

# Optimising patient selection to improve outcome in advanced ovarian cancer

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11

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Summary

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In the present chapter, the most important conclusions of this thesis are summarised. In part I we focused on the differences in treatment patterns and survival outcomes. In part II we aimed to get insight into prognostic factors that affect clinical outcomes, and in the last part of this thesis, we highlighted the importance of patient selection for the primary treatment of ovarian cancer.

## **PART I: SURVIVAL AND TREATMENT OF PRIMARY OVARIAN CANCER IN THE NETHERLANDS**

The vast majority of ovarian cancer patients is diagnosed with advanced stage disease. The combination of treatment consists of cytoreductive surgery and platinum-based chemotherapy. Over the last years, the timing of surgery became a subject of a heated debate, and neoadjuvant chemotherapy followed by interval cytoreductive surgery (NACT-ICS) is nowadays a reasonable alternative to primary cytoreductive surgery (PCS) for patients with advanced stage disease (FIGO IIIc and IV).

In **chapter 2** we observed that more patients with advanced stage disease were treated according to contemporary guidelines with a combination of cytoreductive surgery and platinum-based chemotherapy (55% in 1989-1993 to 67% in 2009-2014). In addition, PCS was initially preferred as first-line treatment (65% in 2004-2008), while in the most recent period, NACT-ICS was more frequently used compared to PCS (57% in 2009-2014). Simultaneously, the outcome of cytoreductive surgery increased over time as well. Despite all these efforts in intensifying treatment, long-term survival has, however, not improved in the last 25 years. The lack of improvements in long-term survival urges us to put major efforts into improving cure rates for women with EOC.

Comparable to other tumour types, centralisation of surgical care has been proposed to improve surgical outcomes and, hence, survival rates for ovarian cancer. In **chapter 3** we studied whether the hospital of diagnosis influenced the probability to surgical treatment. Centralisation of surgical care was initiated in two stages in the Netherlands. Firstly, registered gynaecological-oncologists were consulted to perform surgery together with regular gynaecologists in smaller hospitals. Secondly, a national consensus was reached to restrict the performance of surgery to hospitals which carried out a minimum of twenty cytoreductive surgeries on an annual basis. At baseline, the hospital of diagnosis was independently associated with the probability to surgical treatment. The first initiatives to centralisation already resulted in a decrease in hospital variation, although the initial hospital of diagnosis still significantly influenced treatment decisions. After a national consensus was reached, we observed no association between the initial hospital of

diagnosis and the likelihood to surgical treatment anymore. This finding underscores that centralisation does not only contribute to improved surgical outcomes, but also to a more coherent treatment policy across individual hospitals.

In **chapter 4** we aimed to describe treatment variation and its effect on patient outcome between geographical regions in the Netherlands. Overall, the percentage of patients that received no therapy did not differ between the geographical regions, while the percentage of patients that received chemotherapy in combination with cytoreductive surgery did differ significantly (range 61-71%). In addition, the use of PCS and NACT-ICS differed significantly between regions and could not be (fully) explained by differences in patient populations (PCS: 24-48%, NACT-ICS: 44-70% and PCS+NACT-ICS: 5-13%). Moreover, the probability of complete cytoreductive surgery was significantly associated with treatment region, even when accounting for possible confounders (including treatment sequence). This variation resulted in survival differences between geographical regions for patients that received either PCS or NACT-ICS. Survival of patients was the lowest in the region with the lowest number of complete cytoreductive surgeries. However, when all patients were analysed together (including those with no or limited therapy), survival was comparable between all regions. Patient selection to those who benefit from cytoreductive surgery and chemotherapy may explain this discrepancy, and this selection process may differ between regions.

## **PART II: PROGNOSTIC FACTORS THAT AFFECT SURVIVAL IN OVARIAN CANCER PATIENTS**

The outcome of cytoreductive surgery is one of the most important factors for prolonged overall survival, while it is hampered by the surgeons' intraoperative assessment and therefore subject to inter- and intra-observer variability. In **chapter 5** we searched for an objective prognostic factor to predict survival outcomes of patients who underwent PCS more accurately. We showed that the relative perioperative decline in CA125 is an independent prognostic factor for prolonged overall survival. This prognostic effect was also observed in patients with the same amount of residual disease, suggesting the need for a complementary model to predict clinical outcome more accurately in advanced ovarian cancer patients.

To prolong survival in advanced ovarian cancer, adjuvant chemotherapy is recommended after both primary and interval cytoreductive surgery. Currently, there is no advice about the optimal time interval between cytoreductive surgery and subsequent platinum-based chemotherapy. It is assumed that commencement of adjuvant chemotherapy should

be initiated as soon as possible, as this may prevent early tumour growth within the before mentioned time interval. In **chapter 6** we showed, predominantly after complete cytoreductive surgery, that delayed initiation of chemotherapy was associated with impaired overall survival after both PCS and NACT-ICS. Consequently, we advise to start adjuvant chemotherapy within the first five to six weeks after cytoreductive surgery.

The FIGO staging system was updated in 2014. This new classification distinguishes between patients with malignant pleural effusion (FIGO IVa), and patients with all other (extra)abdominal metastases (FIGO IVb). In **chapter 7** we found that this new classification did not provide additional prognostic information, as survival was similar between FIGO IVa and FIGO IVb patients. Patients with extra-abdominal lymph node metastases as only site of distant disease, however, had the most favourable survival of all FIGO IV patients, and may suggest the need for another FIGO classification. In addition, we showed that NACT-ICS is probably the preferred treatment approach in FIGO IV patients. We observed comparable survival rates between PCS and NACT-ICS. and other studies already showed that postoperative complications were lower after NACT-ICS. However, we may have identified a subgroup of selected patients that may benefit from PCS over NACT-ICS. In a sensitivity analysis that excluded patients that died shortly after PCS in order to overcome immortal time bias, a more favourable outcome was observed in patients with FIGO IVa disease. Unfortunately, the number of FIGO IVa patients who underwent PCS is limited in our cohort. Moreover, PCS can only be beneficial if patients that die shortly after this extensive procedure could be identified pre-operatively.

### **PART III: OPTIMISING PATIENT SELECTION FOR PRIMARY SURGERY OF CHEMOTHERAPY**

In **chapter 8** we evaluated the current opinions of Dutch gynaecologists and medical oncologists. In total 167 participants responded to our survey. Among the responders, 82% and gynaecologists and 93% of medical oncologists adopted NACT-ICS as an alternative treatment approach. Moreover, even 62% of medical oncologists preferred NACT-ICS to PCS as first line treatment, while only 33% of gynaecologists preferred NACT-ICS. The decision to schedule patients for PCS seems to depend on the probability of successful surgery in the primary setting. This emphasises the great importance of our selection processes to ensure that every patient undergoes the most optimal treatment.

It is thought that survival outcomes of advanced ovarian cancer patients can be improved through optimal patient selection. Observational data suggest that patients with no residual disease after PCS have the best survival outcomes compared to all other treatment

groups. The decision to schedule patient for PCS is therefore, among others, based on the probability to complete cytoreductive surgery. However, it is well known that predicting the outcome of surgery is inaccurate. Therefore, we developed a prediction model to estimate the probability to achieve no macroscopic residual disease at primary surgery for advanced ovarian cancer patients (FIGO IIIC and IV) in **chapter 9**. This model was based on simple baseline characteristics and may improve patient selection in clinical daily practice after external validation of our model.

The probability to complete cytoreductive surgery increases after NACT, while this does not translate into prolonged survival rates. Moreover, randomised data suggest that there is no difference between optimal (0.1-1.0 cm of residual disease) and suboptimal (>1cm of residual disease) cytoreductive surgery after NACT. This indicates that the prognostic effect of surgical outcomes is different when NACT is applied. In **chapter 10**, we summarised the currently available literature about the prognostic effect of surgical outcomes after NACT-ICS. We observed that patients with no residual disease after NACT-ICS had the best survival rates, comparable to PCS. The prognostic effect of optimal versus suboptimal cytoreduction, however, varied between the included studies. Based on a weighted average analysis, a six-month survival advantage was observed in case of an optimal outcome compared to a suboptimal outcome. The additional prognostic effect of optimal versus suboptimal cytoreductive surgery probably lengthens survival in the whole population, but macroscopic residual disease of any diameter should be avoided during interval cytoreductive surgery.