The role of maximal cytoreduction is well established in the management of advanced primary ovarian cancer (1), while surgical staging is absolutely important and in early stages of the disease is considered mandatory due to the prognostic value and the consequences for the choice of systemic chemotherapy.

Cytoreductive surgery for ovarian cancer is generally performed at the time of diagnosis and requires high competence of the surgeon to apply various multivisceral surgical techniques. When cytoreductive surgery is performed after neoadjuvant chemotherapy it is defined as interval cytoreduction (2). The hypothesis of the attributable benefits of cytoreduction includes (3) removal of poorly vascularised tumour whereupon pharmacologic sanctuaries are eliminated, (4) a higher growth fraction in the better perfused small residual tumour masses which favours an increased cell death with chemotherapy, (5) small tumour masses require fewer cycles of chemotherapy so there is less opportunity for induced drug resistance, (6) removal of drug-resistant clonogenic cells, and (7) host immunocompetence enhanced by the removal of large tumour bulk (3). Nevertheless further prospective translational research activities were warranted to understand more precisely these effects.

There is great consensus that postoperative tumor-residual-mass is the most relevant prognostic factor in advanced ovarian cancer and this independent from all other clinically and tumor specific factors, including age, histology and grading (8).

In 1934, Meigs was the first one who championed cytoreductive surgery in advanced ovarian cancer to enhance the effects of postoperative radiation therapy (4). The concept of primary cytoreduction was supported when Griffiths showed that survival depends on residual disease (5). Since then, many other authors and two meta-analyses have confirmed this observation (6,7). Whilst in the late 90’s the aim of primary surgery was defined as residual disease of less than 1 cm (so-called optimal debulking), it seems that this definition has to be re-discussed. Actual data of a meta-analysis of the AGO Study Group including more than 3000 patients with advanced ovarian cancer of 3 large prospective randomized trials show clearly that patients most benefit in case of complete resection (8). According to the 4th Ovarian Cancer Consensus Conference (2010) the ultimate goal is currently defined as cytoreduction to microscopic disease, even though there is evidence that reduction to <1 cm macroscopic disease is also associated with some benefit. Therefore the term “optimal” cytoreduction should be reserved for those with no macroscopic residual disease. Emphasis was also given to the adequate documentation of the surgical result which must be provided as to the level of cytoreduction (at least microscopic vs. macroscopic) (9).

The advantages in survival in case of complete resection are so impressive, that it is not arguable to deny a patient cytoreductive surgery with complete removal of the tumor if this is technically possible under consideration of comorbidities and risk factors of the individual patient (9,10). This benefit is also allocated for special patient populations such as elderly or severely obese patients (11,12). To achieve optimal surgical results with improved survival in advanced stages of the disease, surgical techniques include apart from pelvic surgery with en-block intestinal resections, also addition of an upper abdominal approach, in terms of diaphragmatic stripping, splenectomy, distal pancreatectomy or liver capsule resection (13).

Due to the high operative challenge where specialized training skills are required, there is growing evidence which demonstrates the superiority of both surgical and chemotherapeutic treatment strategies conducted and performed by qualified gynecological oncologists. Higher rates of compete tumor resection by comparably low operative morbidity and mortality can be obtained, if advanced ovarian cancer patients are primarily treated in specialized high-volume hospitals (14-16).

Nevertheless, the timing of cytoreductive surgery as an upfront debulking operation was challenged because complete removal of tumor could be achieved only in a minority of patients outside specialized centers. The actual impact of neoadjuvant chemotherapy on the primary treatment of advanced ovarian cancer is currently one of the most hotly debated issues in the gynecological cancer-society worldwide. Concretely, the benefit of interval cytoreduction was investigated in two randomized prospective trials conducted by the EORTC and the Gynecologic Oncology Group (GOG). Final results were somewhat conflicting, but both studies supported an extensive attempt at surgical cytoreduction during primary therapy (2). Whilst van der Burg (17) reported a survival benefit for interval debulking performed in a specialised centre after primary surgery.
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With ovarian cancer, Rose (18) found no benefit for interval debulking, if primary surgery was performed by a gynecologic oncologist. Except from marginal differences in the study design and chemotherapy-type, the crucial difference between the two study designs was the experience level of the surgeons who performed the operations. Recently a Cochrane Review and a metaanalysis of surgery after neoadjuvant chemotherapy have been published (19,20). The conclusions of the metaanalysis and the Cochrane review are as follows: Interval debulking is helpful only for cases with inadequate primary surgery. Interval debulking should be avoided in cases with technically adequate but unsuccessful primary surgery. One of the most frequently raised arguments against neoadjuvant chemotherapy is that most studies evaluating this approach are not derived from specialized gynecological cancer-centers. Moreover, if interval debulking is indicated, it should be performed as soon as possible (after the third course of chemotherapy latest). Interval debulking can never be a compensation for an adequate primary surgery. An EORTC-GCG/NCIC-CTG trial has compared primary surgery versus interval debulking in patients with stage IIIC/IV ovarian cancer which has shown non-inferiority of interval debulking compared to upfront surgery (21). However, this trial included only patients in whom the treating physicians have expected a low probability to achieve complete resection at primary surgery potentially benefit from neoadjuvant chemotherapy. Optimal debulking (residual disease up to 1 cm) was achieved in only 48% in patients in the primary surgery arm and in 83% after neoadjuvant chemotherapy. Postoperative mortality was significantly lower in the interval debulking arm (0.6% vs. 2.7%). The survival rates showed no significant differences between the two arms (29 and 30 months), but were low compared to eg the last prospective randomized GCIG Intergroup trial AGO-OVAR 9 reporting an overall survival of 46 and 49 months (22). Also the median time of surgery with 180 minutes indicates the negative selection in this trial population (‘quick surgeons’ and/or ‘quick surgery’). The surgical data (e.g. large bowel resection rate of 10%) are not in line with surgical data from experienced gynecologic oncology centers. Based on these facts, the transferability of the data to all advanced stage ovarian cancer patients seems not possible. It seems that patients in whom complete resection at primary surgery in experienced centres is not possible could potentially benefit in terms of lower morbidity and mortality by interval debulking. Surgery with maximal effort of cytoreduction before primary chemotherapy remains the standard of care in patients in whom complete resection could be achieved. Interval debulking after 2 or 3 courses of systemic therapy is an option for patients in whom surgery with maximal effort is not possible at primary diagnosis (e.g. worse performance status due to cancer symptoms and aim of improvement by ‘neoadjuvant’ chemotherapy). This level II evidence for the role of cytoreductive surgery in advanced ovarian cancer is supported by data from an epidemiologic survey indicating that both optimal surgery and state-of-the-art chemotherapy contribute independently to the outcome in ovarian cancer (23).

Again according to the recent 4th Ovarian Cancer Consensus Conference delayed primary surgery following neoadjuvant chemotherapy is considered to be an option for selected patients with stage IIIC and IV ovarian cancer as included in the EORTC 55971 study. However till now no well defined selection criteria are specified which would identify the optimal candidates for a neoadjuvant approach (24,25) and should be restricted to very limited number of patients who are not able to undergo a primary cytoreductive surgery.

Regarding the value of systematic lymph node dissection, evidence indicates that lymphadenectomy in advanced ovarian cancer might offer a benefit mainly to those patients who underwent a complete intraperitoneal debulking (26). Currently there is a large prospective randomized trial (LION) which compares the value of systematic pelvic and paraaortal lymph node dissection in patients with completely resected advanced ovarian cancer.

In respect of the impact of the histological type on the overall outcome in primary ovarian cancer, data on 8704 women with stage III/IV EOC from 7 randomized trials were evaluated. Two hundred twenty-one patients (2.5%) had clear cell carcinoma; 264 (3.0%), mucinous; and 36 (0.4%), transitional cell. The mean age of patients with serous histology was greater than those with mucinous (4.1 years) and clear cell (2.6 years, P < 0.001). Mucinous, clear cell, and transitional cell tumors were more likely to be completely resected than serous (P < 0.05). When controlling for age and residual disease, mucinous and clear cell tumors had shorter times to progression (hazards ratio [HR], 2.1; 95% confidence interval [CI], 1.8-2.4 and HR, 1.6; 95% CI, 1.4-1.9, respectively) and death (HR, 2.7; 95% CI, 2.3-3.1 and HR, 2.2; 95% CI, 1.8-2.6, respectively) compared with serous. The median overall survival for serous, clear cell, mucinous, and endometrioid histologies were 40.8, 21.3, 14.6, and 50.9 months.

Mucinous and clear cell carcinomas are independent predictors of poor prognosis in stage III/IV EOC. Studies targeting these rare histological subtypes are warranted and will require significant intergroup collaboration (27).

Concluding it is challenging to postulate that if complete resection is considered as achievable, optimal primary cytoreductive surgery should be considered as the preferred strategy in patients with advanced ovarian cancer, even though till now no adequate selection criteria are defined which would identify the optimal candidates for a neoadjuvant approach, so that further prospective randomized trials combined with the implementation of validated intra-operative tumor documentation tools and a strong translational part are mandatory in order to define the true impact of a neoadjuvant approach in advanced ovarian cancer. Of crucial importance remains however the fact, that regardless the approach that will be followed, the surgical treatment of patients with ovarian cancer should remain only in hands of experienced gynecologic oncologic surgeons, so that maximal benefit is derived by a comparable low morbidity.
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References

9. 4th Ovarian Cancer Consensus Conference, June 25 – 27, 2010, UBC Life Sciences Institute, Vancouver, BC.