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# Primary versus secondary cytoreduction for epithelial ovarian cancer: A paired analysis of tumour pattern and surgical outcome

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ABSTRACT

*Objective:* Recurrence rates of Epithelial Ovarian Cancer (EOC) remain high. Aim of the present study was to compare tumour pattern and surgical outcome at primary and secondary tumourdebulking in a paired patients' collective.

*Methods:* Seventy-nine consecutive EOC-patients who underwent both primary and secondary cytoreduction in our institution between 09/2000 and 12/2010 were evaluated according to a validated documentation-tool ('IMO', Intraoperative Mapping Ovarian Cancer). Differences in tumour-pattern between paired samples were examined using McNemar-test or sign-test.

*Results:* A complete macroscopic tumour resection could be achieved significantly more often during primary versus secondary surgery (77% versus 50%; $p < 0.001$) in comparable operative times (242 min versus 199 min; $p = 0.15$) and by equivalent operative morbidity (25% versus 29%; $p = 0.424$). Tumour-residuals at primary correlated significantly with tumour-residuals at secondary cytoreduction ($p = 0.003$). Patients at relapse had significantly higher rates of tumour involvement of the gastric serosa (2.5% versus 16.9%; $p = 0.001$), serosa of small intestine (20.3% versus 44.9%; $p < 0.001$) and mesentery (30.4% versus 50%; $p = 0.012$). The relative-risk for peritoneal carcinosis, intestinal tumour involvement or positive lymph nodes at secondary tumourdebulking in the case of presence of these features at primary surgery was 1.53 (95% CI: 0.89–2.63); 0.92 (95% CI: 0.65–1.31) and 1.49 (95% CI: 0.83–2.68), respectively, and thus not reaching a statistical significance.

*Conclusions:* Secondary cytoreduction due to EOC appears to be associated with significantly lower optimal tumourdebulking rates compared to primary setting, since the disease tends to recur in patterns less accessible to complete resection such as gastrointestinal serosa, mesentery and upper abdomen. By maximal surgical effort, tumour residuals significantly correlate between primary and secondary cytoreduction. No other predictors of surgical outcome or tumour-pattern could be identified.



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## 1. Introduction

A tremendous shift towards a more radical operative approach resulting in more optimal tumour resection rates in advanced Epithelial Ovarian Cancer (EOC) has occurred in the last decades.[1–4] Upper abdominal debulking procedures, extensive deperitonealisation and en-block tumour resections redounded to a significant improvement of patient's progression free survival rates. Intensified operative training in specialised centres yielded an overall amelioration of surgical skills and abilities, so that no inevitable higher operative morbidity had to concomitantly occur.[5,6] Nevertheless, EOC remains, due to its heterogeneity in terms of histotype, tumour biology, platinum-sensitivity and outcome, a disease with high recurrence rates and often fatal outcome. Till now no strategy for individualising care could deliver a significant improvement in overall patients' outcome. Therefore, clinical observations concerning treatment failure, may potentially lead to novel hypotheses regarding evolution and progression of the disease and ultimately to develop more effective strategies against it.[7] A better understanding of the tumour dissemination patterns followed in the primary and subsequently in the recurrent situation of the disease may contribute to this in an additional level and enhance the evolution and refinement of surgical and, by extension, systemic approach.

Data correlating the tumour dissemination pattern and surgical outcome in primary and later recurrent situations of the disease in the same patient hardly exist. The aim of this study was, therefore, to evaluate tumour dissemination, maximal tumour load, tumour residuals and operative outcome in EOC-patients operated at both primary and relapsed setting in our centre, a reference point for ovarian malignancies.

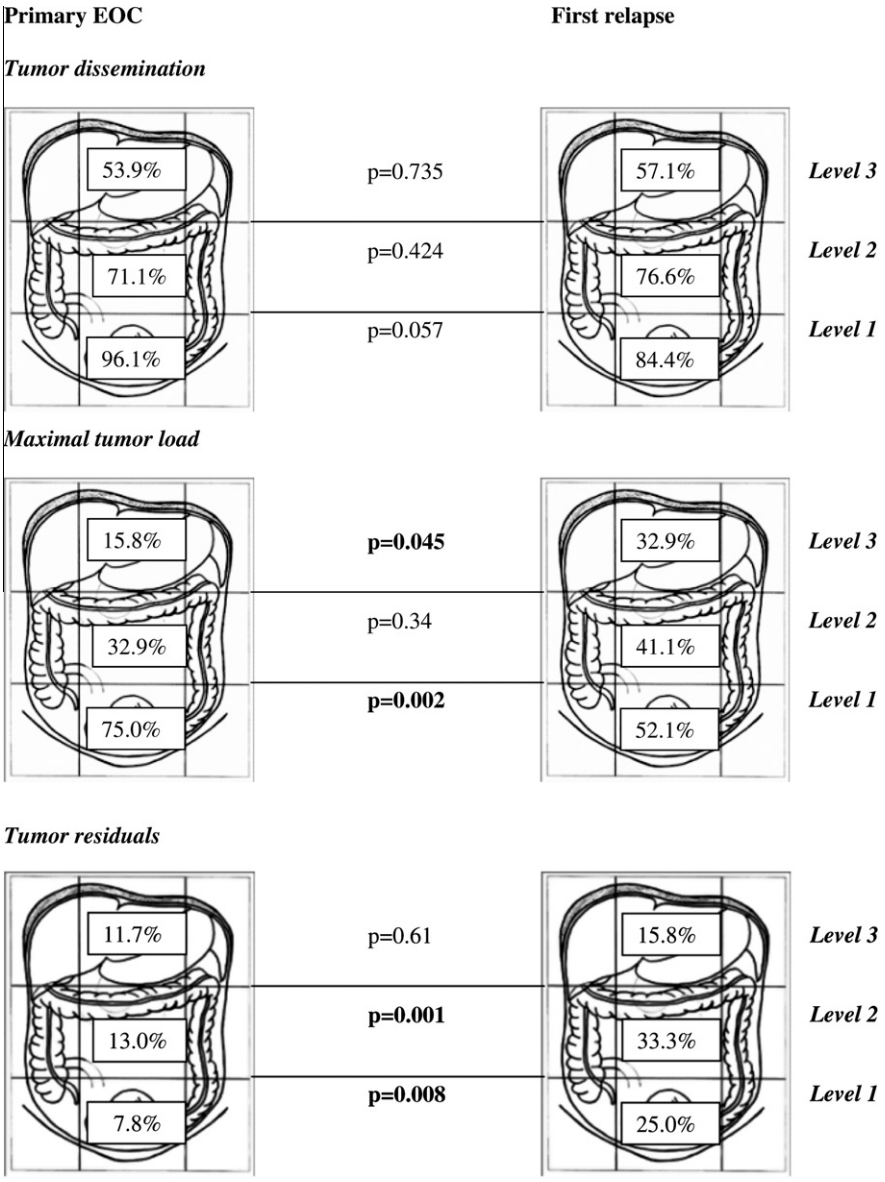


**Fig. 1 – Tumour dissemination patterns followed in primary and recurrent EOC, as well as localisation of maximal tumour load and postoperative tumour residuals according to the IMO documentation tool.**

## 2. Patients and methods

We performed a systematic analysis of a prospectively maintained database evaluating the intraoperative tumour dissemination pattern and operative outcome of all women who underwent both primary and secondary tumourdebulking surgery in our institution between 09/2000 and 12/2010. We identified 79 patients. The total number of patients operated during the same period due to primary malignant lesions of the ovary of any stage was 705.

All operations were performed by one of four gynaecologic oncologic surgeons. Staging was performed and defined in accordance with the FIGO-criteria for ovarian cancer.[8] Each primary surgery was performed per midline laparotomy aiming at maximal tumour reduction. Standard procedures included peritoneal cytology, extrafascial hysterectomy, bilateral adnexectomy, infra-gastric omentectomy and systematic pelvic/para-aortic lymph-node dissection if a complete tumour resection could be obtained or in the case of bulky nodes. If indicated, additional procedures, such as intestinal resection, splenectomy and/or partial resection of other affected organs (e.g. urinary bladder, liver, and pancreas) were performed in order to achieve optimal tumourdebulking.

Secondary debulking was defined by a maximal effort to achieve maximal tumour reduction and was always performed per midline laparotomy. Tumour relapse and indication for secondary cytoreduction were defined according to the RECIST-criteria,[28] patients' preference, patients' symptoms and ECOG performance status. CT or MRI-studies were performed to assess the tumour relapse either due to increased CA125-levels as previously defined[29] and/or due to an abnormal clinical and sonographical examination. Exclusion criteria for surgery were extraabdominal metastases, diffuse liver metastases. Secondary tumourdebulking aiming at maximal tumour reduction was performed by a disease free interval of more than 6 months.

In every patient, the detailed tumour pattern was intraoperatively assessed by an independent trained person based on the surgical procedures performed and by a systematic interview of the surgical team. Postoperatively all histologic findings and collected data were entered into a validated documentation system (Intraoperative Mapping Ovarian Cancer, IMO), especially developed for ovarian neoplasms with special focus on the description of the tumour pattern, maximal tumour-burden, postoperative tumour-residuals (0 cm, <0.5 cm, <1 cm, <2 cm, >2 cm) and the amount of preoperative ascites (none, </>500 ml). 'IMO' represents a detailed surgical and histopathological documentation system developed in our clinic in order to obtain a better and more objective description of the ovarian tumour spread within the abdominal cavity and to define more precisely the histopathological features of the malignancy.[9–12] Within the Tumour Bank Ovarian Cancer project (www.toc.network.de), tumour tissue, ascites, serum and blood were collected from each patient with malignant tumours. The patients' informed consent was always given prior to surgery and sample collection and documentation. The levels and fields according to which the abdominal cavity is divided into are presented in Fig. 1.

### 2.1. Follow-up

All further patients' data including history, and follow-up and survival data were abstracted from the patients' records. Survival data of the patients were last updated 01/2011 based on patient's files and/or responses from their physicians or insurance-companies.

Patients were regularly evaluated at the end of the treatment for evidence of disease recurrence. Clinical examinations, transvaginal and transabdominal ultrasound, CA-125 (if preoperative value elevated) assays were performed every 3 months. A CT/MRI-scan was ordered if the above examinations revealed any pathology.

### 2.2. Statistics

Differences in tumour pattern and residual tumour mass between paired samples of primary ovarian cancer and recurrence were examined using McNemar-test, sign-test or Wilcoxon signed rank test where appropriate. Correlations were analysed for dichotomous variables with $\chi^2$ test and Kendall's tau $b$ for ordinal variables; relative risks with 95% confidence interval (95% CI) are reported. Median overall survival and progression free survival were estimated by using Kaplan–Meier method. Follow-up and survival data were measured from the time of primary operation. All analyses were performed with PASW 18.0 (SPSS Inc., Chicago). A two-tailed $p$ value $< 0.05$ was considered statistically significant.

## 3. Results

A total of 79 patients were included into the present analysis. Median patient's age at primary diagnosis was 52 years (range: 21–74). A total of 15 (8.4%) patients experienced during the median follow-up period of 32 months (range: 4–111) one further episode of relapse and 6 patients (3.4%) two further episodes of relapse. Forty-five patients (55.7%) died during the same period. Median overall survival was 56 months (95% CI: 35.1–76.9); and median progression free survival to first relapse was 16 months (95% CI: 13.5–18.5). Forty-four patients (68.4%) were platinum-sensitive after first-line chemotherapy, while 26.6% of the operated patients in the relapsed situation were platinum-resistant. The largest tumour size of metastatic disease at primary and recurrent situation was 14 cm and 16 cm, respectively, and thus not significantly different. Demographic, tumour-related and operative characteristics of the entire patients' collective are presented in detail in Table 1.

### 3.1. Tumour dissemination pattern and surgical procedures

Patients had a higher incidence of ascites prior to primary compared to secondary-surgery (65.3% versus 40.5%; $p = 0.002$), by similar median operative times (242 min versus 199 min; $p = 0.15$). Patients at relapse had significantly higher rates of tumour involvement of the gastric serosa (2.5% versus

**Table 1 – Demographic, tumour-related and operative characteristics of the entire patients collective at the primary and secondary situation of the disease. Median interval between primary and secondary tumourdebulking was 16.0 months (95% CI: 13.5–18.5). nf = not found.**

| | patients (%) (N = 79) | | |
|---|---|---|---|
| Median age at primary diagnosis [years] | 52 (21–74) | | |
| *FIGO-stage* | | | |
| I | 4 (5.1%) | | |
| II | 2 (2.5%) | | |
| III | 65 (82.3%) | | |
| IV | 7 (8.9%) | | |
| n.f. | 1 (1.2%) | | |
| *Grading* | | | |
| G1 | 1 (1.3%) | | |
| G2 | 22(27.8%) | | |
| G3 | 49 (62%) | | |
| n.f. | 7 (8.8%) | | |
| *Histology* | | | |
| Serous–papillary | 64 (81%) | | |
| Clear cell | 3 (3.8%) | | |
| Endometroid | 3 (3.8%) | | |
| n.f. | 9 (11.4%) | | |
| *N-status* | | | |
| N0 | 29 (36.7%) | | |
| N1 | 39 (49.4%) | | |
| Nx | 11 (13.9%) | | |
| Distant metastases at primary diagnosis | 7 (8.9%) | | |
| | Primary cytoreduction | Secondary cytoreduction | *p*-Value |
| *Intraoperative ascites* | | | |
| None | 28 (35.4%) | 49 (62.02%) | <0.001 |
| <500 ml | 31 (39.7%) | 23 (31.1%) | |
| >500 ml | 20 (25.6%) | 7 (9.5%) | |
| Median preoperative CA125 [U/ml] | 229 (5–18400) | 142 (10–3906) | 0.002 |
| Median operative time [min] | 242 (38–592) | 199 (10–631) | 0.15 |
| *Postoperative tumour residuals* | | | |
| None | 6 (76.9%) | 39 (50.0%) | <0.001 |
| <0.5 cm | 5 (6.4%) | 14 (17.9%) | |
| 0.5–1 cm | 5 (6.4%) | 7 (9.0%) | |
| 1–2 cm | 4 (5.1%) | 3 (2.6%) | |
| >2 cm | 4 (5.1%) | 16 (20.5%) | |

16.9%; $p = 0.003$), serosa of small intestine (20.3% versus 44.9%; $p = 0.001$) and mesentery (30.4% versus 50%; $p = 0.012$). No significant differences were identified regarding tumour involvement of douglas, peritoneal carcinosis, liver, omental bursa, liver, diaphragm, spleen and large bowel.

Concerning the operative procedures performed with higher rates of pelvic and paraaortic lymph node dissection, extensive peritonectomy, appendectomy and omentectomy were documented at primary tumourdebulking. Complete macroscopic tumour resection rates were significantly higher at primary versus secondary surgery (77% versus 50%; $p < 0.001$). Data are presented in detail in Table 1. Nevertheless, operative morbidity rates were not statistically significant between primary and secondary tumourdebulking (25% versus 29%; $p = 0.424$). Operative data are presented in Table 2.

When evaluating the tumour dissemination pattern according to IMO (Fig. 1), then no significant differences could be identified between primary and secondary setting regarding tumour dissemination; the tumour was restricted to 3 or less IMO-fields in 57.9% primary versus 47.4% relapsed patients ($p = 0.123$). Regarding the number of IMO-fields with the maximal tumour load, 97.4% of the primary cases had a maximal tumour load in $\leqslant 3$ IMO-fields, while this was the case in 94.5% of the patients in the relapsed situation ($p = 0.687$). Also no significant differences were reported in the number of IMO-fields with postoperative tumour residuals; 94.7% of the patients in the primary versus 85.1% in the relapsed-situation ($p = 0.180$) had $\leqslant 3$ IMO-fields with macroscopical tumour residuals.

Statistically significant differences were identified, however, between primary and secondary surgery in regard to the localisation of maximal tumour load and postoperative tumour residuals, as shown in Fig. 1. Significantly higher rates of tumour residuals were documented in abdominal levels 1 and 2 at recurrence ($p = 0.008$ and $p = 0.001$, respectively). Also, we report of higher rates of maximal tumour load in le-

**Table 2 – Surgical procedures performed at primary and secondary tumourdebulking and associated operative morbidity in the 79 patients with EOC.**

| Procedure performed | Primary cytoreduction | Secondary cytoreduction | *p*-Value |
|---|---|---|---|
| Hysterectomy | 60 (75.9%) | 3 (3.8%) | **<0.001** |
| Pelvic LN dissection | 68 (86.1%) | 14 (17.7%) | **<0.001** |
| Paraaortic LN dissection | 65 (82.3%) | 12 (15.2%) | **<0.001** |
| Preternatural anus | 4 (5.1%) | 6 (7.7%) | 0.73 |
| Intestinal resection | 33 (41.8%) | 38 (48.1%) | 0.5 |
| Small intestine | 12 (15.2%) | 25 (31.6%) | **0.004** |
| Large intestine | 32 (40.5%) | 24 (30.4%) | 0.25 |
| *Upper abdominal procedures* | | | |
| Partial liver resection | 2 (2.5%) | 0 | 0.5 |
| Liver capsule resection | 4 (5.1%) | 9 (11.9%) | 0.146 |
| Partial gastrectomy | 1 (1.3%) | 6 (7.7%) | 0.125 |
| Cholecystectomy | 1 (1.3%) | 2 (2.6%) | 1.0 |
| Splenectomy | 3 (3.8%) | 6 (7.7%) | 0.508 |
| Peritonectomy | 51 (64.6%) | 36 (46.2%) | **0.045** |
| Diaphragmatic resection | 10 (12.7%) | 7 (9.0%) | 0.791 |
| Operative complications | 17 (25.0%) | 18 (29.5%) | 0.424 |
| Thromboembolism | 3 (4.4%) | 1 (1.6%) | 0.25 |
| Infection/ Sepsis | 2 (2.9%) | 5 (8.2%) | 0.625 |
| Intestinal complications (anastomotic insufficiency, fistula) | 2 (2.9%) | 7 (11.5%) | 0.71 |
| Postoperative bleeding | 1 (1.5%) | 5 (8.2%) | 0.25 |
| Postoperative neurologic impairment | 5 (7.5%) | 4 (6.6%) | 0.375 |
| Pulmonary complications | 1 (1.5%) | 3 (4.9%) | 0.625 |
| Death within 30 d | 0 | 3 (4.3%) | 0.5 |
| Relaparotomy | 2 (2.9%) | 4 (6.5%) | 1.0 |

vel 1 at primary situation ($p = 0.002$) and in level 3 at relapse ($p = 0.045$). No significant differences were otherwise identified between primary and recurrent EOC in respect of the actual tumour dissemination.

### 3.2. *Correlation primary to relapsed EOC*

The residual tumour mass at primary cytoreduction correlated significantly ($p = 0.003$) with the residual tumour mass at secondary cytoreduction. Thirty-two patients had more tumour residuals after secondary compared to primary debulking; seven patients had less tumour residuals at secondary surgery, while in 40 patients tumour residuals between primary and secondary cytoreduction were equal. The relative risk of any residual tumour mass after secondary surgery was 1.91 (95% CI: 1.29–2.84) for patients with any tumour residuals after primary surgery compared to those patients who underwent complete macroscopical tumour resection at primary surgery. The correlation between tumour residuals after primary and secondary tumourdebulking is presented in Table 4.

We could not identify any significant predictive value of peritoneal carcinosis (RR = 1.53; 95% CI: 0.89–2.63), intestinal tumour involvement (RR: 0.92; 95% CI: 0.65–1.31) or positive lymph nodes (RR = 1.49; 95% CI: 0.83–2.68) at primary operation in respect to involvement of these features at recurrence (Table 3).

## 4. Discussion

To our knowledge this is the first attempt of a paired analysis of both primary and secondary cytoreduction due to EOC at the same affected patients operated in the same institution, so that bias such as inhomogenous surgical quality or inconsistent tumour documentation are eliminated. We could demonstrate that secondary cytoreduction is associated with significantly lower optimal tumourdebulking rates compared to primary setting, since the disease tends to recur in patterns less accessible to complete resection such as gastrointestinal serosa, mesentery and upper abdomen. We could show that, by maximal surgical effort, tumour residuals appear to correlate significantly between primary and secondary operation. However, no other predictors of surgical outcome or tumour-pattern, such as peritoneal carcinomatosis, intestinal tumour involvement or positive lymph nodes could be identified. Tumour residuals were highly significant more often disseminated in all three abdominal levels at recurrence. The significantly higher rates of postoperative tumour residuals also in the pelvis is rather attributed to the fact, that in the case of macroscopic tumour residuals in the middle and upper abdomen no further maximal surgical effort was performed to resect the tumour in the lower abdomen. The less optimal cytoreduction rates at recurrence may be attributed to the fact, that EOC tends to recur in areas much less accessible to resection, as was shown by the higher rates of diffuse tumour involvement of the gastrointestinal serosa and the radix mesenterii, localizations broadly known and recognised as ‘criteria of inoperability’.

Interestingly, our collective patients had significantly lower rates of ascites prior to secondary compared to primary cytoreduction. This may be a possible effect of the CA125-triggered follow-up and thus potentially earlier diagnosis of relapse.

Through the present analysis we could show that a different tumour ‘behaviour’ is followed in the primary compared

**Table 3 – Incidence and relative risk of peritoneal carcinosis, positive lymph node status and intestinal tumour involvement in primary and secondary surgery.**

| | | | 1. relapse Intestinal metastases | | |
|---|---|---|---|---|---|
| | | | Yes | No | Total |
| Primary OP Intestinal metastases | Yes | *n* | 23 | 16 | 39 |
| | | % | 59.0% | 41.0% | 100.0% |
| | No | *n* | 25 | 14 | 39 |
| | | % | 64.1% | 35.9% | 100.0% |
| Total | | *n* | *n* | 30 | 78 |
| | | % | % | 38.5% | 100.0% |
| RR: 0.92 (95% CI: 0.65–1.31) | | | | | |
| | | | Peritoneal carcinosis | | |
| | | | Yes | No | Total |
| Primary OP Peritoneal carcinosis | Yes | *n* | 49 | 15 | 64 |
| | | % | 76.6% | 23.4% | 100.0% |
| | No | *n* | 7 | 7 | 14 |
| | | % | 50.0% | 50.0% | 100.0% |
| Total | | *n* | 56 | 22 | 78 |
| | | % | 71.8% | 28.2% | 100.0% |
| RR: 1.53 (95% CI: 0.89–2.63) | | | | | |
| | | | Positive lymph nodes | | |
| | | | N1 | N0 | Total |
| Primary OP Positive lymph nodes | N1 | *n* | 13 | 3 | 16 |
| | | % | 81.3% | 18.8% | 100.0% |
| | N0 | *n* | 6 | 5 | 11 |
| | | % | 54.5% | 45.5% | 100.0% |
| Total | | *n* | 19 | 8 | 27 |
| | | % | 70.4% | 29.6% | 100.0% |
| RR: 1.49 (95% CI: 0.83–2.68) | | | | | |

to recurrent situation of the disease even at the same patient, while interestingly the primary tumour patterns do not appear to have any predictive value for the tumour patterns at recurrence. Also, despite the lower rates of ascites at recurrent tumourdebulking, significantly less often a complete tumour resection was obtainable at recurrence. These findings may be of high clinical importance. Through numerous, even though mainly retrospective, studies,[13–24] authors could worldwide demonstrate the significant impact of complete cytoreduction at secondary surgery by a comparable morbid-

**Table 4 – Correlation of tumour reduction rates at primary and secondary tumourdebulking surgery in ovarian cancer patients.**

| | | | 1. relapse Post OP tumour residuals | | |
|---|---|---|---|---|---|
| | | | Yes | No | Total |
| Primary OP Post-OP tumour residuals | Yes | *n* | 10 | 7 | 17 |
| | | % | 58.8% | 41.1% | 100.0% |
| | No | *n* | 32 | 30 | 62 |
| | | % | 51.6% | 48.4% | 100.0% |
| Total | | *n* | 42 | 37 | 79 |
| | % | % | 53.1% | 46.8%% | 100.0% |
| RR: 1.91 (95% CI: 1.29–2.84) | | | | | |

ity in specialised centres with teaching facilities.[25,26] However, no validated criteria have been up to date clearly defined to select the optimal candidates for recurrent surgery in EOC. So a possible approach to this could be the analysis of the primary tumour pattern, from which one would possibly conclude on the pattern followed at recurrence. This question, however, namely whether the surgical outcome and tumour dissemination pattern at initial presentation of the disease is of any predictive value on the surgical outcome and dissemination pattern at recurrence remains unanswered. Our data could show that the amount of postoperative tumour residuals after primary tumourdebulking clearly correlates with the amount of tumour residuals after secondary surgery with maximal surgical effort. However, no further significant predictors of outcome or tumour pattern could be identified even after considering clinical highly relevant features such as lymph node involvement, peritoneal carcinosis or intestinal tumour involvement.

Interestingly, despite the heavily pretreated patients' status, surgical morbidity at recurrence does not appear to significantly differ from the primary setting when surgery remains in the hands of highly specialised and trained surgeons. These findings are in compliance with the DESKTOP-results by Harter et al. where it was also shown that surgery at relapse is not necessarily associated with higher morbidity rates.[24] However, there is a clear trend towards increased morbidity and perioperative mortality at relapse surgery compared to the primary one. Therefore, we have to consider the possibility of lack of significance regarding the operative morbidity between primary and secondary cytoreduction due to the small number of evaluated patients.

Venturing even beyond surgical borders, one could say that ovarian cancer reappears under a different dissemination profile than at its initial presentation in terms of a higher 'aggressivity' and higher dissemination tendency, changing so surgical outcome and required surgical effort. Any potential attempts to derive clinical relevant conclusions on the outcome of the forthcoming cytoreduction, depending on the outcome and tumour dissemination at the outset of the disease, would rather fail. Therefore, novel biomarkers are warranted in order to predict tumour patterns followed at recurrence and hence surgical outcome.

Concluding, it is challenging to postulate, that a paradigm shift may occur in the recurrence of epithelial ovarian cancer from the outset of the disease. Increasingly supported theories that platinum-resistant recurrence may be attributed to originally preexisting clones which are generated by clonal diversity from the outset of the disease and which slowly grow, chemoresistant at recurrence while sharing a common ancestor at an early stage of tumour development[7,27], may also fit in the findings depicted in the present analysis. Based on more 'aggressive' and dedifferentiated cancer clones the disease reappears with an accordingly more 'aggressive' and therapy resistant profile which clearly renders a higher therapeutic challenge. However, this remains a vague theory which has to be proven within prospective translational projects.

## Conflict of interest statement

None declared.

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