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ORIGINAL RESEARCH ARTICLE

Residual tumor and primary debulking surgery vs interval debulking surgery in stage IV epithelial ovarian cancer

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Abstract

Introduction: It is debated whether women with FIGO (International Federation of Gynecology and Obstetrics) Stage IV epithelial ovarian cancer should be offered primary debulking surgery (PDS) or interval debulking surgery (IDS). Furthermore, the impact of complete resection of intra-abdominal disease (R0) despite their extra-abdominal metastases is questioned. The objective of this study was to investigate the impact of intra-abdominal residual tumor, Stage IVA vs IVB, the localization and number of metastases defining Stage IV disease on overall survival (OS) comparing PDS and IDS in FIGO Stage IV epithelial ovarian cancer.

Material and Methods: We included 2091 women registered with Stage IIIC–IV ovarian cancer in the Danish Gynecological Cancer Database during 2009–2016. The impact of residual tumor was evaluated using univariate and multivariate analyses.

Results: In total, 681 patients had stage IV disease, of whom 26% underwent PDS, 38% IDS, and 36% chemotherapy only. Overall survival for PDS and IDS were similar. Patients achieving R0 at PDS showed a tendency towards a higher OS than patients achieving R0 at IDS, though the difference was non-significant. In women with Stage IVA and IVB disease there was a survival benefit in achieving R0 both when treated with PDS and IDS. Women with Stage IVB disease treated with chemotherapy only had a significantly lower OS than patients achieving R0 at both PDS and IDS. Malignant pleural effusion and having five metastatic sites compared with having one was associated with a poorer OS.

Conclusions: Our study shows similar OS in patients with Stage IV disease treated with IDS compared with PDS. Complete intra-abdominal tumor resection improves the prognosis in both PDS and IDS in Stage IV ovarian cancer. Malignant pleural effusion seems to be a negative prognostic factor and should have more focus in future studies.

Abbreviations: BMI, body mass index; EOC, epithelial ovarian cancer; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; LN, lymph nodes; NA, missing values; NACT, neoadjuvant chemotherapy; OS, overall survival; PDS, primary debulking surgery; PS, performance status; R0, no residual tumor; RD, residual tumor.

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KEYWORDS
gynecological oncology, malignant pleural exudate, ovarian cancer, residual tumor

1 | INTRODUCTION

Epithelial ovarian cancer (EOC) is the primary cause of death from gynecological malignancies in Denmark with approximately 450 new cases annually.[1] Worldwide, ovarian cancer accounts for 3.4% of cancers associated with women with nearly 314 000 new cases in 2020.[2] Women with ovarian cancer often experience few or diffuse symptoms, and approximately 70% present with advanced stages—FIGO (International Federation of Gynecology and Obstetrics) Stage III–IV—at time of diagnosis.[3] The current standard treatment is primary debulking surgery (PDS) followed by six courses of platinum-based chemotherapy. Intra-abdominal complete tumor resection (R0) is associated with a benefit in overall survival (OS) and is considered a key part in the management of EOC.[4,5] Choice of treatment course is decided at a multidisciplinary conference based on performance status (PS), age, resectability, location of metastases using imaging (CT, positron emission tomography [PET]-CT and MRI), and/or a diagnostic laparoscopic procedure. Women are referred to neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS), when R0 is considered unachievable because of tumor location and patient's health conditions or because of high-volume Stage IV disease.

There is an ongoing debate whether women with Stage IV disease should be offered PDS or IDS, and if they benefit from achieving intra-abdominal R0 despite their extra-abdominal metastases. Several studies have shown an increase in OS when achieving R0 after PDS in Stage IV EOC.[6–8] However, similar OS has been observed when randomizing EOC groups for PDS followed by chemotherapy or IDS in Stage IIIC–IV EOC.[9] Large prospective population-based studies comparing PDS and IDS in Stage IV are missing.

The objective of this nationwide study was to investigate the impact of residual tumor diameter in Stage IV EOC comparing PDS and IDS. The secondary objective was to determine the impact of Stage IVA and IVB and the localization and number of Stage IV metastases on OS. Furthermore, to examine the impact on OS when obtaining complete response on extra-abdominal metastases after NACT in patients undergoing IDS.

Key message

Complete intra-abdominal tumor resection improves the prognosis in Stage IV ovarian cancer patients treated with either primary debulking surgery or interval debulking surgery. Malignant pleural effusion was an indicator of poor overall survival in Stage IV ovarian cancer.

2 | MATERIAL AND METHODS

Women were identified through the Danish Gynecological Cancer Database, a national clinical database containing prospectively collected data on all Danish gynecological cancer patients since January 2005 with a coverage of 97%.[3] Each woman was identified and linked to the Danish Cause of Death Register and the Danish National Patient Register through a unique 10-digit number given to all Danish citizens making it possible to obtain data regarding survival and ensuring lifelong follow up.

We included 681 patients with Stage IV EOC and 1410 patients with Stage IIIC EOC from January 1, 2009 to June 30, 2016, (Figure S1). Follow up was from the date of the first visit with a specialist in gynecological oncology in the hospital to the date of death or last follow-up date November 9, 2019.

Stage IV was defined as: distant metastases, divided into: IVA—pleural effusion with positive cytology, IVB—parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes [LN] and LN outside the abdominal cavity), cytologically and/or histologically verified, and diagnosed by imaging alone. Data regarding Stage IVA and IVB, localization of metastases, method of diagnosis, and possible reason for refraining from surgery were obtained or validated through patient records.

According to histology, tumors were divided into four categories: type I (low-grade serous, mucinous, endometrioid and clear cell), type II (high-grade serous and carcinosarcoma), "serous not graded", and "other epithelial" (malignant Brenner tumor, undifferentiated carcinoma, adenosquamous adenocarcinoma, non-specified adenocarcinoma, seromucinous adenocarcinoma, and planocellular carcinoma).

The exposure variables were defined as:

Residual tumor: Defined as all macroscopically visible intra-abdominal residual tumor and divided into: (1) R0 (complete intra-abdominal tumor resection), (2) R≤1 (residual tumor >0 and ≤1 cm), (3) R>1 (residual tumor >1 cm), and (4) data not available (NA).

Localization of metastases: Localization of Stage IV metastases were divided into: (1) liver or other organ parenchyma or transmural involvement of the intestines, (2) inguinal, cervical, clavicular, or axillary LN, (3) pleura or lung parenchyma, (4) mediastinal LN, (5) other (bone, umbilical, cutaneous, or abdominal wall, including port-site metastases), and (6) data on localization not available (NA). Each patient could occur within multiple groups.

Number of metastatic sites: Stage IV metastases were divided into six groups according to the number of sites.

Association between clinicopathological parameters and residual tumor were assessed using chi-squared or Kruskal-Wallis tests. Missing values (NA) were not included in the analyses. Survival analyses were performed using Kaplan-Meier method or Cox proportional hazard models. Overall survival was calculated from the date of initial examination to the date of last follow up. SPSS statistical software was used (version 25 SPSS Inc.).

2.1 | Ethical approval

Ethical approval was not required for this registry-based study, according to Danish law.[30] The project was approved by the Data Protection Agency in the Capital Region of Denmark (jr. nr.2012–58–0004).

3 | RESULTS

We included 2091 women of whom 681 (32.6%) presented with Stage IV EOC. The distribution was: Stage IVA: 70 women (10.3%), Stage IVB: 561 women (82.4%), and unspecified Stage IV: 50 women (7.3%).

Stage IV was more comorbid (American Society of Anesthesiologists score and PS were inferior), compared with stage IIIC. Stage IVA had a lower ascites volume and tumor grade compared with IVB. Clinicopathological characteristics were similar with regards to age, body mass index, smoking status, and comorbidities between stages (Table S1).

The proportions of women treated with surgery were: Stage IIIC: 83.0%, Stage IVA: 57.1%, and Stage IVB: 65.8%, (Table 1). Among women selected for surgery, 62.7%, 45%, and 39.6% underwent PDS, whereas the remainder underwent IDS in Stages IIIC, IVA, and IVB, respectively. Residual tumor size was similar between stages in subgroup analyses including women treated with PDS or IDS, also when excluding Stage IVA (Table 1). Extra-abdominal metastases were removed in a negligible proportion of cases (data unpublished).

Univariate analyses showed similar OS in PDS and IDS in Stage IV EOC (PDS: 31.2 months, 95% CI 24.3–38.0 months, IDS: 32.3 months, 95% CI 28.9–35.7 months). However, OS tended to be highest in IDS, where OS was lower than 30 months, whereas OS tended to be highest in PDS, where OS was higher than 30 months, although the difference was not significant (log-rank p=0.13), (Figure 1). In Stage IVA, OS was similar between patients achieving R0 at PDS (24.0 months, 95% CI 20.5–27.4 months) and IDS (28.9 months, 95% CI 13.2–44.6 months) in univariate analyses. In Stage IVB, patients achieving R0 at PDS showed a tendency towards a higher OS (45.7 months, 95% CI 26.8–64.6 months) when compared with patients achieving R0 at IDS (35.9 months, 95% CI 31.4–40.5 months). However, the difference was non-significant (Table 2).

In Stage IVB IDS, R0 was associated with longer OS (35.9 months, 95% CI 31.4–40.5 months) compared with R>1 (OS 20.3 months, 95% CI 16.0–24.6 months). Women with Stage IVB disease treated with chemotherapy only had an OS of 12.1 months (95% CI 10.1–14.0 months), which is significantly lower than women undergoing both PDS and IDS and achieving R0 (Table 2 and Figure 2).

In Stage IVA, OS was similar between women achieving R0 and R≤1 at IDS; however, the analyses lacked power (Table 2).

TABLE 1 Surgical outcome according to FIGO stage in patients with FIGO Stage IIIC–IV epithelial ovarian cancer in Denmark in 2009–2016, N = 1606

	FIGO stage				
	IIIC (n = 1170)	IVA (n = 40)	IVB (n = 369)	IV unspecified (n = 27)	p value*
PDS					
Total n	734	18	146	12	
Residual tumor (cm)					
0	456 (62.1)	9 (50.0)	102 (69.9)	2 (16.7)	
≤1	123 (16.8)	1 (5.6)	11 (7.5)	4 (33.3)	0.17
>1	155 (21.1)	8 (44.4)	33 (22.6)	6 (50.0)	
IDS					
Total n	436	22	223	15	
Residual tumor (cm)					
0	260 (59.6)	14 (63.6)	145 (65.0)	12 (80.0)	
≤1	72 (16.5)	6 (27.3)	44 (19.7)	1 (6.7)	0.14
>1	104 (23.9)	2 (9.1)	34 (15.2)	2 (13.3)	

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; PDS, primary debulking surgery.

*Value of p comparing FIGO stage and residual disease size.

In multivariate analyses OS was similar in Stage IV with R0 after IDS compared with Stage IV with R0 after PDS (hazard ratio [HR] 1.36, 95% CI 0.91–2.02; data not shown). A benefit in OS was found in Stage IV with R0 compared with R≤1 and R>1 in both PDS ($HR_{R\leq1}$ 2.89, 95% CI 1.50–5.57, and $HR_{R>1}$ 1.74, 95% CI 1.11–2.71) and IDS ($HR_{R\leq1}$ 1.56, 95% CI 1.08–2.25, and $HR_{R>1}$ 2.18, 95% CI 1.43–3.33) (Table 3).

A poorer OS was found in women with Stage IV IDS with malignant pleural effusion at time of diagnosis compared with Stage IV IDS without pleural effusion (HR 1.63, 95% CI 1.15–2.32). In women with no surgery, a poorer OS was found in women with PS2 and PS3–4 compared with PS0 (HR_{PS2} 1.80, 95% CI 1.20–2.70, and HR_{PS3-4} 3.15, 95% CI 2.02–4.93), and in women with metastases in the pleura or lung parenchyma compared with having none in this location (HR 1.59, 95% CI 1.10–2.29). Multivariate analyses were adjusted for age, PS, histology, ascites, localization of Stage IV metastases, IVA vs IVB and residual tumor (in operated patients) (Table 3).

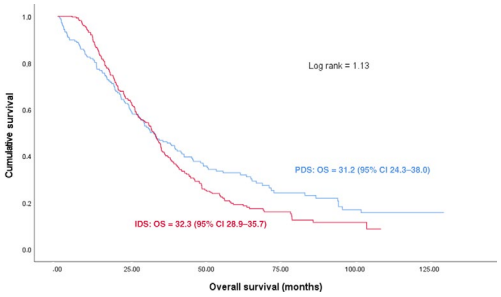

FIGURE 1 Kaplan-Meier plot on overall survival comparing primary debulking surgery (PDS) and interval debulking surgery (IDS) in patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark

The impacts of location and number of Stage IV metastases on OS were investigated in sub-analyses. Having five metastatic sites was associated with a lower OS compared with having one (HR 3.59, 95% CI 1.69–7.64) in univariate analyses (Table 4, Figure 3). We found a decrease in OS with an increasing number of sites (log-rank $P = 0.00$). Both malignant pleural effusion (HR 1.57, 95% CI 1.35–1.84)) and "other" metastases (bone, umbilical, cutaneous, or abdominal wall) (HR 1.51, 95% CI 1.12–2.03) were associated with a lower OS compared with having no/none in this location when adjusted for the remaining locations (Table 4).

Stage IV with full response on extra-abdominal tumor after NACT (evaluated by CT) had an OS of 35.0 months (95% CI 28.2–41.8 months), whereas women with partial/no response had an OS of 31.5 months (95% CI 25.7–37.4 months, log rank-$P = 0.15$) (Figure 4).

Furthermore, we investigated how Stage IV was diagnosed, and why patients with Stage IV disease were omitted from surgery.

In Stage IVB, 58.1% of stage IV metastases were confirmed by histology and/or cytology, while 40.8% were based on imaging. In

TABLE 2 Univariate analyses using the Kaplan-Meier method exploring the impact of surgical outcome on overall survival according to PDS vs IDS in FIGO-stage IV epithelial ovarian cancer during 2009–2016 in Denmark

	FIGO stage								
	IVA			IVB			IV unspecified		
		Overall survival			Overall survival			Overall survival	
	n (%)	Median[a] (months)	95% CI	*n* (%)	Median[a] (months)	95% CI	*n* (%)	Median[a] (months)	95% CI
PDS									
Residual tumor (cm)									
0	9 (50.0)	24.0	20.5–27.4	102 (69.9)	45.7	26.8–64.6	2 (16.7)	1.9	[b]
≤1	1 (5.6)	55.6	[c]	11 (7.5)	19.2	7.5–30.9	4 (33.3)	9.7	0.0–1.9
>1	8 (44.4)	13.2	0.0–42.1	33 (22.6)	27.1	15.9–38.2	6 (50.0)	15.1	4.5–25.6
IDS									
Residual tumor, (cm)									
0	(63.6)	28.9	13.2–44.6	145 (65.0)	35.9	31.4–40.5	(80.0)	24.5	4.1–44.9
≤1	6 (27.3)	29.2	9.1–49.4	44 (19.7)	27.1	20.8–33.4	1 (6.7)	15.7	[b]
>1	2 (9.1)	9.3	[b]	34 (15.3)	20.3	16.0–24.6	2 (13.3)	10.3	[b]

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; IDS, interval debulking surgery; PDS, primary debulking surgery.

[a]Cumulative median.

[b]Two patients or fewer.

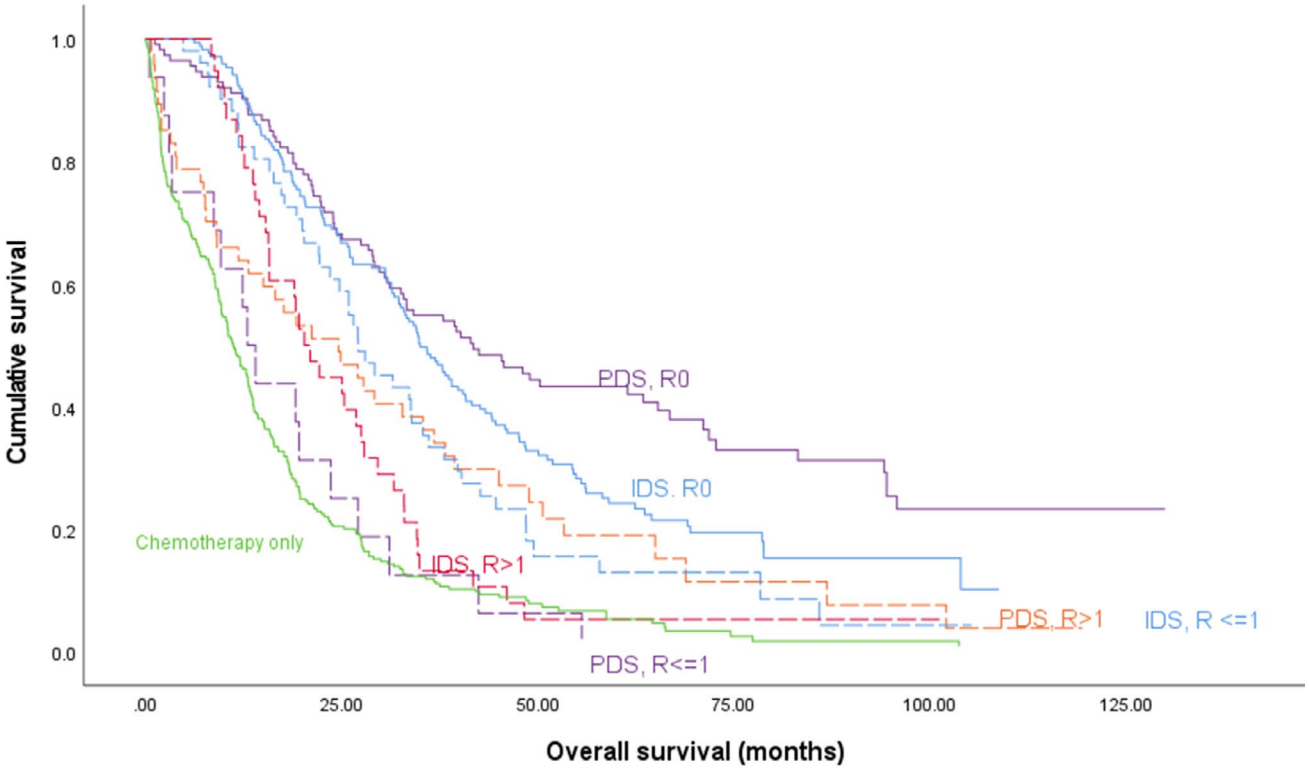

FIGURE 2 Kaplan-Meier plot on overall survival distributed to residual tumor in cm in patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark. Comparing overall survival between primary debulking surgery (PDS) and interval debulking surgery (IDS) distributed to residual tumor and no surgery in Stage IV epithelial ovarian cancer

stage IVA, 100% was confirmed by cytology. In univariate analyses, OS were similar in women with pathology-confirmed stage IVB, and in women whose stage was based on imaging (Table S2).

In stage IVA (n = 30) the main reasons for refraining from surgery were unresectable intra-abdominal tumor (30.0%) and patient condition (33.3%), (including body mass index, PS, age, and comorbidities). In Stage IVB (n = 192) the main reasons were unresectable intra-abdominal tumor evaluated primarily (31.8%) and after NACT (35.9%) (Table S3).

4 | DISCUSSION

The non-inferiority of IDS compared with PDS in the treatment of advanced EOC has been reported in three randomized trials.[9–11] However, few studies have investigated OS exclusively among women with stage IV comparing PDS with IDS.[12,13] This nationwide study is to our knowledge the largest study analyzing prospectively collected data comparing the OS between PDS and IDS according to residual tumor in Stage IV EOC.

In univariate and multivariate analyses, we found a tendency towards a higher OS in patients with Stage IV disease, achieving R0 at PDS compared with IDS, though the difference was non-significant.

Only one previous study investigated the impact of R0 in PDS vs IDS among patients with Stage IV disease, exclusively. Rauh-Hain et al found a superior OS among women who achieved R0 after PDS compared with IDS ($OS_{PDS,R0}$ 72 months and $OS_{IDS,R0}$ 31 months),[13] which is an approximately four times greater survival benefit than observed in the present study. The selection of treatment-modality and the surgical strategy were different to those of the present study, as a larger proportion of patients underwent PDS (73%) and the proportion of women achieving R0 was lower in both PDS and IDS in the study by Rauh-Hain et al.[13] As the selection of patients for surgery affects the R0 rate, the proportion of women referred to PDS and IDS as well as chemotherapy only are important factors to consider when evaluating the impact of R0 on survival. This may explain the observed differences in OS between the studies.

Another important factor is the Stage IIIC/IV ratio. In the present study, the ratio was 2.1 (all women, including no surgery). In comparison, a US study reported a ratio of 4.1.[14] The difference may be due to the routine use of PET/CT in Denmark[15] resulting in upstaging of Stage IIIC. According to the FIGO classification, Stages IVA and IVB must be confirmed pathologically. In Denmark, clinical practice does not allow biopsies with the sole purpose of academic staging, and biopsies are only indicated if the treatment plan relies upon it. Although this upstaging may not occur in other countries, the Stage IIIC/IV ratio in women who underwent surgery is similar to those found in other studies (2.7–3.1),[9,10] and OS was similar in pathologically confirmed Stage IVB, and Stage IVB based on imaging alone, thus supporting the

TABLE 3 Multivariate Cox regression with overall survival as end point. Analyses including patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark

	PDS (n = 176)		IDS (n = 260)		Chemotherapy only (n = 245)	
	HR	95% CI	HR	95% CI	HR	95% CI
Residual tumor size (cm)						
0[a]	1	–	1	–	–	–
≤1	2.89	1.50–5.57	1.56	1.08–2.25	–	–
>1	1.74	1.11–2.71	2.18	1.43–3.33	–	–
Age (years)						
≤60[a]	1	–	1	–	1	–
>60 and <75	1.13	0.74–2.10	1.50	1.08–2.09	1.34	0.88–2.04
≥75	1.50	0.96–2.35	1.58	0.95–2.63	1.39	0.90–2.15
Performance status						
0[a]	1	–	1	–	1	–
1	1.13	0.73–1.74	1.17	0.85–1.60	1.34	0.92–1.95
2	1.08	0.51–2.30	1.57	0.97–2.53	1.80	1.20–2.70
3–4	2.67	1.16–6.12	1.97	0.73–5.34	3.15	2.02–4.93
NA	0.00	-	0.92	0.21–4.07	4.03	1.71–9.52
Histology						
Type I tumors[a,b]	1	–	1	–	1	–
Type II tumors[c]	0.48	0.30–0.79	1.28	0.58–2.80	0.83	0.50–1.40
Serous, not graded[d]	0.55	0.18–1.66	1.28	0.59–2.77	1.24	0.76–2.01
Other epithelial	1.99	0.62–6.46	1.18	0.28–4.95	0.66	0.35–1.26
Ascites						
0 ml[a]	1	–	1	–	1	–
<500 ml	1.02	0.62–1.68	1.11	0.75–1.66	1.12	0.67–1.87
>500 ml	1.24	0.74–2.06	1.70	1.14–2.55	1.42	0.92–2.19
NA	0.89	0.28–2.84	1.26	0.79–2.01	0.96	0.65–1.41
Localization of tumor defining Stage IV[e]						
Liver and other organ parenchyma, and transmural involvement of the intestines	1.48	0.78–2.79	1.12	0.74–1.65	0.96	0.61–1.52
Lymph nodes outside the abdomen	1.18	0.61–2.26	1.07	0.77–1.48	1.00	0.72–1.38
Pleura or lung parenchyma	1.21	0.58–2.54	0.81	0.54–1.22	1.59	1.10–2.29
Mediastinal lymph nodes	1.34	0.75–2.42	0.78	0.56–1.10	1.33	0.97–1.84
Others (bone, umbilical, cutaneous and abdominal wall)	1.06	0.48–2.34	1.95	0.99–3.84	1.36	0.85–2.16
Malignant pleural effusion	1.46	0.74–2.90	1.63	1.15–2.32	0.97	0.66–1.42
FIGO stage IVA vs IVB						
Stage IVA[a]	1	–	1	–	1	–
Stage IVB	1.22	0.44–3.40	1.48	0.80–2.74	0.76	0.44–1.32
Stage IV unspecified	2.36	0.85–6.58	1.30	0.59–2.86	0.89	0.43–1.83

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IDS, interval debulking surgery; PDS, primary debulking surgery; RD, residual disease.

[a]Reference group.

[b]Consisting of low-grade serous, mucinous, endometrioid, and clear cell.

[c]Consisting of high-grade serous and carcinosarcoma.

[d]It is our experience that the group of not graded serous tumors are in fact high-grade serous in close to all cases.

[e]Reference is having no metastases in the specific location.

TABLE 4 Cox regression exploring impact of number of metastatic sites and localization of metastases defining Stage IV disease on overall survival in patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark ($n = 681$)

	n (%)	HR	95% CI
Number of metastatic sites[a,d]			
1[c]	346 (50.8)	–	–
2	190 (27.9)	1.09	0.90–1.32
3	58 (8.5)	1.33	1.00–1.78
4	22 (3.3)	1.52	0.96–2.39
5	7 (1.0)	3.59	1.69–7.64
NA	58 (8.5)	1.51	1.12–2.04
Localization of metastases defining stage IV[b]			
Liver or other organ parenchyma, and transmural involvement of the intestines	131 (19.2)	1.10	0.90–1.33
Lymph nodes outside the abdomen)	200 (29.4)	1.11	0.94–1.31
Metastases in the pleura or lung parenchyma	114 (16.7)	1.15	0.93–1.43
Mediastinal lymph node metastases	267 (39.2)	1.10	0.94–1.29
Others (bone, umbilical, cutaneous, and abdominal wall metastases)	52 (7.6)	1.51	1.12–2.03
Malignant pleural effusion	212 (31.1)	1.57	1.35–1.84

Abbreviations: CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio.

[a]Univariate Cox regression.

[b]Multivariate Cox regression with the different locations as covariates. Each patient can occur within multiple covariates. Reference is no metastases in the particular location.

[c]Reference group.

[d]We performed a log rank test for increasing number of sites, log rank: $p = 0.00$.

finding that women with Stage IVB were staged correctly in most cases.

In the study by Rauh-Hain et al,[13] only 18% were referred to IDS and 9% to chemotherapy only. Clinical practice today aims to only refer patients to PDS when R0 is expected. Therefore, the larger percentage of women not selected for surgery in our study (38%) is in line with international guidelines today.

In our study, women selected for IDS had a higher number of Stage IV metastatic sites than women selected for PDS. Despite this, we found a similar OS between PDS and IDS, which in our opinion confirms that the two surgical strategies may be equal. Indeed, a meta-analysis based on two randomized clinical trials, concluded that stage IV had better progression-free survival and OS (HR 0.76, 95% CI [0.58–1.00]) with NACT (including both chemotherapy only and NACT-IDS) compared with PDS.[12] However, no stratification according to residual tumor was performed. It should be noted that the trials were criticized for their low proportion of R0. The conclusions drawn were that IDS is superior to PDS in Stage IV EOC if the surgeon is not specialized within gynecological oncology.

Our results suggest that OS in Stage IV IDS and PDS is similar, though patients who achieve R0 at PDS may have a survival benefit. Hence, if the surgeons are not confident that R0 can be achieved, standard treatment for Stage IV may be IDS if a good response to chemotherapy is expected,[16–18] because IDS is associated with a reduction in surgical invasiveness and postoperative complication rates.[10,11,19] However, selecting the right Stage IV patients for IDS is a great challenge because studies report that approximately 10% of women selected for NACT never receive surgery.[9,13] One persistent argument against routine use of NACT as first-line treatment has been the risk of an increased risk of chemoresistance. However, results are conflicting.[20–22]

When investigating OS in Stage IV PDS, we discovered a higher OS in patients with residual tumor (RD) >1 cm compared with RD ≤1 cm, though the difference was non-significant. Our data showed a larger percentage of patients who died shortly after surgery in the small group of patients with RD ≤1 cm. In contrast, the proportion of long-term survivors was higher in the group of patients with RD >1 cm. This may possibly explain the different estimates.

In addition to residual tumor we investigated the impact of location and number of metastatic sites on OS. In line with other studies, we found malignant pleural effusion to be a negative prognostic factor.[23,24] The poorer prognosis associated with pleural effusions could be due to a poorer PS at the time of diagnosis in patients with malignant pleural effusion, and association between pleural effusions and more aggressive disease or undetected intrathoracic disease.

Association between tumor burden in the upper abdomen and metastases in cardiophrenic LN are shown in several studies. Laasik et al found that the supradiaphragmatic LN became inactive during primary chemotherapy more often in the RECIST responders compared with non-responders (HR 1.46, 95% CI 1.09–1–96).[25] Luger et al found that cardiophrenic LN <5 mm combined with ascites volume <500 ml, and CA 125 levels <500 U/mL at baseline, predicted R0 in 100% of patients.[26] Unfortunately, we did not discriminate between cardiophrenic LN and other mediastinal LN. In Danish clinical practice, patients with unresectable extra-abdominal LN >1 cm on CT scans are referred to IDS.

In our study, we found a poorer OS in Stage IV patients with five metastatic sites compared with having one. This is in line with Wimberger et al who found that multiple sites of distant metastases

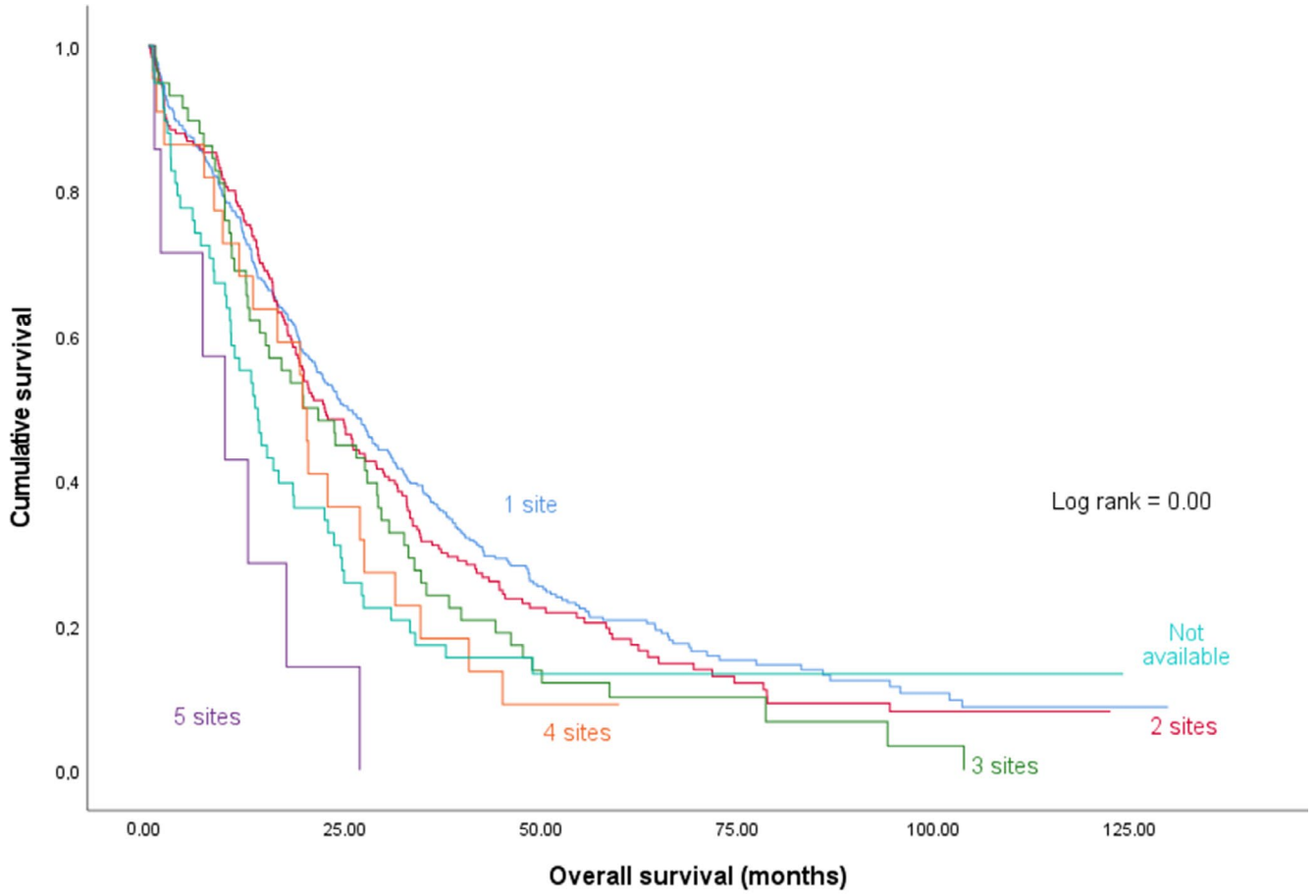

FIGURE 3 Kaplan-Meier plot on overall survival distributed to number of FIGO Stage IV defining metastatic sites in patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark

showed a reduced OS compared with single-site metastases (OS 26.8 months vs 20.2 months $p = 0.009$) in Stage IV PDS.

In our study, a negligible proportion of cases had extra-abdominal metastases removed. At present, some institutions remove extra-abdominal metastases in the belief that this will improve prognosis. If this is the case, and extra-abdominal metastases had been removed in our study population, we would expect a better OS in Stage IVB.

During the 7-year study period, diagnostics and surgical strategy may have changed. In 2009, new guidelines in ovarian cancer treatment in Denmark led to a more radical approach to gynecological cancer surgery. Therefore, the study period was restricted to 2009 and onwards. However, the surgical effort to reduce tumor volume may have increased during the study period, as surgeons specialized in gynecological oncology in Denmark have improved their surgical skills during this period. Regarding diagnostics, the percentage of patients who had a PET-CT performed ranged from approximately 80% to 90% per year from 2013 and onwards, where data were available (data unpublished).

The present study has several strengths. Data are nationwide and represent an unselected population of women with ovarian cancer. In Denmark, the treatment of EOC is centralized to a few high-volume centers performing diagnostics and treatment conforming to the existing national guidelines.[27] On average, each center performed approximately 40 surgeries on patients with advanced ovarian cancer per year during the study period.[3] Furthermore, data on the diagnosis and spread of disease in Stage IV were validated through patient journals and the survival analyses are based on a life-long register-based follow up with a coverage of approximately 99.5%.[28]

The main weaknesses of the present study were as follows. Incomplete registration of variables from the Danish Gynecological Cancer Database may occur. As registration in the database is prospectively collected, it is not likely to result in registration bias. Pathological re-evaluation has not been performed. However, the initial pathological diagnosis and staging were performed by pathologists experienced within gynecological oncology. Registration of histological grade is lower in non-operated than in operated patients. Pathologists may have had difficulties grading smaller biopsies and cytology, which would often be the available biological material from non-operated patients. Our study lacks data regarding chemotherapy, including response evaluated by RECIST criteria during oncological treatment; however, the standard treatment of advanced EOC in Denmark during the study period was adjuvant treatment after PDS, and NACT before IDS using a combination of

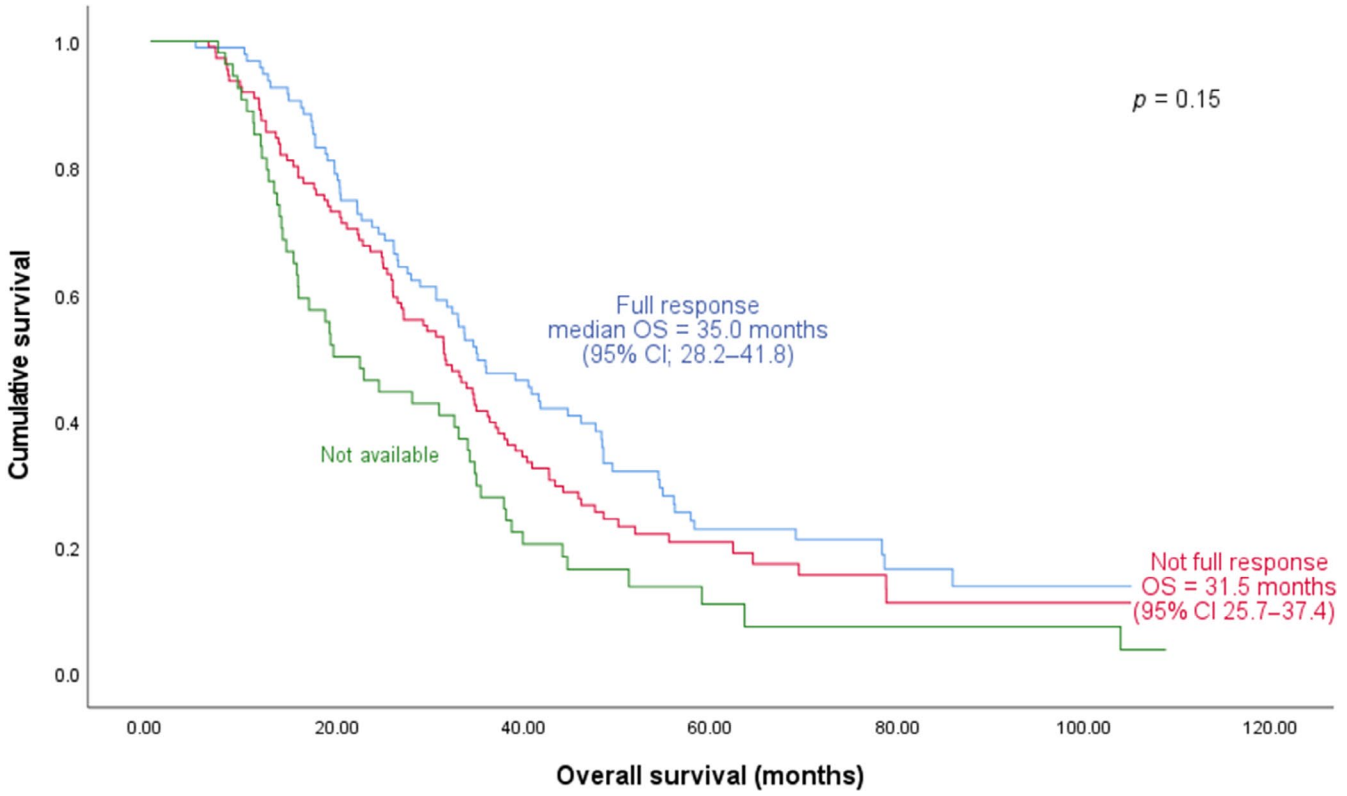

FIGURE 4 Kaplan-Meier plot on overall survival exploring full response* vs not full response to chemotherapy before interval debulking surgery (IDS) in patients with FIGO Stage IV epithelial ovarian cancer during 2009–2016 in Denmark

taxane and platinum-based chemotherapy. Since 2013, all women with residual tumor or Stage IV (including IVA) disease have been offered additional treatment with bevacizumab during and in addition to standard chemotherapy and as maintenance.[29] Finally, results regarding Stage IVA should be interpreted with caution, because these analyses lack power.

5 | CONCLUSION

Our study confirms similar OS in patients with Stage IV EOS treated with IDS compared with PDS, although patients achieving R0 at PDS showed a tendency towards a higher survival than patients achieving R0 at IDS. Achieving R0 is crucial in improving the prognosis in both PDS and IDS. Malignant pleural effusion at time of diagnosis seems to be a negative prognostic factor and should have more focus in future studies.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

SMS: conceptualization; data curation; investigation; formal analysis; project administration; funding acquisition. CH: conceptualization; validation; supervision. BJM: conceptualization; validation. MIRD, MPJ and KF: investigation; validation. THS: conceptualization; investigation; validation. SMS, CH, and THS: writing—original draft. BJM, MIRD, MPJ, and KF: writing—review and editing.

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SUPPORTING INFORMATION

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