Improving quality of care for patients with ovarian and endometrial cancer

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CHAPTER 4

Surgery for patients with newly diagnosed advanced ovarian cancer: which patient, when and extent?

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Current opinion in Oncology, 2017 Sep; 29(5):351-358

ABSTRACT

Purpose of review

Cytoreduction to no residual disease is the mainstay of primary treatment for advanced epithelial ovarian cancer (AdvEOC). This review addresses recent insights on optimal patient selection, timing and extent of surgery, intended to optimize cytoreduction in patients with AdvEOC.

Recent findings

Clinical guidelines recommend primary cytoreductive surgery for AdvEOC patients with a high likelihood of achieving complete cytoreduction with acceptable morbidity. In line with this, preoperative prediction markers such as CA-125, histologic and genomic factors, innovative imaging modalities and the performance of a diagnostic laparoscopy have been suggested to improve clinical decision-making with regard to optimal timing of cytoreductive surgery. To determine whether these strategies should be incorporated into clinical practice validation in randomized clinical trials is essential.

Summary

The past decade has seen a paradigm shift in the number of AvdEOC patients that are being treated with upfront neo-adjuvant chemotherapy instead of primary cytoreductive surgery. However, while neo-adjuvant chemotherapy may reduce morbidity at the time of interval cytoreductive surgery, no favorable impact on survival has been demonstrated and it may induce resistance to chemotherapy. Therefore, optimizing patient selection for PCS is crucial. Furthermore, surgical innovations in patients diagnosed with AvdEOC should focus on improving survival outcomes.

INTRODUCTION

Advanced Epithelial ovarian cancer (AdvEOC) is the most lethal malignancy in women(1). Ovarian carcinoma comprise a heterogeneous group of cancers including high-grade serous carcinoma (70-80%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (<5%) and low-grade carcinoma (<5%). A lack of specific symptoms, often resulting in advanced disease at diagnosis, and frequent development of resistance to chemotherapy, play an important role in the unfavorable prognosis of patients diagnosed with this aggressive disease.

Despite efforts aimed at improving survival outcomes, minimal impact on survival has been achieved thus far. Surprisingly, no significant changes have been made in the core elements of therapy for AdvEOC in the past decades. Standard therapy comprised, and still comprises, a combination of cytoreductive surgery and platinum based chemotherapy. Currently, in most countries, patients undergo primary cytoreductive surgery (PCS) and adjuvant chemotherapy (ACT) if complete cytoreduction seems feasible with acceptable morbidity. Patients are treated with neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) when complete cytoreduction is considered unlikely, or if unacceptable morbidity is expected during PCS(2). This review will focus on organization of care, sequence of primary therapy, advances in selection of patients for primary cytoreductive surgery and perspectives in primary therapy for AdvEOC.

ORGANIZATION OF CARE

In the past decade the importance of cytoreduction to no macroscopically visible disease (termed 'complete cytoreduction') has become universally accepted(3). In 2002, a landmark meta-analysis quantified the correlation between surgical outcome and survival advantage and concluded that each 10% increase in maximal cytoreduction is associated with a 5.5% increase in median survival outcomes(4). As such, all patients with AdvEOC should receive one maximal effort at complete cytoreduction.

Various efforts aimed at improving the rate of complete cytoreduction have been made. One of the aspects that have been investigated extensively in this regard is the organization of oncologic care for patients with AdvEOC. Several studies have demonstrated that the likelihood of achieving complete cytoreduction is higher when cytoreductive surgery is performed by specialized surgical teams in high volume hospitals(5–8). These insights instigated a paradigm shift in the organization of care for AdvEOC patients. Important criteria within these guidelines are a minimal required case load and the presence of specialized (surgical) personnel within the treatment hospital. According to the recently published ESGO quality indicators , surgical cytoreduction for AdvEOC patients should be centralized to hospitals that perform a minimum of 20 cytoreductive surgeries annually. Intermediate and optimal annual targets have been set at 50 and 100 surgeries, respectively(9).

SEQUENCE OF PRIMARY THERAPY

Increasing emphasis on the importance of achieving complete cytoreduction while keeping patient morbidity at acceptable levels, has led to the implementation of a therapeutic regime in which NACT is followed by ICS. Advocates of the NACT+ICS-regime suggest that chemotherapy may reduce tumor load and increase the chances of achieving complete cytoreduction with less surgical morbidity. Importantly, a meta-analysis published in 2006 concluded that NACT was associated with inferior overall survival(10). Nevertheless, in this meta-analysis, and other analyses comprising retrospective studies, favorable survival in the PCS group may be attributable to favorable prognostic factors such as better performance status and lower tumor load.

Two landmark phase III clinical trials (EORTC 55971 and CHORUS trial) have been conducted assessing survival impact of NACT+ICS instead of PCS+ACT in AdvEOC(11,12). Although these trials demonstrated higher complete cytoreduction rates and lower surgical morbidity in patients treated with the NACT+ICS regime, the overall and progression free survival outcomes were similar between both groups. Notably, an exploratory analysis of the EORTC 55971 trial demonstrated favorable survival in patients with stage IIIC and less extensive tumor load that were treated with PCS+ACT, and favorable survival in patients with stage IV disease and high tumor load that were treated with NACT+ICS(13). Recently, a meta-analysis was conducted comprising four phase III clinical trials that have published mature survival data of patients treated with either PCS+ACT or NACT+ICS (the EORTC 55971 and CHORUS trials and two older trials)(14). This meta-analysis confirmed non-inferiority of NACT+ICS compared to PCS+ACT with regard to overall survival (HR 0.94, 95% CI 0.81-1.08, p=0.38) and progression free survival (HR 0.89, 95% CI 0.77-1.03, p=0.12), and established that administration of NACT was associated with higher chances of achieving complete cytoreduction during ICS when compared to PCS (RR 2.37, 95% CI 1.94-2.91, p<0.001).

One of the potential explanations of the lack of survival benefit seen with NACT+ICS is the risk of inducing chemotherapy resistance by exposing large tumor volumes to chemotherapy (15–17). Administration of NACT may selectively eliminate the chemotherapy sensitive cells, which may drive platinum resistance. It has recently been shown that recurrences in patients that were treated with NACT+ICS were less sensitive to subsequent chemotherapy compared to patients that were treated with PCS+ACT, suggesting that the administration of NACT may undermine therapeutic options for recurrent disease(16,17).

In contrast to the EORTC 55971 and CHORUS trials, the recently conducted randomized phase III SCORPION trial failed to demonstrate a difference in complete cytoreduction rates between the two regimes(18). Survival data of the SCORPION trial are thus eagerly awaited. Despite the lack of improvement in cytoreduction, several other advantages of NACT+ICS regime were demonstrated in the SCORPION trial including lower morbidity (less early grade III and IV adverse events) and higher quality of life. The CHORUS trial also showed less grade III or IV adverse events in the NACT+ICS group,

although no difference in quality of life was demonstrated(12). An overview of the three most recently conducted phase III randomized trials (EORTC 55971, CHORUS and SCORPION) is depicted in table 1.

Notably, the EORTC 55971 and CHORUS trials have important limitations such as a selection bias towards patients with poor performance status, old age and high tumor load, as well as suboptimal cytoreductive surgery outcomes (mainly at primary surgery), low mean operative times and low median overall survival. To address limitations of the EORTC 55971 and CHORUS trials, specifically the suboptimal cytoreductive surgery outcomes, the Arbeitsgemeinschaft Gynaekologische Onkologie study group, North Eastern German Society of Gynaecologic Oncology and international collaborators have initiated a new randomized clinical trial: The Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST)(19). Within this trial 686 AdvEOC patients will be randomized to PCS+ACT or NACT+ICS. Stringent quality assessment is in place to ensure that participating centers meet the recently published ESGO criteria for cytoreductive surgery in AdvEOC patients(9). Final analysis of overall survival in the TRUST trial is expected in 2023.

The Society of Gynecologic Oncology (SGO) and the American Society of Clinical Oncology (ASCO) have also published a clinical guideline regarding the use of NACT in patients with AdvEOC, an overview is shown in Table 2(9,20).

Table 1. Recent phase III randomized clinical trials on PCS+ACT vs NACT+ICS in AdvEOC

Trial	Inclusion criteria	Primary outcome	Number of patients per arm	Complete cytoreduction
EORTC 55971 Vergote *et al*. New England Journal of Medicine 2010	Biopsy-proven stage IIIC or IV invasive epithelial ovarian carcinoma, primary peritoneal carcinoma, or fallopian-tube carcinoma.	OS	PCS+ACT: 336 NACT+ICS: 334	PCS+ACT, 19% NACT+ICS, 51%
CHORUS Kehoe *et al*. Lancet 2015	Clinical or imaging evidence of stage III or IV ovarian, fallopian tube or primary peritoneal cancer.	OS	PCS+ACT: 276 NACT+ICS: 274	PCS+ACT, 17% NACT+ICS, 43%
SCORPION Fagotti *et al*. European Journal of Cancer 2016	Histological evidence (frozen section) of stage IIIC or IV ovarian, fallopian tube or primary peritoneal cancer and high tumor load without mesenteric retraction.	Surgical adverse events	PCS+ACT: 55 NACT+ICS: 55	PCS+ACT, 46% NACT+ICS, 58%

PCS+ACT: primary cytoreductive surgery and adjuvant chemotherapy, NACT+ICS: neoadjuvant chemotherapy and interval cytoreductive surgery, OS: overall survival, PFS: progression free survival, ITT: intention to treat analysis, HR: hazard ratio.

SELECTION OF PATIENTS FOR PCS

One of the future directions discussed in the SGO/ASCO guideline is the optimization of preoperative patient selection for PCS(20). More specifically, exclusion criteria for patients with high tumor load and at high risk of morbidity and/or mortality from PCS, and selection criteria for patients with low tumor load and high likelihood of complete cytoreduction with PCS should be developed.

Clinical and laboratory markers

One of the markers which has been suggested to be of use in patient selection for PCS is Cancer Antigen 125 (CA-125). An analysis based on data that was prospectively collected for a multicenter nonrandomized trial identified CA-125 ≥600 as a marker for the presence of residual disease after PCS(21). Furthermore, a retrospective study by Mahdi *et al* determined that a reduction in preoperative CA-125 of 90% was associated with complete ICS(22). Human Epididymis protein 4 (HE4) has also been studied with respect to patient selection for PCS. Though it has been identified as a strong predictor for unfavorable prognosis in AdvEOC, CA-125 currently remains the most important biomarker in AdvEOC (excluding mucinous subtypes) (23,24). Furthermore, markers of performance and nutritional status, such as age, race, smoking status, creatinine and albumin levels have also been studied with regard to selection of patients for PDS(25,26).

Median OS (months)	Median PFS (months)	Any grade III-IV Adverse events	Postoperative death <28 days
PCS+ACT, 29	PCS+ACT, 12	No overall data available	PCS+ACT, 3%
NACT+ICS, 30	NACT+ICS, 12		NACT+ICS, 1%
ITT: HR 0.98, 90% CI 0.84-1.13. Predefined non-inferiority boundary was 1.25.	ITT: HR 1.01, 90% CI 0.89-1.15		
PCS+ACT, 23	PCS+ACT, 12	PCS+ACT, 24%	PCS+ACT, 6%
NACT+ICS, 24	NACT+ICS, 11	NACT+ICS, 14%	NACT+ICS, <1%
ITT: HR 0.87, upper bound of one-sided 90% CI 0.72-1.05. Predefined non-inferiority boundary was 1.18.	ITT: HR 0.91, 95% CI 0.76-1.09		
Awaiting maturation of data	Awaiting maturation of data	PCS+ACT, 53% NACT+ICS, 6%	PCS+ACT, 4% NACT+ICS, 0%

Table 2. SGO-ASCO clinical guidelines en ESGO clinical guidelines

	SGO-ASCO guidelines (20)	**ESGO guidelines** (9)
Specialized decision-making	All women with suspected stage IIIC or IV invasive epithelial ovarian cancer should be evaluated by a gynecologic oncologist prior to initiation of therapy to determine whether they are candidates for PCS. Decisions that women are not eligible for medical or surgical cancer treatment should be made after a consultation with a gynecologic oncologist and/or a medical oncologist with gynecologic expertise.	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. All patients should be reviewed postoperatively at a gynecologic oncology multidisciplinary meeting
Preoperative workup	A primary clinical evaluation should include a CT of the abdomen and pelvis with oral and intravenous contrast and chest imaging (CT preferred) to evaluate the extent of disease and the feasibility of surgical resection. The use of other tools to refine this assessment may include laparoscopic evaluation or additional radiographic imaging (e.g. FDG-PET scan or diffusion-weighted MRI).	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. A tumor marker assessment should be performed for at least CA125 levels. HE4 has also been proposed. Additional markers, including AFP, hCG, CEA, CA19-9, inhibin B or AMH, estradiol, testosterone, would be useful in specific circumstances such as young age, or imaging suggesting a mucinous, or non-epithelial, or tumor of extra-adnexal origin.
Selection of patients for PCS+ACT	For women with a high likelihood of achieving a cytoreduction to <1cm (ideally to no visible disease) with acceptable morbidity, PCS is recommended over NACT.	Primary surgery is recommended in patients who can be debulked upfront to no residual tumor with a reasonable complication rate. Risk-benefit is in favor of PCS when: - There is no unresectable tumor present; - Complete debulking to no residual tumor seems feasible when reasonable morbidity, taking into account the patients' status; - Patient accepts potential supportive measures as blood transfusions or stoma.
Selection of patients for NACT+ICS	Women who have a high perioperative risk profile or a low likelihood of achieving cytoreduction to <1cm (ideally to no visible disease) should receive NACT. For women who are fit for PCS but are deemed unlikely to have cytoreduction to <1cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS.	Criteria against PCS are: - 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 < 1.5m) - Diffuse involvement/deep infiltration of stomach/duodenum (limited excision is possible) and head or middle part of pancreas (tail of pancreas can be resected)' - Involvement of truncus coeliacus, hepatic arteries, left gastric artery (coeliac nodes can be resected).
Timing of ICS	ICS should be performed after ≤4 cycles of NACT for women with a response to chemotherapy or stable disease. Alternate timing of ICS has not been prospectively evaluated but may be considered on patient-centered factors.	ICS should be proposed to patients fit for surgery with a response or stable disease compatible with complete resection. If a patient did not have the opportunity of surgery after 3 cycles, then a delayed debulking after more than 3 cycles of NACT may be considered on an individual basis.

SGO: Society of Gynecologic Oncology, ASCO: American Society of Clinical Oncology, ESGO: European Society of Gynecologic Oncology, PCS+ACT: primary cytoreductive surgery and adjuvant chemotherapy, NACT+ICS: neoadjuvant chemotherapy and interval cytoreductive surgery.

Collectively, these studies suggest that preoperatively available markers such as CA-125, performance status and nutritional status could facilitate selection of patients for PCS. However, reaching consensus on the cut off values for each of these markers is essential, and it remains to be elucidated whether the prospective use of these markers contributes to favorable survival outcomes of AdvEOC patients.

Histologic and genomic factors

Taking into account the heterogeneity of ovarian carcinoma, tumor biology may also provide important information for the selection of patients for PCS+ACT or NACT+ICS. With up to 75% of patients responding to primary chemotherapy, high grade serous ovarian cancer is considered chemotherapy sensitive. Mucinous, clear cell and low grade serous ovarian cancer are far less sensitive. Despite low response rates in some subtypes, the administration of chemotherapy is still standard of care in all AdvEOC patients. However, consensus reviews of rare EOC subtypes by the Gynecologic Cancer InterGroup have emphasized that the administration of NACT should be discouraged in these chemotherapy resistant subtypes(27–29). Further clinical trials are warranted to investigate the role of alternative (targeted) therapies as first line treatment for patients with advanced mucinous, clear cell or low grade serous ovarian cancer. Due to the low incidence of these subtypes international collaboration will be essential.

Genomic markers may also play a role in differentiating between patients that are sensitive to chemotherapy and those that are not. A recent genomic characterization of chemotherapy resistant high grade serous ovarian cancer identified several potential predictors of chemotherapy resistance including, among others, CCNE1 amplifications and loss of BRCA1 or BRCA2 mutations(30).

Radiographic and nuclear Imaging

Preoperative imaging such as CT-scans can provide essential information regarding the extent of tumor dissemination and may aid prediction of surgical outcomes. However, a systematic review aimed at evaluating CT-based multivariable prediction models in AdvEOC concluded that externally validated studies with high predictive value are currently lacking(31).

PET/CT-scans have also been suggested as a valuable tool for prediction of cytoreductive outcomes. For instance, a prospective study on 343 AdvEOC patients that underwent preoperative PET/CT imaging identified several PET/CT features that were independently associated with incomplete cytoreduction (e.g. presence of disease in the diaphragm and small bowel mesentery implants)(32). A study comparing the predictive value of preoperative PET/CT and high-dose contrast CT showed superiority of PET/CT in detection of extra-abdominal disease(33).

The presence of malignant pleural effusion or metastatic disease above the diaphragm may result in suboptimal cytoreduction despite complete removal of all other tumor locations. However, studies

on the impact of disease above the diaphragm on clinical decision making in AdvEOC are currently lacking. Novel surgical techniques for diaphragmatic surgery (e.g. diaphragmatic peritoneal stripping and diaphragmatic full-thickness resection) have been developed, however the impact of these techniques on overall survival is still unclear(34). A review by Escayola *et al* recently concluded that it is currently unclear whether pleural involvement can reliably be assessed by CT-scan and/or chest radiograph alone, and proposed that video-assisted thoracoscopy (VATS) could be a valuable tool in describing the extent of pleural disease(35). One of the key findings in a review by Di Guilmi was that among patients with negative pleural cytology, 23.5% have pleural disease determined with VATS. Herein, VATS led to a change in stage of disease in 41% of patients(36). Both Escayola *et al* and Di Guilmi conclude that VATS may facilitate the selection of patients for PCS. Importantly, VATS should not be performed in patients with low likelihood of complete cytoreduction of tumor in abdomen and pelvis as these patients are candidates for NACT.

Another imaging modality that may aid the selection of patients with high likelihood of complete cytoreduction for PCS is diffusion weighted MRI (DW-MRI). A study by Espada *et al* (N=34), showed that DW-MRI accurately predicts cytoreductive outcome in 91% of cases(37). Furthermore, within the recurrent setting, DW-MRI accurately predicted complete cytoreduction in 94% of patients that were eligible for salvage surgery, whereas CT accurately predicted complete cytoreduction in only 49% of these patients(38). The authors attributed the superiority of DW-MRI over CT to better contrast resolution resulting in improved detection of sites that are critical for surgery such as serosal intestinal metastases, metastases around the central mesenteric vessels and unresectable distant metastases. The survival impact of using DW-MRI to select patients for PCS requires further investigation.

Diagnostic laparoscopy

A number of non-randomized studies have investigated the value of assessing operability of patients with AdvEOC by diagnostic laparoscopy (39,40). More recently, the LAPOVCA trial randomized 201 patients that were expected to be eligible for PCS to preoperative diagnostic laparoscopy versus PCS(41). Within the PCS group 39% underwent unsuccessful cytoreduction compared to 10% in the diagnostic laparoscopy group. Critics of this trial include a selection bias (13% of included patients had benign/borderline disease or a malignancy of other origin) and low quality of surgery (42% of patients in the PCS group underwent an incomplete cytoreduction).

PERSPECTIVES IN PRIMARY THERAPY FOR ADVEOC

Lymphadenectomy

While sampling of pelvic and para-aortic lymph nodes is an undisputed part of staging for early stage disease, the value of performing a full lymphadenectomy in AdvEOC is subject of debate. As retroperitoneal lymph node involvement is expected in a majority of patients with advanced stage disease, it has been proposed that systematic pelvic and para-aortic lymphadenectomy could facilitate cytoreduction and improve survival outcomes. A recent meta-analysis by Zhou *et al* demonstrated favorable OS and PFS, and a lower rate of recurrence, in AdvEOC patients that underwent lymphadenectomy compared to those that did not (42). The therapeutic value of lymphadenectomy in primary therapy for patients with AdvEOC is currently being investigated by the Arbeitsgemeinschaft Gynaekologische Onkologie study group in the prospective Lymphadenectomy In Ovarian Neoplasms (LION) trial(43). Within this trial, 640 patients with FIGO stage IIB-IV and without visible residual tumor have been randomized to lymphadenectomy or no lymphadenectomy. Maturation of survival data is eagerly awaited.

Intraperitoneal chemotherapy (IP) and hyperthermic intraperitoneal chemotherapy (HIPEC)

As patients with AdvEOC frequently develop peritoneal recurrences, alternative methods of chemotherapy delivery, such as the administration of (heated) chemotherapy directly into the abdominal cavity, are currently being investigated. A Cochrane systematic review by Jaaback *et al* confirmed the favorable survival outcomes of AdvEOC patients treated with chemotherapy that was (partially) administered intraperitoneally (HR 0.81, 95% CI 0.72-0.90), though more serious adverse events (gastrointestinal, pain, fever, infection) were registered compared to standard intravenous administration(44). A meta-analysis by Huo *et al* indeed confirmed the favorable survival outcomes (OR 3.46 95% CI 2.19-5.48), but showed comparable morbidity and mortality between treatment regimens consisting of cytoreduction + intravenous chemotherapy + HIPEC and cytoreduction + intravenous chemotherapy(45). Clinical trials are currently ongoing to establish optimal timing, dosing and patient selection for this treatment modality.

Intraoperative optical imaging

Another innovative strategy that is currently under investigation in various solid malignancies is intraoperative fluorescent imaging. The use of tumor-specific fluorescent markers may facilitate intraoperative identification of tumor deposits and improve cytoreductive outcomes. In 2011, the first-in-human trial using intraoperative fluorescent imaging in ovarian cancer was performed. Within this trial, high sensitivity and specificity of the folate receptor α targeted agent (folate-FITC) was demonstrated in ovarian cancer patients(46). Recently, the clinical application of folate receptor α targeting agents EC17 and OTL38 rendered promising outcomes in a small number of patients undergoing cytoreductive surgery for ovarian cancer(47,48). Further optimization of fluorescent agents is warranted to reduce the occurrence of auto fluorescent false-positive lesions. Moreover, the impact of intraoperative imaging on survival outcomes requires validation in a clinical trial.

CONCLUSION

In conclusion, the past decade has seen a paradigm shift in the number of AvdEOC patients treated with upfront neo-adjuvant chemotherapy instead of primary cytoreductive surgery. Clinical guidelines from SGO-ASCO and ESGO currently recommend primary cytoreductive surgery for AdvEOC patients with a high likelihood of achieving complete debulking with acceptable morbidity. Neo-adjuvant chemotherapy may reduce morbidity at the time of interval cytoreductive surgery, but it does not improve survival outcomes and may undermine therapeutic options for recurrent disease by inducing chemotherapy resistance. Optimal selection of patients is crucial in an attempt to improve prognosis. Furthermore, it is imperative that surgical innovations in patients diagnosed with AvdEOC are directed at improving survival outcomes.

FUNDING AND ACKNOWLEDGEMENTS

This work was funded by the Dutch Cancer Society (grant RUG2013-6505) to HWN.

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PART II

Improving organization of care for patients with endometrial cancer