Chapter 1

General Introduction

EPIDEMIOLOGY

Ovarian cancer is the second most common gynecologic malignancy with an incidence of about 15 cases per 100,000 women in Western countries [1-3] and is ranked the seventh leading cause of cancer-related death in women worldwide [4,5]. The high mortality rate is due partly to the fact that most ovarian cancers are diagnosed at an advanced stage of the disease. Early ovarian cancer accounts for approximately one-third of all newly diagnosed ovarian carcinomas [6]. The early-stage disease is defined by the International Federation of Gynecology and Obstetrics (FIGO) as stage I and IIa and is histologically confined to the internal gonads in the small pelvis [7]. Worldwide around 68,000 new cases of early ovarian carcinoma will be diagnosed annually [5]. The cumulative risk (age 0-64) for ovarian cancer is 0.5 [5]. The incidence of early-stage ovarian cancer in the Netherlands is approximately 370 patients per year. The median age at diagnosis is 57 year with around 30% less than 50 year [8].

CLASSIFICATION

Patients with ovarian cancer are surgically staged according to the FIGO classification. In 1964 the general assembly of the FIGO approved on a stage grouping of ovarian carcinoma [9]. Hereafter investigation of large series of ovarian cancer led to a definitive stage defining by the Cancer Committee of FIGO in 1971 [10]. General agreement existed on the importance of the penetration of the ovarian capsule by the tumor in stage I ovarian cancer, but opinions differed as to whether the presence of ascites had an influence on the outcome [11]. Ascites which had to contain malignant cells was only incorporated in stage Ic. Capsule rupture has been shown a prognostic indicator for disease-free survival in some studies [12-13]. In 1975 further refinements came when final histology after surgery was to be considered in the staging and Ic was no longer subdivided according to the rupture of the ovarian capsule and grouped together with those cases in which ascites was present, not necessarily containing malignant cells, or positive peritoneal washings [14]. In 1985 the FIGO modified the staging for ovarian carcinoma in part to reflect the prognostic significance of metastatic spread to the pelvic or para-aortic lymph nodes. In disease confined to one or both ovaries, positive nodes result in an upstaging to stage IIIc [7]. The latest revision of the FIGO classification was in 2009, but no modification for the staging system of ovarian carcinomas was made [15,16].

PATHOGENESIS AND HISTOPATHOLOGY

Several theories exist on the pathogenesis of epithelial ovarian cancer. While it is widely believed that the epithelial component of the ovary gives rise to the common epithelial ovarian carcinomas [17], it is not clear whether these cancers originate from a single-cell layer of surface epithelium or in architectural aberrations of the surface epithelium. These include surface epithelial-lined clefts and cortical inclusions cysts, thought to result from post-ovulatory wound repair, tissue remodeling associated with pregnancy or aging, para-ovarian adhesions, or simply the dynamic interaction between surface epithelium and underlying stroma [18-20]. A study of Pothuri et al. supports a model in which ovarian cancers frequently arise within epithelial inclusion cysts, but not the surface epithelium per se, and that carcinoma may be preceded by a dysplastic precursor lesion [21]. Another histopathology-based theory holds that epithelial ovarian cancer may arise in components of the secondary Müllerian system, located within or adjacent to the ovary [22]. The histologic subtypes of epithelial ovarian cancer include serous, mucinous, endometrioid, clear cell, mixed type and undifferentiated tumors. A new model for the pathogenesis of ovarian cancer is proposed by Kurman and coworkers [23]. In this model ovarian tumors are divided into two broad groups designated Type I and Type II. Type I tumors are slow growing, generally confined to the ovary at diagnosis and develop from well esthablised precursor lesions (borderline tumors). Type I tumors included low-grade micropapillary serous carcinoma, mucinous, endometrioid and clear cell carcinoma. They are genetically stable tumors and are characterized by mutations in a number of different genes including *KRAS, BRAF, PTEN,* and *beta-catenin.* Type II tumors, like the high grade serous carcinomas, are rapidly growing, highly aggressive neoplasms for which well defined precursor lesions have not yet been described. This group of tumors have a high level of instability and are characterized by mutation of *TP53.* Some other studies suggested that type II ovarian carcinomas are perhaps not ovarian cancers at all, but rather originate in the fallopian tube [24,25].

Different grading systems are used for ovarian cancer. The FIGO grading system is primarily based on architectural features, and the grade depends on the ratio of glandular or papillary structures versus solid tumor growth within an individual tumor [26]. The World Health Organisation (WHO) grading system is dependent on observer's impressions derived from both architectural and nuclear features but not defined in a quantitative manner [27]. The Gynecologic Oncology Group (GOG) grading system considers architectural and, to a lesser extent, nuclear features, but varies depending on the histologic type of the tumor being graded [28]. Clear cell carcinoma of the ovary cannot be graded by either the FIGO and GOG grading system. Thus, the grade assigned to a particular tumor is dependent on the observer's diagnosis of the histologic

type of tumor, which has been shown to be poorly reproducible between pathologists in several studies [29-31].

Silverberg proposed a new grading system modeled on the Nottingham system of breast cancer grading and designed to be applied to all invasive epithelial carcinomas of the ovary, including clear cell tumors [32].

SURGICAL STAGING

Major advances in the understanding of the natural history of early ovarian cancer occurred in the 1970s and 1980s when some authors defined the incidence of occult disease in the omentum, paracolic gutters, diaphragm, in the peritoneal washings and the lymph nodes [33-36].

Piver et al. report that microscopic metastases in the abdominal cavity at different sites like the right diaphragm (11%), the omentum (3%) and malignant cells in peritoneal washings (33%) were found in patients with presumed early-stage ovarian cancer [33]. Another route of metastasis is via the lymphatic channels. In 1974 Knapp and Friedmann reported at first their experience with aortic lymph node metastases in patients with early ovarian cancer [37]. In the decades thereafter other studies have extended our knowledge about the routes and incidence of lymphatic spread to the pelvic and aortic lymph nodes. The anatomy of ovarian lymph drainage is complex. It has been stated that the drainage trunks leaving the subovarian plexus take a cephaled course toward the aortic nodes via the infundibulopelvic ligament [38]. Another lymphatic channel courses from the hilus of the ovary within the folds of the broad ligament to drain into the obturator, external, and common iliac nodes which are interconnected by a great variety of anastomoses [39]. Lymphatic vessels also enter and travel along the round ligament to reach the inguinal region [40]. Involvement of pelvic nodes has been reported to occur in 8-15% [33,41] and of para-aortic nodes in 5-24% of patients with stage I disease [41,42].

Peritoneal seeding is the most common pathway for the spread of ovarian cancer whereby tumor cells slough off the ovary and enter the peritoneal circulation to seed multiple sites like the diaphragm, omentum, paracolic gutters, cul-de-sac and paravesical recesses [43-45]. Peritoneal fluid is able to flow upward from the pelvis due to pressure gradients in the abdominal cavity [44].

These findings have led to a better understanding of the spread of early ovarian cancer within the peritoneal cavity and the need for a comprehensive surgical staging of these patients. Complete surgical staging consists of abdominal hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, sampling of pelvic and para-aortic lymph nodes, careful inspection of the whole abdominal cavity, taking of blind peritoneal biopsies and biopsies of any suspect lesions and of adhesions adjacent to the tumor and peritoneal washings. The stage of ovarian cancer is defined as the extent of the disease at the time of diagnosis. This can only be determined by exploratory surgery and meticulous evaluation of all areas of disease dissemination. The surgical procedures and the requirements for optimal intraperitoneal surgical staging of cancers apparently confined to the pelvis are well established by the FIGO [46]. Different guidelines for surgical staging of ovarian cancer were defined like the European guidelines of staging of ovarian cancer (EGSOG), the European Organisation for Research and Treatment of Cancer (EORTC) guidelines and the Gynecologic Oncology Group (GOG) guidelines [47,48]. EGSOG guidelines require lymph node sampling among the external and common iliac vessels and along the aorta and vena cava, specifically between the inferior mesenteric artery and the level of the left renal vein. The GOG guidelines recommend also excision of the distal half of the obturator fatpad anterior to the obturator nerve and prescribe dissection from the area between the inferior mesenteric artery and the left renal vein only in case of palpably suspicious nodes [47] .

In a study of Petru et al., 55% of lymph node metastases in presumed early-stage ovarian cancer were less than 2 mm in diameter [49]. Similar findings have been found by Wu et al., 33% of clinically nonsuspicious nodes harbored metastases of epithelial ovarian cancer [36].

The result of surgical staging in ovarian cancer is a redistribution of stages. Several studies have shown that a substantial number of patients initially believed to have disease confined to the ovaries will be upstaged. Young et al. [34] reported on a group of 100 patients of whom 62 agreed to be restaged after being referred for treatment of stage I or II ovarian cancer. Of these patients almost one third (31%) were upstaged, with the final stage in most becoming stage III. Comparable studies by Soper, Hellewa and Buchsbaum reported similar results [50-52].

Therefore, the importance of complete surgical staging cannot be overstated. Mc Gowan et al. [53] examined the completeness of staging in 291 patients with ovarian cancer. Forty six percent of patients were inadequately staged. Proper staging was highly correlated with the level of experience of the surgeon who treated the patient. Gynecologic oncologists adequately staged 97% of patients, general gynecologists 52%

and general surgeons 32%. These findings are also supported by others [53-56]. Five-year survival and disease-free survival, respectively, for stage I-II ovarian cancer patients surgically staged by a gynecologic oncologist were 83% ± 7% and 76% ± 8%, compared to 59% ± 11% ($P < 0.05$) and 39% ± 11% ($P < 0.03$) for the group operated upon by a non-oncologist [57]. In a study of Vernooij et al. among patients with FIGO stage I-IIa disease, risk of ovarian cancer-specific mortality was 30% and 42% lower after treatment in semi-specialized and specialized hospitals, respectively, as compared to general hospitals [58]. In another study the level of specialization and the volume of hospitals and the number of gynecologists were strongly related to the proportion of adequately staged patients [59]. Comprehensive surgical staging is essential for prognostic determination and treatment planning for patients with apparent early-stage ovarian cancer as it defines a subset of patients that do not require adjuvant treatment in order to reduce the risks of late complications of chemotherapy as well as the morbidity and costs caused by such therapy [60].

TREATMENT MODALITIES

In the past many randomized trials have enrolled patients with early ovarian cancer in order to evaluate the value of adjuvant therapies like external radiotherapy, intraperitoneal installation of radionuclides such as gold-198 (^{198}Au) or phosphorus-32 (^{32}P), single alkylating agents or platinum-based single or combination chemotherapy.

Some of these studies were of low quality because of the omission of a control arm, inclusion of borderline tumors and incomplete surgical staging [61-67]. It was stated that: "the inclusion of inaccurately staged, incompletely evaluated patients in trials attempting to test the potential value, if any, of adjuvant treatment will be difficult to interpret at best and misleading at worst" [68].

Meta-analyses performed by Winter-Roach et al. [69] for those trials with complete surgical staging procedures comparing adjuvant chemotherapy (AC) versus radiotherapy showed no significant difference between the effects of AC and radiotherapy on overall survival (OS) and disease-free survival (DFS). The main analysis of OS showed an HR of 0.85 (95% CI 0.62 to 1.17) and the DFS showed an HR of 0.94 with a 95% CI of 0.56 to 1.59. In the subgroups, AC versus ^{32}P, AC versus whole abdominal radiation (WAR) or platinum-based AC versus ^{32}P, radiotherapy showed no statistical advantage for any modality. Cisplatin containing regimens are preferable to radiotherapy and intraperitoneal ^{32}P because of lower toxicity and relative ease of administration.

Most randomized trials compared two or three different treatment arms and almost all had a very low power because of the small number of patients or too few events. Furthermore, the efficacy of AC cannot be firmly established without an untreated observation arm.

In a study of Young et al. [70], 81 patients with grade 1 or 2 stage Ia or Ib (FIGO 1973) ovarian cancer were randomly assigned to receive 12 cycles of orally administered adjuvant melphalan and 81 no adjuvant treatment. No significant difference in overall survival (OS, 94% versus 98%) or disease-free survival (DFS, 91% versus 98%) was found. Bolis et al. [71] showed in 85 FIGO stage Ia or Ib, grade 2 or 3 patients a significant DFS advantage in the cisplatin group (83%) compared to the observation arm (65%). However, when the controls were treated with cisplatin at relapse, they had the same overall 5-year survival as the group receiving cisplatin treatment, as an adjuvant modality following initial surgery: 82% and 88% respectively. This result suggests that eight of the ten women in the cisplatin arm had been overtreated. If survival after relapse is compared, the patients in the upfront cisplatin group did much worse than patients in the nontreated group. Therefore the authors suggested that salvage treatment was more effective in the observation arm than in the chemotherapy arm, but also in this trial the number of patients was too small to draw too strong conclusions.

The Nordic Cooperative Ovarian Cancer Group performed a randomized study between 1992-1997 in patients with high risk epithelial ovarian cancer (stage I) including 162 eligible patients comparing carboplatin and observation [72]. High risk was defined as grade 2 or 3 tumor, all clear cell and DNA aneuploid tumors, independent of grade. Only 10% of the patients had a complete comprehensive surgical staging. The study was closed prematurely due to poor accrual. The estimated 5-year OS and DFS rates were 86% versus 85% and 70% versus 71% for the adjuvant chemotherapy and control group, respectively.

In a randomized phase III Gynecologic Oncology Group study in early-stage ovarian carcinoma comparing 3 versus 6 cycles of adjuvant carboplatin and paclitaxel, the latter did not significantly alter the recurrence rate in high risk early ovarian cancer, but was associated with more toxicity. There was documentation of complete surgical staging of only 71% of patients in this trial [73].

PROGNOSIS

The survival rates reported in the literature for patients with early ovarian cancer (EOC) vary, partly due to the differences in completeness of surgical staging and grade of differentiation and inclusion in some series of borderline tumors. The 5-year survival rates range from 76-95% for stage I [4,75-78] and 42-70% for stage II patients [75,78]. Over the past decades the improvement of the relative survival has occurred during the period in which adjuvant chemotherapy has been used in the treatment of EOC together with an improvement of the surgical staging in the same period. Although the overall survival curves are good compared to patients with advanced disease, approximately 10-50% of women with early EOC will experience a recurrence or die as a result of the disease [6,76,79,80]. Because of these long-term figures, major efforts have been made to develop adjuvant therapies, to optimize surgical staging and to identify prognostic factors that can predict patient outcome.

Women with early-stage ovarian cancer have a much better chance of achieving a cure than do women with late-stage disease. This difference makes screening for ovarian cancer, with the hope of detecting it in its presymptomatic state, an attractive concept. Unfortunately, efforts to demonstrate that screening for ovarian cancer in the general population can decrease mortality have been disappointing [81]. No accurate screening test is available but transvaginal sonography and CA 125 determinations can be valuable in selected patients [82] as well as the Risk of Malignancy Index (RMI) [83,84]. The results of the prevalence screen of the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) shows that the sensitivity of the multimodel screening (MMS) with annual CA 125 screening with transvaginal ultrasound scan as a second line test and annual screening with transvaginal ultrasound (USS) is encouraging. Specificity was higher in the MMS group than in the USS group, resulting in lower rates of repeat testing and surgery. The results of ongoing screening are awaited so that the effect of screening on mortality can be determined [85].

The detection of serum proteomic patterns or other biomarker panels holds promise of novel screening strategies and individual target therapies [86-88].

PROGNOSTIC FACTORS

Prognostic variables can divide patients into risk groups. It is generally accepted that stage Ia grade 1 tumors with complete surgical staging have a very good prognosis with a 5-year overall survival of 95% permitting fertility sparing surgery [6]. Trimbos et al. described a 100% disease-free 5-year survival in patients with well differentiated early ovarian cancer who had undergone a careful staging procedure [89]. Young found a 98% disease-free survival rate in 38 patients with well-staged, low risk early ovarian cancer [68]. In a study of Vergote et al. none of the 77 patients with well differentiated DNA diploid tumors had relapses [74].

Several prognostic factors for early-stage ovarian carcinoma have been analyzed. Some of them are biological and clinical in nature, but others such as the thoroughness of the staging procedure, the extent of the surgery, and the philosophy of treatment, are defined by human nature [90].

Many clinical and pathological characteristics have been found to correlate with survival in early ovarian carcinoma including stage, histologic type, tumor grade, ascites, age and ploidy [15,70,72,89,91-101]. Furthermore rupture of the tumor, dense adhesions and surgical staging have been indicated as independent prognostic factors in prior reports [89-91,102-105]. In a multivariate analysis of 351 patients with stage I ovarian cancer Zanetta et al. [90] found that the extent of surgical staging was a statistically significant independent prognostic factor for disease-free and overall survival.

The largest retrospective multivariate analysis in stage I epithelial ovarian cancer of Vergote et al. including 1,545 patients, concluded that the most important independent prognostic factors were degree of differentiation followed by rupture before surgery, FIGO substage Ib versus Ia and age [104].

Also highly reproducible quantitative pathological features which are easy to assess have shown to be of prognostic value in early ovarian cancer in combination with clinical characteristics. In a study of Brugghe et al. [106] MNA (volume percentage of epithelium, mitotic activity index, mean) and MNV (volume-weighted mean nuclear volume) were the strongest single prognostic factors for overall survival in a group of 102 adequately staged FIGO stage I ovarian cancer patients who did not receive adjuvant treatment.

SCOPE AND OUTLINE OF THE THESIS

In order to evaluate the effect of adjuvant chemotherapy and surgical staging in early ovarian cancer patients, the European Organisation for Research and Treatment of Cancer - Gynecologic Cancer Group (EORTC-GCG) performed the Adjuvant Chemo-Therapy in Ovarian Neoplasm (ACTION) trial (EORTC trial 55904). The ACTION trial was a randomized study on the role of platinum containing adjuvant chemotherapy in early ovarian cancer patients with FIGO stages Ia and Ib (grade II-III) and stages Ic and IIa (grade I-III) and all stages Ia-IIa clear cell carcinoma after surgery. Randomization between platinum containing chemotherapy and no adjuvant treatment took place after surgical staging and patients randomized to receive platinum based chemotherapy were treated within four weeks after surgical treatment for at least four consecutive courses.

Because there still exist a lot of discussion and questions about the treatment and prognosis of patients with early ovarian cancer, we further examined the surgical staging categories and the different subgroups in order to get some answers on these subjects.

In *chapter 2* the results of the first analysis of the ACTION trial are described between the adjuvant chemotherapy arm and the no treatment arm (observation arm) on the role of platinum-based chemotherapy on disease-free survival (DFS) and overall survival (OS). Furthermore, analyses were performed in optimally staged patients versus non-optimally staged patients.

A review of the treatment modalities and recent findings in early ovarian cancer patients is given in *chapter 3*.

The clinical characteristics and response to platinum-based chemotherapy in patients with clear cell carcinoma (CCC) versus serous adenocarcinoma (SAC) randomized in the ACTION trial are described in *chapter 4*.

Early ovarian cancer patients are often incompletely staged during their initial surgery. In *chapter 5* we discuss the possible reasons for inadequately staging early ovarian cancer patients.

The effect of lymph node sampling and taking of blind biopsies as part of the surgical staging procedure for early ovarian cancer on DFS and OS in patients who received no adjuvant chemotherapy are analysed in *chapter 6*.

In *chapter 7* the prognostic value of the FIGO Ic substages including capsule rupturing, ascites containing malignant cells, surface tumor and positive peritoneal fluid in relation to disease-free and overall survival are described.

Finally we show the long term results of the patients randomized in the ACTION trial in *chapter 8*.

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