European Society of Gynaecological Oncology (ESGO) Guidelines for Ovarian Cancer Surgery

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Objective: The aim of this study was to develop clinically relevant and evidence-based guidelines as part of European Society of Gynaecological Oncology's mission to improve the quality of care for women with gynecological cancers across Europe.

Methods: The European Society of Gynaecological Oncology council nominated an international multidisciplinary development group made of practicing clinicians who have demonstrated leadership and interest in the care of ovarian cancer (20 experts across Europe). To ensure that the statements are evidence based, the current literature identified from a systematic search has been reviewed and critically appraised. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group (expert agreement). The guidelines are thus based on the best available evidence and expert agreement. Before publication, the guidelines were reviewed by 66 international reviewers independent from the development group including patients representatives.

Results: The guidelines cover preoperative workup, specialized multidisciplinary decision making, and surgical management of diagnosed epithelial ovarian, fallopian tube, and peritoneal cancers. The guidelines are also illustrated by algorithms.

Key Words: Ovarian cancer, Guidelines, Surgery, Algorithms

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Copyright © 2017 by IGCS and ESGO ISSN: 1048-891X DOI: 10.1097/IGC.00000000001041 The project has been initiated by the European Society of Gynaecological Oncology (ESGO), which has provided administrative and meeting expenses support. The decision to develop guidelines has been made by the Guidelines, Recommendations and Quality Assurance Committee of the ESGO, with the approval of the ESGO Council. The only external funding source was a grant from the Institut National du Cancer (INCa, France). The ESGO is a nonprofit knowledgeable society. The INCa is a French government agency.

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Andreas duBois and Ignace Vergote contributed equally. The development group (including all authors) is collectively responsible for the decision to submit for publication. Denis Querleu (chair) and François Planchamp (co-chair, methodologist) have written the first draft of the manuscript. Systematic literature search was completed by François Planchamp. All other contributors have actively participated to the development group, given personal input, reviewed the manuscript, and given the final approval before submission.

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The development of guidelines and quality indicators is one of the core activities of the European Society of Gynaecological Oncology (ESGO), as part of ESGO's mission to improve the quality of care for women with gynecological cancers across Europe. The Guidelines Committee led by Prof Denis Querleu and experts in the field started its work within the framework of ESGO in 2013 with the aim to elaborate a complete set of guidelines and associated quality indicators for the management of gynecological cancers, in collaboration with related sister knowledgeable societies, whenever relevant and possible.

Ovarian cancer is the leading cause of death among all gynecological cancers, with most patients presenting with advanced-stage tumors, as defined by the spread of the disease outside the pelvis.^{1,2} Because the surgical management of advanced ovarian cancer involves complex surgery, quality of surgical care is a major component of the multidisciplinary management of the disease. The ESGO developed a set of quality assurance criteria, using a rigorous methodology, for advanced ovarian cancer surgery that can be used to audit and improve the clinical practice in a straightforward and practical way.³ To complete the set concerning the management of patients with ovarian cancer, the decision to develop guidelines for ovarian cancer surgery has been made by the Guidelines, Recommendations and Quality Assurance Committee of the ESGO, with the approval of the ESGO Council.

OBJECTIVE

The objectives of the guidelines are to improve and homogenize the management of patients with ovarian cancer. The guidelines cover diagnosis and preoperative workup, specialized multidisciplinary decision making, and surgical management for patients with epithelial ovarian cancer and provide information for discussion with patients and carers. The guidelines exclude the management of borderline tumors and do not include any economic analysis of the strategies. These guidelines are focused on the role, objectives, and standards of the surgical management of diagnosed epithelial ovarian cancer and, by extension, fallopian tube and serous peritoneal carcinoma. The management of nonepithelial tumors and borderline tumors is not included. Screening of ovarian cancer and prophylaxis is not addressed. Diagnosis and management of adnexal masses will be addressed only regarding the minimal necessary preoperative workup. Medical management (referred to as "chemotherapy") will be defined at the time of a forthcoming consensus conference in collaboration with the European Society of Medical Oncology. This report does not include any economic analysis of the strategies.

METHOD

The guidelines were developed using a 5-step process (see Fig. 1). The strengths of the process include creation of a multidisciplinary international development group, use of scientific evidence and/or international expert consensus to support the guidelines, and use of an international external review process (physicians and patients). This development process involved 2 meetings of the international development group, which earlier elaborated ESGO quality indicators for ovarian cancer surgery (Institut Bergonié, Bordeaux, France).³

Step 1: Nomination of Multidisciplinary International Development Group

The ESGO Council nominated practicing clinicians who care for patients with ovarian cancer and have demonstrated leadership in the clinical management of patients through research, administrative responsibilities, and/or committee membership to serve on the expert panel. The objective was to assemble a multidisciplinary panel. It was therefore essential to include professionals from relevant disciplines (surgery, medical oncology, pathology, radiology,



FIGURE 1. Development process.

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gynecology, radiation oncology) so that their perspectives would contribute to the validity and acceptability of the guidelines. The experts of the multidisciplinary international development group were required to complete a declaration of interest form and to promptly inform the ESGO council whether any change in the disclosed information occurred during the course of the project.

Step 2: Identification of Scientific Evidence

To ensure that the statements were evidence based, the current literature was reviewed and critically appraised. A systematic literature review of the studies published between January 2005 and May 2016 was carried out using the MEDLINE database (see Appendix 1, http://links.lww.com/ IGC/A507). The literature search was limited to publications in English. Priority was given to high-quality systematic reviews, meta-analyses, and randomized controlled trials, but lower levels of evidence were also evaluated. The search strategy excluded editorials, letters, and in vitro studies. The reference list of each identified article was reviewed for other potentially relevant articles. The bibliography was also to be supplemented by additional references provided by the international development group. Another bibliographic search was carried out to identify previous initiatives using a systematic literature search in MEDLINE database (no restriction in the search period) and a bibliographic search using selected evidence-based medicine Web sites (see Appendix 2, http://links.lww.com/IGC/A508). After the selection and critical appraisal of the articles (N = 485; see Appendix 1, http://links.lww.com/IGC/A507), a summary of the scientific evidence was developed.

Step 3: Formulation of Guidelines

The multidisciplinary expert group developed guidelines for diagnosis and preoperative workup, specialized multidisciplinary decision making, and the surgical management. The guidelines were retained if they were supported by sufficient high-level scientific evidence and/or when a large consensus among experts was obtained. By default, a guideline is the clinical approach. If an approach was judged to be acceptable but was not unanimously recognized as a criterion standard clinical approach, indication was given that it was still subject to discussion and/or evaluation. In the absence of any clear scientific evidence, judgment was based on the professional experience and consensus of the development group (expert agreement). The reliability and quality of the evidence given throughout this article have been graded following the SIGN grading system (see Table 1).

Step 4: External Evaluation of the Guidelines, International Review

The ESGO Council established a large panel of practicing clinicians who provide care to patients with ovarian cancer and patients. The objective was to assemble a multidisciplinary panel. The 66 international reviewers were independent from the multidisciplinary expert group. International reviewers were asked to evaluate each guideline according to their relevance and feasibility in clinical practice (only physicians). Quantitative and qualitative evaluations of

TABLE 1. Grades of recommendations

- A At least 1 meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population; or
 - A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
- B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
- C A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
- D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
- Recommended best practice based on the clinical experience of the guideline development group

Ratings are as follows: 1++, high-quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias; 1+, well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias; 2++, highquality systematic reviews of case control or cohort studies or highquality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal,; 2+, well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 3, nonanalytic studies, for example, case reports, case series; and 4, expert opinion.

the guidelines were proposed to be performed. Patients were asked to qualitatively evaluate each guideline (according their experience, preferences, feelings, etc).

Step 5: Integration of International Reviewers' Comments

Responses of the 66 external reviewers were pooled and discussed by the international development group to finalize the guidelines. The complete report of the guidelines for ovarian cancer surgery is available online at ESGO Web site (https://guidelines.esgo.org/).

GUIDELINES

These guidelines are a statement of evidence (485 articles appraised; see Appendix 1, http://links.lww.com/IGC/A507) and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. These guidelines make no representations and warranties of any kind whatsoever regarding their content, use, or application and disclaim any responsibility for their application or use in any



Consider fertility preservation in selected young patients,
With exceptions for retroperitoneal staging (see specific recommendations on surgery of early-stage ovarian cancer)

FIGURE 2. Algorithm 1 for epithelial ovarian cancer surgery.

way. The guidelines are presented hereinafter and illustrated by algorithms (see Figs. 2–4).

Diagnosis and Preoperative Workup

An accurate diagnosis guides patient management and informs prognosis. It is crucial to determine whether peritoneal infiltration and/or omental masses in patients with previous malignancy represent a recurrent disease or a new disease process.⁴ A great proportion of women with newly diagnosed ovarian cancer have peritoneal carcinomatosis. Ovarian and peritoneal malignancy secondary to gastrointestinal cancer have to be ruled out by suitable methods. In case of possible gastrointestinal tract origin, colonoscopy and gastroscopy should be performed before surgery. Furthermore, parenchymal metastases have to be detected by imaging.

Clinical examination including abdominal, vaginal, and rectal examinations; assessment of the breast, groins, axilla, and supraclavicular areas; and auscultation of the lungs should be performed (expert agreement). Routine pelvic (transvaginal and transabdominal) ultrasound should be used as a primary workup tool in any adnexal mass (grade B). Specialized pelvic, abdominal, and thoracic complementary imaging should be performed in case of suspected carcinoma of the ovary or indeterminate or suspicious masses at routine ultrasound examination (grade B). A tumor marker assessment should be performed for at least CA125 levels. HE4 has also been proposed. Additional markers, including α -fetoprotein, human chorionic gonadotropin, lactate dehydrogenase, carcinoembryonic antigen, CA19-9, inhibin B or antimullerian hormone, estradiol, and testosterone, would be useful in specific circumstances such as young age or imaging suggesting a mucinous, or nonepithelial, tumor of extra-adnexal origin (expert agreement).

Specialized Multidisciplinary Decision Making

Although hospital and surgeon volumes are not a sufficient guarantee of surgical quality, they are a major prerequisite. Patients treated in high-volume hospitals have a higher chance of receiving standard treatment (surgery conformed to recommended guidelines) compared with patients treated in low-volume hospitals.⁵ The postoperative hospital stay is correlated with the number of surgical procedures performed.⁶ So, the hospital and surgeon volumes must be merged with outcome, for example, complete surgical resection and complications that must also be recorded.



FIGURE 3. Algorithm 2 for epithelial ovarian cancer surgery.

In Europe, organization of gynecological oncology differs among countries, but there is a trend of centralization and subspecialization. The ESGO, in collaboration with the European Board and College of Obstetricians and Gynecologists, has developed a subspecialty training program in gynecologic oncology.

Institutions participating in clinical research contribute to improve quality of care. Patients treated in study hospitals have a higher chance of receiving standard treatment compared with patients treated in hospitals not participating in cooperative clinical studies.⁷ Furthermore, study centers do not only recruit patients but tend to have infrastructures associated with clinical trial participation. They have physicians interested in ovarian cancer and motivated to perform studies. They also might participate more often in quality assurance programs. The benefit could not be limited to patients enrolled in active protocols. The positive effects could also be observed in patients where no protocol has been active.⁷ Thus, patients treated in these centers who are not enrolled in clinical trials might nevertheless receive quality of care that is above average as well.

Multidisciplinary care is recognized as the best practice in treatment planning and care for patients internationally. In several cancer types, there is evidence that decisions made by a multidisciplinary team are more likely to be in accord with evidence-based guidelines than those made by individual clinicians and the role of multidisciplinary approach in the quality of care is recognized.^{8–16}

Malnutrition has been demonstrated to affect two thirds of patients with ovarian cancer at the time of diagnosis and portends poor surgical outcomes.¹⁷ Malnutrition at the time of surgery is an important contributor to perioperative morbidity. It makes patients more vulnerable to surgical site infections. Malignancy-related malnutrition causes alterations in immune function that impairs a patient's response to surgical stress and places malnourished surgical patients at an increased risk for the development of surgical site infections.^{18,19} Immunomodulating diets in patients with ovarian cancer could provide an effective way to minimize the postoperative morbidity associated with surgical site infections.

The overall reduction of mortality and morbidity rates after surgery has consistently decreased during the last decade with the introduction of innovative perioperative care, which has made it difficult to assess the independent role of each single perioperative intervention. However, the high morbidity of ovarian cancer surgery, which increases with



FIGURE 4. Algorithm 3 for epithelial ovarian cancer surgery.

complexity,^{20–22} justifies the implementation of the concept of "fast-track surgery" or "enhanced recovery programs" involving procedure-specific evidence-based care principles, which have been demonstrated to result in enhanced recovery with reduced of stay and morbidity.²³

Although no specific research on this topic has been carried out in ovarian cancer surgery, the abundant available literature concerning open colorectal surgery provides compelling data, which can reasonably be transposed.²⁴ Perioperative management includes (1) preoperative hemoglobin optimization²⁵ and iron-deficit correction,²⁶ (2) correction of denutrition according to the current guidelines,²⁷ and (3) fluid management, involving a goal-directed therapy policy rather than liberal fluid therapy without hemodynamic goals; however, the superiority of goal-directed therapy compared with restrictive fluid strategy remains unclear,²⁸ and there is no recognized standard method of monitoring.²⁹ Although routine premedication is no longer recommended,³⁰ prevention of postoperative nausea and vomiting should be systematic.³¹

Women with nonemergency clinical presentation and suspected adnexal/peritoneal malignancy should be referred to a specialist in gynecologic oncology (grade C) (certified gynecological oncologist or, in countries where certification is not organized, by a trained surgeon dedicated to the management of gynecologic cancer [accounting for >50% of his/ her practice or having completed an ESGO-accredited fellowship). Surgery in low-volume and low-quality centers is discouraged. The existence of an intermediate care facility and access to an intensive care unit management are required. Participation in clinical trials is a quality indicator (expert agreement). Treatment should be preoperatively planned at a multidisciplinary team meeting, after a workup aimed at ruling out (1) unresectable metastases and (2) secondary ovarian and peritoneal metastases from other primary malignancies when family history, symptoms, radiological features, or CA125–carcinoembryonic antigen ratio is suggestive. Informed consent of the patient must be obtained (grade C). All patients should be reviewed postoperatively at a gynecological oncology multidisciplinary meeting (expert agreement).

Surgical Management for Stage I to II Ovarian Cancer

Midline laparotomy is recommended to surgically manage early ovarian cancers. Apparently, stage I could potentially be managed laparoscopically by a gynecological oncologist with the appropriate expertise able to perform an adequate surgical staging laparoscopically. Rupture of an intact primary tumor with spillage of tumor cells at the time of dissection and extraction of the specimen should be avoided (grade B). Intraoperative rupture of a yet unruptured adnexal mass must be avoided (grade B). The availability of frozen section may allow the necessary surgical assessment to be completed at the time of initial surgery. It is understood that frozen section may not be conclusive and that definitive pathology is the criterion standard of diagnosis (grade B). In the absence of frozen section or in case of inconclusive frozen section, a 2-step procedure should be preferred (expert agreement). Total hysterectomy and bilateral salpingo-oophorectomy

are standard (expert agreement). Fertility-preserving surgery (unilateral salpingo-oophorectomy) should be offered to selected premenopausal patients desiring fertility (grade C) (discussion on fertility must be mentioned in the patient record; the final decision is made after comprehensive staging surgery based on the final stage and grade—fertility preservation is accepted in case of stage IA or IC1, low-grade serous or endometrioid carcinoma, or expansile type mucinous tumors; other stage I substages or pathologic subtypes, subject to individualized decision; uterine preservation with bilateral salpingo-oophorectomy can be considered in selected young patients with apparent stage IB low-risk invasive carcinoma and normal endometrial biopsy finding, but this is not standard management, and there are few data to support this policy).

Laparoscopic restaging is an acceptable approach if performed by a gynecologic oncologist with adequate expertise to perform a comprehensive assessment (grade B). Visual assessment of the entire peritoneal cavity is recommended (expert agreement). Peritoneal washings or cytology, taken before manipulation of the tumor, are recommended (grade C). When no suspicious implants are found in the pelvis, paracolic areas, and subdiaphragmatic areas, blind peritoneal biopsies are recommended (grade C). At least infracolic omentectomy is recommended (grade C). Bilateral pelvic and para-aortic lymph node dissection up to the level of the left renal vein (with the exception of stage I expansile-type mucinous adenocarcinomas) is recommended (grade B). When early carcinoma is incidentally found at surgery for a suspected "benign" condition, a second surgical procedure will be required when the patient has not been comprehensively staged (expert agreement). Reassessment for the only purpose of performing appendectomy is not mandatory even in case of mucinous histology if the appendix has been examined and found normal (expert agreement).

Surgical Management for Stage III to IV Ovarian Cancer

Surgery remains a key determinant of survival outcome in advanced ovarian cancer. The size of residual disease after cytoreductive surgery is estimated as the largest diameter of remaining tumor and is one of the most important prognostic factors. According to the fourth International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference (2010) held in Vancouver,³² the term "optimal" cytoreduction should be reserved for those with no macroscopic residual disease. This corresponds to the definition of complete surgery.

There is evidence that standardized operative reports result in more complete and reliably interpretable operative data compared with nonstandardized operative reports.³³ Furthermore, compliance with the standardized operative report improves over time. In the absence of an internationally validated standardized operative report in ovarian cancer, some required elements must be reported. Size and location of disease at the beginning of the operation must be described. All the areas of the abdominal cavity must be described (ovaries, tubes, uterus, pelvic peritoneum, paracolic gutters, anterior parietal peritoneum, mesentery, peritoneal surface of the colon and bowel, liver, spleen, greater and lesser omentum, porta hepatis, stomach, Morrison pouch, lesser sac, undersurface of

both hemidiaphragms, pelvic and aortic nodes, and if applicable, pleural cavity). If applicable, the size and location of residual disease at the end of the operation and the reasons for not achieving complete cytoreduction must be reported.

An accurate pathology report is critical for the optimal management of patients with advanced ovarian cancer. The link between the absence of standardized reporting guide and deficiencies among reports is described for other tumor types.^{34–36} The report is essential for communication to treating physicians, data collection within clinical trials, or review by a second pathologist or when unforeseen problems arise, and a reassessment is needed later on. The distinction between primary ovarian and metastatic tumors is based on the interpretation of a complex combination of macroscopic, microscopic, and biochemical data and requires pathological expertise. Histological reports must provide prognostic indicators, which inform treatment planning for women given a diagnosis of epithelial ovarian cancer.

In 2015, an international panel of pathologists and clinicians developed a common, internationally agreed upon, evidence-based ovarian cancer data set.³⁷ It contains "required" (mandatory/core) and "recommended" (nonmandatory/noncore) elements. Required elements were defined as those that had agreed evidentiary support and that were unanimously agreed upon by the review panel to be essential for clinical management. Recommended elements were those considered to be clinically important and recommended for good practice but with lesser degrees of supportive evidence. The data set has been developed for resection specimens of primary borderline and malignant epithelial tumors of the ovary, fallopian tubes, and peritoneum. It does not include nonepithelial ovarian neoplasms such as germ cell or sex cord stromal tumors or other primary peritoneal neoplasms such as mesothelioma.

The panel experts consider that widespread use of this internationally agreed upon, evidence-based, structured pathology data set for advanced ovarian cancer not only will lead to improved patient management but is a prerequisite for research and international benchmarking in health care.

The absence of consensus within the surgical community on the way to report surgical complications has hampered proper evaluation of the surgeon's work and, possibly, progress in the surgical field. The therapy used to correct a specific complication remains the cornerstone to rank a complication. Conclusive assessments of surgical procedures remained limited by the lack of consensus on how to define complications and to stratify them by severity.

The Clavien-Dindo classification,^{38,39} a proposed morbidity scale based on the therapeutic consequences of complications, consisted of 5 severity grades and focused on the medical perspectives, with a major emphasis on the risk and invasiveness of the therapy used to correct a complication. In 2013, Slankamenac et al⁴⁰ developed a comprehensive complication index that takes into account all complications after a procedure and their respective severity. The development of this comprehensive complication index was based on the adapted Clavien-Dindo classification system. The complications were weighed with different severities by adopting an "operation risk index" approach. The panel experts consider that widespread use of a simple, objective, and reproducible approach for comprehensive surgical outcome assessment will lead to improvement of patient management. It should be easily applicable and usable by surgeons who are less experienced.

Midline laparotomy is required to manage stage III to IV ovarian cancers (expert agreement). Complete resection of all visible diseases is the goal of surgical management. Voluntary use of incomplete surgery (upfront or interval) is discouraged (grade A).

Criteria against abdominal debulking are the following (expert agreement):

- Diffuse deep infiltration of the root of small bowel mesentery
- Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to short bowel syndrome (remaining bowel < 1.5 m)
- Diffuse involvement/deep infiltration of the stomach/ duodenum (limited excision is possible) and head or middle part of the pancreas (tail of the pancreas can be resected)
- Involvement of truncus coeliacus, hepatic arteries, and left gastric artery (celiac nodes can be resected)

Metastatic (stage IVB) disease may be resectable. Central or multisegmental parenchymal liver metastases, multiple parenchymal lung metastases (preferably histologically proven), nonresectable lymph node metastases, and multiple brain metastases are not resectable (expert agreement). Primary surgery is recommended in patients who can be debulked upfront to no residual tumor with a reasonable complication rate (grade A).

Risk-benefit ratio is in favor of primary surgery when (expert agreement):

- There is no unresectable tumor extent;
- Complete debulking to no residual tumor seems feasible with reasonable morbidity, taking into account the patient's status. Decisions are individualized and based on multiple parameters (examples of potentially resectable extra-abdominal disease are inguinal or axillary lymph nodes, retrocrural or paracardiac nodes, focal parietal pleural involvement, and isolated parenchymal lung metastases; examples of resectable intra-abdominal parenchymal metastases are splenic metastases, capsular liver metastases, and single deep liver metastasis, depending on the location); and
- Patient accepts potential supportive measures as blood transfusions or stoma.

Interval debulking surgery should be proposed to patients fit for surgery with response or stable disease compatible with complete resection (grade A). If a patient did not have the opportunity of surgery after 3 cycles, then a delayed debulking after more than 3 cycles of neoadjuvant chemotherapy may be considered on an individual basis (expert agreement). A patient with inoperable tumor who progresses during neoadjuvant chemotherapy should not be operated on unless for palliative reasons that cannot be managed conservatively. Careful review of pathology in serous adenocarcinoma (possible low grade) and additional workup in mucinous adenocarcinoma (possible GI tract secondary) are recommended when applicable in this circumstance (expert agreement).

Minimum Required Information

All necessary information about sites and size of the disease, tumor dissemination patterns, resections performed, and residual disease should be available in the operation protocol (expert agreement). The operation protocol should be systematically structured. Tumor dissemination patterns with site and size of the tumor lesions should be described at the beginning of the operation protocol (expert agreement). All areas of the abdominal and pelvic cavity should be evaluated and described (expert agreement). All the completed surgical procedures should be mentioned (expert agreement). If any, the size and location of residual disease should be described at the end of the operation protocol. Reasons for not achieving complete cytoreduction must be defined (expert agreement). At the minimum, the information contained in the ESGO operative report must be present (expert agreement) (the ESGO operative report is available at ESGO Web site [https://guidelines.esgo.org/]). The pathology report should contain all necessary information (expert agreement). Surgical morbidity and mortality should be assessed and recorded, and selected cases should be discussed at morbidity and mortality conferences (expert agreement).

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