KCE REPORT 268Cs

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

SUMMARY

OVARIAN CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

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GOOD CLINICAL PRACTICE

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SUMMARY

OVARIAN CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

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FOREWORD

Ovarian cancer is far less given media coverage than breast cancer, yet it is the second most frequent among gynaecological cancers. With its late and atypical symptoms, it is often discovered at an advanced stage, when it has already metastasized. It is also ranked fifth on the list of causes of cancer-related death in women.

It was urgent to develop clinical practice guidelines on the management of ovarian cancer, and add these ones to our collection - increasingly extended – that was developed in collaboration with the College of Oncology. In this case, the development of dedicated clinical guidelines to ovarian cancer was clearly asked by the healthcare professionals, especially because the management of ovarian cancer patients seemed highly variable between hospitals. To find out if this is really the case, a next step is required, that is to say a study based on quality indicators. Indeed, the logical sequence for the development of a quality health care system is based on trustworthy clinical recommendations; on this strong basis, a series of quality indicators can be identified, to finally measure outcomes using these indicators and compare them with the levels of performance that patients are reasonably entitled to expect.

We are not yet there, but a lot of the work has already been accomplished, thanks to the joined efforts made in collaboration with the dynamic and motivated members of the guideline development group. We express our sincere gratitude for this fruitful collaboration. This type of work is only possible when clinical experts are willing to spend their time to share their knowledge and experience to serve the community. A form of "healing art" that is certainly not less noble than the care they provide to each of their patients.

Christian LÉONARD
Deputy general director

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General director

LIST OF ABBREVIATIONS

ABRÉVIATION	DÉFINITION
ADNEX	Assessment of Different NEoplasias in the adneXa
FIGO	International Federation of Gynaecology and Obstetrics
GDG	Guideline Development Group
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HIPEC	Hyperthermic intraperitoneal chemotherapy
HTA	Health Technology Assessment
IOTA	International Ovarian Tumour Analysis
KCE	Belgian health care knowledge centre
MRI	Magnetic resonance imaging
PET-CT	Positron emission tomography - computed tomography
RCT	Randomised controlled trial

1. INTRODUCTION

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 with this disease in Belgium. Survival is generally poor, with a five-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]

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. 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 subject of ongoing research. Therapeutic options and prognosis of recurrent disease highly depend on the time lapse between the end of the previous treatment and the occurrence of recurrent disease (platinum-free interval).

2. OBJECTIVES AND SCOPE OF THIS GUIDELINE

This guideline provides recommendations based on current scientific evidence for the diagnosis, treatment and follow-up of epithelial ovarian cancer. It is hypothesised that 'ovarian' cancers may originate from the Fallopian tube and in the advanced stages, it is difficult to distinguish tumours that started in the ovary, Fallopian tube or on the peritoneal surface. Consequently cancers of the fallopian tube and primary peritoneal cancer are also included in this guideline.

This guideline covers:

- Carcinoma of the ovary, fallopian tube and primary peritoneal carcinoma
- Epithelial carcinoma, e.g. serous, mucinous, clear cell or endometrioid histology
- 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, sex cord stromal tumours and carcinosarcomas.
- Screening
- Treatment of recurrent disease
- Palliative interventions

The role of bevacizumab in ovarian cancer treatment will be investigated in a separate KCE report.

3. METHODS

3.1. General approach

The Belgian guideline on the diagnosis, treatment and follow-up of ovarian cancer, developed by the College of Oncology in 2010[3] and the recent evidence-based guideline from the Scottish Intercollegiate Guidelines Network (SIGN),[4] served as a starting point to determine the research questions for this guideline.

Members of the Guideline Development Group (GDG) and representatives of professional organizations were asked to select research questions that were considered a priority for discussion 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-relevant outcomes.

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 removal of all macroscopic tumour result in improved prognosis of stage cIII-IV ovarian cancer, compared to incomplete debulking with residual macroscopic disease less than 1 cm or more than 1 cm?
- 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 first-line intraperitoneal carboplatin-paclitaxel chemotherapy compared to intravenous carboplatin-paclitaxel treatment?
- What is the effectiveness of first-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) report.

3.2. Systematic review of the literature

The Cochrane Library, Medline and Embase were searched for systematic reviews. In addition, the review list of the Cochrane Gynaecological Cancer Group was browsed for relevant reviews. In a second step, CENTRAL, Medline (including premedline) and Embase were searched for primary studies to update selected evidence syntheses. If no systematic review was available, a search for primary studies was performed from inception of the databases.

For the diagnostic questions, systematic reviews, diagnostic accuracy studies and RCTs were searched; for the other research questions, systematic reviews, RCTs or comparative observational studies were searched. Only articles published in Dutch, English and French were included.

The quality appraisal was performed using the AMSTAR checklist for systematic reviews, Cochrane Collaboration's tool for assessing risk of bias

for RCTs and comparative observational studies, and the QUADAS-2 checklist for diagnostic accuracy studies.

3.3. Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by KCE. This first draft, along with the evidence tables, was circulated to the GDG prior to the face-to-face meetings. Based on the discussions with the GDG, a second draft of the recommendations was prepared and once more circulated to the GDG for final approval.

To determine the level of evidence and strength of each recommendation, the GRADE methodology was followed (Table 1 and Table 2). The strength of a recommendation depends on the balance between all desirable and undesirable effects of an intervention (i.e. net clinical benefit), the quality of available evidence, patient values and preferences, and the estimated cost (resource utilization). For this guideline, no formal cost-effectiveness study was conducted.

Finally, the recommendations prepared by the GDG were submitted to key representatives of the relevant stakeholders (see colophon), who acted as external reviewers of the draft guideline.

As part of the standard KCE procedures, the current guideline was reviewed prior to its publication by three independent validators (cf. names in the colophon).

Table 1 – 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 2 – Strength of recommendations according to GRADE[$]

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).

[$] *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*

3.4. Patient involvement

A literature search was performed to identify information on the values and preferences of ovarian cancer patients regarding their care.

Furthermore, representatives of the patient organisation “Esperanza” were invited to review the draft recommendations from a patient perspective.

The patient representatives were asked the following questions:

- Have important considerations from a patient’s 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 in the scientific report.

4. CLINICAL RECOMMENDATIONS

The details of the evidence used to formulate the recommendations and best practice below are available in the scientific report and its supplements. The tables follow the sequence of the chapters of the scientific report.

4.1. Early-stage disease

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 and assessment of the need for adjuvant therapy.[3, 4]

We focus on two research questions that assess preoperative and intraoperative assessment of the tumour to facilitate surgical decision making (Risk of Malignancy Index (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.

4.1.1. Pre-operative assessment of a pelvic mass: comparison of predictive models

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 expectant 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"*

4.1.2. Intra-operative frozen section

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

4.1.3. Lymphadenectomy

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*

**Only non-comparative observational studies reporting on prevalence of lymph node metastases were reviewed.*

4.1.4. Adjuvant chemotherapy

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 patients with 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 IB, IC grade 1 or stage IA grade 2*
$defined as stage IB, IC grade 2-3 or stage IA grade 3

4.1.5. Laparoscopic surgery in early-stage ovarian cancer

Recommendation	Strength of Recommendation	Level of Evidence
• Do not routinely consider laparoscopic surgery 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 after laparotomy or for restaging of tumours at low risk for peritoneal spread.	Weak	Very low

4.2. Advanced-stage disease

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.

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

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

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 IVA 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

4.2.2. Aim of cytoreductive surgery: no macroscopic disease

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

4.2.3. Neoadjuvant chemotherapy and interval debulking versus upfront surgery

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

4.2.4. Intraperitoneal chemotherapy

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

**applies a fortiori to HIPEC*

4.2.5. First-line weekly (dose-dense) chemotherapy

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.*

4.2.6. Routine Ca 125 measurements during follow-up

Recommendation	Strength of Recommendation	Level of Evidence
• Do not offer chemotherapy for recurrent ovarian cancer based on raised Ca 125 alone, in the absence of symptoms.	Strong	Low

5. IMPLEMENTATION AND UPDATING OF THE GUIDELINE

5.1. Implementation

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). To this end they can use various channels such as websites or continuing education, and, if desired, transform this material into attractive and user-friendly tools tailored to caregiver groups.

The following barriers for implementation were identified:

- 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 as low-grade or high-grade serous tumours. For other histological types, differential grading is strongly recommended.[5] 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, these trials have several flaws, such as an inappropriate control arm. In spite of these flaws, several international organisations issued recommendations in favour of intraperitoneal chemotherapy.[6-8] 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.[9] Other clinical experts voiced serious concerns regarding the quality of the available evidence.[10] 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”.[11] 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.

5.2. Monitoring quality of care

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

The development of quality indicators is scheduled after the publication of this guideline. KCE previously recommended setting 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.[12]

5.3. Guideline update

In view of the rapidly evolving evidence, this guideline should ideally be updated every 5 years. Each update of the guideline should be accompanied by an update of the relevant patient information.

COLOPHON

Title:	Ovarian cancer: diagnosis, treatment and follow-up – Summary
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