Surgical staging and prognosis in serous borderline ovarian tumours (BOT): A subanalysis of the AGO ROBOT study

F Trillsch1,33, S Mahner*,1,33, E Vettorazzi2, L Woelber1, A Reuss3, K Baumann4, M-D Keyser-Paik5, U Canzler6, K Wollschaeger7, D Forner8, J Pfisterer9,10, W Schroeder11, K Muenstedt12, B Richter13, C Fotopoulos14, B Schmalfeldt15, A Burges16, N Ewald-Riegler17, N de Gregorio18, F Hilpert19, T Fehm20,21, W Meier22, P Hillemanens23, L Hanker24,25, A Hasenburg26, H-G Strauss27, M Hellriegel27, P Wimberger6,29, S Kommoss17,20, F Kommoss30, S Hauptmann27,31 and A du Bois32

1Universitaetsklinikum Hamburg-Eppendorf, Klinik und Poliklinik fuer Gynaekologie, Martinistr. 52, 20246 Hamburg, Germany; 2Universitaetsklinikum Hamburg-Eppendorf, Institut fuer Medizinische Biometrie und Epidemiologie, Martinistr. 52, 20246 Hamburg, Germany; 3Philipps-Universitaet Marburg, Koordinierungszenrum fuer Klinische Studien, Karl-von-Frisch-Str. 4, 35043 Marburg, Germany; 4Universitaetsklinikum Giessen u. Marburg GmbH, Klinik fuer Gynaekologie, Gym. Endokrinologie und Onkologie, Boldingenstr., 35043 Marburg, Germany; 5Rheinische Friedrich-Wilhelms-Universitaet, Universitaets-Frauenklinik, Sigmund-Freud-Str. 25, 53127 Bonn, Germany; 6Technische Universitaet Dresden, Klinik und Poliklinik fuer Frauenheilkunde und Geburtshilfe, Fetscherstr. 74, 01307 Dresden, Germany; 7Universitaetsklinikum Magdeburg, Universitaets-Frauenklinik, Gerhart-Hauptmann-Str. 35, 39108 Magdeburg, Germany; 8Sana-Klinikum Remscheid, Klinik fuer Frauenheilkunde und Geburtshilfe, Burger Strasse 211, 42859 Remscheid, Germany; 9Staatliches Klinikum Solingen gGmbH, Klinik fuer Gynaekologie und Geburtshilfe, Gotenstrasse 1, 42653 Solingen, Germany; 10Zentrum fuer Gynaekologische Onkologie, Herzog-Friedrich-Str. 21, 24103 Kiel, Germany; 11Gynaecologic UBS Bremen, Schwachhauser Herrstrasse 367, 28211 Bremen, Germany; 12Universitaetsklinikum Giessen, Zentrum fuer Frauenheilkunde und Geburtshilfe, Klinikstrasse 33, 35352 Giessen, Germany; 13Elblandkliniken Meissen-Radebeul GmbH & Co. KG, Frauenklinik, Heinrich-Zille-Str. 13, 01445 Radebeul, Germany; 14Charite, Campus Virchow Klinikum, Frauenklinik, Augustenburger Platz 1, 13353 Berlin, Germany; 15Klinikum rechts der Isar der Technischen Universitaet, Frauen- und Poliklinik, Ismaninger Str. 22, 81675 Munich, Germany; 16Klinikum der Universitaet Muenchen, Campus Grosshadern, Klinik und Poliklinik fuer Frauenheilkunde und Geburtshilfe, Marchioninistr.15, 81377 Munich, Germany; 17Dr Horst Schmidt Klinik GmbH, Klinik fuer Gynaekologie und gynaekologische Onkologie, Ludwig-Erhard-Str. 100, 65199 Wiesbaden, Germany; 18Universitaetsklinikum Ulm, Frauenklinik, Prittwitzstrasse 43, 89075 Ulm, Germany; 19Universitaetsklinikum Schleswig-Holstein, Campus Kiel, Klinik fuer Gynaekologie und Geburtshilfe, Michaelsstrasse 16, 24105 Kiel, Germany; 20Universitaetsklinikum Tuebingen, Department fuer Fraugesundheit, Calwerstrasse 7, 72076 Tuebingen, Germany; 21Universitaetsklinikum Duesseldorf, Universitaetsfrauenklinik, Moorenstrasse 5, 40225 Duesseldorf, Germany; 22Evangelisches Krankenhaus, Frauenklinik, Kirchfeldstrasse 40, 40217 Duesseldorf, Germany; 23Medizinische Hochschule Hannover, Frauenklinik, Carl-Neuberg-Str. 1, 30625 Hannover, Germany; 24Klinikum der J.W. Goethe-Universitaet, Zentrum fuer Frauenheilkunde und Geburtshilfe, Theodor-Stern-Kai 7, 60590 Frankfurt am Main, Germany; 25Universitaetsklinikum Schleswig-Holstein, Campus Luebeck, Klinik fuer Gynaekologie und Geburtshilfe, Ratzeburger Allee 160, 23562 Luebeck, Germany; 26Universitaetsklinikum Freiburg, Frauenklinik, Hugstetter Str. 55, 79106 Freiburg im Breisgau, Germany; 27Universitaetsklinikum Halle (Saale), Universitaetsklinik und Poliklinik fuer Gynaekologie, Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany; 28Georg-August-Universitaet Gottingen, Gynaekologie und Geburtshilfe, Robert-Koch-Str. 40, 37075 Gottingen, Germany; 29Universitaetsklinikum Essen, Klinik fuer Frauenheilkunde und Geburtshilfe, Essen, Germany; 30Institut fuer Pathologie, Referenzzentrum fuer Gynaekopathologie, A2,2, 48159 Mannheim, Germany; 31Institut fuer Pathologie Trier-Dueren-Duesseldorf, Roonstrasse 30, 52351 Dueren, Germany and 32Kliniken Essen-Mitte, Klinik fuer Gynaekologische Onkologie, Henricistasse 92, 45136 Essen, Germany

*Correspondence: Dr S Mahner; E-mail: s.mahner@uke.de

These authors contributed equally to this work.

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Preoperative diagnosis of borderline ovarian tumours (BOT) is frequently hindered by unspecific clinical symptoms and absence of appropriate diagnostic tools (Fischera et al., 2012; Tang et al., 2012; Trillsch et al., 2013). As intraoperative fresh frozen section is of limited value for diagnosing BOT and informed consent for further operative procedures is not always obtained preoperatively, the primary surgical approach for BOT patients frequently results in incomplete surgical staging leading to formal indication of re-staging surgery (Trillsch et al., 2010; Shih et al., 2011; Song et al., 2011).

Although incomplete surgical staging has been recently confirmed to be an independent negative prognostic factor for disease recurrence besides higher FIGO stage, residual tumour, and fertility preservation in the large cohort study on BOT of the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO ROBOT study) (du Bois et al., 2013), little is known about the prognostic impact of each individual staging procedure. This information is, however, of high importance when counselling BOT patients after incomplete surgical staging. As most studies concentrate on the question whether fertility preservation is safe and feasible from an oncologic standpoint (Morice et al., 2001; Fauvet et al., 2005; Palomba et al., 2010; Trillsch et al., 2014; Uzan et al., 2014), the evidence for further recommended staging procedures as omentectomy, peritoneal biopsies, and cytology is sparse.

In the present study, we analysed the impact of each individual staging procedure on prognosis of patients with serous BOT within the large cohort of the AGO ROBOT study.

Results: For patients with one missing staging procedure, the hazard ratio (HR) for recurrence was 1.25 (95%-CI 0.66–2.39; P = 0.497). This risk increased with each additional procedure skipped reaching statistical significance in case of two (HR 1.95; 95%-CI 1.06–3.58; P = 0.031) and three missing steps (HR 2.37; 95%-CI 1.22–4.64; P = 0.011). The most crucial procedure was omentectomy which retained a statistically significant impact on PFS in multiple analysis (HR 1.91; 95%-CI 1.15–3.19; P = 0.013) adjusting for previously established prognostic factors as FIGO stage, tumour residuals, and fertility preservation.

Conclusion: Individual surgical staging procedures contribute to the prognosis for patients with serous BOT. In this analysis, recurrence risk increased with each skipped surgical step. This should be considered when re-staging procedures following incomplete primary surgery are discussed.
from unadjusted analysis were tested for independence adjusting for previously described prognostic factors (FIGO stage, fertility preservation, and postoperative residual tumour). Owing to excellent disease-specific and overall survival with low event numbers, these endpoints were not considered for adjusted analysis.

### RESULTS

A total of 559 patients with confirmed diagnosis of serous BOT after central pathological review and a median age of 49 (14–92) years met the inclusion criteria. Detailed clinical and treatment-related parameters are provided in Table 1.

The majority of patients were diagnosed in FIGO stage I (73.9%) with laparotomy as primary surgical approach in more than half of the patients (54.9%). Staging quality after primary surgery was inadequate in 395 patients (70.7%). This number was reduced to 281 patients (50.3%) when patients with re-staging surgeries were considered as well. A total of 131 patients (23.4%) were diagnosed with peritoneal implants, of which 21 (16.0%) showed to be invasive. Re-staging surgery led to upstaging in 29 of the 199 patients undergoing this procedure (14.6%). Of these 29 patients, 23 (79.3%) had positive peritoneal implants (20 with non-invasive histology, four with invasive histology, one patient with both). The remaining six patients (20.7%) were up-staged because of positive cytology or further adnexal involvement of the BOT.

Five-year-recurrence rate of the total cohort was 5.6%, 13 of 53 patients (24.5%) with recurrent disease experienced malignant transformation. In terms of the investigated staging procedures, omentectomy was carried out in 78.4%, peritoneal biopsies in 66.9%, and cytology in 68.3% of all patients (Table 1).

Each of the latter staging procedures, if not carried out, had a negative impact on progression-free survival in single, unadjusted analysis (omentectomy hazard ratio (HR) 2.00, \(P=0.004\); peritoneal biopsies HR 1.51, \(P=0.087\); cytology HR 1.63, \(P=0.041\), Table 2). This effect remained statistically significant for omentectomy in multiple analysis (HR 1.81; 95%-CI 1.03–3.21; \(P=0.041\), Table 2).

Consequently, the prognostic effect of an omitted omentectomy was tested for independence in a multiple analysis adjusting for previously described prognostic factors for BOT (Figure 1). In this Cox regression model, a prognostic impact could be confirmed for higher FIGO stage (FIGO II vs I; HR 2.35; 95%-CI 1.29–4.30, \(P=0.005\); FIGO III vs I HR 2.89; 95%-CI 1.58–5.27; \(P=0.001\), fertility preservation (HR 3.28, 95%-CI 2.03–5.28; \(P<0.001\)), incomplete surgical cytoreduction (HR 3.99; 95%-CI 1.58–10.05; \(P=0.003\)), and also for omitted omentectomy (HR 1.91; 95%-CI 1.15–3.19; \(P=0.013\), Figure 1).

Patients undergoing omentectomy (n = 438, 78.4%) were diagnosed in higher FIGO stages compared with patients without omentectomy (n = 121, 21.6%; FIGO stage I 29.5% vs 15.0%, \(P<0.001\), Table 3) and presented with higher rates of peritoneal implants (26.7% vs 11.6%, \(P=0.001\) but had a lower 5-year-recurrence rate (10.7% vs 20.1%, \(P=0.004\). Patients undergoing omentectomy were slightly younger (48 vs 53 years, \(P=0.192\) but a fertility-preserving approach was performed significantly less frequently in these patients (16.0% vs 33.1%, \(P<0.001\) in patients with omentectomy, bilateral salpingo-oophorectomy (84.2% vs 66.9%, \(P<0.001\), hysterectomy (76.7% vs 51.2%, \(P<0.001\) and the other two recommended staging procedures peritoneal biopsies (78.5% vs 24.8%, \(P<0.001\) and cytology (74.4% vs 46.3%, \(P<0.001\) were carried out significantly more frequently than in patients without omentectomy. Accordingly, appendectomy (34.5% vs 11.6%, \(P<0.001\) and pelvic (23.5% vs 12.4%, \(P=0.005\) or para-aortic lymph node dissection (16.0% vs 5.8%,

### Table 1. Clinical patient characteristics, n = 559

| Age at first diagnosis | Median, years | Range |
|------------------------|---------------|-------|
|                        | 49            | (14–92) |

| FIGO stage | IA/B | IC | IIA-C | IIIA-C |
|------------|------|----|-------|--------|
|            | 279  | 134| 65     | 81     |
|            | (49.9%) | (24.0%) | (11.6%) | (14.5%) |

| Primary surgical approach | Laparotomy | Converted laparoscopy | Laparoscopy |
|---------------------------|------------|-----------------------|-------------|
|                           | 307        | 54                    | 198         |
|                           | (54.9%)    | (9.7%)                | (35.4%)     |

| Histologic characteristics | Stromal microinvasion | Micropapillary pattern |
|----------------------------|----------------------|-----------------------|
|                            | 30                    | 85                    |
|                            | (5.4%)                | (15.2%)               |

| Surgical procedures in primary and re-staging surgerya | Bilateral salpingo-oophorectomy | Unilateral salpingo-oophorectomy |
|--------------------------------------------------------|-------------------------------|-------------------------------|
|                                                        | 450                            | 135                           |
|                                                        | (80.5%)                        | (24.2%)                       |

| Surgical cytoreduction | Complete | Incomplete | Unknown |
|------------------------|----------|------------|---------|
|                        | 517      | 81         | 34      |
|                        | (92.5%)  | (14.4%)    | (6.1%)  |

| Staging quality after primary surgery | Adequate | Inadequate |
|--------------------------------------|----------|------------|
|                                      | 164      | 395        |
|                                      | (29.3%)  | (70.7%)    |

| Staging quality after primary and re-staging surgery | Adequate | Inadequate |
|------------------------------------------------------|----------|------------|
|                                                      | 278      | 281        |
|                                                      | (49.7%)  | (50.3%)    |

| Fertility-sparing surgery | Yes | No |
|---------------------------|-----|----|
|                           | 110 | 449|
|                           | (19.7%) | (80.3%) |

| Up-staging after re-staging surgery | Yes | No |
|-------------------------------------|-----|----|
|                                     | 29  | 530|
|                                     | (5.2%) | (94.8%) |

| Recurrent disease | Yes | No |
|-------------------|-----|----|
| Borderline tumour | 53  | 40 |
|                   | (9.5%) | (75.5%) |
| High grade carcinoma | 4/3 | 8/3 |
|                   | (7.3%) | (15.1%) |
| Low grade carcinoma | 8/3 | 1/3 |
|                   | (15.1%) | (1.9%) |
| Unknown | 1/3 | 506 |
|         | (1.9%) | (90.5%) |

| Site of recurrent diseasea | Ovarian tissue | Ipsilateral | Contralateral | Peritoneum | Omentum | Other | Unknown |
|---------------------------|----------------|-------------|---------------|------------|---------|-------|---------|
|                           | 26/3           | 9/3         | 20/3          | 28/3       | 1/3     | 2/3   | 10/3    |
|                           | (49.1%)        | (17.0%)     | (37.7%)       | (52.8%)    | (1.9%)  | (3.8%) | (18.9%) |

| Malignant transformation during follow-up | Yes | No |
|------------------------------------------|-----|----|
|                                          | 13/3 | 40/3|
|                                          | (24.5%) | (75.5%) |

| 5-year progression-free survival | 86.9%
| 5-year disease-specific survival | 99.2%
The present analysis of the AGO ROBOT study attributes for the first time a prognostic importance to each individual step of surgical staging irrespective of their surgical nature, the prognostic impact of consecutively skipped staging procedures was tested (Figure 2A). For patients with one staging procedure missing, the HR for recurrence was 1.25 (95%-CI 0.66–2.39; P = 0.497). This risk increased with each additionally skipped procedure reaching statistical significance in case of two (HR 1.95; 95%-CI 1.22–4.64; P = 0.011) or three (HR 2.72; 95%-CI 1.58–4.76; P < 0.001) missing staging procedures. Even when adjusted for previously described prognostic factors for BOT, the prognostic impact of two (HR 3.54; 95%-CI 1.81–6.93; P = 0.009) or three (HR 5.27; 95%-CI 2.35–11.71; P < 0.001) missing steps remained statistically significant (Figure 2B).

**DISCUSSION**

The present analysis of the AGO ROBOT study attributes for the first time a prognostic importance to each individual step of surgical staging in the management of patients with serous BOT.

This information can help gynaecologic oncologists counselling patients with diagnosis of BOT and incomplete surgical staging following the primary approach. In this large dataset of 559 cases with confirmed diagnosis of serous BOT, 70.7% of the patients were inadequately staged during primary surgery and consequently candidates to be counselled for further management. This fraction is in accordance with other studies reporting rates of 61.3–70.3% of patients who formally require re-staging procedures to be comprehensively staged according to current guidelines (Fauvet et al, 2004; Ewald-Riegler et al, 2012; Azuar et al, 2013).

Apart from treatment recommendations for the reproductive organs including fertility-preserving aspects, the rationale for further recommended surgical staging procedures as omentectomy, peritoneal biopsies, and cytology is less evident. In this analysis, we could demonstrate that the recurrence risk of patients with serous BOT increased with each skipped step of the surgical staging. This expands the general results of previous studies indicating a clearly worse prognostic outcome of inadequately staged patients (Fauvet et al, 2004; Azuar et al, 2013; du Bois et al, 2013; Romeo et al, 2013).

Studies focusing on distinct surgical procedures are mainly available for the question of fertility preservation indicating higher recurrence rates for this approach (Palomba et al, 2010; Trillsch et al, 2014; Uzan et al, 2014). In this context, it has been shown that preservation of the primarily affected ovary raises the recurrence risk the most so that organ preservation should be reserved only for special constellations when the contralateral ovary had already been removed for other reasons or in case of bilateral disease (Fauvet et al, 2004; Palomba et al, 2010; du Bois et al, 2013; Uzan et al, 2014). In contrast, this study investigated the prognostic significance of staging procedures not directly related to fertility preservation (omentumectomy, peritoneal biopsies, cytology), demonstrating the highest prognostic impact for omentectomy in unadjusted analysis. Even in multiple analysis adjusted for previously confirmed prognostic factors such as FIGO stage, fertility preservation, and macroscopic tumour residuals, omentectomy retains its statistical significance for prognosis.

Compared with invasive ovarian cancer in which the omentum is frequently affected and large tumour burden is described as omental cake (Sehouli et al, 2009; Woelber et al, 2010), omental implants are rarely seen in BOT patients (Fotopoulou et al, 2010;
Table 3. Clinical characteristics for patients with or without omentectomy

| Clinical patient characteristics                        | No omentectomy n = 121 (21.6%) | Omentectomy n = 438 (78.4%) | P-value |
|---------------------------------------------------------|---------------------------------|-------------------------------|---------|
| **Age at first diagnosis**                              |                                 |                               |         |
| Median, years                                           | 53 (16–92)                      | 48 (14–86)                    | 0.192*  |
| **FIGO stage**                                          |                                 |                               | <0.001* |
| IA/B                                                    | 81 (67.0%)                      | 198 (45.2%)                   |         |
| IC                                                      | 23 (19.0%)                      | 111 (25.3%)                   |         |
| IIA-C                                                   | 14 (11.6%)                      | 51 (11.7%)                    |         |
| IIIA-C                                                  | 3 (2.5%)                        | 78 (17.8%)                    |         |
| **Surgical approach in primary and re-staging surgery** |                                 |                               | <0.001* |
| Laparoscopy                                             | 32 (26.4%)                      | 43 (9.8%)                     |         |
| Laparotomy                                              | 89 (73.6%)                      | 395 (90.2%)                   |         |
| **Surgical procedures in primary and re-staging surgery** |                               |                               |         |
| Bilateral salpingo-oophorectomy                         | 81 (64.9%)                      | 369 (84.2%)                   | <0.001* |
| Unilateral salpingo-oophorectomy                        | 29 (24.0%)                      | 106 (24.2%)                   | 0.958*  |
| Cystectomy                                              | 27 (22.3%)                      | 76 (17.4%)                    | 0.221*  |
| Hysterectomy                                            | 62 (51.2%)                      | 336 (76.7%)                   | <0.001* |
| Peritoneal biopsies                                     | 30 (24.8%)                      | 344 (78.3%)                   | <0.001* |
| Cytology                                                | 58 (46.3%)                      | 326 (74.4%)                   | <0.001* |
| Appendectomy                                            | 14 (11.6%)                      | 151 (34.5%)                   | <0.001* |
| Pelvic LND/LN biopsies                                  | 15 (12.4%)                      | 103 (23.5%)                   | 0.005*  |
| Para-aortic LND/LN biopsies                             | 7 (5.8%)                        | 70 (16.0%)                    | 0.002*  |
| Peritoneal implants in primary or re-staging surgery    |                                 |                               | <0.001* |
| None                                                    | 107 (88.4%)                     | 321 (73.3%)                   |         |
| Non-invasive                                            | 12 (9.9%)                       | 98 (22.4%)                    |         |
| Invasive                                                | 2 (1.7%)                        | 19 (4.3%)                     |         |
| Surgical cytoreduction                                  |                                 |                               | 0.530*  |
| Complete                                                | 109 (90.1%)                     | 408 (93.2%)                   |         |
| Incomplete                                              | 6 (1.4%)                        | 6 (1.4%)                      |         |
| Unknown                                                 | 10 (8.3%)                       | 24 (5.5%)                     |         |
| Staging quality after primary and re-staging surgery    |                                 |                               | <0.001* |
| Adequate                                                | 0 (0.0%)                        | 278 (63.5%)                   |         |
| Inadequate                                              | 121 (100.0%)                    | 160 (36.5%)                   |         |
| Fertility-sparing surgery                               |                                 |                               | <0.001* |
| Yes                                                     | 40 (33.1%)                      | 70 (16.0%)                    |         |
| No                                                      | 81 (66.9%)                      | 368 (84.0%)                   |         |
| Up-staging after re-staging surgery                     |                                 |                               | 0.026*  |
| Yes                                                     | 2 (1.7%)                        | 27 (6.2%)                     |         |
| No                                                      | 119 (98.3%)                     | 411 (93.8%)                   |         |
| Recurrent disease                                       |                                 |                               | 0.029*  |
| Yes                                                     | 18 (14.9%)                      | 35 (8.0%)                     |         |
| Borderline tumour                                       | 14/18 (77.8%)                   | 26/35 (74.3%)                 |         |
| High grade carcinoma                                    | 1/18 (5.6%)                     | 3/35 (8.6%)                   |         |
| Low grade carcinoma                                     | 2/18 (11.1%)                    | 6/35 (17.1%)                  |         |
| Unknown                                                 | 1/18 (5.6%)                     | 0/35 (0.0%)                   |         |
| No                                                      | 103 (85.1%)                     | 403 (92.0%)                   |         |
| **Site of recurrent disease**                           |                                 |                               |         |
| Ovarian tissue                                          | 8/18 (44.4%)                    | 18/35 (51.4%)                 |         |
| Ipsilateral                                             | 4/18 (22.2%)                    | 5/35 (14.3%)                  |         |
| Contralateral                                           | 4/18 (22.2%)                    | 16/35 (45.7%)                 |         |
| Peritoneum                                              | 5/18 (27.8%)                    | 23/35 (65.7%)                 |         |
| Omentum                                                 | 1/18 (5.6%)                     | 0/35 (0.0%)                   |         |
| Other                                                    | 0/18 (0.0%)                     | 2/35 (5.8%)                   |         |
| Unknown                                                 | 5/18 (27.8%)                    | 5/35 (14.3%)                  |         |
| 5-year progression-free survival                        | 79.9%                           | 89.3%                         | 0.004*  |
| 5-year disease-specific survival                        | 98.8%                           | 99.7%                         | 0.893*  |

**Abbreviations:** FIGO = International Federation of Gynecology and Obstetrics; LND = lymph node dissection; LN = lymph node.

*Student’s t-test.

bChi²-test.

*Multiple entries possible.

dLog-rank test.
Kristensen et al, 2014). With 73.9%, the majority of all patients in the present cohort were diagnosed in FIGO stage I. Of all patients, 23.5% had implants that were of invasive histology in 21 patients (3.8%). Of note, patients undergoing omentectomy had a significantly better prognosis despite a shift towards higher FIGO stage and more invasive implants. Conversely, for patients without omentectomy, fertility-preserving strategy was more frequently followed and other staging procedures less frequently performed which might also influence prognosis. Multiple analyses adjusted for these characteristics, however, underline that the removal of potentially affected structures like the omentum might impact prognosis and help to prevent relapse. Furthermore, the present data showing increasing risk of recurrence with each skipped staging procedure can help to illustrate treatment recommendations and facilitate informed consent with the patients.

The obvious limitation of our study is that patients were retrospectively included and patient cohorts were not randomly assigned to pre-defined staging procedures. Therefore, the results have to be cautiously interpreted to avoid possible selection bias. However, the AGO ROBOT dataset represents the so far largest dataset of BOT patients. The participating centres included all consecutive patients during the study period and all cases were subject to central pathological review resulting in a well-characterised cohort. As prospective investigations comparing different staging procedures will hardly ever be available, the present study might provide important new aspects to this question with immediate implications for clinical routine: In patients who underwent surgery with uni- or bilateral salpingo-oophorectomy without oncological intention due to unexpected diagnosis of serous BOT in a surgery for different reasons (e.g., appendectomy, Caesarean section, ovarian cyst), gynaecologic oncologists may now rather tend towards the recommendation of secondary surgery with re-staging procedures based on this analysis despite the generally excellent overall prognosis of BOT. Furthermore, the present data showing increasing risk of recurrence with each skipped staging procedure can help to illustrate treatment recommendations and facilitate informed consent with the patients.

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**Figure 2. Analyses of missing staging procedures regarding progression-free survival (PFS).** (A) Forest plot illustrating the unadjusted analysis of the prognostic impact of consecutively skipped staging procedures in terms of PFS by Cox regression model. (B) Forest plot for multiple analysis adjusted for established prognostic factors as well as for two and three missing surgical staging procedures in terms of PFS by Cox regression model.
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CONFLICT OF INTEREST

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