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Interval between debulking surgery and adjuvant chemotherapy is associated with overall survival in patients with advanced ovarian cancer

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HIGHLIGHTS

- Age, comorbidity and the occurrence of perioperative complications contribute to a prolonged TTC.
- A prolonged TTC is an independent prognostic factor for worse overall survival.
- Early initiation of chemotherapy results in similar survival when compared to an intermediate TTC.

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ABSTRACT

Objective. Treatment for advanced epithelial ovarian cancer (EOC) consists of debulking surgery and (neo)adjuvant platinum-based chemotherapy. The aim of this study was to evaluate whether the time from surgery to adjuvant chemotherapy (TTC) was associated with clinical outcome.

Methods. We identified all Dutch patients who received optimal or complete debulking surgery for primary EOC (FIGO IIb-IV) between 2008 and 2015 from the Netherlands Cancer Registry. TTC was divided into three groups based on the interquartile range (IQR). Early (<25%) and prolonged (>75%) TTC were compared to intermediate TTC (25–75%). Logistic regression was used to identify factors associated with a prolonged TTC and multivariable Cox regression to evaluate the independent effect of treatment interval on overall survival (OS). Patients receiving primary debulking surgery (PDS) and patients receiving interval debulking surgery (IDS) were analyzed separately.

Results. 4097 patients were included, 1612 underwent PDS and 2485 IDS. Median TTC was 29 days (IQR 24–37). Age ≥ 65, complete debulking surgery, postoperative complications, and hospitalization ≥10 days were independently associated with a longer TTC for both PDS and IDS. TTC in the longest quartile was associated with poor OS after both PDS (Hazard Rate (HR) 1.43, 95% CI 1.09–1.88) and NACT-IDS (HR 1.22 (1.02–1.47)) when compared to the intermediate TTC, but only in patients with no macroscopic residual disease after surgery.

Conclusions. Our study provides evidence that delayed initiation of adjuvant chemotherapy is an independent prognostic factor for worse overall survival after complete (interval)debulking surgery. We advise to start adjuvant chemotherapy within five to six weeks after debulking surgery.

1. Introduction

Treatment for advanced ovarian cancer consists of debulking surgery and (neo)adjuvant platinum based chemotherapy [1]. The goal of debulking surgery is to leave no residual disease [2]. When the likelihood of gross residual disease after primary debulking surgery (PDS) is high, neoadjuvant chemotherapy (NACT) can reduce tumor load

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and is an alternative treatment approach to reach complete debulking surgery [1, 3, 4]. Regardless of treatment approach, adjuvant chemotherapy is a prerequisite to improve clinical outcomes.

Despite the generally accepted use of adjuvant chemotherapy, there is no guideline on the optimal interval between debulking surgery and the start of adjuvant chemotherapy. It is assumed that commencement of adjuvant chemotherapy should be initiated as soon as possible, as this may prevent early tumor growth within the before mentioned time interval [5–7]. Studies in breast and colorectal cancer indeed suggested that delayed initiation of adjuvant chemotherapy impairs overall survival [5, 8–11]. Studies in ovarian cancer, however, report conflicting results [5, 12]. Some studies failed to show an association between the 'Time To start adjuvant Chemotherapy' (TTC) and overall survival [6, 13–19], while others indicated that delayed TTC adversely influenced clinical outcomes [5, 7, 20–23]. To our knowledge, the effect of a prolonged TTC was not previously studied after interval debulking surgery (IDS) in ovarian cancer, although this treatment sequence is increasingly applied.

Various patient-, tumor-, and surgery-related characteristics may cause a delay in adjuvant chemotherapy administration, such as comorbidity and the extent of surgery [23, 24]. Analyses of the interplay between these factors, preferably using unbiased population-based studies, may provide insight into possible modifiable characteristics and can help to minimize the time interval between surgery and adjuvant chemotherapy.

The aim of this study was to identify factors that are associated with prolonged TTC and whether the timing of adjuvant chemotherapy is independently associated with clinical outcomes in patients treated with either PDS or NACT-IDS.

2. Methods

All consecutive patients who were diagnosed with epithelial ovarian cancer (EOC), including primary peritoneal and fallopian tube carcinoma (International Classification of Diseases for Oncology (ICD-O) C48.2, C56.9 and C57.0), between 01.01.2008 and 31.12.2015 were identified from the Netherlands Cancer Registry (NCR) [25]. The NCR is a population-based cancer registry with coverage of all newly diagnosed malignancies in the Netherlands. Information on vital status and date of death are obtained by yearly linkage of the NCR with the municipal demography registries. For the purpose of this study, dedicated registration clerks collected additional medical information from medical files, including the Charlson Comorbidity Index (CCI) [26], treatment details (surgery and chemotherapy) and the date of disease recurrence.

2.1. Study population

Patients were eligible for inclusion if they were diagnosed with advanced stage disease, underwent debulking surgery and received at least one course of adjuvant chemotherapy. Patients were excluded if they underwent more than one debulking surgery, had an unknown time interval between surgery and chemotherapy or had >1 cm of residual disease after debulking surgery (Fig. 1).

2.2. Definitions of clinical outcomes

Advanced stage disease was defined by Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIB or higher. FIGO stage (2014) was derived from the Tumor-Node-Metastasis (TNM) staging system and based on postoperative findings. In case patients underwent NACT-IDS clinical TNM stage was used [27].

The TTC was defined as the period between debulking surgery and the start of subsequent chemotherapy. In case patients underwent IDS, the treatment-free interval between NACT and IDS was also determined for adjustment in multivariable analysis. Six cycles of carboplatin plus paclitaxel was considered regular care. Actual chemotherapy regimen was recorded for each patient including dose modifications and delays, all survival models were adjusted for these chemotherapy alterations.

Outcome of debulking surgery was defined as complete in case of no macroscopic residual disease and as optimal if the largest diameter of residual disease was ≤1 cm. Debulking surgery was defined as extended if one of the following procedures was executed during surgery; (retroperitoneal) lymphadenectomy, bowel resection, peritoneum stripping (including diaphragm), splenectomy, pancreatectomy, liver resections and/or bladder resections, or if the duration of the operation was longer than 240 minutes.

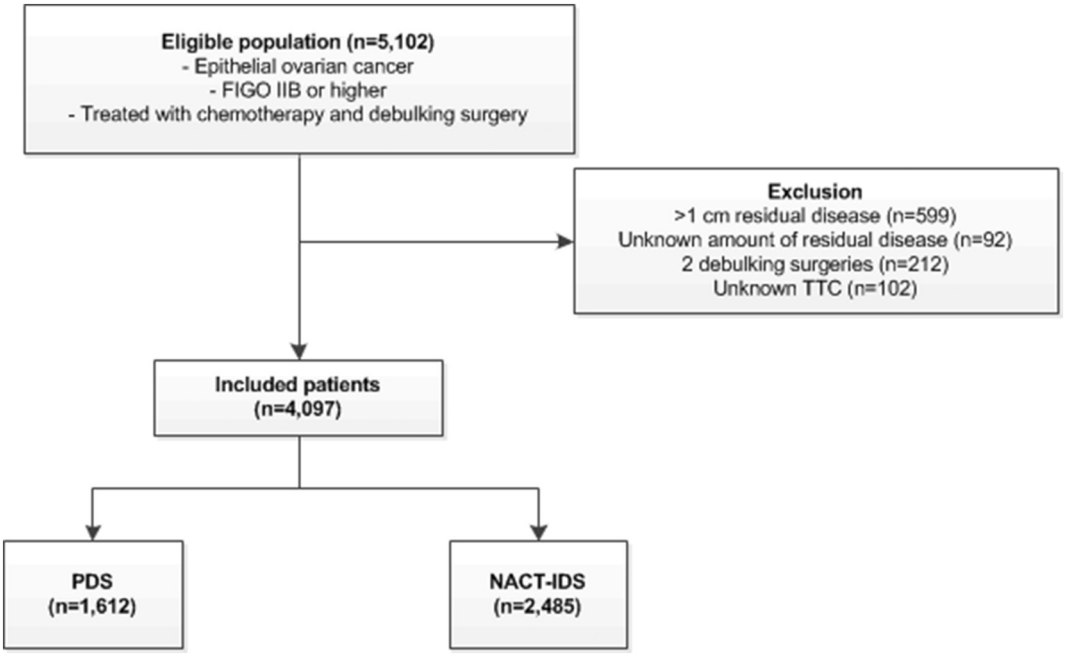

Fig. 1. In- and exclusion criteria for the studied population.

Postoperative complications were recorded if they occurred within 30 days after debulking surgery and included infectious complications, surgical site complications, thromboembolic events, reoperations, bowel complications (anastomotic leakage or abscess) and functional complications (such as urinary retention or ileus). Postoperative recovery was regarded as complicated if any complications occurred or if patients were admitted to the intensive care unit (in case of >1 day). Furthermore, readmissions were recorded if they occurred within thirty days postoperative and were added to the total admission time.

2.3. Statistical analyses

The TTC was summarized and categorized in three groups based on the interquartile range (IQR); lowest 25% (<23 days), 25–75% (24–37 days) and highest 75% (>37 days). Baseline characteristics of these groups were compared using Chi-square tests for categorical variables and ANOVA or Mann-Whitney *U* tests for continuous variables. Associations with prolonged TTC (time >75% quartile, i.e. >37 days) were explored with uni- and multivariable logistic regression models.

Overall survival (OS) was defined as the interval between date of first treatment (surgery for PDS patients and chemotherapy for NACT-IDS patients) and death or between date of first treatment and last follow-up for patients who were alive at data cut-off (1 February 2017). Progression free survival (PFS) was defined as the date of first treatment until progression or death, whichever occurred first. Progression was defined as clinical signs of tumor growth, i.e. increase in CA125 and/or visible lesions on imaging techniques (either regrowth of pre-existing lesions or new lesions), combined with the clinical judgment of the treating physician (medical oncologist or gynecologist). In case patients were still alive and had no progressive disease, patients were censored at the date of their last hospital visit. PFS and OS were analyzed by Kaplan-Meier survival curves and multivariable Cox regression models. All statistical analyses were performed using STATA/SE (version 14.1; STATA CORP., College Station, Texas, USA) and a *P*-value < 0.05 was considered statistically significant.

3. Results

We identified 4097 eligible patients from the NCR who were diagnosed between 2008 and 2015. Of them 1612 (39.3%) underwent PDS and 2485 (60.7%) underwent NACT-IDS (Fig. 1). The median time between surgery and the start of adjuvant chemotherapy was 29 days (IQR 24–37), and slightly differed between patients undergoing PDS (31 days (IQR 26–40)) and NACT-IDS (28 days (IQR 23–36)). Both treatment sequences were evaluated separately and baseline characteristics of both groups are listed in the Supplementary material (S1, S2).

3.1. Associations with prolonged TTC

Age (≥65 years), postoperative complications, prolonged hospitalization and complete debulking surgery were independently associated with delayed initiation of adjuvant chemotherapy after both PDS and NACT-IDS in a multivariable logistic regression model (Table 1). In addition, a CCI of 1–2 was also predictive of a delay in chemotherapy when compared to a CCI of 0, but a score of 3 or higher was not an independent prognostic factor. In univariable analysis, extensive surgery was associated with prolonged TTC, both in patients receiving PDS (odds ratio (OR) 1.27, 95% CI 1.02–1.58) and patients receiving NACT-IDS (OR 1.84 (1.51–2.24)). In multivariable analyses, however, extensive surgery was only associated with a prolonged TTC in patients who underwent NACT-IDS (Table 1). FIGO stage and the presence of ascites were not associated with a delay in chemotherapy (Table 1).

Table 1
Multivariable logistic regression to determine prognostic factors for prolonged TTC (>37 days) stratified by treatment sequence.

	PDS (OR, 95% CI)[a]	NACT-IDS (OR, 95% CI)[a]
Age		
<65 years	Reference	Reference
≥65 years	**1.35 (1.07–1.69)**	**1.74 (1.40–2.17)**
FIGO stage		
FIGO II	1.08 (0.81–1.45)	0.88 (0.28–2.75)
FIGO III	Reference	Reference
FIGO IV	1.17 (0.77–1.77)	0.86 (0.69–1.09)
Charlson Comorbidity Index		
0	Reference	Reference
1–2	**1.28 (1.00–1.67)**	**1.29 (1.02–1.62)**
≥3	1.45 (0.68–3.09)	1.51 (0.83–2.72)
Ascites		
<500 mL	Reference	Reference
≥500 mL	0.89 (0.68–1.17)	0.97 (0.75–1.24)
Extensive surgery		
No	Reference	Reference
Yes	1.18 (0.93–1.49)	**1.39 (1.11–1.73)**
Postoperative complications		
No	Reference	Reference
Yes	**1.59 (1.24–2.04)**	**1.89 (1.50–2.38)**
Hospitalization		
<10 days	Reference	Reference
≥10 days	**2.22 (1.70–2.90)**	**3.69 (2.92–4.66)**
Outcome of surgery		
Optimal (≤1 cm RD)	Reference	Reference
Complete (no macroscopic RD)	**1.40 (1.09–1.80)**	**1.30 (1.04–1.61)**

RD: residual disease.
[a] All OR's are adjusted for the listed variables, FIGO unknown and CCI unknown were included in the model but not listed in this table.

3.2. Influence of TTC on prognosis in patients who underwent PDS

For patients treated with PDS, crude median OS did not differ significantly between TTC intervals ($TTC_{<24}$: 67.6 months, $TTC_{24–37}$: 66.5 months, $TTC_{>37}$: 60.9 months, $P = 0.173$). When adjusted for patient- and tumor characteristics, including postoperative complications and chemotherapy alterations, there was no association between delayed chemotherapy and overall survival in patients with macroscopic residual disease after surgery (Hazard Rate $(HR)_{>37}$: 0.89 (0.68–1.16) vs 24–37 days, Table 2). However, patients with no residual disease after debulking surgery and a prolonged TTC experienced worse OS ($HR_{>37}$: 1.43 (1.09–1.88) vs 24–37 days, Fig. 2). In addition, patients with TTC < 24 days had comparable survival with TTC of 24–37 days in both models (Table 2). These trends in OS were comparable in a sensitivity analysis, where we used the specific TTC interval for PDS (i.e. <26 days vs 26–40 days vs >40 days) instead of the TTC intervals of the whole study population (data not shown). Moreover, progression-free survival did not differ between TTC intervals (data not shown).

Table 2
Influence of TTC interval on overall survival stratified by the amount of residual disease.

	Model I (HR, 95% CI)[a]	Model II (HR, 95% CI)[a]
PDS		
<24 days	1.09 (0.78–1.54)	0.94 (0.72–1.23)
24–37 days	Reference	Reference
>37 days	**1.43 (1.09–1.88)**	0.89 (0.68–1.16)
NACT-IDS		
<24 days	1.07 (0.89–1.28)	1.10 (0.93–1.31)
24–37 days	Reference	Reference
>37 days	**1.22 (1.02–1.47)**	1.10 (0.90–1.33)

Model I: only patients with no residual disease, Model II: only patients with macroscopic residual disease (≤1 cm).
[a] Adjusted for age, stage at diagnosis, histologic type, differentiation grade, performance score, postoperative complications, prolonged hospitalization and chemotherapy alterations. For patients undergoing NACT-IDS, additional adjustment was made for the duration of the treatment free interval between NACT and IDS.

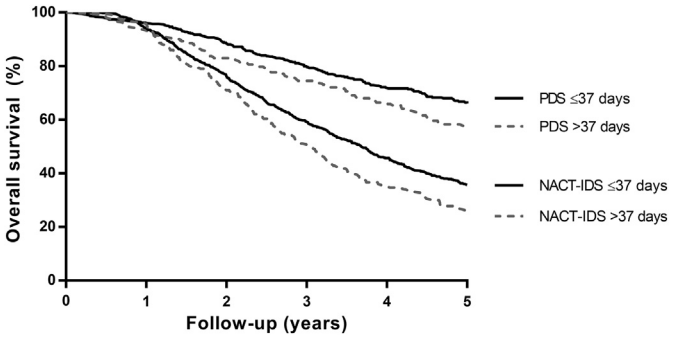

Fig. 2. Overall survival for patients with no residual disease after surgery stratified by treatment sequence.

3.3. Influence of TTC on prognosis in patients who underwent NACT-IDS

In patients undergoing NACT-IDS, crude median OS differed significantly between TTC intervals ($TTC_{<24}$: 33.8 months, $TTC_{24–37}$: 37.1 months, $TTC_{>37}$: 31.0 months, $P = 0.007$). In a multivariable Cox regression model, including adjustment for treatment free interval between NACT and IDS, there was no association between delayed adjuvant chemotherapy and overall survival in patients with macroscopic residual disease after surgery ($HR_{>37}$: 1.10 (0.90–1.33) vs 24–37 days). But similar to PDS patients, this was objectified in patients with no residual disease ($HR_{>37}$: 1.22 (1.02–1.47), Fig. 2). Again, trends in OS did not alter when the specific NACT-IDS TTC intervals were used and PFS did not differ between groups.

4. Discussion

In our large-scale population-based study we evaluated factors that are associated with delayed initiation of adjuvant chemotherapy and its influence on clinical outcomes in both patients undergoing PDS and NACT-IDS. In patients with no macroscopic residual disease after debulking surgery, delayed initiation of adjuvant chemotherapy was associated with impaired OS. However, we did not observe this effect in patients with macroscopic residual disease after surgery. Moreover, the observed associations with TTC and overall survival were not seen in progression-free survival.

In this study we gained insight into prognostic factors that are related to a prolonged TTC. As reported in earlier studies, prolonged hospitalization and occurrence of postoperative complications were the strongest prognostic factors for delayed initiation of chemotherapy [15, 20]. A complicated postoperative recovery often leads to prolonged hospitalization due to additional medical interventions, and therefore may result in delayed chemotherapy administration [23]. Higher age and a higher CCI were also independent predictive factors for a delay in chemotherapy and this is confirmed in other studies [24, 28]. Furthermore, patients with no residual disease were more prone to delayed initiation of chemotherapy, probably because they require more often extensive surgery [29]. This was most pronounced in NACT-IDS patients, who suffered significantly more often from postoperative complications after equal levels of extensive surgery compared to PDS patients (data not shown). In addition, the higher tendency of clinicians to start chemotherapy as soon as possible in patients with residual disease may also play a role [5–7].

A substantial number of studies investigated the time interval between debulking surgery and chemotherapy. The results of these studies are difficult to compare since the median time between surgery and the commencement of adjuvant chemotherapy ranged from 17 to 42 days in the listed studies. These differences illustrate the heterogeneity of studied populations and therefore may explain the inconsistent outcomes. In addition, TTC intervals were based on either IQR [13–15], median TTC [6, 7, 18, 20], or various weeks [16, 17, 19, 21–23], which also contributes to the conflicting results. In our study, we chose for IQR and compared the outliers (lowest and highest IQR groups) with the intermediate group (mean IQR) as we were interested if either early or late start influenced clinical outcomes. By using the median, or a number of weeks as a cut-off this association could not be studied.

Several studies have indicated that the early start of chemotherapy might be associated with worse clinical outcomes. The studies of Flynn et al. and Rosa et al. demonstrated worse OS when patients started before 22 and 28 days respectively [6, 17]. In both studies, however, patients with gross macroscopic residual disease were overrepresented in the early groups. Consequently, there was no effect on clinical outcomes when they adjusted their models for residual disease. By only including patients with ≤1 cm residual disease, this trend in overall survival was not seen in our study. In addition, patients with an early initiation of chemotherapy neither experience a survival benefit compared to the intermediate group, indicating that earlier start of adjuvant chemotherapy does not contribute to improved clinical outcomes [22].

We did find an independent association between delayed initiation of chemotherapy and impaired clinical outcomes. In patients treated with either PDS or NACT-IDS, the strongest influence was demonstrated in patients with no residual disease after debulking surgery. This is in concordance with earlier published studies [7, 22, 23]. A hypothesis for our findings might be that the prolonged interval after surgery attenuates the good prognosis of a complete debulking surgery, as it allows the tumor to regrow again. Even though macroscopic residual disease is absent in patients after a complete debulking, microscopic residual disease might be forced into accelerated proliferation and tumor regrowth due to the surgical intervention, as suggested by mouse models [30, 31]. In addition, oophorectomy may induce tumor angiogenesis leading to rapid growth of (microscopic) residual tumor cells in ovarian cancer patients [32].

Our findings are in contrast with a study of Hofstetter et al., who demonstrated a negative effect of prolonged TTC on overall survival only in patients with residual disease after debulking surgery [20]. They suggested that larger tumor masses tend to be less perfused than smaller tumor masses, and are therefore less responsive to chemotherapy [20]. Still, by including patients with ≤1 cm of residual disease we cannot speak of 'large tumor masses' in our series. But it remains unclear why patients with an optimal debulking do not benefit from early initiation of chemotherapy.

Patients are more prone to a delay in chemotherapy after very extensive surgery, which may raise the question whether we always should pursue complete debulking surgery if it is associated with a high probability to postoperative complications, and therefore delay in treatment continuation. Even though this is a valid argument, the prognosis of patients with no residual disease and a prolonged TTC is still superior to patients with macroscopic residual disease and an intermediate TTC (data not shown). So our results should not be used to justify spending less effort in the operating room as a concern of prolonged TTC, which is confirmed in the study of Aletti [15].

This study has a number of strengths. The population-based character enabled us to include all consecutive Dutch patients who underwent surgery and chemotherapy for advanced ovarian cancer in an era of platinum-based chemotherapy and the aim to no residual disease after surgery. Furthermore, we were able to adjust our clinical outcomes for chemotherapy alterations, extended surgery and postoperative complications. Both extended surgery and postoperative complications were associated with the time interval, and influenced our survival models, but did not undo the effect of chemotherapy delays. Finally, we also included patients who underwent interval debulking surgery, which actually is a more common alternative treatment approach in ovarian cancer patients.

Besides these strengths, there are also some limitations. We had to exclude 102 patients from our analyses because time intervals were not known. We assumed that these missing time intervals were at

random, and case-mix did not vary between the in- and excluded patients, but some bias cannot be excluded. In addition, we could not distinguish patients with an exploratory laparotomy from patients with a real effort to debulking surgery but a non-optimal outcome (>1 cm residual disease). Therefore, we excluded these patients and this limits the usability as these patients are also part of clinical daily practice. Furthermore, reasons for late start of adjuvant chemotherapy were not recorded. We adjusted our models for postoperative complications, comorbidity and prolonged hospitalization, assuming to be the most common reasons for delaying adjuvant treatment.

In conclusion, our study provides evidence that delayed initiation of adjuvant chemotherapy is an independent prognostic factor for worse overall survival after complete (interval)debulking surgery. Consequently, we advise to start adjuvant chemotherapy within the first five to six weeks after debulking surgery.

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Conflicts of interest

None.

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