Improving quality of care for patients with ovarian and endometrial cancer

Eggink, Florine Alexandra

CHAPTER 9

Summary

SUMMARY

The studies presented in this thesis were aimed at improving quality of care for patients with ovarian cancer and endometrial cancer. In part I and II we focused on the organization of care for patients with ovarian and endometrial cancer. In part III we focused on individualization of care for patients with endometrial cancer.

Part I: Improving organization of care for patients with ovarian cancer

Ovarian cancer is the leading cause of death in gynecologic cancers. Standard primary treatment consists of a combination of cytoreductive surgery and platinum based chemotherapy. Traditionally, patients were treated with primary cytoreductive surgery (PCS) followed by 6 cycles of adjuvant chemotherapy (ACT) in the hospital of diagnosis. Within the past decade the importance of removing all macroscopically visible tumor deposits, termed 'complete cytoreduction', has been established. Moreover, favorable cytoreductive outcomes have consistently been demonstrated in the presence of specialized gynecologic oncologists in high volume hospitals. Therefore, treatment for patients with advanced stage ovarian cancer has been centralized to hospitals with annual case volumes of ≥20 surgeries. Within the same period, cytoreductive neoadjuvant chemotherapy (NACT) was introduced to reduce tumor load and increase the chance of achieving a complete cytoreduction during interval cytoreductive surgery (ICS).

In **chapter 2**, we evaluated the impact of these changes in patterns of care on surgical outcomes and survival of patients diagnosed with advanced stage epithelial ovarian cancer in the Netherlands between 2004 and 2013. The rise in the annual case load of hospitals treating patients with advanced stage ovarian cancer due to centralization of care, in combination with the expanding proportion of patients undergoing NACT, coincided with improved cytoreductive outcomes and a small improvement in overall survival.

In **chapter 3** we performed a pattern of care study to measure health system intervals of patients that were referred to the University Medical Center Groningen with a suspicion of ovarian cancer. During the course of the study increased awareness of health system intervals inspired changes in local practice. This resulted in improved compliance to national health system interval guidelines.

In **chapter 4** we conducted a review of the literature concerning optimal patient selection, timing and extent of surgery for patients with advanced stage ovarian cancer. Despite recent changes in organization of care and the paradigm shift in timing of cytoreductive surgery, no convincing impact on survival has been achieved thus far. We concluded that studies aimed at improving survival, especially those focused on optimizing patient selection for PCS, should be prioritized.

Part II: Improving organization of care for patients with endometrial cancer

Endometrial cancer is the most common gynecologic malignancy in economically developed countries. Standard diagnostic procedures for women suspected of endometrial cancer include ultrasonography and endometrial sampling. The pre-operatively collected endometrial sampling material and post-operative surgical specimens are used to stratify patients into groups according to their risk of progression and recurrence. This information is used to guide therapeutic decisions. Currently, the pre-operatively obtained tissue is used to guide clinical decisions regarding the extent of surgery and the tissue obtained during surgery is used to guide clinical decisions regarding adjuvant therapy. In **chapter 5** we evaluated the concordance between the pre- and postoperative risk stratifications of patients that were diagnosed with endometrial cancer in the Netherlands between 2005 and 2014. Within this period, the concordance between pre-operative and post-operative risk-stratifications was 90%. Notably, unfavorable survival outcomes were determined in patients with a high pre- and low post-operative risk compared to patients with a concordant low risk. We therefore concluded that the pre-operative risk stratification contains independent prognostic information.

The postoperative risk stratification is used to guide clinical decisions regarding adjuvant therapy. In **chapter 6** we evaluated compliance of physicians with adjuvant therapy guidelines in patients that were diagnosed with endometrial cancer in the Netherlands between 2005 and 2014. Excellent compliance to guidelines was determined in low and low-intermediate risk patients. In contrast, compliance was much lower in high-intermediate and high risk patients. Furthermore, large variations in compliance to guidelines were demonstrated between the eight oncologic regions in the Netherlands.

Part III: Individualization of care for patients with endometrial cancers

While the prognosis of patients with early stage, low risk disease is relatively favorable, there is an unmet need for effective treatment options in advanced stage, high risk endometrial cancer. The current 'one size fits all' approach is clearly insufficient for high risk endometrial cancers. It has therefore been suggested that new treatment modalities for high risk endometrial cancer should be aimed at specific tumor features such as biomarkers and molecular characteristics.

Traditionally, endometrial cancer was classified according to a dualistic model based on grade, histology and hormone receptor expression. In 2013, the Cancer Genome Atlas Network introduced a new classification with four genomically distinct subtypes based on molecular markers. Surprisingly, one of these subgroups, comprising ultramutated tumors with somatic mutations in the exonuclease domain of *POLE*, had excellent survival outcomes despite being associated with high risk features. Within the past decade, it has been suggested that these highly mutated tumors can generate high levels of neoantigens which may elicit strong immune responses. We therefore hypothesized that the excellent prognosis of patients with *POLE*-mutated endometrial cancers may be due to the presence of a strong anti-tumor immune response. In **chapter 7** we investigated whether POLE-mutant endometrial tumors show evidence of increased immunogenicity. Our data demonstrated that POLE-mutant

endometrial cancers and hypermutated microsatellite unstable endometrial cancers are characterized by a robust intra-tumoral immune response and an enrichment of antigenic neo-peptides. In **Chapter 8** we validated our findings in a cohort of high-risk patients. Moreover, we demonstrated the presence of high densities of PD-1- and PD-L1-expressing immune cells within the *POLE*-mutant and microsatellite unstable subgroups. These characteristics make these two subgroups of endometrial cancer patients attractive candidates for immune checkpoint inhibition therapy.