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Original Research

Validation of a treatment-selection rule for patients with advanced stage ovarian cancer

R. van de Vrie[1,*], E. van Werkhoven[2,*], M. J. Rutten[1], J. D. Asseler[1], H. S. van Meurs[1], D. E. Werter[1], M. R. Buist[1], A. H. Zwinderman[3], C. A. R. Lok[4], P. M. M. Bossuyt[2], G. G. Kenter[1], P. Tajik[2,5]

[1]*Department of Obstetrics and Gynaecology, Centre for Gynaecologic Oncology Amsterdam, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*

[2]*Biometrics Department, The Netherlands Cancer Institute, Amsterdam, the Netherlands*

[3]*Department of Epidemiology, Biostatistics & Bioinformatics, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*

[4]*Department of Gynaecologic Oncology, Centre for Gynaecologic Oncology Amsterdam, Antoni van Leeuwenhoek Hospital, Amsterdam, the Netherlands*

[5]*Department of Pathology, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands*

Summary

Purpose of investigation: To externally validate the rule of Van Meurs *et al*. for selecting patients with advanced epithelial ovarian cancer for treatment with primary surgery or neoadjuvant chemotherapy (NACT). *Materials and Methods*: We analysed a historical cohort of 900 consecutive patients with FIGO stage IIIC/IV ovarian cancer treated for advanced stage epithelial ovarian cancer at the Centre of Gynaecologic Oncology Amsterdam between 1998 and 2012. To externally validate the treatment-selection rule of Van Meurs *et al*. four groups were defined based on metastatic tumour size (smaller or larger than 45 mm) and FIGO stage (IIIC *vs*. IV). Within these groups, we compared survival outcomes of primary surgery and NACT. *Results*: Differential treatment benefit in model-defined subgroups based on metastatic tumour size and FIGO stage was confirmed (interaction $p = 0.008$). Survival after primary surgery was significantly better compared to NACT plus interval debulking surgery for patients in FIGO stage IIIC ($p = 0.001$) or IV ($p = 0.028$) with metastases $\leq$ 45 mm, and those in FIGO stage IIIC with metastases $>$ 45 mm ($p = 0.011$). Survival was not significantly worse for FIGO stage IV patients with metastases $>$ 45 mm ($p = 0.094$). In patients with such large metastases, the location (omentum versus elsewhere in the body) was not prognostic ($p = 0.44$). *Conclusion*: Our study has externally validated the treatment-selection rule first described by van Meurs *et al*. Primary surgery was shown to be superior for all patients except for the FIGO stage IV patients with a large metastatic tumour size ($>$ 45 mm), irrespective of localisation of the metastasis.

Key words: Ovarian cancer; Treatment strategy; Overall survival; FIGO stage; Metastasis.

Introduction

Epithelial ovarian cancer is a leading cause of death from gynaecological malignancies worldwide. Most women are diagnosed with advanced disease (Federation of Gynaecology and Obstetrics (FIGO) stage III or IV) [1], with a five-year overall–survival prognosis of 30% to 40% [2, 3]. Standard treatment consists of primary surgery followed by chemotherapy [4]. An alternative treatment was widely implemented after publication of the European Organization for Research and Treatment of Cancer (EORTC) 55971 trial in 2010 [5], which demonstrated non-inferiority of neoadjuvant chemotherapy (NACT) followed by interval debulking surgery and post-surgery chemotherapy. These results were confirmed in another randomized trial by Kehoe *et al*. [6] and have been supported by other studies [7-11].

Despite this evidence, the choice between NACT and primary surgery remains controversial. NACT increases the chance of total removal of all macroscopic tumour and could lead to improved survival, since residual disease after debulking surgery is the most important prognostic factor for survival [12]. The guideline of the American Society of Clinical Oncology recommends NACT for women with a high risk profile and a low likelihood of cytoreduction to $<$ 1 cm [13]. Models to identify such patients have been developed based on patient characteristics, laparoscopy results, imaging features, or combinations of these [14, 15].

However, residual disease after debulking surgery is only a surrogate endpoint for survival and is difficult to predict [14]. To solve this problem, treatment-selection models have been developed that focus directly on survival, such as the prediction model developed by Van Meurs and colleagues [3]. In a secondary analysis of the EORTC 55971 trial, they demonstrated that FIGO stage and the size of the largest metastatic tumour are significantly associated with benefit from treatment. They selected ten baseline clinical and pathological characteristics as potential biomarkers. Using Subpopulation Treatment Effect Pattern Plots (STEPP), they considered biomarkers with a statistically significant qualitative additive interaction with treatment

*Contributed equally.

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as being potentially informative for treatment selection. Their study showed that the size of the largest metastatic tumour and the FIGO stage were significantly associated with magnitude of benefit from treatment. These were combined to create a multimarker treatment-selection rule: primary surgery was recommended for patients with FIGO stage IIIC and a largest metastatic tumour size $\leq$ 45 mm. Both primary surgery and NACT were feasible options for patients with FIGO stage IIIC with largest metastatic tumour size $>$ 45 mm and for FIGO stage IV patients with largest metastatic tumour size $\leq$ 45 mm. NACT was recommended for patients with FIGO stage IV disease with a largest metastatic tumour size $>$ 45 mm.

This treatment-selection rule has not yet been externally validated, which prevents unconditional recommendation of its use. In the present study, we therefore performed such an external validation. In addition, we evaluated whether the localisation of the metastasis – within the omentum compared to a metastasis at another site – influences survival differentially.

Materials and Methods

We conducted a multicentre historical cohort study of consecutive patients who were treated for advanced stage epithelial ovarian cancer at the Centre of Gynaecologic Oncology Amsterdam (Academic Medical Centre, Free University Medical Centre and Antoni van Leeuwenhoek) between 1998 and 2012. We included all women who had epithelial cancer of the ovary, tube or peritoneum classified as advanced stage based on FIGO criteria (stages IIIC or IV) and who underwent either primary debulking surgery or NACT with interval debulking surgery. To select only patients for whom it is more difficult to predict whether cytoreductive surgery will be successful, we excluded those with lower stage ovarian cancer (FIGO stage I- IIIB). To ensure a truly external validation (without overlap with the dataset that was used to develop the decision rule) patients who participated in the EORTC 55971 trial were excluded. Finally, to avoid bias from this additional treatment within the NACT group, we excluded patients who received HIPEC treatment as part of the OVHIPEC trial [16].

Data were retrieved from medical files, including FIGO stage and largest metastatic tumour size in mm (including omental cake). In women who received primary surgery, the largest metastatic tumour size was evaluated by either the CT scan prior to surgery or the surgery report. For women who received NACT with interval surgery, the metastatic tumour size was evaluated on the CT scan made prior to chemotherapy treatment. If this was inconclusive, a sonography image prior to treatment was used. If no specific measurement for metastasis was found in the medical records, metastatic tumour size was considered missing.

As defined by van Meurs [3], the following four subgroups were constructed:

1. FIGO stage IIIC and largest metastatic tumour size $\leq$ 45 mm;

2. FIGO stage IIIC and largest metastatic tumour size $>$ 45 mm;

3. FIGO stage IV and largest metastatic tumour size $\leq$ 45 mm;

4. FIGO stage IV and largest metastatic tumour size $>$ 45 mm.

Baseline characteristics were compared between treatment groups using Wilcoxon's rank sum test and Fisher's exact test or the Chi-square test. Cox proportional hazards models of overall survival were used to analyse the treatment effect and the treatment-by-subgroup interaction. Subsequently, separate Cox proportional hazards models were used to analyse overall survival by treatment in the four subgroups. Missing data were imputed, i.e. they were replaced with substitute values that are based on a regression model. The imputation procedure was repeated 10 times using the multiple imputation method, which ensures that variation introduced by the imputation process is accounted for. The event indicator and the Nelson–Aalen estimator of the hazard were included in the imputation model.

After multiple imputation, predictions are usually calculated from the average coefficients (i.e. the log hazard ratios) across the imputed datasets, which are combined into a linear predictor. To ensure the validity of this method, each of the separate imputation sets must contain data from the same patients. However, this was not the case in our analysis for the models in the separate subgroups because the size of the largest metastasis was missing for some patients, and the subgroups to which such patients belonged could vary between multiple-imputation datasets. Therefore, survival curves per subgroup were obtained from the average of the linear predictors instead of the average of the coefficients. This was done as follows: for each patient occurring in a subgroup at least once, the mean linear predictor was calculated across the imputations for which that patient belonged to that subgroup. These linear predictors were then used to calculate the Breslow estimator of the survival curve of that subgroup.

In contrast to the study design of van Meurs *et al.* [3], we did not collect data from a randomized study but from patient records. To account for possible treatment-by-indication bias, baseline imbalances between the two treatment groups were compensated for by weighting patients in each model by the inverse probability of the treatment they actually received. The following variables were used to calculate the probability of receiving treatment: age, BMI, FIGO stage, size of metastasis, CA-125, albumin, grade, ASA, platelets, location of first debulking surgery, ascites (whether it was present and was more than or less than 500 ml) and period of treatment (before 2010 or after). The period was included to account for possible changes after the publication of the EORTC 55971 trial [5]. BRCA status of the majority of patients was unknown and could therefore not be included in the analyses. The weights were trimmed to the 1^{st} and 99^{th} percentile of their distribution. To assess the effect of the weighting on the imbalance between

the treatment groups, standardized differences were calculated (details are provided in the appendix).

A sensitivity analysis was done with separate Cox proportional hazards models of overall survival by treatment in the four subgroups without imputation or weighting, using only patients with known metastatic tumour size. Another analysis was done in the subgroup of patients with a large metastatic tumour (> 45 mm), in which survival was analysed by whether patients had a large metastasis within the omentum or a large metastasis anywhere else in the body. A p-value of < 0.05 was considered to indicate statistically significant differences. Statistical analyses were performed with the Statistical Package for the Social Sciences software package, version 23 for Windows (SPSS Inc., Chicago, Illinois, USA) and R 3.4.4 with package mice version 2.46.0.

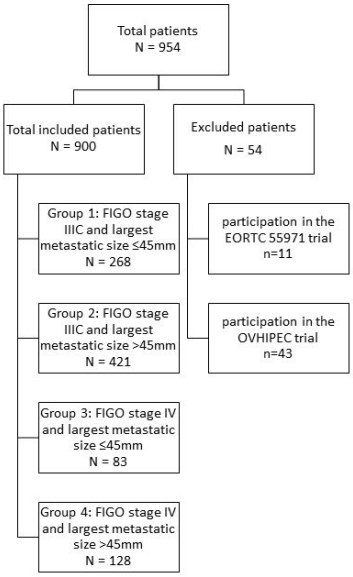

Figure 1. — Flow diagram of included patients.

Results

We identified 954 eligible patients in the study period, of which 54 were excluded because of participation in the EORTC 55971 trial (n = 11) or the OVHIPEC trial (n = 43) (Figure 1). Of the remaining 900 patients, 319 (35%) underwent primary surgery and 581 patients (65%) received NACT followed by interval surgery. Of all patients, 689 (77%) had clinical FIGO stage IIIC, and 211 (23%) had FIGO stage IV (Table 1). FIGO stage was available for all patients, but the size of the metastatic tumour was missing in 244 patients (27%).

Some patient characteristics differed between the treatment groups. The NACT group was on average older ($p < 0.001$), with a corresponding higher percentage postmenopausal women ($p < 0.001$). World Health Organization (WHO) performance status was higher in the NACT group ($p = 0.002$), and histology differed between the two treatment groups ($p < 0.001$). Significantly more patients with FIGO stage IIIC were present in the primary surgery group, and significantly more patients with FIGO stage IV were present in the NACT group ($p < 0.001$). Imbalance in treatment period was most prominent in subgroup 4 (FIGO stage IV and largest metastatic tumour size > 45 mm), where all 16 patients who received primary surgery were treated between 1997 and 2008. Serum CA-125 before treatment ($p < 0.001$) was unevenly distributed, with higher levels in the NACT group. After weighting, baseline characteristics of the treatment groups were more comparable (Supplemental tables S1 and S2). We also inspected the distribution of propensity scores per treatment group and found sufficient overlap (Supplemental figure S1).

After 10 multiple imputations, the average distribution of patients across the four subgroups was as follows: Group 1: 268 (30%) patients had FIGO stage IIIC and largest metastatic size ≤ 45 mm; Group 2: 421 patients (47%) had FIGO stage IIIC and largest metastatic size > 45 mm; Group 3: 83 patients (9%) had FIGO stage IV and largest metastatic size ≤ 45 mm; and Group 4: 128 patients (14%) had FIGO stage IV and largest metastatic size > 45 mm (Table 2).

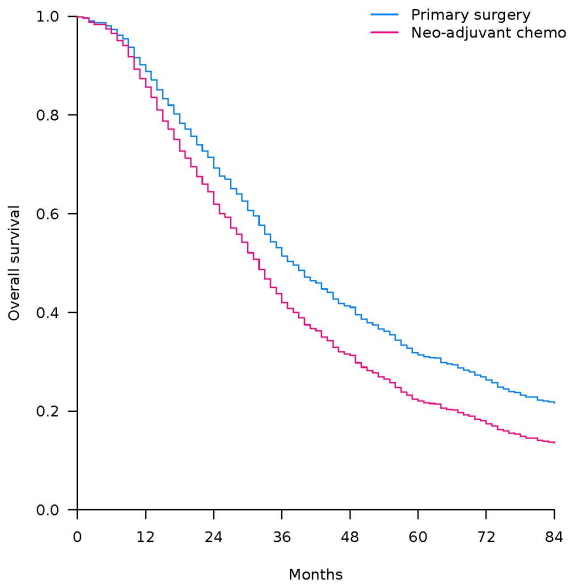

Figure 2. — Overall survival by treatment strategy. HR 1.31 95%CI (1.17–1.45), $p < 0.0001$.

The median follow-up was 94 months; in 38 patient's survival time was censored before five years of follow up. Overall survival was significantly worse in the group undergoing NACT compared to primary surgery (HR 1.31, 95% CI 1.17–1.45, $p < 0.0001$) (Figure 2).

In the subgroup of patients with FIGO stage IIIC and metastatic size ≤ 45 mm, the five-year survival was 27% in the NACT group, versus 42% in the primary surgery group

Table 1. — *Baseline characteristics of participants. Percentages given without missing data.*

Baseline characteristics	Primary surgery (n = 319)	Neoadjuvant chemotherapy followed by interval surgery (n = 581)	*p*-value
Age (years)			< 0.001
Median (IQR)	60 (51–68)	64 (56–70)	
Body Mass Index (BMI)			0.95
Median (IQR)	24.6 (21.9–27.8)	24.5 (21.8–27.8)	
Missing data	129 (40%)	193 (33%)	
Post-menopausal			< 0.001
No	45 (17%)	38 (8%)	
Yes	217 (83%)	459 (92%)	
Missing data	57 (18%)	84 (14%)	
World Health Organization (WHO) performance status			0.002
0	166 (60%)	220 (49%)	
1	98 (35%)	172 (38%)	
2	12 (4%)	49 (11%)	
3	2 (1%)	8 (2%)	
Missing data	41 (13%)	132 (23%)	
Tumour grade by Silverberg			0.49
1	18 (7%)	19 (7%)	
2	60 (22%)	54 (18%)	
3	189 (71%)	219 (75%)	
Missing data	52 (16%)	289 (50%)	
Histology			< 0.001
Serous	228 (71%)	462 (80%)	
Mucinous	14 (4%)	13 (2%)	
Endometroid	36 (11%)	15 (3%)	
Clear cell	13 (4%)	13 (2%)	
Undifferentiated	19 (6%)	74 (13%)	
Mixed	2 (1%)	2 (< 1%)	
Other	7 (2%)	2 (< 1%)	
Serum CA-125 before treatment (U/ml) *			< 0.001
Median (IQR)	608.5 (218.8–1757.0)	963.0 (380.0–2413.0)	
Missing data	13 (4%)	30 (5%)	
Amount of ascites before treatment			0.12
> 500 ml	179 (60%)	233 (54%)	
≤ 500 ml	118 (40%)	197 (46%)	
Missing data	22 (7%)	151 (26%)	
Clinical stage			< 0.001
IIIC	288 (90%)	401 (69%)	
IV	31 (10%)	180 (31%)	
Missing data	0 (0%)	0 (0%)	
Metastatic tumour size			0.91
≤ 45 mm	103 (41%)	160 (40%)	
> 45 mm	151 (59%)	242 (60%)	
Missing data	65 (20%)	179 (31%)	
Subgroup			< 0.001
FIGO IIIC and largest metastatic tumour size ≤ 45 mm	94 (29%)	108 (19%)	
FIGO stage IIIC and largest metastatic tumour size > 45 mm	135 (42%)	172 (30%)	
FIGO stage IV and largest metastatic tumour size ≤ 45 mm	9 (3%)	52 (9%)	
FIGO stage IV and largest metastatic tumour size > 45 mm	16 (5%)	70 (12%)	
Missing data	65 (20%)	179 (31%)	
Residual tumour after surgery			< 0.001
No residue	96 (30%)	269 (46%)	
< 1 cm residue	75 (23%)	231 (40%)	
> 1 cm residue	148 (46%)	80 (14%)	
Missing data	0 (0%)	1 (< 1%)	

IQR: interquartile range.

Table 2. — *Number of patients per subgroup defined by clinical (FIGO) stage and the largest metastatic tumour size with the comparative outcome of primary surgery and neoadjuvant chemotherapy in terms of five-year survival for each subgroup.*

Subgroups	Subgroup size (%)*	5-year survival probability (%)	HR of neo-adjuvant *vs.* primary surgery (95% CI) **	*p*-value	
		Primary surgery	Neoadjuvant chemotherapy		
1 FIGO stage IIIC and largest metastatic size ≤ 45 mm	268 (30%)	42%	27%	1.51 (1.18–1.93)	0.001
2 FIGO stage IIIC and largest metastatic size > 45 mm	421 (47%)	29%	21%	1.25 (1.05–1.48)	0.011
3 FIGO stage IV and largest metastatic size ≤ 45 mm	83 (9%)	35%	17%	1.66 (1.06–2.59)	0.028
4 FIGO stage IV and largest metastatic size > 45 mm	128 (14%)	10%	17%	0.77 (0.57–1.05)	0.094

** Average size of metastatic tumour across 10 multiple imputations.*
*** p for interaction = 0.008.*

(HR 1.51, 95% CI 1.181.93, $p = 0.001$). In patients with stage IV and ≤ 45 mm there was also a benefit from primary surgery (HR 1.66, 95% CI 1.06-2.59, $p = 0.028$) and, to a lesser extent, in the subgroup of patients with stage IIIC and metastatic size > 45 mm (HR 1.25 95% CI 1.051.48, $p = 0.011$). In the subgroup of stage IV and metastatic size of > 45 mm, the effect appeared to be reversed, although the difference in survival was not significant (HR 0.77 95% CI 0.571.05 $p = 0.094$). The predicted five-year survival in this subgroup was 10% with primary surgery and 17% with NACT (Figure 3). The heterogeneity of the treatment effect across the four subgroups was statistically significant (p for interaction = 0.008). In the subgroup of patients with a large metastatic tumour who received primary surgery, no significant survival difference was observed between patients with a large metastasis within the omentum and patients with a large metastasis anywhere else in the body (HR 0.81, 95% CI 0.47–1.40, $p = 0.44$) (Figure 4). The sensitivity analysis without weighting in the 656 patients with known metastatic tumour size showed a significant benefit in the subgroup with FIGO stage IIIC and metastatic size ≤ 45 mm for primary surgery (HR 1.87, 95% CI 1.35–2.59, $p = 0.0001$) and the subgroup with FIGO IIIC and metastatic size > 45 mm (HR 1.37 95% CI 1.07–1.75, $p = 0.013$), but not for the two FIGO IV subgroups (Supplemental Figure S2).

Discussion

The aim of our study was to externally validate the treatment-selection rule by van Meurs *et al*. for selecting the type of treatment of advanced stage ovarian cancer [3]. We found that patients with FIGO stage IIIC or IV with a small metastatic tumour (≤ 45 mm), or with FIGO stage IIIC and a large metastatic tumour (> 45 mm) benefit most from primary surgery. No significant survival difference was found for patients with stage IV and a large metastatic tumour size (> 45 mm). This partly confirms the conclusions of Van Meurs *et al*. [3] and is consistent with the results of Meyer *et al*. [17]. In both of these studies, primary surgery was associated with increased survival in stage IIIC, but not for stage IV disease.

We expected that a metastasis within the omentum, which can be resected relatively easily, would have a better prognosis compared to a metastasis anywhere else in the body. However, this difference was not seen in the subgroups of patients with a large metastatic tumour. This suggests that the extent of disease may be more important for the survival prognosis than the exact localisation of the metastasis.

The strength of our study lies in the large number of included patients and the completeness and duration of follow up. In this dataset of 900 patients, only 38 patients had times censored before five years. Generalizability was increased by combining data from three large institutes. These institutes were oncological centres, so all patients were treated by experienced gynaecological oncologists.

Several limitations should also be mentioned. As with all non-randomised studies, estimates from this study may suffer from selection bias. Firstly, only patients with a primary or interval surgery were included. This means that patients were not included if they started NACT but never underwent surgery, for example because of deterioration of their physical condition due to toxicity of neoadjuvant chemotherapy or tumour growth during NACT. Secondly, there were imbalances in the baseline characteristics between the two treatment groups: the significantly lower WHO performance status in the primary surgery group could have affected survival outcome. Moreover, primary surgery was the standard treatment in the Netherlands before 2010, and interval surgery was mostly given to patients who were deemed unfit for primary surgery. After 2010, the results of the EORTC 55971 trial [5] influenced the selection for various treatment approaches, with a high rate of NACT. We attempted to correct for these imbalances

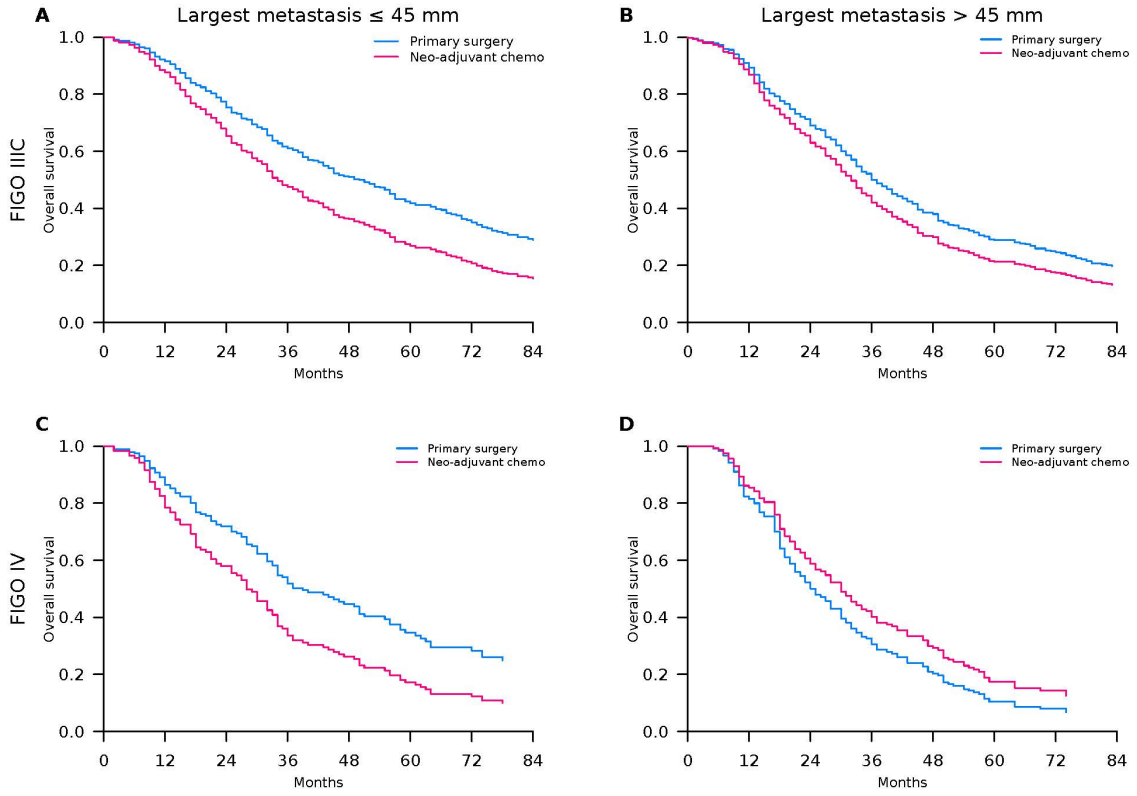

Figure 3. — Overall survival by treatment in the four biomarker subgroups. a. Subgroup of patients with FIGO stage IIIC and metastatic size $\leq$ 45 mm, HR 1.51 95% CI (1.18–1.93), p = 0.001. b. Subgroup of patients with FIGO stage IIIC and metastatic size $>$ 45 mm, HR 1.25 95% CI (1.05–1.48), p = 0.011. c. Subgroup of patients with FIGO stage IV and metastatic size $\leq$ 45 mm, HR 1.66 95% CI (1.06–2.59), p = 0.028. d. Subgroup of patients with FIGO stage IV and metastatic size $>$ 45 mm, HR 0.77 95% CI (0.57–1.05), p = 0.094. The heterogeneity of the treatment effect across the four subgroups was statistically significant (p for interaction = 0.008).

by using inverse probability of treatment weighting, where the weights were calculated using a model for the probability of getting the actual treatment. This model included baseline characteristics and the period of treatment (before 2010 or after). Despite this correction we still observed a difference between the two treatments, even though non-inferiority was demonstrated by Vergote *et al.* [5]. This may indicate that there are unknown confounding factors that we could not take into account. This emphasizes the importance of randomized clinical trials.

Another disadvantage of the retrospective data collection in this study was the missing data. For example, metastatic tumour size was missing for 244 of the 900 patients (27%). This is not surprising because usually not all localisations of metastatic disease are measured separately during surgery. Multiple imputation was used for these and other variables with missing values. In a sensitivity analysis without weighting, using only patients with known metastatic tumour size, the hazard ratios did not differ very much, but were only statistically significant in the two FIGO IIIC subgroups. But even the non-missing values of the metastatic tumour size have a degree of uncertainty, because these were based on measures as they were reported in the past, with a risk of false classification and patients being classified in the wrong subgroup. BRCA status was missing for the majority of patients and could therefore not be imputed reliably. An imbalance in BRCA status could have influenced the result of our study because of the improved OS due to sensitivity for platinum and PARP inhibition. However, it is unlikely that this would have led to the impossibility of validating the treatment model, because also in BRCA mutation carriers, tumour size of metastasis and FIGO stage are also likely to be prognostic.

Possibilities for further research include the development of various treatment-selection rules to predict residual tumour after debulking surgery, which are currently being developed and tested based on patient characteristics, laparoscopy results, imaging features, or combinations of these variables [14, 15]. For example, Rutten *et al.* [15] recommended adding an open laparoscopy to the standard diagnostic work-up, and Fagotti *et al.* [18] described an easy-to-use prediction model for laparoscopy to guide treatment. Their model calculates a score from seven laparoscopic features. Laparoscopic assessment after standard diagnostic work-up could potentially be combined with our treatment-selection rule for the subgroups with uncertain results.

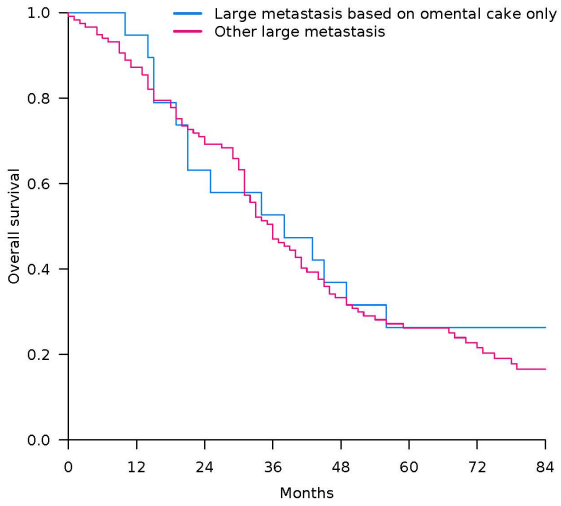

Figure 4. — Subgroup analysis in patients with a large metastatic tumour size > 45 mm who received primary surgery by whether the large metastasis was within the omentum or anywhere else in the body. HR 0.81 (0.47–1.40), $p = 0.44$.

Many prediction models are being developed, but only a few have been evaluated with external data. Consequently, there is insufficient knowledge about their performance, which may explain why many of them are not used in clinical practice [19].

Conclusions

Based on this analysis, we conclude that overall survival after primary surgery is better than after NACT followed by interval surgery in a subgroup of patients. We confirmed the treatment difference as described by Van Meurs *et al*. for patients with a small metastatic tumour size of $\leq$ 45 mm and FIGO stage IIIC or IV, and for FIGO stage IIIC with a large metastatic tumour size > 45 mm, with better survival after primary surgery. However, for patients with a large metastatic tumour size (> 45 mm) and FIGO stage IV, survival was not significantly different. Overall, the results of this external validation provide further support for the recommendations of Van Meurs *et al*. and can facilitate a more widespread use of this model for making recommendations about treatment options in women with advanced stage ovarian cancer.

Ethics approval and consent to participate

From all patients, written informed consent was provided to conduct retrospective research on clinical data. The study was conducted in accordance with the Declaration of Helsinki, due to the retrospective nature of the analyses approval by the Ethics Committee was not necessary.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://ejgo.imrpress.com/EN/10.31083/j.ejgo.2020.06.5369.

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Corresponding Author:
ROELIEN VAN DE VRIE, MSC
Department of Obstetrics and Gynaecology, Academic Medical Centre - University of Amsterdam, Meibergdreef 9, 1100 DD Amsterdam, the Netherlands, Room H4-232, PO Box 22660, Netherlands
e-mail: r.vandevrie@amsterdamumc.nl