Clinical outcome and prognostic factors in borderline ovarian tumors and invasive ovarian carcinomas in western Sweden

Margaretha Åkeson

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Cover image: Serous borderline ovarian tumor and serous papillary cystadenocarcinoma.

To my family

and to all women stricken with this disease

Abstract

Ovarian cancer, the most lethal of gynecological malignances in Sweden, is first diagnosed in advanced stages in two thirds of the cases. Although the incidence is decreasing, mortality remains high.

Clinical guidelines were introduced in western Sweden in 1993 to describe best clinical care in order to improve survival. In a prospectively collected, data-based quality register at the Regional Oncological Centre, all cases of borderline ovarian tumors (BOT) and epithelial ovarian cancer (EOC) from 1993 to 2005 were recorded. Data concerning age, stage, grade, histopathology, residual disease, ploidy status, CA-125, follow-up, recurrence, and death were collected. In 1998, the guidelines were revised to include a new chemotherapy combination for women with advanced EOC.

During the first period, 1993 to 1998, the 5- and 10-year relative survival (RS) rates for the total population of EOC (N=682) were 46.2% (95% CI 42.1-50.3) and 38.4% (95% CI 34.1-42.8) respectively. The median age was 63 years.

During the second period, 1998 to 2005, the 5- and 8-year RS rates were 48.8% (95% CI 45.2-52.4) and 39.7% (95% CI 34.9-44.5) for all (N=853) patients. An improvement in survival was indicated for early stage disease (I-IIA) treated with carboplatin after surgery, with the 5-year RS rates of 81.9% (95% CI 73.5-88.6) in Period 1 rising to 87.1% (95% CI 80.1-92.6) in Period 2.

Most interesting was the comparison of the two cohorts of advanced disease (stages IIB-IV), since the adjuvant chemotherapy combination was changed. The therapy of carboplatin+cyclophosphamide+epirubicin used during the first period showed a 5-year RS rate of 34.3% (95% CI 29.5-39.3); during the second period, paclitaxel+carboplatin treatment yielded a 5-year RS rate of 33.3% (95% CI 28.8-38.0). Progression-free survival (PFS) rates were also similar in women with stage IIB-IV tumors: 19 months (95% CI 17-22) versus 18 months (95% CI 17-20) for Periods 1 and 2. Only a randomized study, preferably including toxicity and quality of life aspects, may clarify which of these treatments confers the greater benefit.

Prognostic factors for survival were analyzed by multivariate Cox regression analysis. Age, stage, residual disease after surgery, and postoperative CA-125 were identified as prognostic markers in both study populations.

Of patients with BOT (N=399), the 5- and 10-year RS rates were equal to 100%, with a total combined recurrence and death rate of 2%. Only two women having conservative surgery had a recurrence. Patients with aneuploid tumors were given adjuvant carboplatin even for stage I disease, but chemotherapy may not be appropriate treatment for women with BOTs, considering the risks of complications and the possible impact on fertility.

In **conclusion,** this thesis identifies age, stage, residual disease, and postoperative CA-125 as prognostic factors for survival of EOC. The 5-year RS and the PFS rates for patients with advanced EOC treated with the chemotherapy of paclitaxel+carboplatin after surgery showed no improvement over earlier chemotherapy treatment. Because 5- and 10-year RS for BOT equals 100%, fertility-saving surgery seems most suitable for younger women with BOT.

List of Original Papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. Åkeson, M., Zetterqvist, B-M., Holmberg, E. and Horvath G.
Improved survival with clinical guidelines? Evaluation of a quality register linked to clinical guidelines for ovarian cancer in the western health care region in Sweden between 1 September 1993 and 1 June 1998. Acta Obstet Gynecol Scand 2005;84:1113-1118.

II. Åkeson, M., Zetterqvist, B-M., Holmberg, E., Jakobsen, A-M., Brännström, M., Horvath, G. A population-based 5-year cohort study including all cases of epithelial ovarian cancer in western Sweden: 10-year survival and prognostic factors. Int J Gynecol Cancer 2008, in press.

III. Åkeson, M., Zetterqvist, B-M., Dahllöf, K., Brännström, M., Horvath, G.
Effect of adjuvant paclitaxel and carboplatin for advanced epithelial ovarian cancer: a population-based cohort study of all patients in western Sweden with long-term follow-up. Acta Obstet Gynecol Scand 2008, in press.

IV. Åkeson, M., Zetterqvist, B-M., Dahllöf, K., Jakobsen, A-M., Brännström, M., Horvath, G. Population-based cohort follow-up study of all patients operated for borderline ovarian tumor in western Sweden during an 11 year period. Int J Gynecol Cancer, 2008;18:453-459.

Abbreviations

ACTION	adjuvant chemotherapy in ovarian neoplasm
AOCTG	Advanced Ovarian Cancer Trialists Group
APST	atypical proliferative serous tumor
BOT	borderline ovarian tumor
CAP	cyclophosphamide+ doxorubicin + cisplatin
CG	clinical guidelines
CR	complete response
CP	cyclophosphamide+ cisplatin
CT	computed tomography
DSS	disease-specific survival
EORTC	European Organization for Research and Treatment of Cancer
EPC	Epidemiological Centre
FCM	flow cytometry
FIGO	International Federation of Gynecology and Obstetrics
GLE	gain in life expectancy
GOG	Gynecologic Oncology Group
ICON	International Collaborative Ovarian Neoplasm group
LMP	low malignant potential
MPSC	micropapillary serous carcinoma
MRI	magnetic resonance imaging
OC	regional oncologic centre
OCP	oral contraceptive pill
OS	overall survival
Parafac	carboplatin+epirubicin+cyclophosphamide
PET	positron emission tomography
Paratax	paclitaxel+carboplatin
PFS	progression-free survival
RS	relative survival
SEER	surveillance epidemiology and end results
TVS	transvaginal sonography
WHO	World Health Organization

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Paper I-IV

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancy in Europe and North America. It is often asymptomatic until it has metastasized, rendering two-thirds of cases undiagnosed until an advanced stage. Even with radical surgery and aggressive adjuvant chemotherapy, the prognosis is still poor and more than half of the patients will die from their disease. To decrease this mortality, improvements in prevention, early detection (screening), surgery, and medical treatment must be explored.

In the early 1990s, gynecologists and gynecologic oncologists from the departments of obstetrics and gynecology in each of the hospitals in the Western Health Care Region in Sweden and from the Department of Oncology at the Sahlgrenska University Hospital in Gothenburg met to set up strict clinical guidelines for ovarian cancer. The goal was to improve survival rates by centralizing treatment in fewer hands, forming specialized tumor teams in the region, and defining the best clinical algorithm for patient care. To follow up on these initiatives, a quality register (tracking) form was designed to be sent to the Regional Oncologic Centre (OC) in Gothenburg for each patient at diagnosis, completion of treatment, regular follow-up visits, recurrence, and death.

The first clinical guidelines for ovarian cancer in western Sweden came into practice in September 1993 and were revised to include new adjuvant chemotherapy in advanced epithelial ovarian cancer (EOC) in 1998. Because I was involved from the start with the group that designed the guidelines, completing and reporting the results was a matter of great interest to me.

Background

Incidence and Prevalence

The National Cancer Registry of Sweden was established in 1958 and clinicians as well as pathologists were required separately to report all cancer cases to the National Board of Health and Welfare. The incidence of ovarian cancer in Sweden at that time was known to be one of the highest in the world. Between 1960 and 1984 there was an increase in cases, followed by a period of stabilization (1).The highest age-adjusted incidence rate of around 25 per 100 000 women (related to the Swedish population in the year 2000) occurred between 1975 and 1985, and declined to around 15/100 000 by 2005 (2) (**Figure 1**).

Per 100 000

Year of diagnosis
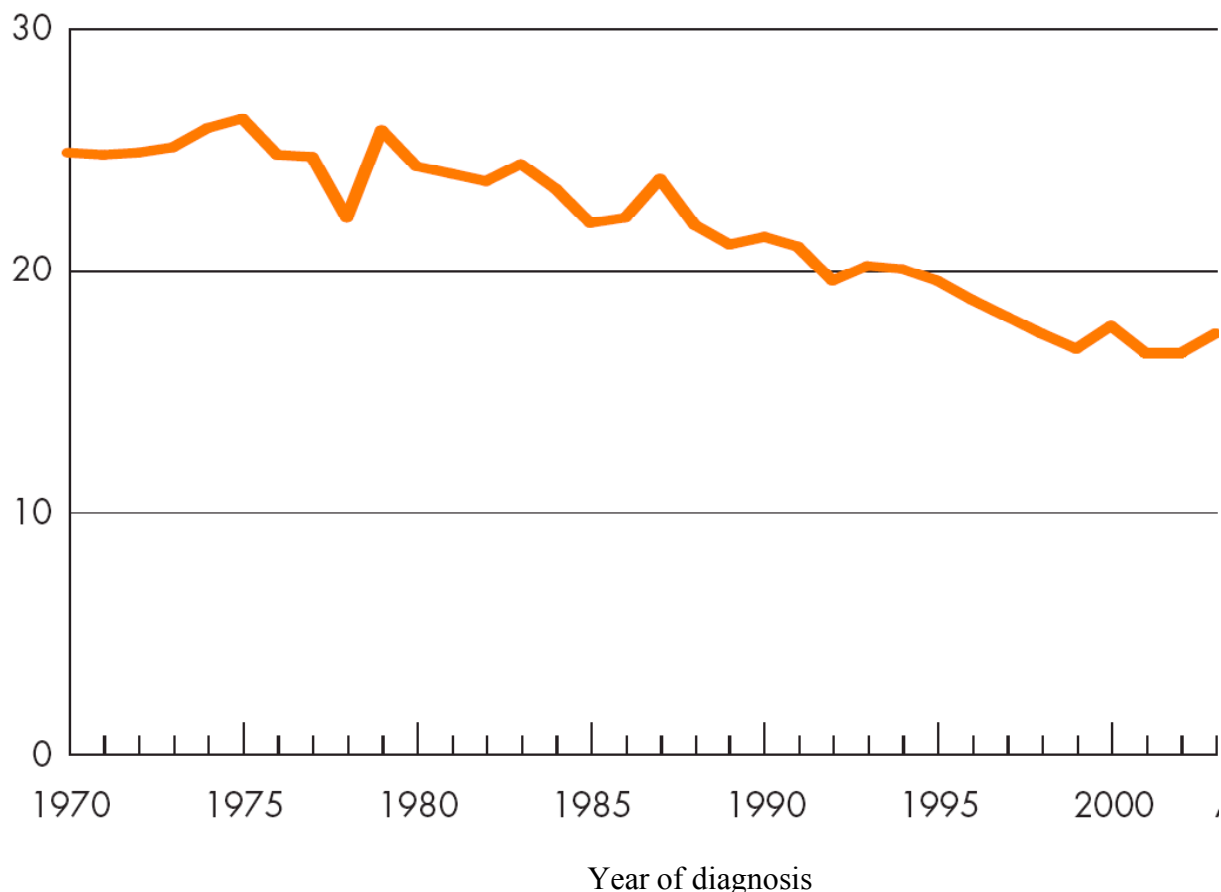
Figure 1. Age standardized (to the Swedish population 2000) incidence of ovarian cancer in Sweden 1970-2003. Centre of Epidemiology. www.sos.se/epc

In 2005, ovarian cancer was the eighth most frequent type of female cancer in Sweden, with around 800 (3.6%) new cases (Centre of Epidemiology, National Board of Health and Welfare, Stockholm, www.sos.se/epc). The annual change during the previous 10 years was a decrease 2.1%, attributed mainly to the more common use of oral contraceptives (OCP) in age

groups now at highest risk for ovarian cancer (3). The prevalence, or total number of cases of the disease in the population at a given time, is another measure of how common a disease is, combining the incidence, age distribution in the population, age at diagnosis, and length of survival. In Sweden the prevalence for ovarian and Fallopian tube cancers combined was around 2550 between 2001 and 2005 (2).

The incidence of EOC and borderline ovarian tumors (BOT) in western Sweden and in the entire Swedish population from 1971 to 2006 is shown in **Figure 2**. A decline in the incidence of EOC has been seen in northern Europe during this period compared to an increase in southern Europe (4). This may be associated with the much higher use of OCPs since the 1970s by women of fertile age in northern Europe compared to women from southern Europe(5, 6) Reduced parity over time in the southern population may also attribute to their increased ovarian cancer incidence, since parity is inversely related to ovarian cancer risk (7), (8). Moreover, EOC are considerably more common in northern Europe and the US than in, China, Japan, and countries in Africa. The cause of this difference is not yet explained.

In US cancer statistics for 2005, ovarian cancer is the seventh most frequent of all female cancers (22 220 new cases and 16 210 estimated deaths) (9), and the life-time risk is calculated to be 1/70, compared to 1/8-9 for breast cancer. From 1996 to 2005 there was an annual decrease of 1.2% in the US incidence, with a 2005 incidence of 13.3 per 100 000 women (SEER Cancer Statistics Review 1975-2005, NCI) (www.seer.cancer.gov). This is epidemiology very similar to that in Sweden.

Borderline ovarian tumor cases have an age-adjusted incidence rate of less than 5 per 100 000 women (Figure 2), with 186 new cases diagnosed in Sweden 2005.
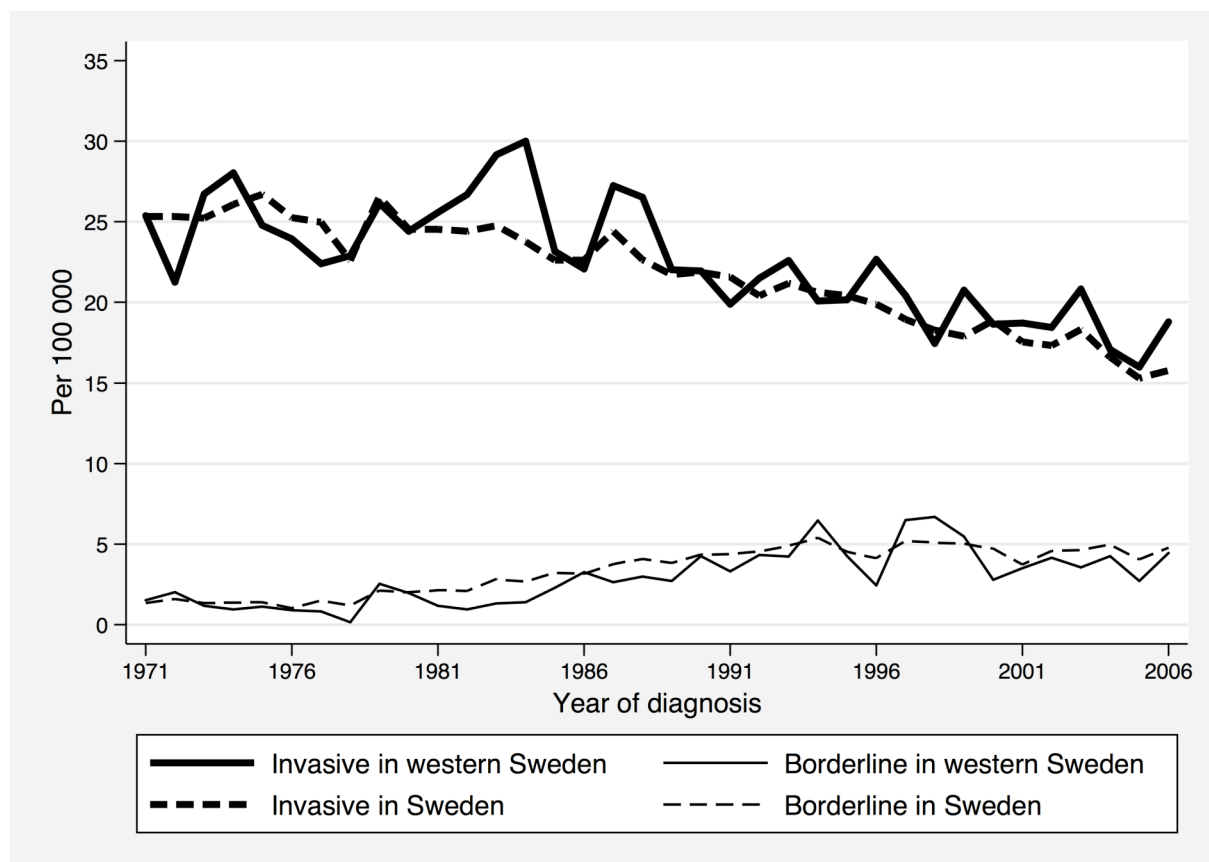
Figure 2. Age-standardized incidence per 100 000 women of BOT and EOC in western and whole Sweden 1971-2006. The Regional Oncologic Centre, Gothenburg and the National Board of Health and Welfare, Sweden.

Mortality

Ovarian cancer is the leading cause of death among gynecological cancers in the western world (9); in 2005, 580 women died of ovarian cancer in Sweden. The trends in mortality in Sweden are shown in **Figure 3**. Long-term survival results must always be analyzed in relation to the time of diagnosis, screening (that could give a long lead time), incidence, and mortality (10). In Sweden there has been a decline in both the incidence and, to a lesser degree, the mortality of ovarian cancer during the study period. (Figures 1 and 3**).**

Per 100 000

Time of diagnosis
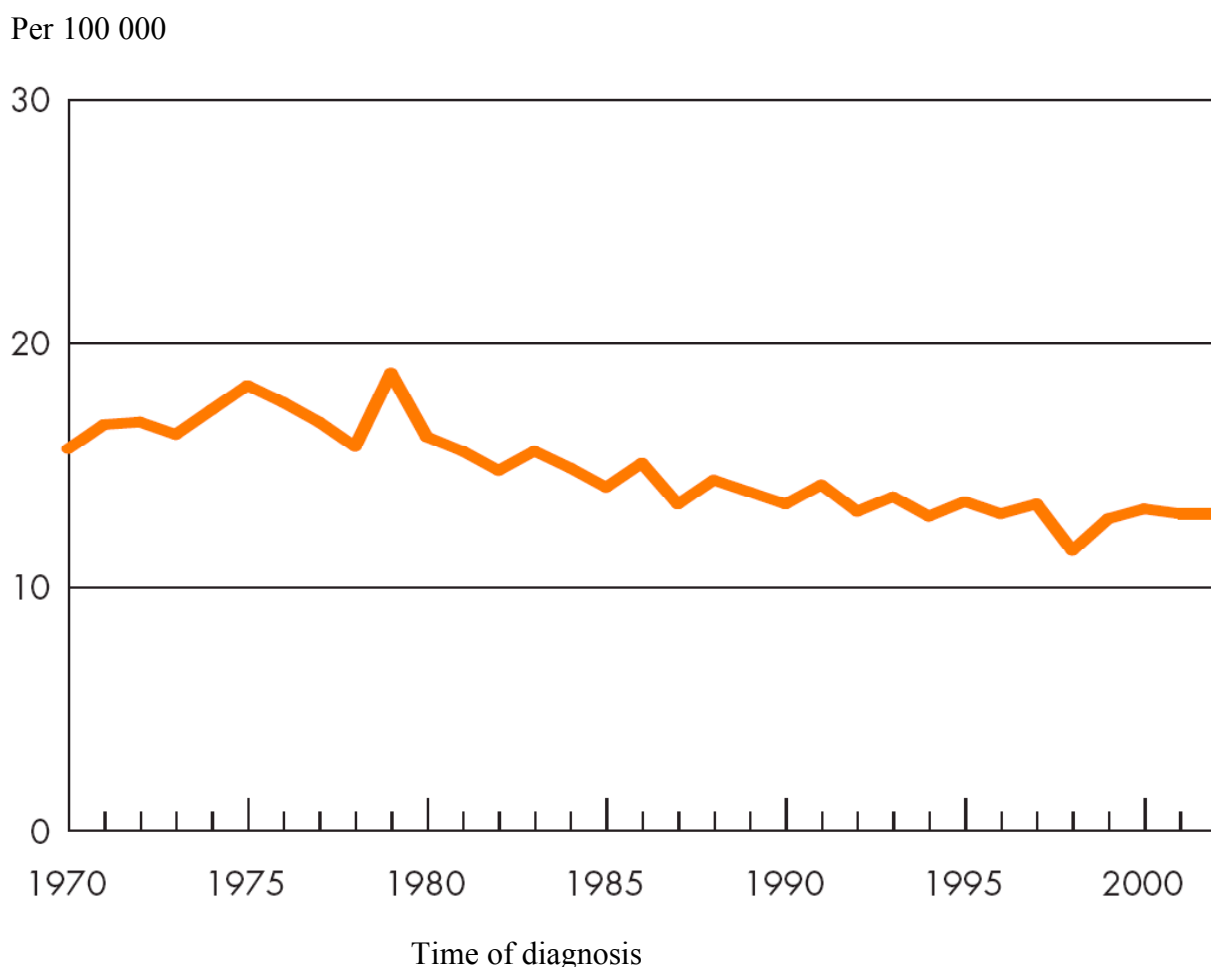
Figure 3. Age-standardized mortality of ovarian cancer in Sweden 1970-2003. Centre of Epidemiology. www.sos.se/epc

After a previous increase, overall ovarian cancer mortality in the European Union has been rather stable over the last three decades (1970-1999)(11). However, there was a decline in mortality among middle-aged women (35-64 years) in most western European countries over the most recent time periods, but with substantial differences between countries, with rates of around 15/100 000 women in Denmark and the UK, around 10/100 000 in Sweden and Germany, and 8/100 000 in Italy and Spain (11).This is probably mainly a reflection of the changing prevalence of OCP use in the various countries rather than of therapeutic

achievements. The crude incidence of ovarian cancer in the European Union for 2005 was 18/100 000 women and the mortality was 12/100 000 women (12).

Trends in age-adjusted ovarian cancer mortality in the US from 1979 to 1995 showed little change, but rates did increase in older women (>65 years) and decrease in younger women (13). From 1996 to 2005 there was a decrease of 0.1% in the annual US mortality to a 2005 rate of 8.8 per 100 000 in 2005 (SEER Cancer Statistics Review 1975-2005, NCI. www.seer.cancer.gov).

Etiology and Risk Factors

The causes of EOCs are not clearly understood. Most EOCs likely originate in the surface epithelium of the ovary, but inclusion cysts (invaginated epithelial cells after follicle rupture) are another probable source. EOCs are derived from pluripotent cells of the celomic epithelium originating from the primitive mesoderm.

A malignant transformation of the epithelium of the ovarian surface, which is continous with the peritoneal mesothelium, occurs. It is generally a monoclonal disease (14). However, the serous surface papillary carcinoma in BRCA1 carriers is thought to be polyclonal (15).

Models of ovarian carcinogenesis include the theory of incessant ovulation, where the number of ovulatory cycles is an indication of risk (16). The mitotic activity in reparation of the surface epithelium after ovulation increases the possibility of genetic changes. Consistent with this hypothesis is the fact that women with multiple pregnancies and increased time of lactation are at a decreased risk, while early menarche, late age at menopause, and nulliparity, with repetitive damage of the surface epithelium at the sites of follicular rupture, are associated with increased risk,(7,17,18). Increased pregnancies account for a risk reduction of about 12% for each additional birth; high age at last birth is also associated with a reduced risk (19).

The other important risk reduction is the use of OCP (6, 17), with a persistent protection up to 30 years (3, 20). The longer the duration of OCP use, the greater the reduction of EOC incidence. The protection does not seem to be as strong for mucinous tumors and BOTs. What kind of OCPs women have used is difficult to assess in retrospective epidemiological research, since there is probably much recall bias (3).To evaluate the effect of different hormonal compositions in OCPs, prospective studies are preferable. The incessant ovulation theory is weakened by the fact that progesterone-only oral contraceptives also give protection even if they do not inhibit ovulation (21). However, progesterone is the dominant hormone during pregnancy, which also reduces risk—probably by the induction of apoptosis of ovarian surface epithelium cells. Pregnancy inhibits ovulation totally, but the suggested protective effect of progesterone may also be important in the etiology of EOC (22).

Another hormonal theory is the gonadotropin hypothesis, which proposes that increased levels of estrogens from gonadotropin release cause epithelial cells to be entrapped in inclusion cysts and undergo malignancy. This excessive gonadotropin stimulation of the ovary, along with elevated androgen levels, is thought to be associated with an increased risk of EOC (22, 23). Other conditions of hyperandrogenity such as polycystic ovary syndrome, acne, and hirsutism are also associated with increased risk (24).

Hormone replacement therapy (HRT), if used by postmenopausal women for at least five years, may increase the risk for EOC or may accelerate the growth of an already existing tumor. Current users of HRT had a relative risk of 1.2 for both incident disease and death in a recent report from the Million Women Study (25). Unopposed estrogen use and obesity increase the risk of serous BOTs but are not associated with mucinous BOTs (26).

Among other factors associated with *enhanced risk,* a positive family history of ovarian cancer is the most significant. The majority of ovarian cancers are sporadic and only 5% to 10% of EOCs are inherited. The lifetime risk without a family history of ovarian cancer has been reported as around 1.4% to 1.8% in the US population (27) and around 1.1% in the Swedish population before the age of 75 (2). In the presence of a BRCA1 mutation, the average lifetime risk ranges from 16% to 44%, with the highest rate seen among women of Ashkenazi Jewish descent (28, 29). In the event of a BRCA2 mutation, the risk is smaller, with a lifetime risk of about 10% by age 70 (30, 31). Patients with any of the common BRCA mutations have highly proliferative tumors, but still a better overall survival (OS), when adjusted for stage (32). BOTs have a much less frequent incidence of BRCA mutations, which suggests a different molecular origin (33).

There are also women with EOC as a part of the hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (Lynch II syndrome), due to mutations in DNA mismatch repair genes (34, 35).

Infertility has also been discussed as connected with an enhanced risk of EOC (36) and it was earlier suggested that this was linked to treatment with fertility drugs. However, the effect of the drugs has been difficult to separate from the effects of infertility itself (18) and the findings of different studies are inconsistent (37, 38).

Factors that predispose to inflammation, such as pelvic inflammatory disease, endometriosis (especially the clear cell and endometroid subtypes of EOC), perineal talc use, and asbestosis, may be important in EOC formation, probably because inflammation promotes reconstruction of the epithelial surface cells, and at that stage they are susceptible to mutation (23).

Other environmental factors possibly related to enhanced risk of ovarian cancer are smoking, obesity, diet, and alcohol consumption, but study results for these factors are conflicting (23).

Among factors with *decreased risk,* apart from the most important hormonal factors discussed above, are histories of tubal ligation or hysterectomy. It has been speculated that this may be due to reduction of the utero-ovarian blood-flow and possibly the interruption of inflammatory agents to the ovaries (17, 36, 39, 40) Unilateral salpingo- oophorectomy is said in some studies to reduce risk, probably by the same effect (20, 41).

Physical activity has been shown to protect against EOC independent of body mass index (42), but there could well be a co-variation with other life-style factors. Most epidemiologic research has focused on invasive EOC (5, 20, 36, 43), while fewer have studied the epidemiology of BOT (26, 44, 45).

Pathogenesis

Ovarian tumors are very heterogeneous and there is molecular and genetic evidence to support two recently proposed categories of carcinogenesis which have been brought forward by Shih and Kurman (46). They divide the tumors into two groups. **Type I** (**low-grade pathway)** are slowly growing tumors, mostly confined to the ovaries at diagnosis, less responsive to chemotherapy, developed from and sharing molecular characteristics with the precursor tumor of low-malignant potential (LMP = BOT). Type I tumors include low-grade micropapillary serous carcinomas (MPSC), and mucinous, endometroid, and clear cell carcinomas. The BOTs and low-grade carcinomas are rather genetically stable but have mutations in the KRAS and BRAF in 30% to 50%, which are rarely found in high-grade tumors.

The other **Type II** (**high-grade pathway)** tumors are rapidly growing, highly aggressive, and without definitive precursor lesion. They include high-grade serous carcinoma (MD-Anderson grading, page 17), carcinosarcomas, and undifferentiated carcinomas and they are genetically instable (See **Figure 24,** page 70).

Molecular analyses of the two different types suggest different pathogenesis. Pathologic studies found that around 60% of low-grade serous carcinomas also contain BOTs compared with only 2% of high grade tumors (47). On the other hand, the TP53 gene has been found to be mutated in 50% to 80% of high-grade invasive carcinomas but only rarely in BOTs (48).

The proposed model of ovarian carcinogenesis that leads to these two different pathways can possibly explain the problems with different screening procedures, since early stage tumors may be biologically different from advanced stage tumors with their rapid spread in the abdomen (46, 49).

Histopathological types

This thesis will not consider the relatively rare germ cell and sex cord-stromal tumors, but will focus on ovarian tumors of epithelial origin (EOC), which represent around 90% of all ovarian cancers. According to recommendations from WHO (50), tumors are classified as benign, BOTs with proliferative activity, and nuclear abnormalities of epithelial cells but without infiltrative destructive growth, and overtly malignant cystadenocarcinomas.

The different subtypes are: **serous, mucinous, endometroid, clear cell, Brenner, mixed** epithelial tumors, and **undifferentiated** carcinomas.

Serous cystadenocarcinomas–often with papillary or cystic components, are the most common (around 60% or more). They resemble the epithelium lining of the Fallopian tube and their genetic heterogeneity is expressed in very heterogenic morphology (51). The nuclear atypia is often marked with abnormal mitotic figures. Many contain so-called psammoma bodies (concentric rings of calcification) and often secrete CA125. They are more common in advanced stages. The p53 gene is often over-expressed and the serous tumors stain positive with an antibody against Wilms tumor (WT1), which also reacts against serous ovarian carcinoma. Most serous tumors belong to Shih and Kurman's Type II above.

Mucinous tumors (around 10% or less) are either endocervical or intestinal. The first type, endocervical, has cells resembling the endocervical glands; both types contain intracytoplasmic mucin. They lack expression of estrogen receptors (ER), and KRAS mutations are common. They are different from other EOCs in many ways, especially prognostically and and etiologically. They have a weaker association to hormonal and reproductive factors, including OCP use, no association with BRCA mutations, and only seldom raised CA125 values (53-55). Women with advanced mucinous tumors often have a poor outcome (56, 57). This type of tumor may be associated with pseudomyxoma peritonei and can be mistaken for an ovarian primary, when it actually is a carcinoma of gastrointestinal origin that has metastazised to the ovaries (58, 59). A recent publication suggests that there may be an overestimate of mucinous EOCs and that they may represent fewer than 3% of all EOCs (60). The authors conclude that mucinous tumors are more often metastatic and they constructed an algorithm that demonstrates that if all unilateral mucinous tumors bigger than 10 cm in circumference are identified as primary mucinous EOC and all others as metastatic from the gastrointestinal tract, 90% of the cases are accurately classified (60). Most mucinous tumors belong to Type I.

Endometroid histology (around 10-15%) has similarities with the endometrium, being predominantly glandular, and can occur in association with endometriosis and also with a primary synchronous cancer in the uterine cavity (52). Most endometroid tumors are FIGO stage I-II. They lack WT1 expression and p53 over-expression and have a generally good prognosis. Endometroid tumors belong to Type I.

Clear cell carcinomas (less than 10%) have characteristic "hobnail" cells with clear cytoplasma because of glycogen dissolved during the preparation of the tumor specimen.

They are believed to be of Mullerian origin and have been said to have a bad prognosis in both early and advanced stages (61, 62). It can be difficult to differentiate them from serous carcinomas; they usually lack WT1 expression, but p53 can be overexpressed. They can probably belong to both Type I and Type II.

Brenner tumors resemble transitional cell carcinomas, but are very seldom malignant.

Carcinomas of **mixed** histologic type have two or more of the common cell types that account for at least 10% each of the tumor.

Undifferentiated carcinomas are too poorly differentiated to be placed in any other group and can be considered Type II tumors.

The most prominent immune profile is shown in **Table 1.** Serous tumors are always CK7 positive and CK20 negative. Mucinous tumors are both CK7 and CK20 positive in around 50%; if a mucinous tumor is CK 20 positive and CK 7 negative it does not support a diagnosis of primary ovarian mucinous neoplasm.

Histo-pathology	CK 7	CK 20	EMA	CEA	WT1	Vimentin	p-53
Serous	+	--			+		+
Mucinous	+	+ (50%)	+	+			
Endo-metroid	+		+	--		+	
Clear cell	+	--	+	+	-	+	(+)
Brenner	+		+	+			

Table 1. Immunoprofile in EOC of different histopathology. (Modified after Rosai and Ackerman.Surgical Pathology Volume I and II. Mosby 2004).

Borderline ovarian tumors have all the same histological types as the carcinomas, but a different proportion of serous versus mucinous tumors, with approximately 55% serous and 40% mucinous. Risk factors are similar to invasive mucinous tumors, but with weaker associations to reproductive factors and OCP (26, 45, 55). Mucinous BOTs of higher stages are known to have a bad prognosis (63, 64). Serous BOTs with extra-ovarian invasive implants often have a bad prognosis (65). However, even if the implants behave as metastatic carcinomas, there are studies indicating that tumors with non-invasive implants - even at advanced stage - often grow in a benign fashion (66). Morphological and molecular genetic analyses have led to the proposition of a new classification of serous BOTs into two types: 1) a more benign variant, with atypical proliferative serous tumors (APST) as a precursor, and 2) a stepwise development further to a non-invasive micropapillary serous carcinoma (MPSC) (67). An APST often coexist with a non-invasive MPSC and a low-grade carcinoma (an invasive MPSC) (46, 48). (See Figure 24, page 70).

Degree of differentiation

The FIGO grading system is based on architectural features of tumors and contains three grades of differentiation and two of undifferentiated or unassessable tumors:

Grade 1 (G1): highly differentiated tumor cells most resemble cells of origin and have <5% solid component.

Grade 2 (G2): moderately differentiated cells with 5% to 50% solid component;

Grade 3 (G3): poorly differentiated tumor cells that are most different from the benign cells and have >50% solid component;

Grade 4 (G4): undifferentiated cells;

Grade X (GX): the grade cannot be assessed.

The World Health Organization (WHO) system is based on both architectural and cytologic appearance. It also contains three grades, G1–G3, but these are not quantitatively defined (68).

The FIGO and the WHO grading system use high degree of differentiation = G1 and low grade of differentiation = G3 in the same meaning in opposition to the recently proposed MD Anderson grading system. This is a two-tier system, but only for serous carcinomas based on histologic, immunohistochemical, and clinical features. It is used mainly by US pathologists (47). The two categories are defined as:

Low grade: serous carcinoma with mild or moderate nuclear atypia and a low mitotic index.

High grade: serous carcinoma with pleomorphic cells, marked nuclear atypia, and a high mitotic index.

The low grade of the MD Anderson grading system is mostly corresponding to highly differentiaded (G1) serous tumors and the high grade serous tumors are corresponding to the moderately and poorly differentiated tumors (G2-G3) of the FIGO grading system.

(Because the different grading systems use "high" and "low" in opposite ways, it is important to bear in mind which system is being referred to).

Definitions of FIGO Stages in primary carcinoma of the ovary

Stage I: Growth limited to the ovaries.
IA Growth limited to one ovary; no ascites present containing malignant cells. No tumor on the external surface; capsule intact.
IB Growth limited to both ovaries; no ascites containing malignant cells. No tumor on external surfaces; capsules intact.
IC Tumor either Stage IA or IB, but with tumor on surface of one or both ovaries, or with capsule ruptured, or with ascites present containing malignant cells, or with positive peritoneal washings.
Stage II: Growth involving one or both ovaries with pelvic extension.
IIA Extension and/or metastases to the uterus and/or tubes.
IIB Extension to other pelvic tissues.
IIC Tumor either Stage IIA or IIB, but with tumor on surface of one or both ovaries or with capsule(s) ruptured; or with ascites present containing malignant cells or with positive peritoneal washings.
Stage III: Tumor involving one or both ovaries with histologically confirmed peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equals stage III. Tumor is limited to the true pelvis, but with histologically proven malignant extension to small bowel or mesentery.
IIIA Tumor grossly limited to the true pelvis, with negative nodes, but with histologically confirmed microscopic seeding of abdominal peritoneal surfaces, or histologically proven extension to small bowel or mesentery.
IIIB Tumor involving one or both ovaries with histologically confirmed implants, peritoneal metastases of abdominal peritoneal surfaces, none exceeding 2 cm in diameter; nodes are negative
IIIC Peritoneal metastases beyond the pelvis > 2 cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV: Growth involving one or both ovaries with distant metastases. If pleural effusion is present, there must be positive cytology to allot a case to Stage IV. Parenchymal liver metastasis equals Stage IV.
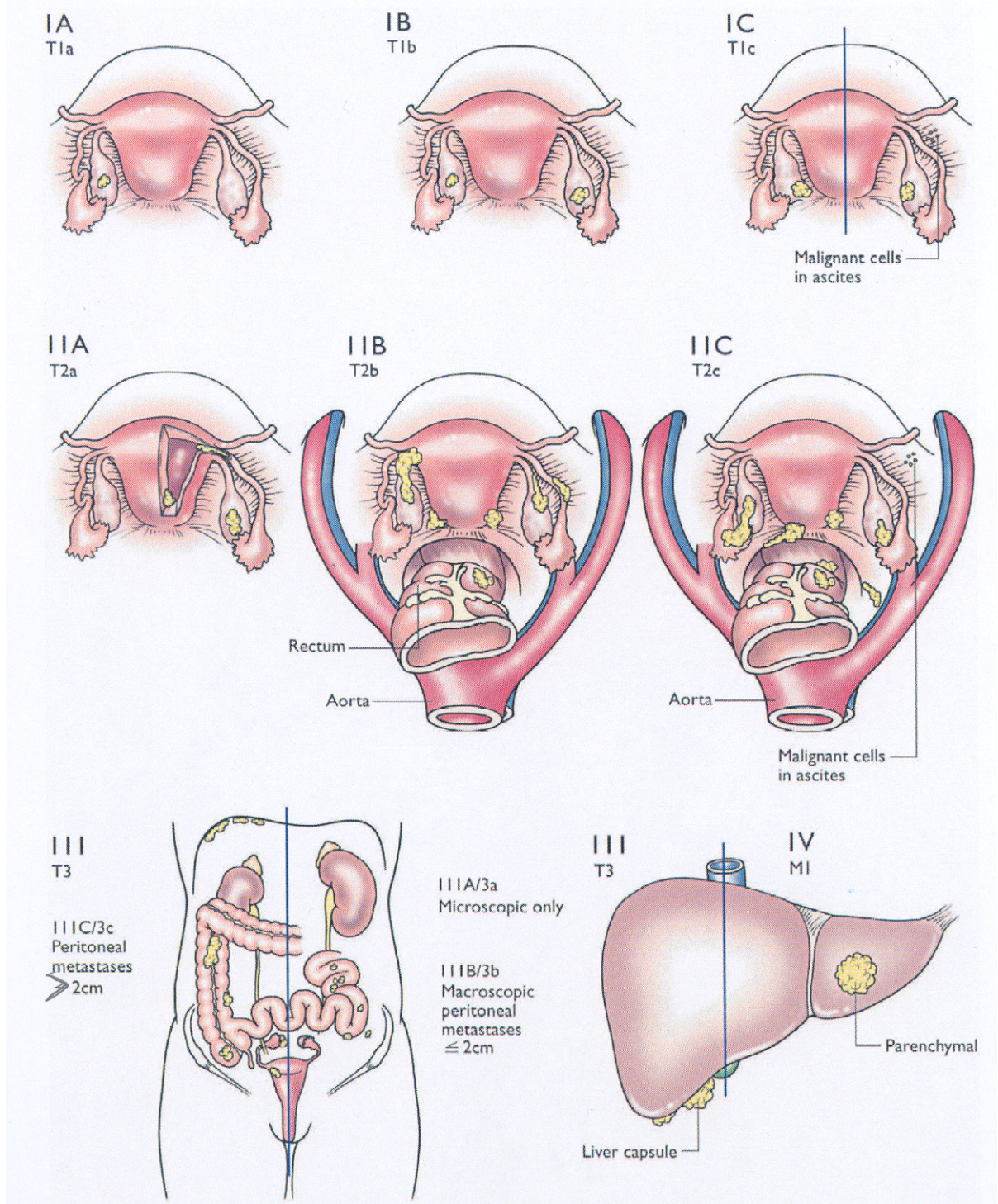
Figure 4. FIGO stages in ovarian cancer. After ref (69). Copyright 2008.

Symptoms and Diagnosis

The **symptoms** of EOC are vague and do not typically lead women to their gynaecologist at first. Recent reports show that over 90% of cases with invasive ovarian cancer reported at least one symptom leading to diagnosis with onsets long before diagnosis (70). The most common symptoms were: bloating/feeling of fullness, gas/nausea/indigestion, urinary frequency/urgency, abdominal pain, dyspareunia, and lack of energy (71-73).

In ovarian cancer **diagnosis** there is delay by the patient as well as by the doctor. In clinical practice the diagnosis is sometimes highly suspected, but often must be confirmed before exploratory surgery by computed tomography (CT), especially if a transvaginal sonography examination (TVS) is inconclusive or if some other gastro-intestinal tumor is suspected. TVS is usually the method of choice for detecting tumors in the true pelvis, but CT is preferable for revealing any involvement of the lymph nodes or the liver. To distinguish benign from malign tumors, the risk of malignancy index (RMI) was introduced as a simple scoring system based on menopausal status, ultrasonographic morphology, and serum CA-125 level, with a cut-off limit of 200 (74). This index was later used in selecting patients to specialized oncology centers (75). Its sensitivity in separating malign from benign disease is between 71% and 90%, with specificity between 88% and 96% (75-77).

Magnetic resonance imaging (MRI) examination may be used when involvement in adjacent organs is suspected. Positron emission tomography (PET) may be used to diagnose metastases; in combination with CT, it was recently evaluated in a prospective study with promising results (78).

Lung x-rays are mandatory; if pleural effusion is present, there must be a positive cytology to include patients in stage IV.

Screening

At present only 25% of ovarian cancer is detected in stage I. Early detection is believed to be associated with a higher cure rate. Assuming that stage I ovarian cancer is the precursor of advanced disease, detection at this stage is the goal for different screening techniques. Since the incidence of ovarian cancer is rather low, a screening program for detection of early stage disease must be both highly sensitive and extremely specific to obtain the high positive predictive value needed to avoid unnecessary surgery (79-80). Annual TVS screening performed on over 25 000 asymptomatic women over 50 years of age with a family history of ovarian cancer from 1987 to 2005 in the US showed a decrease in stage at detection with a sensitivity of 85.0%, specificity of 98.7% (81).

CA-125 is the most commonly used serum marker combined with TVS for screening purposes. Genetically high-risk women are often offered EOC screening, even if its effectiveness has not been convincingly demonstrated in earlier studies (31). However, Jacobs et al were the first to report a randomized controlled trial with postmenopausal women and annual CA-125 over three years (82). A larger study by the same group, United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is ongoing and includes 200 000 postmenopausal women in three randomized groups with different screening combinations, including CA-125 and TVS. The CA-125 results will be analyzed using the risk

of ovarian cancer algorithm introduced by Skates et al and tested on postmenopausal women (83).

There are multiple different markers tested that could be combined, but the problem is to reach higher sensitivity without losing high specificity (80, 84) to avoid unnecessary surgical exploration. Recently used markers include HE4, mesothelin, osteopontin, kallikrein, and soluble EGF receptor (85).

Surgery

Primary surgery

For most early stage EOC and BOT disease, surgery is sufficient. Fertility-saving surgery is appropriate in low-risk stage I EOC and most cases of BOT if the woman is of childbearing age and wishes to preserve her fertility; laparoscopic technique is often used to accomplish this (86-88).

The surgery is essential for accurate staging (89) and for cytoreduction. Debulking surgery also relieves patients from symptoms associated with bowel obstructions and pressure from the tumor. Optimal cytoreduction, earlier defined as no nodule >2 cm, later as no nodule >1 cm, and now as no macroscopic residual tumor, is significantly associated with improved survival (90-94). Primary surgery for advanced EOC is a technical challenge and its success depends upon the skill of the surgeon (93, 95, 96) but the biology of the tumor also reflects its resectability (97). Specialized gyneoncological teams report enhanced survival, especially when compared to general surgeons (98-101). Higher survival rates are also shown for centralized treatment in well controlled populations in the Scandinavian countries (102-105). Some researchers emphasize the volume of these surgeries in different kind of hospitals (106), suggesting that more patients per surgeon may perhaps shorten the long learning curve of gynecological cancer surgery (107). Whether "ultra-radical" surgery, including partial hepatectomy, splenectomy, colectomy, multiple resections of the small bowel, etc., is of benefit to the patient has not been clearly shown (108). Clinical trials must balance the risks and include quality of life aspects in the studies (109).

Secondary surgery

Interval debulking surgery after some courses of neoadjuvant chemotherapy, studied in many retrospective reports, has shown no conclusive superiority over primary surgery (110). In patients where debulking surgery upfront is suboptimal, interval cytoreductive surgery after some courses of chemotherapy with good regression has been shown superior to continued chemotherapy in one prospective randomized study performed by the European Organization for Research and Treatment (EORTC), with significantly longer PFS as well as longer median survival (111). In contrast to this, the Gynecologic Oncology Group (GOG) trial 152 showed no advantage for patients undergoing interval debulking when they primarily had a maximal surgery performed by a gynecological oncologist (112). Therefore EORTC started a prospective randomized study to compare primary debulking surgery with neoadjuvant chemotherapy; the final analysis is expected in 2009.

Second-look laparotomy is recommended in clinical trials as the most exact way of verifying a complete pathological response or finding occult disease, but it provides no advantages concerning survival (113). Positive emission tomography has been discussed as a complement to, as well as compared with, the second look, but with disappointing results (114).

Laparoscopy can often be the preferable technique in the second-look procedure. Laparoscopy is also recommended as a diagnostic tool to evaluate operability in advanced cases and for eventual interval debulking after neoadjuvant chemotherapy (110), preferably with an open technique.

Prophylactic surgery

Prophylactic bilateral salpingo-ophorectomy is often suggested to women carrying BRCA1 and BRCA2 mutations after they have completed childbearing. In a study of 551 women with these mutations, 259 women undergoing the operation were compared to 292 matched controls without prophylactic surgery. After prophylactic operation, 2 women (0.8%) developed serous papillary peritoneal cancer after 3.8 and 8.6 years compared to 58 women (19.9%) in the control group, who received the diagnosis of ovarian cancer. Further, 21% of the operated women developed breast cancer in comparison to 42% in the control group without the prophylactic surgery (115).

Chemotherapy

The majority of EOC patients will require postoperative chemotherapy treatment, since at least a microscopic tumor could be left after surgery in stages higher than IB.
The **cell cycle specificity** of the chemotherapy agents discussed is different for each agent. Cyclophosphamide, the platinum compounds (cisplatin and carboplatin), and the anthracyclines like doxo-and epi-rubicin are active predominantly during the G1 phase, when the cell enlarges and makes new proteins. The platinum compounds act on the intra- and inter-strand crosslinks and change the shape of the DNA, leading to apoptosis. The taxanes (paclitaxel and docetaxel) are active in the G2 phase, when the cell prepares for dividing, and in the mitosis phase, when the cell divides. The taxanes stabilize the microtubule causing a mitotic block in the cell.
In **early stage** disease a low-risk group can be defined as patients with stage IA, grade I. Many investigators also include stage IB, grade 1 or 2 disease, where no chemotherapy is necessary (assuming that the staging procedure is adequate) (61, 116, 117). However, there are many reports of inadequate staging (89, 118). In the International Collaborative Ovarian Neoplasm Group (ICON) I study from the EORTC-Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) Collaborators, there was no additional effect on survival with chemotherapy in early stage disease if patients had been adequately staged (119). When the two randomized studies of ICON I and Action trials in 925 patients from 1990 to 2000 were combined, a statistical difference was found with a 5-year overall survival (OS) rate of 82% in the platinum-based chemotherapy group and 74% in the observation group with no chemotherapy (120). However, since there were a high proportion of inadequately staged patients, there were most certainly patients of higher stages taking advantage of the chemotherapy.
The management of patients with **advanced** EOC consists of a combination of cytoreductive surgery and combination chemotherapy. The past 30 years have seen major advances in the chemotherapy used. For many years, single agents such as melphalan or cyclophosphamide were used (121). A large meta-analysis performed by the Advanced Ovarian Cancer Trialists Group (AOCTG) (122) compared non-platinum-based single-drug therapy to non-platinum-based combination therapy and showed no difference in OS except in one Swedish study (in which western Sweden took part). The Swedish study compared melphalan with

melphalan+adriamycin and favoured the combination (123). During the mid-1970s, the platinum-based agents were introduced and were later added to the combinations of doxorubicin and cyclophosphamide (124, 125). Several meta-analysis in the 1990s shed light on the roles of cisplatin, its analogue carboplatin, and the anthracyclines (126, 127). The ICON 2 trial showed that there was no difference in progression-free survival (PFS) or OS between the combination of cyclophosphamide, doxorubicin, and cisplatin (CAP) compared with single-agent carboplatin (128). Later, the introduction of paclitaxel in combination with cisplatin in the landmark study GOG111 (129), confirmed by the European Canadian Intergroup (OV 10) (130), showed an improved survival compared to cyclophosphamide+cisplatin (CP). This led to a general change in treatment and soon the combination with paclitaxel and carboplatin became the gold standard in treating advanced EOC. However, other studies could not confirm the superiority of paclitaxel over single-agent carboplatin or other platinum combinations not including paclitaxel (131, 132). These four last mentioned studies have been thoroughly discussed in a paper by Sandercock (133), who questions the reliability of findings of the superiority of paclitaxel.

A systematic overview of chemotherapy in ovarian cancer was performed by the Swedish Council of Technology Assessment in Health Care (SBU) in 2001 (134).This review is based on 176 reports including over 33 600 patients. They conclude that in radically operated, low-risk, early-stage patients (stage IA-IB, non-clear-cell, grade 1, or BOT) there is no need for chemotherapy. In high-risk early-stage EOC, the role of chemotherapy is unclear and should preferably be used in clinical trials. In advanced disease there is substantial evidence that adjuvant chemotherapy will prolong the median survival. Data support the substitution of cisplatin with carboplatin because it offers lower toxicity and better quality of life. The researchers consider it too early to define the effect on survival with paclitaxel-carboplatin use.

Intraperitoneal (IP) chemotherapy in comparison with intravenous (IV) therapy has shown an improved survival with a median survival rate of 66 months in optimally debulked stage III EOC patients, compared to 50 months for the group who received IV administration of cisplatin and paclitaxel, but it is not an easily accepted treatment, mainly because of catheter problems and toxicity (135). The favourable results with IP therapy are supported by a newly presented Cochrane analysis from the National Cancer Institute (136).

Paradigm shifts in the treatment of ovarian cancer on an approximate time scale are shown in **Figure 5.**

The **timing** of the chemotherapy treatment in relation to surgery seems not to be important as a prognostic factor for survival (137-139). The optimal **duration** of adjuvant chemotherapy, the dose intensity, and maintainance therapy are still under debate (140-142).

(Chemotherapy for patients with BOT will be discussed later.)
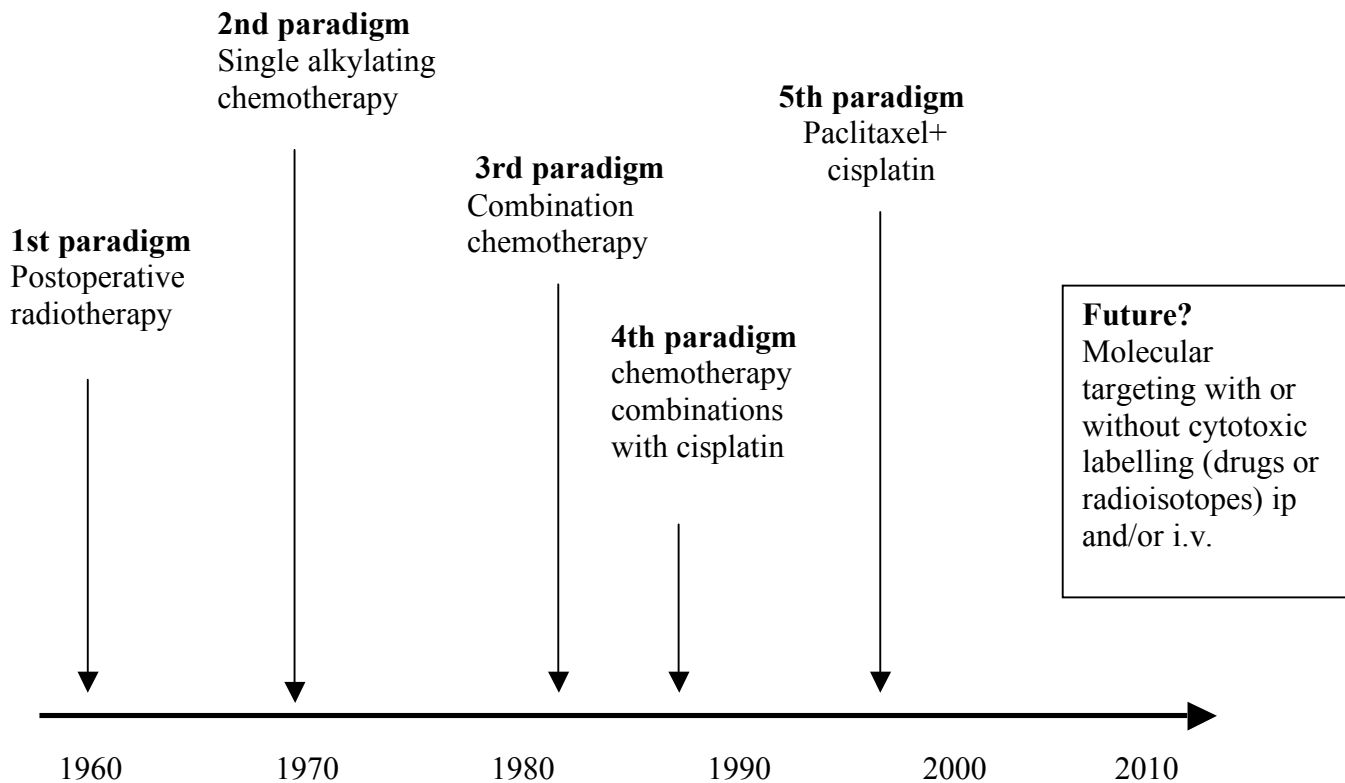
Figure 5. Shift in paradigm in the treatment of ovarian cancer. 2nd paradigm (121), 3rd paradigm (143), 4th paradigm (144), 5th paradigm (129).

Radiotherapy

During the 1950s, surgery and radiotherapy (RT) were the predominant treatment modalities in ovarian cancer. With the introduction of chemotherapy during the late 1960s and its proven effect in advanced EOC (depending on better primary response rates), RT has been used less, mainly because of its marked side effects (145). Typically, a dose of 30 Gy is given to the whole abdomen with an anterior-posterior/posterior-anterior beam arrangement and, if necessary, posterior shielding of the kidneys. Due to extensive field sizes (40x30 cm or larger) a high percentage of patients experienced severe side effects; myelosuppression being the most commonly reported. Moreover, the shielding of organs at risk resulted in inadequate low doses in parts of the target volume, thus reducing the efficiency of radiation.

However, in 1999 a retrospective case control study compared the outcome of patients with advanced ovarian cancer treated with surgery+chemotherapy with the combination of surgery+chemotherapy+RT. The result showed a significantly improved disease-free survival for patients in the RT-group, and suggested that the role of RT should be re-evaluated in a prospective randomized study (146).

A Swedish systematic review of RT trials came to the conclusion that there might be some evidence to suggest that RT could play a role as consolidation therapy in patients with advanced EOC and pathologically complete response after chemotherapy (147).

Prognostic Factors

A prognostic factor (PF) gives information about the clinical outcome but a predictive factor is useful in selecting patients to benefit from a special treatment (148). Frequently factors are prognostic as well as predictive, e.g. steroid receptors in breast cancer. There are prognostic factors that can not be changed, for instance age, FIGO stage, grade, and histopathology, while others can be influenced, including the skills of the surgeon (96, 99, 101, 149), the timing of surgery (110, 138), and the type of chemotherapy (127, 130, 150).

Factors that have been demonstrated as important for survival are **age** (151-153), FIGO **stage** (56, 154, 155), **ascites** and **performance status** (156), **residual** disease (90, 92, 94, 95, 157), **ploidy** status (158-160), and **CA-125** (161-164). **Grade** and **histopathology** have in most reports also been included among PFs, even if they have not always been independent variables (56, 152, 165).
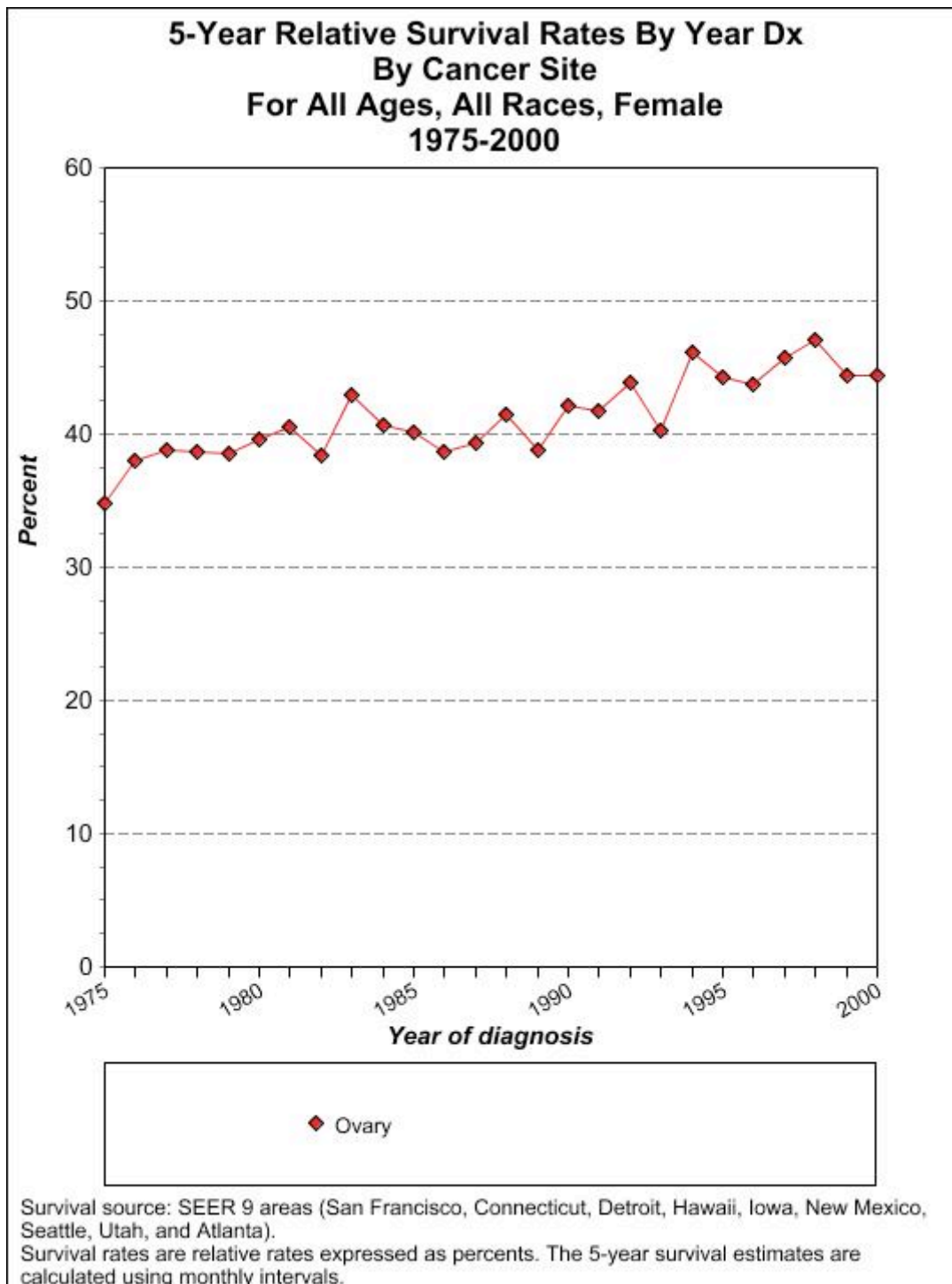
Up until now only stage, grade, and to a lesser extent, ploidy status have influenced the choice of adjuvant treatment, or dictated that chemotherapy should not be given in the case of BOT or early stage disease. Since ovarian cancer is very heterogeneous, it will be necessary to find new and different approaches to treatment (166). Further knowledge in molecular markers and genetic studies will hopefully give us instruments to further understand and predict the best treatment for EOC (167-170).

Hitherto predictive factors have not been used to select the type of therapy.

Treatment Results

In spite of intensified cytoreductive surgery and escalated chemotherapy, the long-term survival results in EOC patients have increased very little over time. Most studies only report enhancements in 5-year survival rates. This could be useful when comparing therapies, but has little relation to changes in cancer mortality. The incidence in Sweden has decreased since the 1980s, but mortality has declined to a somewhat lesser degree, indicating that long-term survival may not have increased. There are very few long-term studies of EOC survival.

Back in the 1950s, the National Cancer Register of Norway reported a relative 5-year survival rate of 22%, rising to 37% in the early 1990s (171). In Finland there has been an improvement in the relative 5-year survival rate in population-based studies from the 1970s to the end of the 1990s, from 36% to 46%, respectively (172). These results are comparable to survival rates from the SEER program in the US from the same period, which showed a rise from a 37% 5-year RS rate during the 1970s to 43% during the 1990s (173). The 5-year RS from the SEER program from 1975 to 2000 is shown in **Figure 6.** The 5-year OS rate in FIGO`s Annual Report from 1996 to 1998 was 46%. However, these figures are possibly biased by selection (69). There is a report on 10-year OS from Germany for the 10-year periods before and after 1988, which shows an almost constant rate (32% and 34%, respectively) (174).

5-Year Relative Survival Rates By Year Dx
By Cancer Site
For All Ages, All Races, Female
1975-2000

Survival source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Survival rates are relative rates expressed as percents. The 5-year survival estimates are calculated using monthly intervals.

Figure 6. Relative 5-year survival in the United States 1975-2000
(SEER Cancer Statistics Review 1975-2005, NCI), www.seer.cancer.gov

In Sweden, a population-based study from the end of the 1980s shows 40% relative 5-year survival (56). The 5- and 10-year RS rates in all Sweden reported from the National Board of Health and Welfare in 2003 were 44.5% and 35.2%, respectively.

When reporting survival results of early stage disease, the material is often divided into groups of low- and high-risk tumors. A long-term survival report from Belgium gives 5- and 10-year OS results of 95% and 89% for women with low-risk tumors (grade 1 and 2, stage IA-IB) and 72% and 33% for high-risk sub-groups (IA-IB grade 3 or IC-II, all grades) (175). The importance of accurate staging has been stressed earlier (89), (119).

Most survival results that are reported apply to selected populations of advanced EOC disease (92, 94-96, 127, 156, 176), and they vary greatly both in observation time and method of description of the survival results.

The survival rates for patients with BOT generally show very good short-term survival (mostly >95%), but the need for long-term follow-up is important to stress since recurrence could occur late (64, 177-180). A complete long-term population-based study of all BOT patients is rare, if any.

As pointed out above, 5-year survival rates do not correspond to cure and these results must be seen in relation to incidence and mortality rates, since improvements in 5-year survival are influenced by changes in diagnostic patterns as well as by delayed mortality and a longer period of life with the disease (10).

Stage distribution, treatment, and approximate EOC treatment results in western Sweden are shown in **Table 2.**

Table 2. Approximate stage distribution, treatment, and treatment results of
 EOC in western Sweden 1993–2005.
Parafac= (carboplatin+ epirubicin+ cyclophosphamide)
Paratax= (carboplatin+paclitaxel), RS=Relative Survival

Stage	I-IIA	IIB-III	IV
Distribution	25%	60%	15%
Treatment	Radical surgery	Debulking cytoreductive surgery	Possibly debulking surgery
	Chemotherapy (high risk only) Single-agent Carboplatin	Chemotherapy Parafac or Paratax	Chemotherapy Parafac or Paratax
Relapse	15%	70%	90%
5-year RS	80-90%	25-35%	5-15%

Aims of the study

The aims of this study were threefold:

— to investigate population-based cohorts of all cases of EOC and BOT in the Western Sweden Health Care Region from 1993 to 2005 regarding short- and long-term survival;

— to evaluate prognostic factors for survival of invasive EOC, with special attention to age, stage, residual tumor after surgery, histopathology, grade, ploidy status, and post-operative CA-125 values;

— to compare the survival of patients with advanced EOC, given different chemotherapy treatment during the two time periods studied.

Material and Methods

## Patients, Type of Registration, Treatment and Follow-up, Papers I and II.

We introduced clinical guidelines (CG) for ovarian cancer in western Sweden in September 1993 (181). The patients were generally diagnosed and operated upon at the different departments of obstetrics and gynecology in the region. All cases were reported to the OC quality register and to the Oncology Department at the Sahlgrenska University Hospital, where the patients were uniformly treated dependent on stage. The variables sent to the OC register were the size of residual tumor after surgery, stage, grade, histopathology, CA-125 levels, ploidy status, treatment, recurrence, and death. This information was checked against the National Cancer Register. Reports on death were checked with population registers. Information on cause of death was mostly taken from the report to OC and from the Cause of Death Register, when data were missing.

Patients included in **Papers I** and **II** were identical and they were diagnosed from September 1, 1993, to May 31, 1998 (Period 1). In **Paper II** there was a longer follow-up period and prognostic factors were evaluated.

A total of 712 patients were reported to OC according to the CG. Compared to the National Cancer Register, there were 6 more patients with EOC included, and 36 were excluded. A flow chart for patients in both periods is presented in **Figure 7**. Early-stage patients, except those at low risk (stage IA, grade I, diploid), were treated with adjuvant carboplatin and advanced stages (IIB-IV) were treated with carboplatin+epirubicin+cyclophosphamide (Parafac). Chemotherapy was not given to 86 (12.6%) patients. The patients in **Paper I** were followed until November 1, 2002, and in **Paper II** until November 1, 2007. The median follow-up duration in **Paper I** was 6.75 years (4.3-9.1) and in **Paper II** 11.7 years (8.7-14.1). No patient was lost to follow-up. The age distribution of the patients is shown in **Figure 8.** The median age was 63 years (range 18-91) and the mean age was also 63 years.
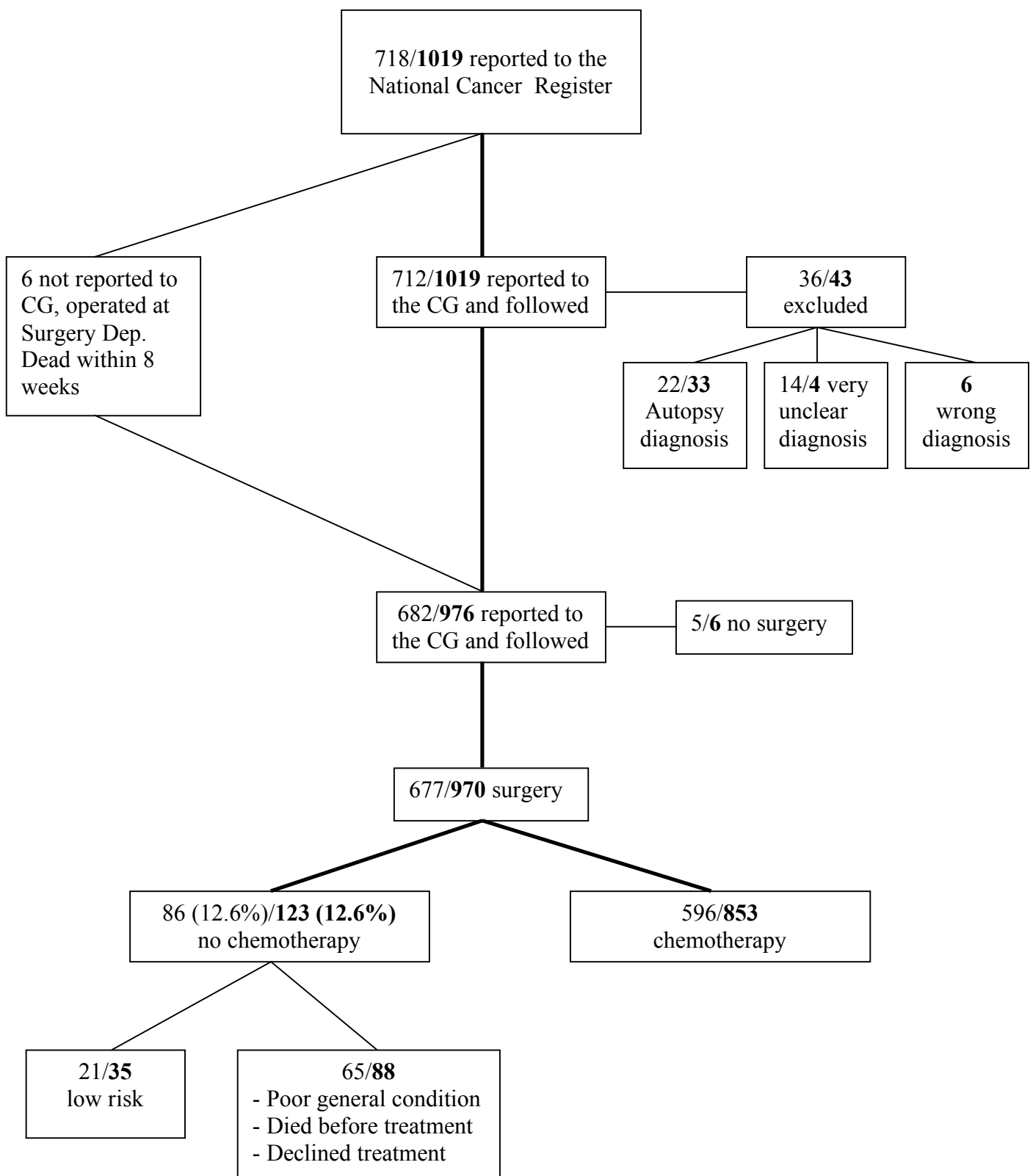
Figure 7. Flow chart for EOC patients in western Sweden reported to National Cancer Register and the Clinical Guidelines (CG) during both Period 1 (Sept 1, 1993-May 31, 1998) and **Period 2 (June 1, 1998-May 31, 2005, in bold text).** All 682/**976** patients were followed and no one was lost to follow-up.
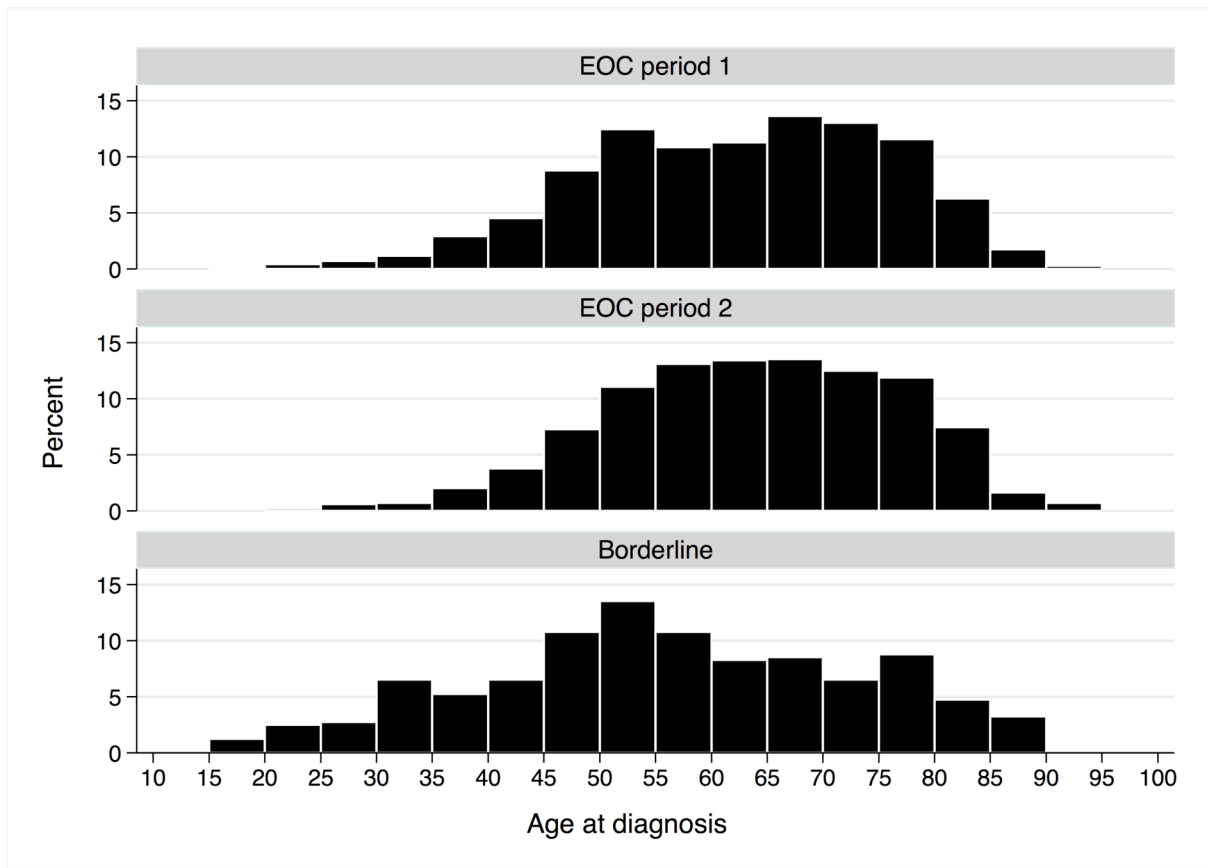
Figure 8 Age distribution in 5-year age classes in all EOC patients in Period 1 (1993-1998) and Period 2 (1998-2005) and all borderline patients (1993-2004).

Patients, Treatment, and Follow-up, Paper III

The guidelines for EOC were changed in 1998 with alteration in the recommendations for adjuvant chemotherapy to include the administration of paclitaxel and carboplation (Paratax) to patients with advanced stages of EOC (IIB-IV) (182). Patients in **Paper III** were diagnosed from June 1, 1998, to August 31, 2005, and followed until September 1, 2007. A total of 1019 patients with EOC were reported to the National Cancer Register, but 43 were excluded. The material then consisted of 976 patients and they were all followed as seen in flow chart of Figure 7 (numbers with **bold text**). Chemotherapy was not given to 123 (12.6%) patients. The median follow-up duration was 5.7 years (2.3-9.2). No patient was lost to follow-up. The age distribution is shown in Figure 8. The median age was 64 years (range 23-94) and the mean age 63.2 years.

Patients, Treatment, and Follow-up, Paper IV.

All patients in **Paper IV** had borderline ovarian tumors (BOT) diagnosed from September 1, 1993, to August 31, 2004, and followed until May 1, 2006. After excluding 10 patients with coexisting invasive ovarian cancer, the material consisted of 399 patients with BOTs. The

patients were all recognized in the National Cancer Register as shown in flow chart of **Figure 9**. Patients with early stage disease (I-IIA) with aneuploid tumors were treated with adjuvant chemotherapy of carboplatin; patients of higher stages (IIB-IV) were treated with ParaFac or Paratax combinations independent of ploidy status. The median follow-up duration was 7.7 years (1.6-12.6). No patient was lost to follow-up. The age distribution in 5-year age-classes is shown in Figure 8. The median age was 55 years (range 16-90) and the mean age was 55.4 years. Apart from the prospective data collection, a special survey was used to record the type of surgery, recurrence, and fertility after fertility-saving surgery for women under 45 years of age (n=96), (See **Figure 23,** page 67).
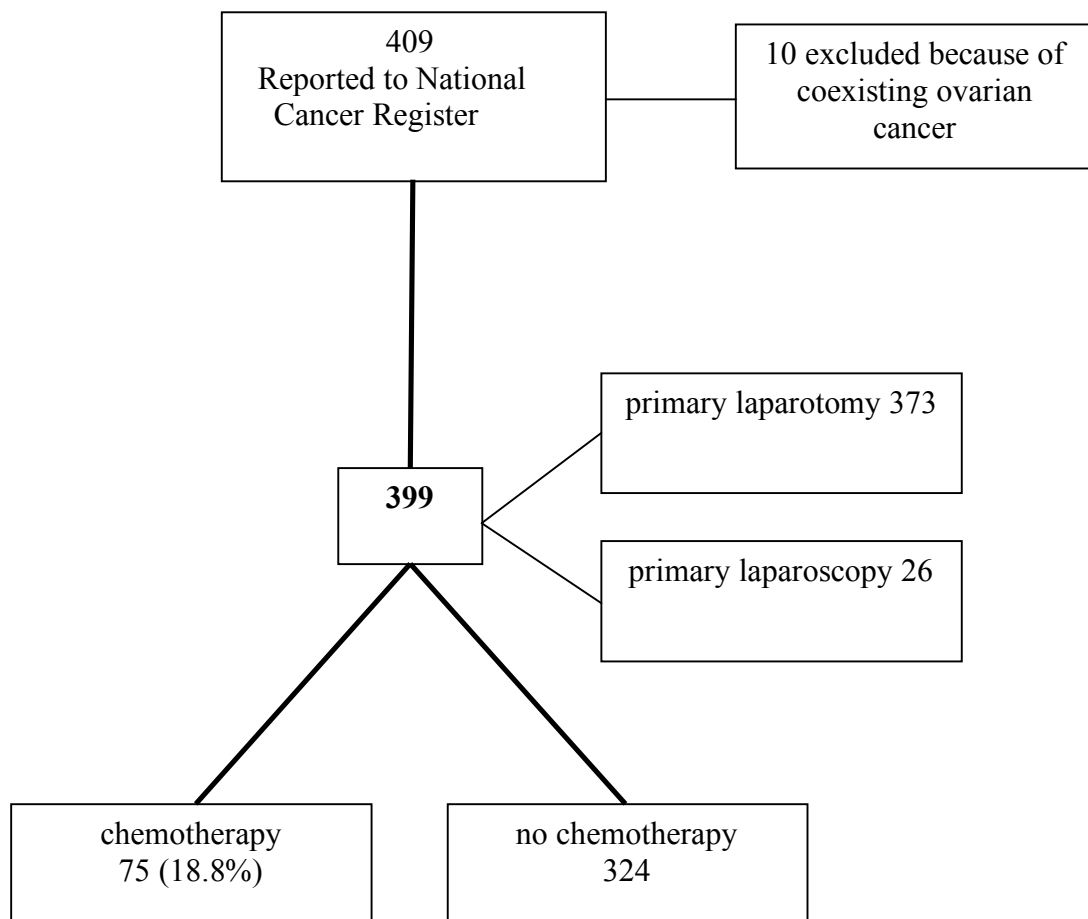
Figure 9. Flow chart for patients with BOT in western Sweden, reported to the National Cancer Register from September 1 1993 to August 31 2004. All 399 patients were followed and no patient was lost to follow-up.

Survival Terminology

The aim of these population-based studies was to describe the survival of the EOC patients in a geographically defined area with a population of around 1.6 million inhabitants. We collected the data from the National Cancer Register at OC and compared them with the CG reports from the departments of gynecology and obstetrics in the region. All cases were identified and missing data was completed from patient record file.

To interpret changes in cancer survival one must have information on incidence, age and stage distribution, treatment policy, and mortality, as well as survival in an age-matched normal population.

Relative survival (RS) was calculated to describe the 5-and 10-year survival rates (see statistical analyses, page 35), which in principal is the ratio between observed and expected survival and gives a perception of the excess mortality due to ovarian cancer or treatment (183). It requires estimates of the expected survival of a comparable age-adjusted general population. The major advantage of using relative survival rates is that you do not need information on the actual cause of death (which is often unavailable or incorrect in the death certificate) (184, 185).

Disease-specific survival (DSS), or cause-specific or cause-of-death–specific survival, measures mortality due to cancer and requires an accurate classification of all causes of death.

Overall survival (OS), or crude survival or observed survival, includes all causes of death without any specification and measures the total mortality (186). This is not an appropriate estimate when comparing survival between study cohorts with different age distributions.

In **Paper I** the 5-year RS rate and the 5-year DSS rate were both calculated and were similar, around 46%. This indicates that death certificate and normal population similarity uncertainties were not great nor did one outweigh the other.

In **Paper III**, Table 4 compares the numbers in the material when using different estimates describing survival.

Surgical guidelines

One of the most important goals with the CGs for ovarian cancer was to form tumor teams at each department and create new standards for the surgery. These standards highlight careful preoperative planning, involving colorectal surgeons and urologists, and recommend that the surgical approach should include a midline incision that permits adequate exposure of the upper abdomen and pelvis. Total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, routine biopsies of clinically uninvolved areas in the pelvis and paracolic guts, as well as all tumor-suspected areas, and peritoneal washings are also recommended. Biopsy or removal of suspected lymph nodes is recommended, but routine complete lymph node dissection is not. The goal was to leave no macroscopic tumor. The importance of correct staging was stressed, including thoracocentesis in the case of pleural effusions to reveal stage IV disease. Tumor material was sent for flow cytometry (FCM).

During the first period, 1993 to 1998 (**Papers I and II**), residual tumor was defined as not macroscopic, ≤ 2 cm, or >2 cm. However, during the later period, 1998 to 2005 (**Paper III**), we changed the notation of residual tumor to not macroscopic, ≤ 1 cm, or >1 cm in accordance with more recent studies (62, 90).

In early stage disease or BOT in younger patients wishing to preserve their fertility individualized conservative surgery was performed.

FCM

Fresh tumor material was brought to the pathologist and representative samples of the tumor were immediately frozen (-80°C) and sent for FCM analysis. We used the procedures developed by Thornthwaite (187) and Lee et al (188). FCM DNA-analyses give information on ploidy status and the S-phase fraction (SPF). We used the classification system of Hiddemann et al (189), according to which samples with one DNA stemline are classified as diploid (one peak) and those with more than one cell population as non-diploid (two or more peaks). Aneuploidy was defined with a DNA-index (DI) of <0.98, >1.03–1.92, and >2.06. There is no universally accepted definition of tetraploidy. Some studies report good prognosis for breast cancer patients with tetraploid tumors and suggest that tetraploid and diploid tumors should be combined in a euploid group (190). To distinguish tetraploidy from aneuploidy we used the DI range of 1.92–2.06 for the tetraploid region.

CA-125

The OC125 antibody was produced by Bast et al (191), established from a patient with a serous ovarian cystadenocarcinoma. CA-125 is an antigenic determinant recognized by this antibody on the cell surface. It is a large glycoprotein, and the gene encoding CA-125 was recently cloned (192). Serum CA-125 determinations have been extensively used in EOC patients preoperatively to distinguish between benign and malignant ovarian tumors (74, 75, 193) , as well as postoperatively and in follow-up to recognize a recurrence (161, 194, 195) and to evaluate the response to treatment (196). However, the CA-125 value can often be raised even in benign conditions such as menstruation, pregnancy, endometriosis, myoma, and pelvic inflammatory disease (197). Also, other malignancies, such as those originating in the breast, colon, rectum, lung, pancreas, liver, or elsewhere, could show high values of CA-125 (198).
In the present studies we used the postoperative values of CA-125 taken just before the start of chemotherapy and evaluated this as a prognostic factor for survival. We used the cut-off values of >35, 35–65, and >65 U/ml according to earlier studies (161).
In early stage EOC, the CA-125 value exceeds the level of 35U/ml only in 50% to 60% of patients (199), but when the disease is disseminated outside the ovary, there is an elevation of CA-125 in over 90% of cases (197).

Chemotherapy

The chemotherapy given to patients studied in **Papers I and II** (Period 1, 1993-1998) was for stage I-IIA disease, single-agent carboplatin 7 x (GFR+25) every 4th week according to the Calvert formula (200) for six courses. The low-risk patients were defined as those with diploid tumors, stage IA, and grade 1; they did not receive chemotherapy. In advanced stages (IIB-IV) patients were given carboplatin 5 x (GFR+25) + epirubicin 50 mg/m^2 and cyclophosphamide 400 mg/m^2 every 4th week for eight courses if there was a complete response (CR), as evaluated by palpation under general anesthesia at course number six.
In **Paper III** (Period 2, 1998-2005) chemotherapy to the early-stage patients was the same carboplatin dosage as during the previous period. Patients with advanced stage (IIB-IV) were

given carboplatin 5 x (GFR+25) and paclitaxel 175 mg/m^2 every 3rd week for six courses if CR (evaluated by palpation under general anesthesia, CA-125, and possibly CT-scan).

Staging, the first chemotherapy course, and the evaluation at the sixth course were centralized to the Department of Oncology, Sahlgrenska University Hospital. The chemotherapy courses given in between were administered at the local hospitals in the region. The routines for administrating chemotherapy during the two periods are given in **Appendix 1** (page 92).

If CR was not reached, continued chemotherapy to at least ten courses was often given in both periods. Accurate data on this, as well as second or third line chemotherapy in case of recurrence, were not available in the database. (See comments in Appendix 1).

Statistical analyses

As in most population-based survival studies, we used relative survival (RS) analyses. The RS is the ratio of the observed survival of the patients to the expected survival of a comparable group from the general population (183). Annual mortality risk in one-year age and calendar cohorts for the entire Swedish female population were used to calculate the expected survival. This normal population was adjusted to the subgroups analyzed. The RS gives an indication of any excess mortality due to ovarian cancer or its treatment in the studied population. The major advantage of the RS is that information about cause of death is not required. A limitation is that the studied population, except for the cancer, may not mimic the normal population in other unknown factors that may also influence their mortality.

The relative survival model can be written as:

$$S(t;z) = S^*(t;z) \times r(t;z)$$

(the hazard function at time t, with a covariate vector z)

where S(t;z), S*(t;z), and r(t;z) represent cumulative observed, expected, and relative survival (201).

The hazards are assumed to be constant within intervals of follow-up time.

The patients were followed up through the unique identification number used for all persons in Sweden. Records on the National Population Register were linked to those on the National Cause of Death register at the National Board of Health and Welfare. All patients in the study cohort were identified through these registers. End of follow-up was date of death or last known date alive according to the National Population Register.

In **Papers I** and **II**, Stata statistical software was used for the statistical analysis (202). The RS analysis, using the strs-command in Stata developed by Paul Dickman, was used for comparing survival in different patient groups (201). In **Papers III** and **IV,** SAS 9.1.3 software was used for the statistical analysis. Cox regression analyses were used in **Papers II** and **III** for univariate and multivariate analyses of prognostic variables. Death from EOC was the analyzed event (203). The median progression-free survival was analyzed using the Kaplan-Meier method in **Paper III.** The association between ploidy status and patient age ($\geq$ 60 vs < 60 years of age) was evaluated with one-sided Fisher exact test in **Paper IV**. This test was also used in **Paper IV** to evaluate the association between ploidy status and patients with serous versus mucinous tumors.

Results and Comments

Incidence

In western Sweden during the study period of 1993 to 2005 there was a decline in the age standardized incidence of EOC from around 21/100 000 women in 1993 to 16 in 2005. The changes in incidence in western Sweden from 1971 to 2005 are shown in **Figure 10.** However, among the patients with BOTs, there seems to be an increase or at least not a decrease (Figure 2, page 11), possibly due to improved reporting, but perhaps also to a smaller effect of OCP on BOT pathogenesis (26).

Per 100 000

Year
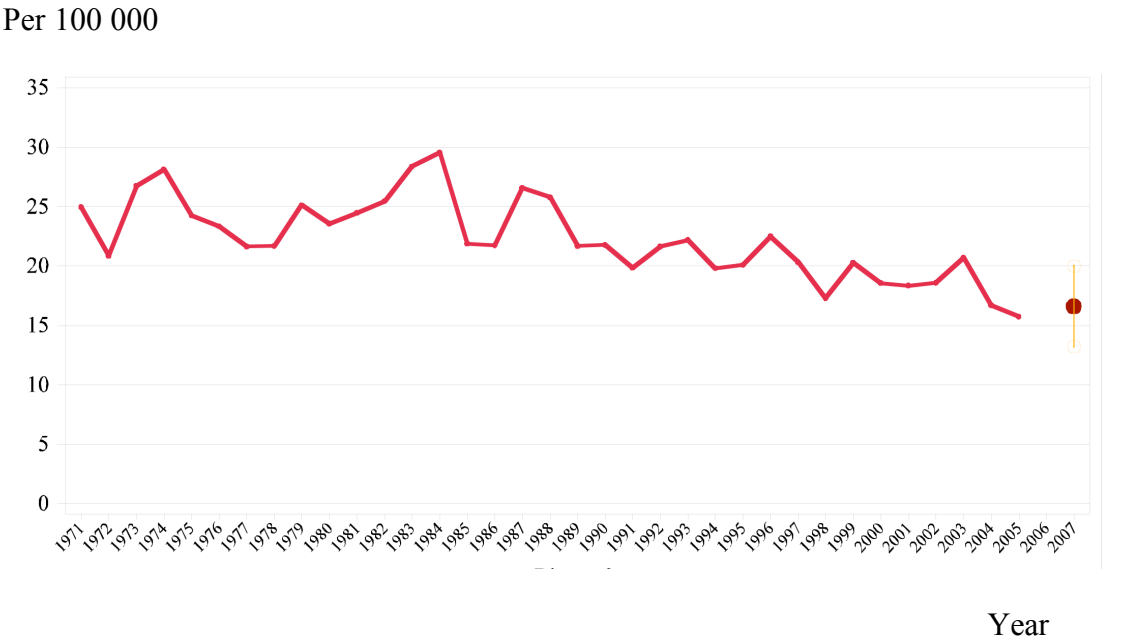
Figure 10. Age standardized incidence for ovarian cancer in western Sweden from 1971 to 2005 per 100 000 women. From the Regional Oncologic Centre of Gothenburg.

The age specific incidence of EOC in different birth cohorts showed a clear decline in the younger cohorts born from 1955 to 1959 as compared to the birth cohorts of 1935 to 1939 and 1945 to 1949 (**Figure 11**). This is probably a reflection of the more frequent use of OCP in the younger age groups (3).

Age specific incidence of ovarian cancer
Year of diagnosis 1968-2006
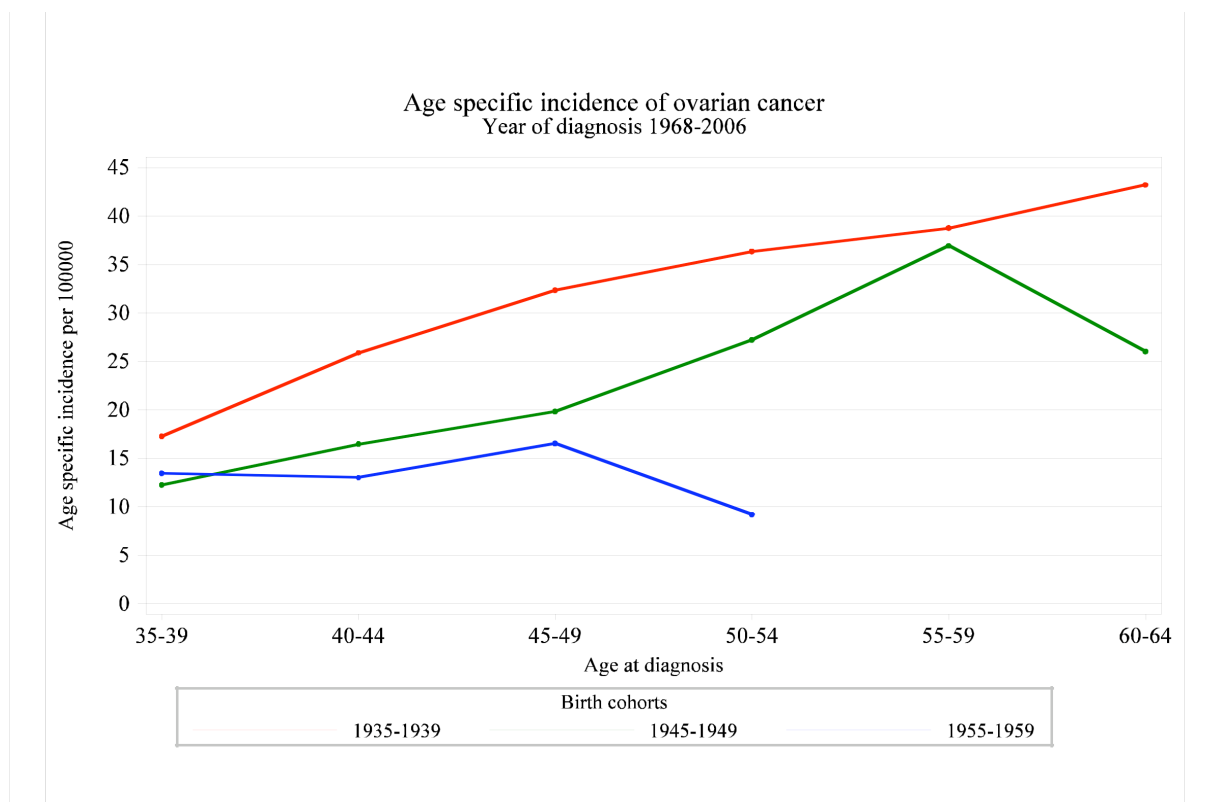
Figure11. Age specific incidence of ovarian cancer in different birth cohorts: 1935 to 39 (n=414), 1945 to 49 (n=273) and 1955 to 59 (n=100) in western Sweden 1968 to 2006. Regional Oncologic Centre, Gothenburg.

Survival 1993 to 1998 (Period 1), Papers I and II.

The 5-year RS rate in **Paper I** for the period 1993 to 1998 was 46.1% (95% confidence interval [CI], 42.1-50.3) for the entire material (N=682). The 10-year RS rate of the same population in **Paper II** was 38.4% (95% CI 34.1-42.8) (**Figure 12**) and the median RS rate was 4.3 years (95% CI 3.6-5.2) for the entire material and 2.5 years (95% CI 2.2-2.8) for the subgroup of stage III-IV.
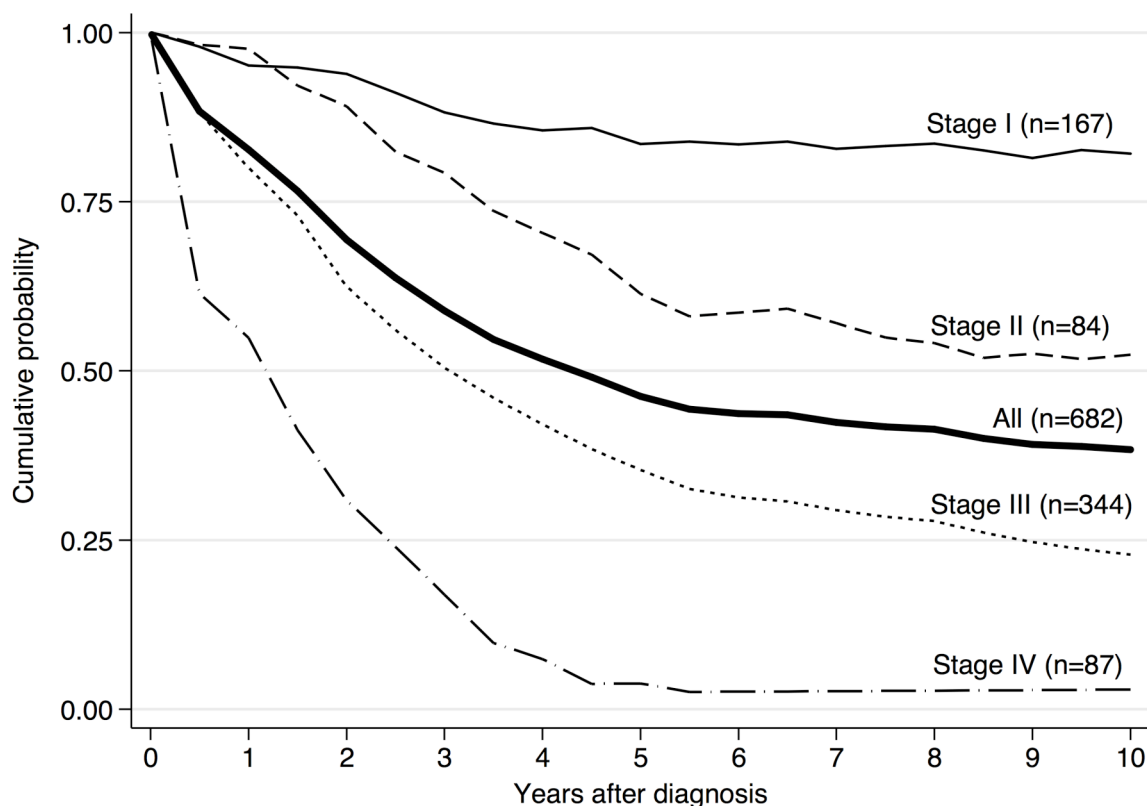
Figure 12. Relative 5- (46.1%) and 10-year (38.4%) survival rates in all (N=682) EOC patients (1993-1998), 5-year RS rates of 83.5%, 61.4%, 35.4%, and 3.8% in stages I, II, III, and IV, respectively.

The 5-year RS rate for the subgroup of 596 patients treated with chemotherapy after surgery in **Paper I** was 47.2% (95% CI 42.8-51.4) and the 10-year RS rate (**Paper II**) was the same as for the entire material, 38.4% (95% CI 33.9-43.0) (**Figure 13**).

In **Paper II** we calculated a median progression-free survival (PFS) of 19 months (95% CI 17-22) for the subgroup of patients with advanced stage disease (stage IIB-IV), who were actually treated with the chemotherapy combination of Parafac. For this latter group, the 5-year RS rate was 34.3% (95% CI 29.5-39.3). For the carboplatin-only treated patients of stage I-IIA, the 5-year RS rate was 81.9% (95% CI 73.5-88.6). (These survival rates are published in **Paper III**).
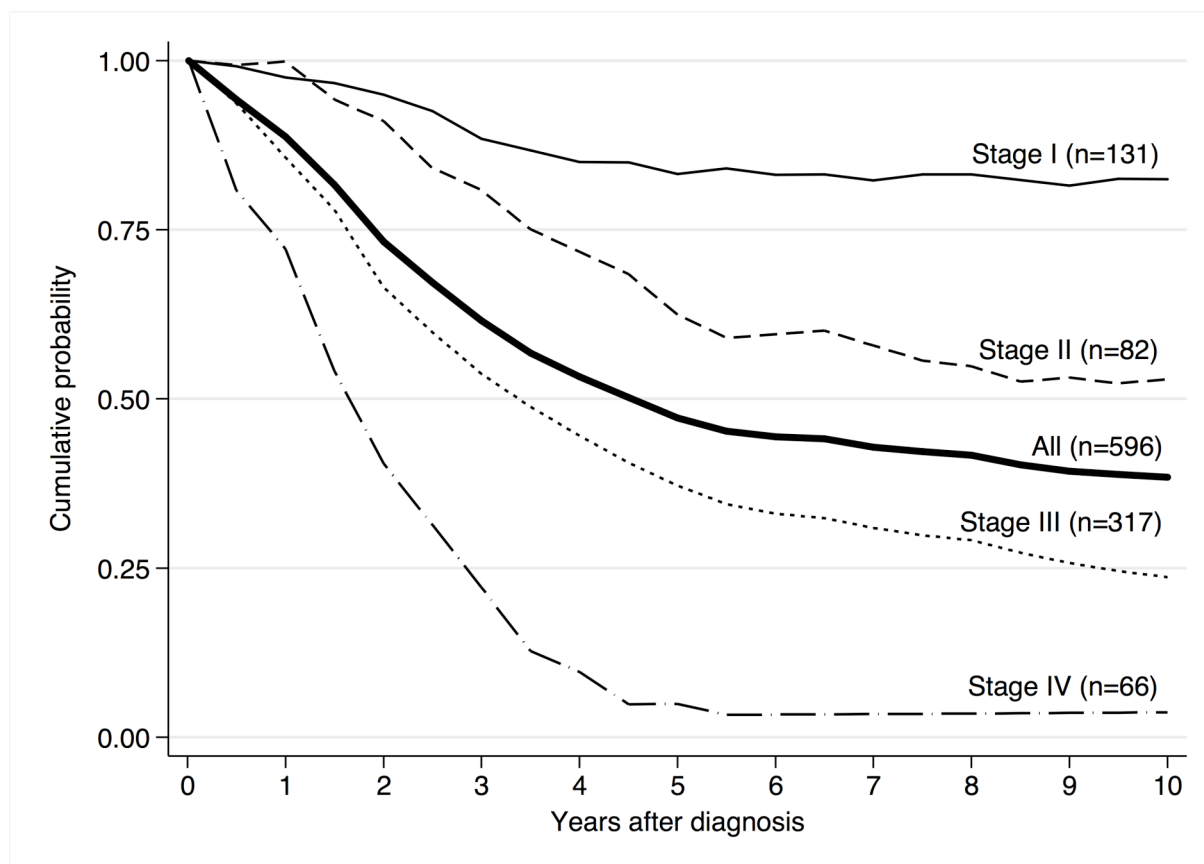
Figure 13. Relative 5- (47.2%) and 10-year (38.4%) survival rates in EOC patients (n=596) treated with chemotherapy after surgery and 5-year RS rates of 83.2%, 62.4%, 37.2%, and 4.9% in stage I, II, III, and IV, respectively during Period 1 (1993-1998).

In **Paper I** we compared the 5-year RS result for western Sweden with the rest of Sweden using data from the Centre for Epidemiology (EPC) at the National Board of Health and Welfare in Stockholm obtained from the actual study period and the time period immediately preceding our study (1988-1993). We concluded that there was a 3% improvement in both our material and that from the rest of Sweden over time (**Paper I,** Figure 3). The slight difference in the survival rate between the 46.1% of our own material and the 45.4% from the EPC data of our region could be explained by the more detailed analysis that we have carried out.

Unselected population-based studies with prospectively recorded data and with complete follow-up are rare. Our 5-year RS rate of 46.1% (95% CI 42.1-50.3) could be compared to a population-based study from Sweden from an earlier period (1984-1987) (56) with a 5-year RS rate of 40.4% (95% CI 34.3-46.6). The CIs overlap, but the trend of higher survival in our study could possibly be explained by the introduction of more advanced principles of surgery and chemotherapy in our study, which looked at a period one decade later.

In Finland a nationwide population-based study of 3851 EOC patients using data from different types of hospitals was carried out during the period 1983 to 1994 (102). They report 5-year RS rates of 37% to 45%, with higher rates in areas with centralized treatment at university hospitals.

There has been a steady increase in 5-year RS rates in ovarian cancer in Norway from around 22% in the 1950s to 37% from 1989 to 1993 (171). A large report of 32 000 EOC patients from the SEER project in the US gives 5-year RS rates of 37% in the 1970s (173) and 43% during the period of 1990 to 1997, which could be compared to the period of the present study. However, their follow-up is short (<3years), their material is probably not as complete as ours, and as many as 17% of their patients are included despite haviing had no surgery.

A population-based Cancer Registry study from Italy from the period 1978 to 1998 showed an increase in age-standardized ovarian cancer incidence as well as mortality over time (204). They report a 5-year RS rate of 42% (n=446) during 1994 to 1998. This is in the same range as our result in a population of the same mean age of 63 years.

Relative Survival is now accepted as the method of choice for expressing population-based cancer survival. Examples of this are the reports from England and Wales (205), the Eurocare study from 17 European countries (206), and the SEER from the US (207), which all report survival as RS. The only possible disadvantage of using the RS is if the reference population used to calculate expected survival is not optimal for the patient group studied. With EOC this is probably not a problem, as indicated by the fact that the 5-year RS and disease-specific survival rates in **Paper I** are very similar (46.1% versus 45.8%).

A comparison of the different modes of describing 5-year survival of the women in Period 1 is given in **Figure 14.**
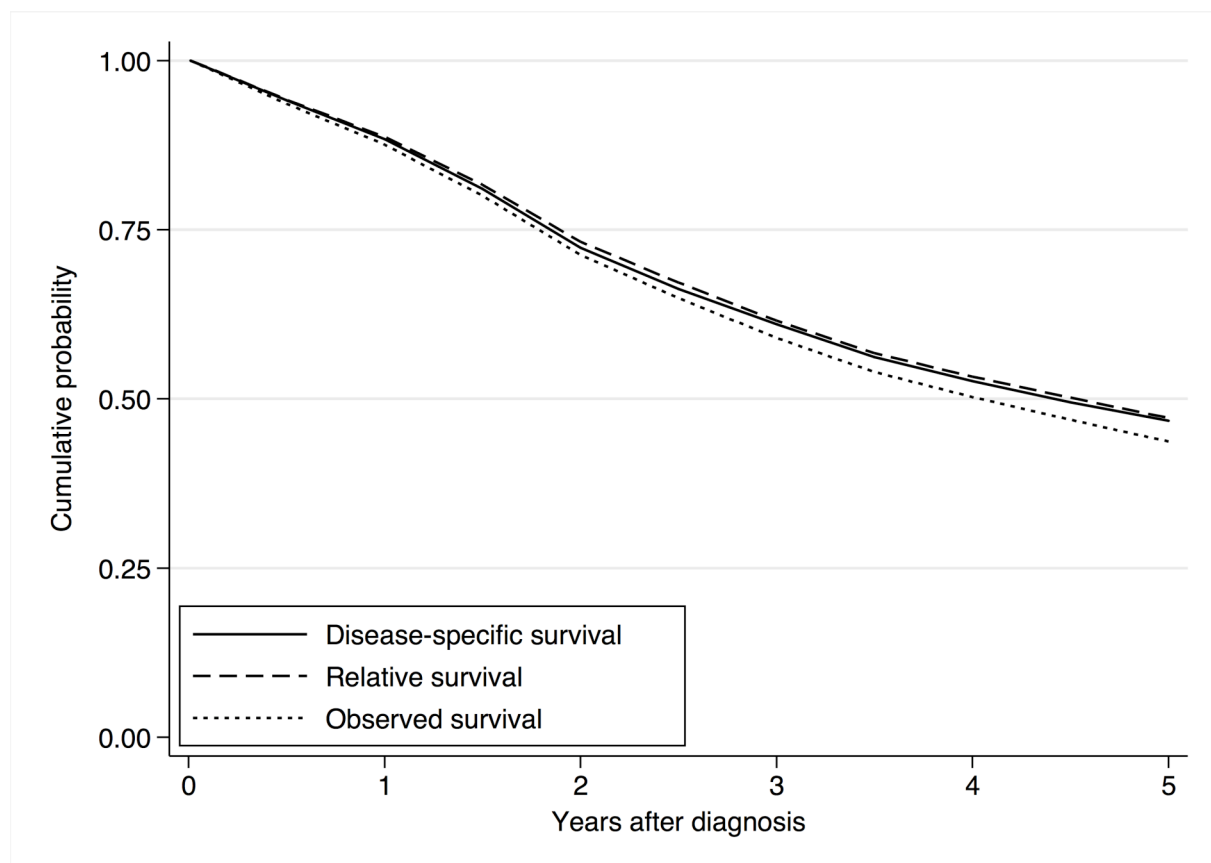
Figure 14. The different modes of describing 5-year survival in EOC patients in Period 1 (1993-1998). For exact % data see **Table 3**.

A study from the SEER database reported a slight progress in ovarian cancer over a 14-year period and reported an increased 5-year **disease-specific** survival rate of EOC from 42.5%

during 1988 to 1992 to 45.8% during 1993 to 1997 (208). It should be noted, however, that clear cell ovarian tumors were excluded from this material. The latter survival result is similar to the 5-year disease-specific survival rates in **Paper I** of 45.8% for all and 46.7% for those treated with chemotherapy (relatively unchanged at 45.9% and 46.8%, respectively, in the longer follow-up period of Paper II). It is also interesting to note that they show an increase in survival rate of around 3% from the time period preceding their study as is also shown in our study (**Paper I**, Figure 3).

A long-term follow-up study of 1220 patients from one part of Sweden during 1975 to 1993 presents a 5-year disease-specific survival of 50% in the whole cohort (137). It contains 39.7% patients in stage I and only 29.4% in stage III, (compared to 24.5% and 50.4% of stage I and III, respectively, in the present study). This difference does most likely explain the high survival rate in that study. The high percentage of patients in stage I in their material may be a result of staging procedures in the earlier period that were not as strict or it could reflect a selection bias in the material.

Many reports concerning EOC follow-up use **overall survival (OS**) as the measure of survival. This way of describing survival data gives lower rates than when survival is expressed relative to the general population. **Table 3** summarizes some other reports as well as our own results, with different modes of describing survival rates and different stages. FIGO's Annual Report shows 5-year OS rates ranging from 26.8% during 1958 to 1962 (n=2320) to 46.4% during 1996 to 1998 (n=4116) (69). However, the reporting centers are mostly university centers and the series are probably biased by selection. Most studies on EOC survival compare different chemotherapy protocols, mostly in patients with advanced stages of disease and in selected populations. Moreover, many of theses studies have a short follow-up time, and because of that the results are difficult to compare with the results of this thesis.

Papers presenting 10-year survival results for EOC are rare. A study from Germany (174) reported data obtained from a prospective population-based cohort of ovarian cancer patients over two decades with 10-year OS rates during the 10-year periods before (32.2%) and after (34.4%) 1988. For the patient group after 1988, a 12-month prolongation of median survival was observed in comparison to the patient group before 1988, but no great improvement was seen in survival rate. That study includes patient data up to and including 1997, and the 34.4% rate is comparable to our 10-year RS rate of 38.4% in **Paper II**. The difference is that they use OS and include even non-epithelial ovarian tumors. These tumors are known to have a better prognosis and the patients who get these tumors are younger, as also indicated by the mean age of their population, which was somewhat lower (60 years) than ours (63 years).

One study from the UK (1985-1994) of the long-term survival of 463 EOC patients of stage IIB-IV who were treated with carboplatin gives OS rates at 5, 10, and 15 years of 21%, 13.5%, and 12%, respectively (209). The small difference between 10 and 15 years of survival in their study is of interest. However, when using OS, women in the higher age groups are possibly also dying of other causes than cancer. They conclude that women with advanced disease who survive 11 years or longer have a life expectancy similar to that of the normal population. This statement accords with a report of cancer incidence in Sweden during three decades (1961-1991), where the authors conclude that the approximate years of follow-up until stabilization in RS for ovarian cancer is 12 years (210). In **Paper II** we saw a tendency of survival stabilizing after 8 to 9 years for early stage disease (Figure 12)**.**

The large SEER database only gives 5-year survival results and there is a need for more population-based studies with long-term follow-up. These kinds of studies are probably easier to perform in the Nordic countries where the populations are easier to find at follow-up because of the specific identification numbers used and the almost complete Cancer Registries.

Table 3. The results of EOC survival in some reports. RS=relative survival, OS=overall survival, DSS=disease-specific survival, Med.=median, m=months, *population-based.

Author Ref. nr.	n	Time	Stage	5-y RS %	5-y DSS %	5-y OS %	Med. RS m	Med. OS m	Med. PFS m
Paper I-II *	682 all 596treated	1993-1998	I-IV	46.2 47.2	45.9 46.8	42.2 43.7	52 54	45 48	
Paper I-II *	396treated Parafac	1993-1998	IIB-IV	34.3			37		19
Paper III *	976 all 853treated	1998-2005	I-IV	48.8 50.4	47.0 48.7	45.0 46.8	56 60	47 51	
Paper III *	530treated Paratax	1998-2005	IIB-IV	33.3			40		18
(56) *	332	1984-1987	I-IV	40.4	40.1	37.5	33	29	
(96) *	447	1975-1993	III-IV		18	16		18	
(102) *	3851	1983-1994	I-IV	37-45					
(152) *	571	1987-1996	I-IV		41	39		32	
(173) *	10 900	1990-1997	I-IV	43					
(208) *	11 610	1993-1997	I-IV		45.8				
(211)	1051	1994-1996	IC-IV			33			
(204) *	446	1994-1998	I-IV	41					
(95)	194	1994-1998	IIIC		35				
(212)	1895	1990ies	III					45	17
(213) *	8621	1996-2003	I-IV	38.0-40.3					
(104)	107	1999-2002	I-IV			4-y. 49.2		46	
(93)	408	1990-2002	IIIC			49		58	

Distribution of Stage, Grade, and Histopathology, 1993 to 1998 (Period 1), Papers I and II.

The distribution of FIGO stages is shown in Table I of **Paper I**. Two thirds of the women have tumors of stage III-IV. The degree of differentiation is shown in Table II of **Paper I.** The distribution of FIGO grade in relation to stage is shown in **Table 4**. There are only around 17% tumors of grade 1 (column %) and almost three quarters of the women have tumors of grade 2 or 3. Grade 1 is overrepresented in stage I at 55% (row %), and grades 2 and 3 are most common in stages III and IV. There are only 1.6% grade 1 tumors in stage IV.

Table 4.Stage related to grade in all EOC patients in Period 1, 1993 to 1998.

| | Stage | | | | |
Grade	I	II	III	IV	Total
High(1) n	67	10	42	2	121
Row %	55.4	8.3	34.7	1.6	100.0
Column%	40.1	11.9	12.2	2.3	17.7
Moderate(2)	64	28	90	23	205
	31.2	13.7	43.9	11.2	100.0
	38.3	33.3	26.1	26.4	30.1
Low(3)	26	33	188	52	299
	8.7	11.0	62.9	17.4	100.0
	15.6	39.3	54.7	59.8	43.8
Undiff.(4)	10	13	24	10	57
Or could	17.5	22.8	42.2	17.5	100.0
not be	6.0	15.5	7.0	11.5	8.4
assessed					
Total	167	84	344	87	682
	24.5	12.3	50.4	12.8	100.0
	100.0	100.0	100.0	100.0	100.0

A study from the SEER database of 1992 to 2003 included well differentiated serous tumors in the group of low-grade tumors (Type I, low-grade tumor, MD Anderson two-tier system) (47) and compared them with all the other grades together in the high-grade tumor group (Type II) in 12 400 women (214). They found that women with type I tumors tend to be younger (median age 55 years), with a much better mean survival (99 months, CI 95-104, median not reached) than women with Type II tumors (median age 63 years), who have a worse mean survival (57 months, CI 56-58, median 39 months). The survival was much better in early as well as advanced stage disease for low-grade, Type I tumors. This is in accordance with the survival results concerning FIGO grades in our study, where we found grade 1 tumors to have significantly higher 5-year RS rates compared with grades 2 and 3 (76.6%, 56.6%, and 31.3% 5-year RS, respectively [p<0.001] in Period 1) (Figure 4 in **Paper II**). However, grade was not an independent prognostic factor in our multivariate analysis.

The distribution of histology is shown in Table II of **Paper I**. Approximately 60% of tumors in our study showed serous histology, 12% endometroid, 10% mucinous and mixed histology, and 7% clear cell. **Table 5** shows the different subgroups of histopathology related to stage. Around three quarters of the tumors (column %) of stage III and two thirds of stage IV are serous, whereas endometroid, mucinous, and clear cell tumors are more frequent in stage I.

Table 5. Stage related to histopathology in all EOC patients from Period 1, 1993-1998.

| Histopathology | Stage | | | | |
	I	II	III	IV	Total
Serous n	52	38	257	57	404
Row %	12.9	9.4	63.6	14.1	100.0
Column %	31.1	45.2	74.7	65.5	59.3
Mucinous	41	6	20	6	73
	56.2	8.2	27.4	8.2	100.0
	24.6	7.1	5.8	6.9	10.7
Endometroid	37	16	23	6	82
	45.1	19.5	28.1	7.3	100.0
	22.1	1 9.1	6.7	6.9	12.0
Clear cell	24	10	14	4	52
	46.2	19.2	26.9	7.7	100.0
	14.4	11.9	4.1	4.6	7.6
Mixed tumor	13	14	30	14	71
	18.3	19.7	42.3	19.7	100.0
	7.8	16.7	8.7	16.1	10.4
Total	167	84	344	87	682
	24.5	12.3	50.4	12.8	100.0
	100.0	100.0	100.0	100.0	100.0

Studies indicate that there is an overestimate of mucinous tumors in historical material, since many metastic tumors from the gastro-intestinal tract are included as primary EOC (60). This may also be true for our study population in Paper I.

Almost half of endometroid and clear cell tumors, and more than half of mucinous tumors were of stage I during Period 1. These tumors seemed to belong to Type I tumors, slowly developing in a stepwise manner from cystadenomas to BOTs and from non-invasive tumors to low-grade carcinomas. Serous tumors are highly overrepresented at higher stages, with more than three quarters of tumors belonging to this histopathological subtype. This fact supports the theory that serous tumors are mostly high grade (Type II tumors) and that they develop *de novo* from ovarian cysts, which come from the ovarian surface epithelium or inclusion cysts without any precursors (46). (See **Figure 24** page 70).

Clinical guidelines

Is there improved survival with clinical guidelines? We deliberatly put the question mark in the title of **Paper I.** We found survival was improved by 3% compared to the preceding period, but is that an effect of the new guidelines? The increased survival rate of EOC is probably dependent on many things, including structured and more effective surgery performed by fewer surgeons, enhanced postoperative care, and protocol chemotherapy to more patients, among other factors. A group in Wales, who determined survival prior to the introduction of new guidelines (215), concluded that there was a very wide variation in the management of ovarian cancer in Wales.

The cancer registries of the Nordic countries are known to be valid, with a recent report of overall completeness of reporting ovarian cancer to the Cancer Registry of Norway of 99.6% (216). A Swedish study detected a 1% underreporting of genital cancer over the time period of 1958 to 1978 (217). Our data was double-checked with reports to both the OC quality register and the National Cancer Registry; in some cases we also controlled the clinical records and the pathological reports from the participating hospitals. All diagnoses were examined by a reference pathologist with vast experience in the field of gyneoncologic pathology. Because all cases were identified, our data must be considered valid and the CI in our survival analysis is a reliable indication of the statistical security.

A group in the Netherlands studied compliance with clinical guidelines in early-stage EOC (218). They concluded that the 5-year OS rate was 97.6% in the group staged optimally according to the guidelines, but only 68.5% in the non-optimally staged group.

Non-compliance with guidelines concerning chemotherapy was below 10% in our material and was mostly associated with death before treatment, bad performance status, or unwillingness to participate. During Periods 1 and 2 there were also some patients included in chemotherapy trials (Table 1 in both **Paper I** and **Paper III**) and some given other-than-standard treatment because of allergic and toxic reactions. These patients were included in the entire survival analyses, but when comparing survival of patients in stages IIB-IV we exclusively counted survival in patients who were given either Parafac or Paratax.

An interesting recent study from the NCI SEER registries evaluated the long-term impact of treatment advances in patients with late-stage ovarian cancer and used cause-specific survival data from 1973 to 2000 (219). They used survival cure models to estimate the gain in life expectancy (GLE) using the fraction of cured patients and the prolonged survival among non-cured patients. The total GLE was 2 years for ovarian cancer, but 80% of this gain was attributed to an extension of survival time in uncured women (from 0.9 years to 2.1 years) rather than an increased cure fraction (from 12% to 14%). This was in contrast to the results for testicular cancer, in which the cure rate represented 100% of a 24-year GLE.

One must bear in mind that the 5-year survival rate is not always a good way to describe how successful we are in decreasing the mortality of a certain disease. There could be changes in early diagnosis (the lead time), in the incidence rate, in age factors in the population, or in therapeutic improvements, any of which could influence mortality rates (10, 220). Prolonged life in uncured patients who live with disease, rather than improvement in cure rates, could represent a great part of the improved 5-year survival rate.

Thus, there is a need for prospective population-based studies, with long-term survival analyses and reliable registration of both disease-free survival and the period from recurrence to death. Then, perhaps, we could wipe out some of the question marks!

Survival 1998 to 2005 (Period 2), Paper III.

The 5-year RS rate of all patients (N=976) from period 2 (**Paper III**) was 48.8% (95% CI 45.2-52.4) and the 8-year RS rate was 39.7% (95% CI 34.9-44.5). The RS for all patients and according to stage are shown in **Figure 15**. For those treated with surgery and chemotherapy (n=853), the RS rates were 50.4% (95% CI 46.4-54.3) and 40.5% (95% CI 35.4-45.6) respectively (**Figure 16**). The median RS was 56 months for all patients and 60 months for the chemotherapy treated.

For those patients of stage IIB-IV treated with carboplatin and paclitaxel, the 5-year RS rate was 33.3% (95% CI 28.8-38.0) (Figure 4 of **Paper III**) and the median PFS time was 18 months (95% CI 17-20).
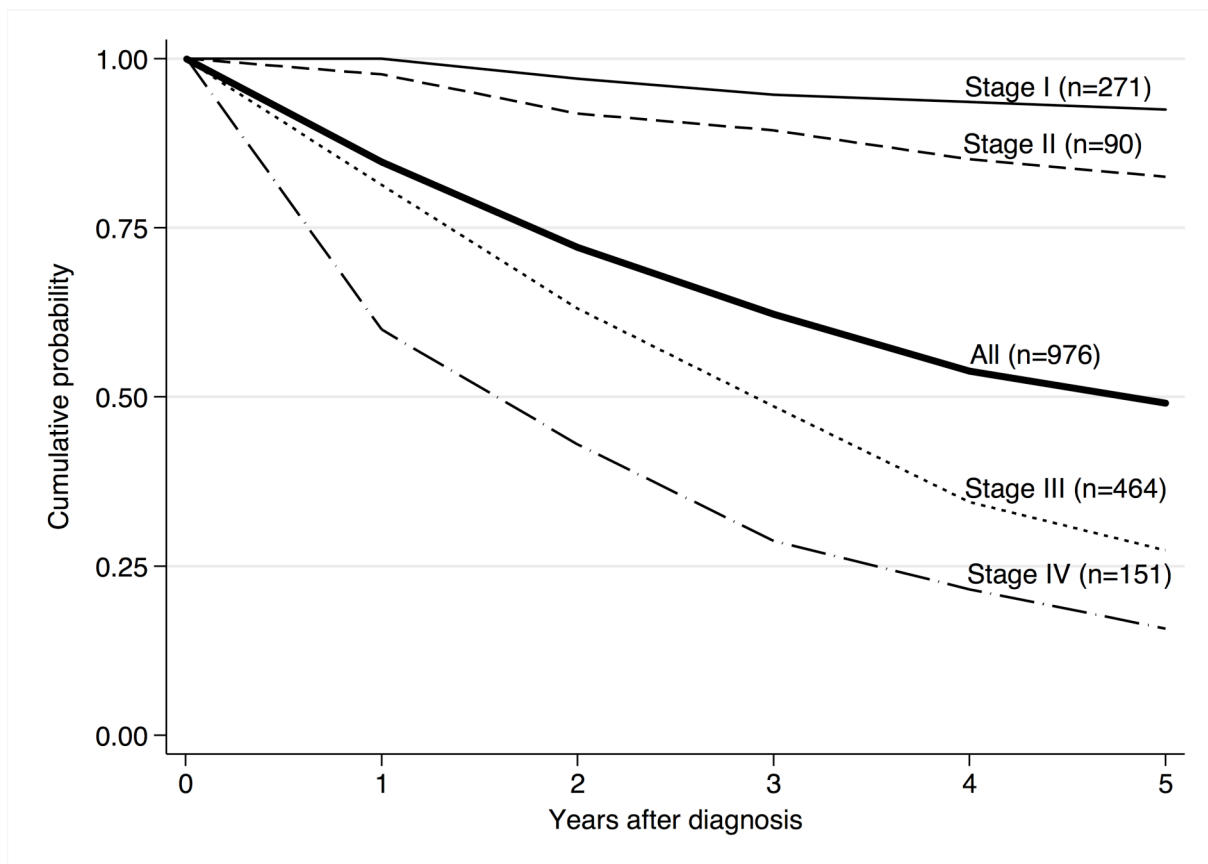
Figure 15. The 5-year RS rate (48.8%) in all EOC patients (N=976), also as related to stage I (92.2%), II (82.5%), III (27.2%), and IV (15.7%) during Period 2 (1998-2005).
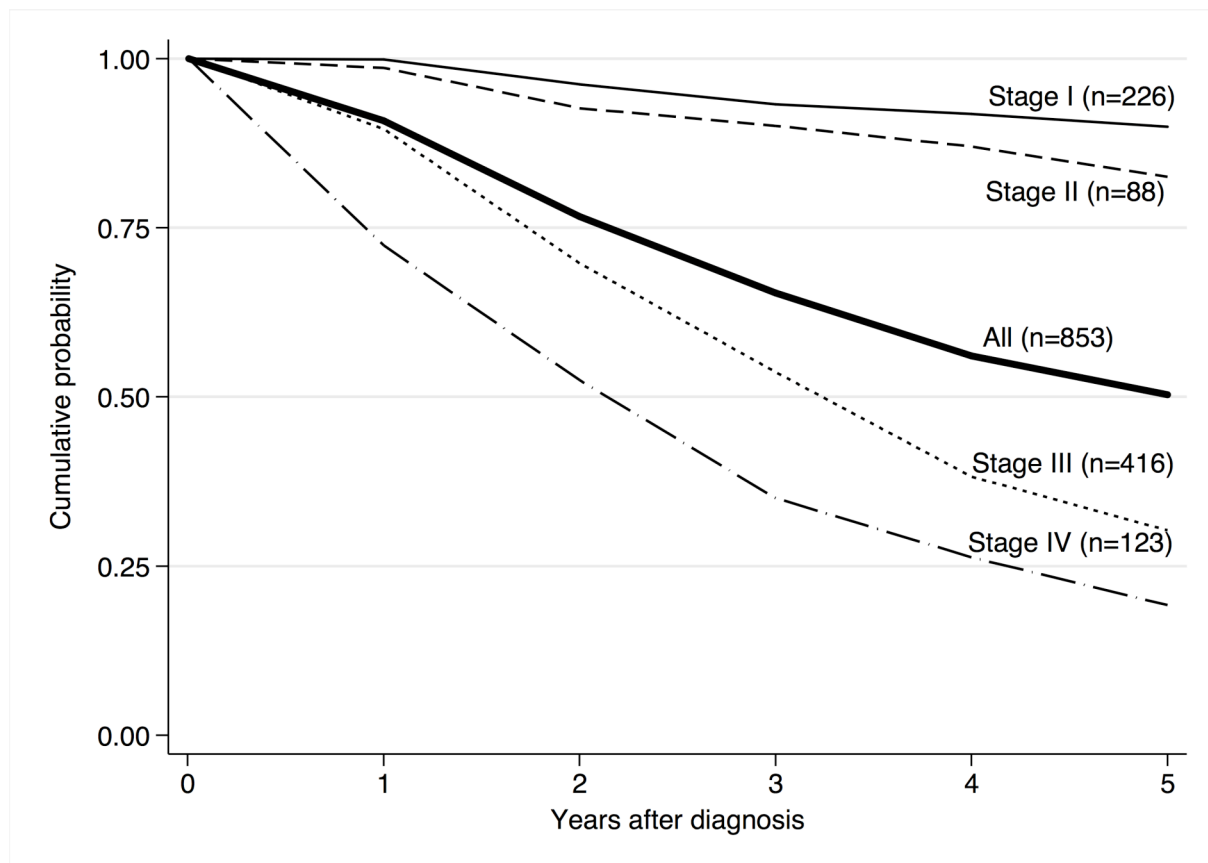
Figure 16. The 5-year RS rate (50.4%) in EOC patients treated with chemotherapy (n=853), also as related to stage in Period 2 (1998-2005). Stage I (89.9%), II (83.0%), III (30.4%), and IV (20.0%). *P*-values in relation to stage I: stage II = *P*<0.26, stage III = *P*< 0.0001, and stage IV = *P*<0.0001.

Population-based data with RS rates for the time between 1998 and 2005 are sparse. From the Finnish Cancer Registry there are reports showing a 5-year RS rate of 46% in the late 1990s (172). The SEER database reports a 5-year RS rate of 45.5% from 1996 to 2004 (www.SEER.gov.nci). These rates are similar to the RS rates of our study during a similar period.

In a most interesting large retrospective population-based nationwide cohort study including all EOC patients from 1996 to 2003 (N=8621) from the Netherlands Cancer Registry, focusing on different hospital types, 5-year RS rates were found to be 38.0%, 39.4%, and 40.3% in general (treating 40% of the patients), semi-specialized (treating 41%), and specialized hospitals (treating 18%), respectively (213). The 5-year RS rates per stage for the whole population were 81.2%, 60.0%, 24.5%, and 11.7% for stage I, II, III, and IV, respectively. These numbers should be compared to 92.2%, 82.5%, 27.2%, and 15.7% in stage I, II, III, and IV, respectively in our study observed over a similar period (Figure 15). Among patients at a lower FIGO stage, there was a decreased risk of cancer-specific mortality in semi-specialized and specialized hospitals in the Netherlands compared to general hospitals (213). However, in advanced disease, the hospital type was not associated with survival. This contradicts earlier studies, where stage III EOC patients treated by gynecologic oncologists showed a better survival than those treated by general gynecologists (99, 105). Many studies show improved survival results when ovarian cancer patients are referred to specialized units (73, 100, 103, 104, 221).

Since many studies report OS or DSS instead of RS we have provided a comparison of the different estimates by describing our material in these terms as well as by RS per stage in **Paper III** (Table 4). Generally, compared to RS, rates for survival are a little lower when reported using DSS and lower still using OS.

In a study from 1999 to 2002 in Denmark, a 4-year **OS** rate of 49.2% and a median survival of 46 months were reported after the introduction of centralized surgery. This could be compared to the median overall survival of 47 months in our 1998 to 2005 study.

In Table 3 (page 42) we list some reports of different estimates to describe survival results of different stages during both time periods. We caution, however, that not all of these are population-based (as indicated).

The recent organization of local tumor teams and the new CGs that provide the basis for this thesis could perhaps be compared to the semi-specialized hospitals described above (213). In that study, however, it is pointed out that the most important factors are the surgical skills and surgical training facilities of each doctor, rather than whether the surgeon is a formal specialist or not. This difference is exemplified by the Dutch study, where the results were generally the same in specialized and semi-specialized hospitals; the long learning curve in gynecologic oncology is, however, stressed by some authors (107). Close cooperation between surgeons and medical oncologists is also very important, and this is perhaps easier to establish in a larger specialized clinic.

The Distribution of Stage, Grade, and Histopathology, 1998 to 2005 (Period 2), Paper III.

The prognostic significance of age, stage, grade, histology, residual tumor, post-operative CA-125, and ploidy status were also evaluated in **Paper III** and are discussed more thoroughly in relation to the results of **Paper II** in the next chapter (**Prognostic factors**).

The stage distribution and 5-year RS rates per stage of both time periods are shown in **Table 6.** There is a higher percentage of patients in stages II and III in Period 1 and a higher percentage of stages I and IV in Period 2. The reason for this stage migration is not clear but will be discussed further in the next chapter (Prognostic Factors).

Table 6. Distribution of FIGO stage in 682 EOC patients in western Sweden from September 1, 1993 to, May 31, 1998, compared to 976 EOC patients in the study from June 1, 1998 to May 31, 2005, and the 5-year relative survival rates per stage for all patients and for those treated with chemotherapy after surgery in the two periods.

Period	1993-1998	1998-2005	5-year relative survival % (n)			
Stage	n (%)	n (%)	period 1 all	period 1 treated	period 2 all	period 2 treated
IA	98 (14.4)	150 (15.4)				
IB	10 (1.5)	14 (1.4)				
IC	59 (8.6)	107 (11.0)				
Total	167 (24.5)	271 (27.8)	83.5(167)	83.2(131)	92.2(271)	89.9(226)
IIA	17 (2.5)	18 (1.8)				
IIB	47 (6.9)	44 (4.5)				
IIC	20 (2.9)	28 (2.9)				
Total	84 (12.3)	90 (9.2)	61.4(84)	62.4(82)	82.5(90)	83.0(88)
IIIA	26 (3.8)	33 (3.4)				
IIIB	59 (8.6)	34 (3.5)				
IIIC	259 (38.0)	397 (40.6)				
Total	344 (50.4)	464 (47.5)	35.4(344)	37.2(317)	27.2(464)	30.4(416)
IV	87 (12.8)	151 (15.5)	3.8(87)	4.9(66)	15.7(151)	20.0(123)

We found grade 1 tumors to have a 5-year RS rate of 83.7% compared to 49.1% and 39.7% for grades 2 and 3, respectively ($P<0.0001$) (**Paper III).** When grade was related to stage for Period 2 (**Table 7**) we saw a high percentage of grade 1 tumors (68%, row %) for stage I, but for stage III and IV more than 80% (column%) were of grades 2 or 3. Only around 5 % of stage IV tumors were of grade 1.

There seems to be a strong association between high FIGO stage and Grade 3. However, in the multivariate analysis, grade was only an independent PF with a hazard ratio of 1.7 when grades 2 and 3 were grouped together.

Although grade has been reported as a significant prognostic variable in early-stage EOC (165), it was not found to be a good predictor of poor outcome for advanced disease in a recent publication (212).

Table 7. Stage related to grade in all EOC patients in Period 2, 1998-2005.

Grade	Stage I	II	III	IV	Total
High(1) n	130	16	36	9	191
Row %	68.0	8.4	18.9	4.7	100.0
Column %	48.0	17.8	7.7	5.9	19.6
Moderate(2)	75	30	127	38	270
	27.8	11.1	47.0	14.1	100.0
	27.7	33.3	27.4	25.2	27.7
Low(3)	57	34	255	85	431
	13.2	7.9	59.2	19.7	100.0
	21.0	37.8	55.0	56.3	44.1
Undiff.(4)	9	10	46	19	84
Or could	10.7	11.9	54.8	22.6	100.0
Not be	3.3	11.1	9.9	12.6	8.6
assessed					
Total	271	90	464	151	976
	27.8	9.2	47.5	15.5	100.0
	100.0	100.0	100.0	100.0	100.0

The distribution of histopathology is shown in Table 3 of **Paper III**. Histology according to stage is shown in **Table 8**. During Period 2, the proportion of tumors of mucinous histology showed a decrease to 7.2% from a rate of 10.7% in Period 1. One explanation could be an increased consciousness among pathologists and clinicians to seek other types of primaries. One could reasonably expect the opposite result, since the use of OCP does not account for the same sort of decrease in mucinous tumors as it seems to in other histological types. Likewise, during Period 1 endometroid, mucinous and clear cell tumors are highly overrepresented in stage I, whereas three quarters of serous tumors are seen in patients at stages III or IV.

That disease incidence has shown a greater decrease in Sweden than has mortality could possibly be explained by a reduction in less aggressive tumor forms (attributable to the protective factors of increased use of OCP). The reduction of less dangerous forms means that there may be a greater proportion of more aggressive tumors, unopposed by OCP.

Table 8 Stage related to histolpathogy in all EOC patients in Period 2, 1998-2005.

| Histopathology | Stage | | | | |
	I	II	III	IV	Total
Serous n	100	40	357	107	610
Row %	17.4	6.6	58.5	17.5	100.0
Column %	39.1	44.4	77.0	70.9	62.5
Mucinous	50	6	8	6	70
	71.4	8.6	11.4	8.6	100.0
	18.4	6.7	1.7	4.0	7.2
Endometroid	75	25	38	13	151
	49.7	16.5	25.2	8.6	100.0
	27.7	27.8	8.2	8.6	15.5
Mucinous	50	6	8	6	70
	71.4	8.6	11.4	8.6	100.0
	18.4	6.7	1.7	4.0	7.2
Clear cell	33	9	13	7	62
	53.2	14.5	21.0	11.3	100.0
	12.2	10.0	2.8	4.6	6.35
Mixed/other	7	10	48	18	83
	8.4	12.1	57.8	21.7	100.0
	2.6	11.1	10.3	11.9	8.5
Total	271	90	464	151	976
	27.8	9.2	47.5	15.5	100.0
	100.0	100.0	100.0	100.0	100.0

Prognostic factors, Papers II and III.

We evaluated the prognostic factors (PF) for survival in the two time periods, Period 1 in **Paper II** and Period 2 in **Paper III.**

Stage was found to be the most important PF, with hazard ratios in stage IV in the multivariate Cox regression analysis of 5.7 and 4.1 in relation to stage I for Periods 1 and 2, respectively. The stage distribution for both periods is shown together with the 5-year RS rates per stage for the two periods in Table 6 (page 49). As mentioned earlier, there is a slight difference in the stage distribution between the two periods, with more patients of stage II and III during Period 1, and more patients of stage I and IV during Period 2. This makes the survival comparison, stage by stage, in the two periods difficult. However, if we consider the early stage patients (I-IIA) as one group and the advanced stages patients (IIB-IV, 73% versus 70.4% in Periods 1 and 2, respectively) as another group, the differences between these groups during the two periods were only 2.6%.

The 5-year RS rates according to stage in the patients treated with chemotherapy during the two periods are shown in Figure 13 (**Paper II**, Figure 3) for Period 1 and Figure 16 (**Paper**

III, Figure 2) for Period 2 and compared in Table 6. A further discussion comparing stage IIB-IV for the two periods with different chemotherapy for advanced cases is included in the following chapter.

The 10-year RS rates for Period 1 per stage in all patients was 82.2%, 52.4%, 22.8%, and 2.9%, and in those treated with chemotherapy 82.5%, 52.9%, 23.6%, and 3.7% for stage I, II, III, and IV, respectively (Figures 12 and 13**).** Thus, interestingly enough, after 10 years, there were no major differences in survival between all women and those treated with chemotherapy. In the group of patients not having had chemotherapy, there is a low-risk group (defined as stage I, grade1, diploid) of around 3% for both periods and around 12% of women in both periods not given chemotherapy because of this low-risk, bad general condition, death before treatment, or unwillingness to participate (mainly because of high age) (See **Table 12** next chapter, page 62).

We noticed a 5-year RS rate of 4.9% in stage IV in those treated with adjuvant chemotherapy during Period 1 compared to 20.0% in Period 2 (Table 6). There were more patients in stage IV in the second period (n=123, versus n=66 of those treated) and it could possibly be a statistical random, since there are few patients in stage IV still alive after 5 years, especially in the first period. However, improved survival in stage IV in Period 2 could also be an effect of stage migration if less aggressive tumors were included in stage IV in the latter period. There was a 5-year RS rate of 37.2% in stage III of those treated during Period 1 compared to the 5-year RS rate of 30.4% in Period 2. It is more difficult to explain this survival decrease in stage III in Period 2. One might assume the opposite result, since more "real" stage IV patients with worse prognoses could have been excluded from stage III in Period 2. The stage distributions were not exactly the same in the two periods, as mentioned earlier, with stage III making up 50.4% and 47.5% in Periods 1 and 2, respectively. Factors influencing survival could include differences in age distribution, diagnostic procedures, or the effects of better treatments. This will be discussed further in the next chapter.

We made a sub-analysis of stage III subgroups and existing values of CA-125 and ploidy status in both **Paper II** (Table 7) and **Paper III** (Table 7), and found in the first period CA-125≥35 U/ml and stage IIIC disease compared to IIIA to be independent PFs for survival. In Period 2 the same results were found when comparing both IIIB and IIIC with IIIA. These survival differences in the subgroups of Stage III have been noted in earlier studies (62, 222) and may also be explained by cytogenetic alterations in stage III disease (168). This is in line with the better survival in patients with no residual disease after surgery, since patients with IIIA tumors only have microscopic residual disease.

Age was found to be a PF for survival in both periods, with a hazard ratio of 1.3 and 1.2 per 10 years in the multivariate Cox analysis during Period 1 and 2, respectively.

Age distribution was found to be similar in Periods 1 and 2 (Figure 8). The mean age of our study was the same (63 years) during both periods, and the median was 63 (18-91) years in Period 1 and 64 (23-94) years in Period 2. In **paper III** we found significant differences in survival between women aged below 70 years and those aged 70 years and over, with a 5-year RS rate of 54.6% and 33.0%, respectively (**Figure 17**). We can see in figure 17 that the differences between all and those treated with chemotherapy diminish over time and after 7 to 8 years there seems to be no difference.

A large population-based study from the SEER database (208) gives a similar median age and the European Union also reports mean age at diagnosis at 63 years (12). A large retrospective review with data from six GOG studies of stage III EOC with nearly 2000 women shows an increased risk of 6% for disease progression and 12%f for death for every interval increase of 10 years of age (212).
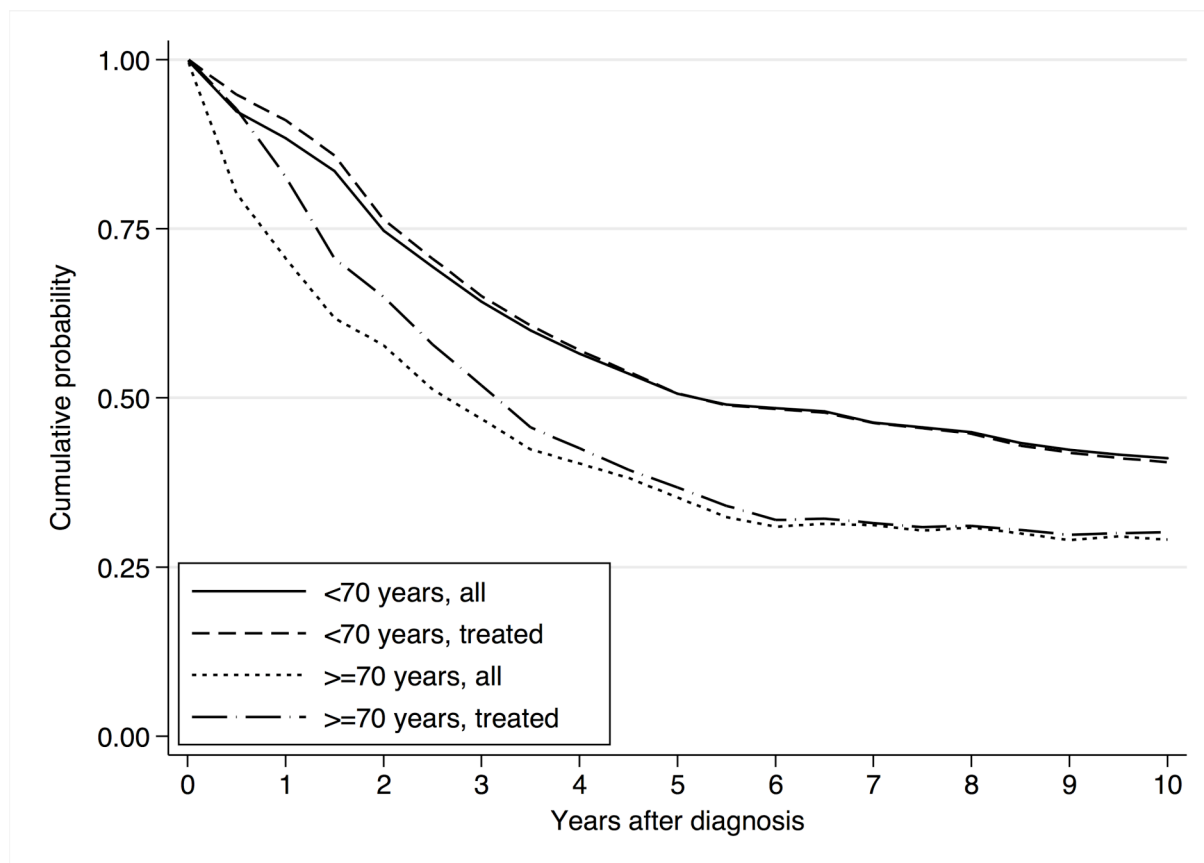
Figure 17. Ten-year RS in all patients and in those treated with chemotherapy after surgery aged <70 years and ≥70 years in Period 1 (1993-1998).

Although it is well known that younger women with EOC are diagnosed with earlier stage and more often have grade 1 tumors (156, 173) age was found to be an independent PF in a multivariate analysis adjusted for stage and grade in earlier studies (151, 153). In a study from the SEER database of over 28 000 women with EOC from 1988 to 2001, the patients were divided into three age groups: <30 years, 30–60 years, and >60 years, showing 5-year disease-specific survival rates of 78.8, 58.8, and 35.3%, respectively (153). Interestingly, the younger women of reproductive age in stage I or II, who underwent fertility-saving surgery, had similar rates of survival to those who had standard surgery, even after repeated surgery. After controlling for factors like stage, grade, and performance status, the younger group still had better survival. This indicates that tumor biology factors, such as DNA ploidy, p53 expression, and other factors, perhaps including immune response and co-morbidities, may be responsible for increased survival in youger age groups as discussed by others (223, 224). Studies have shown that younger women have tumors with higher microvascular density, which probably improves their response to chemotherapy (225).

Convincing data now show that minimizing **residual disease** with primary cytoreductive surgery will increase survival in women with EOC. Griffiths concluded as long ago as 1975 that survival increased with minimization of residual disease and set the limit at 1.5 cm resdual tumor (157), and Hoskins et al found a breaking point at 2 cm (90). Later on, <1 cm residual tumour was suggested as the limit for expecting improved survival (94, 95). In Period 1 we set the limit to no macroscopic, ≤2 cm or > 2 cm, and in Period 2 the limits were changed to ≤ 1 cm or >1 cm residual disease. We found the residual tumor to be an

independent variable for survival in both periods with an HR (compared to no residual tumor at all) of 1.9 and 2.6 for ≤ 2 and >2 cm, respectively in Period 1 (**Paper II,** Table 6) and an HR of 1.5 and 2.1 for ≤ 1 cm and > 1 cm, respectively in period 2 (**Paper III,** Table 6). The percentage of patients with no macroscopic disease after surgery was 42.3% and 44.5% of all patients in Periods 1 and 2, respectively. The distribution of residual tumor per stage for Periods 1 and 2 is shown in **Table 9**.

Table 9. Amount of residual tumor after surgery according to stage in all EOC patients. Periods 1 and 2.

Amount of residual disease n (%) in Period 1 (1993-1998)

Stage	No macroscopic	≤ 2 cm	>2 cm	Not known	Total
I	164 (98.2)	1 (0.6)	0	2 (1.2)	167
II	63 (75.0)	16 (19.0)	5 (6.0)	0	84
III	56 (16.3)	77 (22.4)	208 (60.5)	3 (0.8)	344
IV	3 (3.4)	10 (11.5)	72 (82.8)	2 (2.3)	87
Total	286	104	285	7	682

Amount of residual disease n (%) in Period 2 (1998-2005).

Stage	No macroscopic	≤ 1 cm	>1 cm	Not known	Total
I	268 (98.9)	0	1 (0.4)	2 (0.7)	271
II	75 (83.3)	11 (12.2)	4 (4.5)	0	90
III	80 (17.2)	89 (19.2)	295 (63.6)	0	464
IV	11 (7.3)	20 (13.2)	120 (79.5)	0	151
Total	434	122	420	2	976

The survival probability according to residual tumor in patients treated with chemotherapy during Period 1 is shown in **Figure 18** and during period 2 in figure 3 of **Paper III**. There were significant differences between the proportions of patients with no macroscopic residual tumors and those with residual tumors measuring from <1 to >2 cm during both periods. The comparison between the various groups is difficult because tumor-size limits were changed between studies.
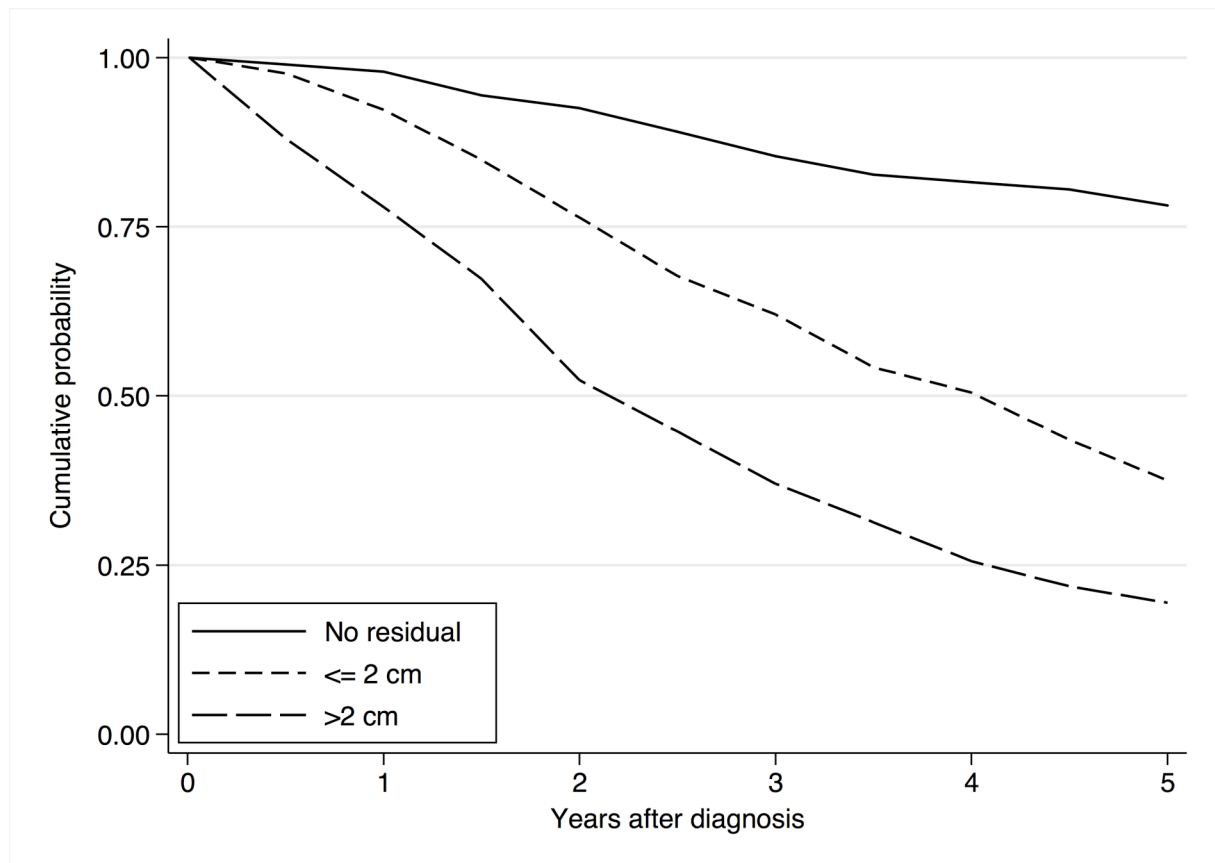
Figure 18. The 5-year RS according to residual disease in EOC patients treated with chemotherapy after surgery in Period 1 (1993-1998).

In stages III and IV, 19.7% of patients were defined as macroscopically tumor-free in the abdomen after surgery during the early period; during the second period, this rose to 24.5% (Table 9). These figures are comparable to those from a prospective study from Germany including 686 EOC patients at stage IIB-IV focusing on age and residual tumor in relation to survival (226). They found that age was an independent PF and that the younger group of patients more often had no residual tumor, which resulted in their improved median OS. They had complete removal of all visible tumor in 29.8% of all patients, a figure better than that of both periods in the present study. They included patients with stage IIB-IV tumors and with a median age of 57.0 years, but excluded patients with clear cell tumors, which to some extent could explain the difference between their figures and ours.

During Period 2, only 36.4% of patients in stage III in the present study population became macroscopically tumor-free, or with < 1cm residual tumor, a sample comparable with the 67.5% in stage IIIC in a recent report from the US (95).

I believe that the surgery performed should and must be enhanced in the region of western Sweden if survival results are to be further improved in terms of PFS and long-term survival. Specialized groups of gynecologic oncologists, after aggressive surgery, can now reach a much higher percentage of no visible remaining tumor. In a prospective study from the US, over 86% of 408 stage IIIC EOC operated patients are reported to have no residual tumor, with a 5-year OS rate of 49% in that population (93). A large meta-analysis of over 6800 stage III-IV EOC patients concludes that each 10% increase in maximal cytoreduction is associated with a 5.5% increase in median survival time (92).

In a recent publication of a retrospective analysis of four GOG studies of 360 stage IV EOC patients evaluating PF, patients without macroscopic residuals in the abdomen after surgery

were found to have the best survival, but surprisingly there was no difference in PFS and OS between patients with 0.1-1 cm residual disease and patients with 1.1-5.0 cm residual disease (227). However, in our study we found the difference between <1 or <2cm and >1 or >2 cm to be significant for both time periods.

Whether 1 or 2 cm is the limit for improved survival is rather irrelevant, especially considering the difficulty of accurately defining a residual in peritoneal carcinosis. The goal must be to leave no macroscopic residual if it is possible to do without causing severe complications or reduced quality of life. Whether "ultra-radical" surgery with total colectomy, multiple small bowel resections, splenectomy, partial hepatectomy, and extirpation of peritoneum with different techniques is of further benefit for women remains a subject of discussion (95, 108).

In our univariate analysis, we found that serous **histopathology** was associated with a worse prognosis in Periods 1 and 2, but in the multivariate analysis, we could not find any histological subgroup to be an independent PF. As shown in Tables 5 and 8, serous histologies are overrepresented in tumors of higher stage. Stages III and IV tumors were mostly of grade 3 (Table 4) and probably therefore the difference between serous and other subtypes of histology become less obvious in the multivariate analysis, where stage is the strongest factor.

Serous tumors are believed to be more aggressive, especially those high-grade tumors according to the MD Anderson two-tier grading system (47). A recent report of stages II-IV low-grade serous EOC found them to be characterized by young age and prolonged OS (228). There was a correspondence between FIGO grade 1 and the low-grade tumors of the Malpica system on one side, and FIGO grade 2-3 and the high-grade tumors on the other side.

Mucinous and endometroid tumors were more often diagnosed in early stage in both periods (Table 5 and 8), and this may contribute to their more favourable prognosis. However, there are reports that mucinous tumors of a higher stage (56, 57) as well as clear cell tumors have a worse prognosis (212). Molecular and genetic studies report differences between mucinous and serous tumors, supporting the theory that the mucinous tumors develop along separate pathways (57). The risk factors for mucinous tumors are also different from those of serous tumours, with less relation to parity, OCP use, and ovulation, indicating a different etiology (36, 53).As discussed earlier, mucinous tumors of higher stage could be metastatic tumors from the gastrointestinal tract being mistaken for ovarian primaries (60).

Clear cell tumors are more likely to be intrinsically resistant to chemotherapy; those of grade 3 often exhibit p53 over-expression (229).

The FIGO **grades** 2 and 3 were found in the univariate Cox analysis, but not in the multivariate analysis, to be prognostic variables in relation to grade 1 in both **Papers II** and **III** (Table 5 both papers). The relationship between stage and grade is shown for the two study periods in Table 4 and 7. The 5-year RS rate for different grades in Period 1 is shown in **Figure 19**. In the late period we grouped grades 2 and 3 together in the multivariate analysis; together, they were then significant, with a hazard ratio of 1.7 in relation to grade1.

It seems that grades 1 and 3 are more consistent indicators of good or bad prognosis, but grade 2 is somewhat more ambiguous as a prognostic sign. Different studies also show conflicting results concerning grade; some cannot identify grade as a PF (152), while others do when they group grades together, as we did (62). The new MD Anderson grading system for serous tumors includes FIGO grades 2 and 3 in their high-grade nomenclature, which makes it easier to identify serous tumors with good or bad prognosis.
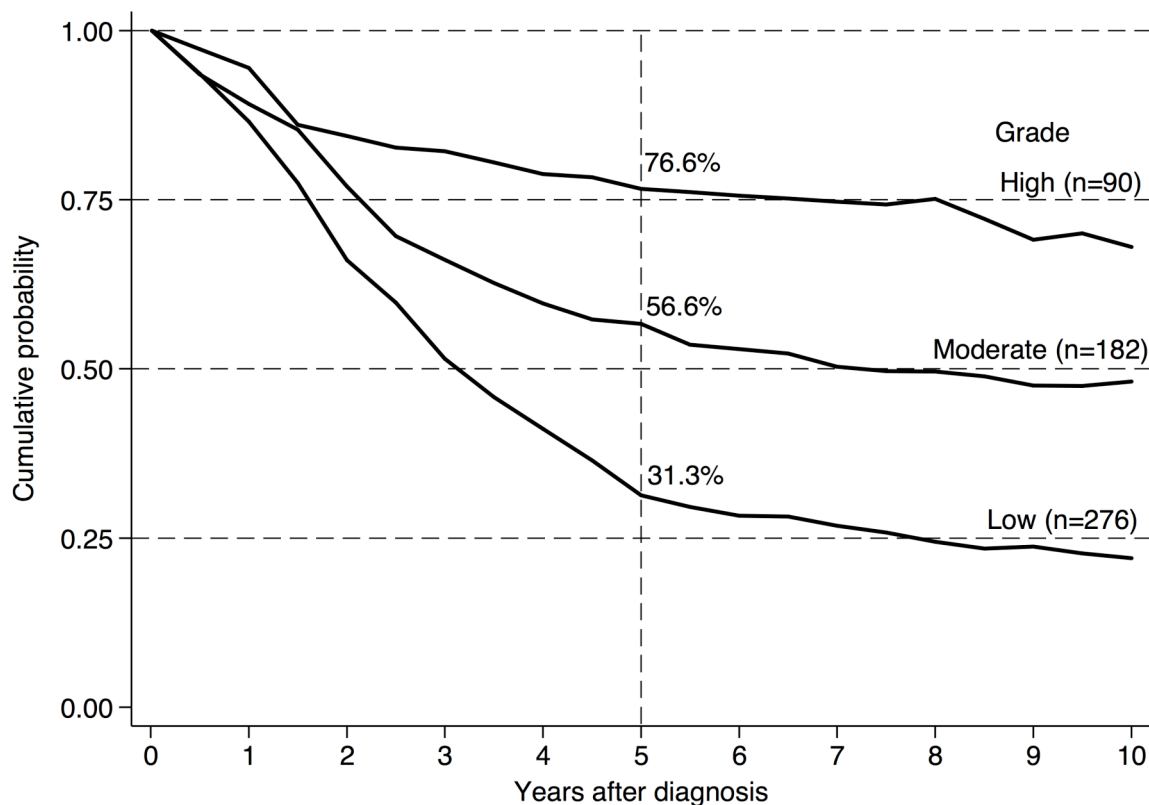
Figure 19. Relative 5-year survival according to grade in 548 EOC patients treated with chemotherapy after surgery in Period 1.

We collected sera for **CA-125** analysis in conjunction with the first chemotherapy treatment, which typically took place three to four weeks after primary surgery. It was available for analysis in 391 patients in Period 1 (**Paper II**) and in 735 patients in Period 2 (**Paper III**). We used cut-off limits of <35, 35–65, and >65 U/ml, consistent with previous publications (161). In the univariate analysis, CA-125 levels were significantly related to survival with hazard ratios of 2.2 in CA-125 levels of 35–65U/ml and 4.9 in CA-125 levels >65U/ml compared with levels <35 during the first period (**Paper II,** Table 5) and with hazard ratios of 2.2 and 4.4 of CA-125 levels 35–65 and >65, respectively, during Period 2 (**Paper III,** Table 5). In Period 1, the 5-year RS rates were 73.6%, 50.0%, and 23.4% in patients treated with chemotherapy with values of <35, 35–65, and >65 U/ml, respectively (**Paper II,** Figure 5). In Period 2, the 5-year RS rates were 77.3%, 60.1%, and 29.1% for values of <35, 35–65, and >65U/ml, respectively (**Figure 20**).
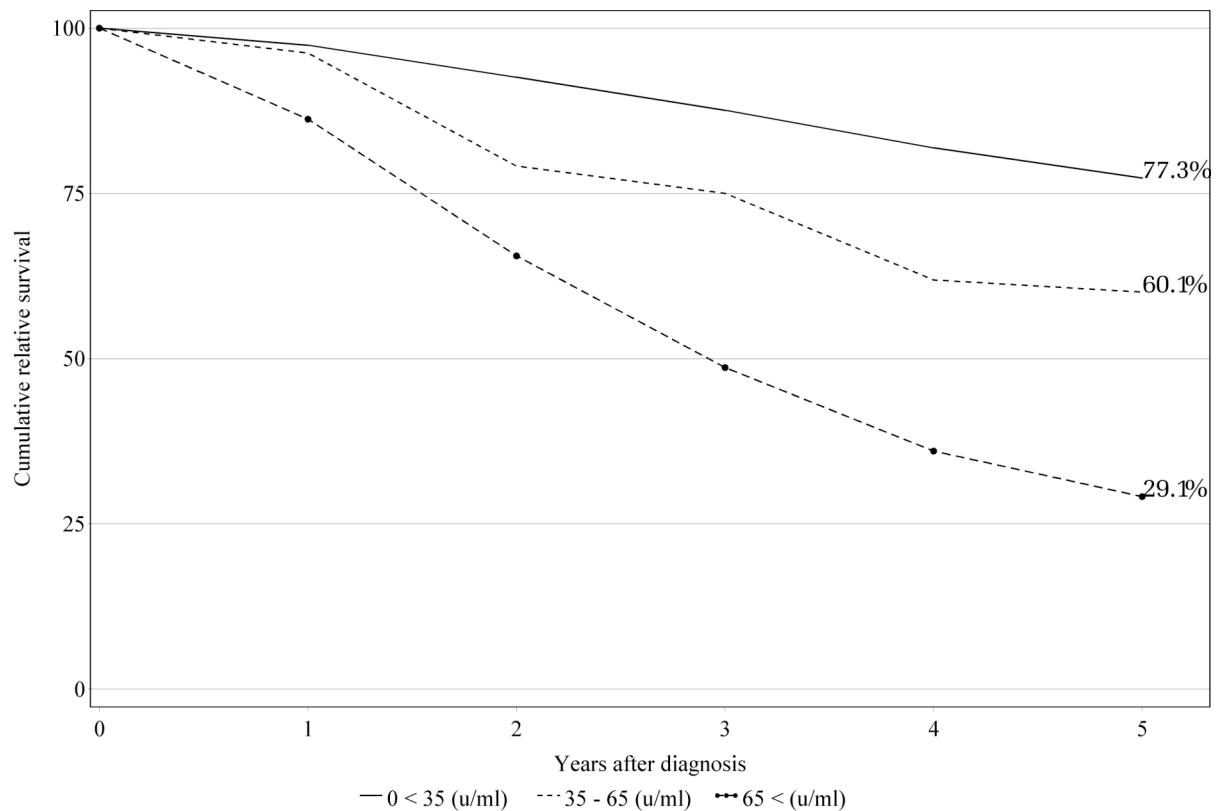
Figure 20. Relative 5-year survival according to CA-125 values with available data (n=735) in patients receiving chemotherapy in Period 2.

In the multivariate analysis, where existing CA-125 values were included, CA-125 >65 U/ ml was found to be an independent prognostic variable together with stage, age, and residual disease in both Periods 1 and 2, with hazard ratios of 2.0 and 1.5, respectively (**Papers II** and **III,** Table 6 in both papers). We examined CA-125 according to stage (**Table 10**) and found 2/3 of patients in stage I (of those with existing values) to have CA-125 values <35U/ml; 60% of patients in stage III and over 80% in stage IV had CA-125 values >65U/ml.

Table 10. CA-125 related to stage in all treated patients (n=596) in Period 1 (1993-1998).

| | STAGE | | | | |
Ca-125	I	II	III	IV	Total
<35 U/ml	56	26	43	2	127
35-65	13	17	41	5	76
>65	14	11	129	34	188
No value	48	28	104	25	205
Total	131	82	317	66	596

The clinical role of CA-125 as a diagnostic marker and a prognostic tool has developed over the past two decades. It is clear that CA-125 still remains the most important tumor marker. Research confirms its value in screening (83), and its clinical implications both in differentiating between benign and malignant ovarian tumors (74, 75) and in monitoring regression and progression (195, 230). Mostly it has been evaluated as a preoperative PF and found to be of prognostic significance with different cut-off limits (163, 194, 231). In early stage disease the results are more conflicting concerning its value as a PF (232, 233), and it is well known that many early stage tumors do not exhibit raised values of CA-125.

Postoperatively measured CA-125 has not been so well examined as a PF. There is an early report from Norway that, like our study, found postoperative CA-125 values >65 U/ml to be of independent prognostic value in their multivariate analysis (161).Two more recent studies of postoperatively measured CA-125 gave conflicting results. One study (234) found postoperative prechemotherapy treatment levels to be of no significance as PF, whereas a French multi-center study (235) found postoperative prechemotherapy values of CA-125 to be a PF in univariate, but not multivariate, analysis. However, they did find CA-125 half life ($\leq$ or > 14 days) and CA-125 nadir ($\leq$20 or >20 U/ml) to be independent PFs. We did not analyze the importance of the length of time from surgery to CA-125 analysis, but excluded cases where the blood sample was not taken in conjunction with the first chemotherapy course. There are studies showing no importance of the time factor between surgery and chemotherapy as a PF (137-139).

Survival was significantly related to **ploidy** in both periods of the study. We used a strict definition for diploidy with a single DNA-index (DI) of 1.00 and for aneuploidy with a DI of <0.98, >1.03–1.92, and >2.06. Tetraploidy was defined as 1.92–2.06 with only a few cases found. The 30% of tumors with no result in ploidy status was due to technical problems in the laboratory as well as missing specimens from the surgeons; these samples are considered missing at random.

Among those treated with chemotherapy, the percentage of tumors that could be evaluated was 69.7% in Period 1 and 69.5% in Period 2. For Period 1 the 5-year RS rate was 57.6% in women with diploid tumors and 31.6% with aneuploid tumors (P<0.001, **Paper II**). In the univariate Cox analysis it was a PF in both periods, but it was not a PF in the multivariate analysis in either period. Aneuploidy was stage-related, with a higher percentage in tumors of higher stages, from 51.2% in stage I to 84.5% in stage IV in Period 2 (**Paper III**). Even in the subgroup analysis of stage IIIA-IIIC, there were more aneuploid tumors in higher stages (P<0.04, **Paper III**).

When ploidy status was related to grade (**Table 11**) it was found that there were only 10% aneuploid tumors in grade 1 and that the majority of aneuploid tumors were, not surprisingly, found in grades 2 and 3.

In the late 1980s some prospectively designed studies found that aneuploidy was independently associated with a worse prognosis (236, 237). However, other studies could not confirm these observations (238, 239). Later prospective studies of early-stage high-risk EOC (223), as well as of advanced disease, have found ploidy status to be an independent PF (159). Possible explanations for the variation in the results could include differences in material and laboratory methods and sample sizes that are often too small for multivariate analysis. The time factor from surgery to the laboratory in fresh frozen tumors could also be important for the quality of the analysis.

Heterogeneity within the tumor is high in EOC and so, for this reason, is the need for multiple sampling (240).

Table 11. Ploidy status according to grade in all EOC tumors (with existing values) in Period 1 (1993-1998). NA= not applicable.

Ploidy status	Grade High	Moderate	Low	Undiff.	NA	Total
Aneuploid	33	100	160	23	2	318
Diploid	49	39	40	9	1	138
No value	39	66	99	18	4	226
Total	121	205	299	50	7	682

Comparing Survival, Stage IIB-IV (Periods 1 and 2), Papers I, II, and III.

The 5-year RS rates of all patients of Period 1 (N=682) and Period 2 (N= 976) were 46.1% (95% CI 42.1-50.3; **Paper I**) and 48.8% (95% CI 45.2-52.4; **Paper III**). For stage I-IIA treated with single-agent carboplatin in Periods 1 and 2, the 5-year RS rates were 81.9% (95% CI 73.5-88.6) and 87.1% (95% CI 80.1-92.6), respectively, **Figure 21**. In **Paper III** we compared the 5-year RS rates of two cohorts receiving different chemotherapy in the two periods. In Table 6 (page 49) we give the 5-year RS rates for each period for all patients and for those treated with chemotherapy. In stage III, containing around 50% of the cases, there was about 7% to 8% higher survival in Period 1 for all patients, as well as those treated with chemotherapy, compared with Period 2.
In Period 1, 396 patients with stage IIB-IV tumors were treated with Parafac (carboplatin+cyclophosphamide +epirubicin) and the 5-year RS rate of these was 34.3% (95% CI 29.5-39.3). In Period 2, there were 530 patients treated with Paratax (carboplatin+paclitaxel) and their 5-year RS rate was 33.3% (95% CI 28.8-38.0), **Figure 21**. The median PFS for those treated with chemotherapy was 19 months (95% CI 17-22) for Period 1 and 18 months (95% CI 17-20) for Period 2 (**Paper II** and **III**).
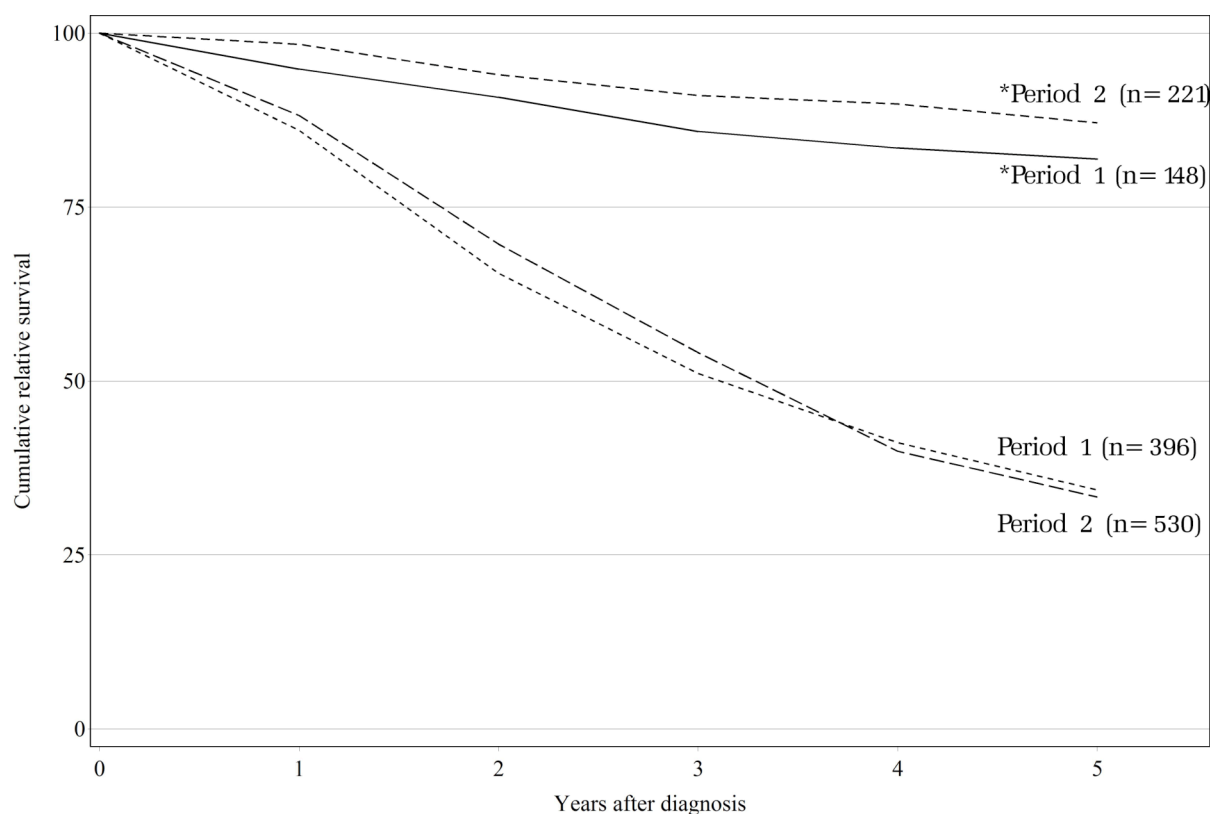
Figure 21. Relative 5-year survival for both periods. In the top of the figure Stage I-IIA carboplatin treated in Period 2 (87.1%) and Period 1 (81.9%). In the bottom in figure stage IIB-IV treated with Parafac in Period 1, (34.3%) and Paratax in Period 2, (33.3%).

A highly interesting comparison to make is that of patients in advanced stages (IIB-IV) who received the two different combinations of chemotherapy. The 5-year RS rates were similar in the two periods for those treated with chemotherapy in stage IIB-IV: 34.3% with Parafac (Period 1) and 33.3% with Paratax (Period 2), Figure 21 **(Paper III**, Figure 4). The median PFS for those treated with chemotherapy in stage IIB-IV was also almost identical: 19 months and 18 months in Periods 1 and 2, respectively (**Paper II** and **III**). The comparisons of different survival rates and percentage of patients treated with chemotherapy are shown in **Table 12**. There were 12.6% of all the patients in both periods who had no chemotherapy; of these, including the slightly over 3% of women considered low risk. As mentioned earlier, the stage distribution was different in the two periods. However, as seen in Table 12, there was only 2.4% difference (79.5% versus 77.1% in Periods 1 and 2, respectively) among those patients of stage IIB-IV who received the different chemotherapies. The stage distributions could possibly also have been altered by different diagnostic procedures over time.

Another factor that could influence the survival, except the treatment, is the age of the patients. We examined the age distribution between the two periods of patients in stages IIB and IV, that actually got the different chemotherapy combinations and found a slight difference, with a somewhat higher mean age in Period 2 (mean age Period 1: 61.7 years [95% CI 60.5-62.9], and mean age Period 2: 63.0 years [95% CI 62.1-64.0]), however this difference was not statistically significant (P=0.08) **Figure 22.**

It seems that the slight improvement in the total 5-year RS seen in Period 2 is attributable to the group of patients with early-stage disease, who had chemotherapy treatment with single-agent carboplatin (5-year RS rates of 87.1% and 81.9%, Periods 1 and 2, respectively), and maybe also to a lesser degree to stage IV patients.

Table 12. Comparison between Periods 1 and 2 concerning survival and chemotherapy treatment. RS = relative survival, PFS=progression-free survival, Parafac=carboplatin+cyclophosphamide+epirubicin, Paratax=paclitaxel+carboplatin.

	Period 1	Period 2
5-year RS, all	46.2% (CI 42.1-50.3)	48.8% (CI 45.2-52.4)
5-year RS, treated	47.2% (CI 42.8-50.3)	50.4% (CI 46.4-54.3)
Stage I-IIA, treated with	81.9% (CI 73.5-88.6) carboplatin	87.1% (CI 80.1-92.6) carboplatin
Stage IIB-IV treated with	34.3% (CI 29.5-39.3) Parafac	33.3% (CI 28.8-38.0) Paratax
Median PFS Stage IIB-IV	19 months (CI 17-22)	18 months (CI 17-20)
Median RS, all	52 months (CI 44-63)	56 months (CI 48-65)
Median RS, treated	54 months (CI 47-65)	60 months (CI 52-73)
No chemo-therapy	86/682 = 12.6%	123/976 = 12.6%
Low risk	21/682 = 3.1%	35/976 = 3.6%
Chemotherapy given to	Parafac	Paratax
stage IIB-IV	396/498 = 79.5%	530/687 = 77.1%
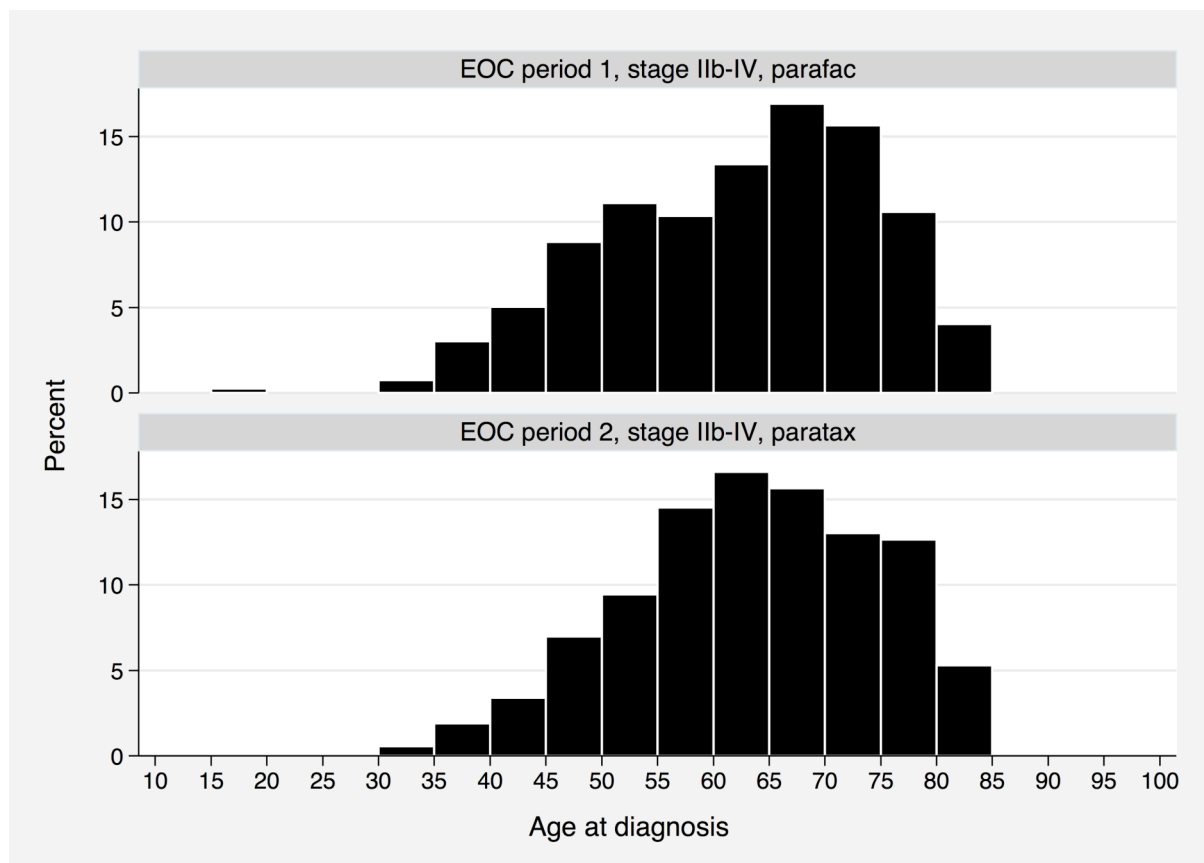
Figure 22. Age distribution of EOC patients with tumors of stage IIB-IV that were treated with Parafac (carboplatin+epirubicin+cyclophosphamide) during Period 1 and Paratax (carboplatin + paclitaxel) during Period 2. Median age Period 1: 63 (18-84) and median age Period 2: 63 (30-85). Mean age Period 1: 61.7 years (95% CI 60.5-62.9), n=396 and mean age Period 2: 63.0 years (95% CI 62.1-64.0), n=530. *P*=0.08.

In **Table 13** we give the results of the most important trials comparing paclitaxel/platinum compounds with platinum-based control treatment. As seen in Table 13, the GOG-111 (129) and the OV-10 (130) trials show better results for the paclitaxel/carboplatin treatment in both PFS and OS. Both these studies used the same combination of cyclophosphamide and cisplatin (CP) as a control arm. The GOG-132 (131) and the ICON 3 (132) trials showed no superiority of the paclitaxel/cisplatin or paclitaxel/carboplatin research arms. The largest study, the ICON3, is actually two studies combined, one using single-agent carboplatin and the other using CAP (cyclophosphamide+doxorubicin+cisplatin) as the control arm. Explanations offered for the heterogeneity in the results of these trials discuss the extent and timing of cross-over to taxanes in the control group, differences in the type of patients included, and less effective control arms in the taxane-positive trials. Obviously more patients crossed over in the two negative studies for the paclitaxel combination, and the ICON 3 study included 118 patients in stage I-II. However, that study is by far the largest, with 2074 patients included.

A thorough analysis of these four trials is made by Sandercock et al (133). They found that the heterogeneity between groups was not substantially greater than within the groups for PFS and OS, concerning the extent of crossover, the type of patients included, and the research arms. Concerning the control arms, they are of another opinion. In ICON 3 there were two control arms that had been shown to be equivalent in the earlier ICON 2 trial (CAP vs. single-

agent carboplatin) (128). The GOG-132 used cisplatin in the control arm and there is substantial evidence that carboplatin is equivalent to cisplatin both as single-agent and in combination regimens (127).The control arms in GOG111 and OV-10 were the same, namely CP. There is no evidence from a randomized trial to show that these control arms are comparable to the control arms of ICON3 and GOG132. However, there is indirect evidence from meta-analyses (126, 127) that supports the hypothesis that the control arms in GOG111 and OV10 may have been less effective than the control arms in GOG132 and ICON3. Thus, Sandercock et al claim, the difference in the results lies in the less effective control arms in GOG-111 and OV-10. The question of whether the control arm in the first of these trials would be effective enough was in fact raised even before the results of the other trials were known.

It is interesting to notice that the median PFS of these four trials of mostly stage III and IV EOC varies between 11.2 to 18 months as compared to our median PFS of 18 to 19 months in the two periods of our chemotherapy-treated stage IIB-IV patients (Table 13**)**. One control arm in the ICON-3 study included doxorubicin (compared to epirubicin in our Parafac treatment) and this study also gave PFS of 17 months, similar to our results for the Parafac and Paratax treatments (Table 13). We acknowledge that our studies are not randomized, that they took place over two different time periods, and that there were slight differences in stage distributions. However, this was a non-selected population-based study including all patients with complete long-term follow-up. The strength of our study is that the populations in both periods are complete and show similar mean and median ages. The percentage of treated patients with stage IIB-IV disease is also similar and distribution of grade and histopathology are reasonably comparable. Furthermore, the proportion of patients that were not treated with chemotherapy was the same (12.6%) for the two periods (Table 12). Another advantage of the study is that there is a centralized histopathologic review, with only a few specialized pathologists reviewing all the cases. The studies conducted with the data from OC can be considered "real world trials," since they included all patients in one geographical region, with participating centers working within strict guidelines but—as in unblended randomized trials—unbiased to possible treatment effects.

It is possible that the different number of cycles of chemotherapy have influenced the results. During Period 1 the Parafac treatment was given for 8 courses if complete response was seen at gynecological examination under anesthesia in conjunction with chemotherapy cycle number 6, whereas during Period 2 it was routine to only give 6 courses. There are, however, studies showing no difference in survival between 6 and 12 courses (241) or between 5 and 8 courses (242) of chemotherapy. Data on second or third line therapies were not available in the prospectively collected database and the extent of that could not be evaluated.

A drawback of our study is of course, that quality of life aspects and toxicity assessments were not included. It is well reported that taxanes have a high degree of neurotoxicity that could be long-lasting and leave women with severe problems (243, 244). Taking into account the higher price of the Paratax treatment compared to Parafac, we consider it important also from a health-economic point of view to do a randomized multicenter study to clarify eventual survival benefits between the two regimens.

Table 13. Important trials comparing paclitaxel/platinum combinations with other platinum-based control treatments.
* Statistically inferior result ($P< 0.001 - < 0.05$).

Trial Ref. nr.	Treatment Regimens	FIGO Stage and n	PFS	OS
			months	
GOG-111 Ref. nr 129	Paclitaxel (135 mg/m^2, 24 h+ + Cisplatin (75 mg/m^2)	III-IV 184	18	38
	Cyclophosphamide (750 mg/m^2) +Cisplatin (75 mg/m^2)	202	13*	24*
OV-10 Ref. nr 130	Paclitaxel (175 mg/m^2), 3h +Cisplatin (75 mg/m^2)	IIB-IV 342	15.5	35.6
	Cyclophosphamide (750 mg/m) +Cisplatin (75 mg/m^2)	338	11.5*	25.8*
GOG-132 Ref. nr 131	Paclitaxel (135 mg/m^2), 24h +Cisplatin (75 mg/m^2)	III-IV 201	14.2	26.6
	Cisplatin (100mg/m^2)	200	16.4	30.2
	Paclitaxel (200 mg/m^2), 24h	213	11.2*	26
ICON -3 Ref. nr 132	Paclitaxel (175 mg/m^2), 24h +Carboplatin AUC 6	I-IV 478	17.3	36.1
	Carboplatin AUC 6	943	16.1	35.4
	Paclitaxel (175 mg/m^2), 3h +Carboplatin AUC 6	232	17	40
	Cyclophosphamide (750 mg/m^2) +Doxorubicin (75 mg/m^2) +Cisplatin (75 mg/m^2)	421	17	40

Borderline Tumors 1993–2004, Paper IV.
Survival, Histopathology, Surgery, Treatment and Pathogenesis

During the period studied, 1993–2004, BOTs made up 20.2% of all ovarian malignancies. The 5- and 10-year RS of all BOT patients equals 100% (**Paper IV,** Figure 2), i.e. there is no excessive death due to the disease in the population studied compared to the general population.

The median age was 55 years (**Paper IV,** Figure 1**),** which was 8 years younger than in patients with EOC. The mean age was 55.4 years. The age distribution in women with both BOT and EOC of the two periods is shown in Figure 8 (page 31) and the flowchart for patients with BOT in Figure 9 (page 32).
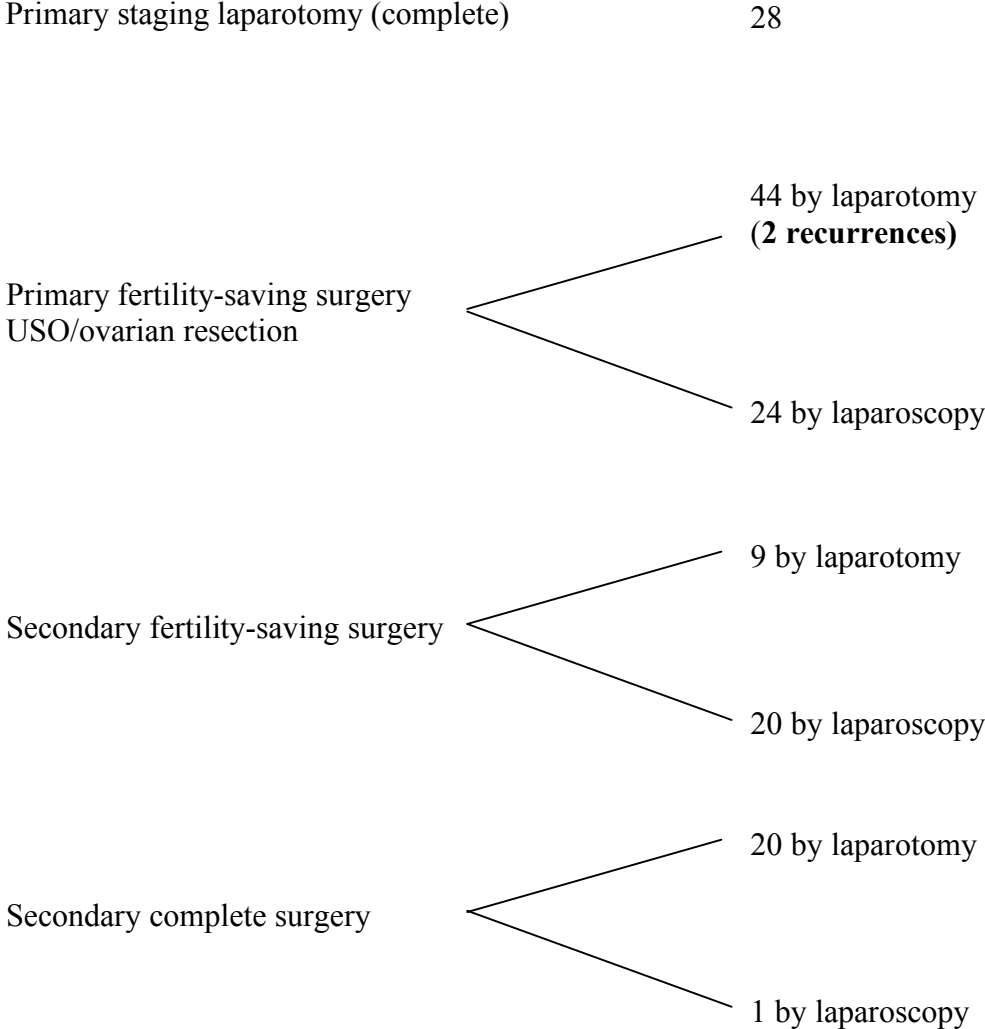
The stage, histopathology, and ploidy status are shown in Table 1, **Paper IV.** Twenty-three patients (5.8%) were in higher stages and seven of these were classified as having invasive implants.

The relation of histopathology to ploidy status is shown in Table 2, **Paper IV** and in **Table 14.** Patients over 60 years of age had more aneuploid tumors. The total amount of aneuploid tumors was 17%, and of these cases, 60 women had stage I disease. Chemotherapy was given to 18.8% of all the women. Table 14 also shows the chemotherapy given

Table 14. Stage, histopathology, FCM, and chemotherapy given to patients with BOT 1993–2004.

	number of cases n=399	%	diploid n=299 82.6 %	aneuploid n=63 17.4 %	no FCM n=37	no chemo-therapy n=324	para-platin n=61 (an)	(dip)	para-fac n=13	para-tax n=1
stage							an	dip		
IA	298	74.7	223	43	32	267	31	--	--	--
IB	38	9.5	30	7	1	32	6	- - --	--	--
IC	40	10.0	30	10	--	21	8	11	--	--
total	**376**	**94.2**	**283**	**60**	**33**	**320**	**45**	**11**	**0**	**0**
IIA	1	0.2	1	--	--	1	--		--	--
IIB	7	1.8	5	1	1	1	3		3	--
IIC	3	0.8	3	--	--	--	2		1	--
total	**11**	**2.8**	**9**	**1**	**1**	**2**	**5**		**4**	**--**
IIIA	7	1.8	4	2	1	1	--		5	1
IIIB	2	0.5	2	--	--	--	--		2	--
IIIC	3	0.7	1	--	2	1	--		2	--
total	**12**	**3.0**	**7**	**2**	**3**	**2**	**--**		**9**	**1**
Histo-pathology										
serous	219	54.9	167	27	25					
mucinous	171	42.9	127	32	12					
endometroid	5	1.2	3	2	--					
clearcell	1	0.2	---	1	--					
mixed	3	0.8	2	1	--					
total	**399**	**100**	**299**	**63**	**37**					

The type of surgery performed on women under 45 years, including fertility-saving surgery, is shown in **Figure 23**. Around 70% of this age group was treated with conservative surgery.

Primary staging laparotomy (complete)   28

Primary fertility-saving surgery
USO/ovarian resection

44 by laparotomy
(**2 recurrences**)

24 by laparoscopy

Secondary fertility-saving surgery

9 by laparotomy

20 by laparoscopy

Secondary complete surgery

20 by laparotomy

1 by laparoscopy

Pregnant at primary surgery = 5 (spontaneous abortion 2).
Children born during follow-up = 21.

Figure 23. Type of surgery, recurrences, and future fertility in women <45 years with BOT (n=96). USO = unilateral salpingo-oophorectomy.

A total of 36 women with BOT died during the follow-up period. Three women were classified as dying of the disease (0.75%), and all of them had mucinous tumors. The stage, histology, plody status, eventual chemotherapy, and time to recurrence or death are shown in **Table 15.** Of the three women who died of the disease, two were in stage IA. On of these women in stage 1A had an aneuploid tumor and was treated with chemotherapy. She developed a surgically confirmed, highly malignant transformation, and her primary tumor

was re-evaluated as a mucinous BOT, stage IA. The other had a diploid tumor and died of an ileus with a strangulation of the sigmoid colon with no confirmed association to her tumor disease; unfortunately, autopsy was not performed. The third woman had a widespread stage IIIC tumor with no FCM analyzed. She had no chemotherapy because of high age and poor general condition. The three women who died did so within 1.5 years of primary surgery.

Five other patients had a recurrence, for a total combined recurrence and death rate of 2.0%. Two women with fertility-preserving surgery (both with unilateral salpingo-oophorectomy and one also with resection of the other ovary) had a recurrence in the preserved ovary around two years after the primary surgery. They were both reoperated with contralateral salpingo-oophorectomy and were alive with no evidence of disease (NED) at the end of follow-up (Table 15). Of the other three women who had a recurrence, all were reoperated; two developed an invasive low-grade carcinoma (alive with disease = AWD) and the third, another BOT (alive with NED).

Table 15. BOT patients with recurrence or death (n=8). Alive with disease (AWD), dead of disease (DOD), no evidence of disease (NED). Stage, histology, ploidy status of patients.

_____

1. Stage IA, serous, aneuploid. Had chemotherapy, recurrence after 9.5 years with invasive tumor, reoperated , AWD**.**
2. Stage IA, mucinous, diploid. No chemotherapy. Recurred and died after 1 year and 2 months. DOD.
3.Stage IIIC, mucinous, no FCM. No chemotherapy. Died after 5 months. DOD.
4,Stage IA, serous, diploid. No chemotherapy. Recurred after 10 years. New BOT reoperated, NED.
5.Stage IA, serous, aneuploid, fertilitypreserving surgery. Had chemotherapy. Recurred after 2,5 years new BOT, reoperated, NED.
6.Stage IA, serous, diploid, fertilitypreserving surgery.No chemotherapy. Recurred after 2years 2 months new BOT, reoperated, NED.
7.Stage IA, serous, diploid. No chemotherapy. Recurred after 5 years, 4 months with invasive tumor, reoperated AWD.
8.Stage IA, mucinous, aneupoid. Had chemotherapy. Recurred after 1.5 years with invasive tumor . Reoperated, DOD.

_____

Most studies of BOTs are retrospective in their design and give only short term results. In a majority of these, 5-year survival rates of between 95% and 99% in localized disease are reported (65, 66, 245). In stage II-IV, survival rates are generally lower, especially for those with micropapillary features associated with invasive implants (64, 66). Results of 10-year RS rates in one SEER study reported 99%, 98%, 96%, and 77% in stage I, II, III, and IV, respectively (179). Another SEER study, which differentiated between serous (LMP-S) and mucinous (LMP-M) tumors, reported 10-year RS rates of 96.9% and 94.0% for LMP-S and LMP-M, respectively, for early stage disease and slightly lower rates for advanced disease: 89.9% in LMP-S vs. 85.5% in LMP-M (64).

In his extensive review of the literature on BOTs, Seidman reported only six prospective randomized studies with a mean follow-up of 6.7 years and survival of 100% (66).

The proportion of serous versus mucinous histopathology of 54.9% to 42.9% in the present study is in the same range as other large population-based reports (63, 64). As has been discussed earlier, the risk factors for BOT and invasive EOC are the same regarding parity

and lactation, but OCP use seems to provide less protection BOTs (26, 44). The mucinous type of BOT is known to have a good prognosis at early stage disease and is generally less aggressive compared to the serous tumors. All three patients classified as dying of the disease in the present study had BOT of mucinous histology. However, two of them could have had a mucinous carcinoma of the gastrointestinal tract that was overlooked at the primary surgery; it is impossible to say, since no autopsy was done and the clinical course did not contradict the possibility. This possibility has been highlighted recently in discussions about mucinous invasive EOC, as well as in mucinous BOTs (58-60). The other five recurrences in our study were all stage IA serous tumors; none of the advanced stage patients with invasive implants had a recurrence.

Our median follow-up was 7.7 years (1.6-12.6) and we saw two women recurring after 9 and 10 years. The need for long-term follow-up, especially for conservatively operated women, has previously been stressed. A recent published study on BOT with very long-term follow-up (5-31 years) followed 80 advanced serous BOTs (stage II-IV) with non-invasive implants in 73 radically operated women (246). They saw 44% recurrence, only 10% of tumors recurred within 5 years, 19% in 5 to 10 years, 10% in 10 to 15 years, and 5% after 15 years. Of 27 women who developed a low-grade carcinoma, 20 died. These figures call for an extended long-term follow-up of BOTs, and not only for higher stages, since seven of our recurrences occurred in stage I patients.

A recent report of 247 BOTs from 1991 to 2004 showed a similar distribution of stage I disease (92%) as our study, but at a lower mean age (38 years). (247). Half of these patients were radically operated with a 98% OS rate and recurrence in only 6 patients (2.4%), with no difference between unstaged or radically operated patients. Only 5% of their cases received adjuvant chemotherapy, compared with 18.8% in our study. Three women (1.5%) died of an invasive ovarian/peritoneal carcinoma. Collectively, these results are similar to those of the present study.

In the past, a staging operation including total abdominal hysterectomy and bilateral salpingo-oophorectomy was recommended for BOTs, but in recent years a more conservative, fertility-saving surgery has proved to be safe in women of childbearing age. Reported recurrence rates vary widely, from a low of zero to as high as 30%. Most recurrences involve a second BOT, most often after ovarian cystectomy, and seldom develop into a progressive malignant disease (86, 88, 248, 249). In a study from 1982 to 2004 with a long-term follow-up of conservatively-operated women, 11% recurrence was reported; two patients developed malignant disease and one of these died (250).

Almost three quarters of women under 45years of age (70.8%) in our study were operated with fertility-saving surgery; there were two recurrences, both with a new BOT in the contra-lateral adnexae (Figure 23). This gave a recurrence rate of only 2.9% (2/68), a number important to bear in mind when counseling fertile women before surgery. The question of whether or not to do a radical operation later on is still unsolved. Most reports of conservative surgery report recurrences of another BOT that is successfully treated with a repeat surgery. Malignant transformation with a poor outcome is rare and could occur in patients even after radical surgery (180, 248, 250).

What is most interesting is the new pathogenesis of ovarian cancers developed by pathologists in the US during the last decade. Based on clinicopathological, molecular, and genetic studies they propose a new model for ovarian tumor progression, including BOTs (46, 48, 49). They describe two different pathways: the low-grade pathway (Type I), where slowly growing tumors develop along with serous BOTs; and the high-grade pathway (Type II), where conventional high-grade serous carcinoma develops more aggressively, mostly directly from the ovarian surface epithelium or inclusion cysts. They propose a stepwise progression from

benign serous cystadenoma, through proliferative tumor (atypical proliferative serous tumor = APST), to non-invasive carcinoma (non-invasive micropapillary serous carcinoma = MPSC), ending with invasive low-grade serous carcinoma (invasive MPSC) **(Figure 24).** Their model explains the outstanding survival rates in most reports of early stage BOTs and the bad prognosis associated with MPSCs with invasive implants. They also argue that the BOT classification outlined by the WHO in 1973 should be abandoned and replaced by APST and that non-invasive MPSC should be regarded as *in situ* tumors. MPSC with invasive implants should, they recommend, be referred to as low-grade carcinomas, not as BOTs (67). However, this is controversial and other pathologists want to maintain the traditional classification (251). Longacre found, in a meticulous study of the histopathology of 273 serous BOTs, that micropapillary features, invasive implants and stromal microinvasion were each predictive of decreased OS on univariate analysis; however on multivariate analysis only stromal microinvasion was predictive of decreased OS. Moreover, he found the distinction between invasive and non-invasive implants difficult to decide and made chiefly on the basis of volume in most reports (65). That could perhaps explain why the invasive implants in our study were not an indicator of poor survival.

Low-grade pathway (Type I)
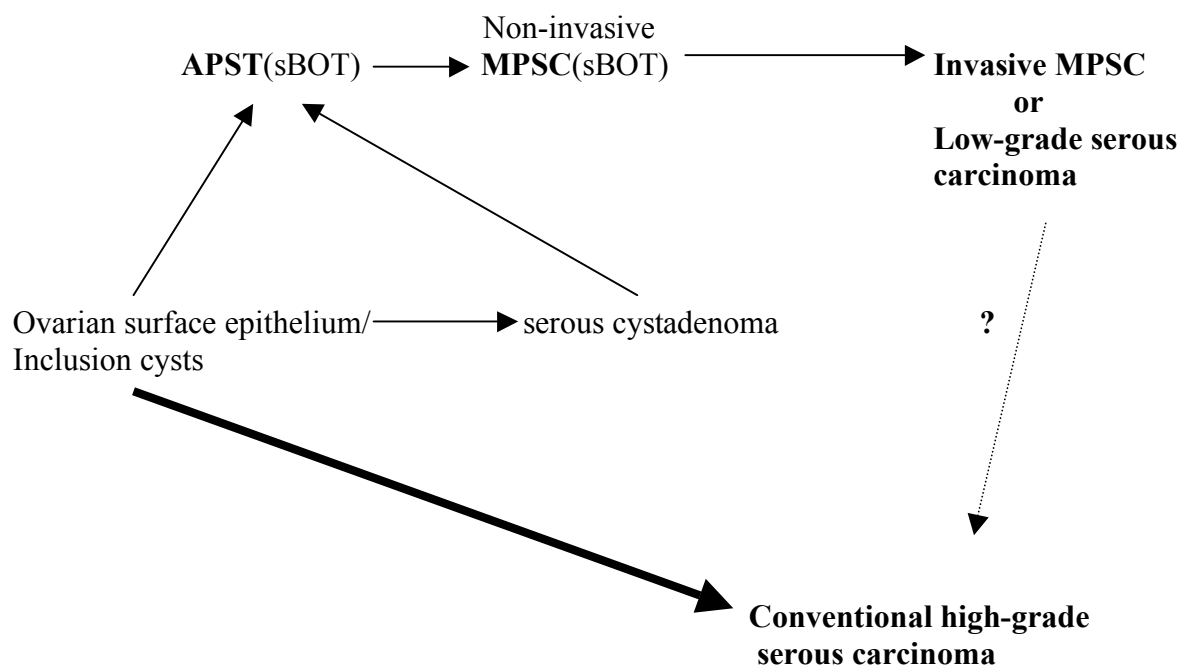
High-grade pathway (Type II)

Figure 24. Schematic model of the stepwise development of low-grade carcinoma from serous BOTs (sBOT) as a precursor, and the more direct high-grade pathway to the conventional aggressive serous carcinoma. APST = atypical proliferative serous tumor, MPSC = micropapillary serous carcinoma. Modified after Shih and Kurman (46).

When we set up the guidelines for treating BOTs in 1993, we were probably influenced by studies of aneuploidy as an important prognostic factor for decreased survival, especially reports from Norway indicating a 19-fold increased risk of mortality in patients with aneuploidy compared to patients with diploid BOTs (252, 253). However, other reports do not confirm the finding of decreased survival with aneuploid tumors (254, 255). The total proportion of aneuploid tumors (17.4%) in our study was no higher in advanced stage than in early stage. In stage I, 60 patients had aneuploid tumors and 45 of these were given chemotherapy along with 11 patiens in stage IC with diploid tumors, for a total of 14.9% (Table 14). Of the women who had a recurrence, three had aneuploid tumors and two of those had been given chemotherapy. There are no prospective studies proving enhanced results for treating BOTs with chemotherapy, neither with nor without using ploidy status as a mode of selecting cases to therapy. Most authorities do not recommend chemotherapy to treat BOT since there are no convincing results of its effect even at higher stages (134, 256-259).

In most BOT studies, as in ours, the proportion of recurrences are so small that conclusions cannot be drawn regarding the benefit of adjuvant chemotherapy and the eventual importance of aneuploidy as a marker for selecting patients to adjuvant therapy. Considering the outstanding survival results in women afflicted with this disease, their often young age, and their fertility wishes, I am of the opinion that further adjuvant chemotherapy in women with BOTs should be abandoned or reserved for those with micropapillary tumors with invasive implants or with microinvasion. One must consider the complication risks of chemotherapy treatment, such as myelosuppression with risk of infection, allergic reactions, infertility, later development of another malignancy, as well as psychological and economic aspects. The total cost of chemotherapy in these cases may be impossible to foresee.

Future aspects

Early detection is the most important factor in improving survival in EOC. Screening requires a strategy that combines high sensitivity and very high specificity to give a high predictive value for a disease such as this, which is fairly rare in the general female population. A promising screening strategy for EOC includes serial CA-125 measurements and TVS, as tested in the ongoing trial of UKCTOCS in the United Kingdom with over 200 000 women, based on the algorithm developed by Skates (83). The inclusion of additional serum markers in a combined test could probably enhance the efficiency.

Future developments using proteomic analyses to detect peptides differently expressed in patients with EOC compared to healthy women could probably identify a distinctive pattern in serum (260). A panel of serum biomarkers for the detection of early stage disease has also been identified (261), as have potential biomarkers for stage III disease (262).

The most valuable tool for early diagnosis, yet to be found, would include methods to detect precursor lesions for an identification of ovarian dysplasia or carcinoma *in situ*, as is currently standard in screening for cervical cancer.

Prevention strategies, such as the use of OCP, must be highlighted (3). Intensified efforts could be made to identify carriers of BRCA-1, BRCA-2, and mismatch repair mutations with enhanced EOC risk, and to ensure they are provided with information about the benefits to their survival of prophylactic surgery.

Improved techniques in primary **surgery** to remove all visible disease and the organization of expert teams has led to improved survival in many settings (92, 95, 101, 149). These principles must be more developed. It is possible that neo-adjuvant chemotherapy before surgery can be valuable in selected cases (110).

Immunotherapy with vaccines and immunoregulation with antibodies in combination with other agents could probably be developed further; the use of anti-VEGF antibody bevacizumab has showed promising results, but like most new treatments it is costly (263).

New chemotherapeutic agents directed at specific bioligical factors of different tumors are necessary. In this regard, molecular profiling studies investigating the global mRNA expression pattern by microarray techniques and the protein expression pattern by proteomic approaches would be useful. Molecular targeting, with or without cytotoxic labelling, using drugs as well as radioisotopes could be further developed. An interesting new concept is the existence of a small population of stem cells within cancer tumors. Ovarian-cancer–initiating cells have been identified in EOC (264) and it may be possible in the future to develop therapeutic agents that specifically target these cells that are important for the continued growth of the cancer.

Quality of life aspects and the organization of treatment in EOC should also be considered more carefully.

Summary

Clinical guidelines for epithelial ovarian cancer (EOC) and borderline ovarian tumors (BOT) were introduced in western Sweden in 1993 and updated in 1998. We analyzed the prospectively recorded quality register database for two periods where different chemotherapy combinations were used in post-surgical treatment of advanced cases. Factors analyzed as potential prognostic markers were age, stage, grade, histopathology, amount of residual disease after surgery, postoperative CA-125, and ploidy status. At scheduled follow-up visits, recurrence and death was noted. Inclusion data were checked against the Swedish Cancer Register and record linkages were made to the National Population Register and the National Cause of Death Register at the National Board of Health and Welfare.

During the first period between June 1, 1993, and August 31, 1998, the 5- and 10-year relative survival (RS) rates were 46.1% and 38.4%, respectively. This was a complete cohort of 682 women with a median age of 63 years. All cases were found and no one was lost at follow-up. Survival was strongly related to FIGO stage, with 5-year RS rates of 83.5%, 61.4%, 35.4%, and 3.8% in stage I, II, III, and IV, respectively.

During the second period between September 1, 1998, and August 31, 2005, with the introduction of paclitaxel+carboplatin to advanced cases, the 5-year RS rate in all 976 women was 48.8% and the 8-year RS rate, 39.7%. The survival benefit was recognized in stage I (92.2%) and stage IV (15.7%) but there was a drop in survival in stage III (27.2%).

We compared the 5-year RS rates in those women in stage IIB-IV who were treated with carboplatin+cyclophosphamide+epirubicin during the first period with carboplatin+paclitaxel in the second period and found no differences; 34.3% (Period 1) and 33.2% (Period 2). The progression-free survival (PFS) was also similar, 19 versus 18 months. The age distribution, the percentage of women in stage IIB-IV, the percentage of untreated cases, the grade, and histopathology were fairly similar in the two periods.

A randomized study, also including toxicity and quality of life aspects, comparing the two regimens in an unselected population would clarify whether paclitaxel is of further benefit to women with advanced EOC.

Univariate and multivariate Cox regression analyses for prognostic factors (PF) were used to study possible PFs for the populations of both periods. Univariate analysis identified age, stage, grade, serous histopathology, residual disease after surgery, post-operative CA-125, and ploidy status as prognostic variables. In the multivariate analysis only age, stage, residual disease, and postoperative CA-125 were recognized as independent prognostic variables in both periods, whereas grade only was a PF when grade 2 and 3 were grouped together versus grade 1.

The whole cohort of 399 women with BOTs from 1993 to 2004 was identified and had a median age of 55 years (range 16-90). The median follow-up duration was 7.7 years (1.6-12.6). The 5- and 10-year RS reached 100% for this cohort. Only 5.8% were in higher stages and the distribution of serous versus mucinous tumors was different from the EOC group, with more mucinous tumors in BOTs. Women with aneuploid tumors (17.4%) were treated with chemotherapy even in stage I. Three women died of the disease; all had mucinous tumors, but two were not confirmed to be related to the BOT. Five other women had a recurrence, and of these, three are still alive with no evidence of disease after complimentary surgery. Fertility-saving conservative surgery was performed in 70% of women under 45 years of age. Two of these were among the recurrences and were re-operated on the contra-

lateral ovary; they are both alive with no evidence of disease. Conservative surgery seems appropriate in younger women. It is also suggested that chemotherapy is unjustified for women with BOTs, considering the risk of complications, women's eventual fertility wishes, and the general good prognosis for these women without the adjuvant treatment.

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Appendix 1.

Period 1 1993-1998.

Administration of carboplatin (according to Calvert) **cyklophosphamide, epirubicin**.
500 ml NaCl for free IV route.
Premedication:
Inj. Decadron 24 mg i.v.
Antiemetics according to ordination
Carboplatin 5x(GFR+25) mg in 500 ml NaCl i.v. during 1 hour.
Epirubicin 50 mg /m^2 in 100 ml NaCl in 10 min.
Cyclophosphamide 400 mg /m^2 in 500 ml NaCl in 30 min.
Every 4th week.
Dose reduction:

LPK (10^9/l)		TPK(10^9/l)		Dose % of previous		
Day 1	nadir	Day 1	nadir	Carbo	Cyklo	Epi
≥3	≥2	≥100	≥75	120	100	100
≥3	1.0-1.9	≥100	50-74	100	100	100
≥3	<1	≥100	25-49	75	75	100
≥3	<1	≥100	<25	50	50	50
<3		<100		1 week delay		

Administration of single-agent carboplatin.
Carboplatin 7x(GFR+25) i.v. in 500ml NaCl during 60 min.
Every 4th week
Antiemetics according to ordination.
Dose reduction:

LPK (10^9/l)		TPK (10^9/l)		Dose % of previous
Day 1	nadir	Day 1	nadir	
≥3	≥3	≥100	≥100	120
≥3	>2	≥100	> 75	100
2.5-3	1-2	≥100	50-75	75
2-2.4	<1	75-100	<50	50
<2		<75		1 week delay

Period 2 1998-2005. **Administration of paclitaxel and carboplatin**.
250 ml NaCl for assurance of free i.v. route
Premedication:
Klemastin 2 mg in 100 ml NaCl during 10 min. 50 min. before Paclitaxel infusion.
Cimetidin 300 mg in 100 ml NaCl during 10 min. 40 min.before Paclitaxel infusion
Inj. Decadron 24 mg i.v. 30 min. before Paclitaxel infusion
Paclitaxel 175mg/m^2 in 500 ml NaCL i.v. during 3 hours.
Antiemetics according to ordination
Carboplatin 5x(GFR+25) in 500 ml NaCL during 30 min.
Every 3rd week.
Dose reduction:

LPK (10^9/l)		TPK(10^9/l)		Dose % of previous	
Day 1	nadir	Day 1	nadir	Paclitaxel	Carboplatin
≥ 3	≥ 1	≥ 100	≥ 50	100	100
≥ 3	< 1	≥ 100	< 50	80	80
< 3		< 100		1 week delay	

Administration of single-agent carboplatin
Antiemetics according to ordination
Carboplatin 7x(GFR+25) or 300-350 mg/m^2 in 500 ml NaCl during 30 min.
Every 4th week.
Dose reduction:

LPK (10^9/l)		TPK (10^9/l)		Dose % of previous
Day 1	nadir	Day 1	nadir	
≥ 3	≥ 2	≥ 100	≥ 75	120
≥ 3	1.0-1.9	≥ 100	50-74	100
≥ 3	<1	≥ 100	25-49	75
≥ 3	<1	≥ 100	<25	50
<3		<100		1 week delay

Second or third line therapy at recurrence was not properly recorded in the database.
However, in the earlier years of Period 1 most patients were treated with single-agent carboplatin. In the last part of Period 1 we also introduced paclitaxel, especially in a study, where patients were randomized to paclitaxel 1 week versus paclitaxel every 3rd week.

In Period 2 (1998-2005) we decided whether recurrence was of a platinol-resistant character (within 6 months) or not. In platinol-resistant cases we gave paclitaxel, topotecan, or gemcitabin.
If it was considered a non-platinol resistant recurrence (after 6 months) we often gave single-agent carboplatin or carboplatin+paclitaxel once again. In cases of severe neurotoxicity we gave topotecan, gemcitabin, or docetaxel.