Improving treatment strategies in ovarian cancer: Towards individualized patient care

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Chapter 1

General introduction and outline of the thesis
GENERAL INTRODUCTION

Ovarian cancer

Ovarian cancer is the leading cause of death from gynecologic cancers in the western world.\textsuperscript{1, 2} Optimal treatment to improve survival still remains a great challenge. Currently, there is a debate on treatment strategies for ovarian cancer. Guidelines are ambiguous and consequently, treatment varies per center. It is unclear which treatments are most effective, and in what order they are to be administered.

Ovarian cancer comprises a highly heterogeneous group of tumors. They can be subdivided into four categories: surface epithelial-stromal tumors (65-70%), sex cord-stromal tumors (15-20%), germ cell tumors (5-10%) and metastases (5%). Histology dictates many aspects of clinical treatment, management, and prognosis.\textsuperscript{3}

This thesis deals with the two most prevalent subtypes. Firstly, this thesis encompasses the treatment of rare granulosa cell tumors – non-epithelial sex cord stromal ovarian tumors – and then focuses on the more common epithelial ovarian tumors.

Granulosa cell tumors

Sex cord-stromal tumors originate from either primitive sex cords or from mesenchymal stroma of the developing gonad and account for approximately 7% of all malignant ovarian tumors.\textsuperscript{4, 5} Baron Carl von Rokitansky (1804-1878), a well-known professor of pathological anatomy at the University of Vienna, was the first to describe a granulosa cell tumor of the ovary as a single tumor entity in 1859.\textsuperscript{6} The granulosa cell tumor is the most common type, accounting for 70%, of ovarian sex cord-stromal tumors.\textsuperscript{7} The tumor is very rare, with an incidence of 0.6 to 1.7 per 100,000 women per year.\textsuperscript{7-10} It can present at any age, and produces estradiol. Due to this hormonal production, the majority of postmenopausal women present with vaginal bleeding, whilst most premenopausal women present with irregular menstruation or menorrhagia. In premenarchal girls, precocious puberty can occur. Abdominal pain and distention are common symptoms as well at all ages.\textsuperscript{10}

Granulosa cell tumors can be subdivided into two types, based on clinical and pathological features; an adult type (95%) and a juvenile type (5%).\textsuperscript{7} Microscopically, adult granulosa tumor cells have scant cytoplasm and a round to ovoid nucleus with a characteristic longitudinal groove, also known as ‘coffee bean’ nuclei (Figure 1). The tumor cells grow in a variety of patterns, the best-known is the microfollicular pattern which is characterized by the presence of Call-Exner bodies.\textsuperscript{11} Diagnosis of the tumor can be very challenging based on histomorphology and immunohistochemistry only.
However, recent identification of a recurring somatic mutation in the gene Forkhead box L2 (FOXL2) in adult type granulosa cell tumors, has provided opportunities to improve diagnosis.\textsuperscript{12}

Short term survival rates are reasonable, with an overall 10-year survival rate of approximately 60-90%, however long term survival rates decline.\textsuperscript{13} Relapses can occur up to 37 years after the primary diagnosis, which emphasizes the importance of a lifelong follow-up of these patients.\textsuperscript{14} Due to these late recurrences, the 25-year survival rate is only 40-60\%.\textsuperscript{13} Several prognostic factors for recurrence and survival have been identified, such as: stage of disease, age at diagnosis, residual tumor after initial surgery, mitotic index of the tumor, nuclear atypia, tumor size, tumor rupture and presentation of disease.\textsuperscript{8, 10, 15-26} Nevertheless, their relative importance is still unknown.

\textbf{Figure 1.} Example of a micrograph of an adult granulosa cell tumor with Call-Exner bodies and ‘coffee bean’ nuclei.

\textit{Current treatment strategies in granulosa cell tumors}

In 1964 Malkasian and Hawks recommended conservative unilateral oophorectomy in young patients and a more radical surgery, abdominal hysterectomy and bilateral salpingo-oophorectomy, in older patients.\textsuperscript{27} Nevertheless, many physicians perform radical surgery in all patients with a granulosa cell tumor and there is still no consensus about the surgical treatment. Another discussion is about whether or not to perform a complete surgico-pathological staging in all patients with a granulosa cell tumors.\textsuperscript{28, 29}

Besides surgery, other treatments are available for granulosa cell tumors. Radiotherapy has been administered as treatment for irresectable tumors, with contradicting
Guidelines recommend chemotherapy in advanced stages, but this too remains arguable with chemosensitivity being relatively low in granulosa cell tumors.\textsuperscript{33} Hormone therapy was proposed as potential treatment strategy, since the majority of tumors express hormone receptors with 32-66% Estrogen Receptor positivity and 98-100% Progesteron Receptor positivity.\textsuperscript{34-36} The first case of hormone therapy for a patient with a granulosa cell tumor was described more than 40 years ago.\textsuperscript{37} More case reports and case series have been published ever since, with promising results.\textsuperscript{36, 38, 39} Unfortunately none of them has reported more than six patients, and therefore more research needs to be conducted on this subject.

\textbf{Epithelial ovarian cancer}

The most common neoplasms of the ovary are surface epithelial-stromal tumors. The origin of these tumors is not clear. It is thought that the origin lies in the single layer of cells that cover the ovary or that lines cysts immediately beneath the ovarian surface.\textsuperscript{40} However, emerging data suggest that the origin of epithelial ovarian cancer lies in the fallopian tube. For example Piek et al. described an examination of tubal segments removed from women that underwent a risk-reducing bilateral salpingo-oophorectomy and found that the majority had areas of cellular dysplasia or hyperplasia in the tubal epithelium.\textsuperscript{41}

Epithelial-stromal tumors are subdivided in the following types; serous, mucinous, endometrioid, clear cell, transitional, and undifferentiated tumors.\textsuperscript{3} Besides the origin, there are substantial differences between epithelial ovarian cancers and non-epithelial cancers, such as granulosa cell tumors described above. The incidence is much higher, with an incidence rate of 15.22 cases per 100.000 women per year. In the Netherlands, annually around 1300 new patients are diagnosed.\textsuperscript{42} The peak age of disease presentation lies around 56 to 60 years.\textsuperscript{40} The majority of women with epithelial ovarian cancer present with nonspecific abdominal and gastrointestinal symptoms, and complaints of pain.\textsuperscript{43, 44}

Survival rates are less favorable than in sex cord-stromal tumors. Around two-thirds of all patients present with advanced stage disease at the time of diagnosis, possibly due to the nonspecific symptoms, which results in an overall 5-year survival rate of less than 40%.\textsuperscript{45}

\textit{Current treatment strategies in epithelial ovarian cancer}

For many years, the standard treatment of patients with advanced disease has been primary debulking surgery, with the intention to resect all visible tumor, followed by chemotherapy.\textsuperscript{46} The result of this debulking surgery is the most important prognostic factor for survival.\textsuperscript{47, 48} In 2010 Vergote et al. published the results of the European
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Organization for Research and Treatment of Cancer (EORTC) 55971 randomized trial, that investigated neoadjuvant chemotherapy followed by interval debulking surgery and postsurgical chemotherapy compared to standard treatment with primary debulking surgery followed by chemotherapy. Due to this alternative approach for patients with advanced stage epithelial cancer a profound debate emerged on the sequence of debulking surgery and chemotherapy.49, 50 The trial concluded that neoadjuvant chemotherapy is not inferior to primary surgery in the overall group of patients. Nonetheless, the question remains whether this applies to all individual patients, or that selection of patients who could benefit more from one of the treatment strategies could provide a genuine alternative. At present, strict criteria for the selection of patients are lacking.

All treatments that are mentioned above are administered worldwide every single day, but hitherto the optimal management of these tumor types has remained debatable. Therefore, further studies are warranted in the field of ovarian cancer treatment strategies in order to improve the outcome of these patients.

AIM OF THE THESIS

The studies presented in this thesis aim to investigate and improve treatment strategies in ovarian cancer. The overall objectives were the following:

• To evaluate aspects of treatment strategies in ovarian cancer that are currently used in every day practice;
• To develop models to tailor treatment and post-treatment strategies to individual patient characteristics;
• To identify the best diagnostic strategy for various types of ovarian cancer to allow for the optimal treatment.

OUTLINE OF THE THESIS

The outline of the thesis covers these objectives. Treatment strategies are discussed for two types of ovarian cancer. The first part of this thesis encompasses the treatment of rare granulosa cell tumors – non-epithelial sex cord stromal ovarian tumors –, while the second part of this thesis focuses on improving treatment strategies of the more common epithelial ovarian tumors.

Part I – Primary and adjuvant treatment of granulosa cell tumors of the ovary

In Chapter 2 we report the incidence of endometrial hyperplasia and cancer in patients with an ovarian granulosa cell tumor to evaluate whether a surgical hysterectomy –
in combination with uni- or bilateral salpingo-oophorectomy – is justified as primary treatment. **Chapter 3** describes the development and internal validation of a prognostic model to predict recurrence free survival in patients with an adult granulosa cell tumor, after primary treatment. This model has the intention to facilitate counseling patients and to guide post-treatment decisions. In **Chapter 4** we assess the objective response rate to chemotherapy in chemotherapy-naïve patients with an irresectable, measurable granulosa cell tumor. Chemotherapy is a widely used therapeutic approach for patients with an advanced or recurrent granulosa cell tumor. **Chapter 5** presents a systematic review that provides an extensive overview of all cases of hormonal treatment in patients with an ovarian granulosa cell tumor. The aim is to assess the evidence for or against the beneficial effect of this relatively unknown treatment modality. We also present an evaluation of response to hormone therapy in a consecutive series of patients treated in the Center for Gynecologic Oncology Amsterdam in **Chapter 6**. The aim of this study is to objectify our findings from the systematic review in Chapter 5. In the study presented in **Chapter 7** we combine histopathological review with immunohistochemistry and FOXL2 mutational status to identify the best diagnostic strategy for granulosa cell tumors in current practice. When sex cord-stromal tumor subtype-specific treatment for granulosa cell tumors will be developed in the future, this will become of increasing importance.

**Part II – Primary debulking surgery versus neoadjuvant chemotherapy in ovarian cancer**

In **Chapter 8** we present an exploratory analysis of a randomized trial, in which 670 patients with ovarian cancer were assigned to either primary surgery or neoadjuvant chemotherapy. Overall survival was similar in both groups. We study whether biomarkers, consisting of baseline characteristics of advanced stage ovarian cancer patients, can help to identify subgroups of patients who would benefit more from primary surgery or neoadjuvant chemotherapy. Finally, **Chapter 9** describes the design of the LapOvCa study; Laparoscopy to predict the result of primary debulking surgery in advanced Ovarian Cancer patients. We present a study in which we aim to provide evidence for the effectiveness of laparoscopy before primary surgery in advanced stage ovarian cancer patients. Eventually our ambition is to be capable of selecting patients for either primary debulking surgery or neoadjuvant chemotherapy.
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