3. Cytoreductive surgery for ovarian cancer

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Surgical therapy in ovarian cancer contains different types of surgery (Table 1):

(1) **Surgery for diagnostic purposes:** This kind of surgery could be performed at any time in the course of ovarian cancer (e.g. to get a histological diagnosis). *Second-look surgery* belongs to this group of procedures. It is an operation performed in patients who are clinically free of disease after the completion of a defined course of chemotherapy with the purpose to confirm the response status (In principle, the removal of the remaining tumor at second-look passes the border of diagnostic procedures).

(2) **Staging laparotomy:** This surgery should be performed in patients with macroscopically early ovarian cancer limited to the ovaries or the pelvis. Aim of this surgery is the detection of tumor spread

(3) **Primary cytoreductive surgery:** Surgery with the aim of complete resection of all macroscopic tumors in patients with first diagnosis of ovarian cancer before any other treatment modalities (e.g. chemotherapy).

(4) **Secondary surgery/Interval debulking:** An operation performed in patients after chemotherapy, usually 2 or 3 cycles, with an attempt to remove any remaining tumor which has not been removed by chemotherapy.

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(5) **Surgery for progressive ovarian cancer:** An operation with the purpose of removing obviously resistant tumors which have not responded to chemotherapy and progressed during primary chemotherapy.

(6) **Surgery for recurrent ovarian cancer:** Surgery aiming for complete resection of all macroscopic tumor in patients with recurrent ovarian cancer after completion of primary therapy including a subsequent period without any signs of disease.

(7) **Palliative surgery:** An operation performed in patients with symptoms caused by progressive disease or sequels from prior treatment. These operations are performed in an effort to relieve symptoms and do not aim primarily at survival prolongation.

This book chapter wants to focus on cytoreductive surgeries in primary and recurrent ovarian cancer.

Table 1. Different types of surgery in ovarian cancer.

(1) Surgery for diagnostic purposes
(2) Staging laparotomy
(3) Primary cytoreductive surgery
(4) Secondary surgery/Interval debulking
(5) Surgery for progressive ovarian cancer
(6) Surgery for recurrent ovarian cancer
(7) Palliative surgery

Primary cytoreductive surgery

The role of surgery in newly diagnosed ovarian cancer is widely accepted, although there is no Level I evidence for its role, and prospectively randomized phase III studies comparing cytoreductive surgery with no surgery are lacking. However, there is supportive evidence (level II and III) indicating a benefit for primary cytoreductive surgery. Possible benefits of surgery include (1) removal of poorly vascularized tumor whereupon pharmacologic sanctuaries are eliminated, (2) a higher growth fraction in the better perfused small residual tumor masses which favours an increased cell death with chemotherapy, (3) small tumor masses require fewer cycles of chemotherapy so there is less opportunity for induced drug resistance, (4) removal of drug-resistant clonogenic cells, and (5) host immunocompetence enhanced by the removal of large tumor bulk [1]. In 1934, Meigs was the first one who championed cytoreductive surgery in advanced ovarian cancer to enhance the effects of postoperative radiation therapy [2]. The concept of primary cytoreduction was supported when Griffiths showed that survival

depends on residual disease [3]. Since then, many other authors and two meta-analyses have confirmed this observation [4, 5, 6, 7, 8, 9, 10, 11, 12, 13]. 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 [14]. There is still some advantage in case of achieving residual disease of 1-10 mm compared to more than 10 mm, but nevertheless, 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 co-morbidities and risk factors of the individual patient [15]. The surgical techniques include not only pelvic surgery and bowel resection. Also the addition of upper abdominal surgery, including stripping of the diaphragm or splenectomy, improves survival if these techniques help to achieve lower tumor burden [16].

However, there is some debate about definition of complete debulking: Should systematic lymphadenectomy be included or is it sufficient to remove palpable enlarged lymph nodes. It is known that 81% of patients with advanced disease have lymph node metastases which are often not detectable by palpation. Furthermore, most of metastatic nodes are localized in the upper para-aortic and interaortocaval region [17] (Figure 1). A recently published prospectively randomized phase III international multicenter study addressed this question [18]. This study compared systematic pelvic and para-aortic lymphadenectomy with removal of enlarged lymph nodes only in FIGO stage III epithelial ovarian cancer and intra-abdominal so-called optimal debulking with tumor residuals up to 1 cm. Patients with systematic lymphadenectomy showed a significant longer progression-free survival (median +7 months adjusted analysis, p = 0.01; +5 months analysis of raw data) and a non-significant benefit regarding median overall survival (+ 2.4 months in adjusted analysis, +5.6 months raw data analysis). In addition, patients who underwent systematic lymphadenectomy had longer operation time and more complications (including blood loss). The lack of any significant survival advantage led some to comment, that systematic lymphadenectomy should not play a role in primary ovarian cancer surgery [19]. However, the authors of the study came to an opposite conclusion and stated that "the therapeutic value of systematic lymphadenectomy in women with advanced ovarian cancer remains controversial". The latter statement seems more reasonable when analyzing the study carefully. The survival comparison was based on 191 events in only 44.2% of all recruited patients. A clinical relevant impact
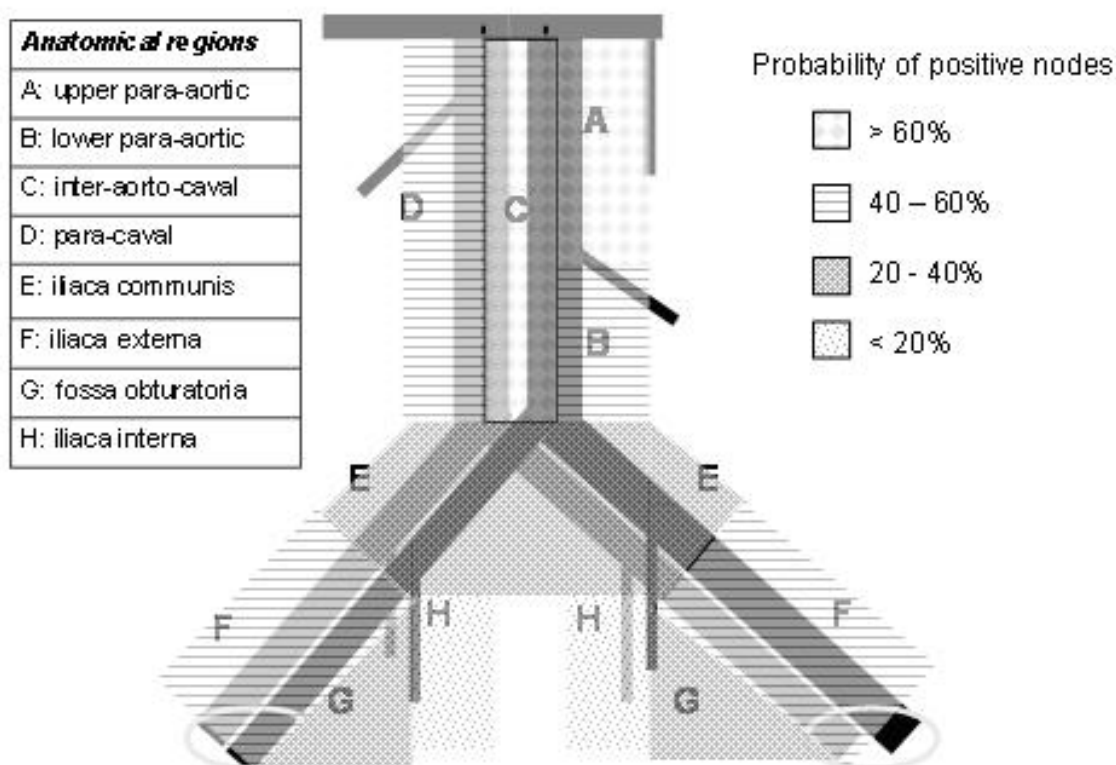
Anatomical regions
A: upper para-aortic
B: lower para-aortic
C: inter-aorto-caval
D: para-caval
E: iliaca communis
F: iliaca externa
G: fossa obturatoria
H: iliaca interna

Probability of positive nodes

□ > 60%

▤ 40 – 60%

▦ 20 - 40%

▥ < 20%

Figure 1. Probability of positive nodes in ovarian cancer patients.

of any procedure cannot be ruled out based on such small numbers; e.g. a risk reduction of 25% or, in other words, an absolute improvement of 13% survival rate would have been missed statistically in such a small cohort. Furthermore, the composition of the study cohorts might be re-considered. The role of systematic lymphadenectomy might be to complete "seemingly complete" debulking by removing small tumor residuals in patients who have metastatic but non-palpable lymph nodes (non-palpable lymph node metastases rarely exceed 1 cm by diameter) thus shifting these patient from small volume residual disease to no macroscopic residual disease. This effect could only benefit patients with complete intra-abdominal debulking and no macroscopic residual disease left in the peritoneal cavity. However, two thirds of included patients had intra-abdominal residuals of up to 1 cm. Lymphadenectomy would not alter their status of residual disease and they still had small volume disease intra-abdominally even if small lymph node metastasis would have been removed. Consequently, only the 37% of included patients who had no visible residuals intra-abdominally could have experienced any benefit from systematic lymphadenectomy with respect to residual tumor. Furthermore, only 28% of patients more had positive nodes in the lymphadenectomy group compared to the patients who had only removal of enlarged lymph nodes (42% vs. 70%) thus making the subgroup who

would (theoretically) benefit from systematic lymphadenectomy even smaller. In conclusion, a trial aiming at an evaluation of a possible impact of systematic lymphadenectomy should "enrich" the study population by patients who could benefit and only enroll patients with complete intra-abdominal debulking. The LION-trial which addresses this question has currently started (Figure 2). Until results are available, the role of lymphadenectomy remains a cornerstone of staging in early ovarian cancer and should be discussed with patients balancing side effects and possible benefit. Patients most probable to gain any benefit are those completely debulked intra-abdominally. However, patients with small volume disease still experienced better progression-free survival, which might be of value on its own if not traded for excessive toxicity (which is uncommon in experienced centers for ovarian cancer surgery). An exploratory analysis of the surgical treatment characteristics in a prospective trial compared UK and Non-UK centers [20]. This study showed the following observations: (1) patients recruited from centers outside the UK were more likely to be completely debulked (UK 28.6%, Non-UK 39.9%, p<0.001). (2) Completely debulked patients of Non-UK centers had better PFS compared to UK centers (p=0.01). In Non-UK centers procedures as bowel resection, pelvic, and para-aortic lymphadenectomy have been performed more often (p<0.001), especially in complete debulked patients. It seems that complete debulking without lymphadenectomy is not the same as complete debulking with this procedure. The operation time was shorter in UK centers (95 minutes vs. 135 minutes, p<0.001). Unfortunately morbidity of the surgery is not reported, but more extensive surgery, as performed in Non-UK centers resulted in better PFS (Overall survival was not reported). An exploratory analysis of the AGO-OVAR meta-database which contains the data of 3 prospective randomized trials in advanced ovarian cancer, showed that 1003 out of 2924 patients had complete resection. 72% of the patients in this subgroup underwent lymphadenectomy. In multivariate analysis lymph node resection remained an independent prognostic factor (Hazard ratio 0.71, 95% CI: 0.55-0.91). Further prognostic factors were age, performance status, stage, histological subtype, and grading [21]. In conclusion, residual disease after primary surgery is an important prognostic factor. Multiple surgical procedures are necessary to remove all visible tumor. Only complete debulking should be the aim of surgery before start of primary chemotherapy.

Many surgical skills and techniques described in this book are necessary for conducting adequate and successful surgeries in ovarian cancer patients. Majority of patients are still treated in low-volume hospitals which are not specialized in treating ovarian cancer patients. An actually performed review

*L*ymphadenectomy *I*n *O*varian *N*eoplasms
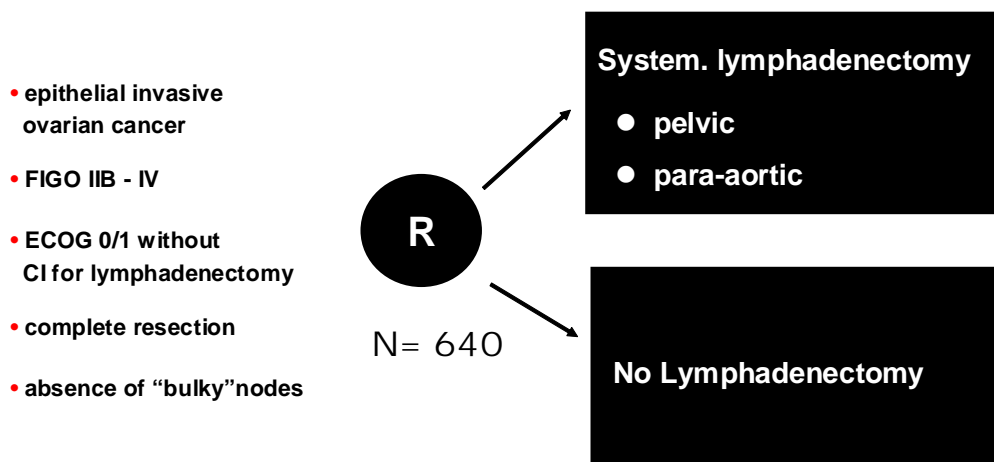## LION
(AGO-OVAR OP.3)

Figure 2. Design LION.

on specialization has shown that treatment by specialized centers and physicians (Gynecologic Oncologists) lead to a better quality of staging in ovarian cancer and a higher rate of optimal debulking in advanced ovarian cancer [22]. Additionally a national survey in Germany has shown that patients have a higher chance to receive state-of-the art therapy including a successful surgery in clinics involved in ovarian cancer trials [23].

Secondary surgery / Interval debulking

The timing of cytoreductive surgery as upfront debulking operation was challenged because (almost) complete removal of the entire visible tumor could only be achieved in a minority of patients outside specialized centers. At this time, interval cytoreductive surgery seemed to be an attractive option and 2 randomized prospective trials [24, 25] provide some evidence that patients with advanced ovarian cancer benefit from one successful cytoreductive surgery. Whilst van der Burg reported a survival benefit for interval debulking performed in a specialized centre after primary surgery elsewhere, Rose found no benefit for interval debulking, if primary surgery was performed by a gynecologic oncologist. 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 [26]. 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. The survival rates showed no significant differences between the two arms (29 and 30 months), but are low compared to e.g. the last prospective randomized GCIG Intergroup trial AGO-OVAR 9 reporting a overall survival of 46 and 49 months [27]. Also the median time of surgery with 180 minutes indicates the negative selection bias in this trial population. Postoperative mortality was significantly lower in the interval debulking arm (0.6% vs. 2.7%). It is difficult to interpret this data, but it seems that patients in whom complete resection at primary surgery in experienced centers is not possible could potentially benefit in terms of lower morbidity and mortality by interval debulking. Surgery with maximal effort of cytoreduction before starting 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 was 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].

Cytoreductive surgery in recurrent ovarian cancer

Reviewing the role of secondary cytoreductive surgeries faces obstacles due to the broad variety of definitions used to describe different procedures. Definitions commonly include different groups of patients, namely patients with recurrent disease and those with persistent disease; the latter might even include patients with either progressive disease at the end of chemotherapy or patients with persisting but not progressing ovarian cancer as well as both patients with small residual tumors that responded to systemic treatment and patients suffering from recurrence after a disease-free period of some weeks or several years [28,29]. There are only a very limited number of reports about surgery for persistent or primary progressive ovarian cancer. One of this series was reported by Morris et al: "The present study provided no evidence that secondary surgery is of significant…" [30]. For this subgroup survival rates up to 9 months are reported which are not justify cytoreductive surgery with a morbidity rate of 24% in this setting.

Cytoreductive surgery for recurrence is defined as an operation performed in patients with recurrent disease after completion of primary treatment (surgery with or without chemotherapy) and a period without any evidence of disease. It is performed with the purpose of removing as much of the tumor as possible. Although usually not curative, this kind of surgery aims at prolongation of survival and its practice follows similar rules as primary surgery for advanced disease. Unfortunately, the only randomized trial about the role of cytoreductive surgery in recurrent ovarian cancer by the EORTC, the LOROCSON trial, has been aborted prematurely due to low recruitment [pers. communication I. Vergote] This review will present the available evidence about the role of cytoreductive surgery apart from randomized trials and focuses on some relevant questions:

Which patients had been offered cytoreductive surgery for recurrence (selection bias?) and what were the surgical achievements?

Some authors defined optimal debulking as removal of all visible tumor while others reported small residuals with varying dimensions of maximum diameters (0.5-2 cm). The complete debulking rate varied between 9 and 82% [31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49]. All series were collected retrospectively and exposed to obvious selection bias. Unfortunately, information about selection criteria and proportions of patients not offered cytoreductive surgery was lacking. The reported selection rates of patients without being offered surgery varied from 7%-64%.

What was / should be the appropriate endpoint for cytoreductive surgery for recurrence?

The concept of so-called optimal debulking has been introduced for primary cytoreductive surgery in advanced ovarian cancer. Mainly retrospective analyses studies had reported a kind of threshold above which cytoreduction did not result in a more favorable outcome and defined "optimal debulking" as achieving removal of all tumor lesions with a maximum diameter larger than this cut-off. More recent studies had used a definition of ≤ 1 cm diameter of residual tumor as cut-off for inclusion criteria [50, 51] or as stratum [52, 53]. However, the concept of optimal debulking has not been very well established in cytoreductive surgery for recurrent disease.

The larger series of patients with cytoreductive surgery for recurrent disease provided controversial findings. Eisenkop and Harter reported a survival benefit only for completely debulked patients whilst Scarabelli and Zang indicated a benefit also for so-called optimally debulked patients. However, the latter two series reported remarkably lower complete resection

rates (11% and 35%) than Harter and Eisenkop (50% and 81%), thus raising the question about different selection criteria, different surgical approaches, and methodological issues. A benefit might be missed if a subgroup bearing a potential prognostic factor is rather small. Another series from Güngör et al with 75 patients compared completely debulked patients with patients with residual disease and those treated with chemotherapy only. Again, only patients with complete debulking showed a prolonged survival.

Are there any predictive and/or prognostic factors regarding surgical outcome in recurrent ovarian cancer?

None of the series reported age as predictive factor for resectability. The presence of symptoms, elevated CA 125, localization of disease, number of disease sites, and short treatment free interval were reported in univariate analyses as predictive factor. Only four series reported multivariate analyses of predictive or prognostic factors associated with favorable surgical outcome. Eisenkop identified absence of pre-operative salvage chemotherapy, good performance status and size of recurrent disease less than 10 cm as predictors for complete debulking. In Gronlunds series with 38 patients number of disease sites (solitary vs. multiple) was an independent factor for resectability. Zang reported absence of ascites and residual disease after surgery in primary treatment as predictors for resectability. The DESKTOP trial [36] identified the following predictors: Good performance status, no residual disease after surgery for primary treatment (alternatively, if unknown: early initial FIGO stage) and neither ascites > 500 ml in pre-OP diagnostics. Complete resection was achieved in 79% of patients presenting all these factors. If not all factors were positive, a complete resection was achieved in only 43%. The latter group could be further differentiated: a complete debulking could be achieved in 63% of this subgroup if there was no peritoneal carcinomatosis found intra-operatively; otherwise only 23% could be debulked completely. In the subsequent DESKTOP II trial patients with good performance status (ECOG 0), complete resection at primary surgery, and absence of ascites were defined as score positive and the score was validated in multicentre study. In this setting, the use of this score has shown a complete resection rate of 76% in patients with first relapse and with this result the score was validated successfully [54]. A subsequent randomized phase III trial is planned by the AGO-OVAR.

Does favorable surgical outcome translate into survival benefit in recurrent ovarian cancer?

The median survival of completely debulked patients ranged from 16 to 100 months and overlapped with the median survival described in the

recently reported large prospective trials in recurrent platinum-sensitive ovarian cancer, i.e. ICON4/AGO-OVAR 2.2 [55] and the Gynecologic Cancer Intergroup (GCIG) study AGO-OVAR 2.5 [56]. These studies reported median survival of 18 and 29 months in the respective superior arms. The majority of series of cytoreductive surgery for recurrent ovarian cancer did not report median survival far exceeding the ICON4/AGO-OVAR 2.2 results. Although median survival was on average higher in series with more completely debulked patients, a statistically significant correlation could not be detected. Furthermore, the lack of randomized trials makes it impossible to conclude whether a more favorable outcome in series with high rates of complete debulking could be attributed to biology (i.e. selection bias) or to surgical efforts.

Which prognostic factors are associated with prolonged survival in patients who received cytoreductive surgery for recurrent ovarian cancer?

Almost all series reported a relationship between survival and surgical outcome in univariate analysis. Complete debulking was one of the strongest predictors for survival in all 5 multivariate analyses performed on this question (table 3). All other factors analyzed provided controversial information. Treatment-free-interval before cytoreductive surgery did not show any significant impact on outcome in univariate analyses of six series but another five series reported a significant role. However, only few patients with rather short treatment-free survival had been included in the respective series and the proportion of patients with less than 6 months ranged from 0 – 13.5 % only. Therefore, the data about a possible impact of treatment-free-interval are mainly valid for different periods beyond 6 months.

Eisenkop reported a benefit for treatment-free intervals exceeding 36 months compared to shorter intervals (13-36 and 6 – 12 months). Scarabelli showed a benefit for the subgroup with a recurrence-free-interval of 13 to 24 months but not for patients with longer (> 24 months) or shorter intervals (7-12 months). The DESKTOP trial showed a benefit for a treatment-free-interval exceeding 6 months but no difference when intervals longer than 6 months were compared in the univariate analysis (6-12 vs. 12-24 vs. longer than 24 months). However, treatment-free-interval did not remain an independent factor in the multivariate analysis. A similar observation was reported by Zang who reported a benefit for longer progression-free-intervals in the univariate analysis which could not be confirmed in the multivariate analysis. A further factor associated with prolonged survival was absence of ascites (2 of 3 series analyzing ascites as factor) and an inverse relation was

reported for pre-operative chemotherapy (2 of 4 series analyzing this issue). Only three series had evaluated the impact of systemic treatment after surgery and the most recent analysis reported by Harter observed a positive impact of post-operative platinum-based chemotherapy. In addition the influence of pre-operative tumor load on surgical and prognostic outcome was still discussed controversial. An exploratory analysis of the DESKTOP II data has shown that presence of peritoneal carcinomatosis is a significant negative predictor for complete resection. However, if complete resection is achieved despite peritoneal carcinomatosis, there is no difference in survival compared to completely debulked patients without peritoneal carcinomatosis [57].

In conclusion, there is no level I/II evidence for cytoreductive surgery in recurrent ovarian cancer. However, even the most active chemotherapy regimens provided only limited activity with a median survival of 29 months (ICON4/AGO-OVAR 2.2), and improvement is clearly needed. The reported series of surgery for recurrent disease include survival rates up to 100 months, thus far exceeding the median survival rates reported after chemotherapy only. These data stem from highly selected patient cohorts and, therefore, the main question might be: How can we select suitable patients for cytoreductive surgery in recurrent ovarian cancer? The available information is far from being conclusive, but some factors were repeatedly cited as predictors for successful operations. Sound counseling of patients regarding the selection for surgery in recurrent ovarian cancer will only be possible after validation of these predictors in a kind of predictive score which provides an acceptable range of assumed factors regarding favorable outcome of surgery. The DESKTOP I study identified three variables: (1) good performance status, (2) absence of ascites, and (3) complete debulking during primary surgery (or, if unknown, early FIGO stage initially). This predictive score was successfully validated (AGO-DESKTOP II).

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