EARLY OVARIAN CANCER

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In liefdevolle herinnering aan mijn vader
Voor mijn moeder

Contents

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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Chapter 2

Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma

European Organisation for Research and Treatment of Cancer- Adjuvant ChemoTherapy in Ovarian Neoplasm trial

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ABSTRACT

Background: All randomized trials of adjuvant chemotherapy for early-stage ovarian cancer have lacked the statistical power to show a difference in the effect on survival between adjuvant chemotherapy and no adjuvant chemotherapy.
They have also not taken into account the adequacy of surgical staging. We performed a prospective unblinded, randomized phase III trial to test the efficacy of adjuvant chemotherapy in patients with early-stage ovarian cancer, with emphasis on the extent of surgical staging.

Methods: Between November 1990 and January 2000, 448 patients from 40 centers in nine European countries were randomly assigned to either adjuvant platinum-based chemotherapy (n = 224) or observation (n = 224) following surgery. Endpoints were overall survival and recurrence-free survival, and the analysis was on an intention-to-treat basis. The Kaplan–Meier method was used to perform time-to-event analysis, and the log-rank test was used to compare differences between treatment arms. Statistical tests were two sided.

Results: After a median follow-up of 5.5 years, the difference in overall survival between the two trial arms was not statistically significant (hazard ratio [HR] = 0.69, 95% confidence interval [CI] = 0.44 to 1.08; $P = 0.10$).
Recurrence-free survival, however, was statistically significantly improved in the adjuvant chemotherapy arm (HR = 0.63, 95% CI = 0.43 to 0.92; $P = 0.02$). Approximately one-third of patients (n = 151) had been optimally staged and two-thirds (n = 297) had not. Among patients in the observation arm, optimal staging was associated with a statistically significant improvement in overall and recurrence-free survival (HR = 2.31 [95% CI = 1.08 to 4.96]; $P = 0.03$ and HR = 1.82 [95% CI = 1.02 to 3.24] $P = 0.04$, respectively).
No such association was observed in the chemotherapy arm. In the non-optimally staged patients, adjuvant chemotherapy was associated with statistically significant improvements in overall and recurrence-free survival (HR = 1.75 [95% CI = 1.04 to 2.95]; $P = 0.03$ and HR = 1.78 [95% CI = 1.15 to 2.77]; $P = 0.009$, respectively). In the optimally staged patients, no benefit of adjuvant chemotherapy was seen.

Conclusions: Adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival in patients with early-stage ovarian cancer. The benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease.

INTRODUCTION

Ovarian cancer is a common gynecologic malignancy. Approximately 30% of patients with ovarian cancer are diagnosed with early-stage disease, which is localized to the gynecologic organs and has not spread to adjacent structures in the pelvis or the upper abdomen. Nevertheless, 10%–50% of patients who receive surgery for treatment of early-stage ovarian cancer have a recurrence, and these recurrences are often resistant to various forms of salvage treatment [1].

This high recurrence rate has led to attempts to use different forms of adjuvant treatment, but solid scientific proof of the clinical effectiveness of adjuvant treatment is lacking. Not only is the clinical significance of adjuvant treatment unclear, but the definition of which patients are at high risk of recurrence—that is, in potential need of adjuvant treatment—has remained obscure.

Few randomized trials have tried to address the uncertainties that have been created by this 'act-before-proof' approach. Young et al. [2] reported a Gynecologic Oncology Group (GOG) study in which patients with stage Ia or Ib and grade I or II ovarian cancer were randomly assigned to either observation or intermittent oral melphalan following surgery. There was no survival difference between the two groups of patients. Although the number of patients in this trial was too small to draw definitive conclusions, the authors advocated not administering any adjuvant treatment following surgery and comprehensive staging in patients with this stage and grade of disease [2].

Recently the results of two randomized European trials that included an observation arm have become available [3,4]. In the Italian study [3], patients with early-stage ovarian cancer were randomly assigned to receive either cisplatin or observation following surgery. Patients in both arms received salvage therapy on recurrence. A statistically significant difference in recurrence- free survival was found in favor of chemotherapy, but no difference in overall survival was demonstrated (overall survival: hazard ratio [HR] = 1.15 [95% confidence interval [CI] = 0.44 to 2.98]; recurrence-free survival: HR = 0.35 [95% CI = 0.14 to 0.89]). The authors suggested that salvage treatment was more effective in the observation arm than in the adjuvant chemotherapy arm and that, although patient numbers were small, these findings support a policy of deferring chemotherapy until the actual time of recurrence [3]. In the Scandinavian study [4], 162 patients with early-stage ovarian carcinoma were randomly assigned to receive carboplatin or observation following surgery. No difference in disease-specific survival or disease-free survival was seen (disease-specific survival: HR = 0.94 [95% CI = 0.37 to 2.36]; disease-free survival: HR = 0.98 [95% CI = 0.52 to 1.83]) [4]. However, both

the Italian and Scandinavian studies lacked the power to draw definitive conclusions and did not take into account the extent of the surgical staging of their study groups. The quality of surgical staging in ovarian cancer relates to the reliability of the diagnosis of early-stage disease because it has been well documented that approximately 24% of non-optimally staged patients with early-stage ovarian cancer actually harbor occult residual disease in the peritoneal cavity (stage III disease) [5–8].

In 1990 the European Organisation for Research and Treatment of Cancer–Gynaecological Cancer Group (EORTC–GCG) initiated a randomized clinical trial comparing platinum-based adjuvant chemotherapy with no further treatment (i.e., observation) following surgery in patients with early-stage ovarian cancer.

The study, called Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION), which ran between November 1990 and January 2000, was designed to have more statistical power than previous trials to detect a survival difference and to emphasize the completeness of surgical staging in the analysis of the endpoints of the study. At the same time, the International Collaborative Ovarian Neoplasm Collaborators initiated a similar trial (ICON1), the results of which are also published [9]. We report on the findings of the ACTION trial.

PATIENTS AND METHODS

Patients and Surgery

Patients with International Federation of Gynecology and Obstetrics (FIGO) stages Ia–Ib, grade II–III; all stages Ic and IIa, and all stages I–IIa with clear cell epithelial cancer of the ovary were eligible for the study [10,11]. Surgical treatment had to consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy, followed by surgical staging. In cases of stage Ia cancer, unilateral salpingo-oophorectomy followed by surgical staging was permitted. This kind of conservative surgery has been shown to be adequate treatment for women with stage Ia disease who wish to preserve fertility [12,13]. Patients with a prior or concomitant second malignancy were excluded, as were patients with a World Health Organization (WHO) performance status of more than 3, previous treatment with chemotherapy or radiation therapy, expected inadequacy of follow-up, and an interval of more than 6 weeks between surgical staging procedure and randomization. The Institutional Review Board of each participating center had to approve the study, and informed consent of each patient was a prerequisite.

Surgical Staging

Surgical staging had to consist of at least careful inspection and palpation of all peritoneal surfaces, with biopsies of any suspect lesions, such as adhesions adjacent to the ovarian tumor.

However, far more comprehensive staging was strongly advised, including omentectomy; peritoneal washings; blind biopsies from the peritoneum in the pelvis (pouch of Douglas, bladder, pelvic sidewalls), the paracolic gutters, and the right hemidiaphragm; and iliac and peri-aortic lymph node sampling. If all of these staging requirements were met, the staging performance was considered to be optimal. Three other, less comprehensive staging categories were defined: modified, minimal, and inadequate (Table 1). Strict guidelines were also given for the microscopic assessment of histologic cell type and for the assessment of tumor differentiation, according to WHO criteria [10].

Table 1. Requirements for surgical staging following bilateral salpingo-oophorectomy and total abdominal hysterectomy*

Surgical staging category	Staging guidelines
Optimal	Inspection and palpation of all peritoneal surfaces; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy; (blind) biopsies of right hemidiaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac; sampling of iliac and peri-aortic lymph nodes.
Modified	Everything between optimal and minimal staging.
Minimal	Inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases; peritoneal washing; infracolic omentectomy.
Inadequate	Less than minimal staging but at least careful inspection and palpation of all peritoneal surfaces and the retroperitoneal area; biopsies of any suspect lesions for metastases.

*Patients with stage Ia disease who wished to preserve fertility were permitted to have only a unilateral salpingo-oophorectomy.

Randomization

Patients were centrally randomly assigned to either the adjuvant chemotherapy arm or the observation arm by a computer program, using a minimization procedure, at the EORTC Data Center in Brussels. Randomization was stratified according to institution, FIGO stage, and grade of tumor differentiation.

Adjuvant Chemotherapy

Treatment in the adjuvant chemotherapy arm had to consist of at least four courses

of a platinum-based regimen following surgery; however, six courses of treatment were recommended.

Single-agent platinum chemotherapy was also allowed as well as combination regimens. In the case of cisplatin, the required dose was 75 mg/m^2, and for carboplatin the required dose was 350 mg/m^2. Dose modifications in the case of drug toxicity were given when appropriate. Each center had to define its adjuvant chemotherapy regimen in advance and had to remain with that regimen for the duration of the trial. After surgery, patients in the observation arm were not treated again until recurrence. Tumor recurrence had to be confirmed cytologically or histologically.

Patients in the observation arm who had tumor recurrence were given the same chemotherapy regimen that their particular center was using in the adjuvant chemotherapy arm.

Statistical Analysis

Analysis of results was on an intention-to-treat basis. The primary endpoint was overall survival, and the secondary endpoint was recurrence-free survival. Time-to-event analyses were based on the Kaplan–Meier method [14] and events were compared using the log-rank test. Prognostic factor analysis used the Cox proportional hazards regression model, after necessary assumptions were met, to determine statistically significant covariates, such as FIGO stage, tumor grade, histologic cell type, completeness of surgical staging, age, tumor marker carcino antigen 125 (CA 125) level and performance status. Differences in relative size of treatment effect between subgroups of staging performance were tested using a chi-square (χ^2) test for interaction.

Because of the relatively long life expectancy of patients with early-stage ovarian carcinoma and the small expected improvements in survival, the sample size was set, more or less arbitrarily, to 1000 or more patients. An independent interim data-monitoring committee assessed the data and the progress of the study at fixed intervals. A single independent data-monitoring committee monitored the combined accumulating data from ACTION and the parallel trial (ICON1). Interim analyses were interpreted by using conservative statistical significance tests. If the *P* value for the comparison of survival between treatment arms fell below 0.01, consideration was given to stopping the trial. Because patient accrual took longer than expected, the committee decided to close the study in 2000, before the target number of patients was accrued. Audits by an independent quality control panel were done during the course of the study to verify the quality of the data. A separate publication on the findings of this panel is in preparation, but preliminary analysis has confirmed the reliability of the surgical staging data.

RESULTS

Baseline Characteristics

Between November 1990 and January 2000, a total of 448 patients were accrued to the trial by 40 centers from nine European countries. Analysis is complete through March 26, 2001 (Fig. 1). Table 2 shows the clinical and tumor characteristics of the patients in both trial arms. The majority of patients in the chemotherapy arm received cisplatin combined with cyclophosphamide (102 patients or 47%) or single-agent carboplatin (71 patients or 33%). The various clinical and pathologic risk factors were well balanced between the two arms. Thirteen patients in the observation arm received

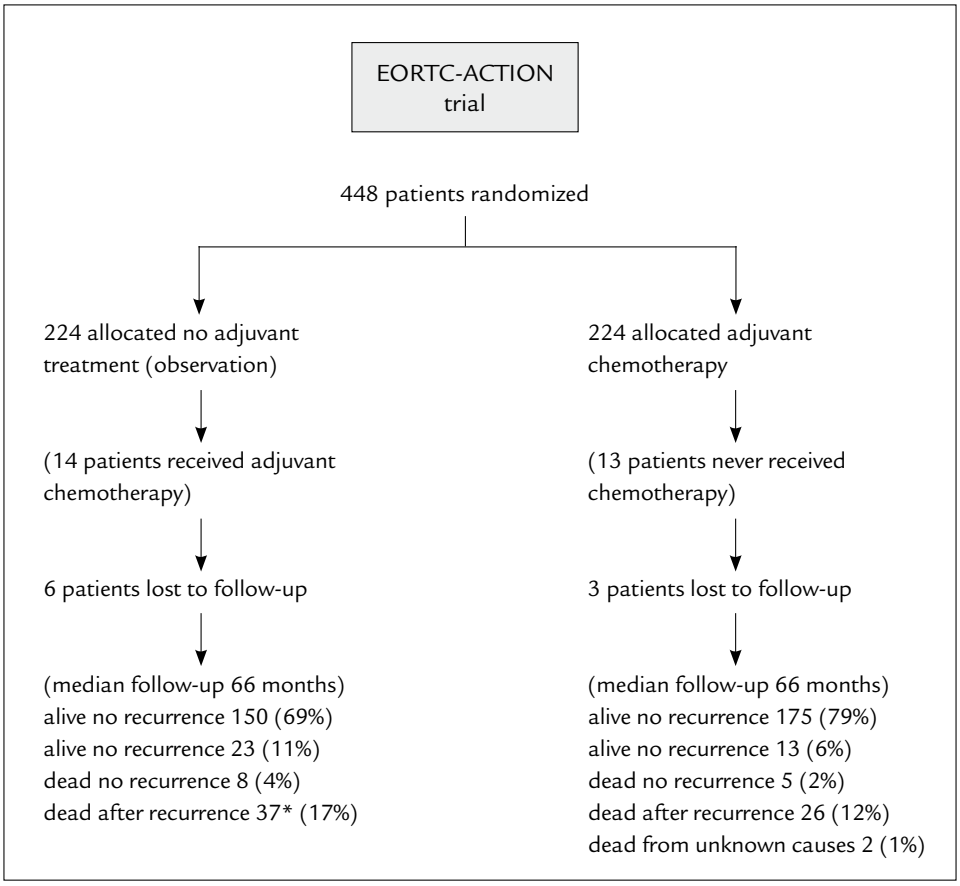


Figure 1. CONSORT diagram of the trial profile of the European Organisation for Research and Treatment of Cancer (EORTC)–Adjuvant ChemoTherapy In Ovarian Neoplasm (ACTION) trial.
*In one patient, no recurrent disease was suspected before the time of death.

Table 2. Clinical and tumor characteristics in patients with early ovarian cancer (stage I–IIa) by treatment arm*

Characteristic	Observation (N =224)	Adjuvant chemotherapy (N =224)
Age, y (median; range)	55 (22–77)	54 (18–84)
Performance status†, n (%)		
0	199 (89)	188 (84)
1	21 (9)	34 (15)
2	3 (1)	2 (1)
Missing 1 (1)	0 (0)	
FIGO stage‡, n (%)		
Ia	76 (33)	79 (35)
Ib	18 (8)	19 (8)
Ic, ovarian surface	28 (13)	22 (10)
Ic, capsule ruptured	52 (23)	64 (29)
Ic, ascites/malignant washing	33 (15)	24 (11)
IIa	15 (7)	16 (7)
Missing	2 (1)	0 (0)
Tumor grade§, n (%)		
Well differentiated	28 (12)	26 (12)
Moderately differentiated	114 (51)	114 (50)
Poorly differentiated	78 (35)	78 (35)
Unknown	2 (1)	6 (3)
Missing	2 (1)	0 (0)
Histologic cell type, n (%)		
Serous	74 (33)	82 (37)
Mucinous	35 (16)	42 (19)
Endometrioid	72 (32)	48 (21)
Clear-cell	26 (12)	37 (17)
Undifferentiated	5 (2)	3 (1)
Other	9 (4)	7 (3)
Missing	3 (1)	5 (2)
CA 125, n (%)		
Normal	55 (24)	73 (33)
Abnormal	116 (52)	0 (40)
Not done	51 (23)	7 (25)
Missing	2 (1)	4 (2)
Surgical staging performance, n (%)		
Optimal	75 (34)	76 (34)
Modified	68 (30)	70 (31)
Minimal	60 (27)	54 (24)
Inadequate	19 (9)	24 (11)
Missing	2 (1)	0 (0)

*Missing = patient information was missing.
†Performance status was in accordance with World Health Organization guidelines [15].
‡FIGO = International Federation of Gynecology and Obstetrics staging system [11].
§Tumor grade was in accordance with World Health Organization grading criteria [10].

chemotherapy, and 14 patients in the adjuvant chemotherapy arm did not. The reasons for these protocol violations were morbidity, disease progression, administrative error, and patient refusal. Follow-up ranged from 3 months to 9 years, with a median follow-up of 5.5 years. Nine patients were lost to follow-up, six in the observation arm and three in the chemotherapy arm.

During the follow-up period 100 recurrences were detected, 60 in the observation arm and 40 in the chemotherapy arm. The incidence of recurrence in the locoregional, extrapelvic, and combined pelvic and extrapelvic sites in the observation and chemotherapy arms was 33%, 47%, and 20% and 35%, 50%, and 15%, respectively (Table 3). Overall, 78 patients died, 45 in the observation arm and 33 in the chemotherapy arm. Sixty-three of the 78 deaths (81%) were due to ovarian cancer; this percentage was similar between the two trial arms. Eight patients in the observation arm died of causes other than ovarian cancer: two of heart failure, three of other malignancies, two of cerebrovascular accident, and one of respiratory failure. Five patients in the chemotherapy arm died of causes other than ovarian cancer: two of heart failure, one of cerebrovascular accident, one of idiopathic thrombocytopenia, and one of pulmonary thromboembolism following a bone fracture. Two patients in the chemotherapy arm died of unknown causes.

Table 3. Site of disease recurrence in patients with early ovarian cancer by treatment arm

Variable	Adjuvant chemotherapy (N = 224)	Observation (N = 224)	Total (N = 448)
No recurrence, n (%)	184 (82)	164 (73)	348 (78)
Recurrence, n (%)	40 (18)	60 (27)	100 (22)
Pelvic	14 (6)	20 (9)	34 (8)
Extrapelvic	20 (9)	28 (13)	48 (11)
Both (pelvic + extrapelvic)	6 (3)	12 (5)	18 (4)

Survival Data

Kaplan–Meier analysis of overall survival yielded 5-year survival figures in the observation and the adjuvant chemotherapy arms of 78% and 85%, respectively, a difference of 7% (95% CI = –1.08% to 15.72%). The difference in overall survival between the two arms was not statistically significant, as depicted in Fig. 2 (HR = 0.69 (95% CI = 0.44 to 1.08); $P = 0.10$). The Kaplan–Meier curves for recurrence-free survival in both arms are shown in Fig. 3. Patients in the adjuvant chemotherapy arm had statistically better recurrence-free survival than patients in the observation arm, with an HR of 0.63 (95% CI = 0.43 to 0.92; $P = 0.02$). These results translate into 5-year survival figures of 68% for patients in the observation arm and 76% for patients in the adjuvant chemotherapy arm, an improvement in recurrence-free survival of 8% (95% CI = –0.88% to 18.04%).

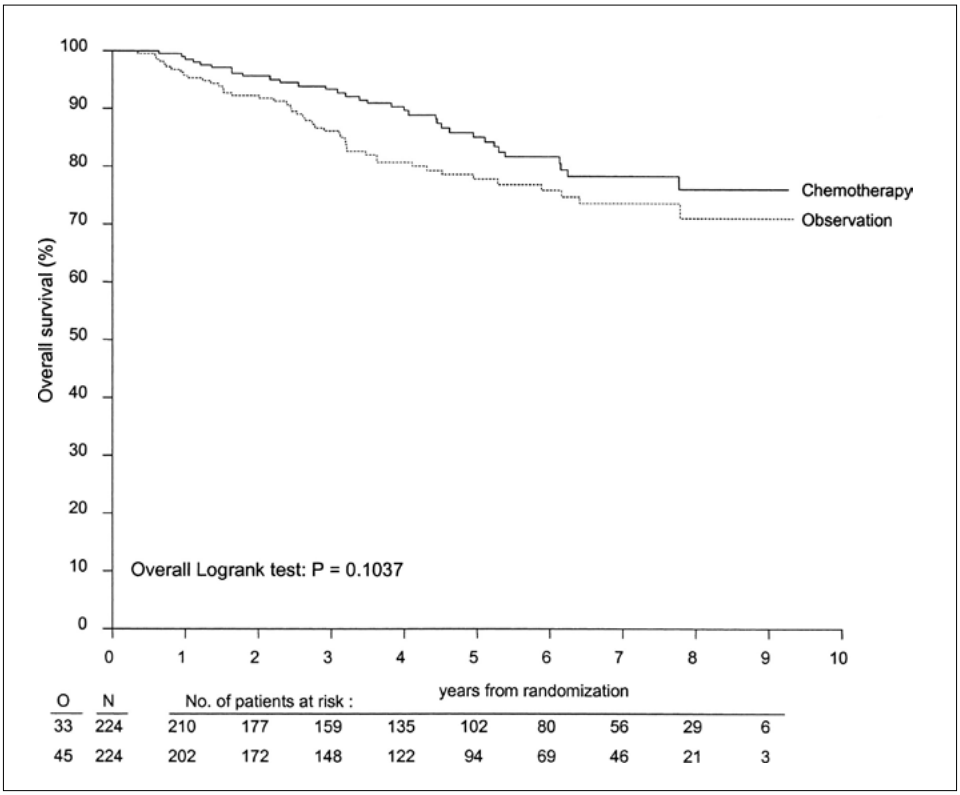


Figure 2. Kaplan–Meier curves for overall survival in patients with early-stage ovarian cancer. Adjuvant chemotherapy patients (n = 224) (**solid line**) were those patients who received immediate adjuvant chemotherapy. Observation patients (n = 224) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated.
The hazard ratio is 1.45 (95% confidence interval [CI] = 0.93 to 2.27, *P* = 0.10 using the log-rank test). These results translate into 5-year overall survival figures of 78% for patients in the observation arm and 85% for patients in the adjuvant chemotherapy arm, a difference of 7% (95% CI = –1.08% to 15.72%). N = number of patients; O = number of observations (events).
Of the 100 patients who had tumor recurrence, 66 died (66%; 62 deaths were due to ovarian cancer). Among the optimally staged patients, six of the 13 (46%) patients who had tumor recurrence in the observation arm died and nine of the 12 (75%) patients who had tumor recurrence in the chemotherapy arm died. Among the non-optimally staged patients, the percentages were different; 33 of the 47 (70%) patients who had tumor recurrence in the observation arm died, and 18 of the 28 (64%) patients who had tumor recurrence in the chemotherapy arm died.

Prognostic Factors and Survival

To determine possible prognostic factors for overall and recurrence-free survival, we performed univariate and multivariable analyses of possible risk factors apart from treatment on the survival data. In Table 4, the univariate and multivariable analyses of possible risk factors apart from treatment are summarized.

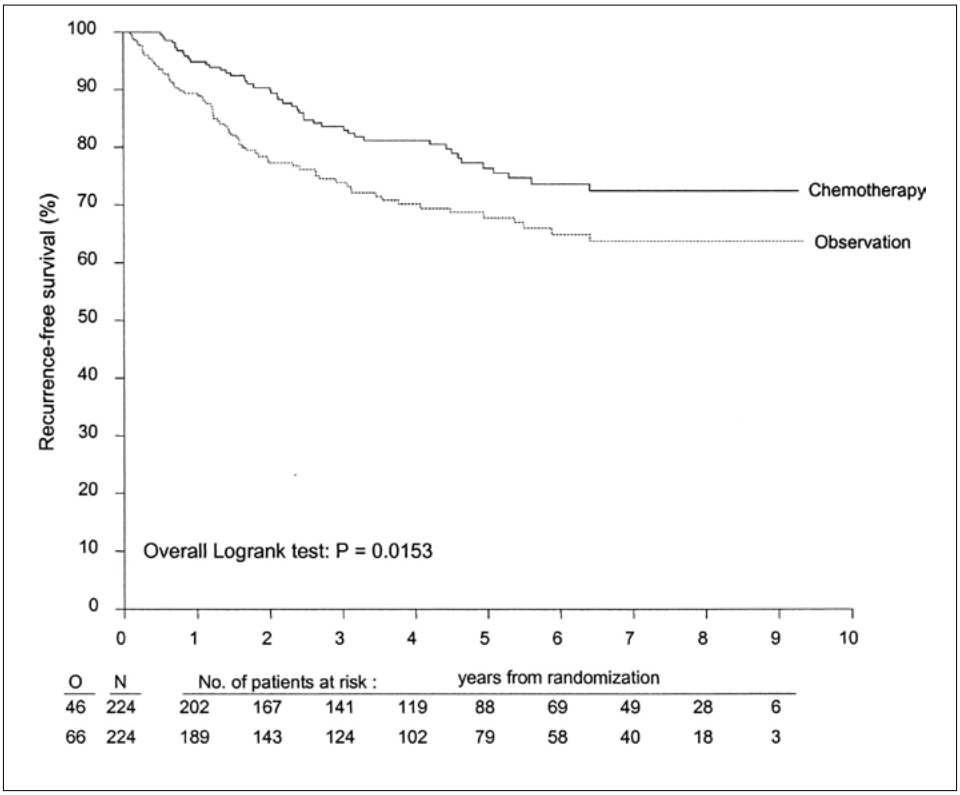


Figure 3. Kaplan–Meier curves for recurrence-free survival in patients with early-stage ovarian cancer.
Adjuvant chemotherapy patients (n = 224) (**solid lin**e) were those patients who received immediate adjuvant chemotherapy.
Observation patients (n = 224) (**dotted line**) were those patients who were observed until adjuvant chemotherapy was indicated. The hazard ratio is 1.59 (95% confidence interval [CI] = 1.09 to 2.31, *P* = 0.02 using the log-rank test) in favor of adjuvant chemotherapy.
These results translate into 5-year recurrence-free survival figures of 68% for patients in the observation arm and 76% for patients in the adjuvant chemotherapy arm, a difference of 8% (95% CI = 0.88% to 18.04%).
N = number of patients; O = number of observations (events).

CA 125 analysis was performed in too few of the patients to be considered in the multivariable analysis. FIGO stage was not a statistically significant prognostic factor. Staging adequacy and tumor grade were statistically significant prognostic factors for overall survival and recurrence-free survival in the univariate and multivariable analysis. Histologic cell type was a statistically significant prognostic factor only for overall survival in the univariate and multivariable analysis.

Table 4. Prognostic factors that were identified in the univariate and multivariable analyses*

	Univariate		Multivariable	
Variable	HR (95% CI)	*P* value†	HR (95% CI)	*P* value‡
Overall survival				
Surgical staging	2.24 (1.29 to 3.90)	0.004	2.05 (1.14 to 3.67)	0.04
Tumor grade	1.64 (1.05 to 2.56)	0.03	1.62 (1.03 to 2.54)	0.03
Histologic cell type	1.79 (1.11 to 2.88)	0.02	1.72 (1.06 to 2.79)	0.02
Recurrence-free survival				
Surgical staging	2.06 (1.25 to 3.39)	0.004	1.96 (1.18 to 3.26)	0.009
Tumor grade	1.85 (1.28 to 2.69)	0.001	1.86 (1.28 to 2.70)	0.001
Histologic cell type	N.S.		N.S.	

*HR = hazard ratio; CI = confidence interval. Surgical staging = inadequate versus minimal, modified, and optimal. Tumor grade was in accordance with World Health Organization grading criteria (10). Histologic cell type = mucinous/endometrioid versus serous, clear-cell, undifferentiated, and other (rare) histology. N.S. = not statistically significant.
†*P* value was determined using the Cox proportional hazards regression model.
‡*P* value was determined using the Cox proportional hazards regression model.

Because staging adequacy was a statistically significant prognostic factor, we investigated survival by different categories of staging (Table 1). Four categories were defined, and the survival curves are shown in Fig. 4. However, for further survival analyses, these categories were dichotomized into just two categories: optimal and non-optimal. This particular dichotomization was done a priori and for reasons of clarity. From a clinical point of view, optimal staging would be easy to define; that is, all staging steps had to be performed. The other staging categories— modified, minimal, and inadequate (regardless of what and how many staging steps were omitted) were regarded as non-optimal.

Of the 448 patients, 151 were optimally staged (observation arm, 75; chemotherapy arm, 76) and 295 were non-optimally staged (observation arm, 147; chemotherapy arm, 148) and in two patients, the staging status was unknown (Table 2). The various baseline characteristics were well balanced among the different staging categories (data not shown). In the observation arm, patients who underwent non-optimal surgical staging had statistically significantly worse overall survival (Fig. 5, A) (HR = 2.31, 95% CI = 1.08 to 4.96; $P = 0.03$) and recurrence-free survival (Fig. 5, C) (HR = 1.82, 95% CI = 1.02 to 3.24; $P = 0.04$) than the optimally staged patients. However, no difference in overall or recurrence-free survival was evident in the patients in the adjuvant chemotherapy arm (Fig. 5, B and D).

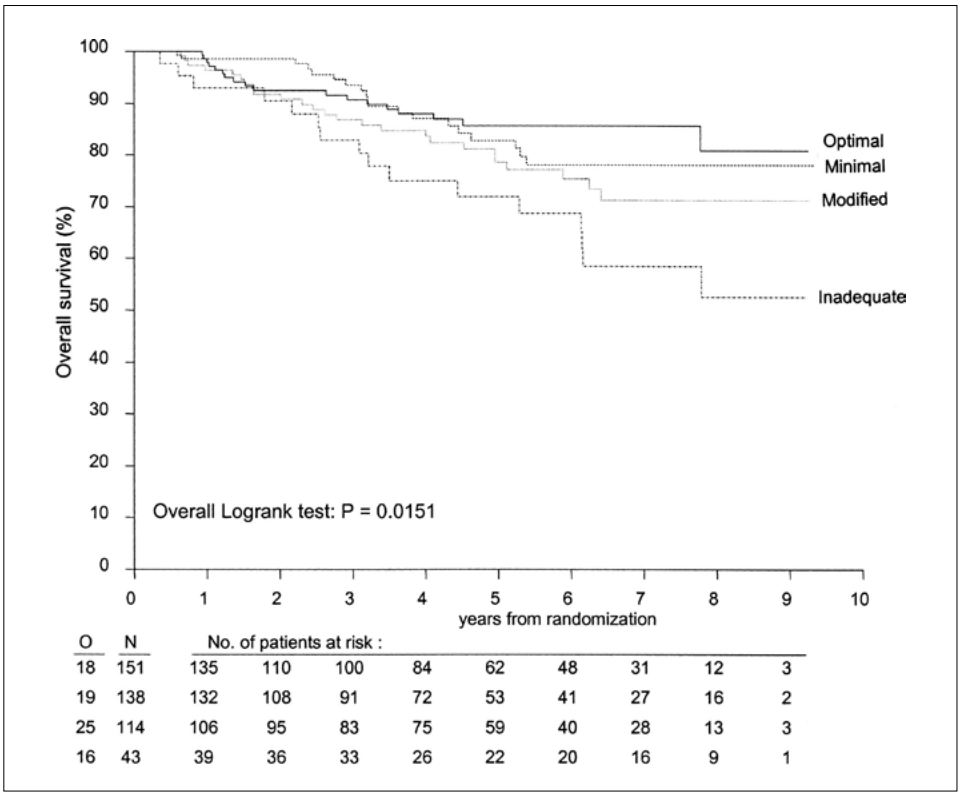


Figure 4. Kaplan–Meier curves for overall survival in patients with early-stage ovarian carcinoma by staging type. Optimal staging (n = 151) (**solid line**), modified staging (n = 138) (**solid dotted line**), minimal staging (n = 114) (**fine dotted line**), and inadequate staging (n = 43) (**solid/fine dotted line**) are in accordance with the staging guidelines presented in Table 1. The hazard ratio is 2.17 (95% confidence interval [CI] = 1.25 to 3.76; *P* = 0.02 using the log-rank test) in favor of optimal staging. N = number of patients; O = number of observations (events).

Extending this subgroup analysis further by looking at the optimal and non-optimal staging groups separately, no difference in overall survival between the observation arm and the chemotherapy arm was found in the optimally staged patients (Fig. 6, A), whereas a statistically significant difference in overall survival between the two arms was demonstrated in the non-optimally staged patients (Fig. 6, B) (HR = 1.75, 95% CI = 1.04 to 2.95; *P* = 0.03). A similar phenomenon was seen for recurrence-free survival (optimally staged patients: HR =1.14, 95% CI = 0.54 to 2.39; *P* = 0.7 [Fig. 6, C]; non-optimally staged patients: HR = 1.78, 95% CI = 1.15 to 2.77; *P* = 0.009 [Fig. 6, D]). However, interactions between treatment effect and the staging subgroups did not reach statistical significance (HR = 2.18, 95% CI . 0.74 to 6.38; *P* = 0.15; Fig. 7).

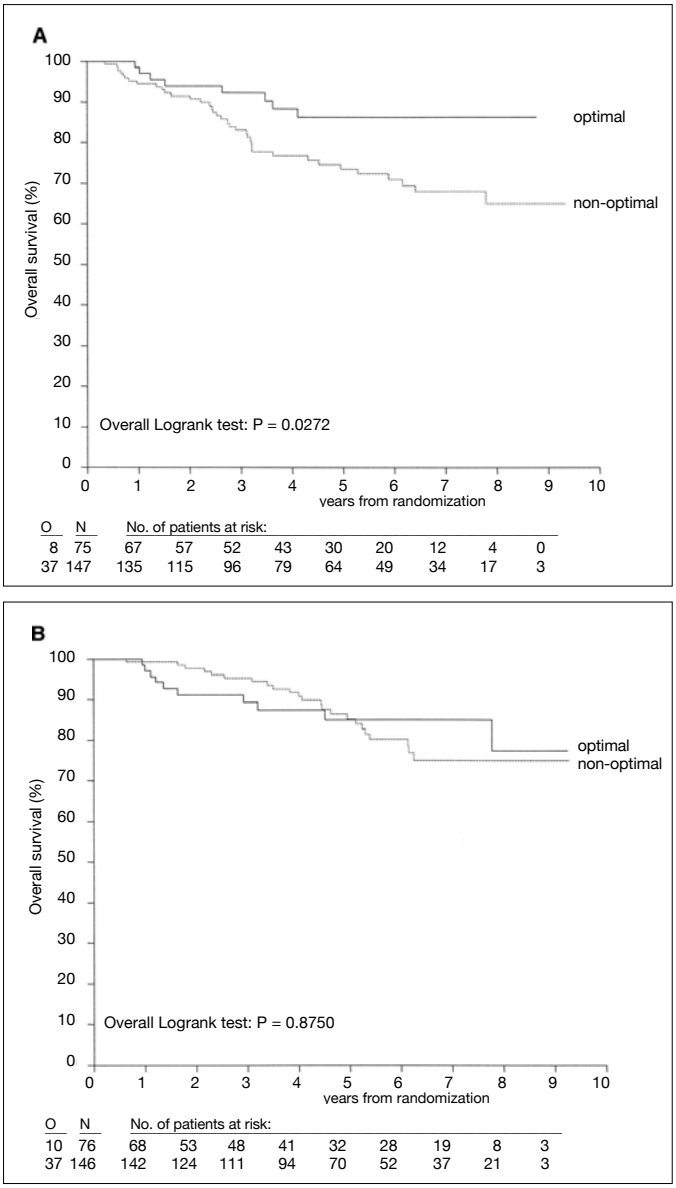
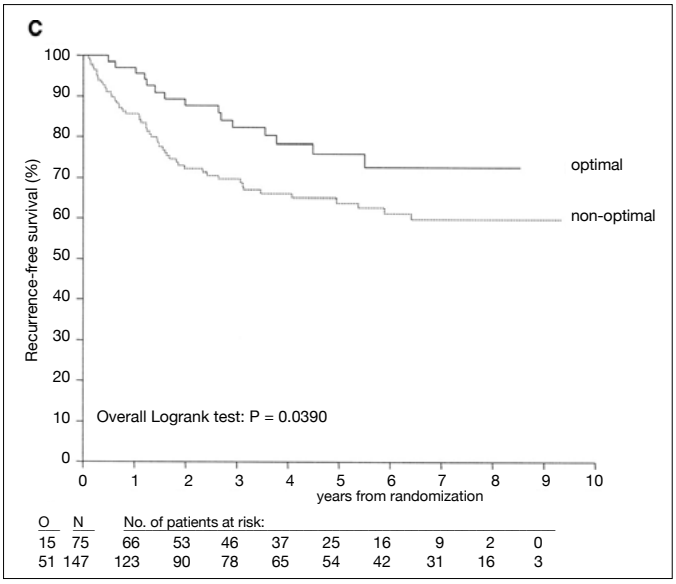
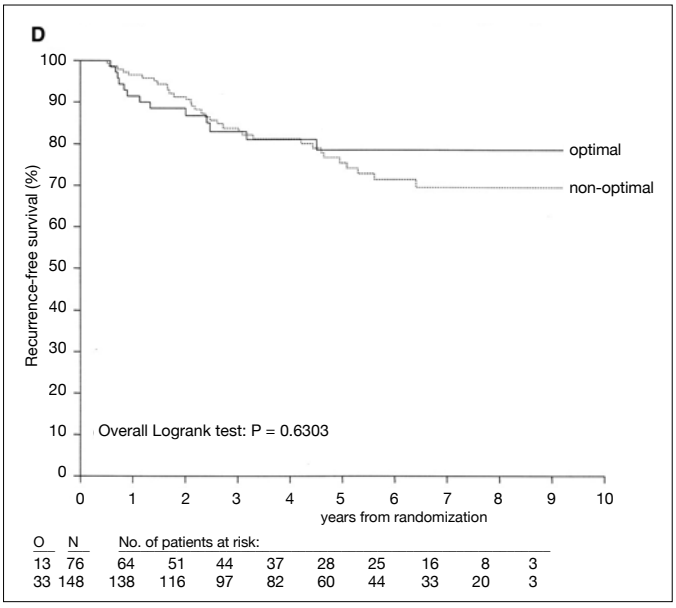


Figure 5. Kaplan–Meier curves for overall and recurrence-free survival in patients with early-stage ovarian cancer by staging type.
Optimal staging (n = 75 in the observation arm and n = 76 in the chemotherapy arm) (**solid line**) and non-optimal staging (modified, minimal, inadequate staging categories combined) (n = 147 in the observation arm and n = 148 in the chemotherapy arm) (**dotted line**) are in accordance with the staging guidelines presented in Table 1. N = number of patients; O = number of observations (events).
A) Overall survival in the observation arm. The hazard ratio [HR] = 2.31 (95% confidence interval [CI] = 1.06 to 4.96, *P* = 0.03 using the log-rank test) in favor of optimal staging. B) Overall survival in the adjuvant chemotherapy arm. HR = 1.06 (95% CI = 0.51 to 2.23, *P* = 0.9 using the log-rank test).





C) Recurrence-free survival in the observation arm. HR = 1.82 (95% CI =1.02 to 3.24, *P* = 0.04 using the log-rank test) in favor of optimal staging. D) Recurrence-free survival in the adjuvant chemotherapy arm. HR 1.17 (95% CI = 0.0.62 to 2.22, *P* = 0.6 using the log-rank test).

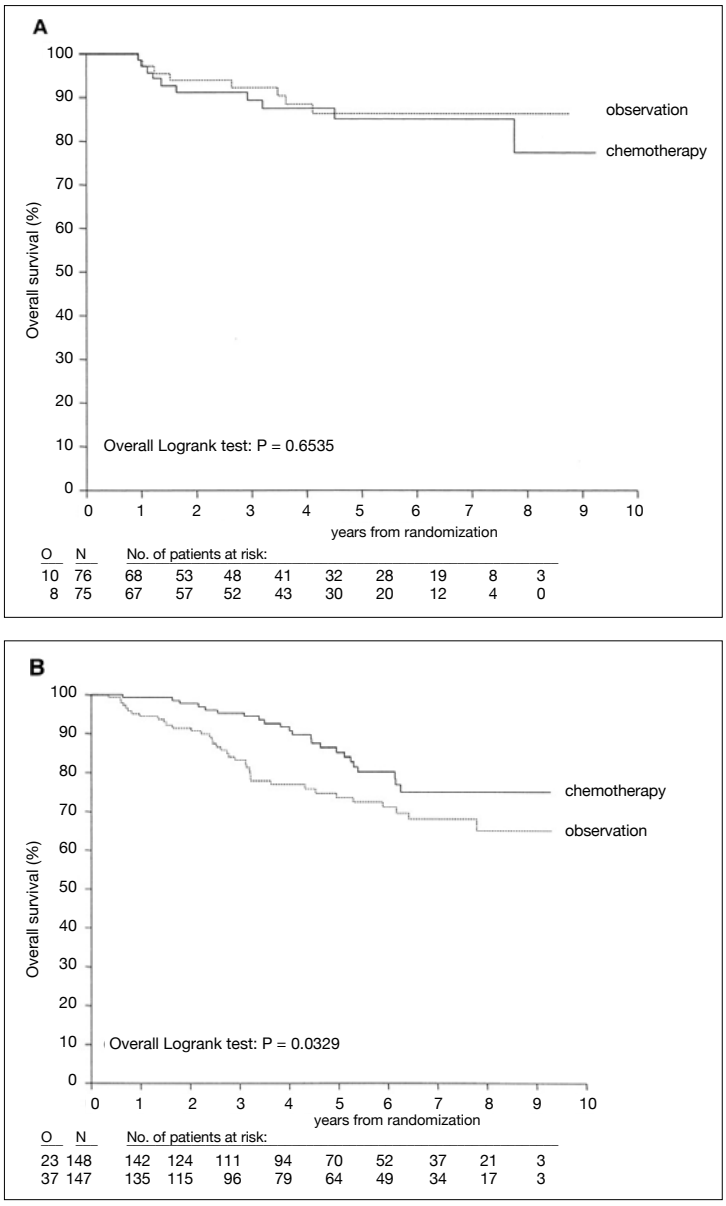
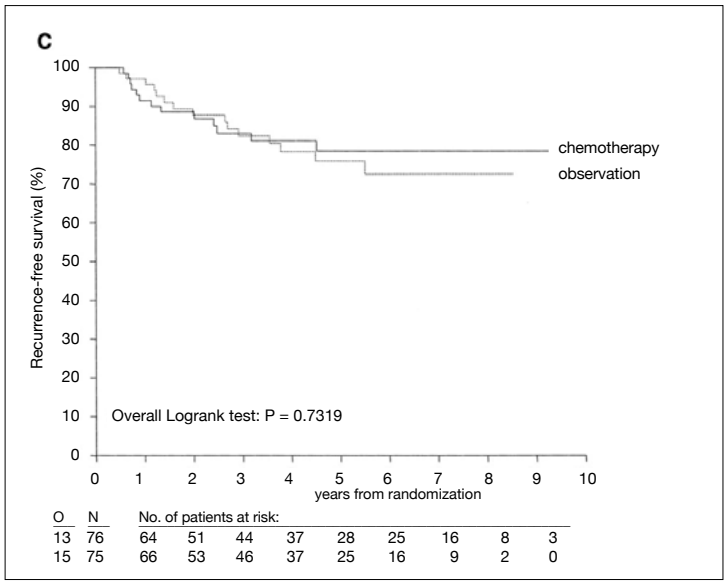
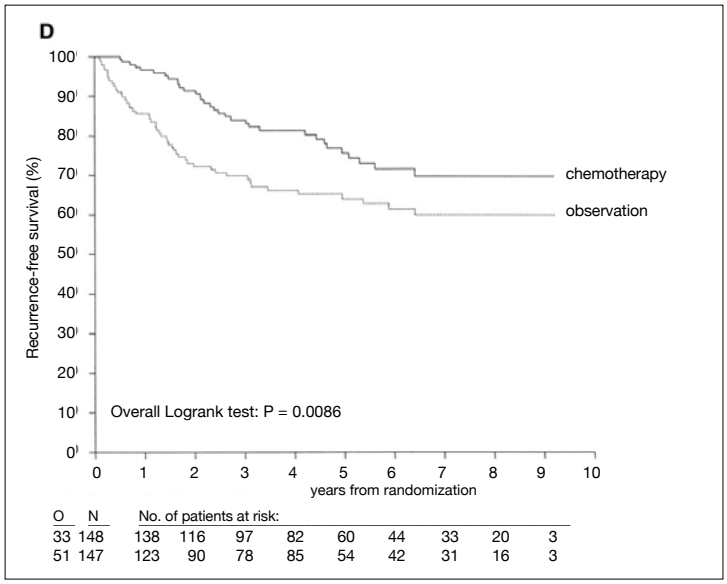


Figure 6. Kaplan–Meier curves for overall and recurrence-free survival in patients with early-stage ovarian cancer by treatment arm.

Chemotherapy patients (**solid line**) were those patients who received immediate adjuvant chemotherapy (n = 76 in optimally staged arm, and n = 148 in non-optimally staged arm). Observation patients (**dotted line**) were those patients who were observed until chemotherapy was indicated (n = 75 in optimally staged arm, and n = 147 in non-optimally staged arm). N = number of patients; O = number of observations (events). A) Overall survival in the optimally staged patients. The hazard ratio (HR) = 0.81 (95% confidence interval [CI] = 0.32 to 2.05, *P* = 0.7 using the log-rank test). B) Overall survival in the non-optimally staged patients. HR = 1.75 (95% CI = 1.04 to 2.95, *P* = 0.03 using the log-rank test) in favor of adjuvant chemotherapy.





C) Recurrence-free survival in the optimally staged patients. HR = 1.14 (95% CI = 0.54 to 2.93, *P* = 0.7 using the log-rank test). D) Recurrence-free survival in the non-optimally staged patients. HR = 1.78 (95% CI = 1.51 to 2.77, *P* = 0.009 using the log-rank test) in favor of adjuvant chemotherapy.

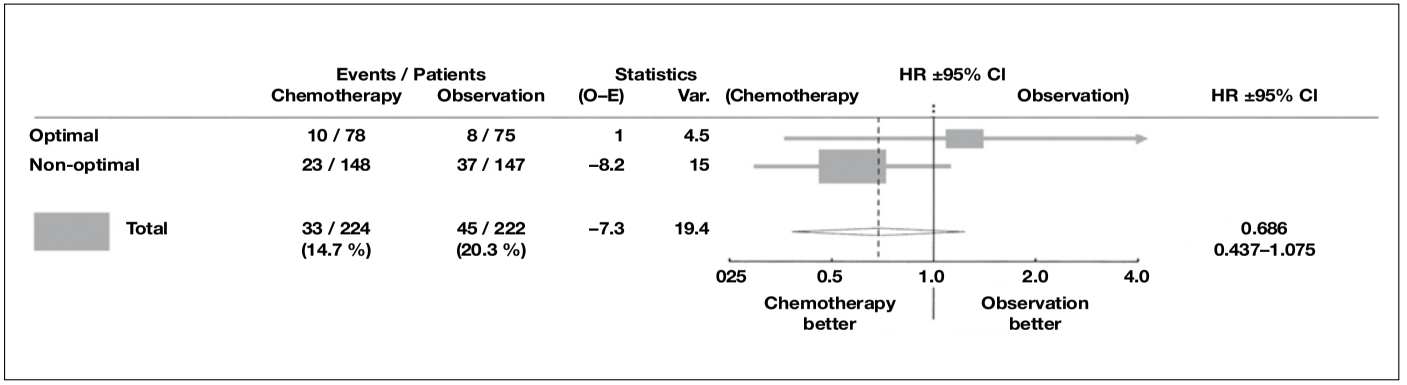


Figure 7. Forest plots of the interaction between the surgical staging groups optimal and non-optimal staging versus treatment effect (adjuvant chemotherapy better versus observation better) for overall survival.

For each dataset, the hazard ratio (HR) for overall survival is plotted as a **solid square**, and the area of the square is proportional to the variance of the estimated effect. The length of the **horizontal line** through the square indicates the 95% confidence interval (CI). The **arrow** at the end of the horizontal line indicates that the 95% CI is larger than the scale of the figure. The **diamond** indicates the HR (middle of the diamond) and the 95% CI (extremes of the diamond) for the combined data. Linear trends and heterogeneity of the HRs to detect differences in relative size of treatment effect were assessed by a chi-square (χ^2) test for interaction. χ^2 test for heterogeneity = 2.01, degrees of freedom = 1; P = 0.15. The HR for overall survival in optimally staged and non-optimally staged patients is 2.18 (95% CI = 0.74 to 6.38; P = 0 .15). O-E = number of events observed minus number of events expected under the null hypothesis. Variance = variance of 1/logarithm of the HR. The HR for overall survival in the chemotherapy arm and the observation arm is 0.686 (95% CI = 0.437 to 1.075)

DISCUSSION

The present study provides evidence that adjuvant chemotherapy delays disease recurrence in patients with early-stage ovarian cancer, of whom two-thirds (n =297) had undergone non-optimal surgical staging. For overall survival, however, no statistically significant differences were observed.

In addition to the well known risk factors for overall and recurrence-free survival, such as tumor grade and histologic cell type [16], the completeness of surgical staging was found to be an independent prognostic factor. The impact of surgical staging on prognosis is not surprising, because the extent of staging influences the likelihood of residual disease. Optimal surgical staging minimizes the likelihood of residual stage III disease, and incomplete surgical staging increases the possibility of hidden occult cancer in the peritoneal cavity. The finding that completeness of surgical staging is an independent prognostic factor is not completely new. For example, in 1992 the Department of Obstetrics and Gynecology at Yale University compared expert and comprehensive surgery (i.e., complete surgical staging) in early-stage ovarian cancer with incomplete surgical staging and tumor removal [17]. Although the number of patients in that study was small, a statistically significant survival advantage was demonstrated in favor of the completely staged group. More recently, Italian investigators have also identified the extent of surgical staging with early-stage ovarian carcinoma as an independent prognostic factor in their multivariable analysis [18].

In the current study, patients in the observation arm who were optimally staged had statistically significantly better overall and recurrence-free survival than patients who were non-optimally staged (Fig. 5, A and C). However, the poor prognosis of the non-optimally staged patients could be corrected by administering adjuvant chemotherapy (Fig. 5, B and D). This finding suggests that adjuvant chemotherapy in early-stage ovarian cancer may work predominantly by affecting small-volume or microscopic tumor implants or metastases that remain unnoticed at the time of surgical staging. This hypothesis is supported by the finding that chemotherapy improved both overall and recurrence-free survival in the non-optimally staged patients (i.e., those patients who may have had residual disease) and not in the optimally staged patients (i.e., those patients who had only a minimal chance of residual disease) (Fig. 6, B and D). The finding that adjuvant chemotherapy is effective in non-optimally staged patients might also explain the results of the ICON1 trial [9] and the combined ICON1/ACTION analysis [19], in which the majority of patients were most probably not optimally staged. Although FIGO stage is generally a well known risk factor for survival of patients with ovarian cancer, it was not found to be a prognostic factor in this study. For example,

stage Ic disease was not associated with a higher risk of recurrence or death compared with moderately and poorly differentiated stages Ia and Ib disease (data not shown). In addition, in a recent meta-analysis of more than 1500 cases of early-stage ovarian cancer, Vergote et al. [16] found that stage Ic disease had a prognosis similar to that of stage Ib disease. Thus, these findings might be an important consideration when redefining high-risk early-stage ovarian cancer.

Salvage treatment of patients with recurrent disease showed a difference in salvage rate (i.e., the percentage of patients successfully treated for tumor recurrence) between the optimally staged and the non-optimally staged patients. In the non-optimally staged patients, the salvage rate in the observation and the adjuvant chemotherapy arms was similar (70% and 64%, respectively). In the optimally staged patients, salvage treatment with adjuvant chemotherapy was more successful in the observation arm than in the adjuvant chemotherapy arm (75% and 46%, respectively). The number of patients involved in this analysis was small, but it is of interest that the same difference in the effectiveness of chemotherapy salvage treatment was found in the Italian Gruppo Interregionale Collaborative Oncology Group (GICOG) study, in which patients also underwent complete surgical staging [3]. If this difference in the effectiveness of salvage treatment were to be observed in larger studies, it would give additional support to a policy of postponing chemotherapy until the time of actual tumor recurrence, providing that optimal surgical staging had been performed.

Like other analyses of this kind, this study has several potential limitations. First, the ACTION trial was not specifically designed to compare different surgical staging procedures, and patients were not prospectively stratified according to the various surgical staging categories. Retrospective stratification, however, showed a well-balanced distribution of the four staging categories between the two treatment arms (data not shown) and no differences in the distribution of other risk factors, such as tumor grade and histologic cell type, between optimally and non-optimally staged patients. Second, the numbers of patients become increasingly smaller when performing subgroup analyses.

Although this study is the largest randomized trial in early-stage ovarian cancer in terms of the number of assessable patients, it still suffers from a limited sample size. Therefore, the interpretation of results should be made with sufficient care, because, although interactions of this kind are generally hard to detect, a lack of statistically significant differences between two groups does not necessarily imply equivalence. Statistical tests to analyze the potential interaction between the chemotherapy effect and the staging adequacy showed only trends and no proof ($P = 0.15$). In Fig. 7, a

graphic representation of this analysis can be seen. The hazard ratios of optimal and non-optimal staging regarding overall survival seem to be different, but statistical proof at a $P = 0.05$ level was prevented by the large 95% confidence interval in the optimally staged patients. The main determinant of the width of the 95% confidence interval is the number of events, and events were infrequent following complete surgical staging. It is, therefore, exactly the factor that has to be proven that is hampering the statistical ability to do so.

This effect, the opposite of a self-fulfilling prophecy, sheds doubt on the possibility that stronger statistical proof will ever be feasible in terms of necessary numbers of patients. Although we have stressed the clinical significance of complete surgical staging of early-stage ovarian cancer, some concern may be raised about its feasibility in clinical practice.

In the ACTION trial, even though strict guidelines for optimal surgical staging were set, only one-third of the patients were optimally staged according to the guidelines in Table 1. The reasons for this low number of patients actually receiving staging according to trial protocols are well known. Early-stage ovarian cancer often presents with symptoms mimicking a benign ovarian cyst. This clinical condition is then dealt with by surgeons with either a lack of knowledge of ovarian cancer spread or a lack of surgical experience (e.g., in lymph node sampling) [20,21]. The findings of this study underscore the clinical significance of surgical staging and will hopefully influence the current practice of referral and centralization to oncology centers of suspected early-stage ovarian cancer patients.

In conclusion, this trial studied patients who were completely and comprehensively (i.e., optimally) staged in only one-third of cases. Taking all patients into account, adjuvant chemotherapy statistically significantly improved recurrence-free survival, but no improvement was seen in overall survival. Tumor grade, histologic cell type, and completeness of surgical staging were independent prognostic factors. In the subgroup analysis of different staging adequacy, indications were found that adjuvant chemotherapy is not effective in optimally staged patients. Thus, we suggest that adjuvant chemotherapy in early-stage ovarian cancer is predominantly effective in patients with occult residual disease and that its effectiveness is dependent on the likelihood of remaining ovarian cancer spread. The adequacy of surgical staging is indicative of the likelihood of unappreciated residual cancer, and the observed benefit of adjuvant chemotherapy - primarily in non-optimally staged patients - may be indicative of a benefit of adjuvant chemotherapy only in patients with appreciable residual disease. In the next EORTC trial we will attempt to confirm the findings that adjuvant

chemotherapy in early-stage ovarian cancer, is not effective after optimal surgical staging. We are considering a trial protocol to randomly assign non-optimally staged patients into either restaging (i.e., to make the patient optimally staged) followed by observation or direct adjuvant chemotherapy without restaging. Because the two trial arms may be equivalent in terms of survival, quality-of-life issues will be an important endpoint of this study.

APPENDIX

EORTC—ACTION TRIAL COLLABORATORS AND AFFILIATIONS*:

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* at the time the trial was ongoing

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Chapter 3

Chemotherapy for early ovarian cancer

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PURPOSE OF REVIEW

The treatment of early ovarian cancer has long been based on non-randomized studies and on a small number of randomized studies without sufficient power. Adjuvant chemotherapy is often given to high-risk patients, but the benefit of such an approach has never been proven and the definition of high-risk early ovarian cancer differs widely. Recently, the results of the two largest randomized clinical trials on early ovarian cancer became available. Both trials are discussed, and their results are related to the other relevant literature of the last three years.

RECENT FINDINGS

A meta-analysis of over 1500 patients from the year 2001 confirmed tumor grade as a strong prognostic factor but it also demonstrated the adverse effect of capsule rupture before and during surgery. The Adjuvant ChemoTherapy in Ovarian Neoplasm trial (European Organisation for Research and Treatment of Cancer) randomized 448 patients to either adjuvant chemotherapy following surgery or observation.

Adjuvant chemotherapy improved overall survival and disease-free survival in non-optimally staged patients but showed no benefit in optimally staged patients. The Medical Research Council International Collaborative Ovarian Neoplasm 1 trial randomized 477 patients in a similar way. Overall survival and disease-free survival were improved by adjuvant chemotherapy.

It was argued that the study population of the International Collaborative Ovarian Neoplasm 1 trial probably represents non-optimally staged patients, and this hypothesis explains why the results of this trial were in accord with those of the Adjuvant ChemoTherapy in Ovarian Neoplasm trial.

SUMMARY

The implications of these data are that a complete surgical staging is of utmost importance and should be pursued. In cases of non-optimal staging and contraindications for restaging, adjuvant chemotherapy is indicated to deal with unnoticed residual tumor deposits that exist in approximately 25% of cases.

INTRODUCTION

The general notion of how to treat early epithelial ovarian cancer (stage I–IIa according to the International Federation of Gynaecology and Obstetrics) has long been based on a relatively small number of studies. The majority of these studies include retrospective observational reports, and, until 2000, only two relevant randomized clinical trials were available for consideration [1,2].

Young et al. [3], in a landmark study, had been the first to show that comprehensive restaging in patients with apparent early-stage ovarian carcinoma (on the basis of incomplete surgical staging) resulted in upstaging to stage III disease in 24% of cases (grade I tumors, 16%; grade III tumors, 46%). These findings were confirmed by a number of other investigators between 1985 and 1998 [4–9].

The importance of a complete surgical staging was also stressed by the group of Monza [10] in Italy, who found the completeness of surgical staging to be an independent prognostic factor in early ovarian cancer for overall survival as well as for disease-free survival (DFS).

Italian investigators also demonstrated that unilateral salpingo-oophorectomy instead of bilateral salpingooophorectomy and total abdominal hysterectomy can be regarded as adequate surgical staging in selected cases [11,12].

The only relevant randomized clinical trials with an observation arm were published in 1990 and 2000 [1,2]. The first study randomized 81 comprehensively staged patients with low-risk ovarian cancer to either oral melphalan or observation. There was no difference in overall survival or DFS between the two arms [1].

In an Italian trial [2] involving patients with stage Ia or stage Ib G2 or G3 ovarian cancer, a randomization was performed between no treatment following complete surgical staging on the one hand and six courses of cisplatin (50 mg/m^2 every 28 days) on the other. A recent update of this trial with a median follow-up of more than 10 years confirmed the results of the original publication: cisplatin significantly reduced the recurrence rate but not overall survival (overall survival in cisplatin arm, 88%; overall survival in observation arm, 82%) [12]. This difference was attributed to the fact that patients who relapsed from the observation arm were subsequently crossed over and treated with cisplatin. The chemo-naive patients from the observation arm responded better to cisplatin than the relapsed patients from the adjuvant chemotherapy arm. This observation is an important argument for postponing chemotherapy in early ovarian cancer until the time of actual tumor recurrence [2].

On the basis of all these data, the importance of complete surgical staging was generally acknowledged. Furthermore, it was felt that adjuvant treatment for some groups of high-risk patients should be considered to reduce the recurrence rate, although a survival benefit had never been demonstrated. Because of the lack of randomized trials with sufficient numbers of patients, proof of the benefits of adjuvant treatment was not available. It was also realized that in routine practice the complete surgical staging of all patients with presumed early ovarian cancer is difficult to pursue [13,14].

RANDOMIZED CLINICAL TRIALS IN 2000–2003

Recently, the results of three randomized clinical trials containing an observation arm following surgery were published; the fourth paper was a case-based meta-analysis of two of these studies [15-18].

In a Scandinavian trial [15], patients were randomly assigned to receive either carboplatin (n = 81) or observation (n = 81) after surgery. No differences in overall survival or DFS between the two arms were found (hazard ratio of DFS, 0.98, 95% confidence interval, 0.52–1.83; hazard ratio of overall survival, 0.94, 95% confidence interval, 0.36–2.36). Apart from tumor grade, aneuploidy was found to be a strong and independent prognostic factor [15].

The Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) trial [16] was a multicenter European trial, also randomizing patients with early ovarian cancer to either observation following surgery or adjuvant chemotherapy. The main characteristics of this trial are summarized in Table 1 [16,17]. The inclusion criteria defined the ACTION population as having median to high-risk early ovarian cancer. Much emphasis was devoted to the surgical staging procedure in order to define the early-stage condition of the study population as far as possible. A total of 448 patients were involved: 224 were in the observation arm, and 224 were in the chemotherapy arm. Despite the strict guidelines for optimal surgical staging, only 151 (34%) patients were found to have been optimally staged and 297 (66%) patients were considered as non-optimally staged. Overall survival was not statistically different between the observation arm and the chemotherapy arm (hazard ratio, 0.69; 95% confidence interval, 0.44–1.08; P = 0.10). DFS was significantly better in the chemotherapy arm (hazard ratio, 0.63; 95% confidence interval, 0.43–0.72; P = 0.02).
Multivariate analysis revealed the histological cell type, the tumor grade, and the completeness of surgical staging as independent prognostic factors. In the observation arm, overall survival and DFS were significantly better for the optimally staged patients.

Table 1. Main characteristics and results of two randomized clinical trials on early ovarian cancer [16,17]

	EORTC ACTION trial	MRC ICON1 trial
No. of patients	448	477
Randomization	Observation versus at least four courses of platinum-containing chemotherapy	Observation versus at least four courses of platinum-containing chemotherapy
Entry criteria	Stage Ia or Ib, G2 or G3, all stages Ic or IIa, all clear-cell cancer Ia–IIa; epithelial ovarian cancer	Doubt of the attending physician as to whether chemotherapy would be indicated following macroscopic tumor resection of epithelial ovarian cancer
Definition of relapse	Histologically or cytologically confirmed	Clinically defined
Statistical analysis	Intention-to-treat basis	Intention-to-treat basis
Median duration of follow-up	66 months	51 months
Staging recommendations	Detailed staging guidelines in the protocol;complete staging strongly recommended	No staging guidelines given
Completeness of staging monitored?	Yes	No
Guidelines for pathology assessment of tumorgrade and cell type	Given	Not given
Central pathology review?	No	No
Staging performance		
Optimal	151 (34%)	Unknown
Non-optimal	297 (66%)	Unknown
5-Year overall survival		
Observation arm	78%	70%
Chemotherapy arm	85%	79%
5-Year disease-free survival		
Observation arm	68%	62%
Chemotherapy arm	76%	73%
Optimally staged vs non-optimally staged patients		
Observation		
x S	HR 2.31 (1.06–4.96)*	Unknown
x DFS	HR 1.82 (1.02–3.24)*	Unknown
Chemotherapy		
x S	HR 1.06 (0.51–2.23)	Unknown
x DFS	HR 1.17 (0.62–2.22)	Unknown
Chemotherapy vs observation		
Optimally staged patients		
x S	HR 0.81 (0.32–2.05)	Unknown
x DFS	HR 1.14 (0.54–2.93)	Unknown
Non-optimally staged patients		
x S	HR 1.75 (1.04–2.95)*	Unknown
x DFS	HR 1.78 (1.51–2.77)**	Unknown

ACTION, Adjuvant Chemotherapy in Ovarian Neoplasm; DFS, disease-free survival; EORTC, European Organization for Research and Treatment of Cancer; HR, hazard ratio; ICON1, International Collaborative Ovarian Neoplasm 1; MRC, Medical Research Council; S, overall survival. *$P < 0.05$ log rank test; **$P < 0.01$ log rank test.

In the chemotherapy arm, this difference had disappeared (Table 1). In the non-optimally staged patients, overall survival and DFS were significantly better for the patients receiving adjuvant chemotherapy. In the optimally staged patients, there was no difference at all and the curves were identical (Table 1). The conclusion of the ACTION authors was that adjuvant chemotherapy may work predominantly by affecting small-volume or microscopic tumor deposits that remain unnoticed at the time of non-optimal surgical staging and that the benefits of adjuvant chemotherapy seem to be limited to non-optimally staged patients with a higher risk of unappreciated residual disease.

The British International Collaborative Ovarian Neoplasm 1 (ICON1) trial [17] started one year later than the ACTION trial and used a similar study design. The most important characteristics of the ICON1 trial are also summarized in Table 1. In total, 477 patients were entered into the trial: 241 were in the chemotherapy arm, and 236 were in the observation arm. Overall survival was significantly better in the chemotherapy arm (hazard ratio, 0.66, 95% confidence interval, 0.45–0.97; $P = 0.03$) and the same was true for DFS (hazard ratio, 0.65; 95% confidence interval, 0.46–0.91, $P = 0.01$). The conclusions of the ICON1 collaborators were that adjuvant chemotherapy significantly prolonged overall survival and DFS in this group of patients, and that all patients with early-stage ovarian carcinoma should be considered for adjuvant chemotherapy following surgery [17].

Because of the difficulties in obtaining sufficient numbers of patients in the ICON1 and ACTION trials, it was decided during the course of the two studies to perform a case-based meta-analysis of the combined patient material. This analysis was called ACTICON [18]. Adjuvant chemotherapy significantly improved overall survival (hazard ratio, 0.67; 95% confidence interval, 0.50–0.90; $P = 0.008$) and DFS (hazard ratio, 0.64; 95% confidence interval, 0.50–0.82; $P = 0.001$). Five-year overall survival was 74% in the observation arm and 82% in the chemotherapy arm. Five-year DFS was 65% in the observation arm and 76% in the chemotherapy arm. The conclusions of the authors of this meta-analysis was that, 'Platinum-based adjuvant chemotherapy improved overall survival and recurrence-free survival at 5 years in this combined group of patients with early stage ovarian cancer defined by the inclusion criteria of the ICON1 and ACTION trials' [18].

Apart from these important large trials, another, albeit smaller, randomized clinical trial from Poland was reported [19]. In this study, 150 patients with International Federation of Gynaecology and Obstetrics stage Ia, Ib, grade 2–3 and all patients classified as Ic and IIa were randomized to either adjuvant radiotherapy or chemotherapy. DFS at 5-year was 81% (no differences between the two arms).

OTHER STUDIES IN 2000–2003

The most relevant, non-randomized study in this period was a meta-analysis of Scandinavian and other European data in over 1500 patients with stage I ovarian carcinoma [20]. The study was done primarily to define prognostic factors for DFS. Tumor grade was, once again, identified as the strongest prognostic factor, but capsule rupture before and, to a lesser extent, during surgery was also independently related to a less-favorable prognosis.

Interestingly, International Federation of Gynaecology and Obstetrics stage Ic and clear cell cancer were not by themselves found to be independent prognostic factors. This finding confirmed an earlier Italian study in which clear cell cancer in itself also did not have an unfavorable prognostic significance, as it was counterbalanced by tumor grade [21].

Another (rarely cited) paper related to the long-term risks of chemotherapy for ovarian cancer [22]. In this Canadian study of long-term survivors among high-risk early ovarian cancer patients, the risk of developing a second primary malignancy was significantly increased compared to age-matched controls (relative risk, 1.55 at a median follow-up of 13.5 years). These findings are consistent with another retrospective analysis in over 32,000 patients treated for ovarian cancer [23]. The authors of this study concluded that one in every five women would be expected to develop a new malignancy within 20 years of a diagnosis of ovarian cancer [23].

From these data, it can be said that adjuvant anticancer treatment for malignancies with more favorable survival rates should be carefully weighed against the long-term risks and side-effects of such therapy.

Faught and co-workers [24] retrospectively emphasized the importance of comprehensive surgical staging in early ovarian cancer. Forty-three of 128 women (34%) with presumed early ovarian carcinoma were upstaged to stage IIb or III disease. Apart from these studies, a number of state-of-the-art studies have been published that merely reflect personal interpretations of the literature before the appearance of the large European ACTION and ICON1 trials [12,25,26].

CONCLUSION

The publication of the two largest randomized clinical trials with a no-treatment arm following surgery for early ovarian cancer is undoubtedly the most important contribution to recent literature on this disease. Any conclusions as to the current state of the art should, therefore, seek to clarify the results of these two trials and analyze their similarities and differences. On first impression there seem to be more differences than similarities between the two trials. One (ICON1) [17] advocates adjuvant chemotherapy in (all) patients with early ovarian cancer. The other (ACTION) [16] suggests that adjuvant chemotherapy does not work in optimally staged patients. However, there is a plausible explanation for this difference and the key features seem to be the composition of the study populations and the completeness of the surgical staging.

From the ACTION trial, we know exactly which portion of patients had been optimally staged and which portion had not. The non-optimally staged patients can be regarded as harboring occult residual disease in over 25% of cases. This figure might easily explain the significant advantage, in terms of overall survival and DFS, of adjuvant chemotherapy over observation in these patients. On the other hand, no advantage, in terms of overall survival and DFS, of adjuvant chemotherapy could be demonstrated in the optimally staged patients.

Of the ACTION trial population, 297 patients (66%) can be considered to have a 25% chance of tumor deposits in the abdomen that remained unnoticed due to nonoptimal staging. Thus, 74 patients (0.25 x 297), that is 17% of the total ACTION population, might represent stage III disease rather than early ovarian carcinoma. This portion of unappreciated stage III patients probably accounts for the significant improvement in DFS but not in overall survival.

We have no information on the staging performance for the ICON1 trial, but we do know that no specific recommendations were given or precautions taken to guarantee optimal staging. Considering the disappointingly low yield of optimal surgical staging in the ACTION trial, it is realistic to conclude that optimal staging in ICON1 would have occurred in far fewer than one-third of the patients. This assumption is supported by preliminary results from the Scottish Randomized Trial in Ovarian Cancer [27] showing that pelvic and peri-aortic lymph node sampling in early ovarian cancer is hardly ever performed in oncology centers in the UK.

Furthermore, comparison of the observation arm of all ICON1 patients on the one hand with the two-thirds of non-optimally staged ACTION patients on the other produced

identical curves for overall survival [28]. The similarity of these Kaplan–Meier curves was all the more striking in view of the fact that ICON1 harbored low-risk patients (stage Ia or Ib, grade 1) in 15% of cases, unlike the ACTION trial. This all leads to the conclusion that the vast majority of patients in the ICON1 trial should be considered as non-optimally staged.

By accepting this assumption it makes it easier to explain the benefits of adjuvant chemotherapy in terms of DFS and overall survival. To take this one step further, assuming that only a few ICON1 patients and only one-third of the ACTION patients were optimally staged, it is likely that not much more than one-sixth of the patients in the combined ACTICON population were optimally staged. This means that, by and large, 20%, or one out of every five patients, of the ACTION study group would have harbored residual tumor tissue following surgery. That figure explains the overall survival and DFS advantages of adjuvant chemotherapy in this group.

In conclusion, the ACTION and ICON1 trials have proved, beyond doubt, that adjuvant chemotherapy is effective for treating residual tumor deposits in supposed early ovarian cancer following non-optimal surgical staging. In this respect, chemotherapy serves to correct poor surgery. For optimally staged patients, the ACTION trial suggests that adjuvant chemotherapy is of little or no benefit. Withholding chemotherapy in these cases might be even more relevant in view of the reported superiority of tumor response to chemotherapy in chemo-naive patients [2] and the relatively high risk of second primary tumors in long-term survivors of early ovarian cancer.

RECOMMENDATIONS FOR TREATMENT

On the basis of the results of recent randomized trials in early ovarian cancer, a comprehensive and complete surgical staging should be pursued. This will diminish or exclude the risk of unnoticed residual disease, and, therefore, improve the prognosis of early-stage ovarian cancer. Achieving the goal of optimal surgical staging at the time of the first laparotomy often proves difficult in routine clinical practice. Patterns of care for this disease might be redefined as recently suggested by British investigators [29]. Policies for referral to oncology centers and the availability of consulting gynecological oncologists to perform staging procedures in community hospitals should be evaluated in this respect. Incompletely staged patients should be restaged unless physical or psychological factors indicate otherwise, in which case adjuvant chemotherapy should be given as it has proven effectiveness against residual tumor deposits. The number of courses is debatable. The ACTION and ICON1 trials recommended six courses. This

number of courses seems the most logical since it is regarded as standard treatment for stage III ovarian cancer, and the risk of insufficiently treated stage III disease is the main reason for administering adjuvant chemotherapy.

What about giving adjuvant chemotherapy in optimally staged patients? The subgroup analysis of the ACTION trial strongly suggests that this does not improve overall survival and DFS and would, therefore, do more harm than good. Because this is the first time that this has been demonstrated, some practitioners will stick to the old policy of treating high-risk, early-stage ovarian cancer with adjuvant chemotherapy. There are several reasons why practitioners might resist changes to the standard treatment pattern: some might not be convinced by a single randomized trial; some might fear withholding a seemingly beneficial therapy to the patient; some might fear medico-legal complications in cases of tumor recurrence; and some might be unwilling to refuse the patient's demands to 'do everything that is possible'.

Nevertheless, advocates of the adjuvant chemotherapy policy should consider the harmful effect of unnecessary chemotherapy in terms of morbidity, costs, and impaired quality of life. Furthermore, the higher tumor response of recurrences in chemo-naive patients and the longterm risks of second primary tumors in survivors of ovarian cancer deserve consideration. Finally, it should be realized that in virtually all studies reporting risk factors and defining categories of high-risk patients, chemotherapy was given and this treatment did not diminish the high-risk status of these patients in any way.

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Chapter 4

Clear cell carcinoma compared to serous carcinoma in early ovarian cancer: same prognosis in a large randomized trial

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ABSTRACT

Background*:* An analysis was performed comparing survival of patients with clear cell carcinoma (CCC) to patients with serous adenocarcinoma (SAC) in early ovarian cancer. Furthermore, a literature search was done in order to clarify the clinical and histopathological features of clear cell tumors of the ovary.

Methods: Between November 1990 and March 2000, 448 patients with ovarian cancer FIGO stages I-IIa were enrolled in the EORTC ACTION trial, a randomized study comparing adjuvant chemotherapy to observation after surgical treatment in patients with early ovarian cancer. Patients in the chemotherapy group received platinum-based chemotherapy for at least 4 courses.

Results: 63 patients with clear cell carcinoma (14.1%) were compared to 156 patients with serous tumors (34.8%). The median age was 54 years in the CCC group and 56 years in the SAC group. The treatment arms were well balanced between both groups. A significant difference was found in the FIGO stage Ic with capsule rupture, 28/63 (44.4%) in the CCC patients and 29/156 (18.6%) in the SAC patients ($P < 0.001$). Recurrences occured in 25% of the patients and this was similar between the CCC group and the SAC group. No significant difference was found in overall survival (OS) between patients with clear cell carcinoma and serous carcinoma in both treatment arms together. In the observation arm the 5-year disease-free survival (DFS) was 71% in the CCC group versus 61% in the SAC group, whereas in the chemotherapy arm the 5-year DFS was higher in the SAC group compared to the CCC group (78% versus 60%). Both differences were not statistically significant.

Conclusions: The present study showed no worse prognosis in patients with clear cell carcinoma as compared to patients with serous carcinoma in early ovarian cancer. Poorer overall survival in the CCC group receiving adjuvant chemotherapy in relation to the SAC group might be explained by possible chemoresistance of clear cell tumors.

INTRODUCTION

Clear cell carcinoma (CCC) of the ovary is generally considered to be a tumor with poor prognosis and distinct clinical characteristics compared to other epithelial ovarian cancers [1]. It is often associated with endometriosis and nulliparity is frequently described [2,3]. The incidence of CCC various from 4 to 12% of all ovarian cancers. These tumors were first described by Pelham in 1899 as hypernephroma of the ovary in view of their resemblance to renal cell carcinoma. Later, terms as mesonephromas [4] and hypernephroid carcinoma of the ovary were used. In 1944, Saphir and Lackner [5] were the first authors who suggested the term clear cell adenocarcinoma. Different hypotheses were made indicating these tumors to be from germ cell origin of the endodermal sinus and those who refuted this theory suggested a Müllerian origin. The latter is now generally accepted as the nature of this tumor. Histopathologic findings of CCC consist of four cell types, typical clear or hobnail, eosinophilic and flattened cells in a papillary, solid, or tubulocystic architectural pattern. Since the World Health Organization in 1973 defined CCC as a separate histologic cell type [6] a number of studies have been performed to clarify the behaviour of this tumor. Several studies have shown a high incidence of FIGO stage I tumors [7-13], poorer prognosis compared to serous adenocarcinomas of the ovary [10,14,15] and resistance to platinum-based chemotherapy [1,13,16]. Most of these trials are retrospective cohort studies and often lack a sufficient number of patients.

The purpose of the current study was to compare clinical characteristics, response to platinum-based chemotherapy and survival of patients with clear cell carcinoma (CCC) versus serous adenocarcinoma (SAC) randomized in a large multicenter trial of early ovarian cancer.

PATIENTS AND METHODS

Between November 1990 and March 2000, 448 patients were entered in the EORTC ACTION trial, a randomized clinical study on the role of platinum containing adjuvant chemotherapy in early ovarian cancer FIGO stages Ia and Ib (grade II-III), stages Ic and IIa (grade I-III) and all stages I-IIa clear cell epithelial cancer of the ovary. Randomization between platinum containing chemotherapy and no adjuvant treatment was performed after surgical treatment consisting of total abdominal hysterectomy and bilateral salping-oophorectomy (TAH plus BSO) and staging. Patients randomized to receive chemotherapy were treated within six weeks after surgery for at least four consecutive

courses. In the observation arm no further treatment was given until a histologically or cytologically proven relapse. The same regimen of chemotherapy according to the institution had to be given in case of recurrent disease in the observation arm as in the adjuvant chemotherapy group. Analysis of the results was on an intention-to-treat basis. A detailed description of the design of the ACTION trial is given in three recently published papers by Trimbos et al. [17,18,19].

Analysis

Overall survival and disease-free survival times were defined as the period between randomization and death or relapse. Disease-free and overall survival curves were generated using the method of Kaplan-Meier [20]. Comparisons of the survival distributions were made with the log-rank test. The chi-square or Fisher's exact test were used to evaluate differences in proportions. The Statistical Package for Social Science (SPSS) was used for statistical analysis. Significance was defined as a *P*-value < 0.05.

Furthermore a review of the literature was done in order to evaluate the prognosis of clear cell carcinoma in early ovarian cancer. Papers were selected from journals in English language literature by a Pubmed search over the last thirty years. Only studies which met the following criteria were included:

1) patients with FIGO stage I-II epithelial ovarian carcinoma
2) a minimum of 10 patients with clear cell early ovarian carcinoma in the study group
3) a registrered median survival or a survival curve in the final publication

RESULTS

Of the 448 patients included in the ACTION trial, 156 (34.8 %) were serous adenocarcinomas (SAC) and 63 (14.4%) were clear cell carcinomas (CCC). The median follow-up period was 5.1 years. Table 1 shows the clinical characteristics of the 219 patients from both the SAC and CCC group. There was a significant difference in FIGO stage ($P < 0.001$), 44.4% of the CCC were FIGO stage Ic because of capsule rupture and this was the case in 18.6% in the SAC group. The time of capsule rupturing was the same in both groups, in 24 patients (85.7%) during surgery in the CCC group versus in 26 patients (89.6%) in the SAC group. Tumors were limited to one ovary (Stage Ia) in 36.5% (23/63) of the CCC cases and 33.3% (52/156) of the SAC patients. Only 1 patient (1.6%) in the CCC group had a tumor extending to both ovaries (Stage Ib) compared to 15 patients (9.6%) in the SAC group and 2 patients (3.2%) had pelvic extension (Stage II) of the CCC cases versus 15 (9.6%) in the SAC patients. Differentation grade was

also significantly different in both groups ($P < 0.001$), 33 of the 63 CCC were poorly differentiated (52.4%) against 49 of the 156 in the SAC group (31.4%). No differences were noted between CCC and SAC patients for the variables age, pre-treatment CA 125 values and site of progression. The treatment arms were well balanced between the two groups.

During the follow-up period 56 relapses were found, 16 (25.4%) in the CCC group and 40 (25.6%) in the SAC group. In both groups together 47 patients died, 16 of the deaths occurred in the CCC group, the other 31 in the SAC patients.

Table 1. Patient Characteristics

	Clear cell N=63	**Serous N=156**	***P*-value**
Age	54 (10)	56 (11)	0.74
Treatment arm			
Observation	27 (42.9%)	72 (46.2%)	0.76
Chemotherapy	36 (57.1%)	84 (53.8%)	
CA 125			
Normal	18 (28.6%)	43 (27.4%)	
Abnormal	33 (52.4%)	70 (45.2%)	0.43
Not done	12 (19%)	43 (27.4%)	
Type of staging			
Optimal	25 (39.7%)	45 (28.8%)	
Modified (protocol)	18 (28.6%)	53 (34%)	0.27
Minimal	17 (27%)	41 (26.3%)	
Inadequate	3 (4.8%)	17 (10.9%)	
FIGO Stage			
Ia	23 (36.5%)	52 (33.3%)	
Ib	1 (1.6%)	15 (9.6%)	
Ic ovarian surface	2 (3.2%)	22 (14.1%)	<0.001
Ic capsule rupture	28 (44.4%)	29 (18.6%)	
Ic ascites/washing	7 (11.1%)	23 (14.7%)	
IIa	2 (3.2%)	15 (9.6%)	
Time rupture			
During surgery	24 (85.7%)	26 (89.6%)	0.88
Before surgery	4 (14.3%)	3 (10.4%)	
Differentation grade			
Well	2 (3.2%)	22 (14.1%)	
Moderately	23 (36.5%)	84 (53.8%)	<0.001
Poorly	33 (52.4%)	49 (31.4%)	
Unknown	5 (7.9%)	1 (0.6%)	
Progression			
No	47 (74.6%)	116 (74.4%)	0.84
Yes	16 (25.4%)	40 (25.6%)	

Overall survival rate for the SAC group and the CCC group was not significantly different (Figure 1; *P* = 0.2). The overall survival (OS) by treatment arm is shown in Figure 2 and 3 (*P* = 0.8 and *P* = 0.04 respectively). In the observation arm the OS showed no difference between the CCC patients and the SAC patients. In the chemotherapy arm however a significant difference in OS between the CCC and SAC group was found. Figure 4 shows the DFS in both groups (*P* = 0.9). The 5-year disease-free survival in the chemotherapy arm of patients with serous adenocarcinoma was 78% versus 60% for patients with clear cell carcinoma (Figure 5; *P* = 0.1), whereas in the observation arm the 5-year disease-free survival was higher in the CCC group compared to the SAC group (71% versus 61%: Figure 6; *P* = 0.2). The DFS curve of the CCC patients was higher in the observation arm and lower in the chemotherapy arm compared to the SAC patients. Adjuvant chemotherapy significantly improved DFS in patients with serous adenocarcinoma (Figure 7; *P* = 0.01). In clear cell carcinoma patients no difference in DFS was found between the observation arm and chemotherapy arm (Figure 8; *P* = 0.4).

The sixteen papers meeting the criteria of the Pubmed search, are summarized in Table 2. The 5-year survival of patients with FIGO stage I clear cell ovarian carcinoma ranged from 49-93% and from 29-88.9% for those patients with FIGO stage II clear cell ovarian cancer. The 5-year survival for stage I and II clear cell carcinoma was significantly different, 74.1% versus 49.4%, respectively. In Table 3 the survival figures are shown for patients with serous early ovarian carcinoma from different studies, resulting in a 5-year survival of 76.6% (range 67%-87%) for FIGO stage I patients and 73.5% (range 68-80%) for FIGO stage II serous tumors.

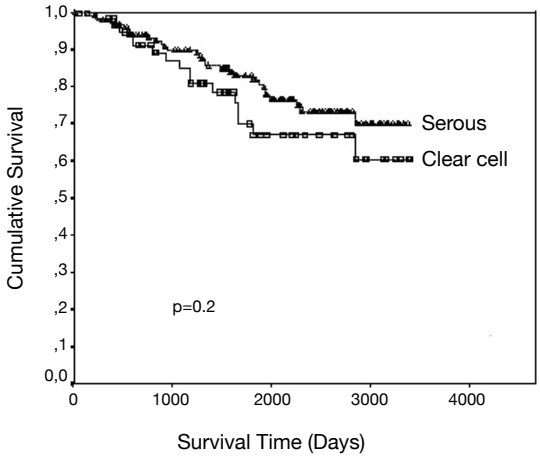

Figure 1. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients with clear cell carcinoma (n = 63) and patients with serous carcinoma (n = 156).
P = 0.2 using the log-rank test.

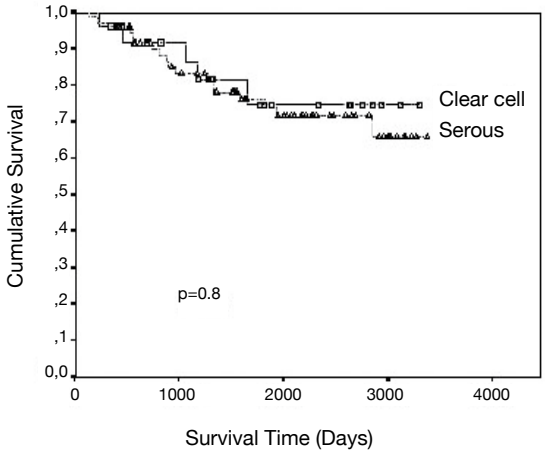

Figure 2. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients in the observation arm with clear cell carcinoma (n = 26) and patients with serous carcinoma (n = 74). Patients in the observation were observed until adjuvant chemotherapy was indicated.
P = 0.8 using the log-rank test.

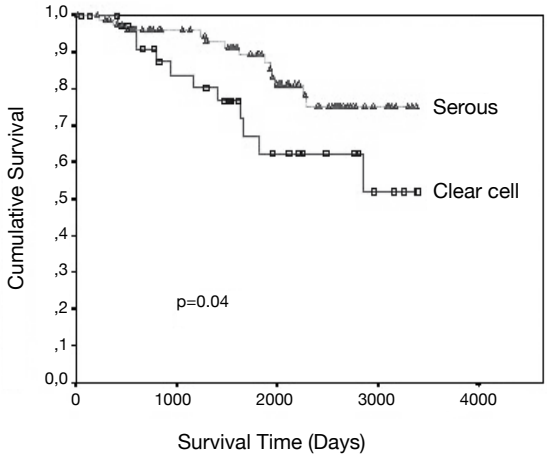

Figure 3. Kaplan-Meier curves for OS in patients with early ovarian cancer. Patients in the chemotherapy arm with clear cell carcinoma (n = 37) and patients with serous carcinoma (n = 82). Patients in the chemotherapy arm received immediate adjuvant chemotherapy.
P = 0.04 using the log-rank test.

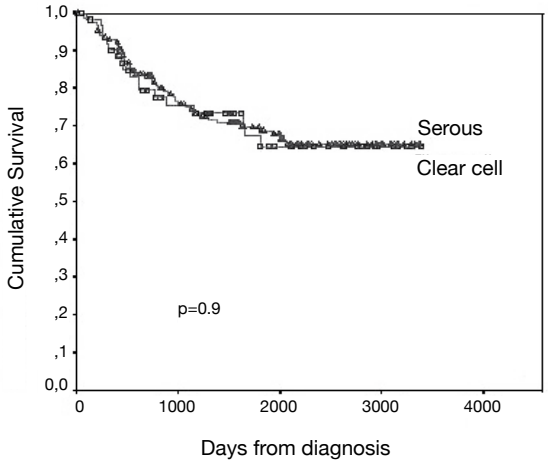

Figure 4. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with clear cell carcinoma (n = 63) and patients with serous carcinoma (n = 156).
P = 0.9 using the log-rank test.

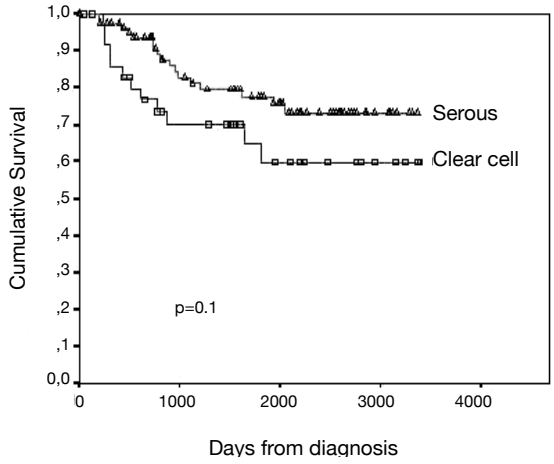

Figure 5. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients in the chemotherapy arm with clear cell carcinoma (n = 37) and patients with serous carcinoma (n = 82). Patients in the chemotherapy arm received immediate adjuvant chemotherapy.
P = 0.1 using the log-rank test.

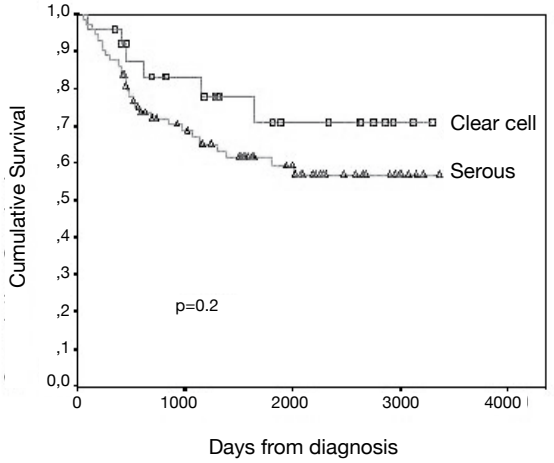

Figure 6. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients in the observation arm with clear cell carcinoma (n = 26) and patients with serous carcinoma (n = 74). Patients in the observation were observed until adjuvant chemotherapy was indicated.
P = 0.2 using the log-rank test.

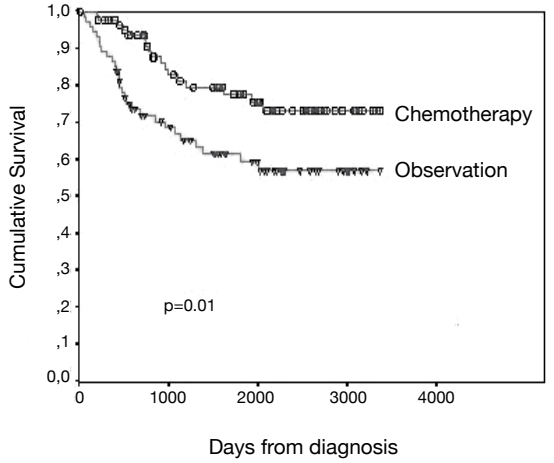

Figure 7. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with serous carcinoma in the chemotherapy arm (n = 82) and patients in the observation arm (n = 74). Patients in the chemotherapy arm received immediate adjuvant chemotherapy and patients in the observation arm were observed until adjuvant chemotherapy was indicated.
P = 0.01 using the log-rank test.

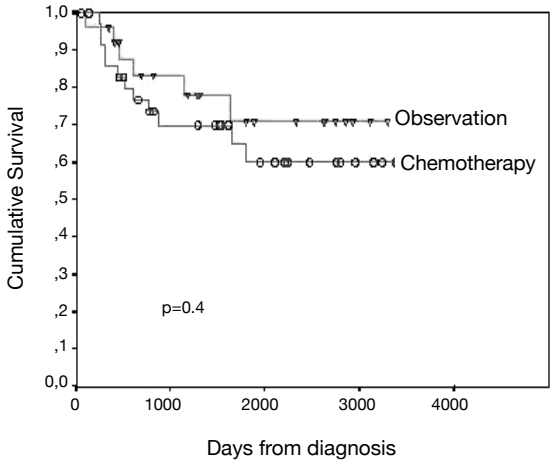

Figure 8. Kaplan-Meier curves for DFS in patients with early ovarian cancer. Patients with clear cell carcinoma in the chemotherapy arm (n = 37) and patients in the observation arm (n = 26). Patients in the chemotherapy arm received immediate adjuvant chemotherapy and patients in the observation arm were observed until adjuvant chemotherapy was indicated.
P = 0.4 using the log-rank test.

Table 2. Survival rate for Clear Cell Adenocarcinoma of the Ovary

		Clear cell 5-year survival	
Author	**Number of patients**	**FIGO stage I**	**FIGO stage II**
Czernobilsky et al. 1970 [2]	? (<12)	80%	na*
Aure et al. 1971 [13]	? (<59)	72%	na
Norris et al. 1971 [36]	? (<40)	61%	na
Shevschuk et al. 1981 [25]	? (<21)	87%	na
Brescia et al. 1989 [14]	15	93%	na
Crozier et al. 1989 [10]	38	49%	60%
Jenison et al. 1989 [7]	29	50%	29%
Kennedy et al. 1989 [6]	15	68%	42%
Montag et al. 1989 [1]	29	55%	29%
O'Brien et al. 1993 [9]	55	65%	40%
Ahmed et al. 1996 [35]	25	90.2%	na
Recio et al. 1996 [37]	37	67%	46%
Behbakht et al. 1998 [11]	27	85%	na
Kita et al. 2000 [12]	28	86%	60%
Sugiyama et al. 2000 [38]	59	80%	88.9%
Vergote et al. 2001 [34]	185	72.7%	na
Present series	63	63%	na
Total	**605**	**74.1%**	**49.4%**

*na: not applicable

Table 3. Survival rate for Serous Adenocarcinoma of the Ovary

		Serous 5-year survival	
Author	**Number of patients**	**FIGO stage I**	**FIGO stage II**
Aure et al. 1971 [13]	?	67%	na*
Swenerton et al. 1985 [39]	76	70%	na
Jenison et al. 1989 [7]	22	87%	80%
Sugiyama et al. 2000 [38]	52	86%	72.7%
Vergote et al. 2001 [34]	430	75.9%	na
Present series	156	74%	68%
Total	**706**	**76.6%**	**73.5%**

*na: not applicable

DISCUSSION

The results from this trial are based on one of the largest series in early ovarian cancer patients FIGO stage I-II. Most of the previous studies were retrospective with a small number of patients and often too few events to draw valid conclusions.

Clinical features

The clinical characteristics of clear cell carcinoma (CCC) have been widely explored. The age distribution, median 55 years, of the patients in the present study is similar to that reported by other groups. Nulliparity of greater than 50% has been reported in all series of clear cell carcinoma with the exception of those by Doshi and Fine (17 and 45% respectively) [21,22]. The frequency of concurrent endometriosis in published series of clear cell carcinoma varies from 8-55% compared to less than 5% in serous ovarian carcinoma [13,14,23]. Many authors described that the presence or absence of endometriosis did not appear to affect overall or progression-free survival [11,12].

Many investigators have stated that the percentage of patients with stage I-II disease in CCC is significantly higher compared with SAC patients, ranging from 53-66% in patients with CCC [7-13]. In a study of clear cell tumors versus matched controls consisting of serous ovarian tumors, 66% of the clear cell tumors were early-stage compared to 40% of the serous tumors [8]. One of the reasons for more stage I disease in the CCC patients may be a higher frequency of symptoms and signs at presentation resulting in earlier detection. In the literature no studies reported a primary peritoneal variant of the clear cell tumor, while mucinous and serous primary peritoneal cancers have been described.

Another argument for the fact that clear cell tumors stay localized until they become a pelvic cyst is the finding in a study of Okhawa et al. [24] that clear cell tumors remain attached to the mesothelial layer while serous tumors invade rapidly into this cell layer. Only 2 patients (3.2%) in our study group of CCC had pelvic extension, while 15/156 (9.6%) in the SAC group had FIGO stage IIa. It is also unusual to encounter bilateral involvement among stage I ovarian clear cell carcinoma patients. In the literature only 4.2% of stage I patients have been noted to have bilateral involvement and we observed this in 1 of the 63 patients (1.6%) in the CCC group versus 15 (9.6%) in the SAC group.

In the current study almost half of the patients in the CCC group had FIGO stage Ic, with 44.4% capsule rupture versus 18.6% in the SAC group. A possible explanation for this biologic phenomenon might be a larger tumor size of CCC as described in many series [7,12,13,24,25], and therefore more often capsule rupture before or during surgery.

In our study no difference was found in DFS and OS between the CCC and SAC group although almost half of the patient in the CCC group had FIGO stage Ic because of capsule rupturing compared to 18.6% in the SAC group.

Grading

One of the difficulties of managing clear cell carcinomas is the histologic grading. Different grading systems are used for ovarian cancer. The FIGO grading system [26] is primarily based on architectural features like the GOG grading system [27] which also in a lesser extent considers nuclear features, but varies on the histologic type being graded. Both grading systems cannot be used for clear cell carcinoma of the ovary. The WHO grading system [6] is dependent on observer's impressions derived possibly from both architectural and nuclear features, but not defined in a quantitative manner. Silverberg [28] proposed a universal grading system for all invasive ovarian carcinomas, based on the Nottingham system for grading all types of mammary carcinoma. Using this system tumors are graded architecturally as grade I-III according the (predominant) architectural pattern (glandular, papillary, solid), nuclear as grade I-III (slight, moderate, marked) and also on mitotic index. The efficacy of this grading system was tested in different series and seems to be valuable in predicting survival. They also found that histopathologic typing in ovarian cancer was less of prognostic significance for survival compared to grading, but better at predicting tumor responsiveness to chemotherapy. Ovarian clear cell cancer can be adequately graded by the Silverberg system.

Chemoresistance

In our study 16/63 (25.4%) recurrences were found in the CCC group and a similar percentage was found in the SAC group 40/156 (25.6%), with a median time to

recurrence of 28 months. Reviewing the literature, different numbers of recurrences are described. In a series of Bekbakht et al. [12], 10/27 (37%) patients with stage I clear cell carcinoma who received adjuvant platinum-based chemotherapy relapsed from which 7/13 (54%) were stage Ic tumors. In comparison, Hreshchyshyn et al. [29] reported a 6% recurrence rate in patients with stage I epithelial ovarian cancer treated with postoperative chemotherapy. The high relapse rate in clear cell carcinoma may be related to chemoresistance. In support of this concept, clear cell carcinoma cell lines were found to exhibit resistance to cisplatin in cell culture [16]. In a study of Kita et al. [13] 5 of the 10 patients with stage II disease had macroscopic residual disease from which 60% died within 9 months after initial surgery and adjuvant cisplatin based chemotherapy, also suggesting chemoresistance. In order to clarify the underlying mechanism of cisplatin resistance in clear cell carcinoma Itamochi [30] conducted a study in 11 CCC and 5 SAC cell lines. They found that the doubling time for CCC cells was significantly longer than that for SAC cell lines (61.4 vs 29.8 hour), suggesting that the resistance of CCC to cisplatin may be caused by low cell proliferation. In our study the disease-free survival (DFS) showed an advantage in the observation arm in the CCC group, while in the chemotherapy arm the DFS was higher in the SAC group. Both differences were not statistically significant but showed a trend and could be partly explained by a possible chemoresistance of the clear cell tumors. A significant difference was found in the SAC group in favor of the adjuvant chemotherapy arm while in the CCC group no survival difference was shown between the observation arm and chemotherapy arm**.**

Prognosis

Regardless of the high recurrence rate for clear cell carcinoma , overall survival is not significant lower than the survival of patients with serous ovarian cancer in the present study. In the current study, more patients in the CCC group were optimally staged (39.7%) versus the SAC group (28.8%). Therefore, we performed a separate analysis for only the optimally staged patients. Even if we look at the optimally staged CCC and SAC patients the outcome was the same, no significant difference could be found in DFS (P = 0.76) and OS (P = 0.28). Furthermore, the survival benefit in the chemotherapy arm of the SAC group compared to the CCC group disappeared (P = 0.11). Five-year survival rates in stage I-II clear cell carcinoma varied from 50-73% in reported series. Many studies were conducted on histologic type as prognostic factor. A number of studies gave patients with clear cell carcinoma of the ovary favorable prognosis compared to serous carcinoma of the ovary [10,14,15]. On the other hand, a same amount of studies regarded clear cell carcinoma as having a worse prognosis than other epithelial cancers [8,31,32]. Jenison et al. [8] noted that 22 patients with stage I clear cell ovarian carcinoma demonstrated a significantly worse estimated 5-year survival than did 11

patients with serous carcinoma (50% vs 87%, $P < 0.001$). Most of the studies however showed no difference in survival for patients with clear cell ovarian cancer compared to other histologic types of ovarian cancer. Our study also lends support to the postulation that clear cell carcinoma has a relatively good prognosis. Zanetta [33] analysed 351 patients with stage I ovarian cancer and could not find a significant difference in DFS and OS comparing clear cell tumors versus other histologic cell types. In a recent study of Vergote et al. [34] on 1545 FIGO stage I ovarian cancer patients histologic type was not of prognostic value, observing a 5-year survival of 72.7% in clear cell carcinoma patients versus 75.9% in patients with serous adenocarcinoma. In the multivariate analyses the degree of differentation was identified as the most powerful prognostic indicator but in this study clear cell carcinoma were not graded [34].

We conclude that although clear cell ovarian carcinomas do have unique clinical features, they have similar prognosis compared to serous ovarian cancer in early stages. The role of chemoresistance needs further study in these type of tumors.

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Chapter 5

Understanding the problem of inadequately staging early ovarian cancer

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ABSTRACT

Background: Early ovarian cancer patients are often incompletely staged during initial surgery [1–3]. This omission can have serious adverse consequences for the prognosis of patients as the completeness of surgical staging has been identified as an independent prognostic parameter for survival [4,5]. The reasons for the problem of inadequate staging of early ovarian cancer are largely unknown. We have analysed the data of a large randomized trial in early ovarian cancer in which detailed information of the surgical staging procedure was monitored [5].

Methods: Data of the EORTC Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) trial were used in which 448 early ovarian cancer patients were randomized between postoperative chemotherapy in one arm and observation following surgery in the other. In this trial strict criteria for surgical staging were advised but optimal, complete staging was performed in only 1/3 of patients. Staging characteristics of the incompletely staged patients were analysed and factors that could explain the failure to perform a complete staging were studied.

Results: Sampling of para-aortic nodes was omitted in 78% of the incompletely staged patients, while 52% of these patients had no pelvic lymph node dissection. Taking blind biopsies from different peritoneal sites was not performed in more than 1/3 of the incompletely staged group. Omission of the staging steps ranged from 3% (infracolic omentectomy) to 55% (biopsy of the right hemi-diaphragm). A significant difference (P = 0.04) between the fraction of completely staged patients was found when comparing institutes who entered less than 5 patients (21%) versus those who included more than 20 patients (37%) in the trial.

Conclusions: Even in a randomized trial in which comprehensive surgical staging was strongly advised in the study protocol the majority of patients (66%) were incompletely staged. Factors relating to a lack of surgical skills attributed most to the number of incompletely staged patients, but insufficient knowledge of the tumor behaviour and routes of spread of ovarian cancer also contributed substantially to this problem. Multicenter trials recruiting patients from many institutes with small volume contribution to the study, run the risk of inadequate adherence to the study protocol.

INTRODUCTION

Ovarian cancer carries a dismal prognosis [6] and almost the only chance of long-term survival is related to early detection of the disease and a flawless and adequate management of the early stages of this 'silent killer'[7]. An important initial step of such adequate management is a thorough, comprehensive surgical staging procedure [1,4,5,8]. Only the most accurate determination of the extent of the disease will enable the definition of subsets of patients requiring adjuvant therapy and those in whom adjuvant treatment can be considered overtreatment.

Consequently, lack of proper staging was found to be an independent prognostic factor in several series [4,5]. In the ACTION trial the optimally staged patients did not benefit from adjuvant chemotherapy [5]. Incomplete surgical staging at initial surgery has been reported between 32% and 72% of cases in different studies [2,9,10]. Knowledge of the reasons for the wide spread inadequacy of staging early ovarian cancer is lacking. Only a few studies have addressed this issue [3,9,11] and that is unfortunate, because a change in this aspect of oncology care can only be hoped for if this deficiency can be sufficiently explained.

The EORTC ACTION trial was one of the largest randomized clinical trials in early ovarian cancer undertaken so far [5]. In this study patients were randomized between observation following surgical treatment and adjuvant platin-based chemotherapy. Detailed information about the staging procedure was available for every patient. These data and other characteristics that might relate to the completeness of surgical staging were analysed.

The aim of the study was to shed more light to the understanding of the reasons for failure of adequate staging surgery in early ovarian cancer.

PATIENTS AND METHODS

Between November 1990 and March 2000 448 patients were enrolled in the EORTC ACTION trial, a randomized clinical trial to study the significance of platinum-based adjuvant chemotherapy in early ovarian cancer. Detailed information of all patients on the staging performance was available and these data were analysed in the present study. Patients were divided in a completely staged group and in an incompletely staged group. If all the staging steps mentioned in Table 1 were completed, staging was

considered complete. All other cases were labelled incomplete. The number of patients entered by the 40 institutes of the nine participating countries was related to the two staging categories.

For the comparison of fractions (complete or incomplete staging) the χ^2 test was used and *P*-values < 0.05 were considered statistically significant.

Table 1. Staging steps necessary to arrive at a complete surgical staging procedure for early ovarian cancer following bilateral salpingo-oophorectomy and total abdominal hysterectomy*

Staging guidelines
Inspection and palpation of all peritoneal surfaces
Biopsies of any suspect lesions for metastases
Biopsies or removal of any adhesions surrounding the (area of the) primary tumor
Peritoneal washing
Infracolic omentectomy
(Blind) biopsies of right hemidiaphragm, of right and left paracolic gutter, of pelvic sidewalls, of ovarian fossa, of bladder peritoneum, and of cul-de-sac
Iliac and peri-aortic lymph node dissection

*patients with stage Ia disease who wished to preserve fertility were permitted to have only an unilateral salpingo-oophorectomy

RESULTS

Clinical and tumor characteristics of the completely and incompletely staged patients are given in Table 2. No differences in mean age, histologic cell type or grade of differentiation of the tumors were seen. In the incompletely staged group the omitted staging steps were divided into two categories: one group of procedures carrying an appreciable risk of surgical morbidity [11] and for which additional surgical skills have to be present and another group of procedures not requiring specific surgical abilities and in which virtually no surgical morbidity was involved. These two groups are shown in Table 3. The surgical morbidity group contributed most to the amount of neglected staging steps.

In 78% of incompletely staged patients para-aortic lymph node sampling was not performed followed by 55% omitted biopsies of the right hemi-diaphragm and 52% pelvic lymph node sampling. However, the low morbidity group did also contribute to the total of complete surgical procedures: blind biopsies of paracolic gutters of 39% and blind biopsies of pelvic side wall also of 39%. Even a totally harmless procedure as taking peritoneal washings for cytology was omitted in 33 of 295 incompletely staged patients (11%); Table 3.

Table 2. Clinical and tumor characteristics of completely and incompletely staged patients*

	Completely staged N = 151	**Incompletely staged** N = 295	***P*-value**
Age	56	54	0.73
FIGO stage			
Ia	46 (30,5%)	109 (36,9%)	
Ib	13 (8.6%)	24 (8.1%)	
Ic ovarian surface	24 (15.9%)	26 (8.8%)	0.29
Ic capsule rupture	38 (25.2%)	78 (26.5%)	
Ic ascites/malignant washing	18 (11.9%)	39 (13.2%)	
IIa	12 (7.9%)	19 (6.5%)	
Histologic type			
Serous	45 (29.8%)	111 (37.6%)	
Mucinous	29 (19.2%)	48 (16.3%)	
Endometrioid	44 (29.1%)	76 (25.8%)	
Clear cell	25 (16.6%)	38 (12.9%)	0.65
Undifferentiated	3 (2.0%)	5 (1.7%)	
Other	2 (1.3%)	14 (4.7%)	
Missing	3 (2.0%)	3 (1.0%)	
Differentiation grade			
Well	15 (9.9%)	39 (13.2%)	
Moderetely	87 (57.6%)	141 (47.8%)	0.30
Poorly	47 (31.1%)	109 (37.0%)	
Unknown	2 (1.3%)	6 (2.0%)	

*Surgical staging performance was missing in 2 patients

Table 3. Omitted staging steps in early ovarian cancer patients

Procedure not performed	**number of 295 incompletely staged patients**	**%**
Procedure difficult or associated with increased morbidity		
Biopsy of right diaphragm	161	55
Sampling para-aortic lymph nodes	230	78
Sampling of pelvic lymph nodes	153	52
Lymph nodes		
Infracolic omentectomy	10	3
Easy procedure; no morbidity involved		
Biopsies of paracolic gutters	114	39
Biopsies of side wall	116	39
Peritoneal washing	33	11

The staging categories of the different institutions divided by the number of patients randomized in the trial are listed in Table 4. In total 40 European institutions from 9 countries were enrolled in the ACTION trial. From these 40 centers, 19 centers entered less than five patients, 7 centers between 6 and 10 patients, also 7 centers between 11 and 20 patients and the other 7 centers more than 20 patients.

Table 4. Staging category by number of patients randomized per center

		Staging category	
Number of patients randomized per center	Number of institutes (n=40)	Complete	Incomplete
0 – 5	19	20.5%	79.5%
6 – 10	7	25.9%	74.1%
11 – 20	7	36.8%	63.2%
> 20	7	36.5%	63.5%

A significant difference was found between the number of patients who were completely staged in the centers which entered a small number of patients (1–5 patients) compared to the centers which entered a large number of patients (>20: 20.5% and 36.5%, respectively, $P = 0.04$). Also a significant difference was shown in the percentage of completely staged patients dividing the centres into two groups (1–10 patients: 23.2% and >10 patients: 36.7%, $P = 0.01$). Tables 5 and 6 show the number of patients in whom blind biopsies were taken and para-aortic and pelvic lymph node sampling was performed by the four European countries which entered most of the patients in the trial. Pelvic lymph node sampling was carried out in 78% of the patients in Spain while

Table 5. Blind biopsies by country of randomization

		Blind biopsies performed		
Country	Number of patients randomized	Side wall	Paracolic gutters	Right hemidiaphragm
Italy	311	241 (77.5%)	224 (72%)	179 (57.7%)
Spain	51	40 (78.4%)	27 (52.9%)	35 (68.6%)
The Netherlands	43	28 (65.1%)	36 (83.7%)	32 (74.4%)
Portugal	13	12 (92.3%)	13 (100%)	7 (53.8%)

Table 6. Lymph node sampling by country of randomization

		Lymph node sampling performed	
Country	Number of patients randomized	Pelvic	Para-aortic
Italy	311	206 (66%)	130 (41.9%)
Spain	51	40 (78.4%)	28 (54.9%)
The Netherlands	43	19 (44.2%)	24 (55.8%)
Portugal	13	1 (7.7%)	1 (7.7%)

these percentages were 66%, 44% and only 8% for Italy, the Netherlands and Portugal, respectively. On the other hand, para-aortic lymph node sampling was performed in 55% of the patients in Italy and the Netherlands while 42% of the patients in Spain and 7% in Portugal had a para-aortic lymph node sampling. Biopsy of the right diaphragm was mostly taken in the Netherlands (74%) compared to 69% in Spain, 58% in Italy and 54% in Portugal. Most of the biopsies from the paracolic gutters and peritoneal side wall were taken in Portugal in 100% and 92% of the patients, respectively.

DISCUSSION

In the daily life practice the performance of a complete, comprehensive staging procedure in early ovarian cancer seems to be difficult to accomplish in all patients. In the EORTC ACTION trial all the necessary staging steps to achieve a complete staging procedure were specifically mentioned in the study protocol and it was strongly advised to execute them.

Nevertheless, in 295 of the 448 patients (66%) one or more staging acts had been omitted. This is a sobering finding because one of the consequences of clinical trials should be that they keep the participating clinician focused on the state-of-the art approach of a particular patient group in the study protocol.

Admittedly, the criteria in the ACTION trial to qualify for a complete staging procedure were very strictly applied, but a minority of 1/3 of completely staged patients remains a disappointingly low figure, and this sheds great doubts on the daily life practice outside a trial situation. Furthermore, we know from the results of the ACTION trial published

earlier [5] that only the non-optimally staged patients benefit from adjuvant platin-based chemotherapy and the optimally staged patients do not need further treatment. To do something about this deficiency in patient care requires insight into the reasons why comprehensive staging for all patients with early ovarian cancer is so hard to achieve.

One of the reasons may be that the first diagnosis or suspicion of early ovarian cancer is frequently made during a surgical procedure for an acute abdomen or for symptoms of an ovarian cyst and therefore is unexpected. These procedures are normally undertaken by general gynecologists without surgical skills to perform a proper staging and without the necessary knowledge of tumor behaviour and sites at risk for tumor spread.

We have tried to differentiate between a lack of surgical skills (more difficult procedures with morbidity involved) and a lack of sufficient knowledge of risk sites for ovarian cancer metastases (easy procedures without appreciable morbidity risk). In the former category retroperitoneal lymph node retrieval was neglected in 78% and 52% of incompletely staged patients. These findings concur with those of a similar study in Dutch patients (70%) [11], and those of an earlier study from the United States [9].

In the group of easy procedure the sites most commonly omitted in the present study were the paracolic gutters (39%), pelvic side wall peritoneum (39%) and even peritoneal washings (11%). In the Dutch study mentioned before, the figures were similar for the peritoneal washings (10%) but very different for the paracolic gutters (85–90%) and the pelvic side wall (73%) [11].

As it seems that lack of surgical expertise as well as deficient knowledge of ovarian cancer spread are responsible for the staging problem at hand, a solution for these shortcomings has to be solved rather in the organisation of health care programs and subspecialisation of gynecologic oncologists than in the sheer education of general gynecologists.

Only a more efficient referral policy could serve to have the surgical staging procedures concentrated by gynecologic oncologists with not only the skills and knowledge to do it, but also the maintenance of experience to deal with a relatively infrequent condition. In this context a policy of only removing a suspicious ovarian cyst or mass and waiting for the definite pathology might help to organise the place and the surgeon for a proper staging procedure later, more effectively [12-14].

In the pre-operative evaluation of an adnexal mass, the widely used Risk of Malignancy Index (RMI) which is based on menopausal status, ultrasound morphology of adnexal masses and absolute level of serum CA-125 may help in differentiating between a benign or malignant mass with a sensitivity from 71% to 88% and a specificity ranging between 74% and 89% in different studies [15-17]. The results of a multicenter study, the International Ovarian Tumor Analysis (IOTA), show that pattern recognition by ultrasound correctly classified 93% of the tumors as benign or malignant while serum CA-125 correctly classified at best 83% of the masses [18].

The ACTION trial was a multicenter randomized trial and performed by clinical research groups consisting of different types of hospitals. We found in this study a clear correlation in the number of patients enrolled by the different institutes and the surgical staging category. Institutes who entered less than 5 patients performed complete staging in 20.5% of the patients, while this percentage increased to almost 37 if more than 10 patients per institute were enrolled in the trial. The volume issue is important in oncology. In a population-based study of 2450 ovarian cancer patients done by Ioka and colleagues, patients receiving care in very low volume hospitals were seen to have a 60% higher risk of death than patients receiving care in high volume hospitals ($P < 0.01$) [19]. Vernooij and colleagues [20] found that the level of specialisation and the volume of the hospital were strongly related to the proportion of adequately staged patients and the overall survival was best in patients treated in specialised hospitals and by gynecologists who treated a high number of patients.

The conclusion of all this is, that if we allow too many institutes that enroll a low number of patients in multicenter clinical studies, we run an increased risk of inadequate adherence to the study protocol. We may have to monitor in future trials more carefully the violation of the study protocol with quality control during the study. In the case of early ovarian cancer this means suboptimal performance to follow the required steps of surgical staging.

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Chapter 6

Lymph node sampling and taking of blind biopsies are important elements of the surgical staging of early ovarian cancer

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ABSTRACT

Background: The purpose of this study was to determine the effect of lymph node sampling and taking of blind biopsies as part of the surgical staging procedure for early ovarian cancer on disease-free survival (DFS) and overall survival (OS) in patients who received no adjuvant chemotherapy.

Methods: In the EORTC ACTION trial 448 patients with early ovarian carcinoma were randomized between November 1990 and March 2000, 224 patients to observation and 224 to adjuvant platin-based chemotherapy. Only patients allocated to observation were included for the current study. Analyses were performed in a subgroup of 75 optimally staged patients (group A), 46 patients in whom all staging steps were performed except para-aortic or pelvic lymph node sampling (group B) and 14 patients who fulfilled all staging criteria but in whom no blind peritoneal biopsies were taken (group C). The study group did not differ in stage distribution, cell type or tumor grade.

Results: Significantly improved 5-year DFS (P = 0.03) and 5-year OS (P = 0.01) were found in group A (optimally staged) versus group B (no lymph node sampling). A significant difference was also shown in 5-year DFS (P = 0.02) and 5-year OS (P = 0.003) between group A and group C (no blind biopsies). Recurrences occurred in 11/75 patients (14.6%) in group A , 16/46 patients (34.8%) in group B and 5/14 (35.7%) in group C. The 5-year DFS in group A was 79% versus 61% and 64% in group B and C respectively. The 5-year OS decreases from 89% in group A to 71% in group B and 65% in group C.

Conclusions: In this study statistically significant differences were found in patients in whom para-aortic and pelvic lymph node sampling and taking of blind peritoneal biopsies were undertaken compared with patients in whom these staging steps had been omitted. These findings support the relevance of lymph node sampling and the taking of blind peritoneal biopsies in the surgical staging of early ovarian cancer.

INTRODUCTION

Early ovarian cancer patients are often surgically understaged. Figures of 33% to 67% of patients with inadequate surgical staging have been reported [1,2], depending on the definition of optimal staging.

The two staging steps that are most frequently omitted include retroperitoneal lymph node dissection and the taking of blind biopsies [3,4]. These omissions take place despite the well documented route of metastasis via the peritoneal fluid and the retroperitoneal lymph nodes. The Gynecologic Oncology Group (GOG) and the European Organisation for Research and Treatment of Cancer (EORTC) has well described guidelines for the staging laparotomy of early ovarian cancer patients [5,6].

The incidence of lymph node involvement in apparently early ovarian cancer is approximately 14% for stage I and 38% for stage II [7-16]. Lymph node metastasis in stage I ovarian cancer is mostly found in stage Ic patients, grade 3 tumors and serous carcinoma [7-15]. Positive findings of blind biopsies of various peritoneal sites in apparently early-stage ovarian cancer has been demonstrated between 3 and 17% of the cases [17,18].

Despite the overwhelming evidence of the importance of these two routes of tumor spread, the particular staging steps to detect it carry inherent problems in clinical practice. The reasons that lymph node dissection and blind biopsies are so often neglected have been reported partly because of lack of technical skills and partly because of lack of knowledge of early ovarian cancer spread [3].

Contrary to the large number of papers analyzing the incidence of lymph node spread or intraperitoneal dissemination of early ovarian cancer, studies on the prognostic significance of lymph node removal or taking of blind peritoneal biopsies are scarce [9-11]. This scarcity is the more problematic because a proven prognostic consequence of these staging steps may contribute to a general acceptance of the importance of these staging elements.

The current study was undertaken to analyze the prognostic significance of lymph node sampling and the taking of blind peritoneal biopsies during surgical staging of early ovarian cancer.

PATIENTS AND METHODS

In the EORTC Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) trial 448 patients were included between November 1990 and January 2000 by 40 centers from nine European countries. Patients with FIGO stages Ia-Ib, grade II-III, all stages Ic-IIa and all stages I-IIa clear cell carcinoma were eligible for the study. After surgical treatment and staging, including total abdominal hysterectomy and bilateral salpingo-oophorectomy using a midline incision, patients were randomized between an observation arm or adjuvant chemotherapy arm consisting of at least four courses of platinum-based chemotherapy. Surgical staging had to consist of at least careful inspection and palpation of all peritoneal surfaces, with biopsies of any suspect lesions, such as adhesions adjacent to the ovarian tumor. However, far more comprehensive staging was strongly advised, including omentectomy, peritoneal washings, blind biopsies from the peritoneum in the pelvis (pouch of Douglas, bladder, pelvic sidewalls), the paracolic gutters, the right hemidiaphragm and iliac and para-aortic lymph node sampling. Only if all staging steps had been performed, the procedure was categorized as optimal. For a detailed description of the inclusion criteria of this trial we refer to a previous publication [2].

Data from the EORTC ACTION trial were used for the present study. The dataset comprises detailed information on staging steps and prognosis. The median follow-up duration at the time of analysis was 5.5 years.
SPSS version 15.0 (SPSS inc., Chicago, IL) was used for statistical analysis. Categorical variable comparisons were conducted by 2-tailed χ^2 and Fisher exact tests. Parametric comparisons were compared by analysis of variance and Student *t* test. Survival estimates were calculated using the Kaplan-Meier product limit method. Comparisons between survival curves were made using the log-rank-test. Two-tailed *P* values are reported, with the α for all tests set at < 0.05 as significant.

RESULTS

From the 448 patients of the ACTION trial, 224 patients were randomized to the adjuvant cisplatin-based chemotherapy arm en 224 to the observation arm. For the present analysis only patients in the observation arm were included. From the 224 observation arm patients 75 patients were optimally staged (group A) and from 46 patients all staging steps were performed except para-aortic or pelvic lymph node sampling (group B). Group C consisted of patients in whom the taking of blind biopsies was omitted but all other steps were carried out (n=14). The other 89 patients out of

the 224 patients in the observation arm were excluded from this analysis because a various of different staging steps together were not performed. In the analysed study population 95% of the patients had a vertical midline incision and for those were a blind biopsy of the right hemidiaphragm was taken 93% of the patient has a vertical midline incision. For a description of the prognosis of the different staging categories in all patients we refer to a previous publication of Trimbos et al. [2].

Table 1 and 2 show a literature review of lymph node involvement in early ovarian cancer.

Table 3 shows the distribution of clinical and histological characteristics of the three groups. No difference between group A and the other two groups in stage distribution, histological cell type and differentiation grade could be found.

Figure 1 shows the overall survival (OS) curve of the patients in group A and group B.

A significantly different overall survival was shown between both groups ($P = 0.01$) with a 5-year overall survival of 89% (group A) versus 71% (group B). During the follow-up period 8% of the patients died (6/75) in group A of whom 2 patients of another cause of death than ovarian cancer, while 23.9% of the patients (11/46) in group B died of the disease.

Also a significant difference in disease-free survival ($P = 0.03$) was found between group A (optimally staged) and group B (no pelvic or para-aortic lymph node sampling), resulting in a 5-year disease-free survival rate of 79% (group A) and 61% (group B), figure not shown. In group A, 11 of the 75 patients recurred (14.6%) versus 16 of the 46 patients (34.8%) in group B.

Table 1. Lymph node involvement FIGO stage I-II ovarian cancer; a literature review

Authors (ref.)	Number	Stage I	Stage II
Benedetti Panici 1993[7]	37	5/35 (14.2%)	0/2 (0%)
Baoicchi 1998 [8]	18	4/18 (22.2%)	
Suzuki 2000 [9]	47	5/47 (10.6%)	
Sakuragi 2000 [10]	94	4/78 (5.1%)	5/16 (31.3%)
Cass 2001 [11]	69	14/69 (20.2%)	
Morice 2003 [12]	100	17/85 (20%)	6/15 (40%)
Negishi 2004 [13]	150	8/123 (6.5%)	11/27 (40.7%)
Takeshima 2005 [14]	193	20/156 (12.8%)	18/37 (48.6%)
Maggioni 2006 [15]	138	29/138 (22%)	
Harter 2007 [16]	69	3/48 (6%)	5/21 (24%)
Total	**915**	**109/797 (13.7%)**	**45/118 (38.1%)**

Table 2. Lymph node involvement FIGO stage I ovarian cancer by substage, grade and histology; literature review

		Stage			Grade			Histology				
Author	**N***	**Ia**	**Ib**	**Ic**	**1**	**2**	**3**	**Serous**	**Mucinous**	**Clear cell**	**Endometrioid**	**Other**
Benedetti Panici [7]	5	–	–	–	1	–	4	4	–	–	1	–
Baoicchi [8]	4	1	1	2	1	1	2	2	1	–	–	1
Suzuki [9]	5	1	–	4	2	3	–	4	–	1	–	–
Sakuragi [10]	4	1	–	3	2	2	–		–	–	–	–
Cass [11]	14	–	–	–	–	–	14	–	–	–	–	
Morice [12]	17	8	4	5	–	–	–	8	–	–	–	9
Negishi [13]	8	1	–	7	–	–	–	1	2	5	–	–
Takeshima [14]	20	7	1	12	–	–	–	–	–	–	–	–
Harter [15]	3	–	1	2	–	2	1	2	–	–	1	–
Total	80	19/61 **31%**	7/61 **11%**	35/61 **58%**	6/35 **17%**	8/35 **23%**	21/35 **60%**	21/42 **50%**	3/42 **7%**	6/42 **14%**	2/42 **5%**	10/42 **24%**

N*: number of patients with positive nodes

Analyzing the DFS (figure not shown) and OS (figure 2) comparison of group A and group C, we found a significant difference for DFS ($P = 0.02$) as well as OS ($P = 0.003$), showing a 5-year DFS of 79% versus 64% respectively and 5-year OS of 89% (group A) and 65% (group C). Recurrences occurred in 5/14 (35.7%) of the patients in group C versus 11/75 patients (14.6%) in group A. In the patients in whom blind biopsies of the peritoneum were not taken (group C) 5 patients (35.7%) died of the disease compared to 6/75 (8%) in the optimally staged patients (group A).

The sites of progression were different in the three groups as shown in Table 4. In the optimally staged group A, 1/75 (1.3%) patients recurred only in the pelvis, while these percentages were 13.1% (6/46) and 14.3% (2/14) for group B (no lymph node sampling) and group C (no blind biopsies) respectively. Intraperitoneal progression was seen in 5.3% in group A versus 8.7% in group B and 14.3% in group C.

Table 3. Clinical and histopathologic characteristics of the different groups

	Group A Optimal All N=75	Group B No lymph node sampling N=46	Group C No blind biopsies N=14	*P*-value A versus B/ A versus C
Age	55	54	56	0.92/0.91
FIGO stage				
Ia	23 (30.7%)	19 (41.3%)	6 (42.9%)	
Ib	6 (8.0%)	3 (6.5%)	1 (7.1%)	
Ic ovarian surface	11 (14.7%)	6 (13.0%)	1 (7.1%)	0.91/0.75
Ic capsule rupture	21 (28.0%)	11 (23.9%)	2 (14.3%)	
Ic ascites/washings	9 (12.0%)	5 (10.9%)	3 (21.4%)	
IIa	6 (6.7%)	2 (4.3%)	1 (7.1%)	
Histologic type				
Serous	22 (29.3%)	15 (32.6%)	7 (50%)	
Mucinous	12 (16.0%)	11 (23.9%)	1 (7.1%)	
Endometrioid	28 (37.3%)	12 (26.1%)	3 (21.4%)	
Clear Cell	10 (13.3%)	4 (8.7%)	1 (7.1%)	0.62/0.31
Undifferentiated	1 (1.3%)	1 (2.2%)	0	
Other	1 (1.3%)	0	1 (7.1%)	
Unknown	1 (1.3%)	3 (6.5%)	1 (7.1%)	
Differentiation Grade				
Well	7 (9.3%)	8 (17.4%)	2 (14.3%)	
Moderately	44 (58.7%)	18 (39.1%)	7 (50%)	0.10/0.78
Poorly	24 (32.0%)	20 (43.5%)	5 (35.7%)	

Table 4. Site of progression in early ovarian cancer patients according to the extent of surgical staging

	Site of progression (n %)			
Surgical Staging Group (recurrences/ Number of pts) %	**Pelvis**	**Outside pelvis** Intraperitoneal	Retroperitoneal	**Both pelvis and outside pelvis**
Group A (11/75) 14.6%	1 (1.3%)	4 (5.3%)	3 (4%)	3 (4%)
Group B (16/46) 34.8%	6 (13.1%)	4 (8.7%)	3 (6.5%)	3 (6.5%)
Group C (5/14) 35.7%	2 (14.3%)	2 (14.3%)	1 (7.1%)	0

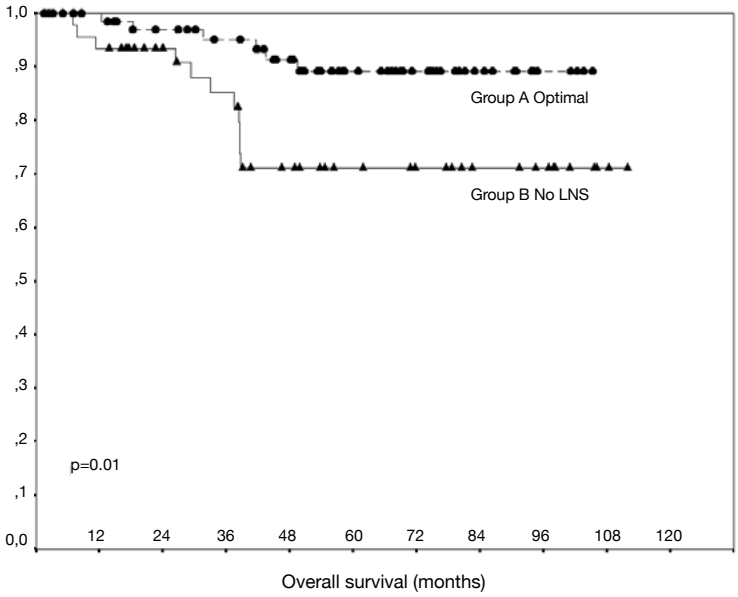

Figure 1. Kaplan - Meier curves for overall survival in patients with early ovarian cancer in the observation arm of the trial. Patients in the optimal group A (n=75) and patients with no para-aortic or pelvic lymph node sampling (LNS) group B (n=46). *P* = 0.01 using the log-rank test.

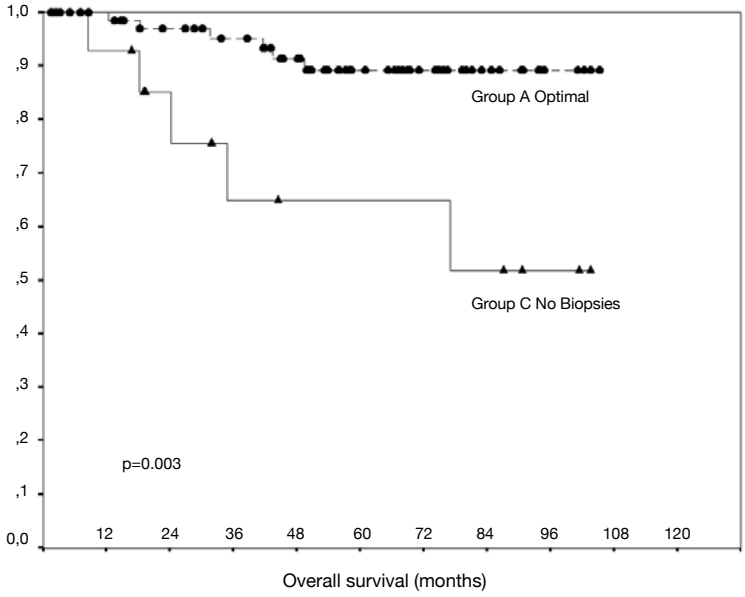

Figure 2. Kaplan - Meier curves for overall survival in patients with early ovarian cancer in the observation arm of the trial. Patients in the optimal group A (n=75) and patients with blind biopsies omitted group C (n=14). *P* = 0.003 using the log-rank test.

DISCUSSION

Lymph node sampling is one of the cornerstones of the surgical staging in early ovarian cancer. Surgical skills are required to carry out a lymph node dissection and the procedure is not without risk or side effects. The morbidity described for a lymphadenectomy includes lymphocyst, nerve and vessel injury and increased operation time and blood loss [3,8].

Performing a lymph node sampling in early ovarian cancer patients can cause problems in daily practice. Most of the patients with early ovarian cancer are diagnosed by a general gynecologist, sometimes unexpected when the patient is operated for acute abdominal pain or a pelvic mass. In this setting the lymph nodes are often not removed and the patient is not always restaged thereafter. Where and by whom the patient with early ovarian cancer is treated depends on the particular organisation of the health care. In the Netherlands there is no referring obligation of patients with early ovarian cancer but a gynaecologic oncologist has to be part of the operating team for a staging surgery which is not in all cases done. To change a system is difficult and solid evidence that centralisation of these patients improves the prognosis, is needed. Studies regarding the prognostic value of all staging steps including lymph node dissection and taking of blind biopsies should contribute to the general application of these steps in the surgical staging of early ovarian cancer patients. In a recent publication Verleye et al. [19] proposed EORTC Gynaecologic Cancer Group (GCG) quality indicators for staging laparotomy in ovarian cancer grossly confined to the pelvis in order to improve the quality of surgery in ovarian carcinoma patients. Kommoss et al. [4] showed that the introduction of a quality assurance and management program for treatment of early ovarian cancer patients represents a major improvement of patient care.

The impact of lymph node sampling, lymphadenectomy or positive nodes on prognosis in early ovarian cancer remains controversial. Baiocchi et al. conducted a multivariate analysis and revealed that lymph node status was the most valuable prognostic factor in patients with disease limited to the ovary [8]. In a recent randomized study in macroscopic early ovarian cancer patients Maggioni et al. [15] performed either a systematic pelvic and para-aortic lymphadenectomy (n=138) or a random sampling of lymph nodes (n=130). The incidence of positive nodes was significantly higher in the lymphadenectomy group than in the sampling group, respectively 22% and 9%, while the recurrence rates were 22% versus 30%. No significant difference in 5-year overall survival (84.2% versus 81.3%) and 5-year progression-free survival (78.3% versus 71.3%) was found between both groups, but this could have been expected as the number of patients randomized was too small to detect a significant difference with a reasonable

power. Also no difference in the sites of progression was found [15]. In our current study, we found in the group of optimally staged patients only one pelvic recurrence (1%), while in the group without pelvic and or para-aortic lymph node sampling 13% of the patients recurred only in the pelvis. Our study differs from that of Maggioni et al. [15] in various aspects. First, our analysis was a subgroup analysis of a randomized trial with a study design that was not primarily intended to study the omission of particular surgical steps during the staging procedure. Second, Maggioni et al. [15] compared restrictive versus extensive lymph node removal whereas the current study compared lymph node sampling versus no sampling at all. And third, an unknown percentage of patients in Maggioni's study received postoperative chemotherapy versus no patients in the current study. Contrary to Maggioni's conclusions we found a significant difference in DFS as well as OS in favour of completely staged patients in our study.

The prognostic significance of lymphadenectomy in the staging of early ovarian cancer is supported by a large retrospective study of stage I ovarian cancer patients of Chan et al. [20]. Lymphadenectomy improved the disease-specific survival of all patients from 87% to 92.6%. Furthermore, they found that the extent of lymphadenectomy (0 nodes, less than 10 nodes, and 10 or more nodes) was a significant prognostic factor for improved survival in the multivariable analysis [20].

We are aware of the limitation of our study with small number of patients especially for the group of patients without blind biopsies. Therefore, we should be careful to draw too strong conclusions, on the other hand all analyses were statistically significant. Furthermore these data were derived from a randomized trial and one of the largest series of early ovarian cancer patients who were treated in a standardized way with well described surgical staging steps.

In our study we have shown that both 5-year DFS and 5-year OS were statistically significantly better for optimally staged patients compared to those in whom either sampling of lymph nodes or taking of blind biopsies were omitted. The 5-year OS decreases from 89% in patients who were optimally staged to 71% when lymph node sampling was not performed. Optimal surgery improved survival by correcting false stage allocation and upstaging.

In conclusion we demonstrated the importance of lymph node sampling and taking of blind peritoneal biopsies in the surgical staging for the prognosis of early ovarian cancer patients in this study.

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Chapter 7

Prognostic value of Ic substages in invasive epithelial ovarian carcinoma

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Submitted

ABSTRACT

Objectives: Since the incorporation of capsule rupturing and other prognostic variables in the FIGO staging system for epithelial ovarian cancer, stage I is an admixture of different substages. The current study describes FIGO stage Ic ovarian cancer patients with a heterogeneity of different clinical presentations like capsule rupturing, ascites containing malignant cells, surface tumor and positive peritoneal fluid in relation to disease-free and overall survival.

Methods: Of the 448 patients randomized in the ACTION trial, 417 FIGO stage I ovarian cancer patients and 31 stage IIa patients were used for the recurrence-free and overall survival analysis.

Results: From the 417 FIGO stage I patients 155 (36%) were stage Ia, 37 stage Ib (9%) and 223 stage Ic (53%) patients. The 5-year overall survival was 82% for stage Ia, 86% for stage Ib and 81% for stage Ic, no statistical difference was found between these substages. Both disease-free and overall 5-year survival was not significant different for the Ic subcategories capsule rupture (71/80%), external surface tumor (76/88%) and positive ascites or malignant washings (67/78%). The time of capsule rupturing, before or during surgery, was not a prognostic factor.

Conclusions: This large series of early ovarian cancer patients shows no difference in prognosis between stage Ic patients compared to the other stages Ia and Ib patients. This study challenged the clinical significance of definition of stage Ic. Further clinical trials maybe define better prognostic factors in these ovarian cancer patients which could be incorporated in the FIGO staging system.

INTRODUCTION

Epithelian ovarian cancer (EOC) accounts for approximately 25% of patients with disease confined to the ovaries (FIGO stage I). These patients are further subdivided according the last International Federation of Gynecology and Obstetrics FIGO classification in 1985 depending whether one ovary (Ia) or both ovaries (Ib) are involved or if there was capsular rupture, surface tumor, ascites present that contains malignant cells or positive peritoneal washings (Ic) [1]. The importance of capsule rupturing was already incorporated in the FIGO staging system in 1971 [2]. The implications of substage in stage I are that it is generally supposed that the factors which assign patients to Ib or Ic carry a worse prognosis [3,4]. In several studies the 5-year survival for stage Ia patients is around 90-95% which decreases to 80-85% and 75-80% for stage Ib and Ic respectively [5-10]. However, many controversies still exist with regard to the relative importance of prognostic variables within stage I and in particular the independent significance of capsule rupture before or during surgery, surface tumor and positive peritoneal cytology. Some authors suggest that rupture of the tumor capsule [11,12] have a relevant impact on survival of early ovarian cancer patients and Ahmed et al. [10] identified the presence of ascites and surface tumor as independent prognostic factors. On the other hand, other studies did not confirm these findings [13,14].

The vast majority of the patients randomized in the EORTC ACTION trial 55904 were FIGO stage Ic patients. To clarify the relevance of the different Ic substages we performed the current study. This analysis of patients randomized in the EORTC ACTION trial shows the results of the subgroups of FIGO stage Ic patients which consist of a heterogeneity of clinical presentations which maybe do have different impact in relation to recurrence rate and overall survival.

PATIENTS AND METHODS

All 448 patients were randomized in the European Organisation for Research and Treatment of Cancer (EORTC) Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION, 55904) trial which run between November 1990 and March 2000. Patients with FIGO stages Ia-Ib, grade 2 and 3, FIGO stages Ic-IIa, grade 1-3 and all grade stages Ic-IIa clear cell carcinoma were eligible for the study. Patients were randomized after surgical treatment between cisplatinum-based chemotherapy or no adjuvant chemotherapy (observation arm). Patients in the chemotherapy arm received at least four courses of platin-based chemotherapy. Patients in the observation arm were followed and treated according the institution policy by a clinically or histologically proven recurrence.

For this analysis 417 patients FIGO stage I epithelial ovarian cancer patients (93%) and 31 stage IIa patients (7%) were used. From the 417 FIGO stage I patients 155 (36%) were Ia, 37 stage Ib (9%) and 223 stage Ic (53%) patients. Information about clinical and histopathological features as well as for surgical staging were available for all patients. The mean follow-up at the time of the analysis was 5.6 years. For a detailed description and results of this trial we refer to a previous publication of Trimbos et al. [15]. Subgroup analysis was performed on the different FIGO stage Ic groups (n=223). Patients were classified according the International Federation of Gynecology and Obstetrics FIGO stage of 1985 [1].

Statistical analysis was performed using SPSS version 15.0 (SPSS inc., Chicago, IL). The Kaplan-Meier method was used for generating the disease-free and overall survival curves [16]. Comparison of survival distributions were made with the log-rank test with a significance defined as the *P* value < 0.05.

RESULTS

Table 1 shows the different FIGO stages of the 448 patients randomized in the EORTC ACION trial for both treatment arms. The FIGO stages were well balanced between the observation and the chemotherapy arm. The distribution of the FIGO stages was as follows: one-third of the patients (36%) were FIGO stage Ia (n=155), 9% stage Ib (n=37), 53% stage Ic (n=223) and 2% IIa (n=31). Further substages of the 223 Ic patients were 50 carcinomas on the ovarian surface (22%), 116 patients with Ic capsule rupture (52%) and 57 patients Ic with malignant washing or ascites (26%). From the

Table 1. FIGO stages by treatment arm

FIGO stage	**Observation Arm** N=224(%)	**Chemotherapy arm** N=224(%)
Ia	76 (34%)	79 (35%)
Ib	18 (8%)	19 (8%)
Ic ovarian surface	28 (12%)	22 (10%)
Ic capsule rupture	52 (23%)	64 (29%)
Ic malignant washing/ascites	33 (15%)	24 (11%)
IIa	15 (7%)	16 (7%)
Unknown	2 (1%)	0

116 patients with Ic capsule rupture, 84% of the rupturing occurred during operation, while 16% took place before surgery. The FIGO stage was missing in two patients. No significant difference was shown in the Ic stage for treatment arm, surgical staging category and differentiation grade as represented in Table 2.

Table 2. Patients Characteristics of FIGO stage Ic substages

	Ic ovarian surface N=50 (%)	Ic capsule rupture N=116 (%)	Ic malignant washing/ascites N=57 (%)	*P*-value
Treatment arm				
Observation	22 (56%)	52 (45%)	33 (58%)	*P*=0.74
Chemotherapy	28 (44%)	64 (55%)	24 (42%)	
Type of staging				
Optimal	24 (48%)	38 (33%)	18 (32%)	*P*=0.16
Not optimal	26 (52%)	78 (67%)	39 (68%)	
Differentiation grade				
Well	15 (30%)	19 (17%)	11 (19%)	
Moderately	22 (44%)	57 (49%)	30 (53%)	*P*=0.22
Poorly	10 (20%)	36 (31%)	16 (28%)	
Unknown	3 (6%)	4 (3%)	0	

Figure 1 shows the 5-year disease-free survival (DFS) of all 448 patients randomized in the ACTION trial with no significant difference for the different stages (P = 0.06). Figure 2 represents the overall survival curves of the three FIGO Ic substages. The 5-year overall survival for Ic substages, tumor on the surface, capsule rupturing and ascites or malignant cells containing peritoneal fluid were 76%, 71% and 67% respectively (P = 0.47). In the group of 223 FIGO stage Ic patients 53 recurrences occured, 11/50 ovarian surface (22%), 26/116 capsule rupture (22%) and 16/57 malignant washing or ascites (28%). The 5-year disease-free survival ranged between 78 and 88% (P = 0.71) for the different Ic stages as shown in Figure 3. From the 223 patients in the FIGO stage Ic group, 40 (18%) died of the disease.

No significant difference was found in both disease-free and overall survival between the Ic capsule rupturing group before and during surgery. Although the 5-year disease-free survival was better in the group with rupturing during operation (74%) compared to the group of rupturing before operation (64%), the overall 5-year survival showed an advantage in the group rupturing before surgery in comparison to rupturing during surgery, 85 versus 78% respectively. These differences were not statistically significant.

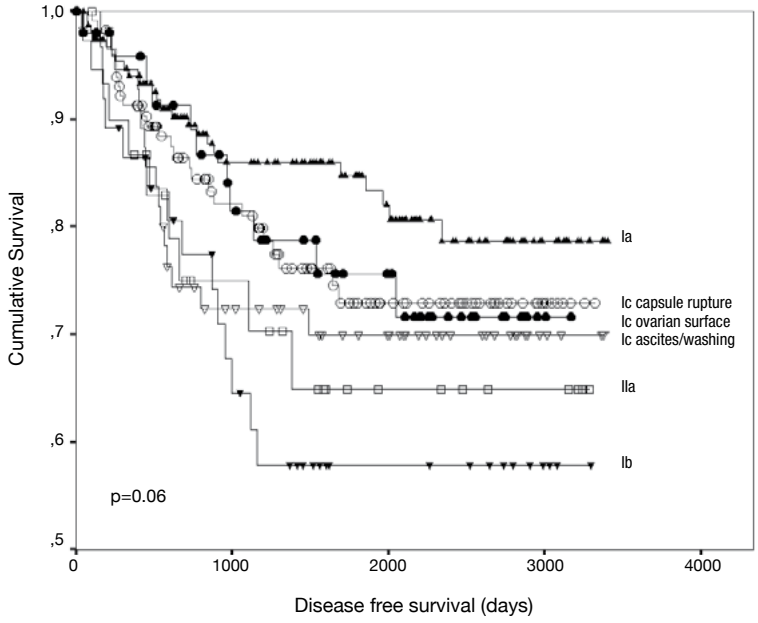

Figure 1. Kaplan - Meier curves for disease-free survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO stage; Ia (n = 155), Ib (n = 37), Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/malignant washing (n= 57) and IIa (n = 31). P = 0.06 using the log-rank test.

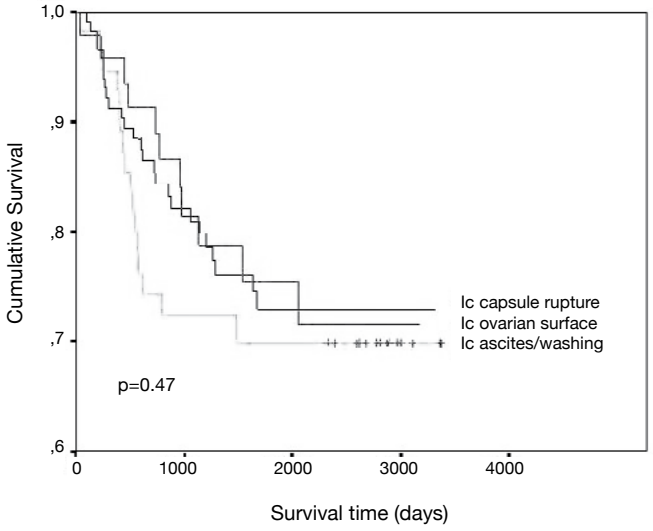

Figure 2. Kaplan - Meier curves for overall survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO Ic substages; Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/ malignant washing (n= 57). P = 0.47 using the log-rank test.

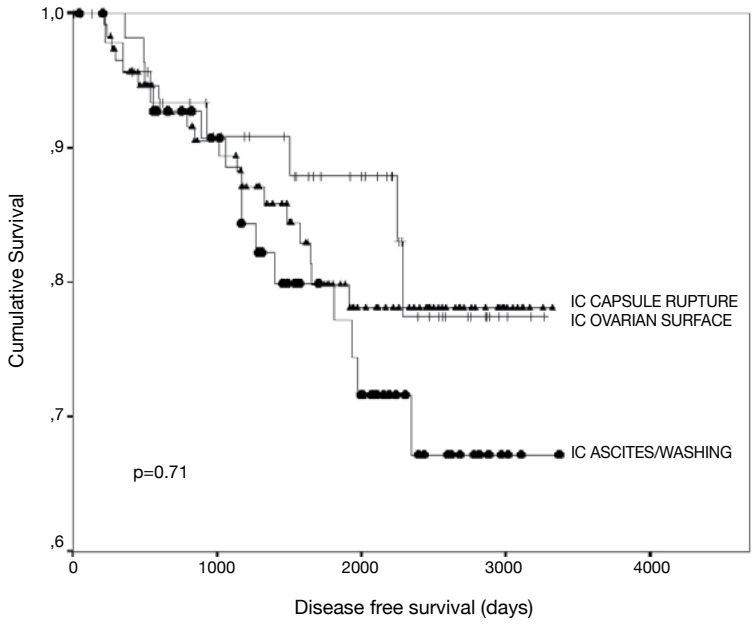

Figure 3. Kaplan - Meier curves for disease-free survival in patients with early ovarian cancer in both treatment arms of the trial by FIGO Ic substages; Ic ovarian surface (n = 50), Ic capsule rupture (n = 116), Ic ascites/ malignant washing (n= 57). P = 0.71 using the log-rank test.

DISCUSSION

In the ACTION trial and the combined ACTION/ICON 1 analysis [11], FIGO stage was not a prognostic factor. FIGO stage Ic disease was not associated with a higher risk of recurrence or death compared to moderately and poorly differentiated FIGO stage Ia and Ib. In a recent meta-analysis of more than 1500 cases of early ovarian cancer patients, Vergote et al. found that stage Ic had a similar prognosis as stage Ib [17]. On the other hand, some other investigators showed a worse outcome in relation to tumor rupture [4] and capsule penetration [11,12], while Dembo et al. [14] found cyst rupture and capsular penetration not prognostic. This last study did not perform lymph node sampling and peritoneal biopsies in the absence of a palpable abnormality. Furthermore, most of these studies are retrospective analyses of small numbers of patients with sometimes unknown surgical staging procedure. Another reason for the inconsistency of the results may be the diverse treatment modalities. No difference in survival was observed between stage I subgroups ovarian carcinomas and stage IIa in a study of Sigurdsson et al. [6]. Our data confirm these findings, the 223 patients with

Ic ovarian cancer showed a 5-year disease-free survival of 70% and a 5-year overall survival of 82% which was not worse than those patients with stage Ia and Ib. Although the statistical power of the current analysis was 0.63, the results of the ACTION trial describe the largest series of early ovarian cancer patients in a randomized trial until now. In our study also no survival difference was found between the different stage I patients, giving a 5-year overall survival of 83% for stage Ia (n=155), 88% for stage Ib (n=37), 82% for stage Ic (n=223) and 78% for stage IIa (n=31) patients. In a study done by Piver [18], the 5-year progression-free survival of 32 stage Ic grade 3 patients with invasive epithelial ovarian cancer was 90.5% and the 5-year survival was 93.3%, treated with cisplatin-based chemotherapy. In contrast to our findings, Brugghe et al. found FIGO substage the strongest prognosticator in 102 adequately staged Ia-Ic ovarian cancer patients who received no postoperative treatment [19].

In studies concerning stage Ic ovarian cancer patients a different prognostic value of capsule rupturing has been found. In a study of Krafft et al. [20] rupture and ascites drastically reduced the changes of survival in 60 patients with early ovarian cancer. Sainz de la Cuesta et al. [21] found a significant difference ($P = 0.03$) in the recurrence-free survival of stage Ia (97 months) compared to stage Ic capsule rupture (78 months). The disease-free survival of the other Ic group (capsular invasion, positive ascites or washings) did not differ significantly from the Ic rupture group. The hazard ratios for overall survival associated with stage Ic-rupture and each potential confounder, except for bloating, exceeded 6.5. They concluded that intra-operative rupture of malignant epithelial ovarian neoplasms may worsen the prognosis of patients with stage I ovarian cancer. Prognostic factor analysis in 162 stage I high risk ovarian cancer patients performed by Tropé et al. showed that extracapsular growth and tumor rupture were significant independent factors with *P* values of 0.0005 and 0.04 respectively [22]. A multivariate analysis by Kodama et al. showed that capsular rupture caused by the surgeon did not affect the prognosis in stage I and II ovarian cancer [23]. Looking at our data the subcategories of Ic patients including capsule rupture (n=116), surface invasion (n=50) and ascites or malignant cells containing washings (n=57) showing 5-year disease-free survival of 71%, 75% and 68% respectively ($P = 0.71$). The survival prognosis was not influenced by the different categories, giving 5-year overall survival percentages of 80% for Ic capsule rupturing, Ic surface of 89% and Ic positive ascites or washings of 79%. Villa et al. [9] reported a significant difference of 5-year survival between patients with tumor presence on the surface (88%) compared to intra-operative tumor rupture (72%).

The specific importance of rupture before or during operation is still unclear. Sevalda et al. reported no influence on survival rates for stage Ic capsule rupture during surgery

and therefore they considered that these patients do not belong to the subgroup Ic as suggested by the FIGO committee [5]. In a multivariate analysis of Vergote et al. both rupturing before as during surgery were independent predictors of disease-free survival, with rupturing before operation giving a higher change of recurrent disease [17]. The results of a study done by Mizuno et al. showed better survival curves for patients with rupturing during operation compared to the other Ic patients [24]. In contrast to these findings, Sjövall et al. found no difference in survival between those patients whose tumors had intact capsules and patients in whom rupture occurred during surgery, 78% versus 85% respectively. The conclusion was drawn that manipulation during surgery which results in puncture or rupture does not have a negative influence on the outcome for the patients. On the other hand, a significant difference in survival was found between patients in whom rupture occured before surgery and those with intra-operative rupture, 59% and 85%, respectively [25]. The results of our analysis with further subdivision of the Ic capsule rupture group into 19 patients where rupture occurred before surgery and 97 patients with rupturing during surgery shows a difference in both 5-year recurrence-free survival (65% versus 74%) and overall survival (80% versus 89%) in favor of capsule rupturing during surgery but this difference reached no significancy.

In conclusion, in this large randomized trial in early ovarian cancer patients with a subset of more than 200 stage Ic patients no significant difference was found in recurrence rate and survival in the subsets of Ic patients, also no clear negative impact on survival and recurrence rate could be found for capsule rupturing before or during surgery. The current used FIGO staging system does not differentiate between low and high risk early ovarian cancer patients. Maybe other prognostic factors, like DNA ploidy and degree of differentation should be incorporated in a new staging system to divide patients with different prognosis.

Appendix 1

Capsule rupturing in the International Federation of Gynecology and Obstetrics (FIGO) staging system

1964	
Stage Ic	growth limited to one or both ovaries, ascites containing malignant cells
Capsule rupture not incorporated in staging system	
1971	
Stage Ia1/Ib1	growth limited to one ovary/both ovaries, capsule ruptured, no ascites
Stage Ia2/Ib2	growth limited to one ovary/both ovaries, capsule not ruptured, no ascites
Stage Ic1	growth limited to one or both ovaries, capsule ruptured, ascites containing malignant cells
Stage Ic2	growth limited to one or both ovaries, capsule not ruptured, ascites containing malignant cells
1975	
Stage Ia1/Ib1	growth limited to one ovary/both ovaries, no tumor external surface, capsule intact, no ascites
Stage Ia2/Ib2	growth limited to one ovary/both ovaries, tumor external surface and/or capsule ruptured, no ascites
Stage Ic	tumor either stage Ia or Ib and acites present or positive peritoneal washings
1985	
Stage Ia	growth limited to one ovary, no tumor external surface, capsule intact, no ascites
Stage Ib	growth limited to both ovaries, no tumor external surface, capsule intact, no ascites
Stage Ic	tumor either stage Ia or Ib, tumor on the external surface or capsule ruptured or ascites containing malignant cells or positive peritoneal washings

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Chapter 8

Surgical staging and treatment of early ovarian cancer: long-term analysis from a randomized trial

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ABSTRACT

A long-term follow-up analysis of the randomized clinical trial Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) from the European Organisation for Research and Treatment of Cancer was undertaken to determine whether the original results with a median follow-up of 5.5 years could be verified after longer follow-up with more events. In the ACTION trial, 448 patients with early ovarian cancer were randomly assigned, after surgery, to adjuvant chemotherapy or to observation (no further treatment). The original analysis found that adjuvant chemotherapy improved recurrence-free survival but not overall survival and found in a subgroup analysis that completeness of surgical staging was an independent prognostic factor, with better recurrence-free and overall survival among those with complete (optimal) surgical staging. After a median follow-up of 10.1 years, we analyzed the more mature data from the ACTION trial and found support for most of the main conclusions of the original analysis, except that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy (hazard ratio of death = 1.89, 95% confidence interval = 0.99 to 3.60; overall two-sided log-rank test $P = 0.05$). More cancer-specific deaths were observed among non-optimally staged patients (40 [27%] of the 147 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm) than among optimally staged patients (seven [9%] of the 75 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm) (two-sided χ^2 test for heterogeneity, $P = 0.06$). Thus, completeness of surgical staging in patients with early ovarian cancer was found to be statistically significantly associated with better outcomes, and the benefit from adjuvant chemotherapy appeared to be restricted to patients with non-optimal surgical staging.

INTRODUCTION

Results of the European randomized clinical trial called Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) conducted by the European Organisation for Research and Treatment of Cancer (EORTC) in patients with early epithelial ovarian cancer were published in 2003 [1], and its conclusions have been discussed previously [2–6]. This trial included 448 patients who in the 2003 report [1] had a median follow-up of 5.5 years (range = 3 months to 9 years), a total of 100 recurrences registered, and 78 deaths from ovarian cancer. Adjuvant chemotherapy that was administered after surgical treatment statistically significantly improved recurrence-free survival but not overall survival [1]. Subgroup analysis on the effect of surgical staging indicated that the benefit of adjuvant chemotherapy appeared to be limited to patients who underwent non-optimal staging and so had a higher risk of undetected residual disease. In a subgroup analysis of patients with optimal surgical staging, adjuvant chemotherapy was not associated with overall or recurrence-free survival.

In this study, we analyzed the mature data with a median follow-up of 10.1 years (95% confidence interval [CI] = 9.2 to 11.3 years) to test specifically whether the findings of the initial analysis would be robust over time. We repeated the initial analysis after a longer follow-up with more events and used cancer-specific survival to avoid the bias of intercurrent deaths (i.e., deaths from a cause other than ovarian cancer) because this risk increases with the duration of follow-up.

PATIENTS AND METHODS

Patients with epithelial ovarian cancer at stages Ia–Ib and grades 2–3 and all stages Ic and IIa and patients with clear cell cancer of the ovary (as defined by the International Federation of Gynecology and Obstetrics [FIGO]) at all stages I–IIa were eligble for the study. After surgery, patients were randomly assigned to adjuvant chemotherapy or to observation. The surgical staging procedure was divided into two groups: optimal and non-optimal staging. Optimal staging included removal of the affected ovary; removal of the uterus and contralateral ovary (if a patient with a stage Ia tumor wanted to remain fertile, the uterus and contralateral ovary could be left in situ); careful inspection and palpation of all peritoneal surfaces and biopsy sampling of any suspicious areas, such as adhesions adjacent to the primary tumor; peritoneal washing for cytology analysis; infracolic omentectomy; blind peritoneal biopsy sampling of the right hemidiaphragm, the right and left paracolic gutters, the pouch of Douglas, the bladder peritoneum and the pelvic side walls; and removal of para-aortic and pelvic lymph nodes. The

group of patients with non-optimal staging was further divided into the categories modified, minimal, and inadequate staging [1]. The ACTION trial was conducted between November 1, 1990, and January 23, 2000, in 40 centers from nine European countries (EORTC Gynaecological Cancer Group, trial registry number = 55904). The Institutional Review Board of each participating center had to approve the study, and informed consent of each patient was a prerequisite.

Cancer-specific survival was measured from the date of randomization to the date of death from ovarian cancer. Patients who were still alive or who had died of other causes were censored at their last known date alive. Recurrence-free survival was measured from the date of randomization to the first documented date of recurrence or death from any cause, whichever occurred first. Both survival measures were estimated by the Kaplan–Meier method and compared by Cox proportional hazards regression (according to the intention-to-treat principle, after necessary assumptions were met) to determine statistically significant covariates, such as FIGO stage, tumor grade, histological cell type, completeness of surgical staging, age, level of tumor marker CA125, and performance status. Differences in relative size of treatment effect between subgroups of staging performance were tested by use of the χ^2 test for interaction.

To analyze the mature data, follow-up was extended to May 23, 2008, increasing the median follow-up from 5.5 years in the original analysis to 10.1 years (95% CI = 9.2 to 11.3 years). The follow-up duration was equal between the two treatment arms.

RESULTS

The number of events for the original analysis and this updated analysis are presented in Table 1. In a multivariable analysis that was adjusted for treatment, only the extent of surgical staging and tumor grade were statistically significantly associated with cancer-specific survival (hazard ratio [HR] of death = 1.89, 95% CI = 1.23 to 2.91, for patients with non-optimal staging compared with those with optimal staging; $P = 0.004$; HR of death = 1.78, 95% CI = 1.24 to 2.56, for patients with poorly differentiated tumors compared with those with well and moderate tumors; $P = 0.002$). In this analysis, well and moderately differentiated tumors were combined because differences between them were minimal.

Cancer-specific and recurrence-free survival for both the observation and the chemotherapy arms are given in Figure 1, A and B. After a 10-year follow-up, cancer-specific survival was similar between the two arms, but recurrence-free survival was statistically significantly

Table 1. Comparison of recurrences and deaths among the 448 patients (224 in the observation arm and 224 in the adjuvant chemotherapy arm) from the original analysis (2003) and from the updated analysis of the mature data: the Adjuvant ChemoTherapy in Ovarian Neoplasm Trial*.

	Original analysis [1]		Analysis mature data	
Events (deaths or recurrences)	**Adjuvant chemotherapy arm**	**Observation arm**	**Adjuvant chemotherapy arm**	**Observation arm**
Recurrences, No. (%)	40 (17.8)	60 (26.8)	61 (27.2)	87 (37.8)
Deaths, No. (% of total deaths)				
Total	33 (14.7)	45 (20.1)	52 (23.2)	67 (29.9)
From ovarian cancer	26 (78.8)	37 (82.2)	36 (69.2)	47 (70.1)
From other causes	5 (15.2)	8 (17.8)	12 (23.1)	19 (28.4)
From unknown causes	2 (6.0)	—	4 (7.7)	1 (1.5)

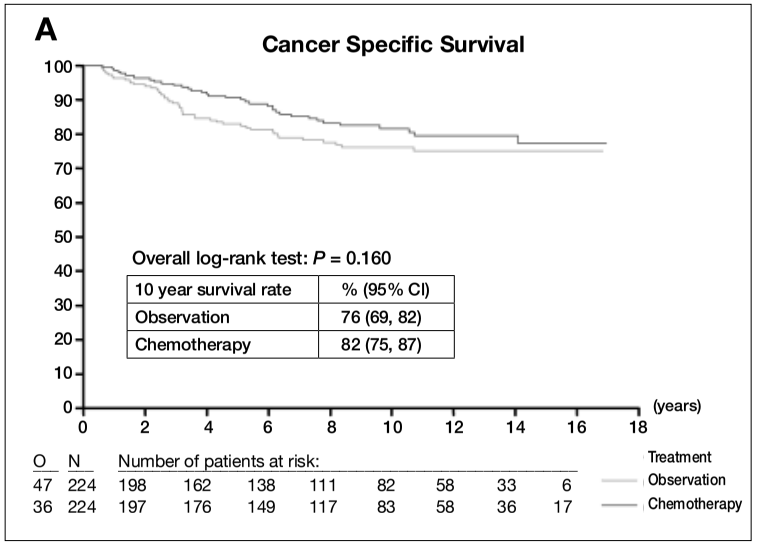
*Adjuvant chemotherapy had to consist of at least four courses of a platinum-based regimen after surgery but six courses were recommended.

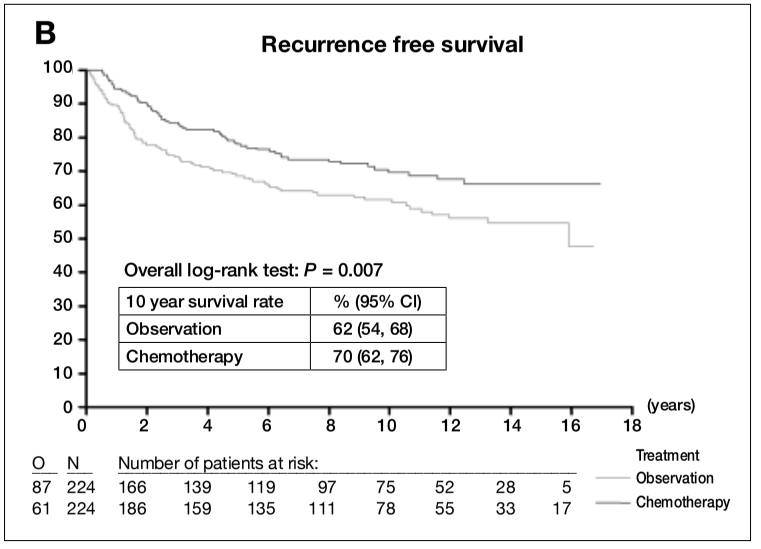
higher in the chemotherapy arm (70%) than in the observation arm (62%) (difference = 8%, 95% CI = 21.6% to 17.6%; HR for death = 0.64, 95% CI = 0.46 to 0.89, $P = 0.007$).

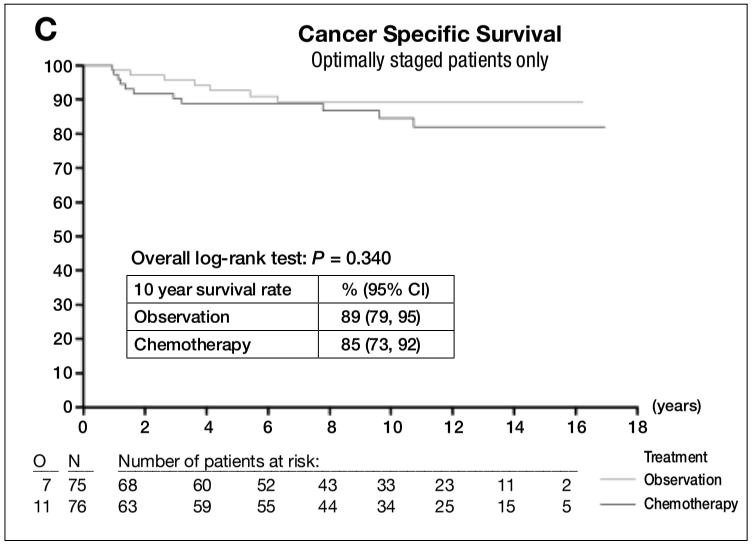
In both this analysis and the original analysis, patients were also separated into optimally and non-optimally staged groups. Among the optimally staged group, no differences were observed in 10-year cancer-specific survival and recurrence-free survival between the adjuvant chemotherapy and the observational arms (Figure 1, C and D).

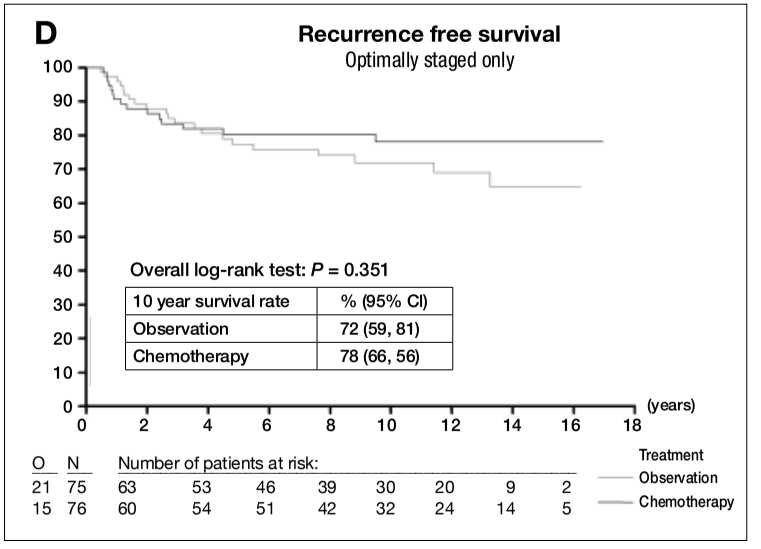
In contrast, among the non-optimally staged group, statistically significantly better 10-year cancer-specific survival was found among those in the adjuvant chemotherapy arm (80%) than among those in the observation arm (69%) (difference = 11%, 95% CI = 0% to 22%; HR for death = 0.58, 95% CI = 0.35 to 0.95, $P = 0.029$) (Figure 1, E). In addition, among the non-optimally staged group, statistically significantly better 10-year recurrence-free survival was found among those in the chemotherapy arm (65%) than among those in the observation arm (56%) (difference = 9%, 95% CI = 22.8% to 20.8%; HR for death = 0.60, 95% CI = 0.41 to 0.87, $P = 0.007$) (Figure 1, F).

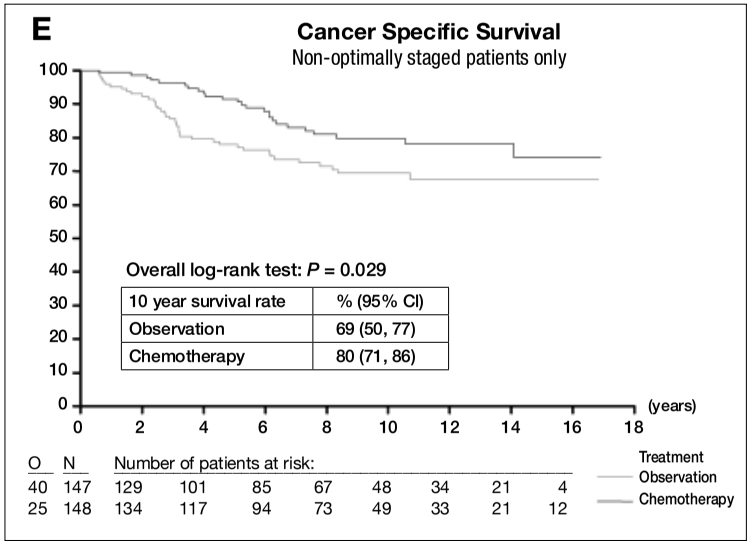
Among patients in the observation arm after a median follow-up of 10.1 years, optimally staged patients had statistically significantly better rates for cancer-specific survival and recurrence-free survival than non-optimally staged patients (Table 2). Among patients in the chemotherapy arm after a median follow-up of 10.1 years, the rates for cancer-specific survival and recurrence-free survival were similar in optimally staged patients and non-optimally staged patients (Table 2).

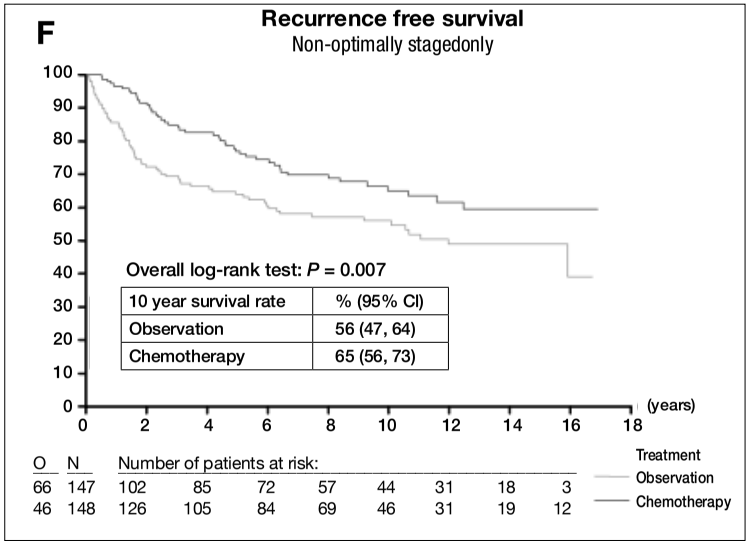

A
Cancer Specific Survival
Overall log-rank test: P = 0.160
10 year survival rate | % (95% CI)
Observation | 76 (69, 82)
Chemotherapy | 82 (75, 87)
(years)
O N Number of patients at risk:
47 224 198 162 138 111 82 58 33 6
36 224 197 176 149 117 83 58 36 17
Treatment
Observation
Chemotherapy


B
Recurrence free survival
Overall log-rank test: P = 0.007
10 year survival rate | % (95% CI)
Observation | 62 (54, 68)
Chemotherapy | 70 (62, 76)
(years)
O N Number of patients at risk:
87 224 166 139 119 97 75 52 28 5
61 224 186 159 135 111 78 55 33 17
Treatment
Observation
Chemotherapy


C
Cancer Specific Survival
Optimally staged patients only
Overall log-rank test: P = 0.340
10 year survival rate | % (95% CI)
Observation | 89 (79, 95)
Chemotherapy | 85 (73, 92)
(years)
O N Number of patients at risk:
7 75 68 60 52 43 33 23 11 2
11 76 63 59 55 44 34 25 15 5
Treatment
Observation
Chemotherapy


D
Recurrence free survival
Optimally staged only
Overall log-rank test: P = 0.351
10 year survival rate | % (95% CI)
Observation | 72 (59, 81)
Chemotherapy | 78 (66, 56)
(years)
O N Number of patients at risk:
21 75 63 53 46 39 30 20 9 2
15 76 60 54 51 42 32 24 14 5
Treatment
Observation
Chemotherapy





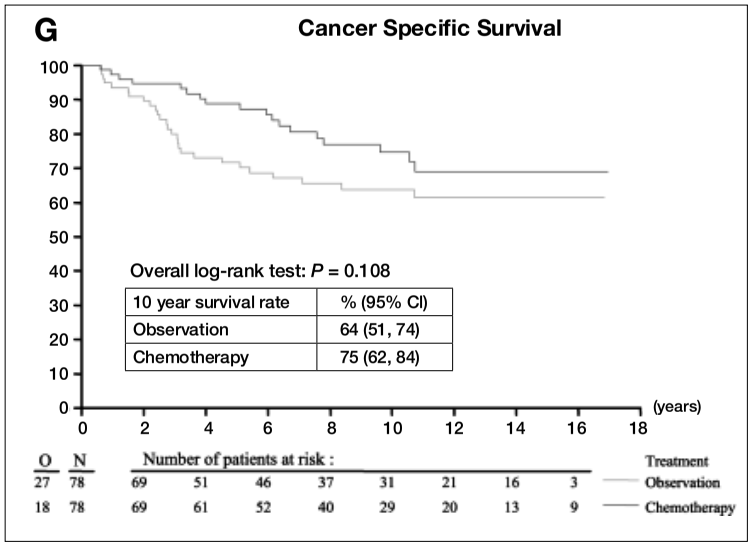


Figure 1. Kaplan–Meier curves for cancer-specific and recurrence-free survival among patients with early-stage ovarian carcinoma by staging type and treatment arm (observation and adjuvant chemotherapy). All comparisons were between the observational arm and the adjuvant chemotherapy arm. The survival percentage is shown on the *y*-axis, and time is shown on the *x*-axis. **A**) Cancer-specific survival in all 448 patients (hazard ratio [HR] of death = 0.73, 95% confidence interval [CI] = 0.48 to 1.13, *P* = 0.16). **B**) Recurrence-free survival in all 448 patients (HR of death = 0.64, 95% CI = 0.46 to 0.89, *P* = 0.007, in favor of adjuvant chemotherapy). **C**) Cancer-specific survival in optimally staged patients (HR of death = 1.58, 95% CI = 0.61 to 4.08, *P* = 0.34). **D**) Recurrence-free survival in optimally staged patients (HR of death = 0.73, 95% CI = 0.38 to 1.42, *P* = 0.35). **E**) Cancer-specific survival in non-optimally staged patients (HR of death = 0.58, 95% CI = 0.35 to 0.95, *P* = 0.029, in favor of adjuvant chemotherapy). **F**) Recurrence-free survival in non-optimally staged patients (HR of death = 0.60, 95% CI = 0.41 to 0.87, *P* = 0.007, in favor of adjuvant chemotherapy). **G**) Cancer-specific survival in patients with a poorly differentiated (grade 3) early-stage ovarian carcinoma (HR or death = 0.62, 95% CI = 0.34 to 1.12, *P* = 0.108). The two-sided log-rank test was used to determine *P* values. All statistical tests were two-sided. N = number of patients; O = number of events observed.

Table 2. The 10-year cancer-specific survival and recurrence-free survival rates by the extent of surgical staging: the Adjuvant ChemoTherapy in Ovarian Neoplasm Trial*.

	% survival (95% CI)			
Survival type and arm	With optimal staging	With non-optimal staging	HR (95%)	P†
Cancer-specific survival				
Observation	89 (79 to 95)	69 (60 to 77)	3.28 (1.47 to 7.33)	0.002
Chemotherapy	85 (73 to 92)	80 (71 to 86)	1.27 (0.62 to 2.58)	0.52
Recurrence-free survival				
Observation	72 (59 to 81)	56 (47 to 64)	1.91 (1.17 to 3.11)	0.009
Chemotherapy	78 (66 to 86)	65 (56 to 73)	1.64 (0.91 to 2.93)	0.09

*CI = Confidence Interval; HR = hazard ratio of death or recurrence.
†The statistical test was the two-sided log-rank test.

CONTEXT AND CAVEATS

Prior knowledge

In the randomized clinical trial Adjuvant ChemoTherapy in Ovarian Neoplasm, 448 patients with early ovarian cancer were randomly assigned, after surgery, to adjuvant chemotherapy or to observation. After a median follow-up of 5.5 years, adjuvant chemotherapy was associated with improved recurrence-free survival but not overall survival. In a subgroup analysis, better recurrence-free and overall survival were observed among those with non-optimal surgical staging than those with optimal staging.

Study design

Long-term analysis of data from this trial after a median of 10.1 years of follow-up.

Contribution

The long-term analysis supported most conclusions from the original analysis, except that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy. More cancer-specific deaths were observed among non-optimally staged patients than among optimally staged patients.

Implications

Completeness of surgical staging among patients with early ovarian cancer was statistically significantly associated with better outcomes, and the benefit from adjuvant chemotherapy was restricted to patients with non-optimal surgical staging.

Limitations

The trial was not designed to compare different surgical staging procedures. Patients could not be prospectively stratified by surgical staging category. The study had a limited sample size. Quality of life was not studied.

Because the differentiation grade of early ovarian cancer is a strong prognostic factor for survival, the optimally staged 156 patients in the ACTION trial with a poorly differentiated (grade 3) tumor (78 in the observation arm and 78 in the adjuvant chemotherapy arm) were analyzed separately. After a median follow-up of 10.1 years, we found no differences between the observation and the chemotherapy arms in stage, age, performance status, histological cell type, or cancer-specific survival (Figure 1, G, and Table 3). This finding did not change when the optimally staged patients with a grade 3 tumor were analyzed separately. However, when non-optimally staged patients with a grade 3 tumor were analyzed, cancer-specific survival was better in the adjuvant chemotherapy arm than in the observation arm (HR of death = 0.40, 95% CI = 0.19 to 0.81, $P = 0.009$) (Table 3).

The long-term results of the ACTION trial strongly substantiate the results of the original analysis [1], with only one exception. After 10.1 years of follow-up, the multivariable analysis found no association between cancer-specific survival and histological cell type. Both staging adequacy and differentiation grade remained highly statistically significant prognostic factors. A well or moderately differentiated tumor, compared with a poorly differentiated tumor, was associated with increased cancer-specific survival (HR of death = 1.78, 95% CI = 1.24 to 2.56).

Table 3. Recurrence-free survival (RFS) and cancer-specific survival (CSS) after 10 years of follow-up among the 156 patients with poorly differentiated (grade 3) tumors: the Adjuvant ChemoTherapy in Ovarian Neoplasm Trial*

	% survival (95% CI)			
Survival type and group	Observation arm	Chemotherapy arm	HR (95% CI)	P†
Optimal staging				
RFS	64 (40 to 80)	49 (27 to 68)	1.25 (0.53 to 2.95)	0.61
CSS	85 (60 to 95)	69 (43 to 85)	2.58 (0.66 to 9.99)	0.15
Non-optimal staging				
RFS	52 (38 to 65)	55 (39 to 69)	0.58 (0.33 to 1.02)	0.05
CSS	56 (41 to 68)	77 (61 to 87)	0.40 (0.19 to 0.81)	0.009

* CI = Confidence Interval; HR = hazard ratio of death or recurrence.
† The statistical test was the two-sided log-rank test.

For the analysis of data with a median follow-up of 10.1 years, we deliberately choose to report cancer-specific survival instead of overall survival because results for overall survival were the same as in the original analysis, except that in the chemotherapy arm, statistically significantly better overall survival was found in the group with optimal surgical staging than in the group with non-optimal staging. Thus, the mature data support a beneficial effect of optimal surgical staging for patients with early ovarian cancer, even among those receiving adjuvant chemotherapy (HR of death = 1.89, 95% CI = 0.99 to 3.60; overall two-sided log-rank test $P = 0.05$).

For the entire cohort studied in the ACTION trial after a median follow-up of 10.1 years, cancer-specific survival was not associated with adjuvant chemotherapy. However, adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival (HR of death = 0.64, 95% CI = 0.46 to 0.89). Among optimally staged patients, recurrence-free survival was similar for both the observation arm (72%) and the adjuvant chemotherapy arm (73%), as was cancer-specific survival (89% and 86%, respectively). Thus, the conclusions of the original report of the ACTION trial appear to be robust and consistent during 10.1 years of follow-up. Among the group with poorly differentiated tumors, it is of interest that survival between optimally and non-optimally staged patients followed the same pattern. Among all patients with a grade 3 tumor, the recurrence-free survival and cancer-specific survival were lower than those of the entire cohort; this observation is consistent with the dismal prognosis of poorly differentiated tumors [7]. However, findings from the analysis with a median follow-up of 10.1 years indicate that administration of adjuvant chemotherapy after optimal surgical staging in this group is not associated with improved survival, perhaps because poorly differentiated early ovarian carcinomas have a tendency to metastasize earlier than those that are well differentiated [8]. Optimal surgical staging might detect this early spread so that patients with occult stage III disease can be identified and separated from the group of really early ovarian carcinomas.

Survival analyses (Figure 1, C–F) indicated that the completeness of staging (optimal vs non-optimal) in the ACTION trial defined two subgroups in which adjuvant chemotherapy has different effects: no benefit in the optimally staged group and a statistically significant benefit in the non-optimally staged group. The heterogeneity in cancer-specific survival was also observed between the treatment effects and the staging groups, as shown in forest plots (Figure 2) and with a χ^2 test for interaction (cancer-specific deaths among the non-optimally staged patients = 40 [27%] of the 147 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm; and among optimally staged patients, cancer-specific deaths = seven [9%] of the 75 deaths in the observation arm and 11 [14%] of the 76 deaths in the adjuvant chemotherapy arm; two-sided χ^2 test for heterogeneity, $P = 0.06$).

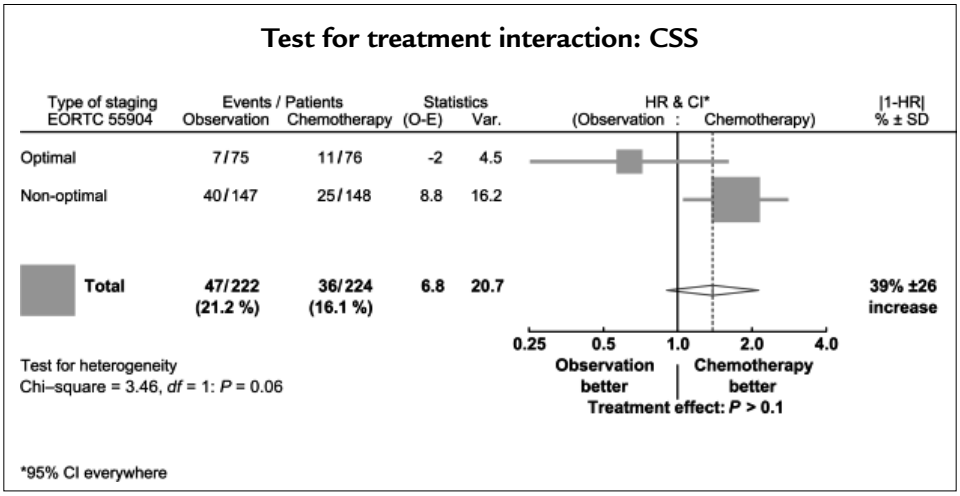


Figure 2. Forest plots of the interaction between the two staging categories (optimal and non-optimal) vs treatment effect (adjuvant chemotherapy better vs observation better) for cancer-specific survival. **Solid squares** = hazard ratios (HRs) for cancer-specific survival (with the area of the square being proportional to the variance of the estimated effect); **length of the horizontal line through the square** = 95% confidence interval (CI); **open diamond** = HR (middle of the diamond); **horizontal points of the diamond** = 95% CI for the combined data. CSS = cancer-specific survival; EORTC = European Organisation of Research and Treatment of Cancer; O - E = number of events observed minus number of events expected under the null hypothesis; SD = standard deviation; Var. = variance of 1 divided by the logarithm of the HR. Linear trends and heterogeneity of the HRs to detect differences in relative size of treatment effect were assessed by a χ^2 test for interaction. All statistical tests were two-sided.

DISCUSSION

This study has several limitations. The ACTION trial was not specifically designed to compare different surgical staging procedures, and patients could not be prospectively stratified according to the various surgical staging categories. Retrospective stratification, however, showed a well-balanced distribution of the various staging categories between the two treatment arms (data not shown), and no differences in the distribution of other risk factors, such as tumor grade and histological cell type between optimally and non-optimally staged patients. Furthermore, the study suffered from a limited sample size. At the time of the study design, no realistic power calculation could be made, so the sample size was arbitrarily set to 1000 or more patients. Because of the slow accrual of patients, this number was not met, despite the fact that this is the largest randomized trial in this disease with an observation arm and comparing the extent of surgical staging. Finally, the ACTION trial did not study quality of life. At the time that the study was planned, quality-of-life analyses were not yet considered an important element of clinical trials.

The design of our study permits no clear-cut guidelines for the treatment of all categories of patients with early ovarian carcinoma. It seems clear, however, that non-optimally staged patients should be restaged or be given adjuvant chemotherapy if restaging is not feasible. Although some people will argue that a *P* value for heterogeneity of 0.06 in a subgroup analysis is still insufficient evidence to withhold adjuvant chemotherapy from all patients with early ovarian cancer who received optimal surgical staging, others will take the view that, in the largest randomized trial on this issue after a median follow-up of 10.1 years, the consistent lack of an association between cancer-specific or recurrence-free survival and adjuvant chemotherapy among optimally staged patients is convincing evidence to restrict administration of chemotherapy even for patients with grade 3 tumors [6]. The latter point of view is supported by the observation that 20% of long-term survivors of ovarian cancer will develop a secondary primary tumor as a result of their treatment with platinum-based chemotherapy [9]. In addition, a randomized study design that included deliberately assigning half of the patients to improper surgery would be unethical because of the proven beneficial prognostic effect of adequate surgery.

In conclusion, the long-term analysis of the ACTION trial data 1) substantiated the original findings of the ACTION trial that the completeness of surgical staging in early ovarian cancer is an independent prognostic factor for recurrence-free and overall survival, even when adjuvant chemotherapy is given after surgery and 2) substantiated the original conclusion of the ACTION trial that " the benefit of adjuvant chemotherapy appears to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease" [1].

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Chapter 9

General Discussion

ADJUVANT CHEMOTHERAPY IN EARLY OVARIAN CANCER

The Adjuvant ChemoTherapy in Ovarian Neoplasm (ACTION) trial is one of the largest randomized trials in early ovarian cancer patients together with the ICON 1 trial [1,2].

The results of the ACTION trial show that adjuvant platin-based chemotherapy delays disease recurrence in patients with early-stage ovarian cancer, of whom 297 of the 448 patients (66%) had undergone non-optimal surgical staging. No statistically difference was found for overall survival in the entire group of patients randomized in the ACTION trial, but was found when combining the results of the ACTION and ICON 1 trials.

If we look at the patients in the observation arm who were optimally staged, both disease-free survival and overall survival were statistically better compared to the non-optimally staged patients in the same arm. The relatively poor prognosis of the non-optimally staged patients could be corrected by administrating adjuvant platinum-based chemotherapy. These results suggest that adjuvant chemotherapy in early-stage ovarian carcinoma may work predominantly by affecting microscopic metastases that remain unnoticed during the staging laparotomy. This hypothesis is supported by the finding that chemotherapy improved both overall and recurrence-free survival in the non-optimally staged patients and not in the optimally staged patients. The finding that adjuvant chemotherapy is effective in non-optimally staged patients might also explain the results of the ICON1 trial [2] and the combined ICON1/ACTION analysis [3], in which the majority of patients were most probably not optimally staged.

Another finding in this study was the difference in the percentage of patients successfully treated for tumor recurrence between the optimally and non-optimally staged group. The optimally staged patients showed a higher salvage rate in the observation arm than in the chemotherapy arm, 75% versus 46%, respectively. In the non-optimally staged patients however the salvage rate was similar in both arms, 70% and 64%. In a study of the Italian Gruppo Interregionale Collaborative Oncology Group GICOG the same difference of effectiveness of chemotherapy was found in patients were a complete surgical staging was performed [4].

A second long-term follow-up analysis of the ACTION trial was performed after a median follow-up of 10.1 years, which substantiated the main conclusions that the benefit of adjuvant chemotherapy is most clear in the non-optimally staged patients and that the completeness of surgical staging is an independent prognosticator for both disease-free and overall survival [5].

SURGICAL STAGING

In the present study the completeness of surgical staging was found to be an independent prognostic factor by multivariate analysis. This is not a surprising finding because the completeness of surgical staging influences the likelihood of remaining residual disease. Optimal staging reduces the chances of metastases in the lymph nodes, omentum and peritoneum and incomplete surgical staging increases the possibility of hidden occult cancer in the peritoneal cavity. The prognostic value of the extent of surgical staging in early ovarian cancer has been found by others as well [6,7].

Although the particular staging steps were precisely mentioned in the protocol of the ACTION trial and strongly advised to carry out, only one-third of the patients entered in the study were optimally staged. In order to reduce this very low number we have tried to figure out what the reasons are why so many patients are not completely staged.

One of the reasons may be that a substantial part of the patients with early ovarian cancer are diagnosed during a surgical procedure for acute abdominal pain or an ovarian mass and operated by a general gynecologist who does not have the surgical skills to perform an optimal surgical staging and has a lack of knowledge about the mechanisms of tumor spread in the abdominal cavity.

To perform a complete surgical staging surgical skills are needed and sufficient knowledge of the routes of metastases of ovarian cancer. In our study we have tried to differentiate between a lack of surgical skills for procedures involving morbidity on one hand or lack of sufficient knowledge of risk sites for ovarian cancer spread to carry out easy procedures without appreciable morbidity risk on the other. Pelvic and para-aortic lymph node sampling, procedures which carry a potential morbidity, were omitted in 78% and 52% respectively in the non-optimally staged group. In a previous Dutch study similar results were found [8], in 70% of the study population no lymph node sampling was done and also another study showed the same figure [9]. As we examine in the present study the easy procedures like taking blind biopsies of the paracolic gutters and from the pelvic side wall we found that it was omitted in 39% of the patients. Peritoneal washings were not done in 11% of the cases.

The role of lymph node sampling or lymphadenectomy on the prognosis in early ovarian cancer remains controversial. In a study of Baiocchi et al. [10] lymph node status was the most valuable prognostic factor in patients with disease limited to the ovary. A randomized study by Maggioni et al. [11] compared systemic pelvic and para-aortic lymphadenectomy to random sampling of lymph nodes in macroscopic early ovarian

cancer. In the systemic lymphadenectomy group the incidence of positive nodes was significantly higher: 22% versus 9% in the random sampling group, but the recurrence rate (22% and 30% respectively) nor the survival were significantly different [11]. In our study we found a significant difference in both disease-free and overall survival but our study compared lymph node sampling versus no sampling in the group patients who received no adjuvant treatment whereas in the trial of Maggioni an unknown percentage received postoperative chemotherapy. The limitation of our study is the relatively small number of patients in a subgroup analysis but on the other hand results are derived from one of the largest series in early ovarian cancer patients.

So both factors like insufficient surgical skills and knowledge are probably responsible for the staging problem in early ovarian cancer. To do something about these shortcomings, a better organization of the referral policy of patients with a suspicion of early ovarian cancer to a center with gynecologic oncologists is necessary.

Another finding of the ACTION trial was the number of patients enrolled by the different institutes and the percentage of complete staging. The hospitals which entered less than 5 patients performed in 20.5% of the patients an optimal staging while this percentage increase to nearly 37% if more than 10 patients were enrolled in the trial. This volume issue plays an important role in oncology. In a population based study of 2450 ovarian cancer patients by Ioka et al. [12], patients treated in very low volume hospitals were seen to have a 60% higher change of death compared to patients receiving care in high volume hospitals ($P < 0.01$).

So if we allow too many institutes which randomize a low number of patients in a trial the chance of inadequate adherence to the study protocol increases. For early ovarian cancer trials this means a non-optimal performance of the required surgical staging steps.

To improve the quality of surgical staging in early ovarian cancer patients Verleye et al. [13] proposed quality indicators for the staging laparotomy in ovarian cancer grossly confined to the pelvis. Kommoss et al. [14] found that the introduction of a quality insurance and management program for treatment of early ovarian cancer patients have led to a major improvement of patient care.

SUBSTAGES AND HISTOLOGIC TYPES

In both the ACTION and the combined ACTION/ICON 1 analyses FIGO (sub)stage was not a significant prognostic factor. The 5-year survival curves for all stages were as follows; 83% for stage Ia (n=155), 88% for stage Ib (n=37), 82% for stage Ic (n=223) and 78% for stage IIa (n=31) patients. In a study of Sigurdsson et al. [15] also no difference in survival was observed between stage I subgroups ovarian carcinomas and stage IIa as we found in our analyses. In a meta analysis by Vergote et al. FIGO stage Ic and FIGO stage Ib patients showed to have similar prognosis [16]. Contrary to our findings Brugghe et al. found FIGO substage the strongest prognosticator in 102 adequately staged Ia-Ic ovarian cancer patients who received no postoperative treatment [17].

If we look in detail to the Ic substage we found no significant difference in recurrence and death rate compared to patients with moderately and poorly differentiated FIGO stage Ia and Ib.

Another issue of Ic patients is the subdivision of capsule rupture, extracapsular growth and positive washings or malignant cells containing ascites. Some authors associated these factors with a worsening prognosis [18-22] while others did not find a difference in prognosis in the different Ic patients [23,24]. A flaw of these studies is the relatively small number of patients, sometimes unknown surgical staging procedure and different treatment modalities. If we look at our three Ic substage groups, Ic capsule rupturing (n=116), surface invasion (n=50) and Ic ascites or malignant cells containing ascites (n=57), 5-year disease-free survival was 71%, 75% and 68% respectively with a *P*-value of 0.71. Also overall survival was not significantly different between the subgroups.

The specific importance of rupture before or during operation is still unclear. Sevalda et al. reported no influence on survival rates for Ic capsule rupture during surgery and therefore they considered that these patients do not belong to the subgroup of Ic as suggested by the FIGO committee [25]. In a multivariate analysis of Vergote et al. both rupturing during and before surgery were independent predictors of disease-free survival, with rupturing before operation giving a higher change of recurrent disease [16].

The results of our study, with further subdivision of the Ic capsule rupture into 19 patients with rupture before surgery and 97 patients where rupture took place during surgery, show a difference in both 5-year recurrence-free survival (65% compared to 74%) and overall survival (80% versus 89%) in favor of capsule rupturing during surgery. However this difference did not reach significance.

So in conclusion, we did not find a significant difference in either disease-free survival or overall survival of the 223 different substages Ic ovarian cancer patients and also no significant negative impact of capsule rupturing during or before surgery. Maybe for further classification of patients with early ovarian cancer other prognostic factors like DNA ploidy or differentation grade should be incorporated in a new FIGO staging system to select patients with adverse prognosis.

Clear cell carcinomas are generally supposed to worsen the prognosis in ovarian cancer patients and do have special clinical features which have been widely studied. Nulliparity of more than 50% have been reported in many series [26-28] as well as concurrent endometriosis in 8-55% of the patients with clear cell carcinoma compared to 5% of the serous ovarian cancer patients [29-31].

We performed a study in 63 clear cell carcinoma (CCC) patients and 156 serous adenocarcinoma (SAC) patients. In our study group 3.2% of the CCC patients had pelvic extension while 9.6% of the SAC patients had FIGO stage IIa. In the literature no studies reported a primary pelvic variant of clear cell tumors, while mucinous and serous primary peritoneal cancers are described. Okhawa et al. suggested another reason why clear cell tumors stay localized. They found that clear cell tumors remain attached to the mesothelial layer while serous cancers rapidly invade into this cell layer [32].

Furthermore, we found a high percentage of Ic capsule rupture among the CCC patients (44.4%) compared to 18.6% of the SAC patients. A possible explanation for this biologic phenomenon might be a larger tumor size or more endometriosis associated with adhesions of CCC as described in many series [26,32-35], and therefore more frequent capsule rupture before or during surgery.

Looking at the recurrence rate in our series we found a similar number of recurrences in the CCC group compared to the SAC group, 25.4% versus 25.6%, respectively. Different percentages of relapse rates are described in the literature, ranging from very low, 6% [36] to 37% [34]. Some studies suggest that the high relapse rate may be related to chemoresistance. In support of this concept, clear cell carcinoma cell lines were found to exhibit resistance to cisplatin in cell culture [37]. Itamochi et al. [38] suggested that the resistance could be explained by a lower cell proliferation in CCC cell lines compared to SAC cell lines which they found in a conducted study.

In our study we found that the disease-free survival (DFS) showed an advantage in the observation arm in favour of the CCC patients, while in the chemotherapy arm the DFS was better in the SAC patients. Both differences were statistically not significant but could partly be explained by the chemoresistance in clear cell tumors.

The 5-year overall survival in the CCC group was 63% compared to 72% in the SAC group. Zanetta et al. [7] analysed 351 patients with stage I ovarian cancer and did not find a significant difference in DFS and OS comparing clear cell tumors versus other histologic types. Many other studies also did not find a survival difference between CCC and SAC patients [16,30,39,40] while Jennison et al. [28] showed a significant better 5-year survival of 87% in 11 SAC patients compared to 50% in 11 CCC patients.

We conclude that clear cell carcinomas do have special clinical features but they show a similar prognosis compared to serous early ovarian cancer patients. In further trials of early ovarian cancer the possible chemoresistance of clear cell carcinomas should be examined in detail.

CONCLUSIONS AND FUTURE CONCEPTS

From this large randomized trial in early ovarian cancer patients we have learned that the patients entered in the trial who were non-optimally staged benefit most from adjuvant chemotherapy and that the patients who were optimally staged have less effect of an adjuvant chemotherapy. The completeness of surgical staging was a prognostic factor and to influence the low figure of adequate and complete surgical staging, gynecologic oncologists must be part of the operation team or the patients have to be referred and restaged if possible and otherwise receive chemotherapy.

Furthermore we found that clear cell carcinomas in early ovarian cancer are not such bad actors as generally supposed. The different FIGO Ic substages were not of prognostic value in our study and neither was capsule rupturing before or during surgery in the subgroups of stage I-II patients with moderately or poorly differentiated tumors.

This trial also does have its limitations; it was not primarily designed for subgroup analyses, included only the moderately or high risk group of stage I patients and although it is one of the largest series in early ovarian cancer it has still a limited sample size.

In future trials we have to stress that an optimal surgical staging has to be performed and we do need to examine new prognostic factors to help us selecting patients who will be at high risk for recurrence. Also quality of life issues must be part of the study design.

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Chapter 10

Summary

In *chapter 1* a general description is given about the epidemiology, surgical staging, treatment modalities and prognostic factors of early-stage ovarian carcinoma.

In *chapter 2* the results are described of the ACTION trial comprising 448 patients with early-stage ovarian carcinoma (from 40 centers in nine European countries), who were randomized between platinum-based chemotherapy (n=224) or observation (n=224) following surgery. After a median follow-up of 5.5 years, the difference in overall survival between the two trial arms was not statistically significant. Recurrence-free survival, however, was significantly improved in the adjuvant chemotherapy arm (HR=0.63, 95% CI=0.43 to 0.92; P = 0.02). Approximately one-third of patients (n=151) had been optimally staged and two-thirds (n=297) had not. Among patients in the observation arm, optimal staging was associated with a statically improvement in overall and disease-free survival. No such association was observed in the chemotherapy arm. We concluded that adjuvant chemotherapy was associated with statistically significantly improved recurrence-free survival in patients with early-stage ovarian cancer. The benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging, i.e., patients with more risk of unappreciated residual disease.

Chapter 3 is a review paper of different randomized conducted trials until now in early ovarian carcinoma and a literature study. The implication of these data is that a complete surgical staging is of utmost importance and should be pursued. In cases of non-optimal staging and contra-indications for restaging, adjuvant chemotherapy is indicated to deal with unnoticed residual tumor deposits that exist in approximately 25% of the cases.

In *chapter 4* we compared the survival of patients with clear cell carcinoma (CCC) to patients with serous adenocarcinoma (SAC) in the ACTION trial. Furthermore, a literature search was done to clarify the clinical and histopathological features of clear cell tumors of the ovary. Sixty-three patients (14.1%) were compared with 156 patients (34.8%) with serous tumors. No significant difference was found in overall survival between patients with CCC and patients with SAC in both trial arms together. In the observation arm, the 5-year disease-free survival was 71% in the CCC group versus 61% in the SAC group, whereas in the chemotherapy arm, the 5-year disease-free survival was higher in the SAC group compared to the CCC group. Both differences were not statistically significant. The present study showed no worse prognosis in patients with CCC as compared to patients with serous carcinoma in early ovarian cancer.

Chapter 5 describes the problem of inadequately surgical staging. Incomplete surgical staging during the initial operation of patients with presumed early-stage ovarian carcinoma has been reported between 32% and 72% in different studies. Knowledge of the reasons for the wide spread inadequacy of staging early ovarian cancer is lacking. The EORTC-ACTION trial is one of the largest randomized clinical trials in early ovarian cancer so far. Detailed information about the staging procedure was available for every patient.

In this trial strict criteria for the surgical staging were advised, however, optimal, complete staging was performed in only one-third of the patients. Staging characteristics of the 295 incomplete staged patients were analysed and factors that could explain the omission of a comprehensive staging were studied. Sampling of para-aortic lymph nodes was not performed in 78% of the incomplete staged patients, while 52% of these patients had no pelvic lymphnode sampling. Omission of the staging steps varies from 3% (infracolic omentectomy) to 55% (biopsy right hemidiaphragm). Even staging steps without morbidity like peritoneal washing (11%) and taking of blind biopsies from the paracolic gutter or side wall (39%) were omitted. The percentage completely staged patients was 20.5% for institutes who randomized less than 5 patients and this percentage increased to 37% when more than 10 patients were included in the trial.

Even in a randomized trial where complete surgical staging was advised in the study protocol the majority of the patients (67%) were incompletely staged. Multicenter trials which recruited patients from different low volume institutes run the risk of inadequate adherence to the study protocol.

In *chapter 6* we studied the value of lymph node sampling and taking of blind biopsies in the surgical staging of early ovarian cancer. Patients with early-stage ovarian cancer are often understaged. The staging steps that are most frequently omitted include the taking of blind peritoneal biopsies and lymph node sampling or lymph node dissection. The incidence of positive nodes in apparently early ovarian cancer is approximately 15% for stage I and 36% for stage II as described in several studies.

Despite the importance of these staging steps it seems difficult to carry them out in daily practice. The reasons of not performing these steps are partly explained by a lack of technical skills and partly because a lack of knowledge of early ovarian cancer spread. This study describes the effect of lymph node sampling and taking of blind biopsies as part of the surgical staging for early ovarian cancer on disease-free and overall survival. For the current study 224 patients randomized in the observation arm of the ACTION trial were included. Of these 224 patients, 75 patients were optimally staged

(group A), 46 patients in whom all staging steps were performed except para-aortic or pelvic lymph node dissection (group B) and 14 patients where no blind biopsies were taken but who fulfilled all other staging steps (group C). A significant difference was found ($P = 0.03$) in the 5-year disease-free survival between group A (optimally staged) and group B (no lymphnode sampling) of 79% versus 61%. Furthermore a significant difference was shown in the 5-year survival between group A (89%) and group B (71%). Also a significant difference was found in the both the 5-year disease-free survival ($P = 0.02$) and the 5-year overall survival ($P = 0.003$) between group A (optimally staged) and group C (no blind biopsies) resulting in a 5-year disease-free survival of 79% versus 64% respectively and a 5-year survival of 89% (group A) and 65% (group C).

Although this study is limited by a relatively small number of patients, it demonstrates the importance of taking blind biopsies and performing a lymph node sampling for the prognosis of patients with early-stage ovarian cancer.

The prognosis of the different FIGO Ic patients is described in *chapter 7*. Patients with diverse FIGO stage Ic presentations like capsule rupturing, ascites containing malignant cells or positive peritoneal fluid and surface tumor showed no significant different disease-free and 5-year overall survival. The recurrence-free and overall 5-year survival was as follows for the different Ic subcategories: capsule rupturing (73%/80%), external surface tumor (76%/88%) and positive ascites or malignant washings (70%/78%). Also the time of capsule rupturing, before or during surgery, was not a prognostic factor in the current study

The long-term results of the ACTION trial are shown in *chapter 8*. After a median follow-up of 10.1 years most of the main conclusions of the original analysis remain the same. This means improved recurrence-free survival but not overall survival by adjuvant chemotherapy and the completeness of surgical staging as an independent prognostic factor, with better recurrence-free and overall survival among patients who were optimally staged. Furthermore, we found in the long-term analysis that overall survival after optimal surgical staging was improved, even among patients who received adjuvant chemotherapy. Thus, completeness of surgical staging in patients with early ovarian cancer was proven to be statistically significantly associated with better outcomes, and the benefit from adjuvant chemotherapy appeared to be restricted to patients with non-optimal surgical staging.

Finally, in *chapter 9* we described the conclusions of the ACTION trial and future concepts for studies in early ovarian cancer.

Chapter 11

Nederlandse Samenvatting

In *hoofdstuk 1* wordt een algemene beschrijving gegeven van de epidemiologie, chirurgische stagering, behandelingsmodaliteiten en prognostische factoren van het vroeg stadium ovariumcarcinoom.

In *hoofdstuk 2* worden de resultaten beschreven van de ACTION studie waarbij 448 patiënten met een vroeg stadium ovariumcarcinoom (uit 40 instituten in negen Europese landen) werden gerandomiseerd tussen adjuvante platinum bevattende chemotherapie (n=224) of observatie (n=224) na chirurgie. Na een mediane follow-up van 5.5 jaar was het verschil in overleving tussen de twee studie-armen statistisch niet significant. De recidief-vrije overleving was echter statistisch significant beter in de adjuvante chemotherapie groep (HR=0.63, 95% CI=0.43 tot 0.92; P = 0.02). Ongeveer eenderde van de patiënten (n=151) was optimaal gestageerd en tweederde (n=297) niet. Bij de patiënten in de observatie-arm was optimale stagering geassocieerd met een significant betere totale en ziektevrije overleving. Deze associatie werd niet gevonden in de chemotherapie-arm. We concludeerden dat adjuvante chemotherapie geassocieerd was met een statistische verbetering van de recidief-vrije overleving bij patiënten met een vroeg stadium ovariumcarcinoom. Het nut van adjuvante chemotherapie lijkt zich te beperken tot patiënten die niet optimaal gestageerd zijn, dat wil zeggen, patiënten die meer risico hebben op onopgemerkte residuale ziekte.

Hoofdstuk 3 is een overzichtsartikel over de verschillende gerandomiseerde studies tot op heden bij het vroege ovariumcarcinoom en een literatuurstudie. De implicatie van deze data is dat complete chirurgische stagering van het allergrootste belang is en zou moeten worden uitgevoerd. In het geval van een niet-optimale stagering of indien er contra-indicaties bestaan voor restageren, is adjuvante chemotherapie geïndiceerd om onopgemerkte residuale tumor deposities, die voorkomen in ongeveer 25% van de gevallen, te bestrijden.

In *hoofdstuk 4* vergeleken we de overleving van de clear cell carcinoom patiënten (CCC) met de sereuze adenocarcinoom patiënten (SAC) in de ACTION studie. Verder werd een literatuurstudie verricht naar de klinische en histopathologische karakteristieken van het clear cell carcinoom van het ovarium. Er werden 63 CCC patiënten (14.1%) vergeleken met 156 SAC patiënten (34.8%). Er werd geen verschil gevonden in de totale overleving tussen de patiënten met CCC en met SAC in beide studie-armen tezamen. In de observatie-arm was de 5-jaars ziektevrije overleving 71% in de CCC groep versus 61% in de SAC groep terwijl in de chemotherapie-arm de 5-jaars ziektevrije overleving hoger was in de SAC groep vergeleken met de CCC groep (78% en 60%). Deze verschillen waren statistisch niet significant. De huidige studie toonde geen slechtere prognose

voor patiënten met een clear cell carcinoom in vergelijking tot patiënten met een sereus carcinoom bij het vroege ovariumcarcinoom.

Hoofdstuk 5 beschrijft het probeem van inadequate chirurgische stagering. Incomplete chirurgische stagering tijdens de initiële operatie van patiënten met een ogenschijnlijk vroeg stadium ovariumcarcinoom is in verschillende studies beschreven variërend tussen de 32% en 72%. Kennis omtrent de redenen voor de wijdverspreide inadequate stagering van het vroege ovariumcarcinoom ontbreekt. De EORTC-ACTION studie is één van de grootste gerandomiseerde klinische studies naar het vroege ovariumcarcinoom tot op heden. Gedetailleerde informatie over de stageringsprocedure was beschikbaar voor iedere patiënt.

In deze studie werden stricte criteria voor de chirurgische stagering geadviseerd, echter optimale, complete stagering werd in slechts eenderde van de patiënten uitgevoerd. Stageringskarakteristieken van de 295 incompleet gestageerde patiënten werden geanalyseerd en factoren die het niet verrichten van een complete stagering mogelijk kunnen verklaren werden bestudeerd. Sampling van de para-aortale lymfklieren werd bij 78% van de incompleet gestageerde patiënten niet verricht, terwijl 52% van deze patiënten geen pelviene lymfkliersampling onderging. Omissie van de stagerings-stappen varieerde van 3% (infracolische omentectomie) tot 55% (biopt rechter diafragma koepel). Zelfs stagerings-stappen zonder morbiditeit zoals het afnemen van spoelvocht (11%) en het nemen van biopten van de para-colische groeven en bekkenwand (39%) werden overgeslagen. Instituten die minder dan 5 patiënten randomiseerden hadden een percentage van 20.5% compleet gestageerde patiënten terwijl dit percentage toenam naar 37% indien meer dan 10 patiënten werden geïncludeerd in de studie.

Zelfs in een gerandomiseerde studie waar complete chirurgische stagering werd geadviseerd in het studieprotocol werd de meerderheid van de patiënten (67%) incompleet gestageerd. Multicenter studies die patiënten recruteren van verschillende laag volume instituten lopen het risico van inadequate adherentie aan het studie protocol.

In *hoofdstuk 6* wordt bestudeerd wat de waarde is van het verrichten van een lymfkliersampling en het nemen van blinde biopten in de chirurgische stagering van het vroege ovariumcarcinoom. Patiënten met een vroeg stadium ovariumcarcinoom worden vaak chirurgisch ondergestageerd. De stagerings-stappen die het meest frequent worden nagelaten zijn het nemen van blinde peritoneale biopten en het verrichten van een lymfkliersampling danwel lymfklierdissectie. De incidentie van positieve lymfklieren in een ogenschijnlijk vroeg stadium ovariumcarcinoom is ongeveer 15% in stadium I

en 36% in stadium II zoals beschreven in diverse studies. Ondanks het nut van deze stagerings-stappen levert de uitvoering ervan in de dagelijkse praktijk regelmatig problemen op. De redenen van het niet uitvoeren ervan zijn deels te verklaren door een gebrek aan technische vaardigheden en deels door een gebrek aan kennis van de verspreidingsroute van het vroege ovariumcarcinoom.

Deze studie beschrijft het effect van lymfkliersampling en het nemen van blinde biopten als onderdeel van de chirurgische stagering bij het vroege ovariumcarcinoom op de ziektevrije en totale overleving. Voor deze studie zijn de 224 patiënten die gerandomiseerd zijn in de observatie-arm van de ACTION studie geïncludeerd. Van deze 224 patiënten waren er 75 patiënten optimaal gestageerd (groep A), bij 46 patiënten waren alle stagerings-stappen uitgevoerd behoudens de para-aortale of iliacale lymfkliersampling (groep B) en bij 14 patiënten waren er geen blinde biopten genomen maar verder wel de overige stappen (groep C). Er werd een significant verschil gevonden (*P* waarde 0.03) in de 5-jaars ziektevrije overleving tussen groep A (optimaal gestageerd) en groep B (geen lymfkliersampling) van 79% versus 61%. Verder werd er ook een significant verschil gezien in de 5-jaars overleving tussen groep A (89%) en groep B (71%). Een significant verschil werd eveneens gevonden voor zowel de 5-jaars ziektevrije overleving (*P* waarde 0.02) als de 5-jaars overleving (*P* waarde 0.003) tussen groep A (optimaal gestageerd) en groep C (geen blinde biopten) resulterend in een 5-jaars ziektevrije periode van 79% versus 64% respectievelijk en een 5-jaars overleving van 89% (groep A) en 65% (groep C). Ondanks de beperking van deze studie met relatief kleine aantallen patiënten per groep demonstreert het wel de noodzaak van het nemen van blinde peritoneale biopten en het verrichten van een lymfkliersampling voor de prognose van patiënten met een vroeg stadium ovariumcarcinoom.

De prognose van de verschillende FIGO Ic patiënten wordt beschreven in *hoofdstuk 7*. Patiënten met diverse FIGO Ic presentaties zoals kapselrupturering, maligne cellen bevattende ascites of positief peritoneaal spoelvocht tonen geen significant verschillende 5-jaars ziektevrije en totale overleving. De 5-jaars recidief-vrije en totale overleving waren als volgt voor de verschillende Ic subcategorieën: kapselrupturering (70%/78%), tumor aan het buitenoppervlak (76%/88%) en positieve ascites of maligne spoelvocht (70%/78%). Ook het tijdstip van kapselrupturering, voor of tijdens de operatie, bleek geen prognostische factor in de huidige studie.

De lange-termijn resultaten van de ACTION studie worden getoond in *hoofdstuk 8*. Na een mediane follow-up van 10.1 jaar bleven de meeste van de belangrijkste conclusies van de originele analyse hetzelfde. Dit betekent, verbeterde recidief-vrije overleving, maar geen verbeterde totale overleving bij adjuvante chemotherapie en de compleetheid van

de chirurgische stagering als onafhankelijke prognostische factor, met betere recidiefvrije en totale overleving bij patiënten die optimaal waren gestageerd. Verder vonden we bij de lange-termijn analyse dat de totale overleving na optimale chirurgische stagering verbeterd was, zelfs bij de patiënten die adjuvante chemotherapie hadden gekregen. Dus, compleetheid van chirurgische stagering bij patiënten met een vroeg ovariumcarcinoom is statistisch bewezen significant geassocieerd met een betere uitkomst, en het nut van adjuvante chemotherapie lijkt beperkt tot patiënten die niet optimaal gestageerd zijn.

Tenslotte beschrijven we in *hoofdstuk 9* de conclusies van de ACTION studie en toekomstige concepten voor studies bij het vroege ovariumcarcinoom.

Abbreviations

AC	Adjuvant chemotherapy
ACTION	Adjuvant ChemoTherapy In Ovarian Neoplasm
CA 125	Cancer antigen 125
CCC	Clear cell carcinoma
DFS	Disease-free survival
EGSOG	European guidelines for surgical staging of ovarian cancer
EOC	Early ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-GCG	European Organisation for Research and Treatment of Cancer Gynecologic Cancer Group
FIGO	International Federation of Gynecology and Obstetrics
GICOG	Gruppo Interregionale Collaborative Oncology Group
GOG	Gynecologic Oncology Group
HR	Hazard ratio
ICON1	International Collaborative Ovarian Neoplasm 1
MMS	Multimodel screening
OS	Overall survival
RMI	Risk of malignancy index
SAC	Serous adenocarcinoma
UKCTOCS	UK Collaborative Trial of Ovarian Cancer Screening
USS	Ultrasound screening
WHO	World Health Organisation

Curriculum Vitae

Petra Jeanette Timmers is geboren op 14 juli 1966 te Katwijk. In 1984 behaalde zij haar eindexamen atheneum aan het Pieter Groen College te Katwijk. Zij begon in 1984 aan de studie geneeskunde aan de RU Leiden en behaalde in 1990 het doctoraal examen en in 1993 het artsexamen. Aansluitend werd zij AGNIO (assistent geneeskundige niet in opleiding) Gynaecologie en Verloskunde in het IJsselland Ziekenhuis te Capelle aan den IJssel en in 1994 in het Leids Universitair Medisch Centrum. Van 1995 tot 1997 was zij fellow bij de European Organisation for Research and Treatment of Cancer (EORTC) in Brussel. Met de opleiding Gynaecologie en Verloskunde begon zij op 1 juni 1997 in het Medisch Centrum Haaglanden te Den Haag (opleider prof. dr. P.J. Dörr †) en van 1998 tot 2002 in het Leids Universitair Medisch Centrum (opleiders prof. dr. H.H.H. Kanhai en mw. prof. dr. G.G. Kenter) en het laatste jaar in het Medisch Centrum Haaglanden. Na haar opleiding was zij chef de clinique in het Medisch Centrum Haaglanden te Den Haag en begon in 2005 als fellow gynaecologische oncologie in het Erasmus Medisch Centrum te Rotterdam. Sinds april 2008 is zij staflid in het Maasstad Ziekenhuis te Rotterdam met als subspecialisatie de gynaecologische oncologie. Zij is opleider vanaf april 2013.

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