic Resonance Imaging
ECOG	Eastern Cooperative Oncology Group
ErbB	Erythroblastic leukemia viral oncogene homolog
FIGO	International Federation of Gynaecology and Obstetrics
FN	False negative
FP	False positive
FS	Frozen section
GDG	Guideline development group
HIPEC	Hyperthermic intraperitoneal chemotherapy
HTA	Health technology assessment
IOTA	International Ovarian Tumour Analysis
IQR	Interquartile range
ITT	Intention to treat
KCE	Belgian Healthcare Knowledge Centre
KRAS	V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog
LR2	Logistic regression 2
LVSI	Lymphovascular space involvement
MA	Meta-analysis
MOC/COM	Multidisciplinary Oncological Consultation / Consultation Oncologique Multidisciplinaire
MRI	Magnetic resonance imaging

OS	Overall survival
^{18}F-FDG PET	Fludeoxyglucose F 18 positron emission tomography
PFS	Progression-free survival
PS	Performance status
QoE	Quality of evidence
QoL	Quality of life
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized controlled trial
RD	Residual disease
RMI	Risk of Malignancy
ROC	Receiver Operating Characteristic
SEER	Surveillance, Epidemiology and End Results
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
TN	True negative
TP	True positive
TP53	Tumour protein p53
UICC	International Union Against Cancer

■ SCIENTIFIC REPORT

1 INTRODUCTION

1.1 Background

In developed countries, ovarian cancer is the 2nd most frequent gynaecological tumour and the 6th most frequent cause of cancer related death in women.[1] Annually, almost 900 women are diagnosed and treated for this disease in Belgium. Survival is generally poor, with a 5-year relative survival of 46.9%, as the majority of ovarian cancers is diagnosed in an advanced stage (65% stage III or IV). Five-year relative survival for stage IV is as low as 19%.[2]

Approximately 90% of ovarian malignant tumours origin in the surface layer covering the ovary, called epithelial ovarian cancer. It has been suggested that the majority of assumed ovarian cancers originate from the Fallopian tube epithelium rather than from the ovary itself. In the advanced stages, it is difficult to distinguish tumours that started in the ovary, Fallopian tube or the peritoneal surface. The differential diagnosis is based on agreed morphological criteria. Although there may be behavioural and prognostic differences, therapeutic approach has been similar historically.[3]

'Epithelial' ovarian cancer has several histological subtypes such as serous, mucinous, clear cell and endometrioid ovarian cancer. Recent insights in molecular biology and tumour genetics identify two main groups of ovarian tumours: type I ovarian cancer including low-grade serous, low-grade endometrioid, clear cell, mucinous and transitional (Brenner) carcinomas and type II tumours including high-grade serous carcinomas, high-grade endometrioid tumours, undifferentiated tumours and malignant mixed mesodermal tumours.[4] These recent insights are implemented in the 4th edition (2014) of the WHO classification of tumours of the female reproductive organs.[5, 6]

Type I tumours are thought to develop in a slow, step-wise fashion originating in adenofibromas or cystadenomas. They usually present at a low stage. Typical specific mutations that are displayed in the different histological cell types are e.g. KRAS, BRAF and ERBB2 mutations in low-grade serous tumours and CTNNB1, PTEN and PIK3CA mutations in low-grade endometrioid carcinomas. TP53 mutations are rare in type I tumours.[4]

Type II tumours behave more aggressively and are often diagnosed when the disease is already at an advanced stage. They are genetically unstable and have a very high frequency of TP53 mutations. It is hypothesized that type II tumours originate from high-grade intraepithelial lesions in the Fallopian tube.[4]

In this report, we focus on epithelial ovarian cancer, but studies that also include patients with Fallopian tube or primary peritoneal cancer are also taken into consideration. Issues specifically for patients with Fallopian tube cancer or primary peritoneal cancer are not included however.

Staging of ovarian is recorded following the TNM principles of the International Union Against Cancer (UICC) and more typically, the overall stage as proposed by the International Federation of Gynecology and Obstetrics (FIGO) is used.[7] FIGO staging for ovarian cancer is summarized inTable 1. Ovarian cancer typically spreads to the adjacent genital organs and pelvic peritoneum, pelvic and para-aortic lymph nodes, omentum, organ and peritoneal surfaces in the upper abdomen and thoracic pleura.

Primary treatment is based on the combination of surgical staging and cytoreduction and systemic treatment. Since the late nineties, paclitaxel-carboplatin combination therapy is considered as the preferrable option.[8] More recently, targeted therapies such as bevacizumab have emerged, both in first-line therapy and recurrent disease. The role of bevacizumab in ovarian cancer treatment will be investigated in a separate KCE report.

Despite a high response rate to first-line therapy, recurrence rate is high. Treatment of recurrent disease is mainly based on chemotherapy but the role of debulking surgery is emerging from ongoing research. Therapeutic options and prognosis of recurrent disease highly depend on the time lapse between the end of treatment and the occurrence of recurrent disease (platinum-free interval).

Table 1 – Staging of ovarian tumours according to FIGO 2014 and UICC 7th edition

FIGO staging	TNM	Ovary
I	**T1**	**Limited to the ovaries**
IA	T1a	One ovary, capsule intact
IB	T1b	Both ovaries, capsule intact
IC	T1c	Capsule ruptured, tumour on surface, malignant cells in ascites or peritoneal washings FIGO IC1: Surgical spill FIGO IC2: Capsule ruptured before surgery or tumour on ovarian surface FIGO IC3: Malignant cells in the ascites or peritoneal washings
II	**T2**	**Pelvic extension below pelvic brim or primary peritoneal carcinoma**
IIA	T2a	Extension and/or implants on uterus, Fallopian tube(s), ovary(ies)
IIB	T2b	Extension and/or implants on other pelvic tissues
	T2c	Malignant cells in ascites or peritoneal washings
III	**T3 and/or N1**	**Peritoneal metastasis beyond pelvis and/or regional lymph node metastasis**

FIGO staging	TNM	Ovary

IIIA1	T1/T2-N1	Positive retroperitoneal lymph nodes only
		    IIIA1(i): metastasis up to 10mm in greatest dimension
		    IIIA1(ii): metastasis more than 10mm in greatest dimension

IIIA2	T3a	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
IIIB	T3b	Macroscopic peritoneal metastasis ≤ 2cm beyond the pelvis, with or without positive retroperitoneal lymph nodes
IIIC	T3c	Peritoneal metastasis > 2cm beyond the pelvis, with or without positive retroperitoneal lymph nodes
IV	**M1**	**Distant metastasis (excludes peritoneal metastasis)** FIGO IVA: Pleural effusion positive cytology FIGO IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity

1.2   The need for a guideline

Due to the complexity of its treatment and the lack of one comprehensive guideline in our country, a variation in the quality of care and survival is suspected. Only a strict guideline followed by the development and the measurement of quality indicators can improve the care for ovarian cancer patients.

1.3   Scope

This guideline covers:

- Carcinoma of the ovary, Fallopian tube and primary peritoneal carcinoma
- Epithelial carcinoma, e.g. serous, mucinous, clear cell or endometrioid histology and carcinosarcoma.
- Borderline and invasive disease
- Diagnosis and first-line treatment
- Follow-up after treatment

This guideline does not address:

- Malignancies of non-epithelial origin, such as germ cell tumours and sex cord stromal tumours
- Screening
- Treatment of recurrent disease
- Palliative interventions

1.4   Remit of the guideline

1.4.1   Overall objectives

This guideline provides recommendations based on current scientific evidence for the diagnosis, treatment and follow-up of epithelial ovarian, Fallopian tube and primary peritoneal cancer. Clinicians are encouraged to interpret these recommendations in the context of the individual patient situation and her own values and preferences. Furthermore, since good quality evidence on optimal treatment options is lacking, patient participation in clinical trials is encouraged as much as possible.

The guideline is based on clinical evidence and may not always be in line with the current criteria for RIZIV – INAMI reimbursement of diagnostic and therapeutic interventions. The RIZIV – INAMI may consider adaptation of reimbursement/funding criteria based on these guidelines.

1.4.2   Multidisciplinary approach

In this report we focused on the effectiveness of specific (medical) interventions, without taking into account the organization of health services. In clinical practice, a multidisciplinary approach by different health care professionals is encouraged.

1.4.3   Patient-centred care

The choice of a treatment should not only consider medical aspects but also patient preferences. Patients should be well and timely informed about all treatment options and the advantages and disadvantages they offer. Indeed, patient representatives involved in the development of this report emphasized the need for patient information. This information should be clear and repeated over time. All questions and concerns of the individual patients should be sufficiently addressed.

For young patients diagnosed with ovarian cancer, consequences of the therapy for fertility and possible fertility spearing measures should be discussed in advance. Patients suffering from advanced disease should have the opportunity to discuss benefit risk balance of possible treatments in terms of survival and quality of life and their personal values and preferences. Also more emphasis should be put on potential adverse events related to each treatment.

Furthermore, patients with ovarian cancer and their family and carers should be offered dedicated psychosocial support on a continuous basis.

Detection of familial predisposition for ovarian cancer and possible BRCA germ line mutations is important for preventive medicine and family counselling. Furthermore, the presence of a BRCA mutation, especially in high grade serous disease, can guide treatment decisions regarding the use of PARP-inhibitors for recurrent disease. We refer to KCE report 236 for further details on indications for oncogenetic testing.[9]

1.4.4 Target users of the guideline

This guideline is intended to be used by all care providers involved in the management of ovarian, Fallopian tube or primary epithelial cancer, including – but not exclusively- gynaecologists and gynaecological oncologists working on a secondary or tertiary care level, medical oncologists, radiation oncologists, oncology nurses, radiologists, nuclear medicine physicians, surgeons and general practitioners. It can also be of interest for women with ovarian cancer and their family, hospital managers and policy makers.

1.5 Statement of intent

Clinical Guidelines are designed to improve the quality of health care and decrease the use of unnecessary or harmful interventions. This guideline has been developed by clinicians and researchers for use within the Belgian healthcare context. It provides advice regarding the care and management of epithelial ovarian, Fallopian tube and primary peritoneal cancer.

The recommendations are not intended to indicate an exclusive course of action or to serve as a standard of care. Standards of care are determined on the basis of all the available clinical data for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Variations, which take into account individual circumstances, clinical judgement and patient choice, may also be appropriate. The information in this guideline is not a substitute for proper diagnosis, treatment or the provision of advice by an appropriate health professional. It is advised, however, that significant deviations from the national guideline are fully documented in the patient's file at the time the relevant decision is taken.

1.6 Funding and declaration of interest

KCE is a federal institution funded for the largest part by INAMI – RIZIV, but also by the Federal Public Service of Health, Food chain Safety and Environment, and the Federal Public Service of Social Security.

The development of clinical practice guidelines is part of the legal mission of the KCE. Although the development of guidelines is paid by KCE's budget, the sole mission of the KCE is providing scientifically valid information. KCE has no interest in companies (commercial or non-commercial i.e. hospitals and universities), associations (e.g. professional associations, unions), individuals or organisations (e.g. lobby groups) that could be positively or negatively affected (financially or in any other way) by the implementation of these guidelines. All clinicians involved in the Guideline Development Group (GDG) or the peer-review process completed a declaration of interest form. Information on potential conflicts of interest is published in the colophon of this report. All members of the KCE Expert Team make yearly declarations of interest and further details of these are available upon request.

2 METHODOLOGY

2.1 Introduction

The KCE guideline is produced according to highly codified principles, based on scientific information regularly updated from the international literature. This guideline was developed using a standard methodology based on a systematic review of the evidence. Further details about KCE and the guideline development methodology are available at https://kce.fgov.be/content/kce-processes.

Several steps were followed to elaborate this guideline. Firstly, clinical questions were developed and the inclusion and exclusion criteria were defined in collaboration with the members of the Guideline Development Group. Secondly a systematic literature review was performed and the identified body of evidence was critically appraised. Thirdly, on the basis of the results of the literature review, recommendations were formulated and graded according to the GRADE approach.

2.2 The Guideline Development Group (GDG)

This guideline was developed as a result of a collaboration between representatives of health professionals involved in the care for women with (suspected) ovarian cancer (GDG) and KCE.

The composition of the GDG is documented in Appendix.

The roles assigned to the GDG were:

- To define the clinical questions, in close collaboration with the KCE Expert Team and stakeholders;
- To identify critical and important outcomes;
- To provide feedback on the selection of studies and identify further relevant manuscripts which may have been missed;
- To provide feedback on the content of the guideline;
- To provide judgement about indirectness of evidence;
- To provide feedback on the draft recommendations;
- To address additional concerns to be reported under a section on 'other considerations'.

2.3 General approach

The Belgian guideline on the diagnosis, treatment and follow-up of ovarian cancer, developed by the College of Oncology in 2010[10] and the recent evidence-based guideline from the Scottish Intercollegiate Guidelines Network (SIGN),[8] served as a starting point to determine the research questions for this guideline.

A longlist with possible diagnostic and therapeutic interventions, covering the following topics: screening, diagnosis, staging, surgery, chemotherapy and targeted therapy, follow-up and management of malignant bowel obstruction, was compiled based on these guidelines, supplemented with other possible topics found in the recent scientific literature and suggestions from the participants.

Members of the GDG and representatives of professional organizations were asked to select research questions from this longlist that were considered priority to be discussed in this guideline because practice has recently changed, there is ongoing debate in the clinical community or there is a large variability in clinical practice.

The final scope was defined during a stakeholder meeting held at KCE on October 6th, 2014. Stakeholders decided to focus on newly-diagnosed ovarian cancer as the quality of first-line treatment is of utmost importance for patient important outcomes.

2.4 Clinical research questions

All clinical questions were translated into in- and exclusion criteria using the PICO (Participants–Interventions–Comparator–Outcomes) framework. Important outcomes were determined for each question. Details can be found in appendix.

The following priority research questions are discussed in this guideline:

- Does the use of a Risk of Malignancy Index to guide treatment decisions result in better outcomes for patients with a (complex) ovarian mass without signs of advanced disease?
- Does the use of intraoperative frozen section to guide treatment decisions result in better outcomes for patients with (presumed) early-stage ovarian cancer?

- In which patients with borderline or (micro-)invasive (presumed) early-stage ovarian cancer can systematic pelvic and para-aortic lymphadenectomy be omitted?

- Which patients with borderline or (micro-)invasive early-stage ovarian cancer may not benefit from adjuvant chemotherapy?

- What is the effectiveness and safety of laparoscopy compared to laparotomy for the treatment of early-stage ovarian cancer and/or staging?

- Does the use of a PET-CT/laparoscopy/ (diffusion) MRI to predict the end-result of surgery result in better outcomes for patients with stage IIIc-IV ovarian cancer?

- Does complete debulking of stage IIIc-IV ovarian cancer result in improved prognosis compared to debulking to end result macroscopic disease < 1cm or > 1cm?

- What is the effectiveness and safety of neo-adjuvant chemotherapy and interval debulking compared to upfront debulking followed by chemotherapy?

- What is the effectiveness of front-line intra-peritoneal carboplatin-paclitaxel chemotherapy compared to intravenous carboplatin-paclitaxel treatment?

- What is the effectiveness of front-line dose-dense carboplatin-paclitaxel chemotherapy compared to conventional (21 day) carboplatin-paclitaxel treatment?

- What is the clinical effectiveness of routine Ca 125 measurements during follow-up of ovarian cancer patients?

Additionally, the literature was searched for patient values and preferences when treated for ovarian cancer.

The use of bevacizumab for patients with ovarian cancer will be discussed in a separate health technology assessment (HTA) project.

2.5 Literature search and study selection

2.5.1 Study design

A systematic literature review was performed by searching for systematic reviews (including meta-analyses or not), randomized controlled trials (RCTs), observational (comparative) studies and/or diagnostic accuracy studies, as specified for each research question in appendix.

An iterative approach was followed:

- First, a search for recently published (from January 2010 onwards) systematic reviews and meta-analyses (SR/MA) was performed;

- Second, the selected evidence synthesis was updated by a search for all relevant primary studies (RCTs and prospective studies) published after the search date of the selected SR/MA. If no systematic review was available, a search for primary studies was performed from inception.

The reference lists of included studies were checked for relevant publications that may have been missed. Information about ongoing studies was collected by searching the search portal of the WHO International Clinical Trial Registry Platform (http://www.who.int/ictrp/en/), and by contacting study authors and organisations. Members of the GDG were also consulted to identify relevant evidence that may have been missed during the search.

2.5.2 Databases and date limits

The following databases were searched for systematic reviews:

- The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database)

- Medline (including premedline)

- Embase

In addition, the review list of the Cochrane Gynaecological Cancer Group was browsed for relevant reviews.

The following databases were searched for primary studies:

- CENTRAL
- Medline (including premedline)
- Embase

A combination of appropriate MeSH terms and free text words was used. The PICOs and the search strategy corresponding to our research questions are documented in the Appendix.

2.5.3   Study selection

To be included, a systematic review had to:

- address at least one of the research questions;
- evaluate at least one of the selected (critical and important) outcomes;
- include RCTs, comparative observational studies or observational cohort or cross-sectional studies regarding Diagnostic test accuracy (DTA) (depending on the RQ);
- search MEDLINE and at least one other electronic database;
- include a risk of bias assessment of the three main quality items for RCTs (allocation concealment, blinding of the outcome assessor and completeness of follow up) and, if applicable, the main quality items for comparative observational studies (selection of the study cohorts (concurrent or not), comparability of the study arms, blinding of the outcome assessor and completeness of follow up) or the main quality items for DTA studies (patient selection, blinded assessment of index test and reference standard, partial or differential verification by the reference standard and inappropriate exclusions); the results thereof should have been reported for the individual studies.

If more than one systematic review was identified for a particular research question, the focus was on the most complete, recent systematic review.

To be included a primary study had to:

- be a randomised or quasi-randomised trial (RCTs), compare groups (comparative observational studies) or present DTA measures (depending on the RQ);

- address the patient populations, comparisons and at least one of the outcomes as described in the KCE research questions.
- evaluate at least one of the selected (critical and important) outcomes.

Study selection was performed by two researchers independently in two phases. Phase one consisted of screening the titles and abstracts of the retrieved studies and excluding studies for which it was obvious that they did not fulfill the inclusion criteria. Of the remaining studies (phase two), the full text was screened. If no full-text was available, the study was not taken into account. Studies published in a language other than English, Dutch, French or German were not included.

2.6   Quality appraisal

Each study was appraised for methodological quality by two researchers independently. Disagreements were resolved by discussion or with consultation of a third researcher in case of persisting disagreement.

The quality of systematic reviews was assessed by the use of AMSTAR (http://amstar.ca/Amstar_Checklist.php).[11]

For RCTs the Cochrane Collaboration's tool for assessing risk of bias was used.[12] The items 'Blinding of participants and personnel (performance bias)', 'Blinding of outcome assessment (detection bias)' and 'Incomplete outcome data (attrition bias)' were assessed for two groups of outcomes: objective outcomes (e.g. overall survival) and subjective outcomes (e.g. quality of life, adverse events) separately. In addition, for subgroup analyses of RCTs, critical appraisal was based on the methodology proposed by Sun et al.[13]

For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was used as well, but with the addition of two extra items that apply to potential bias due to the selection of participants: 'Concurrency of the intervention and comparator group' and 'Comparability of the intervention and comparator group'. For the first item low risk of bias will be assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias will be assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis (e.g. age, tumour type, stage, performance status).

The risk of bias of identified DTA studies was assessed by the QUADAS-2 tool.[14]

Case series were critically appraised following criteria suggested by Chambers et al.,[15] summarized in Table 2.

Table 2 – Criteria used for critical appraisal of case series

Criteria used for critical appraisal of case series
1. Were selection/eligibility criteria adequately reported?
2. Was the selected population representative of that seen in normal practice?
3. Was an appropriate measure of variability reported?
4. Was loss to follow-up reported or explained?
5. Were at least 90% of those included at baseline followed up?
6. Were patients recruited prospectively?
7. Were patients recruited consecutively?
8. Did the study report relevant prognostic factors?

2.7 Data extraction

Data extraction was performed by two researchers independently and entered in evidence tables using standard KCE-templates. Any disagreements were resolved by discussion or, if required, by a third party.

For each systematic review the following data were extracted: title and reference, funding sources, search date, databases being searched, number and types of included studies (RCT, comparative cohort study or other study type), details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics, details of the intervention and comparator groups that have been addressed in the review, results for the outcomes as defined in the various RQs, and limitations and other comments regarding the review.

For each primary study the following data were extracted: title, reference, type of study (RCT, comparative cohort study or other study type), source of funding, country and setting, sample size, duration and follow-up, details about the statistical analysis, eligibility criteria, exclusion criteria, number of participants, patient and disease characteristics (including baseline

comparability), details of the intervention and comparator (e.g. type, dose, duration, route of administration) or details of the index test(s) and reference standards, results, and limitations and other comments regarding the study. For observational studies the results that were adjusted for confounders were reported, if presented in the original study. Important confounders (prognostic factors) to be considered depend on the RQ, but may include (amongst others) age, tumour type, tumour stage, performance status.

2.8 Statistical analysis

For dichotomous outcomes the risk ratio (RR) was used as the measure of treatment effect and for continuous outcomes the mean difference or – if applicable – the standardised mean difference. For time to event data, the hazard ratio (HR) was used.

For comparative observational studies the measure of treatment effect that has been adjusted for confounders was extracted. For dichotomous outcomes this was – in most cases – either the adjusted odds ratio (OR) or the adjusted HR.

For all analyses the results of RCTs and comparative observational studies were analysed separately.[16] If results of both RCTs and comparative observational studies have to be processed for the same comparison and outcome, the same measure of treatment effect was calculated for both study types to enable easy comparison of the results. Meta-analyses were then presented in one forest plot by the use of subgroups according to study type.

Meta-analyses of RCTs were performed according to the guidelines described in the Cochrane Handbook[17] and by the use of Review Manager software (Review Manager 2014). Results of studies that were sufficiently clinically homogeneous, i.e. sufficiently similar with respect to the patients, interventions, outcomes and timing of the follow-up measurements (judged by the content experts) were combined by the use of a fixed-effect model. If the studies were statistically heterogeneous a random-effects model was used and – if sufficient studies available – heterogeneity was explored by subgroup analyses. Statistical heterogeneity was assessed by a combination of visual inspection of the forest plots, the Chi-square test for homogeneity (p-value set at 0.1 to increase the power of this test) and the I^2 statistic. The latter two statistics were interpreted in the light of the size of the studies included in the meta-analysis (e.g. if many large studies are

included that have clinically irrelevant different effect estimates, the Chi-square test will become significant (due to high power) and I^2 will approach 100%; in that case the results of the visual inspection will dominate the judgment of heterogeneity).

For comparative observational studies the generic inverse variance (GIV) method was used for meta-analysis.[17] For each study the adjusted effect estimates (RRs, ORs or HRs) were extracted and transformed to their natural logarithms (LN[RR], LN [OR] or LN[HR]). The log transformed effect measures and their standard error (SE) were entered in RevMan. If no SE was reported, the SE was derived from the 95%-confidence interval of the adjusted effect estimate or from the reported p-value (if at least two decimals had been reported).

If possible, all analyses were performed according to the intention-to-treat principle.

For observational DTA studies analyses were based on the 2 by 2 tables that cross-reference the results of the index test and the reference standard (sensitivity and specificity). Meta-analyses of DTA studies were performed according to the guidelines described in the (draft) Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.[17] Review Manager software was used to prepare forest plots of paired sensitivity and specificity of the included studies, the distribution of studies in the ROC-space and the graphical presentation of the results of the meta-analyses (Review Manager 2014), whereas the actual meta-analyses was done by the use of Stata, module Metandi (StataCorp 2007). Metandi includes random effects methods for meta-analysis of DTA studies in which overall sensitivity and specificity are jointly estimated, whilst taking account of the existing covariance of those two parameters and the existing heterogeneity between studies, which is the rule rather than the exception in meta-analyses of DTA studies.[17] From the summary estimates of sensitivity and specificity positive and negative predicted values were derived.

Studies that were clinically heterogeneous or did not present the data in sufficient detail to enable statistical pooling were summarised qualitatively.

2.9 Grading evidence

For each recommendation, we provided its strength and the quality of the supporting evidence.

According to GRADE, we classified the quality of evidence into 4 categories: high, moderate, low, and very low (iles. Table 3 and Table 4). The quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation. GRADE for guidelines was used, meaning that the evidence across all outcomes and across studies for a particular recommendation was assessed.

2.9.1 Therapeutic interventions

The following quality elements for intervention studies were evaluated: study limitations, inconsistency, indirectness, imprecision and publication bias.

For RCTs, quality rating was initially considered to be of high level (iles. Table 3 and Table 4). The rating was then downgraded if needed based on the judgement of the different quality elements. Each quality element considered to have serious or very serious risk of bias was rated down one or two levels respectively. Judgement of the overall confidence in the effect estimate was also taken into account. We considered confidence in estimates as a continuum and the final rating of confidence could differ from that suggested by each separate domain.

Observational studies were by default considered low level of evidence (iles.Table 3 and Table 4). However, the level of evidence of observational studies with no threats to validity can be upgraded for a number of reasons:

1. Large magnitude of effects;
2. All plausible confounders: all plausible confounding from observational studies or randomized trials may be working to reduce the demonstrated effect or increase the effect if no effect was observed;
3. Dose-response gradient: the presence of a dose-response gradient may increase our confidence in the findings of observational studies and thereby increase the quality of evidence.

The general principles used in this report to downgrade the quality rating are summarized in Table 5. Decisions on downgrading one or two levels were based on the judgement of the assessors. Reasons for (not) downgrading were summarized in the GRADE profiles.

Table 3 – A summary of the GRADE approach to grading the quality of evidence for each outcome

Source of body of evidence	Initial rating of quality of a body of evidence	Factors that may decrease the quality	Factors that may increase the quality	Final quality of a body of evidence
Randomized trials	High	1. Risk of bias 2. Inconsistency	1. Large effect 2. Dose-response	High (⊕⊕⊕⊕) Moderate (⊕⊕⊕⊖)
Observational studies	Low	3. Indirectness 4. Imprecision 5. Publication bias	3. All plausible residual confounding would reduce the demonstrated effect or would suggest a spurious effect if no effect was observed	Low (⊕⊕⊖⊖) Very low (⊕⊖⊖⊖)

Source: Guyatt GH, Oxman AD, Sultan S, Glasziou P, Akl EA, Alonso-Coello P, et al. GRADE guidelines: 9. Rating up the quality of evidence. J Clin Epidemiol. 2011;64(12):1311-6.

Table 4 – Levels of evidence according to the GRADE system

Quality level	Definition	Methodological Quality of Supporting Evidence
High	We are very confident that the true effect lies close to that of the estimate of the effect	RCTs without important limitations or overwhelming evidence from observational studies
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	RCTs with very important limitations or observational studies or case series
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect	

Source: Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol. 2011;64(4):401-6.

Table 5 – Downgrading the quality rating of evidence using GRADE

Quality element	Reasons for downgrading
Limitations	For each study reporting the selected outcome, possible risk of bias introduced by lack of allocation concealment, lack of blinding, lack of intention-to-treat analysis, loss of follow-up and selective outcome reporting were assessed. Additionally, other limitations such as stopping early for benefit and use of non-validated outcome measures were taken into consideration. Level of evidence was downgraded if studies were of sufficiently poor quality. Downgrading was omitted if studies with low risk of bias were available that lead to similar conclusions as the studies with a high risk of bias.
Inconsistency	Downgrading the level of evidence for inconsistency of results was considered in the following situations: point estimates vary widely across studies, confidence intervals show minimal or no overlap, the statistical test for heterogeneity shows a low p-value or the I^2 is large. If large variability in magnitude of effect remained unexplained, the quality of evidence was rated down.
Indirectness	Quality rating was downgraded for indirectness in case the trial population or the applied intervention differed significantly from the population or intervention of interest. Also, the use of surrogate outcomes could lead to downgrading. A third reason for downgrading for indirectness occurred when the studied interventions were not tested in a head-to-head comparison.
Imprecision	Evaluation of the imprecision of results was primarily based on <u>examination of the 95% CI</u>. Quality was rated down if clinical action would differ if the upper versus the lower boundary of the 95% CI represented the truth. In general, 95% CIs around relative effects were used for evaluation, except when the event rate was low in spite of a large sample size. To examine the 95% CIs, the clinical decision threshold (CDT) was defined. When the 95% CI crossed this clinical decision threshold, the quality level was rated down. A relative risk reduction (RRR) of 25% was defined as CDT by default and adapted if deemed appropriate e.g. in case of a low risk intervention. Even if 95% CIs appeared robust, level of evidence could be rated down because of fragility. To judge fragility of results, it is suggested to calculate the number of patients needed for an adequately powered (imaginary) single trial, also called the <u>optimal information size (OIS)</u>. If the total number of patients included in a systematic review was less than the calculated OIS, rating down for imprecision was considered. For calculations, a RRR of 25% was used, unless otherwise stated. When the OIS could not be calculated, a minimum of 300 events for binary outcomes and a minimum of 400 participants for continuous outcomes were used as a rule of thumb.
Reporting bias	Quality rating was downgraded for reporting bias if publication bias was suggested by analysis using funnel plots or searching of trial registries. Publication bias was also suspected if results came from small, positive industry-sponsored trials only.

2.9.2 Diagnostic test accuracy

For diagnostic questions, modified GRADE profiles were constructed. Methods for GRADEing the level of evidence for DTA studies are still under development. In this report, we applied methods described by Schünemann et al. in 2008[18] and in a more recent draft paper by Schünemann et al. (Schünemann, personal communication).

In summary, appropriate DTA studies were considered as high quality evidence, but the level of evidence could be downgraded based on the following considerations:

- Risk of bias was judged based on the selection process of the patients, the execution and independent interpretation of the index test and the reference standard, and the flow and timing of the patients.

- Indirectness was judged based on possible differences between the study populations and those for whom the recommendations are intended, possible differences between the diagnostic expertise of those applying the tests in the studies compared to the settings for which the recommendations are intended or, if applicable, the absence of direct comparison between tests (both are compared to a gold standard in different studies).
  Furthermore, as direct evidence about the impact on patient-important outcomes is often absent, accuracy studies typically provide low quality evidence due to indirectness of the outcomes (surrogate outcomes only).

- Inconsistency was assessed by examining the forest plots and the curves of sensitivity and specificity pairs in ROC space.

- Imprecision was judged considering the confidence intervals around the estimates of test accuracy.

- Publication bias was judged similar to therapeutic interventions.

2.9.3 Prognostic studies

For the evaluation of the level of evidence of prognostic and prediction studies, criteria proposed by the GRADE working group for rating confidence in estimates of event rates in broad categories of patients were used where appropriate.[19]

- Criteria for assessing the risk of bias included the definition and representativeness of the population, completeness of follow-up and objective and unbiased measurement of outcome.

- Inconsistency was judged taking into account the variability of point estimates, extent of overlap in confidence intervals and where point estimates lied in relation to decision threshold.

- Judgement of imprecision was based on the width of the 95% confidence interval around the pooled estimate and the position of the confidence interval with respect to a clinical decision threshold.

- To evaluate indirectness, it was considered whether the studied population corresponded to the population of interest and whether data were applicable to the health care setting the recommendations would be applied.

- Publication bias was judged similar to therapeutic interventions, but statistical tests such as Egger's test were not used.

Similar to (observational) studies for therapeutic interventions, the level of evidence of a body of methodologically sound studies could be rated up. For studies with respect to event rates, the level of evidence could be rated up in case of an increase in events over time following a well-defined pattern ('dose-response gradient') or a large effect.

2.10 Formulation of recommendations

Based on the retrieved evidence, the first draft of recommendations was prepared by KCE. This first draft was, together with the evidence tables, circulated to the guideline development group two weeks prior to the face-to-face meetings (8-6-2015, 21-09-2015 and 19-10-2015). During the meeting, draft recommendations were possibly adapted based on the discussions. No formal consensus procedure was used during the meetings, and disagreement was solved through discussion. Based on the discussion meetings a second draft of recommendations was prepared and once more circulated to the guideline development group for final approval.

The strength of each recommendation was assigned using the GRADE system (Table 6). The strength of recommendations depends on a balance between all desirable and all undesirable effects of an intervention (i.e., net clinical benefit), quality of available evidence, values and preferences, and estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted. Factors that influence the strength of a recommendation are reported in Table 7.

Table 6 – Strength of recommendations according to the GRADE system

Grade	Definition
Strong	The desirable effects of an intervention clearly outweigh the undesirable effects *(the intervention is to be put into practice)*, or the undesirable effects of an intervention clearly outweigh the desirable effects *(the intervention is not to be put into practice)*
Weak	The desirable effects of an intervention probably outweigh the undesirable effects *(the intervention probably is to be put into practice)*, or the undesirable effects of an intervention probably outweigh the desirable effects *(the intervention probably is not to be put into practice)*

Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

Table 7 – Factors that influence the strength of a recommendation

Factor	Comment
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs (resource allocation)	The higher the costs of an intervention, i.e. the greater the resources consumed, the lower the likelihood that a strong recommendation is warranted

Sources: Schünemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A et al. An Official ATS Statement: Grading the Quality of Evidence and Strength of Recommendations in ATS Guidelines and Recommendations. Am J Respir Crit Care Med 2006; 174:605–14.

Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading Strength of Recommendations and Quality of Evidence in Clinical Guidelines - Report From an American College of Chest Physicians Task Force. Chest 2006; 129:174-81.

A strong recommendation implies that most patients would want the recommended course of action. A weak recommendation implies that the majority of informed patients would want the intervention, but many would not.[20, 21] Specifically, a strong negative recommendation means the harms of the recommended approach clearly exceed the benefits whereas a weak negative recommendation implies that the majority of patients would not want the intervention, but many would. In the case of a weak recommendation, clinicians are especially required to spend adequate time with patients to discuss patients' values and preferences. Such an in-depth discussion is necessary for the patient to make an informed decision. This may lead a significant proportion of patients to choose an alternative approach. Fully informed patients are in the best position to make decisions that are consistent with the best evidence and patients' values and preferences.

For policy-makers, a strong recommendation implies that variability in clinical practice between individuals or regions would likely be inappropriate whereas a weak recommendation implies that variability between individuals

or regions may be appropriate, and use as a quality of care criterion is inappropriate.[20, 21]

We offer the suggested interpretation of "strong" and "weak" recommendations in Table 8.

Table 8 – Interpretation of strong and conditional (weak)* recommendations

Implications	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and involvement of various stakeholders.

* the terms "conditional" and "weak" can be used synonymously
Source: Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66(7):726-35.

2.11 External review

2.11.1 Healthcare professionals

The recommendations prepared by the guideline development group were circulated to relevant professional associations (Table 9). Each association was asked to assign one or two key representatives to act as external reviewers of the draft guideline. All expert referees made declarations of interest.

In total, seven external experts were involved in the evaluation of the clinical recommendations. All invited panellists received the scientific report for all

research questions and were asked to score each recommendation on a 5-point Likert scale indicating their level of agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' 'somewhat disagree', '3' 'unsure', '4' 'somewhat agree', and '5' 'completely agree' (the panellists were also able to answer 'not applicable' if they were not familiar with the underlying evidence). If panellists disagreed with the recommendation (score '1' or '2'), they were asked to provide an explanation supported by appropriate evidence. Scientific arguments reported by these experts were used to adapt the formulation or the strength of the clinical recommendations. This was discussed during a stakeholder meeting on

January 04, 2016. In Appendix, an overview is provided of how their comments were taken into account. No formal consensus method was used.

Table 9 – Invited stakeholder organisations

Professional associations invited for external review
Royal Belgian Society of Surgery
Belgian Society of Pathology
Vlaamse Vereniging voor Obstetrie en Gynaecologie (VVOG)
Groupement de Gynécologues Obstétriciens de Langue Française de Belgique (GGOLFB)
Belgian Society for Medical Oncology (BSMO)
Belgische Genootschap voor Nucleaire Geneeskunde - Société Belge de Médecine Nucléaire

2.11.2 Patient representatives

The patient organisation "Esperanza" was invited to review the draft recommendations from a patient perspective.

The patient representatives were asked the following questions:

- Have important considerations from a patients' perspective been missed in the formulation of our recommendations?
- Do we need to add information that could assist patients in making clear choices when doctors discuss treatment options with them?

Patient views and concerns were discussed during a skype meeting on 11 January 2016.

Concerns raised by the patient representatives are summarized in the "patient values and preferences" for each recommendation.

2.12 Final validation

As part of the standard KCE procedures, an external scientific validation of the report was conducted prior to its publication. The scientific content was assessed by three validators on 2 February 2016 (see names in the colophon).

3 CLINICAL RECOMMENDATIONS: EARLY STAGE DISEASE

3.1 Introduction

Treatment of apparent early stage disease is essentially surgical. Comprehensive staging includes thorough inspection of the abdominal cavity, peritoneal washings, multiple blind peritoneal biopsies, bilateral salpingo-oophorectomy, hysterectomy, infracolic omentectomy and bilateral pelvic and para-aortic lymphadenectomy. Histopathological examination of the removed specimens allows for precise diagnosis and staging (seeTable 1) and assessment of the need for adjuvant therapy.8, 10

In this chapter, we focus on two research questions that assess preoperative and intraoperative assessment of the tumour to facilitate surgical decision making (RMI and other models; frozen section) and on two research questions that search for subgroups of patients that could be spared from lymphadenectomy and/or adjuvant chemotherapy in order to reduce treatment-related morbidity. Finally, we evaluate the role of laparoscopy in the treatment of early-stage disease.

3.2 Pre-operative assessment pelvic mass

3.2.1 Background

Early stage ovarian tumours often have no symptoms but can cause abdominal swelling or bloating, pelvic pain or urinary symptoms. When an ovarian cyst or tumour is detected through pelvic examination or imaging (typically ultrasound), it is important to know whether the tumour is likely benign or (borderline) malignant. For benign tumours, a conservative approach can be appropriate and if surgery is performed, the tumour can often be removed by laparoscopy with conservation of fertility.

Surgery for (borderline) malignant tumours is more complex. Laparotomy may be necessary (see below) and also staging procedures such as omentectomy and lymphadenectomy are often needed. This type of surgery requires more advanced operative skills and should thus be performed by experienced, specialized surgeons. Pre-operative assessment can lead to timely referral and planning for intraoperative frozen section (see below).

Several algorithms have been developed to assess ovarian (pelvic) tumours preoperatively. One of the most frequently used algorithms is the Risk of Malignancy Index (RMI) and its adaptations that consist of an ultrasound score, menopausal status and Ca 125 (Table 10), but many more scoring systems and mathematical models (e.g. IOTA simple rules, IOTA ADNEX model) have been developed.[22]

In this chapter, we search for direct evidence regarding the clinical effectiveness of RMI compared to informal assessment or other algorithms, supplemented with evidence on diagnostic accuracy.

Table 10 – The risk of malignancy index scoring system

Feature	RMI 1 score	RMI 2 score
Ultrasound features: • Multilocular cyst • Solid areas • Bilateral lesions • Ascites • Intra-abdominal metastases	0 = none 1 = one abnormality 3 = two or more abnormalities	0 = none 1 = one abnormality 4 = two or more abnormalities
Premenopausal	1	1
Postmenopausal	3	4
Ca 125	U/ml	U/ml

RMI score = ultrasound score x menopausal score x Ca 125 level in U/ml (threshold 200)

Table 11 – IOTA simple rules

Benign features	Malignant features
Unilocular tumour (B1)	Irregular solid tumour (M1)
Largest diameter of largest solid component < 7mm (B2)	Ascites (M2)
Acoustic shadows (B3)	At least papillary projections (M3)
Smooth multilocular tumour with largest diameter < 100mm (B4)	Irregular multilocular solid tumour with largest diameter ≥ 100mm (M4)
No intratumoural blood flow at colour or power Doppler (B5)	Very strong intratumoural blood flow at colour or power Doppler (M5)

A mass is classified as malignant if at least one M-feature and none of the B-features are present and vice versa. If no B or M features are present or if both B and M features are present, then the rules are considered inconclusive (unclassifiable mass), and a second stage test should be used in the unclassifiable tumours.

3.2.2 Results

Evidence from SRs, RCTs and observational studies

No SRs, RCTs or observational studies could be identified that compared treatment decisions guided with and without the use of the Risk of Malignancy Index (RMI) in adult patients with a (complex) ovarian mass without signs of advanced disease, assessing patient-important outcomes. However, two ongoing RCTs were identified.

In one RCT, 140 postmenopausal women aged 40–80, with incidentally detected adnexal tumours on ultrasound scan will be randomly allocated to be assessed and managed according to either of the two protocols under investigation: Risk of Malignancy Index (RMI) calculation alongside the guidance from the Royal College of Obstetricians and Gynaecologists (RCOG), or the Simple Rules as designed by the International Ovarian Tumour Analysis Group.[23] Women with presumed benign cysts will be

observed over the following year, any (suspicion of) malignancy would lead to a surgical intervention. Outcomes of interest are: number of surgical interventions, number of staging laparotomies, diagnostic accuracy of the two protocols, number of blood tests to measure tumour markers and number of surgical complications. The trial started on April 1, 2011 and end date of recruitment was March 31, 2014.

The other RCT will compare the referral pattern and cost-effectiveness of using RMI versus logistic regression model LR2 developed by the International Ovarian Tumour Analysis (IOTA) group to diagnose adnexal masses prior to surgery.[24] Women with any abnormal morphology of the ovary evident on an ultrasound scan will be included. Primary outcome measure is the histological diagnosis (benign or malignant) for patients who undergo surgery and three follow-up findings over one year for conservative management of patients. Secondary outcomes are: percentage of patients with a borderline/invasive mass assigned to the moderate or high risk groups, actual safety and efficiency based on the real-life referral pattern observed in both study arms, percentage of patients with different types of surgical interventions, median length of hospital stay and health-related quality of life. Recruitment for this trial started on September 1, 2010 and ended on July 1, 2013.

So far, no results for clinical outcomes of these RCTs were published.

Conclusions

- **There is no direct clinical evidence that evaluates the effect of Risk of Malignancy Index (RMI) to guide treatment decisions on overall survival, disease-free survival, recurrence rate, quality of life, (loco)regional control or adverse events in adult patients with a (complex) ovarian mass without signs of advanced disease**

Evidence from diagnostic accuracy studies

Data on the diagnostic accuracy of RMI and other prediction models were taken from a recent high-quality systematic review of Kaijser et al.[22] Results for RMI 1 and RMI 2 are based on 23 and 15 studies respectively and are summarized in Table 12. From the models that were investigated in the SR, the logistic regression model LR2 and the IOTA simple rules performed better than the other models.

Table 12 – Diagnostic accuracy of RMI 1, RMI 2, IOTA simple rules and IOTA LR2

Test/model	Sensitivity	Specificity	PPV*	NPV*
RMI 1	0.72 (95% CI 0.67-0.76)	0.92 (95% CI 0.89-0.93)	0.77 (95% CI 0.71-0.79)	0.90 (95% CI 0.88-0.91)
RMI 2	0.75 (95% CI 0.69-0.80)	0.87 (95% CI 0.84-0.90)	0.68 (95% CI 0.63-0.74)	0.90 (95% CI 0.88-0.92)
IOTA simple rules	0.93 (95% CI 0.89-0.95)	0.81 (95% CI 0.76-0.85)	0.64 (95% CI 0.59-0.70)	0.97 (95% CI 0.95-0.98)
IOTA LR2	0.92 (95% CI 0.88-0.95)	0.83 (95% CI 0.77-0.88)	0.67 (95% CI 0.60-0.74)	0.97 (95% CI 0.95-0.98)

Considering a prevalence of malignancy of 27% (overall prevalence of studies included in the SR of Kaijser et al.)

Using RMI 1 in a hypothetical cohort of 1 000 patients with a prevalence of malignancy of 27%, 58 ovarian tumours (95% CI 51-80) would be incorrectly classified as being malignant (FPs) and 76 patients (95% CI 65-89) would be incorrectly classified as having benign disease (FNs).

Using RMI 2 in the same cohort, 95 ovarian tumours (95% CI 73-117) would be incorrectly classified as being malignant (FPs) and 68 patients (95% CI 54-84) would be incorrectly classified as having benign disease (FNs).

Using IOTA LR2 in the same cohort, 124 ovarian tumours (95% CI 88-168) would be incorrectly classified as being malignant (FPs) and 22 patients (95% CI 14-32) would be incorrectly classified as having benign disease (FNs).

Finally, using IOTA simple rules, 139 ovarian tumours (95% CI 110-175) would be incorrectly classified as being malignant (FPs) and 19 patients (95% CI 13-30) would be incorrectly classified as having benign disease (FNs).

Conclusions

- **In women with an ovarian tumour, RMI 1 will miss 28% of the patients that have a malignant ovarian tumour and 8% of the women without malignancy will be incorrectly classified as having a malignancy (high level of evidence).**

- **In women with an ovarian tumour, RMI 2 will miss 25% of the patients that have a malignant ovarian tumour and 13% of the women without malignancy will be incorrectly classified as having a malignancy (high level of evidence).**

- **In women with an ovarian tumour, IOTA simple rules will miss 7% of the patients that have a malignant ovarian tumour and 19% of the women without malignancy will be incorrectly classified as having a malignancy (high level of evidence).**

- **In women with an ovarian tumour, IOTA LR2 will miss 8% of the patients that have a malignant ovarian tumour and 17% of the women without malignancy will be incorrectly classified as having a malignancy (high level of evidence).**

Factor	Comment
Balance between clinical benefits and harms	In terms of test accuracy, IOTA simple rules and the IOTA logistic regression model 2 (LR2) appear to have the best diagnostic performance, with an improved sensitivity but lower specificity compared to RMI. The IOTA group further developed the more user friendly ADNEX model based on their previous models. Software (app and web based application) to use the ADNEX model is freely available via **http://www.iotagroup.org/adnexmodel/**. Data needed for the calculation are age, CA125, setting (referral centre or not) and ultrasound parameters.

Indirectly, it can be assumed that more accurate preoperative assessment is associated with better clinical outcomes:

- For correctly identified benign tumours, an expectative approach or laparoscopic surgery with conservation of the ovaries/fertility can be chosen. There would be no need for referral to a specialized centre (overtreatment avoided).

- For correctly identified borderline or malignant tumours, tumour spill during surgery can be avoided, appropriate setting can be organized (experienced surgeon, frozen section) and the staging procedures can be performed simultaneously with the removal of the tumour.

However, for false positive or false negative results, there may be harmful effects:

- In case a tumour is falsely seen as malignant, unnecessary referral and laparotomy may be performed. Unnecessary staging procedures can be avoided by intraoperative frozen section.

- A tumour wrongly identified as being benign may rupture during surgery to facilitate the procedure and be upstaged to FIGO stage IC by doing so. Furthermore, a second operation may be needed to complete staging.

Therefore, a high sensitivity is preferred over a high specificity as the consequences of false negative results for malignant tumours are worse.

The IOTA models have the highest sensitivity of the studied models and are thus the preferred methods to formally assess pelvic tumours preoperatively. If performed in second line care, it can guide appropriate referral to specialized care. For caregivers working in third line care, it can guide the appropriate surgical approach (or expectative management).

Certainly the application of IOTA simple rules requires little extra effort compared to subjective judgement and approximately 75% of pelvic masses can already be classified by use of these simple rules. Therefore, the GDG strongly recommends to assess all pelvic masses using IOTA simple rules, IOTA LR2 or the ADNEX model.

It is currently not known if the presence of a BRCA germ line mutation influences the diagnostic accuracy of the models discussed. The clinical decisions taken based on the results may however be influenced by the presence of a BRCA-1 or BRCA-2 germ line mutation.

Quality of evidence	The quality of evidence for the diagnostic accuracy outcomes is high, both for IOTA simple rules and IOTA LR2. However, there is no direct evidence that the use of the algorithms improves important clinical outcomes and there may be harmful effects in case of false

positive or negative results. Therefore, we consider the overall level of evidence to be low.

Costs (resource allocation)	Ultrasound and Ca 125 measurement are part of the standard work-up of ovarian cancer. The ADNEX software is freely available online.
	Hence, the influence on resources of the IOTA simple rules or ADNEX model are considered minimal.
Patient values and preferences	<u>Literature review</u> No information. <u>Comments from patient representatives</u> For patients, it is very important to be informed about the most likely diagnosis and the degree of uncertainty that goes with it. To be aware of a likely malignant diagnosis is helpful to prepare for a 'big' operation. Patients must also be clearly informed about the uncertainty of the preoperative diagnosis, as an unexpected final diagnosis is very difficult to accept.

Recommendation	Strength of Recommendation	Level of Evidence
• Assess a pelvic mass preoperatively using IOTA simple rules, IOTA logistic regression 2 or the ADNEX model$^\$$ to inform clinical decisions regarding surgery (surgery versus expectative management, laparoscopy versus laparotomy, surgery in specialized centre or not). If (borderline) malignancy is suspected, the patient should be discussed preoperatively in the multidisciplinary board (MOC/COM) in the presence of at least one representative of the Reference Centre.*	Strong	Low

$^\$$ *The adnex model can be downloaded from http://www.iotagroup.org/adnexmodel/ and is also available as web application. Data needed for the calculation are age, CA125, setting (referral centre or not) and ultrasound parameters.*

*See KCE report 219 "Organisation of care for adults with rare cancers and cancers with complex diagnosis and/or treatment"

3.3 Intra-operative frozen section

3.3.1 Background

As preoperative assessment cannot perfectly predict the malignant or benign nature of a pelvic mass, further information provided by intraoperative histopathological assessment on frozen section (FS) of the tumour can guide surgical decision making on the need for staging procedures with or without lymphadenectomy (see 0).

In this chapter, we assess the diagnostic accuracy of the intraoperative frozen section procedure.

3.3.2 Results

Three systematic reviews,[25-27] one protocol for a Cochrane review[28] and eleven primary DTA studies were found that addressed the diagnostic accuracy of intraoperative frozen section (FS) analysis to guide decisions in patients with (presumed) early-stage ovarian cancer. RCTs that addressed the effect of FS analysis on survival and other patient important outcomes were not identified.

Two systematic reviews were published in 2005[25, 26] and one in 2012 (search date April 2009).[27] The overall risk of bias of the reviews was judged to be low, except for the review of Covens et al. (2012), because it only searched in MEDLINE.[27] The reviews included a total of 35 unique studies. The yield of the review that only searched MEDLINE[27] was cross-checked with the results obtained by the authors of the Cochrane review in preparation. Six studies appeared to have been missed by Covens' review. Three of these studies were also identified in our search update.[29-31]

Of the studies that were included in the three systematic reviews, nine were excluded because these studies either did not comply with the eligibility criteria or because the 2 by 2 Tables could not be reconstructed in a reliable way.

Of the 11 studies identified in the search update, one scored a high risk of bias for Patient Selection[32] and two a low risk of bias.[30, 33] Unclear risk of bias was present in four studies for Index Test, in all studies for Reference Standard and in two studies for Flow and Timing. All other studies were considered at low risk of bias for these domains. Two studies scored high applicability concerns for patient selection,[32, 34] four studies had unclear

concerns for one or more applicability domains and the remainder scored a low concern. The studies included 66 to 1 439 women and were conducted in the UK (n= 3), Turkey (n= 3), Slovenia (n= 1), Iran (n= 1) and India (n= 3). All studies were single centre and retrospective. The prevalence of malignancy ranged from 10.5% to 63% and for the combination of malignancy and borderline tumours from 13.9% to 97.7%. Various tumour types were identified in all studies (epithelial, sex-cord stromal and germ cell tumours, amongst others). All studies analysed the diagnostic accuracy of FS for malignant ovarian tumours versus no malignancy (consisting of a combination of borderline and benign ovarian tumours) and for the combination of malignant or borderline ovarian tumours versus benign ovarian tumours. In all cases the final diagnosis was confirmed by paraffin section.

Accuracy of frozen section analysis for diagnosing malignant ovarian tumours versus borderline or benign tumours

Thirty-seven studies concerning 10 527 women suspected of early-stage ovarian cancer were included in the meta-analysis. The prevalence of malignant ovarian tumours ranged from 10.5% to 62.6% (median 29.0%; interquartile range 23.3% to 37.8%). Sensitivity ranged from 71.1% to 100% and specificity from 96.3% to 100% (Paired forest plot and ROC curve: see appendix). The pooled sensitivity was 90.3% (95% CI 88.0% to 92.2%) and the pooled specificity 99.5% (95% CI 99.1% to 99.7%). The corresponding predictive value for a positive index test result was 98% (95% CI 98% to 99%) and for a negative index test result 96% (95% CI 95% to 97%). In a hypothetical study of 1000 patients and with a prevalence of 29.0% (= median prevalence) 4 patients (95% CI 2 to 6) would be incorrectly classified as having a malignant ovarian tumour (FPs) and 28 patients with a malignant ovarian tumour (95% CI 23 to 35) would have been missed by FS (FNs).

Accuracy of frozen section analysis for diagnosing malignant or borderline ovarian tumours versus benign rumours

Thirty-eight studies concerning 10 834 women suspected of early-stage ovarian cancer were included in the meta-analysis. The prevalence of the combination of malignant and borderline ovarian tumours ranged from 13.9% to 97.7% (median 38.4%; interquartile range 28.5% to 46.9%). Sensitivity ranged from 68.9% to 97.5% and specificity from 90.0% to 100% (paired forest plot and ROC curve: see appendix). The pooled sensitivity

was 90.7% (95% CI 88.8% to 92.3%) and the pooled specificity 99.0% (95% CI 98.6% to 99.3%). The corresponding predictive value for a positive index test result was 97% (95% CI 96% to 98%) and for a negative index test result 96% (95% CI 96% to 97%). In a hypothetical study of 1 000 patients and with a prevalence of 38.4% (= median prevalence) 6 patients (95% CI 4 to 9) would be incorrectly classified as having a malignant or borderline ovarian tumour (FPs) and 36 patients with a malignant or borderline ovarian tumour (95% CI 30 to 43) would have been missed by frozen section (FNs).

Conclusions

- **No randomized comparative studies were identified that evaluated the clinical effectiveness of intra-operative frozen section analysis in women with (presumed) early-stage ovarian cancer.**
- **In women with (presumed) early-stage ovarian cancer intra-operative frozen section analysis will miss 10% of the patients that have a malignant ovarian tumour and 1% of the women without malignancy will be incorrectly classified as having a malignancy (moderate level of evidence).**
- **In women with (presumed) early-stage ovarian cancer intra-operative frozen section analysis will miss 9% of the patients that have a malignant or bordeline ovarian tumour and 1% of the women without malignancy or a borderline tumour will be incorrectly classified as having a malignant or borderline ovarian tumour (moderate level of evidence).**

Factor	Comment
Balance between clinical benefits and harms	During surgery for presumed early-stage ovarian (borderline) malignancy, surgical decision making can further be guided by immediate histopathological analysis of frozen sections of the tumour. First, analysis of the frozen sections can confirm or change the preoperative diagnosis of a borderline or invasive tumour.

Additionally, this first histopathological assessment may provide information on the epithelial or non-epithelial nature of the tumour, histological type (e.g. mucinous, see below) and grade of differentiation, factors that are important to decide if fertility-preservation is safe and if lymphadenectomy is indicated (see below). Although data on the use of frozen section to retrieve more details on the histopathological nature of the tumour are scarcer,[35, 36] overtreatment (e.g. unnecessary lymphadenectomy) may be avoided in some cases. If additional staging procedures appear necessary based on final pathology, it can be performed laparoscopically.

For that reason, the GDG strongly recommends the implementation of intraoperative frozen section if preoperative assessment suggests a pelvic mass is likely (borderline) malignant.

If staging procedures such as lymphadenectomy cannot immediately be performed by the surgeon, frozen section has no benefit and the final histopathological results can be awaited. However, that situation is to be avoided as much as possible.

Quality of evidence	There is moderate level of evidence on the diagnostic accuracy of intraoperative frozen section. However, there is no direct evidence that the use of intraoperative frozen section improves important clinical outcomes. Therefore, we consider the overall level of evidence to be low.
Costs (resource allocation)	In Belgium, the additional resources needed for intraoperative frozen section are considered acceptable by the GDG.
Patient values and preferences	Literature review Geomini et al. interviewed 43 women with an adnexal mass who were scheduled for surgery. In a

scenario with a risk of 10% of a false negative frozen section, only 9% of women preferred immediate radical surgery.[37]

Comments from patient representatives

As for the preoperative assessment, for patients it is very important to be aware of the remaining uncertainty of the diagnosis so that a possible different final diagnosis would be more easily accepted.

Recommendation	Strength of Recommendation	Level of Evidence
• Perform intraoperative frozen section to guide decisions during surgery e.g. regarding staging procedures for presumed early stage (borderline) ovarian cancer.	Strong	Low

3.4 Lymphadenectomy

3.4.1 Background

Historically, in Belgium pelvic and para-aortic lymphadenectomy are performed as part of the (surgical) staging of ovarian malignancies. The presence of metastases in the lymph nodes can upstage an otherwise early stage tumour to FIGO stage III and influence treatment decisions regarding adjuvant chemotherapy.[7, 8]

However, if intraoperatively information on the histology of the tumour is available, lymphadenectomy and associated morbidity may be avoided if the chance for lymph node metastasis is very low and the importance of lymphadenectomy for treatment decisions would be limited.

In this chapter, we investigated the prevalence of lymph node metastases in early-stage ovarian cancer according to several clinical and histological factors.

3.4.2 Results

One systematic review[38] and nine more recent publications of (non-comparative) observational studies[39-47] were identified that reported about the incidence of malignant disease in pelvic and para-aortic lymph nodes in patients with borderline or (micro-)invasive (presumed) early-stage ovarian cancer who underwent systematic pelvic and para-aortic lymphadenectomy. One publication reported about two non-comparative observational studies,[42] so 10 observational studies were included. No RCTs were identified.

The systematic review searched for RCTs and observational studies that included patients with clinically early-stage epithelial ovarian cancer who underwent a complete staging laparotomy including a systematic pelvic and para-aortic lymphadenectomy.[38] Medline and Embase were searched and additional reference checking was done. No search date was reported. However, the most recent included study was published in August 2010. The systematic review included 14 observational studies (1 247 patients with FIGO stage I-II), of which two were prospective cohort studies and 12 were retrospective cohort studies.

Of the ten observational studies published since the systematic review, one was a prospective cohort study.[40] The remaining nine studies were retrospective reviews of medical records in a single centre setting (five studies),[39, 41, 42, 44, 47] multicentre setting (two studies)[43, 45] or in population-based databases (two studies).[42, 46]

The retrospective nature of most of the included studies leads to high risk of selection bias. We included publications that reported about patients who underwent a systematic pelvic and para-aortic lymphadenectomy. The decision to perform a systematic lymphadenectomy could have been influenced by many surgeon and patient-related characteristics. Another limitation of retrospective studies is the fact that not all desired information is available from medical records or registries. As the information in the studies was collected during many years, there is a chance that the indication for lymphadenectomy could have been changed over the years.

The same holds for surgical techniques. All but three studies collected data from a period longer than 10 years.[40, 45, 46] Despite this, the sample size of most included studies is relatively small.

For six studies, patients with clinical early-stage epithelial ovarian carcinoma were eligible.[39, 40, 44-47] Two studies included patients based on pathological T-stage.[41, 43]

Two studies that were presented in the same publication focused on patients with a final diagnosis of (advanced stage serous) borderline ovarian tumour (BOT).[42] The first study is a retrospective analysis of single centre medical records and the second study is the same analysis performed in the Surveillance, Epidemiology, and End Results (SEER) database.

Overall incidence of lymph node metastases in early-stage and borderline ovarian cancer

Borderline ovarian cancer

Of the two studies in borderline ovarian cancer patients, the single-centre study reported an incidence of positive lymph nodes of 28.6%.[42] Most patients in this study had FIGO stage III/IV disease. The population-based study (based on the SEER program) reported an incidence of positive lymph nodes of 6.2%, in a population with FIGO stage I-IV. Results were presented separately for each FIGO stage. For FIGO stage I, an incidence of positive lymph nodes of 1.5% was found (n=1 101), for FIGO stage II 5.6% (n=144) and for FIGO stage I and II combined 2.0%.[42] Other smaller series reviewed in the paper reported similar prevalence of lymph node metastasis according to clinical stage.

(Apparent) early-stage ovarian carcinoma

The systematic review reported an overall incidence of positive lymph nodes in clinically early-stage ovarian carcinoma of 14.2% (14 studies, n=1 247; range 6.1–29.6%).[38] For the para-aortic region an incidence of positive lymph nodes of 7.1% (range 3.0-13.0%) was found, for the pelvic region

2.9% (range 0.0-11.1%) and for positive lymph nodes in both the regions 4.3% (range 0.0-14.8%).

In eight observational studies addressing clinically early-stage epithelial ovarian cancer, the overall incidence of positive lymph nodes was 12.9% (range 5.9-24.6%) (Table 13).[39-41, 43-47] Five of the studies (n=641) reported on the incidence of positive lymph nodes in a specific region.[39, 40, 43, 44, 47] The incidence of positive lymph nodes in the para-aortic region ranged from 3.5 to 11.6%, with a mean of 6.1%. In the pelvic region the incidence of positive lymph nodes was 2.8% (range 0.7-7.2%) and in both regions together 4.4% (range 1.6-13.0%).

The combined results of both the systematic review and the eight observational studies show an overall incidence of positive lymph nodes in clinically early-stage ovarian carcinoma of 12.7% (22 studies, n=2 284) (Table 13).

In Table 14 the incidence of positive lymph nodes is reported per clinical FIGO stage. Seven observational studies reported results for clinical FIGO stage I patients (n=622).[40, 41, 43-47] The incidence of positive lymph nodes ranged from 4.4 to 16.5% (mean 9.2%). For clinical FIGO stage II (3 studies, n=142) the incidence of positive lymph nodes was 21.5% (range 17.5-28.6%).[40, 41, 43] One of the studies that included clinical FIGO stage I patients, reported an incidence of positive lymph nodes of 4.5%, 16.7% and 6.5% for substages Ia (n=111), Ib (n=12) and Ic (n=93), respectively.[46] Another study reported the incidence of positive lymph nodes for FIGO stage Ia-c (n=73) vs. IIa-IIIa (n=42): 12.3% vs. 23.8%.[44] It is unclear whether it is the clinical or the final FIGO stage that was presented here.

Table 13 – Overall Incidence of lymph node metastases in clinical early stage epithelial ovarian cancer and the anatomical distribution of positive lymph nodes

Reference	Total population (syst. lymph-adenectomy)	Positive pelvic and/or para-aortic lymph nodes										
		Overall		Only para-aortic			Only pelvic			Both para-aortic and pelvic		
	n	n	%a	n	%b	%a	n	%b	%a	n	%b	%a
Clinical early stage epithelial ovarian cancer												
Systematic review												
Kleppe 2011	1 247 (stage I-II)	177	14.2	88	49.7	7.1	36	20.3	2.9	53	29.9	4.3
Observational studies												
Chang 2013	69 (stage I-II)	17	24.6	8	47.1	11.6	5	29.4	7.2	9	52.9	13.0
Ditto 2012	111 (stage I-II)	15	13.5	8	53.3	7.2	2	13.3	1.8	5	33.3	4.5
Haller 2011	100 (stage I-II)	14	14.0	-	-	-	-	-	-	-	-	-
Oshita 2013	284 (stage I-II)	23	8.1	10	43.5	3.5	2	8.7	0.7	9	39.1	3.2
Powless 2011	115 (stage I)	19	16.5	10	52.6	8.7	5	26.3	4.3	4	21.1	3.5
Suzuki 2014	80 (stage I)	5	6.3	-	-	-	-	-	-	-	-	-
Svolgaard 2014	216 (stage I)	13	6.0	-	-	-	-	-	-	-	-	-
Ulker 2014	62 (stage I)	8	12.9	3	37.5	4.8	4	50.0	6.5	1	12.5	1.6
Total obs. studies	*1 037*	*114*	*11.0*	*39*	*47.6*	*6.1*	*18*	*22.0*	*2.8*	*28*	*34.1*	*4.4*
Total obs. studies + systematic review	*2 284*	*291*	*12.7*	*127*	*43.6*	*5.6*	*54*	*18.6*	*2.4*	*81*	*27.8*	*3.5*
Borderline ovarian tumour												
Lesieur 2011 (study 1)	49	14	28.6	-	-	-	-	-	-	-	-	-
Lesieur 2011 (study 2)	1496	93	6.2	-	-	-	-	-	-	-	-	-
Total	*1 552*	*107*	*6.9*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*	*-*

a percentage indicates number of patients with positive lymph nodes as a proportion of the total number of patients with clinical early stage ovarian cancer
b percentage indicates number of patients with positive lymph nodes in that particular anatomical region as a proportion of the patients with positive lymph nodes

Table 14 – Incidence of lymph node metastases in early stage epithelial ovarian cancer according to clinical FIGO stage

Reference	Total population	Clinical FIGO stage I			Clinical FIGO stage II		
		Total	LN+		Total	LN+	
	n	n	n	%[a]	n	n	%[a]
Ditto 2012	111	84	8	9.5	27	7	25.9
Haller 2011	100	65	4	6.2	35	10	28.6
Oshita 2011	284	204	9	4.4	80	14	17.5
Powless 2011	115	115	19	16.5	-	-	-
Suzuki 2014	80	80	5	6.3	-	-	-
Svolgaard 2014	216	216	13	6.0	-	-	-
Ulker 2014	62	62	8	12.9	-	-	-
Total	*968*	*622*	*57*	*9.2*	*142*	*31*	*21.8*

Incidence of lymph node metastases according to differentiation grade

The incidence of lymph node metastases according to the differentiation grade was reported by the systematic review[38] and three observational studies.[41, 44, 47] (Table 15). The systematic review reported incidences of metastatic lymph nodes of 4%, 16.5% and 20% for grade 1, grade 2 and grade 3, respectively (total population n=361). The observational studies reported incidences of metastatic lymph nodes of 9.1%, 19.4% and 36% for grade 1, grade 2 and grade 3, respectively (total population n=350). Combined results show incidences of 5.6%, 18.1% and 32% for grade 1, grade 2 and grade 3, respectively (total population n=711).

Table 15 – Incidence of lymph node metastases in clinical early epithelial ovarian cancer according to differentiation grade

Reference	Total population	Grade 1			Grade 2			Grade 3			Missing data
		Total	LN+		Total	LN+		Total	LN+		
	n	n	n	%[a]	n	n	%[a]	n	n	%[a]	n
Systematic review											
Kleppe 2011	361	149	6	4,0	103	17	16.5	50	10	20.0	66
Observational studies											
Haller 2011	173	35	6	17.1	67	23	34.3	71	30	42.3	-
Powless 2011[1]	115	14	0	0.0	36	1	2.8	65	18	27.7	-
Ulker 2014[2]	62	17	0	0.0	31	2	6.4	14	6	42.9	-
Total obs. studies	*350*	*66*	*6*	*9.1*	*134*	*26*	*19.4*	*150*	*54*	*36.0*	*-*
Total obs. studies + systematic review	*711*	*215*	*12*	*5.6*	*237*	*43*	*18.1*	*200*	*64*	*32*	*66*

[a] *percentage indicates number of patients with positive lymph nodes in the mentioned grade as a proportion of the total number of patients of that grade*
[1] *p=0.001 (univariate analyses)*
[2] *p=0.001 (univariate analyses)*

Incidence of lymph node metastases according to histological subtype

Table 16 presents the incidence of lymph node metastases according to histological subtype, reported in the included systematic review38 and seven observational studies.[40, 41, 43-47] The lowest incidence of metastatic lymph nodes was seen in mucinous ovarian carcinoma and the highest incidence in serous ovarian carcinoma. Combined results show incidences of positive lymph nodes of 27.5%, 3.8%, 6.9%, and 14.8% for serous, mucinous, endometrioid and clear cell carcinomas, and 19.1% for the category 'undifferentiated/others'. In the study of Haller, serous carcinoma was compared to non-serous carcinoma, so the undifferentiated/others category contains all non-serous carcinomas.[41]

An eighth observational study (study 2 of the publication on borderline ovarian carcinoma; n=1 496 FIGO stage I-IV)[42] reported incidences of positive lymph nodes for serous cystadenoma (7.8%), papillary cystadenoma (15%), serous papillary cystadenoma (8.4%), mucinous cystadenoma (1%) and mucinous papillary cystadenoma (4.5%).

Table 16 – Incidence of lymph node metastases according to histological subtype

Reference	Total population	Serous				Mucinous				Endometrioid				Clear cell				Undifferentiated/ others				Missing data
		Total	LN+			Total	LN+			Total	LN+			Total	LN+			Total	LN+			
	n	n	n	%[a]		n	n	%[a]		n	n	%[a]		n	n	%[a]		n	n	%[a]		
Systematic review																						
Kleppe 2011	574	150	35	23.3		155	4	2.6		92	6	6.5		139	20	14.4		38	11	28.9		
Observational studies																						
Ditto 2012	111	25	7	28.0		15	0	0.0		38	4	10.5		9	0	0.0		24	4	16.7		
Haller 2011[3]	173	76	45	59.2		-	-	-		-	-	-		-	-	-		97	14	14.4		
Oshita 2013[1]	284	63	10	15.9		54	2	3.7		71	5	7.0		83	6	7.2		13	0	0.0		
Powless 2011[2]	115	30	9	30.0		16	0	0.0		-	-	-		-	-	-		66	10	15.1		3
Suzuki 2014	80	-	-	-		-	-	-		-	-	-		80	5	6.3		-	-	-		
Svolgaard 2014	216	68	9	13.2		29	0	0.0		51	2	3.9		35	0	0.0		24	1	4.3		9
Ulker 2014	62	25	5	20.0		23	1	4.3		9	1	11.1		5	1	20.0						
Total obs. studies		287	85	29.6		137	7	5.1		169	12	7.1		212	32	15.1		224	39	17.4		12
Total obs. studies + systematic review		437	120	27.5		292	11	3.8		261	18	6.9		351	52	14.8		262	50	19.1		12

LN+: lymph node metastasis.

[a] percentage indicates number of patients with positive lymph nodes in the mentioned histological type as a proportion of the total number of patients in that histological type.

[1] Serous adenocarcinoma was also associated with a higher incidence of lymph node metastasis than other histological subtypes (univariate analyses)

[2] p=0.030 (univariate analyses)

[3] p<0.0001 (univariate analyses)

Multivariate analyses

Multivariate analyses were done in four of the included observational studies (Table 17). The following characteristics were presented as potential predictors of lymph node status: bilateral adnexal involvement as compared to unilateral,[40, 44] grade 3 disease, positive cytology,[39] menopause,[40]

the presence of ascites, a higher FIGO grade,[44] serous histology, residual tumour mass and intraperitoneal stage.[41]

However, the predictors included in the analyses differed in the four studies. Although some studies had partly overlapping predictors in their model, they ended up with different results for these overlapping predictors.

Table 17 – Multivariate analyses of risk factors for lymph node metastases in early stage epithelial ovarian cancer

Reference	Study population	All predictors in model	Independent predictors for lymph node metastases
Chang 2013	69 (clinical FIGO stage I-II)	Age, serous histology, grade 3 tumour, presence of ascites, CA 125>35U/ml, positive cytology	Grade 3 tumour, positive cytology
Ditto 2012	111 (clinical FIGO stage I-II)	Menopause (yes/no), bilaterality (vs. unilaterality) of adnexal disease, grading (1-2 vs. 3)	Menopause, bilaterality
Powless 2011	115 (clinical FIGO stage I)	Laterality of adnexal involvement (bilateral vs. unilateral, cytology (negative vs. positive), ascites (absent/present), histology (serous, mucinous, other), FIGO grade, FIGO stage, CA 125 ≤ vs. > 35 U/ml	Laterality of adnexal involvement (bilateral vs. unilateral, ascites (absent/present), FIGO grade
Haller 2011	173 (primary epithelial ovarian carcinoma T1-T3; clinical FIGO stage not reported)	Age, serous histology, residual tumour mass, intraperitoneal stage, tumour differentiation	Serous histology, residual tumour mass, intraperitoneal stage

Conclusions

- **In 22 observational studies of patients with clinically early stage ovarian cancer who underwent systematic pelvic and para-aortic lymphadenectomy the incidence of malignancy in pelvic and para-aortic lymph nodes ranged from 6.0 to 29.6% (mean 12.7%). An increased incidence was seen in patients with a higher TNM stage and a higher differentiation tumour grade. With regard to the histological subtype of the ovarian tumour, the lowest incidence of metastatic lymph nodes was seen in mucinous ovarian carcinoma (mean 3.8%) and the highest incidence in serous ovarian carcinoma (mean 27.5%). In patients with borderline ovarian tumours with (final) FIGO stage I and II an incidence of positive lymph nodes of 2.0% was found.**

- **At multivariate analyses, bilateral adnexal involvement as compared to unilateral, grade 3 disease, positive cytology, menopause, the presence of ascites, serous histology, residual tumour mass and intraperitoneal stage were identified as potential predictors of lymph node status in patients with early stage ovarian cancer.**

Factor	Comment
Balance between clinical benefits and harms	**Borderline tumours**
	Available evidence suggests that the presence of lymph node metastases is low in early stage borderline tumours and that the presence of lymph node metastases has no prognostic value in borderline disease. Furthermore, information on lymph node status is not needed for clinical decision making as adjuvant treatment is not indicated in borderline disease (see below).
	Invasive tumours
	Lymphadenectomy is part of the surgical staging of presumed early stage invasive ovarian cancer. The presence of lymph node metastases would render an otherwise stage I or II tumour to FIGO stage IIIA (see Error! Not a valid result for table.) with consequences for prognosis and decisions on adjuvant chemotherapy. If, however, predictive factors indicate that the probability of lymph node metastases is very low lymphadenectomy can be omitted to avoid side effects such as haemorrhage, infection or lymphedema.
	Evidence shows that both stage IA tumours and well differentiated tumours have a low prevalence of lymph node metastasis. It appears safe to omit lymphadenectomy in case of well differentiated stage IA.
	Furthermore, mucinous tumours have a low prevalence of lymph node metastases, especially in mucinous tumours of the expansile type. Degree of differentiation seems less important in predicting lymph node metastases in mucinous tumours.[48]
	If final histopathology would contradict the frozen section analysis and show an indication for lymphadenectomy, it can be performed laparoscopically in a second operation.
	If intra-operative frozen section suggests other histology than well differentiated stage IA or expansile mucinous disease, both pelvic and para-aortic lymphadenectomy should be performed, as almost half of the patients with lymph node metastases have metastatic disease in the para-aortic region only (see table).
Quality of evidence	As only epidemiological evidence was considered, GRADE was not applied.
Costs (resource allocation)	NA
Patient values and preferences	<u>Literature review</u> No information <u>Comments from patient representatives</u> Patient representatives stress the need for timely information regarding the possible consequences of lymphadenectomy and active follow-up and support for lymphedema. Lymphedema can severely impact daily activities and quality of life, in a way often unexpected by patients.

Recommendations	Strength of Recommendation	Level of Evidence
• Do not perform lymphadenectomy for borderline ovarian tumours.	Strong	Low
• Consider omitting lymphadenectomy in well differentiated stage IA ovarian tumours and stage I mucinous tumours of the expansile type.	Weak	NA

3.5 Adjuvant chemotherapy

3.5.1 Background

Although early stage disease has generally a favourable prognosis, many patients with stage I-II disease will suffer from recurrence. The effectiveness of adjuvant chemotherapy to reduce the chance for recurrence and to improve overall survival is evaluated in this chapter.

3.5.2 Results

3.5.2.1 (Presumed) early stage **borderline** ovarian tumours

Evidence from RCTs

The starting point was a high-quality Cochrane systematic review[49] that included two RCTs comparing adjuvant chemotherapy with no adjuvant chemotherapy in patients with borderline (presumed) early stage ovarian cancer. Risk of bias in these trials was judged to be low. The search date of the review was January 2009. An update of the search revealed no additional RCTs. The intervention of interest was Melphalan (administered orally) in one of the included RCTs and Thio-TEPA in the other. As the included RCTs evaluated different interventions, the results were not pooled.

Overall survival

Faluyi et al.[49] presented number of deaths for both RCTs.

No deaths were seen in the RCT comparing Melphalan with no adjuvant treatment (0/17 vs. 0/25; mean follow-up: 3 years (range 1-7) since diagnosis).

In the RCT comparing Thio-TEPA with no adjuvant treatment no statistically significant differences were found for number of deaths (6/27 (22%) vs. 2/39 (5%), RR=4.33, 95% CI 0.94 to 19.88; median follow-up: 147 months (range 4 -246)). No hazard ratio was reported or could be calculated.

Disease-free survival

Disease recurrences were presented by Faluyi et al.[49] for both RCTs. No recurrences were seen in the RCT comparing Melphalan with no adjuvant treatment (0/17 vs. 0/25). In the RCT comparing Thio-TEPA with no adjuvant treatment no differences were found (1/27 (4%) vs.0/39). No hazard ratio was reported or could be calculated.

Quality of life

This outcome was not assessed in any of the studies.

Adverse events

One of the trials included in the Cochrane review of Faluyi et al. presented results for adverse events. Grade 4 septic neutropenia was seen in one patient receiving Thio-TEPA and in none of the patients receiving no adjuvant treatment. Also, for grade 3 bone marrow toxicity no differences were found for Thio-TEPA versus no adjuvant treatment (1/27 (4%) vs. 0/39).

Conclusions

- **The available evidence of very low quality could neither demonstrate nor refute a difference between adjuvant chemotherapy and no adjuvant treatment in number of deaths and recurrences in women with borderline (presumed) early stage ovarian cancer (Very low level of evidence; Faluyi 2010[49]).**

- **No RCTs could be identified that adressed quality of life in women with borderline (presumed) early stage ovarian cancer undergoing adnexectomy + surgical staging with versus without adjuvant chemotherapy.**

- **The available evidence of very low quality could neither demonstrate nor refute a difference between adjuvant chemotherapy and no adjuvant treatment in grade 4 neutropenia and in grade 3 bone marrow toxicity in women with borderline (presumed) early stage ovarian cancer (Very low level of evidence; Faluyi 2010[49]).**

3.5.2.2 *(Presumed) early-stage **micro-invasive** ovarian cancer*

No RCTs or observational studies could be identified that compared adnexectomy + surgical staging with versus without adjuvant chemotherapy in adult patients with micro-invasive (presumed) early stage ovarian cancer.

Conclusions

- **No RCTs or comparative observational studies could be identified that adressed overall survival, disease-free survival, quality of life or adverse events in women with micro-invasive (presumed) early stage ovarian cancer undergoing adnexectomy + surgical staging with versus without adjuvant chemotherapy.**

3.5.2.3 *(Presumed) early-stage **invasive** ovarian cancer*

The starting point was a high-quality Cochrane systematic review[50] that included five RCTs comparing adjuvant chemotherapy with no adjuvant treatment in adult patients with invasive (presumed) early-stage ovarian cancer. The search date of the review was August 2011. Risk of bias for the included RCTs was judged to be low. A total of 1 277 patients were enrolled. Median follow-up in the five trials ranged from 46 and 121 months. Characteristics of included trials are summarized in Table 18.

All trials included women with FIGO stage I ovarian cancer and one trial included women with FIGO stage II as well. One of the trials was flawed by the inclusion of women with borderline ovarian tumours (about 30% and evenly distributed between study groups).

An update of the search resulted in one additional publication.[51] In this publication, 10-year follow-up results of an RCT were presented which were, however, already included in the systematic review of Winter-Roach[50] in the form of a conference abstract with results of 9.2 years median follow-up. The presented hazard ratios for overall survival (OS) and progression-free survival (PFS) did not differ much between the conference abstract included in the review and the additionally identified full text publication of Collinson et al. Therefore, we decided not to update the meta-analyses of the systematic review. The only discrepancy between the conference abstract and full-text publication was the reporting for the subgroup of suboptimal staging, for which the hazard ratios for OS and PFS seemed to be mixed up (see below).

Table 18 – Summary included trials adjuvant chemotherapy for invasive early-stage ovarian cancer

Reference	n	Inclusion criteria	Intervention	Surgical staging
Young 1990[52]	92	FIGO 1976 stage Ia and Ib well-differentiated or moderately-differentiated tumours, borderline tumours (27/92) included;	Melphalan 0.2mg/kg	Midline laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, biopsies of peritoneal deposits, random biopsies of pelvic and abdominal peritoneal and retroperitoneal lymph node assessment
Bolis 1995[53]	85	Stage Ia en Ib G2 en G3	6 cycles cisplatin (50mg/m^2)	Protocol specifies inclusion of retroperitoneal (pelvic and para-aortic) nodal sampling in the staging procedure
Trope 2000[54]	175	FIGO stage I non-clear cell G2 to G3	6 cycles carboplatin AUC7	Midline laparotomy, total abdominal hysterectomy, bilateral salpingo-oophorectomy, infracolic omentectomy, peritoneal washings and thorough assessment of peritoneal surfaces with biopsy of any suspicious lesion (peritoneal or retroperitoneal).
ICON1 2003[55]	477	FIGO stage I,II	87% carboplatin AUC5 11% cisplatin 2% other platinum-based regimens	Removal of all visible tumour with total abdominal hysterectomy and bilateral salpingo-oophorectomy and where appropriate infracolic omentectomy
ACTION 2003[56, 57]	448	Stage Ia and Ib G2 and G3, all stage Ic	Single agent or combinations based on cisplatin 75 mg/m^2 or carboplatin 350 mg/m^2	All categories include total abdominal hysterectomy and bilateral salpingo-oophorectomy Optimal (151/448): inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy; (blind) biopsies of right hemidiaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac; sampling of iliac and periaortic lymph nodes Modified (138/448): everything between optimal and minimal staging Minimal (114/448): inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy Inadequate (43/448): less than minimal staging but at least careful inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases

Overall survival

Winter-Roach et al. presented a meta-analysis of three RCTs (1 006 women) with data on 5-year OS. This meta-analysis showed that women who received adjuvant platinum-based chemotherapy had a better 5-year OS than women who did not receive adjuvant chemotherapy (pooled HR=0.71; 95% CI 0.53 to 0.93). Meta-analysis of two RCTs (925 women) with 10-year data for OS also showed a benefit for adjuvant chemotherapy (pooled HR=0.74; 95% CI 0.58 to 0.95).

Results for subgroups

- Optimal surgical staging (defined as peritoneal staging plus retroperitoneal node assessment)
  2 trials (surgical staging in Bolis 1995 was considered optimal post-hoc), 234 women: pooled HR for 5-year OS 1.22, 95% CI 0.63 to 2.37
  Suboptimal staging
  2 trials, 772 women: pooled HR for 5-year OS 0.63; 95% CI 0.46 to 0.85
  Results of these subgroup analyses should be interpreted with caution as in the ACTION trial the p-value of the interaction test was 0.15 and the differences between subgroups thus could be due to chance.[13]

- high risk (defined as Ia grade 3, Ib or Ic grade 2 or 3, any clear cell tumour)
  1 trial, 201 women HR for 10-year OS 0.48; 95% CI 0.32 to 0.72
  In the publication of Collinson[51] for high-risk patients a HR for 10-year OS of 0.52 (95% CI 0.33 to 0.81) was reported.
  low/medium risk (low risk: Ia grade 1; medium risk: Ia grade 2, Ib or Ic grade 1)
  1 trial, 219 women HR for 10-year OS 0.95; 95% CI 0.54 to 1.66
  FIGO stage and degree of differentiation were stratification factors for randomization. P-value for the test for interaction was 0.15.

- One of the included RCTs showed that histologic cell type was a statistically significant prognostic factor for overall survival. The effect of adjuvant chemotherapy by histological type could not be calculated from reported data.

Progression-free survival

Four RCTs with data on 5-year PFS were included in a meta-analysis by Winter-Roach. This meta-analysis showed a better PFS for women receiving adjuvant chemotherapy compared to women not receiving adjuvant chemotherapy (pooled HR=0.67; 95% CI 0.53 to 0.84). An almost identical result was found for 10-year PFS in a meta-analysis of two RCTs (pooled HR=0.67; 95% CI 0.54 to 0.84).

Subgroup analysis could not demonstrate a beneficial effect of adjuvant chemotherapy in women who had optimal surgical staging (pooled HR for 5-year PFS 0.67; 95% CI 0.36 to 1.22; pooled HR for 10-year PFS 0.73, 95% CI 0.38 to 1.42), but they did show a benefit women with suboptimal surgical staging (pooled HR for 5-year PFS 0.64, 95% CI 0.50 to 0.82; pooled HR for 10-year PFS 0.60, 95% CI 0.41 to 0.87). One of the included RCTs showed that women at high risk had a benefit from adjuvant chemotherapy, whereas women at low/medium risk may not (high risk: HR for 10-year PFS 0.52; 95% CI 0.33 to 0.82; low/medium risk: HR for 10-year PFS 0.96; 95% CI 0.58 to 1.59). In the publication of Collinson[51] for high-risk patients a HR for 10-year PFS of 0.48 (95% CI 0.31 to 0.73) was reported.

Two RCTs reported on disease-free survival and/or recurrence rates separately for histologic cell types. In one RCT clear-cell tumour type was associated with poorer outcomes in a multivariate analysis with disease-free survival as the end point. Results for relapses were: serous only (n=2/18); mucinous (0/27); endometrioid only (n=0/13); clear cell only (n=2/7); clear cell and any other type (n=1/2); other tumours, one type only (n=0/0); other tumours, mixed types (n=0/6); unclassified or unknown (n=0/8). In another RCT histological grade (1 vs. 2/3 with clear cell carcinomas) was not identified as an independent prognostic factor related to disease free survival and disease specific survival.

Quality of life

This outcome was not assessed in any of the RCTs included in the systematic review.

Adverse events

Winter-Roach et al. stated that it was not possible to make a comparison of the risk of adverse events between adjuvant chemotherapy and no chemotherapy, since none of the included trials reported adverse events among women who did not receive adjuvant chemotherapy.

Conclusions

- **In women with invasive (presumed) early stage ovarian cancer there is evidence of moderate quality that adnexectomy+surgical staging with adjuvant chemotherapy results in better 5- and 10-year overall and progression-free survival than adnexectomy+surgical staging without adjuvant chemotherapy (moderate level of evidence; Winter-Roach 2012).50**

- **In women with invasive early stage ovarian cancer that are suboptimally staged there is evidence of moderate quality that surgery with adjuvant chemotherapy results in better 5-year overall and progression-free survival than surgery without adjuvant chemotherapy (moderate level of evidence; Winter Roach 2012).50 There is evidence of moderate quality that adjuvant chemotherapy results in better 10-year progression-free survival as well (moderate level of evidence; Winter Roach 2012).50 For women that are optimally staged, a difference in overall and progression-free survival between adjuvant chemotherapy and no adjuvant chemotherapy could neither be demonstrated nor refuted (very low level of evidence; Winter-Roach 2012).50**

- **In women with invasive early-stage ovarian cancer at high risk there is evidence of moderate quality that surgery with adjuvant chemotherapy results in better 10-year overall and progression-free survival than surgery without adjuvant chemotherapy. For women at low/medium risk a difference in 10-year overall and progression-free survival between surgery with and surgery**

without adjuvant chemotherapy could neither be demonstrated nor refuted (low level of evidence; Winter Roach 2012).50

- **No RCTs could be identified that adressed quality of life in women with invasive (presumed) early stage ovarian cancer undergoing adnexectomy + surgical staging with versus without adjuvant chemotherapy.**

- **No RCTs could be identified that compared adverse events in women with invasive (presumed) early stage ovarian cancer undergoing adnexectomy + surgical staging with versus without adjuvant chemotherapy.**

Factor	Comment
Balance between clinical benefits and harms	**Borderline disease** Two small randomized controlled trials investigated the use of adjuvant chemotherapy in borderline tumours. Sample sizes are too small to draw any firm conclusions, but results suggest that adjuvant chemotherapy may be harmful. These results are supported by data from older trials including both borderline and invasive tumours.[58] **Micro-invasive disease** There are no comparative data on the use of adjuvant chemotherapy. However, we know that micro-invasive ovarian tumours have the same excellent prognosis as borderline tumours,[59] possible benefit from adjuvant chemotherapy would thus certainly be limited. Progression of micro-invasive tumours to invasive disease leads to low-grade serous tumours, which are little sensitive to chemotherapy (see introduction). Therefore, the GDG does not recommend adjuvant chemotherapy for micro-invasive tumours. **Invasive disease**

Meta-analysis from the several RCTs investigating the effect of adjuvant chemotherapy shows a benefit in PFS and OS for patients who have received adjuvant chemotherapy. Subgroup analyses do not confirm this benefit for optimally staged patients and low/medium risk patients, but the evidence is too weak to change the recommendation for these subgroups.

The absolute benefit in terms of PFS and OS will depend on the baseline risk within the different subgroups. For optimally staged low risk patients (stage IA Grade 1), the absolute benefit would be very limited and would not justify the side effects from chemotherapy.

For correct determination of the differentiation grade, it is recommended to apply differential grading depending on the histological type of the tumour.[6]

All RCTs that investigated the effectiveness of adjuvant chemotherapy for early stage ovarian cancer used the histopathological definitions and grading systems that were current at that time. Taking into account the new WHO histopathology classification, by consensus, international clinical

experts suggest to consider omitting adjuvant chemotherapy for early stage clear cell carcinomas that have been optimally staged (I. Ray-Coquard, personal communication).

Quality of evidence	Borderline disease: very low level of evidence
	Micro-invasive disease: no comparative data, indirect evidence
	Invasive disease: moderate level of evidence
Costs (resource allocation)	No information
Patient values and preferences	<u>Literature review</u>
	No information
	<u>Comments from patient representatives</u>
	Although many people have heard about chemotherapy before and know people who have received it, there are still important knowledge gaps for the majority of patients. Specific and comprehensive information about the route of administration, possible side effects and especially preventative measures for side effects is needed.

Recommendations	Strength of Recommendation	Level of Evidence
• Do not offer adjuvant chemotherapy to patients with an early stage borderline ovarian tumour.	Strong	Very low
• Do not offer adjuvant chemotherapy to patients with an early stage micro-invasive ovarian tumour.	Strong	Very low
• Do not offer adjuvant chemotherapy to low risk early stage (FIGO stage IA Grade 1) ovarian cancer.	Strong	Moderate
• Offer platinum-based adjuvant chemotherapy to fit patients with medium risk* or high risk$ early stage ovarian cancer, whether or not the tumour is optimally staged.	Strong	Moderate

*defined as stage 1B, 1C grade 1 or stage IA grade 2
$defined as stage 1B, 1C grade 2-3 or stage IA grade 3

3.6 Laparoscopic surgery

3.6.1 Background

Laparoscopic surgery has been shown to be a valid alternative for many (oncological) indications, with less complications and accelerated recovery.[60]

Also for surgical staging of presumed early stage ovarian cancer, laparoscopy is shown technically feasible and safe. However, there is remaining concern on the oncological outcomes, as cyst rupture and difficult removal from the abdominal cavity may increase the need for adjuvant chemotherapy and the risk for recurrence and augment the risk for recurrence (e.g. port-site metastasis).

In this chapter, we searched for comparative studies that compared laparoscopic staging with staging via open surgery for presumed early stage ovarian cancer.

3.6.2 Results

A Cochrane review did not identify RCTs comparing laparoscopy with laparotomy for FIGO stage I ovarian cancer.[61] Another recent systematic review (search date March 2014) of Lu et al. was identified in the literature.[62] Their search retrieved 11 non-randomized comparative studies that compared laparoscopic surgery with open surgery for apparent early stage ovarian cancer, of which six were published in Chinese.

No RCT has been published till date and the non-randomized studies suffer from serious shortcomings. All studies published in English also included patients who had adnexectomy before the laparoscopic staging surgery, possibly obscuring a disadvantageous effect of an increased risk of tumour spill in case of laparoscopic surgery. Also non-epithelial tumours were often included. None of the English-language papers performed case-mix correction for differences in prognostic factors, introducing bias in the reported results. Therefore, the evidence is judged to be of very low level for all outcomes.

As primary studies had serious flaws and were not adjusted for case-mix, the pooled results of the meta-analysis were judged to be inappropriate and it was decided to report the range of results for each outcome instead.

Overall survival

Only one of the English-language studies included in the review of Lu et al. (N=113) reported on overall survival.[63] The laparoscopy group had 1 year follow-up with 100% survival. In the laparotomy group, median follow-up was longer (25 months), survival at the end of their follow-up was 96.6% (data in table probably incorrectly reported: 13.3+/-10.2 months vs. 27.7+/-15.4 months, p<0.0001). No case-mix adjustment was done.

Liu et al.[64] report a similar 3-year survival rate (97.14% vs 97.50%) and a slightly lower 5-year survival rate for the laparoscopy group (94.11% vs 96.30%; p>0.05) but sample size was small (N=75) and no case-mix adjustment was performed.

Koo et al.[65] (N=77) reported a 3-year survival rate of 86.1% vs 94.7% (no case-mix adjustment).

Progression-free survival and disease-free survival

No data on progression-free survival were reported.

Only one of the English-language studies included in the review of Lu et al. (N=113) reported on disease-free survival.[63] Laparoscopic staging resulted in a lower disease-free survival than laparotomy (13.3+/-10.2 months vs. 25.7+/-15.0 months, p<0.0001), but no case-mix adjustment was done.

Liu et al.[64] reported a median tumour-free survival time of 54.3 months in the laparoscopy group versus 57.2 months in the laparotomy group (N=75; no case-mix adjustment).

Koo et al.[65] (N=77) reported a mean DFS of 59.3 months (95% CI 51.8-66.7 months) in the laparoscopy group vs 66.3 months (95% CI 62.8-69.9 months) in the laparotomy group (p=0.367) (no case-mix adjustment).

Recurrence rate

Seven observational studies (N=360) included by Lu et al. reported unadjusted data on recurrence rate.[62] The calculated odds ratios ranged between 0.04 (95% CI 0.01 to 0.38) and 6.29 (95% CI 0.28 to 140.86).

Liu et al.[64] reported a recurrence rate of 5.71% in the laparoscopy group versus 5.00% in the laparotomy group (p>0.05; no case-mix adjustment).

Koo et al.[65] (N=77) reported a recurrence rate of 8.3% in the laparoscopy group and 3.8% after laparotomy (p=0.586) (no case-mix adjustment).

Complications

Four observational studies (N=145) included by Lu et al. reported on postoperative mortality.[62] The calculated odds ratios ranged between 0.35 (95% CI 0.01 to 9.24) and 0.53 (95% CI 0.07 to 4.01).

Five studies (N=285) reported on intra-operative complications.[62] The calculated odds ratios ranged between 0.28 (95% CI 0.01 to 6.10) and 5.43 (95% CI 0.21 to 140.18).

Eight studies (N=366) reported on postoperative complications.[62] The calculated odds ratios ranged between 0.13 (95% CI 0.02 to 0.80) and 0.69 (95% CI 0.15 to 3.18).

Liu et al.[64] (N=75) reported a similar complication rate in both groups (11.43% vs 12.50%; p>0.05) but more poor wound healing in the laparotomy group (0% vs 22.50%; p<0.05).

Koo et al.[65] (N=77) reported a similar proportion of patients with postoperative complications in both groups (no case-mix adjustment). Intraoperative complications were more frequent in the laparotomy group (0 vs 5.7%; p=0.548)

Conclusions

- The available evidence does not allow to draw a conclusion about the effect of laparoscopic staging on overall survival, progression-free survival and recurrence rate in patients with early stage ovarian cancer.
- There is evidence of very low quality that laparoscopic staging is associated with less postoperative complications and a lower postoperative mortality than laparotomy. The available evidence does not allow to draw a conclusion about intra-operative complications.

Factor	Comment
Balance between clinical benefits and harms	The limited available evidence remains inconclusive whether or not survival outcomes after laparoscopy are non-inferior to laparotomy. Three concerns impede the general use of laparoscopy for early stage ovarian cancer. First, some areas of the abdomen are more difficult to assess for metastases with laparoscopy as no palpation is possible, e.g. the back side of the liver, spleen, diaphragm. Second, there is a very small risk for port site metastasis.[66] Third, and most importantly, when the tumour is extracted during laparoscopy, the integrity of the tumour cannot be ensured and it is not proven that the use of an endobag is completely safe. In a large observational study, no difference was made between intraoperative rupture and rupture due to surgical needle aspiration; both were classified as rupture during laparoscopy. Overall, intraoperative rupture of any kind was a poor prognostic factor.[67] Therefore, the GDG does not recommend the use of laparoscopy in general. Laparoscopy can be considered, however, if the chance of invasive disease is considered to be low preoperatively and the tumour is small (by consensus, the GDG suggests smaller than 6 cm). Also for re-staging after laparotomy (and if the abdomen is already assessed by palpation) or in case of a re-staging procedure for a tumour with low risk of peritoneal spread (e.g. mucinous tumour), laparoscopy can be considered.
Quality of evidence	As the body of evidence consists of observational studies with a small sample size and unadjusted results only, the quality of evidence is considered to be of very low level.
Costs (resource allocation)	Seven observational studies (N=433) included by Lu et al. reported on hospital stay.[62] Six studies reported a significant shorter hospital stay after laparoscopy, one study found no difference. The mean differences ranged between -9.28 (95% CI -10.76 to -7.80) and 0.20 (95% CI -3.20 to 3.60). No additional information about costs was available.

| **Patient values and preferences** | Literature review

Geomini et al. published the results of an interview with 43 women with a pelvic mass who were awaiting an operation. In a scenario with one percent risk for malignancy, 98% of the women preferred laparoscopy to laparotomy. At a probability of malignancy of 50%, 62% of the women had switched their preference to laparotomy. Eleven percent of the women still | preferred laparoscopy in a scenario with a risk of 90% on malignancy.[37]

Comments from patient representatives

It is the opinion of the patient representatives that for the majority of patients, the oncological safety of the operation comes first. Therefore, the morbidity associated with laparotomy is considered acceptable. |

Recommendations	Strength of Recommendation	Level of Evidence
• Do not routinely consider laparoscopy for (presumed) early stage ovarian cancer. Laparoscopy can be considered if the chance of invasive disease is considered to be low preoperatively and the tumour is small (< 6cm). • For restaging surgery, laparoscopy can be considered if the primary tumour is at low risk for peritoneal spread or if the whole abdomen was assessed during laparotomy when the primary tumour was removed.	Weak	Very low

4 CLINICAL RECOMMENDATIONS: ADVANCED STAGE DISEASE

4.1 Introduction

The majority of ovarian cancer patients present with advanced stage disease that has already spread throughout the abdominal cavity. Cytoreductive surgery and systemic therapy are the cornerstones of therapy for advanced disease. The carboplatin-paclitaxel combination has been the standard first-line systemic treatment for more than 20 years, but new (targeted) treatments and alternative approaches for administration haven been and are being investigated.

In this chapter, we focus on the role of cytoreductive surgery, how to predict the end result of surgery, the timing of surgery and alternative forms of administering first-line chemotherapy.

4.2 Laparoscopy, PET-CT and MRI to predict end result of cytoreductive surgery

One systematic review[68] and four primary DTA studies were found that addressed the diagnostic accuracy of one of the index tests of interest. The review addressed the use of laparoscopy in assessing resectability. Two primary studies addressed MRI and/or CT,[69, 70] one diffusion weighted MRI (DW-MRI)[71] and one assessed ^{18}F-FDG PET-CT.[72]

Unfortunately, none of these studies analysed or performed these index tests as an add-on test to patients who were considered resectable by CT-scanning. Furthermore, one study included a small subset of ovarian cancer cases with a non-epithelial histologic type[69] and two studies included subjects with stage I and II ovarian cancer.[69, 70]

RCTs that addressed the effect of the various imaging modalities on survival and other patient important outcomes were not identified, except for one

ongoing RCT (LapOvCa trial), that will compare laparoscopy vs. no laparoscopy in patients that are considered resectable by conventional staging.[73]

4.2.1 Laparoscopy

The selected systematic review[68] assessed the role of laparoscopy after the diagnostic work-up of patients suspected of advanced ovarian cancer (and planned to receive primary debulking surgery) in predicting non-resectability of disease. The search date of the review was February 2013 and an update of the search did not result in any new studies. The overall risk of bias of the review was judged to be low, although the source of funding or support was not reported for each of the included studies.

The review included seven studies on six cohorts with a total of 408 patients. Only two of the seven studies avoided partial verification bias and reported sufficient data to calculate sensitivity and specificity. However, no meta-analysis could be performed. The sensitivities of these two studies were 0.70 (95% CI 0.57 to 0.82) and 0.71 (95% CI 0.44 to 0.90), respectively, and the specificities of both studies were 1.00 (95% CI 0.90 to 1.00). In both studies no false positives were found (patients considered not resectable by laparoscopy, but who turned out to be resectable by laparotomy). Negative predictive values (NPV) were 0.75 (95% CI 0.55 to 0.86) and 0.96 (95% CI 0.56 to 0.99), respectively.

In a hypothetical study of 1 000 patients and with a prevalence of 45% (= average prevalence of two included studies) 130-135 patients (95% CI 45-81 to 193-252) would be incorrectly classified as being resectable (FNs) and 0 patient (95% CI 0 to 33-55) would be incorrectly classified as not being resectable (FPs).

4.2.2 MRI or CT

One study[69] prospectively evaluated ovarian cancer staging and tumour resectability with CT and/or conventional T1w/T2w MRI. Eighty-two women suspected of ovarian cancer were included and imaged (CT: n = 43 or MRI: n = 50; 11 underwent both tests). Applicability concerns were found for patient selection and the index test.

In six of 43 CT patients (14%) and in 11 of 50 MRI patients (22%) cytoreduction was not successful. However, no definition of "successful"

cytoreduction was presented. The sensitivities for "unsuccessful cytoreduction" of CT and MRI were 0.50 (95% CI 0.12 to 0.88) and 0.91 (95% CI 0.59 to 1.0), respectively. The specificities were 1.0 (95% CI 0.91 to 1.0) and 0.97 (95% CI 0.87 to 1.0), PPVs 1.0 (95% CI 0.29 to 1.0) and 0.91 (95% CI 0.59 to 1.0) and NPVs were 0.93 (95% CI 0.80 to 0.98) and 0.97 (95% CI 0.87 to 1.0).

In a hypothetical study of 1 000 patients and with a prevalence of 18% (= average study prevalence), 90 (95% CI 22 to 158) vs. 16 (95% CI 0 to 74) patients would be incorrectly classified as 'successful cytoreduction' (FNs) by CT and MRI, respectively, and 0 (95% CI 0 to 74) vs. 25 (95% CI 0 to 107) patients would be incorrectly classified as 'unsuccessful cytoreduction' (FPs).

The <u>second study</u>[70] retrospectively assessed the accuracy of CT and MRI in predicting residual disease >2 cm in patients with ovarian cancer. One-hundred and thirty-seven women with newly diagnosed primary epithelial ovarian cancer were included and imaged (CT: n = 91 or MRI: n = 46). The study was judged to be of high risk of bias for patient selection and reference standard. Applicability concerns were found for all domains.

In 116 (85%) patients, cytoreductive surgery was successful, which was defined as residual disease of <2 cm in maximum diameter. Of the 21 unsuccessfully cytoreduced patients 15 and 6 had stage III and IV disease respectively. No statistically significant difference between CT and MRI (p = 1.0) for the detection of inoperable tumour was found. The sensitivities for residual disease >2 cm of CT and MRI were 0.79 (95% CI 0.49 to 0.95) and 0.71 (95% CI 0.29 to 0.96), respectively. The specificities were 0.99 (95% CI 0.93 to 1.0) and 1.0 (95% CI 0.91 to 1.0), PPVs 0.92 (95% CI 0.62 to 1.0) and 1.0 (95% CI 0.48 to 1.0) and NPVs were 0.96 (95% CI 0.89 to 0.99) and 0.95 (95% CI 0.83 to 0.99), respectively.

In a hypothetical study of 1 000 patients and with a prevalence of 15% (= study prevalence), 90 (95% CI 22 to 158) vs. 16 (95% CI 0 to 74) patients would be incorrectly classified as 'successful cytoreduction' (FNs) by CT and MRI, respectively, and 0 (95% CI 0 to 74) vs. 25 (95% CI 0 to 107) patients would be incorrectly classified as 'unsuccessful cytoreduction' (FPs).

4.2.3   Diffusion-weighted MRI (DW-MRI)

One study[71] prospectively assessed the diagnostic accuracy of MRI in combination with diffusion-weighted imaging (DW-MRI) compared to exploratory laparotomy in predicting incomplete primary cytoreductive surgery (defined as residual tumour size >1 cm) for ovarian cancer. Thirty-four patients with advanced stage ovarian carcinoma were included. The study was judged to be of high risk of bias for patient selection, index test and reference standard. Applicability concerns were found for patient selection and the index test.

Cytoreduction was incomplete for eight patients (24.5%). Using a self-made predictive score based on abdominal tumour spread, a ROC curve was generated with an area under the curve for diffusion-weighted MRI of 0.938 (no confidence interval presented). A score ≥ 6 had the highest overall accuracy at 91%. The sensitivity for non-resectability of DW-MRI was 0.75 (95% CI 0.35 to 0.97), specificity 0.96 (95% CI 0.80 to 1.00), PPV 0.86 (95% CI 0.42 to 1.00) and NPV 0.93 (95% CI 0.76 to 0.99).

In a hypothetical study of 1 000 patients and with a prevalence of 24% (= study prevalence) 60 patients (95% CI 7 to 156) would be incorrectly classified as being resectable (FNs) and 30 patients (95% CI 0 to 152) would be incorrectly classified as not being resectable (FPs).

4.2.4 ^{18}F-FDG PET-CT

One article[72] concerned a prediction study with a DTA component, aiming to develop a ^{18}F-FDG PET-CT based nomogram to predict residual tumour size > 0 cm in advanced stage ovarian cancer patients. Three-hundred and forty-three patients were included and allocated to a development (n=240) and validation set (n=103). The study was judged to be of high risk of bias for patient selection and reference standard. Serious applicability concerns were found for the index test (which included not only imaging elements, but also an unvalidated surgical aggressiveness index). Complete cytoreduction was achieved in 120 (35%) patients. The sensitivity for residual disease >0 cm of PET-CT was 0.66 (95% CI 0.60 to 0.73), specificity 0.88 (95% CI 0.80 to 0.93), PPV 0.91 (95% CI 0.85 to 0.95) and NPV 0.58 (95% CI 0.51 to 0.66). In a hypothetical study of 1 000 patients and with a prevalence of 65% (= study prevalence) 221 patients (95% CI 175 to 260) would be incorrectly

classified as having no residual tumour (FNs) and 42 patients (95% CI 24 to 70) would be incorrectly classified as having residual disease >0 cm (FPs).

Conclusions

- **In women with advanced stage ovarian cancer, no firm conclusions can be drawn regarding the accuracy of**
- **laparoscopy to predict residual disease >1 cm (very low level of evidence for sensitivity)[68]**
- **MRI vs CT to predict undefined 'unsuccessful reduction' or residual disease >2 cm (very low level of evidence for sensitivity; Forstner 1995, Qayyum 2005)[69, 70]**
- **DW-MRI to predict residual disease >1 cm (very low level of eidence; Espada 2013)[71]**
- **PET/CT to predict residual disease >0 cm (very low level of evidence; Shim 2015)[72]**

Factor	Comment
Balance between clinical benefits and harms	Patients diagnosed with advanced stage ovarian cancer have (at least) CT-scan of the abdomen and pelvis and imaging of the thorax to determine the stage of the disease. If stage IIIC or IV disease with extensive tumour load is seen, it is difficult to judge resectability based on CT alone.
	Therefore, the role of laparoscopy, DW-MRI and FDG-PET-CT in addition to CT to assess resectability of the tumour has been investigated. All three techniques have a high specificity and moderate sensitivity, meaning they can correctly predict incomplete debulking or debulking to lesions with <1cm diameter in a substantial number of patients, but not all. Evidence does not allow, however, to evaluate the added valued if performed in addition to CT, or to compare the three techniques.
	Laparoscopy

Factor	Comment
	Laparoscopy allows for taking multiple biopsies to confirm the diagnosis histopathologically, which is very important to exclude benign disease or other types of malignant tumours that would need other treatment.
	DW-MRI
	If MR imaging is considered, diffusion-weighted MR[GV1] should be included in the imaging protocol, as it has been shown that adding DW-MRI to routine MRI improves sensitivity and specificity for depicting peritoneal metastases.[74] Given the promising published results and experience in academic centres, MRI with DWI can be considered if CT and/or laparoscopy are insufficient to judge the spread of the disease and operability.
	Necessary infrastructure is widely available in Belgium, but the applicability outside academic centres and the value in terms of clinical outcomes are not yet known. Therefore, it is advisable to collect further data when MRI with DWI is implemented in daily practice.
	PET-CT
	Specificity of PET-CT appears more limited compared to MRI and laparoscopy, although direct

Factor	Comment
	comparison is not possible. The value of PET-CT in advanced ovarian cancer may be the identification of extra-abdominal disease not seen on other imaging.[75] However, the role PET-CT in staging of ovarian cancer (stage III vs stage IV) is out of scope for this guideline.
Quality of evidence	There is no evidence for patient important outcomes (OS, PFS, QoL, adverse events)
	For the diagnostic accuracy outcomes, the level of evidence was judged to be low to very low, due to risk of bias (patient selection and reference standard), applicability concerns in all domains and/or imprecision (wide confidence interval, small sample size).
Costs (resource allocation)	No information
Patient values and preferences	Literature review
	No information.
	Comments from patient representatives
	Both laparoscopy and MRI are acceptable to the majority of patients. MRI has the advantage that no radiation exposure is involved.

Recommendations	Strength of Recommendation	Level of Evidence
• In addition to initial staging CT scan, laparoscopy or DW-MRI can be considered for stage III or IV ovarian cancer, to assess the resectability of the abdominal tumour.	Weak	Very low (MRI) Low (laparoscopy)
• Results of a staging PET/CT should not be used to assess resectability of the abdominal tumour.	Weak	Very low

4.3 Aim of cytoreductive surgery: no macroscopic disease

4.3.1 Background

Since the first half of the previous century, surgical removal of as much tumour as possible has been advocated for the treatment of advanced ovarian cancer. In 1975, a first observational study was published showing that survival is inversely related to the amount of residual disease at the end of surgery. Since then, many more studies have confirmed these findings. However, questions have been raised about the direct causal relationship between surgical efforts and improved survival, as tumours that can be more easily resected may have intrinsically a better prognosis. Furthermore, the definition of the maximum diameter of residual that can be considered as 'optimal debulking', has been changing over the years.[76]

To formulate a recommendation regarding the optimal goal of cytoreductive surgery, we reviewed the literature in order to answer the following two questions:

- What is the prognostic value of the maximum diameter of residual disease at the end of surgery?

- Does (ultra)radical surgery to obtain complete cytoreduction have a beneficial effect on survival?

4.3.2 Prognostic value of the maximal diameter of residual disease at the end of surgery

During the pre-assessment of the literature for this topic, a high-quality Cochrane systematic review[77] was identified, and it was decided to use this review as a basis. The Cochrane review included 11 comparative observational studies with high risk of bias due to their retrospective nature. Despite statistical adjustment for important prognostic factors, selection bias was considered to be of particular concern. Quality of life and adverse events were not addressed in any of the included studies.

A search update of the review resulted in ten comparative observational studies that were included.[78-87] Five studies included women with stage IIIC-IV ovarian cancer,[80, 82-84, 86] two studies only women with stage IIIC cancer[78, 79] and one study only women with stage IV cancer.[87] Two studies also included a small proportion of women with a FIGO stage lower than stage IIIC.[81, 85] Three studies addressed specific populations: only women 65

years and older,[82] only women who underwent rectosigmoid colectomy[83] and only women with residual disease (RD) ≤1 cm.[86] Median follow-up ranged from 25 to 43 months. In four studies the duration of follow-up was not mentioned.[79, 83, 86, 87]

Possible overlap between the study populations of the following pairs of studies cannot be excluded: Chang 2012a[80] and Chang 2012b[79], Hofstetter 2013[81] and Polterauer 2012[85], Bristow 2011[78] and Peiretti 2012[83] and Peiretti 2010[84] and Peiretti 2012.[83] Therefore, whenever possible, sensitivity analyses were performed with leaving out the smallest study and the study with the largest effect.

All studies were considered to have a high risk of bias. Despite the multivariate analyses, confounding by indication cannot be excluded. In addition, in almost all cases the adjusted HRs were derived from prognostic models, which seem to have been assessed based on significance testing and not on including putative confounders in the analysis, irrespective of statistical significance.

Results

The outcomes **quality of life** and **adverse effects** were not assessed according to debulking status in any of the studies.

Overall survival

The search update resulted in six more studies that addressed this outcome. Adjusted hazard ratios are presented.[78-80, 82, 86, 87]

The pooled estimate of the HR for mortality of <u>RD 0.1-1.0 cm vs. microscopic disease</u> changed from 2.20 (95% CI 1.90 to 2.54)[77] to <u>2.21 (95% CI 1.97 to 2.47)</u>, based on 12 studies.

The pooled estimate of the HR for mortality of <u>RD >1 cm vs. microscopic disease</u> changed from 3.16 (95% CI 2.26 to 4.41),[77] to <u>3.08 (95% CI 2.44 to 3.88)</u>, based on eight studies. Removing one of the studies of study pairs that had possible overlap did not result in important changes of the point estimates nor the width of the 95% CIs.

Two other studies reported the HR for 3-year OS of *any* RD (c.q. minimal RD (≤1 cm) or gross RD (>1 cm)) compared to complete debulking: in women with stage IIIA-IV ovarian cancer the HR was 2.95 (95% CI 1.87 to 4.67)[81] and in women with stage IIIC-IV ovarian cancer the HR was 1.4 (95% CI 1.0 to 2.1).[85] The pooled HR was 2.03 (95% CI 1.01 to 4.10).

Finally, one study reported that the presence of any macroscopic residual disease after rectosigmoid colectomy was the only significant risk factor for OS (p=0.003).[83]

Progression-free survival

The search update resulted in three more studies that addressed this outcome.[79, 80, 87]

The pooled estimate of the HR for recurrence of <u>RD 0.1-1.0 cm vs. microscopic disease</u> changed from 1.96 (95% CI 1.72 to 2.23), [77]) to 1.91 (95% CI 1.70 to 2.15), based on five studies.

The pooled estimate of the HR for recurrence of <u>RD >1 cm vs. microscopic disease</u> changed from 2.36 (95% CI 2.06 to 2.71, based on one study) to <u>2.32 (95% CI 2.05 to 2.62</u>, based on four studies) (see appendix). Removing one of the studies of study pairs that had possible overlap did not result in important changes of the point estimates nor the width of the 95% CIs.

One other study reported the HR for 3-year progression-free survival of *any* RD (c.q. minimal RD (≤1 cm) or gross RD (>1 cm)) compared to complete debulking in women with stage IIIC-IV ovarian cancer: this HR (adjusted for FIGO-stage, histological grade, histological type and age) was 1.6 (95% CI 1.3 to 2.1).[85]

Two more studies also reported on progression-free survival, but did not quantify the results. One study reported that age greater than 60 years (p=0.025), stage IV vs. IIIC (p=0.037) and any residual disease (p=0.032) had an independent association with worse PFS.[84] Another study reported that in patients who underwent an upper abdominal procedure (UAP) those with completely resected disease had better PFS than those with <1 cm (p < 0.01).[86]

Conclusions
- **There is low level of evidence that residual disease of 0.1-1.0 cm and >1.0 cm leads to worse overall and progression-free survival than microscopic residual disease in women with advanced stage ovarian cancer.**
- **No RCTs or comparative observational studies were identified that adressed quality of life or adverse effects according to debulking status.**

4.3.3 Effect of (ultra)radical surgery

A high-quality Cochrane systematic review[88] was used as the basis for the literature review. The Cochrane review included only one comparative observational study with a high risk of bias. The search update resulted in two additional comparative observational studies.[80, 89]

All studies addressed women who underwent upfront primary surgery or adjusted their analyses for upfront versus interval debulking surgery. One study (included in Ang 2011)[88] addressed solely women with stage IIIC ovarian cancer and two studies excluded patients with stage IIIC when it was defined by lymph nodes invasion only. [80, 89] All studies were considered to have a high risk of bias. Despite the multivariate analyses, confounding by indication cannot be excluded. In addition, in all cases the adjusted HRs were derived from prognostic models, which seem to have been assessed based on significance testing and not on including putative confounders in the analysis, irrespective of statistical significance.

All studies compared ultra-radical or extensive surgery with standard surgery. In the Cochrane review, standard surgery was defined as total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy either with or without removal of enlarged lymph nodes (paraaortic, pelvic, obturator), and debulking of any other superficial tumour plaques. No new studies with the same comparator group were identified in the literature.

The two newly identified studies, however, included also some elements of bowel surgery in the standard surgery group: segmental small bowel resection[80] or rectosigmoid resection and appendectomy.[89] It was decided to include these two studies, as many centres would consider bowel surgery not as (ultra) radical but rather standard practice. In addition, the list of excluded studies of the Cochrane review was screened for studies that were excluded for bowel surgery in the standard group only. None of these studies could be included in our analysis.

All presented results were adjusted for several prognostic factors. Adjustment for residual disease however, is not appropriate as the effect of more radical surgery is at least partially achieved through a reduction of residual disease.

<u>**Results**</u>

The outcome **quality of life** was not assessed in any of the studies.

Overall survival

One study was identified that applied a multivariate analysis.[80] The HR for survival of ultra-radical surgery versus standard surgery (adjusted for age, FIGO stage and residual disease) was 0.56 (95% CI 0.37 to 0.87) and the median OS was 66 vs. 38 months (p= 0.01; unadjusted). One other study reported no significant differences between the surgical groups in the univariate analysis, which excluded 'type of surgery' from the multivariate analysis.[89]

Progression-free survival

In one study the HR for progression-free survival of ultra-radical surgery versus standard surgery (adjusted for FIGO stage, tumour grade and residual disease) was 0.62 (95% CI 0.42 to 0.92).[80] Median PFS was 18 vs. 11 months (p= 0.01; unadjusted).

Disease-free survival

This outcome was addressed in one study.[89] The HR for relapse or death of ultra-radical surgery versus standard surgery (adjusted for FIGO stage, tumour grade, presence of upper abdominal disease, amount of residual disease and timing of surgery (primary or interval)) was 1.66 (95% CI 1.16 to 2.39). Median disease-free survival was 15.9 vs. 19.3 months (statistically significant; not adjusted).

Adverse events

Only two studies reported some form of adverse events.

Death within 2 weeks following surgery occurred in 0 vs. 3 women (not adjusted for baseline imbalances; no denominators reported) in one study.[88] In another study postoperative death within 30 days occurred in 1/84 (1.2%) vs. 0/119 (0%) (RR = 4.24; 95% CI 0.17 to 102.72).[80]

Significant postoperative morbidity occurred in 32/84 (38.1%) vs. 14/119 (11.8%) women (RR = 3.24; 95% CI 1.84 to 5.68) and women who underwent radical surgery had significantly longer operative time, larger estimated blood loss, more blood transfusions, longer stay in the intensive care unit, and more lymphocysts than those who underwent standard surgery.[80]

Conclusions

- **In women with advanced stage ovarian cancer there is evidence from one observational trial of very low quality that ultra-radical surgery compared to standard surgery results in better overall survival.**

- **In women with advanced stage ovarian cancer there is evidence from one observational trial of very low quality that ultra-radical surgery compared to standard surgery results in better progression-free survival.**

- **In women with advanced stage ovarian cancer there is evidence from one observational trial of very low quality that ultra-radical surgery compared to standard surgery results in worse disease-free survival.**

- **In women with advanced stage ovarian cancer a difference in perioperative mortality between ultra-radical surgery and standard surgery could neither be demonstrated nor refuted.**

- **In women with advanced stage ovarian cancer there is evidence of very low quality that ultra-radical surgery results in significantly more postoperative morbidity, longer operative time, larger estimated blood loss, more blood transfusions, longer stay in the intensive care unit than standard surgery.**

- **No RCTs or comparative observational studies could be identified that adressed quality of life.**

Factor	Comment
Balance between clinical benefits and harms	Available evidence from observational studies consistently shows a survival benefit after complete debulking (no macroscopic disease at the end of surgery), compared to incomplete debulking, whether the maximum diameter is smaller or larger than 1 cm. There is some evidence that reduction to ≤ 1cm at the time of primary surgery is associated with a survival

Factor	Comment
	benefit, but to a lesser degree than cytoreduction to microscopic residual disease.
	All results included in the review were adjusted for other important prognostic factors. The prognostic impact of complete debulking was also confirmed in multivariate analyses of RCTs that included patients with good performance status and high metastatic tumour load.[90, 91]
	The prognostic significance of complete debulking to no residual tumour (but not cytoreduction to ≤ 1cm) also applies to interval debulking surgery.[91]
	To provide further information on the question of "treatment versus biology" (Is the better prognosis after complete debulking due to surgery or do tumours that can be completely debulked have intrinsically a better prognosis?), we also searched for studies comparing (ultra)radical surgery with standard surgery. Although evidence was limited, it supports the use of radical surgical techniques (such as diaphragm resection, peritoneal stripping, splenectomy etc.) to obtain complete resection of all macroscopic tumour.
	Given the consistently shown prognostic value of no macroscopic disease at the end of surgery and supporting evidence from the use of radical surgery, the GDG formulated a strong recommendation that complete debulking should be the aim of cytoreductive surgery. The term "optimal" should no longer be used as old definitions of "optimal" surgery (residual disease < 2cm or < 1cm) do no longer apply.[92]

Factor	Comment
Quality of evidence	<u>Low level of evidence</u>
	Evidence for the prognostic value of the end result of surgery is of moderate quality. However, as this is only indirectly supporting the use of advanced surgery, we kept the overall level of evidence at low level.
	The prognostic value is consistently shown in population-based observational studies and in more homogeneous populations within randomized trials. Moreover, RCTs on the subject are considered not feasible. For that reason, the GDG formulated a strong recommendation despite the low level of evidence.
Costs (resource allocation)	No information
Patient values and preferences	<u>Literature review</u>
	No information
	<u>Comments from patient representatives</u>
	In the experience of the patient representatives, the influence of radical surgery on long term quality of life is not a major drawback, the survival benefit weighing more importantly in the overall balance. However, as for early stage disease, patients should be informed in advance for the possible important consequences of lymphadenectomy.

Recommendation	Strength of Recommendation	Level of Evidence
• The aim of cytoreductive surgery for ovarian cancer (upfront or interval debulking surgery) should be to remove all macroscopic tumour.	Strong	Low

4.4 Neoadjuvant chemotherapy and interval debulking versus upfront surgery

One Cochrane review was identified that compared the effectiveness of primary debulking followed by chemotherapy with neoadjuvant chemotherapy followed by interval debulking.[93] This review was of good quality, and identified only one published RCT (EORTC 55971).[91] Initially, our search for newly published RCTs only identified the study of Greimel et al.[94] who reported on the quality of life data of the same population as Vergote et al.[91] The search was updated on September 1st, 2015 to include the CHORUS trial.[95]

The Cochrane review also identified two ongoing studies of which the publication planning is unknown.[96, 97] Safety results of the JCOG0602 trial were published as an abstract in 2014[96] and the primary analysis of overall survival is planned in 2016.

The EORTC study randomized 670 women with stage IIIC/IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma to primary debulking followed by six cycles of platinum-based chemotherapy (N=336) or neoadjuvant cisplatin followed by interval debulking (N=334).[91] The study had a high risk of bias for subjective outcomes (absence of blinding; no intention-to-treat analysis for quality of life) and a low risk of bias for objective outcomes.

The CHORUS trial randomized 550 women with stage IIIC/IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma to primary debulking followed by at least six cycles of platinum-based chemotherapy (N=276) or neoadjuvant platinum-based chemotherapy followed by interval debulking (N=274).[95]

Results

Overall survival

Meta-analysis of the two trials showed no significant difference for overall survival, and non-inferiority of neoadjuvant chemotherapy (HR for death = 0.93, 95% CI 0.81-1.06, 90%CI 0.83-1.03) (see appendix). Subgroup analysis by stage also showed no significant difference and non-inferiority for stage IV patients (HR of death = 0.80, 95% CI 0.77-1.04, 90%CI 0.65-0.99) and stage III patients (HR of death = 0.97, 95% CI 0.78-1.20, 90%CI 0.80-1.16). Subgroup analysis by metastatic tumour load showed no significant differences (HR of death; 0-5 cm: 1.12, 95% CI 0.58-2.15; 5-10 cm: 0.86, 95% CI 0.69-1.07; >10 cm: 0.88, 95% CI 0.69-1.12), but the non-inferiority border was not crossed for the category 5-10 cm (90%CI 0.71-1.04) and >10 cm (90%CI 0.72-1.08) and crossed for 0-5 cm (90%CI 0.64-1.94).

Progression-free survival

Meta-analysis of the two trials showed no significant difference for progression-free survival (HR for progressive disease = 0.97, 95% CI 0.86-1.09) (see appendix).

Serious adverse events

Primary debulking was associated with significantly more postoperative deaths (RR 6.94; 95% CI 2.06 to 23.44), grade 3-4 venous adverse events (RR 13.37; 95% CI 1.79 to 100.07) and grade 3-4 infections (RR 3.42; 95% CI 1.53 to 7.66), compared to neoadjuvant chemotherapy and interval debulking.

Results of the meta-analysis for serious adverse events are summarized in Table 19.

Table 19 – Neoadjuvant chemotherapy and interval debulking versus primary debulking followed by chemotherapy: serious adverse events

AE	Results (95% CI)
Postoperative death	RR 6.94 (2.06 to 23.44)
Postoperative haemorrhage grade 3-4	RR 1.01 (0.26 to 3.99)
Postoperative venous AE grade 3-4	RR 13.37 (1.79 to 100.07)
Postoperative infection grade 3-4	RR 3.42 (1.35 to 7.66)
Gastrointestinal fistula	RR 2.38 (0.47 to 12.12)
Urinary fistula	RR 0.94 (0.13 to 6.67)

Quality of Life

There was no clinically significant difference in global QoL between the two groups six or twelve months after treatment (MD -3.79; 95% CI -12.16 to 4.59 and MD -1.80; 95% CI -9.90 to 6.32, respectively). Also for the subdomains pain and dyspnoea, there was no significant difference between the two groups six and twelve months after treatment.

Conclusions

- There is evidence of high quality that the effect of neoadjuvant chemotherapy followed by interval debulking on overall survival is not inferior to primary debulking followed by chemotherapy in patients with stage IIIC or IV ovarian carcinoma.
- The available evidence of very low quality does not allow to draw a conclusion about the non-inferiority of neoadjuvant chemotherapy followed by interval debulking compared to primary debulking followed by chemotherapy in patients with stage IIIC or IV ovarian carcinoma and a metastatic tumour load of 0-5 cm. However, there is evidence of moderate quality that the effect of neoadjuvant chemotherapy followed by interval debulking on overall survival is not inferior to primary debulking followed by chemotherapy in patients with stage IIIC or IV ovarian carcinoma and a metastatic tumour load of >5 cm.

- There is evidence of moderate quality that the effect of neoadjuvant chemotherapy followed by interval debulking on progression-free survival is not inferior to primary debulking followed by chemotherapy in patients with stage IIIC or IV ovarian carcinoma.
- There is evidence of low quality that the effect of neoadjuvant chemotherapy followed by interval debulking on quality of life is not inferior to primary debulking followed by chemotherapy in patients with stage IIIC or IV ovarian carcinoma.
- There is evidence of high quality that primary debulking followed by chemotherapy is associated with more postoperative deaths than neoadjuvant chemotherapy followed by interval debulking in patients with stage IIIC or IV ovarian carcinoma.
- There is evidence of moderate quality that primary debulking followed by chemotherapy is associated with more postoperative grade 3-4 venous adverse events and infections than neoadjuvant chemotherapy followed by interval debulking in patients with stage IIIC or IV ovarian carcinoma.

Factor	Comment
Balance between clinical benefits and harms	Overall, in terms of survival outcomes, neoadjuvant chemotherapy is not inferior to primary debulking surgery in patients with FIGO stage IIIC or IV ovarian cancer. The risk of postoperative death and grade 3-4 adverse events is higher after primary debulking compared to interval debulking, but the difference does not remain in the overall survival curves.
	Results, however, differ for specific subgroups. For stage IV disease, survival may be better after neoadjuvant chemotherapy. For patients with more limited tumour load (maximum metastatic tumour diameter < 5cm on imaging), primary debulking may be preferable. Individual decisions will thus depend on stage, tumour burden, general

Factor		Comment
		condition, expected postoperative morbidity and judgement of resectability by the surgeon.
		Importantly, whether surgery is performed upfront or after neoadjuvant chemotherapy, the aim of the surgery should be complete resection of all macroscopic tumour (see 4.3) and neo-adjuvant chemotherapy cannot be a substitute for poor surgery.
Quality of evidence		High level of evidence
		Two multicentre RCTs with low risk of bias show consistent evidence for overall survival and postoperative death. Although for other important outcomes such as quality of life the quality of the evidence was not of high level, the overall level of

Factor	Comment
	evidence was not downgraded as the results were not contradictory to the recommendation.
Costs (resource allocation)	No information
Patient values and preferences	Literature review
	No information.
	Comments from patient representatives
	Preferences probably differ amongst patients. Patients may prefer primary surgery as it feels reassuring that the tumour has been removed. Otherwise, a good response to neoadjuvant chemotherapy can be reassuring and less extensive surgery after chemotherapy can be advantageous.

Recommendation	Strength of Recommendation	Level of Evidence
• Primary debulking surgery is preferable in stage III or IV ovarian cancer if tumour load is more limited and if it is expected that complete debulking can be achieved without considerable morbidity. Consider neoadjuvant chemotherapy and interval debulking surgery in patients with (biopsy proven) FIGO stage IIIC or IV cancer, especially in case of stage IV disease, high tumour load (maximum metastatic diameter > 5cm) or expected high morbidity.	Weak	High

4.5   Intra-peritoneal chemotherapy

One Cochrane review was found that compared intra-peritoneal chemotherapy with intravenous chemotherapy in the first-line treatment of advanced ovarian cancer.[98] Update of the search did not find other RCTs, only a secondary publication of an RCT already included in the Cochrane review was identified.[99]

Nine RCTs were included in the review. The majority of trials included only women with residual disease smaller than 1 or 2 cm at the end of cytoreductive surgery. All trials compared intravenous chemotherapy with a chemotherapy schedule that included a component of intraperitoneal administration, but schedules differed between trials (see Table 20). Six trials were considered to have a low risk of bias.

Table 20 – Intraperitoneal chemotherapy: chemotherapy regimens used in RCTs

Reference	Experimental arm	Control arm
Albers 1996	IV cyclophosphamide (600mg/m^2) + IP cisplatin (100mg/m^2) repeated every 3 weeks for a total of 6 cycles	IV cyclophosphamide (600mg/m^2) + IV cisplatin (100mg/m^2) repeated every 3 weeks for a total of 6 cycles
Gadducci 2000	IV epidox 60mg/m^2 + IV CTX 600 mg/m^2 + IP cisplatin 50 mg/m^2 repeated every four weeks for a total of six cycles	IV epidox 60mg/m^2 + IV CTX 600 mg/m^2 + IV cisplatin 50 mg/m^2 repeated every four weeks for a total of six cycles
GOG 172	IV paclitaxel 135mg/m^2 + IP cisplatin 100 mg/m^2 + IP paclitaxel 60mg/m^2, repeated every 3 weeks for a total of 6 cycles	IV paclitaxel 135mg/m^2 + IV cisplatin 75 mg/m2, repeated every three weeks for a total of 6 cycles
Kirmani 1994	IP cisplatin 200mg/m^2 + IP etoposide 350 mg/m^2; repeated every 4 weeks for a total of 6 cycles	IV cisplatin 100mg/m^2 + IV cyclophosphamide 600 mg/m^2; repeated every 3 weeks for a total of 6 cycles
Markman 2001	IV carboplatin (AUC9) for two courses every 28 days, followed 4 weeks later by IV paclitaxel 135mg/m^2 + IP cisplatin 100mg/m^2 repeated every three weeks for a total of six cycles	IV paclitaxel 135 mg/m^2 + IV cisplatin 75mg/m^2 repeated every three weeks for six cycles
Polyzos 1999	IP carboplatin 350 mg/m^2 + IV cyclophosphamide 600 mg/m^2; repeated every 3 to	IV carboplatin 350 mg/m^2 + IV cyclophosphamide 600 mg/m^2; repeated every 3 to

Reference	Experimental arm	Control arm
	4 weeks for a total of 6 cycles	4 weeks for a total of 6 cycles
Yen 2001	IV cyclophosphamide 500mg/m^2 + IV Adriamycin or epirubicin 50mg/m^2 + IP cisplatin 100mg/m^2; repeated every 3 weeks for a total of 6 cycles	IV cyclophosphamide 500mg/m^2 + IV Adriamycin or epirubicin 50mg/m^2 + IV cisplatin 50mg/m^2; repeated every 3 weeks for a total of 6 cycles
Yen 2009	paclitaxel on day 1 with cisplatin or carboplatin IP on day 2; repeated every 3 weeks for 6 cycles	paclitaxel on day 1 with cisplatin or carboplatin IV on day 2; repeated every 3 weeks for 6 cycles
Zylberg 1986	IV Adriamycin 20mg X 2 + fluorouracil 500mg X 2 + cisplatin 50mg + vincaleucoblastine 10mg + ifosfamide 1g X 2 + IP bleomycin 15mg + cisplatin 50mg + fluorouracil 500mg + Adriamycin 30mg	IV Adriamycin 35mg X 2 + fluorouracil 750mg X 2 + cisplatin 100mg + vincaleucoblastine 10mg + ifosfamide 1g X 2 + bleomycin 15mg

Results

Progression-free survival

Meta-analysis of five trials (1 311 women) showed a prolonged progression-free survival for women who received intra-peritoneal chemotherapy, with a HR of 0.78; 95% CI 0.70 to 0.86).

Overall survival

Meta-analysis of eight trials (2 026 women) showed a better overall survival after intraperitoneal chemotherapy, with a HR of 0.81; 95% CI 0.72 to 0.90. When only high quality trials were included, HR was 0.80; 95% CI 0.72 to 0.90.

Adverse events

The following severe adverse events (grade 3/4) were more likely to occur in the IP group:

Fever: RR 1.64; 95% CI 1.13 to 2.38

Fatigue: RR 2.32; 95% CI 1.06 to 5.07

Gastro-intestinal adverse events: RR 1.70; 95% CI 1.28 to 2.26

Infection: RR 3.34; 95% CI 2.06 to 5.43

Metabolic adverse events: RR 4.45; 95% CI 2.72 to 7.26

Pain: RR 7.47; 95% CI 4.41 to 12.67

Hearing loss was more frequent in women who received no intraperitoneal chemotherapy: RR 0.67; 95% CI 0.46 to 0.99

Quality of life (QoL)

Only one trial (GOG 172) assessed the influence on health-related quality of life of IP chemotherapy, compared to IV therapy.

Women in the IP arm reported worse QoL and pain prior to the fourth chemotherapy cycle and worse QoL 3 to 6 weeks post-treatment. There were no significant QoL or pain score differences between the treatment arms one year post-treatment.

One year after treatment, neurotoxicity symptoms were higher for women who received IP chemotherapy.

Von Gruenigen et al. published additional results in 2012. Twelve months after treatment, there were no meaning differences between the IP and IV group for the physical, social, emotional or functional well-being subscales.[99]

Conclusions

- **There is evidence of low quality that the effect of intra-peritoneal chemotherapy on progression-free survival may be superior to intravenous chemotherapy in patients with advanced stage ovarian cancer.**
- **There is evidence of low quality that the effect of intra-peritoneal chemotherapy on overall survival may be superior to intravenous chemotherapy in patients with advanced stage ovarian cancer.**
- **There is evidence of low to moderate quality that intra-peritoneal chemotherapy is associated with increased risk of grade 3-4 toxicity (fever, fatigue, gastro-intestinal adverse events, infections, metabolic adverse events, pain) compared to intravenous chemotherapy in patients with advanced stage ovarian cancer.**
- **There is evidence of low quality that intra-peritoneal chemotherapy may be associated with worse Quality of Life during and immediately after active treatment, but not one year**

after treatment, compared to intravenous chemotherapy in patients with advanced stage ovarian cancer. Neurotoxicity symptoms may be worse in patients who received intraperitoneal chemotherapy one year after treatment.

Factor	Comment
Balance between clinical benefits and harms	Available evidence from RCTs shows prolonged overall survival and progression-free survival after intraperitoneal chemotherapy compared to intravenous chemotherapy only. However, this benefit must be weighed against the increase in side effects and impact on quality of life. Furthermore, the RCTs have important flaws. In some studies, the method of administration (IP versus IV) was not the only difference between treatment arms (e.g. also different dose of cisplatin, weekly administration of paclitaxel) and apart of one small trial, the IP chemotherapy was not compared to the current standard IV chemotherapy of carboplatin AUC 5-6 and paclitaxel 175mg/m² (with or without bevacizumab). Given these shortcomings of current evidence and the increased adverse events in daily practice compared to the clinical trial setting, the GDG recommends not to routinely offer IP chemotherapy to women with advanced ovarian cancer. This applies *a fortiori* to hyperthermic intraperitoneal chemotherapy (HIPEC). In experienced centres, IP chemotherapy can be considered in fit patients with residual disease < 1 cm at the end of debulking surgery if toxicity is considered acceptable by the patient. However, as ovarian cancer care is very much dispersed in Belgium, there are very few centres with sufficient case load to function as expert centre for IP chemotherapy.

Quality of evidence	Low level of evidence. The evidence derived from RCTs was downgraded for critical outcomes because of imprecision and most importantly, for indirectness (no comparison with current standard IV paclitaxel-carboplatin chemotherapy and more toxicity in daily practice compared to adverse events registered in the trial population).
Costs (resource allocation)	NA
Patient values and preferences	Literature review Blinman et al. interviewed 39 women with advanced stage disease after surgery to residual disease < 1cm about their preferences regarding intraperitoneal chemotherapy. The median survival benefits judged necessary to make IP chemotherapy worthwhile (n=20) were an extra 6 months beyond survival times of either 3 years or 5 years with IV chemotherapy and an extra 5% beyond survival rates of 50% at either 3 years or 5 years with IV chemotherapy, but patient preferences varied widely.[100]

Havrilesky et al. did a discrete choice experiment in 100 women with advanced or recurrent ovarian cancer. Women considered PFS the most important factor for treatment choices, however the majority of women was willing to accept reductions in PFS in return for improvements in side effects or convenience. In the fixed-choice scenario, 52% of all respondents chose intraperitoneal/intravenous treatment. Proportion was higher in women who had previously received intraperitoneal chemotherapy compared to women who had not (86% versus 42%).[101]

Comments from patient representatives

Patients prefer to be informed about intraperitoneal chemotherapy and the reasons why it is not offered as therapy of choice. As there is a lot of information available e.g. on the internet, often in favour of intraperitoneal chemotherapy, patients may otherwise feel they did not receive best available therapy.

Recommendation	Strength of Recommendation	Level of Evidence
• Do not routinely offer first-line intra-peritoneal chemotherapy* to women with advanced-stage ovarian cancer.	Weak	Low

*applies a fortiori to HIPEC

4.6 First-line weekly (dose-dense) chemotherapy

No systematic review on dose-dense chemotherapy in the first-line treatment of ovarian cancer was identified in the literature. Covens et al. performed a systematic review of all randomized controlled trials on first-line chemotherapy for ovarian cancer and could not identify RCTs comparing dose-dense platinum-paclitaxel with standard 3-weekly platinum-paclitaxel chemotherapy. The search date of that review was used as a starting point for our search.

Three published RCTs were identified in the literature, of which one was published in Chinese only and thus had to be excluded (the English abstract included insufficiently reported results).[102, 103] Abstracts of two additional

RCTs were found, but results of these two trials were not published so far.[104, 105]

Two trials (four publications) were finally included.[106-109] The first trial was performed by the Japanese Gynecologic Oncology Group (JGOG).[107, 108] Eighty-five Japanese centres participated. The experimental arm consisted of weekly paclitaxel (80mg/m^2) and 3-weekly carboplatin AUC 6mg/ml per min, compared to 3- weekly paclitaxel (180mg/m^2) and 3-weekly carboplatin AUC 6mg/ml per min in the control group. The second trial was executed in Italy and France, under the coordination of the Multicentre Italian Trials in Ovarian Cancer (MITO) group.[109] In that trial, both carboplatin (AUC 2 mg/ml per min) and paclitaxel (60 mg/m^2) were given weekly in the experimental arm.

Results

Progression-free survival

There was substantial heterogeneity between trials, with the Japanese trial showing better PFS after dose-dense therapy and the European trial showing no difference between the two treatment arms. Meta-analysis of the two trials resulted in a statistically not significant improvement of PFS (HR of 0.83; 95% CI 0.62 to 1.11).

Overall survival

Pooled results showed a HR of 0.95; 95% CI 0.60 to 1.50, again with substantial heterogeneity between trials with only the Japanese trial showing a survival benefit with dose-dense therapy.

Adverse events

In the Japanese trial, anaemia was the only grade 3-4 adverse event that differed significantly between the two groups, with a higher frequency in the dose-dense arm. The frequency of neuropathy did not differ between groups.

In the European trial, the dose-dense group showed a more favourable pattern for (all grade) neutropenia, thrombocytopenia, vomiting, hair loss and neuropathy, but a worse pattern for pulmonary toxic effects. For grade 3-4 toxicity, the following frequencies were noted (3-weekly vs once a week):

- neutropenia: 50% vs 42%
- febrile neutropenia: 3% vs 0.5%
- thrombocytopenia: 7% vs 1%
- grade 2 or higher neuropathy: 17% vs 6%
- grade 2 hair loss: 59% vs 29%

Quality of life

In the Japanese trial, overall QoL scores did not change over time in each group and there was no statistical difference between the two groups. Only the FACT-T (taxane) subscale showed significant lower QoL in the dose-dense group

In the European trial however, the treatment-by-time interaction favoured chemotherapy every week (p<0.0001).

Conclusions

- **Based on low to very low quality of evidence, it remains unclear whether dose-dense chemotherapy is superior or inferior in terms of PFS, OS, toxicity and quality of life.**

Factor	Comment
Balance between clinical benefits and harms	Two RCTs compared 3-weekly paclitaxel-carboplatin with weekly administration of chemotherapy. The MITO-7 study compared the 3-weekly schedule with weekly paclitaxel (60 mg/m^2) and weekly carboplatin (AUC 2 mg/ml per min).[109] The MITO-7 study thus included a weekly schedule but without dose-dense dosing. In the JGOG3016 study, weekly paclitaxel (80 mg/m^2) combined with 3-weekly carboplatin (AUC 6 mg/ml per min).[107, 108] In contrast to the European MITO-7 trial, the Japanese JGOG3016 trial showed a benefit in PFS and OS at the cost of more frequent grade 3-4 anaemia. The MITO-7 trial showed no difference in PFS or OS, but toxicity appeared to be reduced when the chemotherapy was administered weekly. Heterogeneity in results may be explained by differences in included population or the different treatment schedule.

The lack of survival benefit in a Western population seen in the MITO-7 trial is confirmed in two more trials that were not included for different reasons. The GOG 262 was only published in abstract form so far. No difference was noted in PFS (except for patients who received no bevacizumab) and a higher frequency of grade 3 anaemia and grade 2 sensory neuropathy was seen in the dose-dense regimen.[110] Furthermore, a Dutch trial also saw no difference in PFS or OS. In that trial, there was a second randomization after induction therapy (6 weekly cycles or 3 3-weekly cycles), to 3 or 6 additional 3-weekly cycles. Toxicity results are difficult to interpret, as approximately half of the patients received cisplatin instead of carboplatin.[111]

Overall, effectiveness of weekly paclitaxel-carboplatin compared to 3-weekly chemotherapy

	remains unclear, but available results suggest it is an acceptable alternative.
Quality of evidence	Very low level of evidence, mainly due to the heterogeneity and imprecision of the results.
Costs (resource allocation)	No information
Patient values and preferences	Literature review
	No information
	Comments from patient representatives
	No specific comments regarding this recommendation.

Recommendation	Strength of Recommendation	Level of Evidence
• Both weekly and 3-weekly administration of paclitaxel with 3-weekly carboplatin can be considered as first-line chemotherapy for advanced ovarian cancer.*	Weak	Very low

The use of bevacizumab in addition to first line chemotherapy will be discussed in a separate KCE HTA report

5 CLINICAL RECOMMENDATIONS: FOLLOW-UP
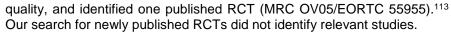
5.1 Background

After completion of first-line treatment, often routine regular follow-up is organized in view of possible treatment for the side effects of therapy, for further psychosocial support, to monitor the outcomes for research purposes and to detect recurrent disease early. The early detection and treatment of recurrent disease is often considered the most important aim of follow-up,

however evidence that early detection improves patient-important outcomes is lacking. The role of repeated clinical examination, imaging or FU of tumour markers is hence not clear.

In this chapter, we evaluate the role of routine CA125 measurements during follow-up after first-line treatment of ovarian cancer.

5.2 Routine CA125 measurements during follow-up

One Cochrane review was identified that compared the potential benefits of different strategies of follow-up in patients with epithelial ovarian cancer following completion of primary treatment.[112] This review was of good

quality, and identified one published RCT (MRC OV05/EORTC 55955).[113] Our search for newly published RCTs did not identify relevant studies.

Rustin et al. randomized 529 women with histologically confirmed epithelial ovarian, fallopian tube, or serous primary peritoneal cancer and in complete clinical remission after completion of first-line platinum-based chemotherapy (normal CA125 concentration) to early treatment based on increased CA125 concentrations (N=265) or delayed treatment on the basis of clinical recurrence (N=264).[113] The study had a low risk of bias for most outcomes, except for quality of life (statistical inconsistencies).

Overall survival

The overall survival did not differ significantly (HR = 0.98; 95% CI 0.80-1.20; p=0.85), and Cox models adjusted for stratification and prognostic factors did not change the overall result.

Quality of life

Median time spent with good global health score was 7.2 (95% CI 5.3-9.3) vs. 9.2 months (95% CI 6.4-10.5), the delayed treatment group had a significantly longer median time from randomization to first deterioration in global health score or death (3.2 vs. 5.8; HR = 0.71, 95% CI 0.58-0.88, p=0.002). Subgroup analyses of individual components of the QLQ-C30 subscales showed deterioration in score sooner in the early group than in the delayed group for almost all subscales.

Time to second- and third-line treatment

Women assigned to early treatment started chemotherapy 4.8 months (95% CI 3.6-5.3) earlier than those allocated to delayed treatment (time to second-line chemotherapy: HR = 0.29; 95% CI 0.24-0.35). Time to third-line treatment or death was also significantly shorter in the early treatment group (HR = 0.71; 95% CI 0.58-0.88).

Conclusions

- **There is evidence of low quality that the effect of early treatment based on increased CA125 concentrations is not significantly different in terms of overall survival from that of delayed treatment based on clinical recurrence in patients with ovarian carcinoma in complete clinical remission after completion of first-line platinum-based chemotherapy.**

- **There is evidence of moderate quality that early treatment based on increased CA125 concentrations leads to an earlier deterioration in global health score than delayed treatment based on clinical recurrence in patients with ovarian carcinoma in complete clinical remission after completion of first-line platinum-based chemotherapy.**

- **There is evidence of high quality that early treatment based on increased CA125 concentrations leads to a shorter time to second- or third-line treatment than delayed treatment based on clinical recurrence in patients with ovarian carcinoma in complete clinical remission after completion of first-line platinum-based chemotherapy.**

Factor	Comment
Balance between clinical benefits and harms	The role of routine CA125 measurements during follow-up after ovarian cancer treatment has been investigated in one randomized controlled trial. Early treatment based on raised CA125 alone in the absence of symptoms is not associated with improved survival but with an earlier deterioration in global health score and a shorter time to second- or third-line treatment. Early treatment based on raised CA125 alone is thus not recommended. How results of imaging (CT scan) influence treatment decisions regarding chemotherapy cannot be derived from the trial results.
	We cannot conclude from the trial that CA125 measurements during follow-up should be completely abandoned. First, only a subgroup of patients with complete response after first-line therapy were included in the trial.

Second, only a very small number of patients in the trial underwent secondary debulking surgery. Early detection of recurrent disease may render more patients eligible for complete removal of all tumour during secondary debulking (results DESKTOP trial awaited). Third, patients often prefer to know the CA125 results (see below). Finally, in the framework of clinical trials, tumour marker follow-up is often required.

Decisions whether or not to perform imaging in case of raised CA125 in an asymptomatic patient will depend on these factors, such as the possibility for secondary surgery or participation in clinical trials.

Quality of evidence	Low level of evidence
Costs (resource allocation)	No information.

Patient values and preferences	<u>Literature review</u> Patients prefer to know the Ca 125 results as it helps them to gain a feeling of being in control of their disease follow-up and management. A questionnaire performed by Oskay et al. showed that Ca 125 measurement is the procedure that induces the most anxiety, but, according to patients' opinion, it is also considered the most important factor during follow-up.[114] <u>Comments from patient representatives</u> Patient representatives confirm that it is reassuring to be actively followed by regular measurements of the tumour marker, avoiding feelings of being left alone after treatment completion. It is comforting to know that starting treatment for recurrent disease as early as possible is not warranted, as the feeling of urgency could induce a lot of stress and anxiety.

Recommendation	Strength of Recommendation	Level of Evidence
• Do not offer chemotherapy for recurrent ovarian cancer based on raised CA125 alone, in the absence of symptoms.	Strong	Low

6 IMPLEMENTATION AND UPDATING OF THE GUIDELINE
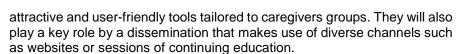
6.1 Implementation

6.1.1 Actors of the implementation of this guideline

Clinical guidelines provide a tool for physicians to consult at different stages of the patient management pathway: screening, diagnosis, treatment and follow-up. They are developed according to highly codified principles, based on scientific information regularly updated from the international literature.

KCE formulates recommendations addressed to specific audiences (clinicians, decision-makers, sickness funds, NIHDI, professional organizations, hospital managers…). KCE is not involved in the decision making process itself, or in the execution of the decisions.

The implementation of this guideline will be facilitated by the College of oncology and scientific professional associations. An online implementation tool similar to the tools accompanying previous guidelines will be developed (www.collegeoncologie.be).

On the other hand the content of this guideline is intended to be disseminated by scientific and professional organisations. They can develop

attractive and user-friendly tools tailored to caregivers groups. They will also play a key role by a dissemination that makes use of diverse channels such as websites or sessions of continuing education.

6.1.2 Barriers and facilitators for implementation of this guideline

The identification of potential barriers and facilitators related to the use of this guideline is limited to a discussion held during the stakeholders meeting. More sophisticated methods could be used, but this would go beyond the scope of this project. More information on the identification of barriers and facilitators in guidelines implementation can be found in a recent KCE-report (see KCE website).[115]

During the stakeholders meeting, the following potential barriers related to the use of this guideline were discussed:

- The IOTA simple rules and the IOTA ADNEX model are easy to use but are currently not yet widely known by Belgian gynaecologists, according to the stakeholders. Further dissemination and training via the professional organisations and websites could enhance implementation.

- Insights in the histopathology of ovarian cancer, especially regarding differentiation grade, have changed over recent years. For example, serous tumours are no longer graded following a 3-tier system but typed as low-grade or high-grade serous tumours. For other histological types, differential grading is strongly recommended.[6] However, as clinical trials and clinical decision making e.g regarding adjuvant chemotherapy are still based on old data, grading following a 3-tier system may still be needed.

- Several randomized controlled trials investigating the use of intraperitoneal chemotherapy have shown a survival benefit compared to intravenous chemotherapy alone. However, the trials have several flaws, such as inappropriate control arm. In spite of these flaws, several international organisations issued recommendations in favour of intraperitoneal chemotherapy.[116-118] Furthermore, a recent publication with real-world data suggests that IP chemotherapy is feasible in daily practice, if expertise is present, and is associated with improved survival.[119] Other clinical experts voiced serious concerns regarding the quality of the available evidence.[120] The opposing views on the value of

the available evidence may hamper implementation of the recommendation regarding intraperitoneal chemotherapy. In addition, the experience and expertise needed for the administration of IP chemotherapy may be lacking in the majority of Belgian hospitals.

- Centralisation of care for ovarian cancer has been recommended in the KCE report "Organisation of care for adults with rare cancers and cancers with complex diagnosis and/or treatment".[121] However, till date, the organisation of care in reference centres has not been formally implemented. Hence, specialized surgical expertise may not be available for all Belgian patients.

6.2 Monitoring the quality of care

This guideline should be considered as a starting point to develop quality improvement programs that targets all caregivers concerned.

It can be used as a tool to support health policies to improve the quality of care, e.g. through the support of actions to increase caregivers' awareness and to improve their practice, or through the development (or revision) of sets of process and outcome quality indicators.

Illustrations of possible quality indicators are:[121, 122]

- Proportion of patients with formal pretreatment multidisciplinary approach before any decision for laparotomy or neoadjuvant chemotherapy.

- Proportion of patients with structured description of the initial and, if applicable, residual lesions in the surgery report

- Proportion of patients with frozen section at the time of surgical intervention for presumed early stage ovarian cancer

- Proportion of performed staging laparotomies in which all of the following procedures are included: total hysterectomy, bilateral salpingo-oophorectomy, cytology of the peritoneal cavity, infracolic omentectomy, random peritoneal biopsies and systematic pelvic and para-aortic lymphadenectomy if medium or high risk features

- Proportion of surgery reports for staging procedures with documented presence or absence of cyst rupture before or during surgery

- Proportion of debulking operations for advanced ovarian cancer at the end of which complete cytoreduction, defined as no macroscopic residual disease at the end of the operation, was achieved

KCE previously recommended to set up an integrative quality system in oncology, covering the development and implementation of clinical practice guidelines, the monitoring of the quality of care with quality indicators, feedback to health care providers and organizations and targeted actions to improve the quality if needed.[123]

6.3   Guideline update

In view of the rapidly evolving evidence, this guideline should be updated at least every five years. Each update should be accompanied by an update of the relevant patient information.

The KCE processes foresee that the relevance of an update would be yearly assessed for each published guideline by the authors. Decisions are made on the basis of new scientific publications on a specific topic (e.g. Cochrane reviews, RCTs on medications or interventions). Potential interest for groups of health practitioners is also considered in this process. If, in the meantime, important new evidence would become available, this should be taken into consideration. The timely implementation of new practice changing evidence is organised in cooperation with the College of Oncology.

This appraisal leads to a decision on whether to update or not a guideline or specific parts of it to ensure the recommendations stay in line with the latest scientific developments.

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