Treatment and outcomes of a Danish ovarian cancer population

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ABSTRACT

INTRODUCTION: Ovarian cancer has the highest mortality rate among gynaecological cancers and is the tenth most frequent cancer among women. 80% of patients with advanced stage disease will experience a progression either during or after treatment.

METHODS: This was a retrospective, observational study of all women referred to adjuvant or neoadjuvant treatment for ovarian cancer between 1 June 2013 and 31 May 2014 at two university hospitals in Denmark.

RESULTS: We included 142 women diagnosed with ovarian cancer. The median overall survival from diagnosis was 48.5 months (95% confidence interval (CI): 36.6-57.9 months). Median survival after the first, second, third, fourth and fifth progression was 19.3 (95% CI: 13.9-27-3), 11.4 (95% CI: 7.7-18.8), 9.5 (95% CI: 6.3-12.7), 8.3 (95% CI: 7.6-11.5) and 5.6 (95% CI: 2.9-not assessed) months, respectively. Median progression-free survival from diagnosis was 15.6 months (95% CI: 14.3-18.4 months). Median progression-free survival after first, second, third, fourth and fifth progression was 9.2 (95% CI: 7.7-10.6), 6.0 (95% CI: 3.5-7.7), 3.3 (95% CI: 2.6-4.6), 4.9 (95% CI: 3.6-8.3) and 3.0 (95% CI: 2.4-5.7) months, respectively. The most frequently used treatment at first progression was carboplatin and pegylated liposomal doxorubicin (n = 37). The most used non-platinum containing treatment at progression was pegylated liposomal doxorubicin (n = 26) followed by paclitaxel (n = 23).

CONCLUSIONS: Ovarian cancer remains a highly aggressive disease with most patients diagnosed in advanced stages. Treatment has not changed much in the past 15 years and the same is evident for the overall survival.

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TRIAL REGISTRATION: not relevant.

Epithelial ovarian cancer (OC) has the highest mortality among gynaecological cancers and is the tenth-most frequent cancer among women [1-3]. Annually, 550 women are diagnosed with OC in Denmark. Unfortunately, most women are diagnosed with late stages of OC with 75% presenting with advanced (stage III or IV) disease [4]. The treatment of OC is based on surgery, where complete resection of the tumour is a major prognostic factor, only surpassed by the FIGO stage [5]. Complete resection is possible in 70% of patients either as primary debulking surgery (PDS) or as interval debulking surgery (IDS). The adjuvant or neoadjuvant treatment of OC is a platinum-based therapy (carboplatin or cisplatin) combined with a taxane [4, 6]. Despite adequate surgery and chemotherapy, more than 80% of patients with stage III-IV disease will relapse either during or after adjuvant therapy [7].

For recurrent ovarian cancer (ROC), the platinum-free interval (PFI) is important in the selection of further treatment. A PFI of less than six months indicates platinum-resistant OC, and a PFI of more than six months indicates platinum-sensitive OC. Platinum-sensitive patients are retreated with a platinum-containing regime [8]. At some point, the patients will progress less than six months after a platinum-containing treatment and are thus considered platinum-resistant. At this point, patients will typically be treated with single-agent pegylated liposomal doxorubicin (PLD), paclitaxel or gemcitabine. Chemotherapy is often accompanied by a decreased quality of life, and it is therefore important to consider the benefit of multiple treatment lines for ROC.

Our primary objectives were to investigate survival outcomes after each progression among women diagnosed with OC in a non-selected patient group from two university hospitals in Denmark and to examine treatment choices and patterns among this population.

METHODS

Study design

The study was done as an observational retrospective trial involving Herlev Hospital and Rigshospitalet. All patients referred for adjuvant or neoadjuvant treatment for a biopsy or cytology-verified ovarian, tubal or peritoneal cancer between 1 June 2013 and 31 May 2014 were included. The patients were identified using the hospitals' electronic chemotherapy ordering systems. Follow-up ran until 1 December 2018. There were no exclusion criteria other than those mentioned above. A total of 142 patients with OC were enrolled in the study.

The following data were retrieved by chart reviews: baseline data (birth date, date of diagnosis, performance status, cancer antigen (CA)-125, BRCA status, comorbidities, other malignancies, neoadjuvant chemotherapy (Y/N), operation (Y/N), operation date,

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TABLE 1 /
Patient characteristics (N = 142, median age 65.0 years (range: 36.7-93.5 years)).

	n (%)
Stage	
IA	6 (4)
IB	1 (1)
IC	16 (11)
IIA	5 (3)
IIB	8 (6)
IIIA	4 (3)
IIIB	6 (4)
IIIC	42 (30)
IVA	8 (6)
IVB	46 (32)
ECOG performance status at start of 1st treatment	
0	61 (43)
1	27 (19)
2	13 (9)
3	4 (3)
Unknown	37 (26)
Histology	
Serous adenocarcinoma	55 (39)
High-grade serous	37 (26)
Low-grade serous	10 (7)
Clear cell	7 (5)
Mucinous	6 (4)
Endometroid	10 (7)
Carcinosarcoma	5 (3)
Carcinoma not otherwise specified	10 (7)
Unknown	1 (1)
Other	1 (1)
Neoadjuvant chemotherapy	
Yes	71 (50)
No	71 (50)
Operation, both PDS and IDS	
Yes	107 (75)
No	35 (25)
Operation result	
0 mm	82 (77)
0-10 mm	10 (9)
〉10 mm	15 (14)
Treatment, adjuvant or neoadjuvant	
Carboplatin-paclitaxel	45 (32)
Carboplatin-docetaxel	54 (38)
Carboplatin-paclitaxel-bevacizumab	9 (6)
Carboplatin-docetaxel-bevacizumab	11 (8)
Carboplatin-doxorubicin	2 (1)
Carboplatin	15 (10)
Trinova3: carboplatin, paclitaxel, AMG/placebo	5 (4)
None	1 (1)

ECOG = Eastern Cooperative Oncology Group;
IDS = interval debulking surgery; PDS = primary debulking surgery.

operation result, pathology, stage, dead (Y/N), death date and cause of death. For each line of treatment: start date, performance status, CA-125, treatment, treatment cycles, end date, end CA-125, progression (Y/N), if yes; new line/observation/palliation, operation for progression (Y/N), radiotherapy (Y/N).

Statistical analyses

Survival probabilities were done according to the Kaplan-Meier method [9]. Overall survival (OS) was calculated from diagnosis to death of any cause. Survival after each progression was calculated from the date of progression to death of any cause.

Progression-free survival (PFS) time was from date of diagnosis to either first progression or death – whichever occurred first. PFS after each progression was calculated from the date of progression to the next progression or death of any cause.

Follow up was until 1 December 2018. Censoring was done based on the date of the last entry to the patient's chart by a health professional.

PFI was calculated as the date of last infusion of a platinum-containing regime to date of progression.

All statistical analyses were done using RStudio version 1.0.153 (RStudio, Inc., Boston, MA).

Ethical approval

The study was approved by the Danish Patient Safety Authority (ID: 3-3013-2444-1) and the Danish Data Protection Agency (I-suite no.: 6506 and r. no.: VD-2018-267).

Trial registration: not relevant.

RESULTS

Demographics

A total of 142 women with OC were included. The patient characteristics are given in **Table 1**. 75% were diagnosed with stage III-IV disease.

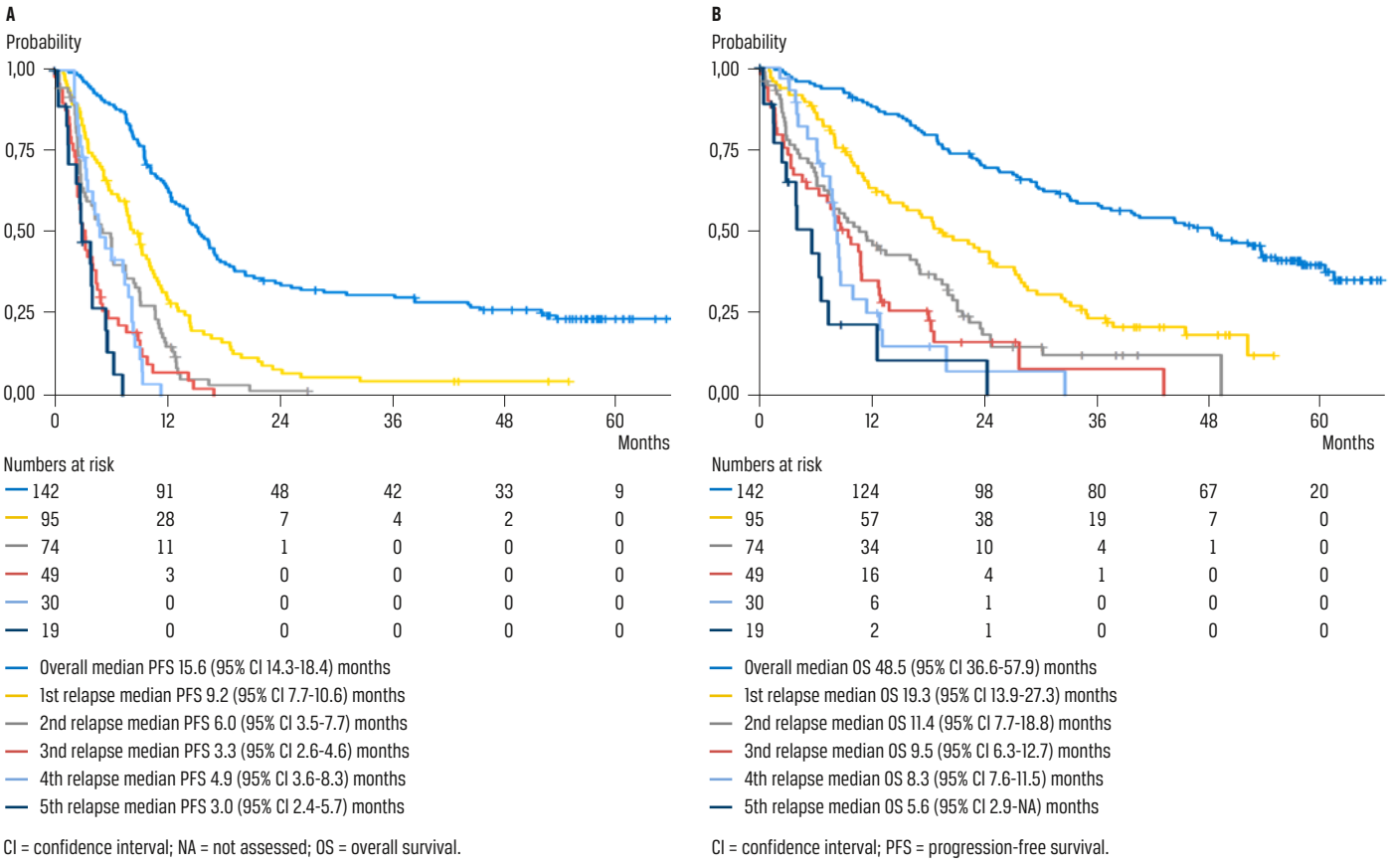
50% of the patients received neoadjuvant treatment. All patients were stage IIIC-IVB except one stage IIB (due to comorbidities). Only 37 patients (52%) assigned to neoadjuvant chemotherapy underwent IDS. Of the 34 patients who did not undergo surgery, 17 (24%) either progressed or did not respond to treatment, 16 (23%) had too many comorbidities and in one patient (1%) surgery was deemed unnecessary.

PDS or IDS was possible in 107 patients or 75%. Surgery was performed at Rigshospitalet for 88% of the patients. The remaining 12% were operated at other centres due to suspected non-malignant disease.
A macroradical resection was possible in 77%. 9% had 1-10 mm residual disease and 14% had more than 10 mm of residual disease.

Six patients with stage IA disease received adjuvant treatment due to histological findings (high-grade serous adenocarcinoma or non-serous histologies).

All patients received neoadjuvant or adjuvant treatment except one patient (1%) who declined.

FIGURE 1 / **A.** Kaplan-Meier analyses of median overall survival from diagnosis and after each progression. **B.** Kaplan-Meier analyses of median progression-free survival from diagnosis and after each progression.



CI = confidence interval; NA = not assessed; OS = overall survival.

CI = confidence interval; PFS = progression-free survival.

Carboplatin combined with a taxane was given to 74% of the patients. In 14%, bevacizumab was added to carboplatin and taxane based on a suboptimal debulked surgical result. One patient (1%) received carboplatin and PLD due to an allergic reaction to a taxane. 10% received single-agent carboplatin.

Overall survival

Of the 142 study participants, 83 died in the study period (58%). The median OS from diagnosis was 48.5 months (95% confidence interval (CI): 36.6-57.9 months). Median follow-up was 45.0 months (range: 1.6-66.5 months).

Median OS after first, second, third, fourth and fifth progression was 19.3 (95% CI: 13.9-27.3), 11.4 (95% CI: 7.7-18.8), 9.5 (95% CI: 6.3-12.7), 8.3 (95% CI: 7.6-11.5) and 5.6 (95% CI: 2.9-not assessed (NA)) months, respectively (**Figure 1**).

Progression-free survival

Of the 142 patients, 106 experienced an event. The median PFS from diagnosis was 15.6 months (95% CI: 14.3-18.4). The median PFS after first, second, third, fourth and fifth progression was 9.2 (95% CI: 7.7-10.6), 6.0 (95% CI: 3.5-7.7), 3.3 (95% CI: 2.6-4.6), 4.9 (95% CI: 3.6-8.3) and 3.0 (95% CI: 2.4-5.7) months, respectively (Figure 1).

Platinum-free interval

Of the 106 patients who experienced an event, 95 received first-line treatment for ROC.

Median OS for platinum-sensitive patients after the first progression was 28.0 (95% CI: 24.6-35.1) months. Median OS for platinum-resistant patients was 9.6 (95% CI: 7.6-18.4).

A total of 43 of the 55 platinum-sensitive patients experienced another progression. At the second progression, 23 patients were still platinum-sensitive. Median OS for platinum-sensitive patients after the second progression was 20.2 (95% CI: 12.7-NA) months and 15.2 (7.7-23.7) months for platinum-resistant patients.

Treatment at progression

Treatments used at each progression are given in **Table 2**.

TABEL 2 / Treatments used at each progression. The values are n.

	Progression							
	1st	2nd	3rd	4th	5th	6th	7th	8th
Doxorubicin	21	5	1	1	-	-	-	-
Doxorubicin and bevacizumab	2	2	-	-	-	-	-	-
Doxorubicin and trabectedin	-	-	-	-	1	-	-	-
Carboplatin	3	5	2	2	-	1	-	-
Carboplatin/doxorubicin	27	14	3	1	-	-	-	-
Carboplatin/doxorubicin/bevacizumab	10	-	-	-	-	-	-	-
Carboplatin/paclitaxel	1	2	-	-	-	-	-	-
Carboplatin/docetaxel	-	1	-	-	-	-	-	-
Carboplatin/docetaxel/bevacizumab	1	-	-	-	-	-	-	-
Carboplatin/gemcitabine	-	-	2	-	-	-	-	-
Cisplatin/doxorubicin	1	-	-	-	-	-	-	-
Gemcitabine	1	7	15	4	3	-	-	-
Gemcitabine/bevacizumab	-	1	2	1	-	-	-	-
Paclitaxel	3	17	6	6	2	-	-	-
Paclitaxel/bevacizumab	2	4	1	1	-	-	-	-
Topotecan	-	2	1	5	2	-	-	1
Topotecan/bevacizumab	-	-	1	-	-	-	-	-
Treosulfan	5	2	-	1	-	-	-	-
PARP treatment	8	1	1	2	-	-	-	-
PARP maintenance	4	1	1	-	-	-	-	-
Experimental treatment	1	1	2	2	-	1	1	-
Endocrine treatment	1	2	-	2	1	-	-	-

PARP = poly (ADP-ribose polymerase.

Platinum-containing therapy

A total of 34 patients with platinum-sensitive disease were given carboplatin/PLD with or without bevacizumab, making it the preferred combinational therapy at first progression. The remaining six platinum-sensitive patients were given another platinum-containing treatment.

Non-platinum containing therapy

The preferred treatment at the first progression when platinum was not used and the patient had not received carboplatin and PLD was PLD (n = 24) followed by paclitaxel (n = 5), see **Table 3**.

If the patient had received carboplatin and PLD, the preferred treatment was paclitaxel (n = 18). At the second progression for previously PLD-treated patients, gemcitabine (n = 13) was the preferred treatment choice, see Table 3.

Experimental treatment was mostly used in the non-platinum containing setting throughout several lines.

DISCUSSION

This retrospective study of a non-selected patient population confirmed earlier findings that the progression risk of OC is close to 80%. Of the 142 patients included, 83 died in the study period. The OS of OC was shown to be 48.5 months with a large decrease in OS after the first progression (19.3 months).

In 2005, Hoskins & Le published a study similar to the present in which they examined the outcomes of 136 OC patients with stage III-IV treated in Canada [10]. Their patients had a median OS of 32 months from diagnosis and 11 months after the first progression. All patients were diagnosed before 1999 and had a minimum of four years of potential follow-up.

Their patients had a median age of 58 (versus 65) years. The preferred treatment at progression was single-agent carboplatin at first relapse. At the second progression, several patients received paclitaxel or etoposide.

Our results could indicate that the OS for patients with advanced OC (32 versus 33.2 months) has not improved since 1999. However, 79% of Hoskins & Le's patients were diagnosed with stage III compared with

TABLE 3 / Treatments without platinum used for patients, who did not or did receive pegylated liposomal doxorubicin (PLD) with platinum in the recurrent setting. The values are n.

	Progression											
	without PLD with platinum								with PLD with platinum			
	1st	2nd	3rd	4th	5th	6th	7th	8th	1st	2nd	3rd	4th
Doxorubicin	21	4	-	-	-	-	-	-	2	-	1	-
Doxorubicin and bevacizumab	3	1	-	-	-	-	-	-	-	-	-	-
Doxorubicin and trabectedin	-	-	-	-	1	-	-	-	-	-	-	-
Gemcitabine	1	4	5	1	-	-	-	-	4	13	1	1
Gemcitabine/bevacizumab	-	1	2	-	-	-	-	-	-	-	1	-
Paclitaxel	4	7	3	-	-	-	-	-	14	5	-	1
Paclitaxel/bevacizumab	1	2	-	1	-	-	-	-	4	-	-	-
Topotecan	-	2	1	1	1	-	-	1	-	1	3	1
Topotecan/bevacizumab	-	-	1	-	-	-	-	-	-	-	-	-
Treosulfan	5	2	-	1	-	-	-	-	-	-	-	-
Experimental treatment	2	-	1	1	-	1	1	-	1	1	-	-
Endocrine treatment	1	1	-	2	1	-	-	-	1	-	-	-

only 49 % in the present study (stage III and IV only) with stage III patients having a median OS of 48.4 months.

A much larger study published in 2012 was performed by Hanker et al examining the outcomes and treatments of 1,620 selected patients originally included in either of three phase III trials in upfront treatment of OC taking place between 1995 and 2002 [11]. The original population consisted of 3,388 patients with a median OS of 44.1 months (95% CI: 42.3-46.4). Of these, 2,393 patients experienced progression, and subsequent treatment information was available for 1,620 patients. At the first progression, the median OS was 17.6 months and the PFS was 10.2 months. More than 90% of the patients included in the analysis were stage IIIB-IV. One must, however, take into account that clinical trials tend to underrepresent the elderly and low-income patient groups [12, 13].

The difference between platinum-sensitive and platinum-resistant patients was most attenuated at the first progression, and the difference was diminished at the second progression. It is, however, still worth mentioning that the median OS for patients who were platinum-sensitive at the first progression but platinum-resistant at the second progression was better than those who were platinum-resistant at the first progression (15.2 versus 9.6 months).

The diminished difference between platinum-sensitive and platinum-resistant patients at the second progression might also reflect the fact that the number of patients included in this analysis was 23 platinum-sensitive versus 20 platinum-resistant patients.

The median OS for patients who were platinum-resistant at the first progression was inferior to the one seen in a study by Griffiths et al who had a median OS from initiation of treatment of platinum-resistant disease of 14.0 months [14].

A noticeable change in the treatment of ROC is seen in the use of PLD after the approval based on the phase III trial by Gordon et al in 2004 [15]. Another new treatment seen in our study is bevacizumab. In Denmark, bevacizumab is approved for advanced OC with suboptimal cytoreduction and for ROC based on the results of ICON7/GOG218 and OCEANS/AURELIA studies [16-19], respectively. Another new treatment modality is the use of poly ADP-ribose polymerase (PARP) inhibitors, although not heavily used in the cohort with only six patients receiving a PARP inhibitor as maintenance therapy and 12 patients receiving it as a treatment option. This is because the emerging evidence of PARPs activity has been incorporated in clinical standard practice from late 2016, which was the later part of the observation period. PARP inhibitors have shown promise in the primary setting as published recently in the SOLO-1 trial (BRCA-mutated patients) and Prima and PAOLA-1 (all patients).

Six patients with stage IA received adjuvant treatment as described in the Danish guidelines present in 2013/2014 [20]. The guidelines state that all stage IA high-grade serous adenocarcinomas or other histological subtypes are to receive adjuvant treatment. Our present study population does not include stage IA low-grade serous adenocarcinomas, which means that the results only reflect patients who undergo oncological treatment.

Our study has several strengths and limitations. One strength is the non-selected population. Another is the possibility of follow-up in Denmark because of the implementation of electronic patient journals. The fact that almost all patients (88%) were surgically handled by the same department also gives strength to our results.

A limitation in our study is that we only included patients who were referred to an oncological department. This means that the patients who either died before being referred or who chose not to be referred were not included. Another limitation is the limited number of patients included.

We chose to censor patients based on the last entry to the chart with the last check in the chart being done on 1 December 2018. The Danish healthcare system is based on the Central Patient Register which collects death dates on all Danish citizens. This means that we know with certainty that the patients censored before 1 December were still alive by 1 December. An exception to this is four patients from the Faroe Islands who were treated at one of the centres.

We chose not to examine the difference between those who received treatment at progression and those who did not. This choice was made on the assumption that those who do not receive subsequent treatment at progression are a highly selective patient group who do not have the adequate performance status to receive more chemotherapy and it would therefore not be of any value to compare the two. Furthermore, the more interesting question is the effect of treatment at later lines in which we would not have enough patients to make any valuable statistical comparison.

CONCLUSIONS

In conclusion, this retrospective study reports a median survival of 48.5 months for patients diagnosed with OC. The study documents that a majority of patients are diagnosed with advanced stages and that most patients will experience a progression at some point.

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A full list of references is available from the corresponding author on request.