

Neoadjuvant chemotherapy as ovarian cancer treatment: ever more used with major regional differences

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ABSTRACT

INTRODUCTION: The traditional first-line treatment for patients with advanced ovarian cancer with primary debulking surgery (PDS) and adjuvant chemotherapy is controversial as some authors report a potential benefit from the alternative treatment with neoadjuvant chemotherapy (NACT) and interval debulking surgery. The aim of this study was to investigate the use of NACT in Denmark in regard to increased use and regional differences.

MATERIAL AND METHODS: Stage IIIC and IV ovarian cancer patients treated in the five Danish tertiary referral centres in the 2005-2010-period were included. The study is based on validated data from The Danish Gynaecological Cancer Database.

RESULTS: Of the 1,367 eligible patients 1,069 were treated with PDS and 298 with NACT. In 2005-2007, 11% of patients were treated with NACT. In 2008-2010, this percentage had risen to 30% ($p < 0.00001$). Between the five referral centres, the use of NACT ranged from 6% to 41% in 2005-2010 ($p < 0.00001$); from 1% to 31% in 2005-2007 ($p < 0.00001$); from 10% to 48% in 2008-2010 ($p < 0.00001$) and from 9% to 48% in 2010 ($p < 0.0008$). Patients treated with NACT were significantly older, had inferior ASA scores and Eastern Cooperative Oncology Group performance status compared with the patients from the PDS group. There was no difference between treatments in regard to body mass index, stage IV disease or patients with no co-morbidity.

CONCLUSION: The use of NACT as first-line treatment tripled from 2005-2010, but the regional variability was large which calls for a uniform agreement on treatment principles and evaluation.

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debulking surgery (PDS) followed by adjuvant chemotherapy. The purpose of PDS is to determine the stage of the disease and to resect the tumour burden. The correlation between unresected tumour implants after PDS and decreased survival is well-established [1]. Extensive surgical procedures have proven to be effective in achieving complete or maximal removal of the tumour, and it has been established that such procedures improve survival [2]. Primary debulking surgery is, however, not suitable for all patients. Patients with severely decreased health or co-morbidity may not be able to tolerate major surgery, especially if the use of extensive surgical procedures is expected. Also, patients for whom preoperative diagnostic findings suggest that the complete removal of a tumour with PDS is impossible are not suitable candidates for PDS.

A different approach is treatment with neoadjuvant chemotherapy (NACT) before a surgical attempt to debulk the patient. Surgery after NACT is called interval debulking surgery (IDS). It has been debated over the past decade whether the NACT and IDS approach could be an alternative to PDS and adjuvant chemotherapy as first-line treatment for patients with advanced ovarian cancer. Several studies have attempted to estimate the impact of NACT on survival, but the majority of these studies are small and retrospective single-institution experiences with heterogeneous patient populations, and their results are therefore difficult to compare [3]. Thus, first-line treatment of patients with advanced ovarian cancer is controversial.

According to recommendations from the Danish Gynecological Cancer Group [4]: "NACT is recommended for patients where pre-operative evaluation suggests that complete tumor debulking with PDS is unfeasible, that is, patients with severe co-morbidity and/or age above 75-80 years, abdominal lymph node metastases above the level of the renal veins, metastasis in the porta-hepatis, metastasis around the superior mesenteric artery and/or non resectable peritoneal carcinomatosis".

The aim of this study was to investigate the use of NACT in the treatment of patients with stage IIIC and IV

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Since the 1970s, the traditional first-line treatment for patients with advanced ovarian cancer has been primary

TABLE 1

Study population baseline characteristics.

	PDS	NACT	Difference, p value
Age, years, median (IQR)	65 (57-73)	68 (60-75)	0.004
Patients > 75 years, fraction (CI)	0.21 (0.19-0.24)	0.28 (0.23-0.33)	0.016
Stage IV disease, fraction (CI)	0.31 (0.28-0.34)	0.27 (0.22-0.32)	ns
BMI, kg/m ² , median (IQR) ^a	24.0 (21.0-27.2)	24.3 (21.8-28.0)	ns
Patients with no co-morbidity, fraction (CI) ^b	0.61 (0.58-0.64)	0.60 (0.54-0.65)	ns
ASA 1, fraction (CI) ^b	0.33 (0.30-0.36)	0.16 (0.12-0.21)	< 0.00005
ASA 2, fraction (CI) ^b	0.50 (0.47-0.53)	0.52 (0.46-0.58)	ns
ASA ≥ 3, fraction (CI) ^b	0.17 (0.15-0.19)	0.31 (0.26-0.37)	< 0.00005
ECOG-PS 0 and 1, fraction (CI) ^b	0.45 (0.42-0.48)	0.33 (0.28-0.39)	< 0.0005
ECOG-PS 2, fraction (CI) ^b	0.38 (0.35-0.41)	0.37 (0.32-0.43)	ns
ECOG-PS ≥ 3, fraction (CI) ^b	0.18 (0.15-0.20)	0.30 (0.24-0.35)	< 0.00005

ASA = American Society of Anesthesiologists' score; BMI = body mass index

CI = 95% confidence interval; ECOG-PS = Eastern Cooperative Oncology Group performance status;

IQR = interquartile range; NACT = neoadjuvant chemotherapy; ns = not significant;

PDS = primary debulking surgery.

a) Data missing for 90 patients; b) Data missing for 31 patients.

ovarian cancer in five Danish gynaecological-oncological tertiary centres from 2005 to 2010 with a view to evaluating any increased use during that time. Also, we aimed to compare the use of NACT among the five centres to evaluate regional differences.

MATERIAL AND METHODS

PDS was defined as a surgical procedure to reduce the tumour burden prior to chemotherapy, whereas NACT was defined as a treatment with chemotherapy prior to intended cytoreductive surgery. Chemotherapeutic regimens used during NACT were expected to follow national guidelines [4]. Body mass index (BMI) was calculated as kg/m². Co-morbidity was defined as any concurrent disease on the first day of admission. Performance status was assessed using the Eastern Cooperative Oncology Group (ECOG) criteria. This observational study is based on prospectively collected and validated intention-to-treat data from the multidisciplinary Danish Gynaecological Cancer Database (DGCD). Reporting to the DGCD is compulsory for all gynaecological, pathological and oncological departments in Denmark participating in the diagnosis and treatment of gynaecological cancer. The study focused on treatment in the five tertiary gynaeco-oncological referral centres (Rigshospitalet, Herlev Hospital, Odense University Hospital, Aarhus University Hospital, Skejby, and Aalborg Hospital), since treatment of advanced ovarian cancer in Denmark is centralized to these centres. As the reasons why patients were not referred to a centre hospital were unknown and less than 5% of stage IIIC and IV patients were treated in regional hospitals in 2010 [5], data from regional hospitals were considered potentially biased

and not representative of the treatment of advanced ovarian cancer in Denmark. The present study therefore includes only data from centre hospitals. We included patients treated in centre hospitals in Denmark and registered in the DGCD with stage IIIC or IV primary epithelial cancer of the ovaries, Fallopian tubes, or peritoneum from 1 January 2005 to 31 December 2010. Patients with borderline tumours or no curative intended treatment were excluded. Authors from all centres were asked to verify the number of patients registered in the DGCD from their institution and to correct any discrepancy. The period 2005 to 2007 is referred to as the early period, and the period 2008 to 2010 is referred to as the late period. We compared the use of NACT in the different time periods on a national level and among the five centres. Additionally, we compared the use of NACT between centres in the last year of registration.

Statistical analysis

The two treatments (PDS versus NACT), the two time periods (early versus late), the five hospitals, stages of disease (IIIC versus IV), presence of co-morbidity (yes versus no), American Society of Anesthesiologists (ASA) score, and ECOG performance status were considered categorical data and statistical comparisons for differences were carried out using χ^2 tests. Age and BMI were considered continuous variables, and differences between groups were identified using the Mann-Whitney U-test. Descriptive data are presented as medians and interquartile ranges. A p value less than 0.05 was considered significant.

Trail registration: not relevant.

RESULTS

A total of 1,754 patients with stage IIIC or IV primary cancer in the ovaries, Fallopian tubes, or peritoneum from 2005 to 2010 were registered in the DGCD from the five centres from 2005 to 2010. A total of 61 patients were registered in the DGCD with no curative in-



Laparotomy performed in Rigshospitalet.

tended treatment, and 326 patients were treated in regional hospitals. Hence, 1,367 patients were eligible for the study of whom 1,069 (78%) were treated with PDS and 298 (22%) were treated with NACT. Patient characteristics are listed in **Table 1**. There was no difference between treatments with regard to stage IV disease, BMI or fraction of patients with no co-morbidity. In the group treated with NACT, there was a higher median age and a larger fraction of patients older than 75 years than among patients in the PDS group. In the group treated with PDS, there was a larger fraction of patients with an ASA score of 1 and a lower fraction of patients with an ASA score ≥ 3 than in the NACT group. Additionally, the PDS group comprised a larger fraction of patients with an ECOG performance status of 0 and 1, and a lower fraction of patients with ECOG performance status ≥ 3 than seen in the NACT group. In the early period, NACT was used in 11% (95% confidence interval (CI): 0.09-0.14) (63/572) of patients treated for advanced ovarian cancer. In the late period, the use of NACT had increased to 30% (95% CI: 0.26-0.33) (235/795) of patients ($p < 0.00001$). In the last year of registration, the use of NACT was 35% (101/290) (95% CI: 0.29-0.41) (**Figure 1**).

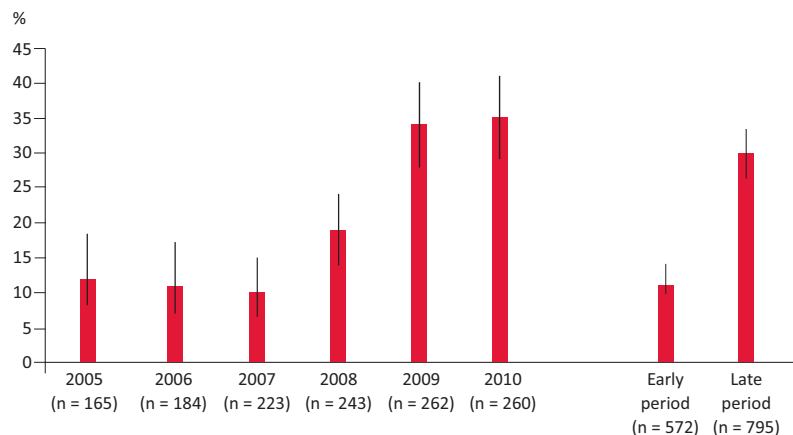
Table 2 shows the different use of NACT among the five centres in the entire inclusion period; the early period; the late period and in the last year of registration. In all four periods, the use of NACT varied significantly between the five centres.

DISCUSSION

The 2005-2010-period saw a significant increase in the proportion of Danish patients with stage IIIC and IV ovarian cancer treated with NACT. Thus, the proportion tripled during the six-year study period, and the most prominent increases were observed in 2008 and 2009. In the last year of registration, at least one in three patients was treated with NACT. The reasons for this increased use are unknown, but several explanations are possible. At the International Gynaecological Cancer Society meeting in Bangkok in October 2008, Professor Ignacio Vergote presented preliminary data from his later publication [6], which concluded that there was no difference in survival between patients treated with either PDS or NACT. Hence, the result supported that NACT is as safe and effective as PDS and this may have influenced Danish gynaecologists. In addition, the increased centralization during the previous decade has meant that a larger fraction of patients are being treated in centre hospitals which explain the increased annual number of patients towards the end of the study period. It has been shown that Danish patients treated in regional hospitals have an inferior ECOG performance status than those treated at centre hospitals, and it was

FIGURE 1

Fraction of stage IIIC and IV ovarian cancer patients treated with neoadjuvant chemotherapy in the five Danish tertiary referral centres from 2005 to 2010. Percentages and 95% confidence intervals are given (early period = 2005-2007, late period = 2008-2010).



demonstrated that regional hospitals use NACT less frequently than centre hospitals [7]. Consequently, the increased centralization may have contributed to the increased use of NACT in centre hospitals. A notable variation in the use of NACT between the five centres was found, ranging from NACT being used in nearly half of the patients to being used in approximately one in ten patients. As indicated by Table 1, the patients referred to NACT were older and in a poorer medical condition than those receiving PDS. This is in agreement with the recommendations from the Danish Gynaecological Cancer Group [4], but, clearly, the five centres interpret these recommendations differently.

As summarized in the introduction, the published literature does not allow for a conclusion about the potential benefit of NACT. In a meta-analysis from 2006 [8], the authors found that survival among patients treated with NACT and PDS was inferior to that of patients treated with PDS. In contrast, a meta-analysis from 2009 [9] found no difference in survival between the treatments. In a review from 2010, Weinberg et al concluded that survival is equal for patients treated with PDS and NACT [3]. Only one randomized controlled trial has ever been published. The authors concluded that survival was not inferior for patients treated with NACT, and NACT could thus be considered a safe alternative to PDS as first-line treatment [6].

An argument against the use of NACT is the potential risk of developing microscopic colonies of chemotherapy-resistant stem tumour cells, which the operating gynaecologist is unable to detect and remove and which will therefore be left in the patient [10]. This can lead to early progression of a platinum-resistant disease and hence a poor outcome for the patient. Additionally,



TABLE 2

Treatment of patients with stage IIIC and IV ovarian cancer in the Danish tertiary referral centres, 2005-2010. Total number of patients, fractions of neoadjuvant chemotherapy treatments and 95% confidence intervals are given.

	NACT, n	PDS, n	Fraction of NACT (CI)	p value
<i>2005-2010</i>				< 0.00001
Odense University Hospital	127	181	0.41 (0.36-0.47)	
Rigshospitalet	84	265	0.24 (0.20-0.29)	
Aarhus University Hospital, Aalborg Hospital	34	129	0.21 (0.15-0.28)	
Herlev Hospital	33	193	0.15 (0.10-0.20)	
Aarhus University Hospital, Skejby	20	301	0.06 (0.04-0.09)	
<i>The early period (2005-2007)</i>				< 0.00001
Odense University Hospital	39	85	0.31 (0.23-0.40)	
Rigshospitalet	15	131	0.10 (0.06-0.16)	
Herlev Hospital	6	93	0.06 (0.02-0.13)	
Aarhus University Hospital, Aalborg Hospital	2	69	0.03 (<0.10)	
Aarhus University Hospital, Skejby	1	131	0.01 (<0.04)	
<i>The late period (2008-2010)</i>				< 0.00001
Odense University Hospital	88	96	0.48 (0.40-0.55)	
Aarhus University Hospital, Aalborg Hospital	32	60	0.35 (0.25-0.45)	
Rigshospitalet	69	134	0.34 (0.28-0.41)	
Herlev Hospital	27	100	0.21 (0.15-0.29)	
Aarhus University Hospital, Skejby	19	170	0.10 (0.06-0.15)	
<i>2010</i>				< 0.0008
Aarhus University Hospital, Aalborg Hospital	21	23	0.48 (0.32-0.63)	
Odense University Hospital	30	38	0.44 (0.32-0.57)	
Herlev Hospital	21	27	0.44 (0.29-0.59)	
Rigshospitalet	24	50	0.32 (0.22-0.44)	
Aarhus University Hospital, Skejby	5	51	0.09 (0.03-0.20)	

CI = 95% confidence interval; NACT = neoadjuvant chemotherapy; PDS = primary debulking surgery.

smaller tumour implants respond better to chemotherapy [11, 12], indicating the benefit of early surgical removal of large tumour implants with poor blood supply and, consequently, a low response to chemotherapy.

In support of the use of NACT is the fact that patients treated with IDS do have significantly less extensive surgery, less per-operative blood loss, a shorter stay at a postoperative intensive care unit, and shorter hospitalization [3, 13] than patients treated with PDS.

It has not yet been established how to best differentiate between patients who are well-suited candidates for PDS and those who should be referred to NACT. One major question is to determine the possibility of achieving the complete removal of the tumour burden with PDS. To date, no diagnostic strategy has been able to solve this problem [14], which makes the decision-making process vulnerable to individual evaluation and individual preference with regard to first-line treatment. In 2011, Kang et al tried to identify patients who would benefit from treatment with NACT [15]. When tested with multivariate Cox analysis, patients with an initial CA-125 above 2,000 U/ml had increased progression-free survival when treated with NACT compared

with PDS. Also in 2011, Aletti et al [16] found that complex surgical procedures improve survival except for patients older than 75 years who have a high tumour dissemination or stage IV disease and have a poor performance or nutritional status. Collectively, this indicates that the patients who could potentially benefit from treatment with NACT are the older patients with advanced disease and who are in poor medical condition.

In 2010, 30% of the members of the Society of Gynecologic Oncologists responded to an electronic survey [17]. Only 9% used NACT in 25% or more of their stage IIIC and IV ovarian cancer patients, and approximately 60% used NACT in less than 10% of these patients. Of the respondents, 82% did not consider the currently available evidence sufficient to justify treatment with NACT. In contrast, a similar questionnaire was sent to the members of the European Society of Gynaecological Oncology. In the group of respondents (40%), 70% believed that there is sufficient evidence in the literature to justify treatment with NACT [18]. The results of these two questionnaires illustrate the differences in opinion that exist between gynaecological oncologists.

In the published literature, the use of NACT ranges from 16% to 80% [15, 18, 19, 20]. Considering these published numbers, the proportion of Danish patients who are treated with NACT seems reasonable, and the difference in the use of NACT between the Danish centres is in line with the differences in the literature.

A weakness of this study is its retrospective design, even though the data used were collected prospectively.

CONCLUSION

NACT as a first-line treatment for patients with advanced ovarian cancer is being used considerably more in the five Danish gynaeco-oncological tertiary referral centres today than was the case seven years ago. In addition, the use of NACT is unevenly distributed among the five Danish gynaeco-oncological referral centres, which calls for collaboration in order to allow assessment of indication and evaluation of treatment outcomes.

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