



# Upfront debulking surgery for high-grade serous ovarian carcinoma: current evidence

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**Abstract:** High-grade serous ovarian carcinoma (HGSOC) is a leading cause of mortality among women worldwide. Currently, there is no clear consensus over the regime these patients should receive. The main two options are upfront debulking surgery with adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery (IDS). The former approach is proposed to be accompanied by lower chemoresistance rates but could lead to severe surgical comorbidities and lower quality of life (QoL). Optimizing patient's selection for upfront debulking surgery might offer higher progression-free and overall survival rates. Further studies need to be conducted in order to elucidate the predictive factors, which are favorable for patients undergoing upfront debulking surgery in cases of high-grade serous ovarian cancer.

**Keywords:** Upfront debulking surgery; high-grade serous ovarian cancer; interval debulking surgery (IDS); chemotherapy; cytoreductive surgery

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## Introduction

Ovarian cancer remains one of the main causes of death for women worldwide and although novel scientific evidence on its origin, genetics, prognosis and treatment has been accumulated over the years, low survival rates are consistent (1,2).

High-grade serous ovarian carcinoma (HGSOC) is a subtype mainly responsible for deaths due to ovarian cancer, rather than all the other subtypes combined (1,3).

Traditionally, cytoreductive surgery prior or after platinum-based chemotherapy comprise the gold standard of therapy for HGSOC (3,4). Nevertheless, surgical treatment options have long been debated and whether upfront debulking in cases of HGSOC or neoadjuvant

chemotherapy followed by interval debulking surgery (IDS) are appropriate, remains still controversial. In this review, current evidence on upfront debulking surgery for high-grade ovarian carcinoma is presented (5). Better understanding on patient's selection, prognostic factors and advantages of this approach will facilitate surgeons' decision on optimal timing for cytoreductive surgery.

## Prognostic factors for upfront debulking surgery

Upfront debulking surgery necessitates a strict selection of patients based on specific prognostic factors and could potentially indicate the group of patients suffering from HGSOC, which will benefit the most by undergoing

upfront cytoreduction (6). Usually, if cytoreduction to no residual disease is feasible, upfront debulking surgery is preferable rather than neo-adjuvant chemotherapy followed by IDS (3). Biomarkers, histologic and genomic factors, intestinal involvement, extra-pelvic disease, hormone levels and patient's profile are just few of the proposed prognostic factors that should be taken into consideration prior to surgical decision (7,8).

### ***Predictive biomarkers for response to (neoadjuvant) chemotherapy***

Several biomarkers for optimal response to neoadjuvant chemotherapy have been proposed, although current evidence remain controversial regarding their potential use. Mesothelin, FLT4,  $\alpha$ -1 acid glycoprotein (AGP) and cancer antigen 125 (Ca-125) are proposed as suggestive of anti-vascular epithelial growth factor (anti-VEGF) monoclonal antibody success as a first line standard chemotherapy (9,10).

Angiogenesis and vascular remodeling are complex processes that involve regulation by the cytokines angiopoietin-1 (Ang1) and Ang2, which interact with the vascular receptor tyrosine kinase Tie2. However, further studies are required in order to be clarified their predictive value (10).

### ***Histologic and genomic factors***

In contrast to all the other subtypes, high-grade serous ovarian cancer may be ideal for neoadjuvant chemotherapy, since this subtype is accompanied by higher chemosensitivity (3,10). Genomic factors, such as cyclin E1 amplifications and the presence of breast cancer BRCA1/2 mutations, have also been suggested as predictive for optimal surgical timing, by defining chemo-resistant over chemo-sensitive high grade-serous ovarian cancer patients (3,11). It has been estimated that approximately 1.3% of women will eventually develop ovarian cancer during their lives (12,13). In this group, it has been documented that approximately 44% of women who inherit BRCA1 mutation and approximately 17% of women who inherit BRCA2 mutation will develop ovarian cancer by their eighties (14-16). BRCA mutation, especially BRCA2 patients, had higher response rates in neoadjuvant therapies and could benefit from this regime (15,17). Patients with BRCA mutation have shown greater rates of overall survival, longer disease-free interval (DFI) after first-line chemotherapy, better responsiveness in common chemotherapeutic regimens and higher treatment

free interval (TFI) between each line of therapy (18,19). For women with BRCA1/2 mutations, progression-free survival is estimated at 15.7 and 21.6 months respectively, and overall survival for both groups were approximately 55.3 and 75.2 months, respectively (15,20). In patients with ovarian carcinomas showing no BRCA 1 or 2 mutation, progression-free survival and overall survival were estimated at 16 and 56 months, showing great similarities to BRCA1 rates (21,22).

### ***Tumor-infiltrating lymphocytes (TILs), tumor cell-free DNA (cfDNA)***

TILs and cfDNA have also been suggested as promising predictive biomarkers although their use is limited and no standard methods for their isolation have been suggested (10,23).

More specifically, high levels of TILs were associated with better response to neoadjuvant chemotherapy, showing that host immune response influences the tumour chemosensitivity (24-26). Additionally, cfDNA levels rises in cases of advanced ovarian cancer. Indeed, high levels of these short fragments of nucleic acids are related to poor overall survival rates and might serve as adequate independent prognostic factor of neoadjuvant chemotherapy. Their value for the screening process is superior to Ca-125, including both sensitivity and specificity (24,27).

### ***Age, performance status, comorbidities, albumin, and body mass index***

Patient's status was a good prognostic factor with regards to patient's selection for upfront debulking surgery. A scoring system evaluating Body Mass Index of the patient, Ca-125 levels and imaging staging was conducted, and a group of scientists tried to identify patients who would gain benefit from primary cytoreductive surgery. Patients with BMI  $<30$  kg/m<sup>2</sup>, Ca-125  $<100$  IU/L and absence of PET/CT findings suggestive of either diaphragmatic and omental carcinomatosis, or positive parenchymal metastases were chosen to undergo upfront debulking surgery with lower risks of no complete cytoreduction (28). In general age and general performance status of the patient will eventually affect the treatment for cases of high-grade serous ovarian cancer.

Patients older than 65 years of age, with albumin levels  $<25$  g/L and ascites  $>1$  L were less likely to benefit from upfront debulking surgery.

### **Intestinal resections**

Although cytoreductive surgeries in patients with advanced-stage ovarian cancer are considered the most challenging in gynecologic oncology, Griffiths has showed that there is survival benefit if the residual tumor after debulking surgery does not exceed 15 mm in diameter (29). Despite the fact that surgical interventions aim to the total resection of the tumor, ensuring zero macroscopic residual tumor or complete (R0) cytoreduction, macroscopic tumor residual less than 10 mm is considered optimal (30).

The strategy of multiorgan resections represents a common practice. Most often, parts of the digestive tract should be resected, especially the colon and/or the rectum. The ortho-sigmoid resection in patients with bulky pelvic disease is rational, because distal sigmoid is often involved either by direct expansion or by implantation of ovarian cancer in the serosa, and this surgical excision can be performed with acceptable peri-operative morbidity. The most severe complication in relation to intestinal surgery is anastomotic dehiscence, which occur especially in recto-sigmoid resection with low anastomosis. The incidence of this complication is 2.8–23% for colonic cancer resections and 0.8–6.8% for gynecologic cancers (31–34). Protracted surgery, blood transfusion, and short distal segment of anastomosis represent the factors most implicated in the risk for anastomotic dehiscence. Some authors suggest the performing of diverting ileostomy or colostomy in order to avoid or minimize such complication.

Others reported that the overall rate of complications associated with *en-bloc* resection of the uterus and adnexa with recto-sigmoid without protective ileostomy is around 2%.

Therefore, the stomas should be performed only in situations such as poor nutrition, significant ascites, anastomosis under tension or multiple anastomoses. Regarding Hartmann's procedure, is considered appropriate for patients with significant comorbidities (35–37).

Several studies have focused on the impact of extended surgery on survival. Scarabelli *et al.* reported 100% 2-year survival for patients without macroscopic tumor after surgery and 77% for patients with implants of 1 cm diameter. Patients with residual disease >2 cm had not reached 2 years (38). Another study from Takahashi and coauthors showed 60.8% of 5-year cumulative survival in patients without residual disease, while patients with macroscopic disease had 0% (39). Cumulative 5-year survival in patients undergoing primary radical cytoreductive surgery with bowel resection was 62.2%,

while in patients operated after neoadjuvant chemotherapy, survival was only 13.9% (38). A study from Arora reported 2-year disease-free survival in 63% of patients who achieved optimal cytoreduction with bowel resection (40).

Peiretti *et al.* showed 72 months median overall survival time among patients with complete cytoreduction compared with 42 months among the rest (41). Estes and colleagues have showed improved disease-free survival in patients with advanced epithelial ovarian carcinoma undergo bowel resection as part of optimal cytoreduction, combined with platinum and taxane, as well as a tendency to improve overall survival (42).

Bowel resection allows for optimal cytoreduction in patients with advanced ovarian cancer and thus improves overall survival. Postoperative morbidity and mortality can be minimized by careful patient selection, techniques such as stomas creation and close postoperative observation. Intestinal surgery represents a decisive part of the debulking procedures for optimal cytoreduction. In patients with advanced disease who are expected to have optimal residual tumor, resection of more than two bowel parts can be feasible and safe with acceptable rates of complication. Subtotal colectomy should be considered in selective patients due to high rates of anastomotic leakage (43).

### **Peritoneal carcinomatosis**

Obviously, strong indicator favouring neoadjuvant chemotherapy over upfront debulking surgery is the possibility of tumour resection. In other words, unresectable disease or extent generalised carcinomatosis are current indications for neoadjuvant chemotherapy (24).

Moreover, spread of the disease appears to be decisive for abandoning upfront debulking surgery. Deep infiltration or diffuse metastasis within both small and large bowel could lead to severe surgical morbidities (10). Celiac lymph node involvement is accompanied with higher rates of large bowel resection and higher incidence of metastasis to small bowel mesentery (44). Lymph node involvement in general does not seem to favorite primary cytoreductive surgery, while peritoneal carcinomatosis increases the rates of cytoreductive failure and surgical complications, if upfront debulking surgery is decided (10,45,46).

### **Extrapelvic disease (Fagotti scoring system and ascites)**

Laparoscopic index of Fagotti is a 100-point score relevant in prediction of optimal cytoreduction among women undergoing IDS. Predictive parameters include peritoneal

**Table 1** Prognostic factors favoring upfront debulking surgery in patients with high-grade serous ovarian cancer

Patient's profile
Age <65 years of age
BMI <30 kg/m <sup>2</sup>
No comorbidities
No severe illness
Stage of the disease
< IIIC
Histology
High-grade serous ovarian cancer less favorable for upfront debulking surgery
Biomarkers
Ca-125 <100–300 IU/L; useful postoperative biomarker
HE4↓ (<277 pmol/L)
Albumin >25 g/L
Genomic and other factors
BRCA: no mutations
TILs ↓ levels
cfDNA↓ levels
Spread of the disease
Resectable disease
No extent of the disease over diaphragm Ascites <1 L
No lymph node involvement; no CLN involvement
No liver, omental nor spleen metastasis
Minimal small and low bowel infiltration
No macroscopic residual disease can be performed

BMI, body mass index; Ca-125, cancer antigen 125; HE4, human epididymis 4; TILs, tumor-infiltrating lymphocytes; cfDNA, cell-free DNA; CLN, celiac lymph node.

carcinomatosis, diaphragmatic and mesenteric disease, omental metastasis, bowel and stomach infiltration and liver metastases, which underline the influence of extraperitoneal and metastatic disease in surgical prognosis (18,47). Patients are classified into three risk groups of incomplete cytoreduction. Those at high-risk would be treated with neoadjuvant chemotherapy, whereas low-risk patients may benefit from upfront complete cytoreduction. For the subset of intermediate-risk patients, laparoscopy for the assessment of disease resectability is reasonable.

### *Preoperative HE4 and CA-125 level*

Both, human epididymis protein 4 (HE4) and cancer antigen 125 (Ca-125), have been suggested as markers in terms of patient selection for upfront debulking surgery in cases of high grade-serous ovarian cancer (3). High HE4 levels have been suggested as a negative prognostic factor for upfront debulking surgery and a recent study suggests an optimal cut-off of 277 pmol/L in order to evaluate high-risk of death among these women (48). Although Ca-125 remains an important marker of the presence of residual tumor load, high levels of this marker, preoperatively, suggest an accurate and sensitive circulating and tissue biomarker in cases of high-grade serous ovarian cancer and are predictive of high risk of death due to advanced ovarian cancer (10). Scientific evidence proposes that Ca-125 regression is a valuable predictor of the efficacy of neoadjuvant chemotherapy and can identify patients who will most gain benefit by this approach (24,48) (*Table 1*).

### *Radiographic and nuclear imaging*

Imaging techniques offer a better understanding of the extent of the disease and permit surgeons to decide whether upfront debulking surgery is optimal for patients suffering from high-grade serous ovarian cancer. More specifically, PET/CT scan is considered a necessary tool in evaluating the efficacy of cytoreduction and defining the optimal surgical timing for intervention within patients with high-grade serous ovarian cancer (24). According to scientific evidence, malignant pleural effusion and metastasis over diaphragm indicate lower chances of complete cytoreduction. Nevertheless, the evidence is not consistent and further studies need to be conducted in order to assess these imaging features' predictive value (3). Additionally, 18 fluorodeoxyglucose-positron emission tomography (18-FDG-PET) is proven to be adequate for estimating neoadjuvant chemotherapy response by quantifying the FDG uptake on tumor sites (24).

Video-assisted thoracoscopy (VATS) was suggested as optimal imaging technique in patients with pleural involvement, in order to assess the stage of the disease, whereas real-time ultrasound elastography was able to evaluate chemotherapy response but the application of the technique is quite limited (3,24). Furthermore, diffusion weighted MRI (DW-MRI) offers an estimated superior predictive value for cytoreductive outcome in approximately 90% of the cases, providing essential information on serosal

intestinal, mesenteric vascular and distant site involvement (3,24,46). Last but not least, sonography has been evolved over the years, and although its use is limited, adequate pre-operative assessment of the extent of the disease can be achieved.

### **Advantages of upfront debulking surgery**

Complete cytoreduction, meaning no macroscopically visible disease or less 10 mm, has been well-documented for its positive predictive value in overall survival outcome (3,24,44). In selected patients, upfront debulking surgery is accompanied with less morbidity compared to neoadjuvant chemotherapy with IDS (3,49). Nevertheless, complete cytoreductive surgery demands higher range of surgical skills in order to achieve optimal tumor resection in abdominal and pelvic sites (44,50,51).

Specialized centers meet these criteria and offer to patients with high-grade serous ovarian cancer lower rates of morbidity as well as, higher rates of overall survival (44,52).

Adequate resection of large tumor bulk results in better vascularized smaller residual tissue offering a better chemotherapeutic response, decreased chemo-resistance and enhanced host immunocompetence (49,53). Thus, upfront debulking surgery offers a variety of benefits for patients with high-grade serous ovarian cancer (53).

To conclude, when spread of the disease is limited and patient profile is stable with no comorbidities, upfront debulking surgery appears to be feasible (10). In any case, surgical expertise defines the success of the procedure since experienced centers show higher rates of complete cytoreduction which offers better overall survival rates for these patients (54,55).

Lower rates of chemoresistance have been well-documented in patients who underwent upfront debulking surgery due to minimal tumor load (3,39). Subsequent chemotherapy in patients with IDS found to be inadequate in patients received neoadjuvant chemotherapy followed by higher rates of recurrence demonstrating a clear advantage of primary cytoreductive surgery (56). For instance, in patients with celiac lymph node involvement, upfront debulking surgery aiming for lymphadenectomy offers higher survival rates, since positive celiac lymph nodes are accompanied with higher incidence of chemo-resistance and more advanced disease with higher rates of recurrence if not removed at the time of the surgery. In these cases, upfront debulking surgery performed by experienced surgeons offers an advantage to high-grade ovarian cancer patients over

neoadjuvant chemotherapy followed by IDS (44). Current scientific data yields an impression of higher overall survivals rates in patients with advanced ovarian cancer undergoing primary cytoreductive surgery with additional intraoperative chemotherapy, regardless remaining residual disease. This evidence though is not consistent and further studies need to be conducted in order to validate this assumption (54).

### **Advantages of IDS**

Rivals of IDS propose that neo-adjuvant chemotherapy may decrease tumor size and may offer, for this reason, improved surgical outcomes (3,57,58). A recent meta-analysis proposed that IDS may succeed better results in cytoreduction rather than upfront debulking surgery (3,59). Nevertheless, this evidence is not consistent and studies suggest similar overall survival rates and progression-free survival rates in both approaches (6,60,61). Neoadjuvant chemotherapy though, is found to be favorable for patients with an IV disease stage with poor performance status (6). It appears that these patients are showing higher levels of quality of life (QoL), a key-point that all end-stage cancer patients are hoping for (54,62,63).

On the other hand, genomic factors seem to define the success of IDS (27). Over-expression of homologous recombination DNA repair pathways, and BRCA, are associated with improved outcome of neoadjuvant chemotherapy followed by IDS (10,64,65). It seems that these genomic factors ameliorate the management of patients with high-grade serous ovarian cancer offering higher overall survival rates (24). By extent, naïve to chemotherapy patients may pose a good environment in order to evaluate new regimens and biomarkers within just a few months (54).

### **Clinical trials comparing neoadjuvant chemotherapy followed by IDS with upfront debulking surgery**

Since the first randomized phase III trial of neoadjuvant chemotherapy in advanced ovarian cancer in 2010, several studies have addressed the issue of the optimal surgical timing (66).

### ***European Organization for Research and Treatment of Cancer (EORTC) 55971***

Suggested higher cytoreduction and decreased surgical morbidity in neoadjuvant chemotherapy followed by IDS,

while progression-free and overall survival rates showed no difference in both groups. Moreover, the same trial proposed that patients with extensive carcinomatosis or stage IV ovarian cancer were more likely to gain benefit from neoadjuvant chemotherapy followed by IDS rather than primary debulking surgery (3). Upfront debulking surgery was optimal for these patients showing higher overall survival rate in cases where no macroscopic residual disease remained at the time of surgery. In cases of neoadjuvant chemotherapy followed by IDS, no accurate surgical stage could be performed and as a result the scientific data of this RCT remain ambiguous (24).

In any case, EORTC trial revealed complete cytoreduction in 19% of the patients receiving upfront debulking surgery followed by adjuvant chemotherapy whereas 51% in patients receiving neoadjuvant chemotherapy and IDS (67).

The median overall survival and median progression-free survival measured in months were approximately 30 and 12, respectively in both groups.

#### ***Chemotherapy OR Upfront Surgery (CHORUS)***

Similar findings to EORTC 55971 were also proposed in CHORUS trial. In this trial, patients with advanced ovarian carcinoma (stage III–IV) were included and neoadjuvant chemotherapy followed by IDS found to be superior with regards to cytoreduction and surgical complications such as, postoperative death, infection, thrombosis or hemorrhage. The number of participants was 550.

In any case, overall survival rates found to be similar in both groups (3). This study suggested that the overall survival after neoadjuvant chemotherapy was not inferior to primary surgery, and surgical morbidity and mortality were significantly reduced in this group, with a trend toward better QoL for the patients (47,68). More specifically, complete cytoreduction was achieved in 17% of the patients receiving upfront debulking surgery followed by adjuvant chemotherapy whereas 43% of the patients receiving neoadjuvant chemotherapy followed by IDS (69,70).

The median overall survival and median progression-free survival measured in months were approximately 23 and approximately 12, respectively in both groups. In these first two trials, no adequate aggressive cytoreduction was able to be achieved, undermining the true value of the results (24).

#### ***Japanese Clinical Oncology Group (JCOG) 0602***

Once again showed noninferiority of neoadjuvant

chemotherapy followed by IDS compared to upfront debulking surgery (53). Predominantly, this trial was able to estimate lower morbidity in patients with advanced ovarian cancer undergoing neoadjuvant chemotherapy followed by IDS compared to primary debulking surgery (6). In this study the median overall survival was 49 months in upfront debulking surgery followed by adjuvant chemotherapy group while 44.3 months in the group of patients receiving IDS after neoadjuvant chemotherapy (71). The median progression-free survival was 15.1 and 16.4 months in these groups, respectively, as well as, complete cytoreduction was achieved in 12% (17 of 147 patients) in UDS group and in 64% (83 of 130 patients) in the NACT group. Regarding, optimal surgery with no residual tumor larger than 1cm, the trial revealed that it was achieved in 37% (55 of 147 patients) and in 82% (92 of 147 patients) respectively in the two groups (72). More specifically, the former group of patients showed shorter operation time, less organ resection, and less adverse events postoperatively in general (24).

#### ***Surgical Complications related to Primary or Interval debulking in Ovarian Neoplasm (SCORPION)***

Moreover, the long-awaited SCORPION trial favors neoadjuvant chemotherapy followed by IDS over upfront debulking surgery (3). According to the trial, patients who underwent the latter regime, were presented with lower QoL and higher morbidity. But overall this trial suggests, that complete cytoreduction was achieved in 46% of the patients receiving upfront debulking surgery followed by adjuvant chemotherapy whereas, 58% in the neoadjuvant group (73,74). Optimal cytoreduction (<1 cm residual tumor) was achieved in 92,8% and 100% in both groups, respectively.

Unfortunately, data regarding overall survival and progression-free survival are still awaited.

#### ***Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (TRUST trial-NCT02828618)***

Finally, TRUST trial will be able to overcome selection bias and randomize its patients.

Further scientific evidence will be published within 2024. In this trial, patients with advanced epithelial ovarian cancer, fallopian tube cancer or primary peritoneal carcinoma FIGO stage IIIB–IVB will be included providing essential data with regards to treatment options (75) (Table 2).

**Table 2** Randomized clinical trials (Phase 3) comparing upfront debulking surgery followed by adjuvant chemotherapy with interval debulking surgery (IDS) after neoadjuvant chemotherapy in cases of advanced epithelial ovarian cancer

Study	Criteria	No of patients	OS (months)	PFS (months)	Complete cytoreduction	Optimal cytoreduction
EORTC 55971	Stage IIIC–IV	UDS-ACT 336 NACT-IDS 334	30 both groups	12 both groups	UDS-ACT 19% NACT-IDS 51%	Not available
The CHemotherapyORUpfront Surgery (CHORUS) trial	Stage* III–IV	UDS-ACT 276 NACT-IDS 274	23 both groups	12 both groups	UDS-ACT 17% NACT-IDS 43%	Not available
JCOG 0602 trial	Stage IIIC–IV	UDS-ACT 149 NACT-IDS 152	UDS ACT 49 NACT IDS 44.3	UDS ACT 15.1 NACT IDS 16.4	UDS-ACT 12% NACT-IDS 64%	UDS-ACT 37% NACT-IDS 82%
SCORPION trial	Stage IIIC–IV Fagotti score 8 to 12	UDS-ACT 55 NACT-IDS 55	Not available	Not available	UDS-ACT 46% NACT-IDS 58%	UDS-ACT 92.8% NACT-IDS 100%
TRUST trial, NCT02828618	Stage IIIB–IVB	772			On-going trial Results are expected in 2024	

\*, no histologic confirmation. UDS, upfront debulking surgery; ACT, adjuvant chemotherapy; NACT, neoadjuvant chemotherapy; IDS, interval debulking surgery; OS, median overall survival; PFS, median progression-free survival.

## Conclusions

As indicated above, there is a lack of consensus regarding the optimal surgical timing in patients with high-grade serous ovarian cancer. All studies suggest personalized approach of each patients by taking into consideration a number of predictive factors that could favor one approach over the other. Understanding the prognostic factor affecting the efficacy of upfront debulking surgery will eventually offer scientific evidence with regards to patient's selection for treatment.

Algorithms should be conducted in order to estimate the efficacy of each surgical approach depending on evidence-based prognostic factors. It is imperative to assess and propose optimal surgical timing with regards to increasing overall survival rates.

Understanding prognostic factors and their influence in the progression or recurrence of the disease will facilitate specialists in terms of choosing optimal treatment option taken also into consideration QoL of the patient as a first-line aim in cases of advanced disease.

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