Improving quality of care for patients with ovarian and endometrial cancer

Eggink, Florine Alexandra

CHAPTER 1

General introduction

GENERAL INTRODUCTION

The studies presented in this thesis were aimed at improving quality of care for patients with epithelial ovarian cancer and endometrial cancer. The first and second part of this thesis comprise studies that were designed to improve quality of care for patients by assessing different aspects of the organization of care. The studies presented in the third part of this thesis focus on improving quality of care by encouraging individualization of care. In the general introduction below a brief outline of this thesis is discussed, including a short overview of the presented studies.

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

Approximately 1200 women are diagnosed with epithelial ovarian cancer in the Netherlands every year(1). Women may present with symptoms such as bloating, pelvic or abdominal pain, early satiety and urinary problems. Due to the aspecific nature of these symptoms, most women are diagnosed with an advanced stage of disease. Though relatively uncommon, epithelial ovarian cancer is the leading cause of death in gynecologic cancers, with a five-year survival of no more than 20-50% for patients with advanced stage disease(2). Factors that influence the prognosis of patients with ovarian cancer include histology, stage of disease, age, performance status, tumor type and tumor grade.

Epithelial carcinomas comprise around 90% of malignant tumors in the ovaries. Other tumors of the ovaries include tumors arising from ovarian stromal or germ cells and metastases from other primary tumors. The studies presented within this thesis concern epithelial ovarian carcinomas, a heterogeneous group of cancers including high-grade serous carcinoma (70-80%), endometrioid carcinoma (10%), clear cell carcinoma (10%), mucinous carcinoma (<5%) and low-grade carcinoma (<5%).

Standard primary therapy for advanced epithelial ovarian cancer comprises a combination of surgery and chemotherapy. Traditionally, primary cytoreductive surgery (PCS) is followed by six cycles of adjuvant chemotherapy (ACT). However, increasing awareness of the importance of cytoreduction to no macroscopically visible residual tumor (termed 'complete cytoreduction') led to the implementation of a therapeutic regime in which three cycles of neo-adjuvant chemotherapy (NACT) are followed by interval cytoreductive surgery (ICS) and three cycles of ACT(3,4). Advocates of this regime suggest that the administration of NACT may increase the chance of achieving a complete cytoreduction at the time of ICS by reducing tumor load. Furthermore, as there is a smaller tumor mass present during surgery, there is a smaller chance of inducing surgical complications(5–7). On the other hand, the administration of NACT may induce resistance to subsequent chemotherapeutic therapy(8–10). Currently, clinical guidelines based on international consensus recommend primary cytoreductive surgery (PCS) and adjuvant chemotherapy (ACT) in patients in whom complete cytoreduction seems feasible with acceptable morbidity. Neoadjuvant chemotherapy (NACT) followed by interval cytoreductive surgery (ICS) is recommended when complete cytoreduction is considered unlikely, or if unacceptable morbidity is expected during PCS(11,12).

Another effort to improve cytoreductive outcomes has been undertaken by centralizing surgery for advanced epithelial ovarian cancer in specialized high volume hospitals(13–15). Within the Netherlands, the first centralization initiatives were undertaken around the year 2005 and official implementation of standards aimed at centralization of care to hospitals with annual case volumes of ≥20 cytoreductive surgeries occurred in 2013(16). Other important aspects of these multidisciplinary standards included the requirement for all patients to be discussed in a pre-operative multidisciplinary panel and all cytoreductive surgeries to be performed by specialized gynecologic oncologists. A new version, including an English translation, of these standards was published in 2017(17).

In **Chapter 2** we evaluated the impact of the centralized care system and the implementation of NACT on the surgical outcome and survival of 7987 patients that were diagnosed with advanced stage epithelial ovarian cancer in the Netherlands between 2004 and 2013.

One of the drawbacks of such a centralized care system is the possibility of inducing treatment delay. Therefore, acceptable health care intervals were defined for patients suspected of epithelial ovarian cancer in multidisciplinary standards(16). In **Chapter 3** we performed a pattern of care study to measure health system intervals of patients that were suspected of ovarian cancer within our Managed Clinical Network.

Finally, in **Chapter 4** we reviewed our findings in light of the most recent insights on optimal patient selection, timing and extent of surgery for patients with advanced ovarian cancer.

Part II: improving organization of care for patients with endometrial cancers

Endometrial cancer is the most common gynecologic malignancy in economically developed countries, affecting around 1900 women annually in the Netherlands(1,2). The incidence of endometrial cancer is increasing due to factors such as increasing life expectancies and the rapidly expanding obesity epidemic. Endometrial cancer is usually diagnosed in postmenopausal women, and as it is frequently symptomatic at an early stage most patients are diagnosed with stage I disease. The overall prognosis of patients with stage I endometrial cancer is relatively favorable at approximately 75-80%. On the other hand, 5-year survival of patients with advanced stage disease ranges from 20-60(18)%. Standard diagnostic procedures for women suspected of early stage endometrial cancer include ultrasonography and endometrial sampling. To guide therapeutic decision-making, 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. These risk-stratifications are based on prognostic factors such as grade, histology, FIGO stage, age and lymph vascular space invasion(19–22).

In patients that are pre-operatively classified as low risk, a hysterectomy and bilateral salpingo-oophorectomy is indicated, while guidelines recommend complete surgical staging and adjuvant therapy in patients that are pre-operatively classified as high risk. The post-operative risk-stratification is used to guide the choice of adjuvant therapy. National and international guidelines do not recommend administration of adjuvant therapy in low and low-intermediate risk patients. Adjuvant therapy, consisting of radiotherapy and/or chemotherapy, is recommended in high-intermediate and high risk patients(23,24).

In **Chapter** 5 we investigated the concordance between pre-operative risk-stratifications based on endometrial sampling and post-operative risk-stratifications based on histological examination of tissue removed during surgery. The study included 3784 patients diagnosed with endometrial cancer in the Netherlands between 2005 and 2014.

In **Chapter 6** we evaluated compliance of physicians with adjuvant therapy guidelines in 13,568 patients that were diagnosed with endometrial cancer in the Netherlands between 2005 and 2014.

Part III: Individualization of care for patients with endometrial cancer

There is an unmet need for effective treatment in endometrial cancer patients at high risk of progression and recurrence. It is widely accepted that the current 'one size fits all' approach is insufficient for high risk endometrial cancer patients. As such, new therapeutic modalities aimed at high risk endometrial cancers should incorporate selection of endometrial cancer patients based on the biomarkers and molecular characteristics that are specific to their tumors. In this regard, expansion of our current understanding of endometrial cancer biology is essential.

Endometrial cancers have traditionally been classified using a dualistic model(25). 'Type I' tumors, characterized as low grade endometrioid, hormone receptor positive tumors with a favorable prognosis, are the most common subtype. Non-endometrioid, high grade, hormone receptor negative tumors, traditionally classified as 'type II', have an unfavorable survival and are less common. More recently, the application of next-generation sequencing has led to rapid advances in our understanding of the molecular etiology of endometrial cancer. In 2013, the Cancer Genome Atlas published a landmark paper in which a new classification, comprising four genomically distinct subtypes, was proposed(26). These four subtypes include ultramutated endometrial cancers with somatic mutations in the exonuclease domain of POLE, microsatellite unstable hypermutated endometrial cancers, a microsatellite stable group with frequent TP53 mutations and a group with no specific molecular profile. Surprisingly, POLE-mutant endometrial cancers, comprising approximately 10% of endometrial cancers, have an excellent prognosis despite being associated with high risk features(27–29).

As in other malignancies, control of endometrial cancer appears to be mediated in part by the immune system. Especially the CD8+ T-lymphocytes (T-cells) play an important role in the direct elimination of cancer cells(30). The CD8+ T-cells recognize cancer cells by their malignant transformation. For example, DNA mutations in cancer cells can lead to the formation of new proteins (termed 'neo-antigens') that can be recognized by the CD8+ T-cells. These neo-antigens can elicit a strong anti-tumor immune response, as previously shown in melanoma and non-small cell lung cancer(31,32). Tumors can deregulate the anti-tumor immune response and enable disease progression by expressing proteins (termed 'immune checkpoints') that induce immune resistance. The clinical development of immunotherapy that blocks such immune checkpoints, thereby restoring the anti-tumor immune response, has made an unprecedented impact on the field of oncology(33).

Taking into account emerging data linking mutational burden, immune response and clinical outcomes, we hypothesized that the excellent prognosis of POLE-mutant endometrial cancers may be attributed in part to an increased immune response against the tumor. In **Chapter 7** we investigated the immunogenic status of 150 endometrial cancers comprising approximately equal numbers of POLE-mutant, microsatellite unstable and microsatellite stable subtypes of low and high grade. In **Chapter 8** we validated and extended our findings in a cohort of 116 high-risk endometrial cancer patients.

Finally, English and Dutch summaries of the studies presented in this thesis can be found in **chapter 9** and **Chapter 10,** and the implications and future directions of the research presented in this thesis are discussed in **Chapter 11**.

REFERENCES

1. Integraal Kankercentrum Nederland. Nederlandse Kankerregistratie [Internet]. [cited 2017 Jul 7]. Available from: http://cijfersoverkanker.nl/
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics , 2017. CA Cancer J Clin. 2017;67(7):7–30.
3. Bristow BRE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era : a Meta-analysis. J Clin Oncol. 2002;20(5):1248–59.
4. Chang SJ, Hodeib M, Chang J, Bristow RE. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: a meta-analysis. Gynecol Oncol. 2013 Sep;130(3):493–8.
5. Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363(10):943–53.
6. Kehoe S et al. Chemotherapy or upfront surgery for newly diagnosed advanced ovarian cancer: results from the MRC CHORUS trial. J Clin Oncol. 2013;31(Suppl):a5500.
7. Zeng L-J, Xiang C-L, Gong Y-Z, Kuang Y, Lu F-F, Yi S-Y, et al. Neoadjuvant chemotherapy for Patients with advanced epithelial ovarian cancer: A Meta-Analysis. Sci Rep [Internet]. 2016;6:35914. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27804983
8. Luo Y, Lee M, Kim HS, Chung HH, Song YS. Effect of neoadjuvant chemotherapy on platinum resistance in stage IIIC and IV epithelial ovarian cancer. Med (United States). 2016;95(36):1–5.
9. da Costa AABA, Valadares C V., Baiocchi G, Mantoan H, Saito A, Sanches S, et al. Neoadjuvant Chemotherapy Followed by Interval Debulking Surgery and the Risk of Platinum Resistance in Epithelial Ovarian Cancer. Ann Surg Oncol [Internet]. 2015;22(S3):971–8. Available from: http://link.springer.com/10.1245/s10434-015-4623-z
10. Rauh-Hain JA, Nitschmann CC, Worley MJ, Bradford LS, Berkowitz RS, Schorge JO, et al. Platinum resistance after neoadjuvant chemotherapy compared to primary surgery in patients with advanced epithelial ovarian carcinoma. Gynecol Oncol [Internet]. 2013;129(1):63–8. Available from: http://dx.doi.org/10.1016/j.ygyno.2013.01.009
11. Querleu D, Planchamp F, Chiva L, Fotopoulou C, Barton D, Cibula D, et al. European Society of Gynaecologic Oncology Quality Indicators for Advanced Ovarian Cancer Surgery. Int J Gynecol Cancer. 2016;26(7):1354–63.
12. Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2016;34(28):3460–73.
13. Woo YL, Kyrgiou M, Bryant A, Everett T, Dickinson HO. Centralisation of services for gynaecological cancer. Cochrane database Syst Rev. 2012;3:CD007945.
14. Dahm-Kähler P, Palmqvist C, Staf C, Holmberg E, Johannesson L. Centralized primary care of advanced ovarian cancer improves complete cytoreduction and survival - A population-based cohort study. Gynecol Oncol [Internet]. 2016;142(2):211–6. Available from: http://linkinghub.elsevier.com/retrieve/pii/S0090825816307545
15. Cowan RA, O'Cearbhaill RE, Gardner GJ, Levine DA, Roche KL, Sonoda Y, et al. Is It Time to Centralize Ovarian Cancer Care in the United States? Ann Surg Oncol [Internet]. 2016;(23):989–93. Available from: http://link.springer.com/10.1245/s10434-015-4938-9
16. Stichting Oncologische Samenwerking. Multidisciplinaire normering oncologische zorg in Nederland, SONCOS normeringsrapport 2 [Internet]. 2014 [cited 2017 Jul 7]. Available from: http://www.iknl.nl/docs/default-source/Palliatieve-zorg-in-de-ziekenhuizen/soncos.pdf?sfvrsn=0
17. Stichting Oncologische Samenwerking. Standardization of multidisciplinary cancer care in the Netherlands, SONCOS standardization report 5 [Internet]. 2017. Available from: https://www.soncos.org
18. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. Eur J Cancer [Internet]. 2013;49(6):1374–403.

Available from: http://dx.doi.org/10.1016/j.ejca.2012.12.027
19. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035–41.
20. Lee K-B, Ki K-D, Lee J-M, Lee J-K, Kim JW, Cho C-H, et al. The Risk of Lymph Node Metastasis Based on Myometrial Invasion and Tumor Grade in Endometrioid Uterine Cancers: A Multicenter, Retrospective Korean Study. Ann Surg Oncol [Internet]. 2009;16:2882–7. Available from: http://www.springerlink.com/index/10.1245/s10434-009-0535-0
21. Convery P a, Cantrell L a, Di Santo N, Broadwater G, Modesitt SC, Secord AA, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. Gynecol Oncol [Internet]. 2011;123(1):65–70. Available from: http://dx.doi.org/10.1016/j.ygyno.2011.06.025%5Cn-http://www.ncbi.nlm.nih.gov/pubmed/21742369
22. Koskas M, Bassot K, Graesslin O, Aristizabal P, Barranger E, Clavel-Chapelon F, et al. Impact of lymphovascular space invasion on a nomogram for predicting lymph node metastasis in endometrial cancer. Gynecol Oncol [Internet]. 2013;129(2):292–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23480871
23. Werkgroep Oncologische Gynaecologie. Landelijke richtlijn endometriumcarcinoom [Internet]. 2011 [cited 2017 Jul 6]. Available from: http://www.oncoline.nl/endometriumcarcinoom
24. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, et al. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011 Sep;22 Suppl 6:vi35-9.
25. Bokhman J V. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol [Internet]. 1983 Feb [cited 2017 Jul 7];15(1):10–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6822361
26. Cancer Genome Atlas Research Network, Kandoth C, Schultz N CA, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C L, PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER L DA. Integrated genomic characterization of endometrial carcinoma. Nature [Internet]. 2013;497(53):67–73. Available from: http://pubget.com/paper/23636398?institution=%5Cnpapers2://publication/doi/10.1038/nature12113
27. Church DN, Stelloo E, Nout R a., Valtcheva N, Depreeuw J, ter Haar N, et al. Prognostic Significance of POLE Proofreading Mutations in Endometrial Cancer. JNCI J Natl Cancer Inst [Internet]. 2014;107:dju402-dju402. Available from: http://jnci.oxfordjournals.org/cgi/doi/10.1093/jnci/dju402
28. Billingsley CC, Cohn DE, Mutch DG, Stephens J a., Suarez A a., Goodfellow PJ. Polymerase ε (POLE) mutations in endometrial cancer: Clinical outcomes and implications for Lynch syndrome testing. Cancer [Internet]. 2015;121:386–94. Available from: http://doi.wiley.com/10.1002/cncr.29046
29. Meng B, Hoang LN, McIntyre JB, Duggan MA, Nelson GS, Lee C-H, et al. POLE exonuclease domain mutation predicts long progression-free survival in grade 3 endometrioid carcinoma of the endometrium. Gynecol Oncol [Internet]. 2014 Jul [cited 2016 Mar 25];134(1):15–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24844595
30. de Jong RA, Leffers N, Boezen HM, ten Hoor KA, van der Zee AGJ, Hollema H, et al. Presence of tumor-infiltrating lymphocytes is an independent prognostic factor in type I and II endometrial cancer. Gynecol Oncol [Internet]. 2009 Jul [cited 2017 Jul 7];114(1):105–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19411095
31. Roh W, Chen P-L, Reuben A, Spencer CN, Prieto PA, Miller JP, et al. Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. Sci Transl Med [Internet]. 2017;9(379). Available from: http://www.ncbi.nlm.nih.gov/pubmed/28251903
32. Yarchoan M, Johnson BA, Lutz ER, Laheru DA, Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer [Internet]. 2017;17(4):209–22. Available from: http://www.nature.com/doifinder/10.1038/nrc.2016.154
33. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer [Internet]. 2012 [cited 2016 Jul 6];12(4):252–64. Available from: http://dx.doi.org/10.1038/nrc3239

PART I

Improving organization of care for patients with ovarian cancer