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Improving quality of care for patients with ovarian and endometrial cancer

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CHAPTER 11

Discussion and future directions

DISCUSSION AND FUTURE DIRECTIONS

In the field of oncology, increasing emphasis is being placed on improving quality of care to improve outcomes and optimize the use of available resources. The studies presented in this thesis focused on improving quality of care in patients with ovarian and endometrial cancer by improving organization of care and encouraging individualization of care.

Efforts aimed at improving organization of care for patients with ovarian cancer

Currently, standard therapy for patients with advanced ovarian cancer comprises a combination of cytoreductive surgery and platinum-based chemotherapy. Within the past decade the importance of cytoreduction to no macroscopic residual disease has become widely accepted. This has triggered initiatives aimed at improving cytoreductive outcomes such as centralization of care to high volume hospitals with highly specialized staff and the implementation of neoadjuvant chemotherapy (NACT) (as reviewed in **chapter 4**). Within the Netherlands, centralization of care and the implementation of NACT coincided with improvements in surgical outcome and survival (as demonstrated in **chapter 2**).

The impact of centralization of care to high volume centers has not been studied in randomized clinical trials. Nonetheless, the value of centralization of services is widely acknowledged as favorable surgical outcomes have consistently been demonstrated in high volume hospitals with specialized surgical teams[1–3]. As the number of gynecologic oncologists involved in cytoreductive surgeries differs per hospital, it is surprising that the discussion regarding volume requirements has mainly focused on case-volumes of hospitals instead of individual physicians. The recently published ESGO guidelines have taken this into account, requiring $\geq 95\%$ of surgeries to be performed or supervised by surgeons performing at least 10 cytoreductive surgeries for ovarian cancer patients annually. Furthermore, within these guidelines minimal as well as optimal targets for quality indicators have been defined. The minimal annual volume targets of ≥ 20 cytoreductive surgeries, which are based on available literature, have been extended with optimal annual volume targets of ≥ 100 cytoreductive surgeries based on expert consensus. Within our ovarian cancer cohort, favorable surgical outcomes were demonstrated in hospitals with annual case volumes of ≥ 30 surgeries (unpublished data). Though solid evidence is still lacking, it is likely that the required annual case volumes in the Netherlands will be increased within the near future, generating new logistical challenges for the small number of high volume hospitals that will remain[4]. Importantly, further intensification of centralization of care will have profound consequences for ovarian cancer patients as they will be required to travel longer distances for their surgical treatment.

One of the drawbacks of centralization of care to hospitals with annual case volumes of ≥ 20 surgeries is the possibility of inducing delays. While the prognostic impact of delay in ovarian cancer patients is unclear, there is evidence that it can lead to anxiety and reduce patient satisfaction and quality of life[5–7]. We therefore measured health system intervals in patients suspected of ovarian cancer

within our Managed Clinical Network in 2013 and 2014 (**chapter 3**). During the study period increased awareness of health system intervals led to changes in clinical practice and improved compliance with national health system interval guidelines. As further intensification of centralization is likely, regular monitoring and evaluation of health system intervals is deemed essential. In line with this, the development and implementation of uniform electronic patient files will facilitate real-time monitoring of health system intervals and may provide crucial feedback with regard to the prevention of delays.

Notably, the impact of NACT on survival is subject of heated debate. Two landmark randomized clinical trials with mature survival data have shown similar overall survival for patients undergoing primary cytoreductive surgery (PCS) and adjuvant chemotherapy (ACT) compared to patients undergoing NACT and interval cytoreductive surgery (ICS), despite higher complete cytoreduction rates and lower surgical morbidity in the NACT group[8,9]. An exploratory analysis of one of these randomized trials demonstrated favorable survival in patients with stage IIIC disease with a low tumor load that underwent PCS and patients with stage IV disease and extensive tumor load that underwent NACT[10]. Data from the National Cancer Data Base, comprising women with stage IIIC and IV EOC diagnosed in the period 2003-2011, aged ≤ 60 with a Charlson comorbidity index of 0, confirmed the favorable survival of PCS within this subgroup[11]. Importantly, the two randomized clinical trials have important limitations such as a selection bias toward patients with unfavorable prognostic features as well as suboptimal cytoreductive outcomes. To that end, results of the randomized Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (TRUST), with stringent cytoreductive surgery criteria such as annual surgical case volumes of ≥ 36 and a $\geq 50\%$ complete resection rate, are eagerly awaited. Final data collection of the TRUST trial is expected in 2023.

Based on currently available data, new clinical guidelines were developed for ovarian cancer care by the European Society of Gynaecologic Oncology (ESGO), American Society of Gynecologic Oncology (SGO) and American Society of Clinical Oncology (ASCO) in 2016[4,12]. These guidelines recommend PCS and ACT for patients with a high likelihood of achieving complete cytoreduction with acceptable morbidity, and NACT and ICS for patients in whom complete cytoreduction is deemed unlikely or with unacceptable morbidity. However, selection of patients for PCS requires further optimization. As discussed extensively in **chapter 4**, pre-operatively available markers such as age, performance status, Cancer Antigen 125 and pre-operative imaging may provide valuable information about tumor load and the risk of developing complications. Moreover, histologic and genomic tumor features have been suggested as potential markers for assessing the chance of chemotherapy resistance. There is considerable tumor heterogeneity within ovarian cancer tumors, and this may in itself have predictive value for survival after chemotherapy treatment as sub-clonal tumor populations may expand during chemotherapy resulting in clinical relapse[13–17]. As the cell types that are responsible for chemotherapy resistance are rare it is important to note that gene expression data from bulk tumor samples may not be an adequate marker for chemotherapy resistance. Single cell analyses comprising samples from before and after the development of chemotherapy resistance may prove useful in helping to

define chemotherapy resistant single cell signatures. Another approach for preoperative patient selection may be pre-operative assessment of operability through diagnostic laparoscopy. Though criticized for having sub-optimal cytoreductive outcomes, the results from the LapOvCA trial suggest that diagnostic laparoscopy can reduce the number of futile laparotomies and is cost-effective[18,19]. It is likely that optimal selection of patients for PCS will require a combination of approaches.

Efforts aimed at improving organization of care for patients with endometrial cancer

Surgery forms the cornerstone of therapy for endometrial cancer patients. Patients at high risk of metastatic spread and recurrence also receive adjuvant therapy in the form of chemotherapy and/or radiotherapy. As of 2013, treatment with curative intent for patients with stage II, III or IV endometrial cancer has been centralized to specialized hospitals in the Netherlands. Furthermore, prospective discussion of all high risk patients in a multidisciplinary setting is required[20].

To guide therapeutic decisions, endometrial cancer patients are categorized into risk groups based on age, FIGO stage, myometrial invasion depth, tumor grade, tumor type and lymph vascular space invasion, according to ESMO clinical practice guidelines[21,22]. Histological evaluation of the tissue obtained pre-operatively is used to guide decisions regarding the extent of surgery, and histological evaluation of the tissue obtained during surgery is used to guide decisions regarding adjuvant therapy. In **Chapter 5**, we demonstrated an overall concordance rate of 90% between the pre- and post-operative risk stratifications. This implies that in 90% of cases clinical decisions regarding the extent of surgery were based on a correct risk stratification, minimizing the risk of over- or under treatment. Compared to the concordance rates stated in previous studies, ranging from 58-84%, this is relatively high. Notably, our analyses demonstrated less favorable survival outcomes of patients with high pre- and low post-operative risks (4% of our study population), suggestive of the presence of intra-tumor heterogeneity and/or mixed morphologic characteristics. As such, despite their post-operative low risk, these patients may require adjuvant therapy for local control of their disease[23–25].

In general, intra-tumor heterogeneity is seen as a diagnostic and therapeutic challenge. High intra-tumor genetic heterogeneity has been demonstrated in endometrial cancer, though it has been suggested that genetic analysis of endometrial cancer samples captures this heterogeneity[26,27]. Intra-tumor heterogeneity is also present at a morphologic level, leading to considerable inter-observer variation in pathologic assessment of endometrial samples[27]. Therefore, to overcome stratification inaccuracies due to intra-tumor genetic and morphologic heterogeneity, incorporation of molecular alterations into clinical risk stratification models has been suggested. Two classification models have been developed incorporating molecular markers. When compared with traditional stratification models, improved risk assessment has been demonstrated in both molecular models [28,29]. Both tools also showed a high concordance between pre-operative and post-operative classifications[30,31]. Recently, low intra-tumor heterogeneity was demonstrated among the well-established prognostic molecular markers *POLE*, *CTNNB1* and p53, which are also part of one of the

molecular risk stratification models[32]. The intra-tumor heterogeneity impacted the risk stratification in 10% of cases, thus in agreement with the 10% discordance seen in **chapter 5**, however the authors suggest that the level of intratumor heterogeneity may have been overestimated due to the selection of large tumors with at least 3 tumor fractions. Risk stratification using clinicopathologic and molecular markers has been shown to result in a better risk assessment compared to molecular markers alone[29]. In line with this, selection of patients for adjuvant therapy using a combination of clinicopathologic and molecular markers is currently being investigated in the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC)-4 trial.

In clinical guidelines, the post-operative risk assessment, considered to be the gold standard, is used to guide the choice of adjuvant therapy for patients with endometrial cancer[33]. As compliance to guidelines is viewed as an important quality indicator we proceeded to evaluate compliance of physicians with these guidelines in a population-based study (**Chapter 5**). While an excellent compliance with guidelines was determined in low and low-intermediate risk patients, the compliance dropped significantly in patients with high-intermediate and high risk. Compliance with guidelines was lowest in a subgroup of high risk patients with FIGO stage III serous disease. We attribute the low compliance in high-intermediate and high risk groups to the lack of survival benefit of adjuvant therapy and inconsistencies present in current literature and guidelines. As data regarding the reasons for noncompliance were lacking, it was not possible to take this into account.

In June 2017, the first results of the PORTEC-3 were presented at the conference of the American Society of Clinical Oncology (ASCO), suggesting prolonged 5-year failure free survival of patients with high risk stage III endometrial cancer treated with chemotherapy and radiation compared to those treated with radiotherapy alone. Importantly, significantly more adverse events were reported in the first 12 months in the combined chemotherapy and radiotherapy group. The first results of the GOG 0258 were also presented at the ASCO 2017 meeting. Within this trial chemo-radiation was compared to chemotherapy alone. No difference was determined in recurrence free survival, however chemo-radiation did improve loco-regional control. Maturation of overall survival data is eagerly awaited for both trials. Current clinical guidelines will require an update once the outcomes of these two clinical trials have officially been published.

Another effort which is currently being undertaken to improve selection of patients for adjuvant therapy is the randomized controlled trial entitled: Selective Targeting of Adjuvant Therapy for Endometrial Carcinoma (STATEC). In brief, the STATEC trial aims to determine whether lymphadenectomy, used to restrict adjuvant treatment to node positive women, results in non-inferior survival compared to adjuvant therapy given to all high risk apparent stage I endometrial cancer patients. Important secondary outcomes include quality of life, and performance of sentinel lymph node assessment. Of note, the therapeutic value of performing a pelvic and para-aortic lymphadenectomy in high risk endometrial cancer patients will be studied in the Endometrial Cancer Lymphadenectomy trial (ECLAT).

Efforts aimed at individualization of care for ovarian and endometrial cancer

Despite efforts aimed at optimization of traditional treatment strategies such as surgery, chemotherapy and radiotherapy, there is an unmet need for effective treatment in advanced ovarian cancer and high risk endometrial cancer. Recent insights in genomic and epigenomic inter-tumor heterogeneity have emphasized the importance of individualization of care based on tumor-specific features of ovarian and endometrial cancer[34,35]. Examples of such individualized approaches include targeted therapies and immunotherapies, which have already been studied extensively in melanoma and non-small cell lung cancer, among other cancers. Although the clinical efficacy of these strategies is evident in a subset of patients, selecting the patients who may benefit remains a challenge.

In **chapter 6** and **chapter 7**, we demonstrated the presence of an enhanced immune response, with high numbers of neoantigens as well as high numbers of lymphocytes expressing the immunomodulatory molecules PD-1 and PD-L1, in patients with POLE-mutant and microsatellite unstable endometrial cancers. These data have been validated by others[36–38]. Based on emerging data linking mutational burden and immune response, it is expected that these patients, with so called ‘hot’ tumors, will benefit from checkpoint inhibition strategies that block the PD-1 and PD-L1 immunomodulatory molecules present within their tumors[39]. Recently, immunogenic differences were also demonstrated between endometrial cancers with hereditary microsatellite instability and sporadic microsatellite instability, suggesting that future clinical trials should separately evaluate the efficacy of immune checkpoint inhibition in patients with these two forms microsatellite instability[38]. So far, data on anti-tumor activity of checkpoint inhibitors in microsatellite endometrial cancer is promising[40,41]. In line with these findings, the FDA approved the administration of pembrolizumab, a checkpoint inhibitor, for microsatellite unstable solid cancers as of May 2017. Clinical data on the anti-tumor effect of checkpoint inhibition in POLE-mutant endometrial cancers is currently based on case reports[42,43]. From a clinical perspective, checkpoint inhibition may not be suitable for patients with low-intermediate risk POLE-mutant endometrial cancer as they have an excellent prognosis when treated with standard therapy. In fact, considering this excellent prognosis, one may wonder whether these patients require adjuvant therapy at all. As such, optimal adjuvant therapy for patients with POLE-mutant endometrial cancer is currently being investigated in the PORTEC-4a clinical trial. In contrast, in patients with low levels of tumor infiltrating lymphocytes, termed ‘cold’ tumors, therapeutic strategies should be aimed at activation of the immune response. In these patients enhancing the number of specific anti-tumor immune cells within the tumor should be considered. These anti-tumor immune cells may be targeted toward antigens which are expressed by endometrial cancers such as human epidermal growth factor 2 (HER2), folate receptor alpha (FR α), mesothelin and p53[44]. Approaches for targeted therapies against these antigens include monoclonal antibodies, bi-specific antibodies, vaccines and adoptive T-cell therapies using chimeric antigen receptors.

Whether immunotherapeutic strategies have a place in the neoadjuvant or adjuvant setting, or whether they should be combined with standard therapy, remains to be elucidated. With this in

mind, we are currently investigating the effects of standard carboplatin/taxol chemotherapy on systemic immunity in a cohort of high-grade serous ovarian cancer patients. So far, we have observed a depletion of circulating myeloid suppressor cells without major systemic changes in T-cell subsets during carboplatin/taxol chemotherapy, a finding that was previously also reported in cervical cancer patients[45]. Although further validation in humanized patient-derived xenografts and clinical trials is required, our preliminary data suggest that combining immunotherapeutic (checkpoint inhibition) strategies with standard chemotherapy seems feasible during first line treatment of high-grade serous ovarian cancer.

As novel treatment modalities are costly and have the potential to induce severe toxicity, adequate patient selection and considerations concerning cost-effectiveness are essential. To aid clinical decision making, and enable affordable cancer care, the European Society of Medical Oncology (ESMO) has developed and validated the Magnitude of Clinical Benefit Scale (MCBS) to prioritize novel anti-cancer therapies in solid tumors[46]. This tool provides a rational, structured and consistent approach for the stratification of the magnitude of clinical benefit that can be anticipated from novel anti-cancer treatment modalities. The scale was recently applied to a cohort of contemporary randomized controlled trials, suggesting that a majority of published trials with statistically significant results fail to identify therapies that have a meaningful clinical benefit[47]. As such, clinicians and investigators should keep the ESMO MCBS in mind when designing future clinical trials with novel agents. Furthermore, the ESMO MSBC may also provide valuable information for policy makers involved in clinical approval of novel anti-cancer therapeutics.

In conclusion, the field of oncology is slowly moving away from traditional 'one size fits all' treatment strategies, which were provided in almost all regional hospitals. First of all, emphasis on quality indicators and their corresponding targets has encouraged centralization of specialized oncologic care, surgical or in the form of novel treatment strategies, to dedicated high volume hospitals. Secondly, advances in our understanding of cancer biology have provided a rationale for individualization of care. Optimal tailoring of (novel) oncologic therapies to patients with specific prognostic tumor features is likely to improve outcomes while minimizing unnecessary toxicity and reducing futile healthcare expenditure. Lastly, future clinical trials should be aimed at the demonstration of meaningful clinical benefit of novel cancer therapies, and this should be a requirement for clinical approval of such therapies.

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