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Localization of distant metastases defines prognosis and treatment efficacy in patients with FIGO stage IV ovarian cancer

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HIGHLIGHTS

- The renewed Federation of Gynecology and Obstetrics (FIGO) IV sub-classification does not provide prognostic information.
- Extra-abdominal lymph node metastases represent a distinct group of FIGO IV patients.
- Neoadjuvant chemotherapy followed by interval cytoreductive surgery is the preferred treatment for the majority of FIGO IV patients.

ABSTRACT

Background Patients with ovarian cancer who are diagnosed with Federation of Gynecology and Obstetrics (FIGO) stage IV disease are a highly heterogeneous group with possible survival differences. The FIGO staging system was therefore updated in 2014.

Objective To evaluate the 2014 changes to FIGO stage IV ovarian cancer on overall survival.

Methods We identified all patients diagnosed with FIGO stage IV disease between January 2008 and December 2015 from the Netherlands Cancer Registry. We analyzed the prognostic effect of FIGO IVa versus IVb. In addition, patients with extra-abdominal lymph node involvement as the only site of distant disease were analyzed separately. Overall survival was analyzed by Kaplan-Meier curves and multivariable Cox regression models.

Results We identified 2436 FIGO IV patients, of whom 35% were diagnosed with FIGO IVa disease. Five-year overall survival of FIGO IVa and IVb patients (including those with no or limited therapy) was 8.9% and 13.0%, respectively ($p=0.51$). Patients with only extra-abdominal lymph node involvement had a significant better overall survival than all other FIGO IV patients (5-year overall survival 25.9%, hazard ratio 0.77 [95% CI 0.62 to 0.95]).

Conclusion Our study shows that the FIGO IV sub-classification into FIGO IVa and IVb does not provide additional prognostic information. Patients with extra-abdominal lymph node metastases as the only site of FIGO IV disease, however, have a better prognosis than all other FIGO IV patients. These results warrant a critical appraisal of the current FIGO IV sub-classification.

INTRODUCTION

The vast majority of patients with epithelial ovarian cancer are diagnosed with advanced stage disease, and about 12–33% have international Federation of Gynecology and Obstetrics (FIGO) stage IV disease at initial presentation.^{1 2} In the majority of these patients, stage IV disease is based on the presence

of malignant pleural effusion (30–60%), parenchymal liver metastases (10–25%), or extra-abdominal lymph node metastases (5–40%).^{1 3–5}

Following the recognition that patients with FIGO stage IV represent a highly heterogeneous group with possible survival differences, the FIGO staging system was updated in 2014. The new classification distinguishes between patients with malignant pleural effusion (FIGO IVa), and patients with either abdominal parenchymal invasion or extra-abdominal metastases (FIGO IVb).^{6 7} Multiple studies evaluated the prognostic value of the new sub-classification, although with conflicting results.^{1 8–15} Most studies reported similar survival results for FIGO IVa and IVb patients, while some studies found a prognostic favorable effect of extra-abdominal lymph node metastases as the only site of distant disease.^{1 8–10} Most of the analyses were, however, often hampered by limited patient numbers and missing clinical information.

The mainstay of primary treatment of FIGO IV patients consists of debulking surgery in combination with (neo)adjuvant chemotherapy. Two landmark randomized clinical trials studied the timing of surgery in patients with epithelial ovarian cancer—that is, primary debulking surgery vs interval debulking surgery, and found similar survival rates in both FIGO IIIc and IV patients.^{16 17} However, it is clear that patients with no residual disease after surgery have the best prognosis. Therefore, the decision to schedule patients for either primary surgery or neoadjuvant chemotherapy and interval surgery is mainly based on the ability to achieve a maximal (intra-abdominal) cytoreduction with acceptable surgical morbidity. In cases of extra-abdominal disease, it is suggested that neoadjuvant chemotherapy may indicate whether a complete cytoreduction could be achieved. In cases of no response or progression during neoadjuvant chemotherapy, surgery might be omitted.

Original Article

The aim of our study was to evaluate the renewed FIGO sub-classification into stage IVa and IVb on clinical outcome in a large population-based cohort. In addition, we studied the effect of treatment in these groups to offer clinical guidance on the preferred treatment of FIGO IV patients.

METHODS

We identified all consecutive patients who were diagnosed with epithelial ovarian cancer, including fallopian tube and primary peritoneal cancer (International Classification of Diseases for Oncology (ICD-O) C56.9, C57.0, C48.2), from the Netherlands Cancer Registry (NCR). The NCR is a nationwide cancer registry and covers all Dutch patients with cancer since 1989. Thoroughly trained registration clerks routinely extracted information on patient and tumor characteristics (including the localization of metastases), diagnostic procedures, and treatment. Follow-up status is obtained by annual linkage with the municipal demography registries (GBA). The study design, data abstraction process, and storage protocols were approved by the NCR review board.

Study Population

We included all FIGO IV patients who were diagnosed between January 1, 2008 and December 31, 2015, including patients with clinically suspicious (but not histologically proved) metastases. Malignant pleural effusion was cytologically confirmed in 99% of patients, as this is required for FIGO stage IV disease in the Tumor-Node-Metastasis (TNM) system. FIGO stage 2009 was derived from the TNM 7 staging system,¹⁸ which means that inguinal lymph node metastases were not included within the FIGO IV group, as they were regarded as regional lymph nodes (N1) at that time.

Definitions

Patients were categorized as FIGO IVa if they were diagnosed with malignant pleural effusion without other extra-abdominal or parenchymal spread, and as FIGO IVb in all other cases. In separate analysis, we divided patients according to the localization of distant disease: (1) pleural malignant effusion, (2) parenchymal metastases (either intra-abdominal or extra-abdominal), (3) extra-abdominal lymph node metastases or (4) other. Patients were categorized as 'other' if they were diagnosed with metastases in more than one of the previously mentioned categories—for example, malignant pleural effusion and parenchymal liver metastasis.

The outcome of cytoreductive surgery (debulking) was defined as complete in cases of no macroscopic abdominal residual disease, as optimal when the largest diameter was ≤ 1 cm, and as sub-optimal in case of residuals > 1 cm in maximal diameter.

For patients undergoing surgery and chemotherapy, additional medical information was collected. As a result, all present co-morbidities were registered in our database, and the Charlson Comorbidity Index was modeled based on these registered comorbidities, which were categorized as 0, 1, and ≥ 2 points.¹⁹ Chemotherapeutic agents, the number of cycles, and alterations to the chemotherapy scheme were registered. Our models were adjusted for chemotherapy modifications, where the use of six cycles of

carboplatin and paclitaxel without dose reductions was considered regular care.

Statistical Analyses

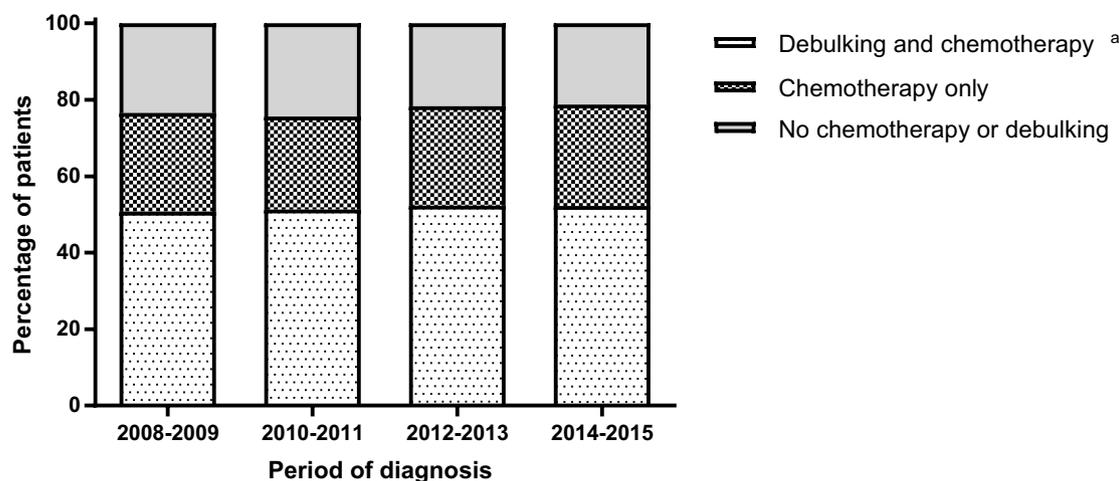
Overall survival was defined as the interval between the date of diagnosis and death, or last follow-up date for patients who were still alive (February 1, 2018). Kaplan-Meier survival curves, log-rank tests and, if applicable, univariable and multivariable Cox regression models were used to analyze overall survival. The proportional hazards assumption was tested for all survival analyses. If the hazards were not constant over time—that is, the proportional hazards assumption was violated, we used time-varying effects in our Cox regression model to adjust our results for non-proportionality.²⁰ When comparing primary surgery and neoadjuvant chemotherapy followed by interval surgery, an additional matching criterion was used as a sensitivity analysis to overcome the introduction of immortal time bias.²¹ Immortal time bias refers to a time interval in the follow-up period where the event of interest could not have occurred because of exposure definition—that is, patients who underwent debulking surgery after neoadjuvant chemotherapy could not have died during neoadjuvant chemotherapy.²² Our matching criterion implied that patients were excluded if they died or were lost to follow-up during the median time that neoadjuvant chemotherapy lasted in our population (103 days). Moreover, regular Kaplan-Meier curves were added to the online supplementary file S5. Statistical analyses were performed using STATA/SE, version 14.1 (Stata-Corp, College Station, Texas, USA) and a p value < 0.05 was considered statistically significant.

RESULTS

Between 2008 and 2015, 1884 out of 2436 FIGO IV patients were treated with surgery and/or chemotherapy (77%), and the rate was stable over time ($p=0.52$, Figure 1). The median age of patients at diagnosis was 69 years (IQR 61–78). Most patients were diagnosed with malignant pleural effusion (35%) or parenchymal metastases (37%). Most parenchymal metastases were localized in the liver (56%), and other localizations were the gastrointestinal tract (9%) and lungs (16%). A minority of patients had solely extra-abdominal lymph node involvement (12%). The most common sites for extra-abdominal lymph node involvement were intra-thoracic lymph nodes (38%) and lymph nodes of the head, face, and neck (21%, such as supraclavicular lymph nodes) or multiple locations (15%). Other baseline characteristics are displayed in the online supplementary material S1.

Clinical Outcome of the Renewed FIGO IV Sub-classification

In our total population (ie, including those with no or limited therapy), 5-year overall survival was 8.9% for FIGO IVa and 13.0% for FIGO IVb patients. We found no prognostic effect of the renewed sub-classification in our total population (hazard ratio 1.03, 95% CI 0.94 to 1.13, $p=0.51$). Survival rates were higher in patients who were treated with the combination of debulking surgery and chemotherapy (5-year overall survival FIGO IVa: 14.6%, FIGO IVb: 23.6%, hazard ratio_{FIGO IVb} 0.82 [95% CI 0.72 to 0.94], $p=0.004$). Moreover, when adjusted for age, Charlson Comorbidity Index, histologic sub-type, treatment sequence, chemotherapy alterations, and the outcome of debulking surgery, FIGO IVb patients experienced better



^a Minority of patients did not receive chemotherapy after surgery

Figure 1 Treatment of all FIGO IV patients with epithelial ovarian cancer over time (n=2436).

survival than FIGO IVa patients (adjusted HR=0.75 [95% CI 0.65 to 0.87]).

Clinical Outcome Stratified by the Localization of Metastases

In our total population (ie, including those with no or limited therapy), stratification by localization of metastasis revealed that patients with solely extra-abdominal lymph node metastases experienced higher overall survival than the other groups of FIGO IV patients (5-year overall survival was 25.9% for lymph node metastases and 9.8% for other metastases, $p < 0.001$, Figure 2). In addition, this effect was also seen in our treated population (ie, combination of chemotherapy and debulking surgery). In these patients, even after adjustment for age, Charlson Comorbidity Index, histologic sub-type, treatment sequence, chemotherapy alterations, and the outcome of debulking surgery, the improved prognosis for patients with lymph node metastases remained statistically significant (adjusted hazard ratio 0.77 [95% CI 0.62 to 0.95] compared with all other metastases). Sensitivity analysis showed that there was

no difference in overall survival between histologically confirmed malignant lymph node involvement and those whose disease was clinically suspicious ($p = 0.62$).

Clinical Outcomes Stratified by Therapy

The number of patients who were treated with primary surgery decreased over time from 27% in 2008–2009 to 10% in 2014–2015 ($p < 0.001$, online supplementary material S2). Simultaneously, the outcome of surgery improved in both groups (online supplementary material S3, S4). Neoadjuvant chemotherapy followed by interval surgery was associated with a higher rate of complete or optimal surgeries in comparison with primary surgery (adjusted OR=2.27 [95% CI 1.54 to 3.34]).

The effect of treatment sequence (primary surgery or neoadjuvant chemotherapy followed by interval surgery) seems to conflict over time in FIGO IVa patients, where survival lines cross at 18 months (online supplementary material S5 panel A). In FIGO IVb patients, treatment sequence did not influence survival (adjusted hazard rates_{NACT-IDS}

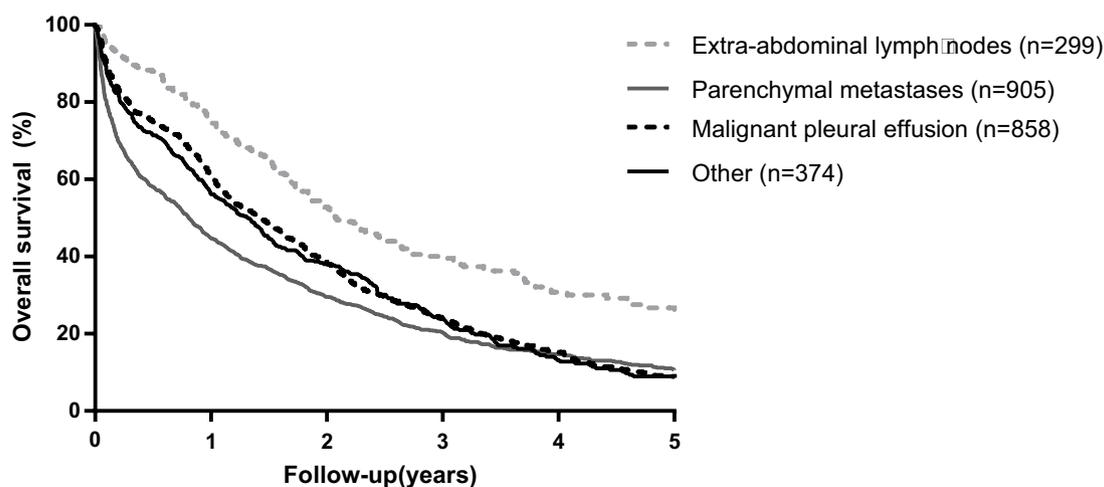


Figure 2 Overall survival of all FIGO IV patients by localization of their metastases (n=2436).

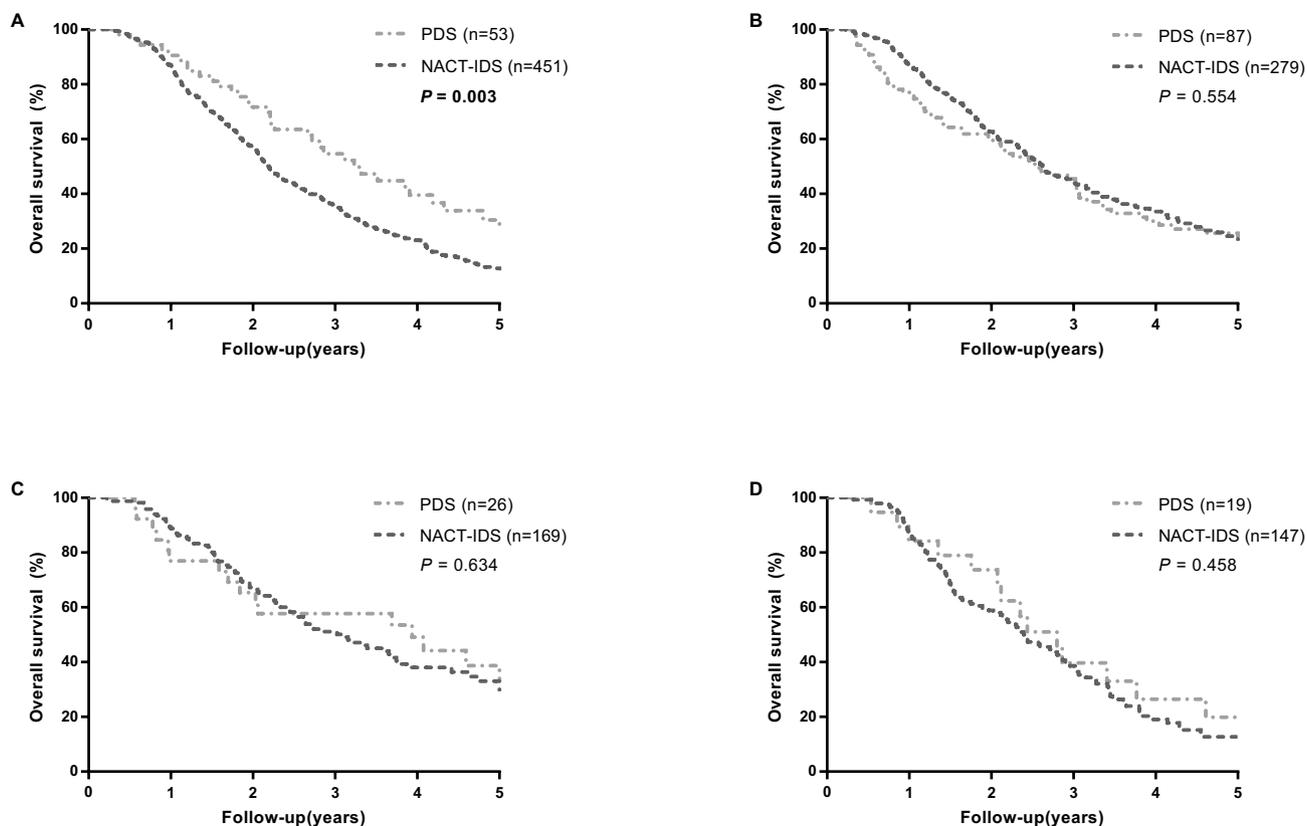


Figure 3 Sensitivity analysis for overall survival by localization of metastases, by using the matching criterion. Every panel contains overall survival with a follow-up of 5 years; the dark gray lines depict patients undergoing neoadjuvant chemotherapy-interval debulking surgery (NACT-IDS) and the light gray lines patients undergoing primary debulking surgery (PDS). The p values represent a log-rank test. (A) Pleural malignant effusion; (B) parenchymal metastases; (C) extra-abdominal metastases; (D) other metastases.

0.97 [95% CI 0.76 to 1.24]). No difference in overall survival between the two treatment sequences was seen also in patients with extra-abdominal lymph node metastases only or other metastases (online supplementary material S5 panel C $p=0.99$ and panel D $p=0.78$, respectively). In patients with parenchymal metastases, however, neoadjuvant chemotherapy followed by interval surgery seems to improve overall survival (online supplementary material S5 panel B, hazard rates_{NACT-IDS} 0.75 [95% CI 0.59 to 0.98]).

In the subsequent sensitivity analysis including a matching criterion to account for immortal time bias, 9/62 patients who died within 3 months after primary surgery were excluded. Of these nine patients, four died shortly after primary surgery, and five received at least one cycle of chemotherapy. The sensitivity analysis then showed a survival benefit for the remaining patients with malignant pleural effusion who had received primary surgery compared with neoadjuvant chemotherapy followed by interval surgery ($p=0.003$, Figure 3 panel A). After adjustment for age, Charlson Comorbidity Index, histologic sub-type, treatment sequence, chemotherapy alterations and the outcome of debulking surgery, this survival benefit remains significant (hazard rates_{NACT-IDS} 1.96 (1.33–2.88)). In patients with parenchymal metastases, where 14 out of 102 primary surgery patients were excluded, neoadjuvant chemotherapy followed by interval surgery is comparable to primary surgery ($p=0.55$).

DISCUSSION

Our population-based study showed that the renewed FIGO IV sub-classification did not provide additional prognostic information. However, patients with extra-abdominal lymph node metastases as the only site of distant disease had a significantly higher overall survival than other groups of FIGO IV patients. In addition, we showed that primary surgery might be an alternative to neoadjuvant chemotherapy followed by interval surgery in selected FIGO IV patients with malignant pleural effusion as the only site of distant disease.

Multiple studies investigated the additional distinction in FIGO IV patients. Most of them found no significant differences in overall survival, while others indicated that FIGO IVb patients, counter-intuitively, might have a better prognosis.^{8 11–15} In our study, we confirmed in a population-based setting, that there was no difference between FIGO IVa and FIGO IVb patients. In patients who were treated with a combination of chemotherapy and debulking surgery, however, FIGO IVb patients might have improved overall survival. This is probably explained by the percentage of patients who do not undergo the combined treatment, which differs significantly between FIGO IVa and FIGO IVb patients (40% vs 59%, respectively, $p<0.001$). As a minority of patients with FIGO IVb disease is treated

with the advised treatment, this selection probably contributes to the differences between the two analyses.

Patients with FIGO stage IV based only on extra-abdominal lymph node metastases have the most favorable prognosis, and this particular finding is in accordance with other studies.^{8–10} The beneficial effect on clinical outcome is in agreement with the renewed distinction in FIGO III patients. In the current FIGO staging classification, patients with regional lymph node metastases only are now classified as FIGO IIIa1 instead of FIGO IIIc. The latter adjustment to the FIGO staging system has proved to be more accurate for prognosis, while the revised FIGO IV stage does not provide any prognostic information.^{7 9 23–25} A limitation of our current research is that patients with inguinal lymph node metastases were not included in the analyses, as they could not be identified from our cancer registry. Following TNM 7 and FIGO 2009, these patients were still classified as FIGO IIIc disease and the localization of regional lymph node metastases was not registered.¹⁸ However, the number of FIGO IV patients with solely inguinal lymph node metastases appears to be low (2–5%), and the survival of these patients may be similar to FIGO III patients with solitary pelvic or para-aortic nodal involvement.^{1 9 26} Consequently, this supports our findings that patients with extra-abdominal lymph node metastases show the most favorable prognosis in the FIGO IV group. The prognostic role of only extra-abdominal lymph nodes in patients with epithelial ovarian cancer should be investigated in future prospective studies, and it remains questionable whether these patients should even be classified as FIGO IV patients.^{9 10}

Over time, the percentage of patients who received no treatment in our population (ie, no chemotherapy and no debulking surgery) was 20–25%. Moreover, another 25% of all patients received chemotherapy without debulking surgery. The decision to schedule patients for cancer-directed treatment or palliative care is based on a multidisciplinary team meeting, including medical oncologists, gynecologic-oncologists, radiologists, and pathologists. Reasons for abstaining from treatment are not routinely collected within our database, and are therefore unknown. The inclusion of patients without cancer-directed treatment explains the low survival rates in our total population in comparison with other studies, as the combination of platinum-based chemotherapy and maximal debulking surgery is essential to improve patients' prognosis.^{2 8 9 13}

Our study showed that debulking surgery contributes to the prognosis of selected patients who eventually underwent surgery in our population, as the survival rates of this group are higher than for patients with limited therapy. In addition, the amount of residual disease is a strong prognostic factor for overall survival (data not shown). This implies that at least a selection of patients with FIGO IV disease is comparable to other patients with advanced stage disease for clinical decision-making, with no residual disease after surgery as ultimate goal.^{27–30} This finding is supported by the distribution of recurrences in FIGO IV patients. Several studies showed that most recurrences occur intra-abdominally, which underlines the importance of controlling intra-abdominal disease.^{11 31 32} However, as shown in other studies, if debulking surgery results in >1 cm of residual disease, it is questionable if this treatment approach is better than chemotherapy alone.^{2 3} The presence of initially unresectable disease (>1 cm) could therefore be challenged with neoadjuvant chemotherapy, and surgery might be omitted in cases of poor response. This emphasizes that patient

selection of those who will benefit from surgery is crucial to avoid surgical morbidity and even mortality.

The preference for timing of surgery changed over time, with an increase in the use of neoadjuvant chemotherapy followed by interval surgery in FIGO IV patients, which contributed to the more favorable outcomes of surgery in the whole population. Neoadjuvant chemotherapy followed by interval surgery seems to be beneficial in FIGO IV patients, as we showed that survival was comparable between primary surgery and neoadjuvant chemotherapy followed by interval surgery, and multiple studies have reported reduced morbidity after neoadjuvant chemotherapy followed by interval surgery.^{16 17 33 34} In our retrospective study, confounding by severity plays a role in the selection of patients for either neoadjuvant chemotherapy followed by interval surgery or primary surgery. Patients who undergo primary surgery are probably diagnosed with a lower tumor burden and a higher probability towards complete debulking surgery. As this favorable prognosis does not translate into better survival rates, primary surgery might not be the preferred treatment for these patients. Moreover, a recent sensitivity analysis on FIGO IV patients of the European Organization for Research and Treatment of Cancer (EORTC) study confirmed the beneficial effect of neoadjuvant chemotherapy followed by interval surgery, and the authors concluded that neoadjuvant chemotherapy followed by interval surgery might be the preferred treatment in FIGO IVb patients.^{8 16} However, other studies indicate that primary surgery remains the preferred treatment, also for FIGO IV patients.¹²

We identified a subgroup of selected patients who may benefit from primary surgery over neoadjuvant chemotherapy followed by interval surgery. In a sensitivity analysis that excluded patients who died shortly after primary surgery in order to overcome immortal time bias, a more favorable outcome was observed in patients with malignant pleural effusion.²² Immortal time bias refers to those patients who did not respond or died during neoadjuvant chemotherapy and thus could not have undergone interval surgery. These patients are represented in our chemotherapy only group, and therefore do not compromise clinical outcome in the neoadjuvant chemotherapy followed by interval surgery group.²² It makes sense that a selection of patients may be better served by primary surgery. Pleural effusion can be the result of trans-diaphragmatic migration of malignant cells through pleuroperitoneal communications, which usually responds well to adjuvant chemotherapy.³⁵ Unfortunately, the number of FIGO IVa patients who underwent primary surgery is limited in our series and this finding needs to be confirmed in future prospective studies. Moreover, primary surgery can be beneficial only if patients who die shortly after this extensive procedure could be identified pre-operatively.

The strengths of our study are its population-based character (including those patients with no or limited therapy), complete follow-up records, and the number of patients, as most studies were underpowered to identify the prognostic effect of certain metastases on clinical outcome. Our study is limited by its retrospective nature and by the definition of the amount of residual disease in FIGO IV patients. Should the presence of extra-abdominal disease, in cases of an intra-abdominal complete debulking surgery, alter the outcome of the surgery? This subject is not often dealt with in other studies, neither does there exist a clear definition in international literature. Therefore, it is possible that gynecologists interpreted the outcome of residual disease differently and

this might have introduced bias in our analyses as our registration clerks register the judgment of the gynecologists.

In conclusion, we showed that the renewed FIGO IV classification into FIGO IVA and IVb does not provide meaningful prognostic information. Patients with extra-abdominal lymph node metastases as the only site of FIGO IV disease, however, do have a better prognosis than all other FIGO IV patients. These findings warrant a critical evaluation of the current FIGO IV sub-classification.

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