OPERATIVE TREATMENT OF OVARIAN CANCER AND BORDERLINE TUMORS IN DIFFERENT HOSPITAL CATEGORIES IN FINLAND

by

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ACADEMIC DISSERTATION

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ABSTRACT

Operative treatment of ovarian cancer and borderline tumors in different hospital categories in Finland

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Surgery is the cornerstone of ovarian cancer treatment and maximal cytoreduction is important. In the early 1980's primary surgical treatment of ovarian cancer was performed in over 80 hospitals in Finland. The significance of the operative volume of the hospital, of the training of the surgeons and of centralization of surgical treatment has been widely discussed. The aim of the present study was to evaluate the outcome of surgical treatment of ovarian cancer in different hospital categories retrospectively and prospectively, and to analyze if any differences are reflected in survival.

The retrospective study included 3851 ovarian cancer patients operated between 1983 and 1994 in Finland. The data was analyzed according to hospital category (university, central, and other) and by quartiles of the hospital operative volume. The results showed that patients operated in the highest operative volume hospitals had the best relative survival. When stratifying the analysis by the period of diagnosis (1983-1988 and 1989-1994), the university hospitals improved their performance the most.

The prospective part of the thesis was initiated in 1999 and included 307 patients with invasive ovarian cancer and 65 patients with an ovarian borderline tumor. The baseline and 5-year surveys used a questionnaire that was filled in by the operating surgeons. For analysis of the 5-year follow-up data, the hospitals were divided into three categories (<10, 10-20, or >20 patients operated in 1999). The effect of the surgical volume was analyzed also as a continuous variable (1-47 operations per year).

In university hospitals, pelvic lymphadenectomy was performed in 88 %, and para-aortic lymphadenectomy in 73 %, of the patients with stage I disease. The corresponding figures ranged from 11 % to 21 % in the other hospitals. For stage III ovarian cancer patients operated by gynecological oncologists, the estimated odds ratio for no macroscopic residual tumor was 3.0 times higher (95 % CI 1.2-7.5) than for those operated by general gynecologists. In the university and other hospitals 82% of the patients received platinum-based chemotherapy. Platinum + taxane combination was given to 63 % of the patients in the university and in 49 % in the other hospitals ($p = 0.0763$). Only a minority of the patients with tumors of borderline malignancy were staged according to recommendations, most often multiple peritoneal biopsies and omentectomy were neglected.

FIGO stage, patient age, and residual tumor were independent prognostic factors of cancer-specific 5-year survival. A higher hospital operative volume was also a significant prognostic factor for better cancer-specific survival ($p = 0.036$) and disease-free survival ($p = 0.048$).

In conclusion, ovarian cancer patients operated in high-volume university hospitals were more often optimally debulked and had a significantly better cancer-specific survival than patients operated in other hospitals. These results favor centralization of primary surgical treatment of ovarian cancer.

Key words: Ovarian cancer, borderline tumor, surgical treatment, survival rate, hospital volume, hospital category, operating surgeon, staging, residual disease

TIIVISTELMÄ

Munasarjasyövän ja borderline tuumoreiden leikkaushoito eri sairaalaluokissa Suomessa

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Kirurginen hoito on munasarjasyövän hoidon kulmakivi ja jäännöskasvaimen kokoa pidetään vakiintuneena ennustetekijänä. Munasarjasyöpäleikkauksia suoritettiin yli 80:ssä eri sairaalassa Suomessa 1980-luvun alkupuolella. Sairaaloiden leikkausmäärän, leikkaavan lääkärin koulutuksen sekä kirurgisen hoidon keskittämisen merkitystä on pohdittu laajalti viime vuosina. Tutkimuksen tarkoituksena oli arvioida munasarjasyövän kirurgisen hoidon toteutusta eri sairaaloissa sekä retrospektiivisesti, että prospektiivisesti. Lisäksi analysoitiin, heijastuvatko kirurgisen hoidon erot elossaololukuihin.

Retrospektiivinen työ koostui 3851:stä vuosina 1983 - 1994 leikatusta munasarjasyöpäpotilaasta Suomessa. Aineistoa käsiteltäessä sairaalat luokiteltiin yliopistollisiin-, keskus- ja muihin sairaaloihin sekä sairaaloiden leikkausmäärää kuvaaviin kvartiileihin. Tutkimuksen tulokset osoittivat, että niillä potilailla, jotka leikattiin suurimman leikkausmäärän omaavissa sairaaloissa, oli korkeimmat elossaololuvut. Kun analysoitiin ajanjakson vaikutusta tuloksiin jakamalla tutkimusaika kahtia (1983-1988 ja 1989-1994), hoitotulosten todettiin parantuneen eniten yliopistosairaaloissa.

Prospektiivinen tutkimus sai alkunsa vuonna 1999 ja koostui invasiivisen munasarjasyövän vuoksi leikatusta 307 potilaasta sekä 65 borderline-tuumorin vuoksi leikatusta potilaasta. Sekä peruskartoitus, että viiden vuoden seurantatutkimus tehtiin leikanneen lääkärin täyttämän kyselykaavakkeen tietojen pohjalta. Viiden vuoden seurantatutkimuksessa sairaalat jaettiin kolmeen ryhmään leikkausmäärän mukaisesti (<10, 10-20, >20 leikkausta vuonna 1999). Vuosittaista leikkausmäärää tutkittiin myös jatkuvana muuttujana (1-47 leikkausta/vuosi).

Yliopistollisissa sairaaloissa pelvinen imusolmukkeiden poisto suoritettiin 88 %:lle ja para-aortaalialueen imusolmukkeiden poisto 73 %:lle levinneisyysasteen I potilaista. Vastaavat prosenttiluvut muissa sairaaloissa vaihtelivat välillä 11-21 %. Gynekologisen onkologin leikkaamalla levinnäisyysasteen III potilaalla oli kolme kertaa suurempi (95 % CI 1.2-7.5) todennäköisyys päästä makroskooppisesti tautivapaaksi ensimmäisessä leikkauksessa kuin yleisgynekologin leikkaamalla potilaalla. Yliopisto- ja muissa sairaaloissa 82% potilaista sai platina-pohjaista solunsalpaajahoitoa. Platina + taksaani -yhdistelmähoitoa annettiin 63 %:lle potilaista yliopistosairaaloissa ja 49 %:lle potilaista muissa sairaaloissa ($p = 0.076$). Vain pienelle osalle borderline-tuumoria sairastavista potilaista suoritettiin asianmukainen staging-leikkaus, peritoneumbiopsioiden ja omentektomian ollessa useimmiten laiminlyötyjä toimenpiteitä.

Taudin levinneisyysaste, potilaan ikä sekä jäännöstuumorin määrä todettiin riippumattomiksi ennustetekijöiksi munasarjasyövän 5-vuoden elossaololukuihin. Sairaaloiden suuremman leikkausmäärän todettiin olevan tilastollisesti merkitsevä ennustetekijä sekä munasarjasyövän tautivapaalle ajalle ($p = 0.036$) että elossaolo-ajalle ($p = 0.048$).

Yhteenvetona voidaan sanoa, että suuremman leikkausmäärän omaavissa yliopistollisissa sairaaloissa leikatuille potilaille tehtiin useammin täydellinen kasvaimen poisto ja heillä oli merkitsevästi paremmat elossaololuvut kuin muissa sairaaloissa leikatuilla potilailla. Tuloksemme puhuvat näin ollen munasarjasyövän ensivaiheen leikkaushoidon keskittämisen puolesta.

Avainsanat: Munasarjasyöpä, borderline-tuumori, leikkaushoito, elossaololuku, sairaalan leikkausmäärä, sairaalaluokka, leikkaava lääkäri, staging, jäännöskasvain

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ABBREVIATIONS AND DEFINITIONS

CI	Confidence intervals
CSS	Cancer-specific survival
CT	Computerized tomography
DFS	Disease-free survival
DSS	Disease-specific survival
EOC	Epithelial ovarian cancer
FCR	Finnish Cancer Registry
FIGO	Fédération Internationale de Gynécologie et d'Obstétrique
GLIM	the Generalized Linear Interactive Modelling package
HR	Hazard ratio
MRI	Magnetic resonance imaging
MS	Median survival
OS	Overall survival
RMI	Risk of malignancy index
RR	Relative risk
RSR	Relative survival rates

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II. Kumpulainen S, Kuoppala T, Leminen A, Penttinen J, Puistola U, Pukkala E, Sankila R, Mäkinen J, Grénman S. Surgical treatment of ovarian cancer in different hospital categories - A prospective nation-wide study in Finland. Eur J Cancer 2006;42:388-395.

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1. INTRODUCTION

Ovarian cancer is the sixth most common cancer among women, accounting for 4 % of all female malignancies (Parkin et al. 2005). Survival of patients with epithelial ovarian cancer has improved due to new cytostatic agents and improved overall surgical skills (Barnholtz-Sloan et al. 2003, Huinink 2000), but it is the most common cause of death in gynecological cancers in the developed countries (Heintz et al. 2006, Cancer statistics for Finland 2005).

Ovarian cancer is a gynecological malignancy associated with a poor prognosis, since it is often diagnosed late (Heintz et al. 2006). Ovarian cancer does not produce any specific signs, and symptoms usually appear only after the disease has spread widely within the peritoneal cavity. There are no adequate screening methods for ovarian cancer, and two-thirds of the ovarian cancer patients have thus widespread intra-abdominal tumor dissemination at the time of diagnosis (Benedet et al. 2000, Heintz et al. 2006).

Surgery is an important for effective treatment of ovarian cancer and is also required for diagnosis and staging (Benedet et al. 2000). The purpose of the primary cytoreductive surgery is the full removal of all visible tumor before other therapy (Tropé et al. 2006). Postoperative management is based on clinical and pathologic features, e.g. stage, tumor histology and tumor grade. While the majority of the women with ovarian cancer need chemotherapy in addition to surgery, some early stage cancers are curable with surgery alone (Heinz et al. 2006). In women with advanced stage disease, optimal surgical cytoreduction is one of the most important prognostic factors (Heinz et al. 2006). Several studies suggest that the survival of patients with ovarian cancer improves if the surgery is performed by gynecological oncologists (Eisenkop et al. 1992, Earle et al. 2006, Giede et al. 2005, Kehoe et al. 1994). Attention has also recently been paid to the positive association between, on the one hand, surgeon and hospital case volume and, on the other hand, the outcome of ovarian cancer patients (Bristow et al. 2004, Hillner et al. 2000, Oberaigner et al. 2006, Tingulstad et al. 2003, Ioka et al. 2004, Goff et al. 2007). It is, consequently, important that the recommended surgical procedures are performed to obtain correct staging information, to achieve optimal cytoreduction, and to guide postoperative therapy.

Operative treatment of ovarian cancer in Finland is performed in different hospital categories having varying surgical volumes and training of the operating physicians. The present study was

performed to obtain accurate and detailed information about the quality and outcome of primary operative treatment and survival of ovarian cancer patients in different hospital categories in Finland. Special emphasis was put on the effect of the operative volume of the hospital and on the relation to subspecialty training of surgeons in gynecological oncology.

2. REVIEW OF THE LITERATURE

2.1 Invasive ovarian cancer

2.1.1 Incidence

The incidence of invasive ovarian cancer in Scandinavia is one of the highest in the world. In Finland, the age-adjusted incidence rate of ovarian cancer in 2004 was 10.3 per 100,000 women and 493 new cases of ovarian cancer and 302 deaths were attributed to ovarian cancer in 2004 (www.cancerregistry.fi). Ovarian cancer was thus the fifth most common cause of cancer death in women in Finland (www.cancerregistry.fi). The incidence of ovarian cancer is highest in the developed countries and lowest incidence in the developing countries and Japan (Parkin et al. 2005).

2.1.2 Survival

In the developed countries the 5-year survival rate of patients with ovarian cancer is currently around 50 % (Heintz et al. 2006, www.cancerregistry.fi). Although most patients have complete clinical response to surgery and first-line chemotherapy, 50 – 75 % of the patients will eventually relapse (Ozols et al. 2001). Survival depends strongly on the stage of the disease. The 5-year survival rate is 85-92 % among patients with stage Ia-Ic disease, 67 – 74 % with stage IIa-IIc disease, 33 – 50 % with stage IIIa-IIIc disease, and only 18 % with stage IV disease (Heintz et al. 2006).

2.1.3 Histology

Approximately 90 % of ovarian cancers are derived from the epithelium of the celom that normally covers the ovarian surface. This surface lining is multipotential and can differentiate into several types of epithelium, which explains why there is a wide variety of epithelial tumors in the ovaries. Epithelial tumors are classified according to cell type and are considered benign, borderline and malignant based on cellular proliferation, nuclear atypia and stromal invasion. Their biological behavior varies by histological type. Serous cystadenocarcinomas are more common than all other histological types together (Heintz et al. 2006). Only one-third of all serous tumors are identified at stage I, while two-thirds have spread outside of the ovaries at the time of diagnosis (Lee et al.

2003). Unlike serous tumors, which generally have a rather homogenous cellular composition and degree of differentiation, mucinous tumors often are heterogenous, particularly those of the intestinal type (Hart 2005). Mucinous tumors are usually confined to the ovaries (Lee et al. 2003, Heintz et al. 2006). The classification of ovarian neoplasms is shown in Table 1 (Heintz et al. 2006, Lee et al. 2003, Underwood 1996).

Table 1. Classification of ovarian neoplasm

Origin	Tumor	
	Types	Subtypes
Epithelium	Serous	
	Mucinous	Benign, borderline or malignant
	Endometrioid	
	Clear cell	
	Transitional cell (Brenner)	
	Mixed epithelial	
	Unclassified	
Germ cells	Dysgerminoma	
	Teratoma	Mature cystic, immature solid or monodermal
	Extraembryonic	Yolk sac (endodermal sinus tumor)
	Malignant mixed germ cell tumors	Choriocarcinoma
Sex-cord stroma	Thecoma	
	Granulosa cell tumor	
	Sertoli-Leydig cell tumor	
	Mixed germ cell stromal tumor	
	Steroid cell tumor	
Metastatic	Various	
Miscellaneous	Hemangioma, lipoma, etc	

2.1.4 Grade

Epithelial tumors of the ovary are further classified by grade. This is important because histological grading is related to prognosis, especially in the early stage tumors. Tumor grade refers generally to the degree of differentiation - or maturity - of the cells that make up the tumor. Worldwide, there are many different systems for the grading of ovarian cancers, and a universal standard has been proposed (Silverberg 2000). Epithelial ovarian cancers are graded by the WHO as follows: well differentiated, moderately differentiated, poorly differentiated and grade cannot be assessed (Heintz et al. 2006). Poorly differentiated cancers are most common in the advanced stages and most of the

early stage cancers are well differentiated (Colombo et al. 2006). Clear cell adenocarcinomas are not typically graded because of the mixture of different architectural patterns (Lee et al. 2006). The prognostic significance of grading ovarian cancer has been studied previously and it has been noted that grading is a significant predictor of survival (Heintz et al. 2006, Engelen et al. 2006, Junor et al. 1994, Woodman et al. 1997). It seems that low histological grade is a more significant predictor than high stage (Chan et al. 2007, Vergote et al. 2001, Zanetta et al. 1998, Winberger et al. 2007).

2.1.5 Stage

The findings at surgery determines the tumor stage, which may be modified by histopathological, clinical or radiological evaluation (Heintz et al. 2006). The standards for staging were introduced 20 years ago by the Gynecologic Oncology Group, and the FIGO staging of ovarian cancer has been surgical since 1988 (Buchsbaum et al. 1989) (Table 2).

Table 2. Staging of carcinoma of the ovary:

Stage I: Growth limited to the ovaries; cancer is confined to one or both ovaries

Stage IA: Tumor limited to one ovary, capsule intact. No tumor on ovarian surface. No malignant cells in the ascites or peritoneal washings.
Stage IB: Tumor limited to both ovaries, capsules intact. No tumor on ovarian surface. No malignant cells in the ascites or peritoneal washings.
Stage IC: Tumor limited to one or both ovaries, with any of the following: Capsule ruptured, tumor on ovarian surface, malignant cells in the ascites or positive peritoneal washings

Stage II: One or both of the ovaries involved and the disease has spread to the uterus and/or the fallopian tubes or other sites in the pelvis.

Stage IIA: Extension and/ or implants in uterus and/or tubes. No malignant cells in the ascites or peritoneal washings
Stage IIB: Extension to other pelvic organ. No malignant cells in the ascites or peritoneal washings
Stage IIC: IIA/B with malignant cells in the ascites or positive peritoneal washings

Stage III: One or both of the ovaries involved and the disease has spread to lymph nodes or other sites outside of the pelvis but is still within the abdominal cavity, such as the surface of the intestine or liver.

Stage IIIA: Microscopic peritoneal metastasis beyond the pelvis
Stage IIIB: Macroscopic peritoneal metastasis beyond the pelvis 2 cm or less in greatest dimension
Stage IIIC: Peritoneal metastasis beyond pelvis more than 2cm in greatest dimension and/or regional lymph nodes and/or metastasis

Stage IV: Growth involving one or both ovaries with distant metastases. If pleural effusion is present, the cytology of the effusion must shown malignant cells. Parenchymal liver metastasis.

2.1.6 Symptoms and signs

Ovarian cancer has been described as a silent killer because it is often diagnosed only in advanced stages, when the disease has spread beyond the ovaries (Benedet et al. 2000). By that time, the prospect of survival is considerably lower than in early stage disease (Heintz et al. 2006). Ovarian cancer is associated in 71 – 78 % with unusual bloating, fullness, urinary urgency and pressure in the abdomen, but 7 % of the women have no symptoms at all (Webb et al. 2004, Olson et al. 2001). Women with ovarian cancer report persistent symptoms that constitute a change from their normal state of health and even early stage ovarian cancer can produce these symptoms (Goff et al. 2007, Olson et al. 2001).

2.1.7 Diagnosis

The success of treatment of ovarian cancer depends on early diagnosis but how to identify the disease early is a daunting task. There is a great need to find biochemical and imaging procedures for routine screening, especially in high-risk patient groups. Much research is being made in the fields of genomics and proteomics that could be used for early diagnosis (Kohn 2007, Legge et al. 2006). Serum proteomics may be a promising area for discovering biomarkers, but clinically useful methods have thus far not emerged.

2.1.7.1 Physical examination

The most important sign of ovarian cancer is the detection of a pelvic mass in physical examination. A solid, irregular, fixed, nodular, bilateral pelvic mass is highly suggestive of ovarian cancer (Colombo et al. 2006). An early stage tumor may be difficult to detect by physical examination only. A combination of gynecological examination, specialist sonography, and tumor marker assay (usually CA 125) is considered to be a good strategy for the early diagnosis of ovarian neoplasia, although the final diagnosis of ovarian cancer is based on histological samples obtained at surgery (Benedet et al. 2000).

2.1.7.2 Imaging

Imaging has become an essential part of the clinical management of patients with ovarian cancer, since it is need for tumor detection, characterization, treatment planning and follow-up.

The final diagnosis of a pelvic mass requires ultimately an exploratory laparoscopy or laparotomy. Preoperative evaluation is needed, and ultrasonography, computed tomography, and magnetic resonance imaging are used to image ovarian cancer; of these, ultrasonography is used most (Liu et al. 2007, van Trappen et al. 2007). According to a meta-analysis, ultrasonography had an accuracy similar to CT and MRI with regard to differentiation of tumors being either malignant or benign with a sensitivity of 85 – 89 %, and a specificity of 84 – 86 % (Liu et al. 2007). In a separate study, 14 borderline tumors had MRI findings that were similar to those of malignant tumors and were considered as ovarian cancers; in the study the false positive frequency was 100 % (Takemori et al. 2002).

2.1.7.3 CA 125

Cancer antigen 125, CA 125, is a serum protein found that is produced at high concentrations by most ovarian cancer cells. CA 125 is produced on the surface of the malignant cells from where it is released in the blood stream. CA 125 was first identified in 1981, and is one of the most extensively studied and used molecular markers of ovarian cancer (Bast et al. 1981). CA 125 in the serum is a sensitive marker for diagnosis and follow-up of ovarian cancer, and is expressed by over 80 % of all patients with ovarian cancers, although levels within the reference range cannot be taken as a guarantee against malignancy. The levels of CA 125 at presentation correlate with the risk of malignancy, stage of disease and histology (Meyer et al. 2000). An elevated CA 125 level strongly suggests the presence of ovarian cancer particularly in postmenopausal women who have a palpable pelvic mass (Colombo et al. 2006).

2.1.7.4 Risk of malignancy index

The RMI is a scoring system based on menopausal status, ultrasonographic morphology, and serum CA 125 level. It is used to discriminate between malignant and benign pelvic masses and to aid in the selection of patients for primary surgery (Andersen et al. 2003, Jacobs et al. 1996, Tingulstad et al. 1996 and 1999). The limitation of RMI is its poor ability to identify patients with borderline tumors and stage I invasive disease. It is more reliable in the detection of patients with advanced stage disease (Andersen et al. 2003, Tingulstad et al. 1999).

2.2 Operative treatment of ovarian cancer

2.2.1 Current guidelines

Surgery is the cornerstone of treatment of epithelial ovarian cancers. All patients with this diagnosis and, who are fit for surgery, should be considered urgently for a full staging laparotomy.

Ovarian cancer is staged surgically and the disease needs to be confirmed by histology. If malignancy is suspected pre-operatively, the laparotomy should be performed through a midline incision. Table 3 summarizes the principles of adequate staging (Benedet et al. 2000). However, any other suspicious area, such as pleural effusion, and rare but obvious involvement of extra pulmonary or pleural and extra peritoneal sites must be biopsied (Benedet et al. 2000).

Table 3: Principles of surgical staging by FIGO guidelines.

• Careful evaluation of all peritoneal surfaces
• 4 washings of the peritoneal cavity: diaphragm, right and left abdomen, pelvis
• Infracolic omentectomy
• Selected lymphadenectomy of the pelvic and para-aortic lymph nodes
• Biopsy and/or resection of any suspicious lesions, masses and any adhesions
• Random blind biopsies of normal peritoneal surfaces, including that from the undersurface of the right hemidiaphragm, bladder reflection, cul-de-sac, right and left paracolic recesses, and both pelvic sidewalls
• Total abdominal hysterectomy and bilateral salpingo-oophorectomy
• Appendectomy for mucinous tumors

The recommendations have been further defined as follows (Tropé et al. 2006):

1. The vertical abdominal incision is enlarged supraumbilically as much as necessary to complete the upper abdominal staging procedure. In selected cases, laparoscopy can be used to access the external appearance of an ovarian mass, and help the surgeon decide which approach (laparoscopy or laparotomy) and incision are best.

2. For evaluation of ascites, sampling of peritoneal fluid is performed first before contamination by blood cells. When there is no ascites, multiple peritoneal washings for cytology analysis must be performed.
3. The entire peritoneal surface of the abdominopelvic wall, from the pelvis to the diaphragm, is thoroughly inspected and palpated, and tumor implants are sought for. The abdominal organs are inspected, and the sizes of all lesions are reported.
4. Random biopsies of pelvic peritoneum, abdominal peritoneum (including paracolic gutters) are taken. It does not seem to be necessary to sample the sub diaphragmatic area routinely.
5. Bilateral para-aortic and pelvic nodes are sampled.
6. Resection of primary ovarian cancer is requires total hysterectomy and bilateral salpingo-oophorectomy.
7. Omentectomy is indicated as a staging procedure and as a part of surgical therapy.
8. The benefit of systematic appendectomy is controversial. The appendix is seldom involved (< 4 % EOC cases). In cases of mucinous tumors, 8 % of appendixes are involved. This suggests that routine appendectomy should be performed as part of the standard staging procedure at least for mucinous tumors and grade 3 tumors.
9. The laparoscopic procedure can be safely used for restaging of apparent EOC. Restaging should be done only in patients who have a high-risk of recurrences. The laparoscopic procedure can be safely used for restaging an apparent EOC by teams that are experienced in ovarian and advanced laparoscopic surgery.

2.2.2 The role of lymphadenectomy

Staging of ovarian cancer has been surgical since 1988 (Buchsbaum et al. 1989), and lymphadenectomy is important for staging. Ovarian cancer spreads usually by local shedding into the peritoneal cavity, followed by implantation on the peritoneum. Hematological metastases are rare, while peritoneal and lymph node involvement is common. The pathologic status of lymph nodes cannot be predicted on the basis of clinical appearance (di Re et al. 2000, Pereira et al. 2007), and systematic lymphadenectomy gives better information regarding disease spread and is especially important for the staging of early ovarian cancer, e.g. the presence of node metastases upstages the patients to stage IIIC. Proper identification of unrecognized disease provides the clinician with more accurate information upon which prognosis can be discussed and treatment can be tailored. The rate of lymph node involvement in apparent early stage ovarian cancer ranges from 4 % to 25 % (Buchsbaum et al. 1989, Burghardt et al. 1991, di Re et al. 2000, Suzuki et al. 2000).

In advanced ovarian cancer, the rate of node involvement ranges from 42 to 84 % (Burghardt et al. 1991, di Re et al. 2000, Panici et al. 2005, Pereira et al. 2007, Saygili et al. 2002).

The role of systematic lymphadenectomy in the treatment of patients with advanced ovarian cancer is still being debated. Patients with metastases to the lymph nodes have worse outcomes and lymphadenectomy contributes to the assessment of the prognosis and the need for adjuvant treatment. A retrospective study suggested a clinically significant survival advantage to patients who had had systematic lymphadenectomy and who underwent cytoreductive surgery for advanced disease (Scarabelli et al. 1995). Non-randomized studies have compared the survival of patients with advanced ovarian cancer undergoing cytoreductive surgery with and without lymphadenectomy and these studies favor lymphadenectomy (Bristow et al. 2002, Chan et al. 2007, Spirtos et al. 1995, di Re et al. 1996). In contrast, univariate and multivariate analyses showed that systematic pelvic and para-aortic lymphadenectomy was not a significant prognostic factor in a group of 61 suboptimally debulked patients with stage III ovarian cancer. In lymph node dissected patients, again, survival was significantly longer if the patient had minimal residual tumor than if the amount of residual tumor was > 2 cm ($p = 0.005$) (Saygili et al. 2002). When studying the impact of lymphadenectomy in early stage disease, lymphadenectomy was associated with improved 5-year disease-specific survival ($p < 0.001$) in a group of 6686 women with stage I ovarian cancer. In the same study, women under the age of 50 years had no benefit from lymphadenectomy (Chan et al. 2007). The extent of lymphadenectomy may also be a significant prognostic factor. In another, large study of 13918 advanced ovarian cancer patients, the extent of lymph node dissection and the number of positive nodes were significant, independent prognostic factors and were associated with an improved disease-specific survival (Chan et al. 2007).

The effect of lymphadenectomy on survival has been evaluated in two randomized studies. In the study by Panici and co-workers, systematic lymphadenectomy improved progression-free but not overall survival among 427 patients who had been optimally debulked (residual tumor ≤1 cm) for stage IIIb-IV epithelial ovarian cancer. In addition, patients who underwent systematic lymphadenectomy had a longer operation time and experienced more complications (Panici et al. 2005). In the other randomized study patients with epithelial ovarian cancer confined to the pelvis were included. Although, survival was only nonstatistically improved in the group who had undergone systematic lymphadenectomy compared with the group who had only had lymph node sampling (84 vs 81 %). Systematic lymphadenectomy revealed a statistically significant higher proportion of patients with metastatic lymph nodes (Maggioni et al. 2006).

Residual disease after primary surgery is an important prognostic factor and complete resection including lymphadenectomy is associated with longer survival. Lymphadenectomy is a cornerstone of staging of early ovarian cancer and should be considered for advanced ovarian cancer patients keeping closely in mind side-effects and possible benefits. Table 4 summarizes the results of seven studies on the effect of lymphadenectomy on survival of ovarian cancer patients. The number of metastatic lymph nodes is evaluated.

Table 4. Effect of lymphadenectomy on survival in ovarian cancer patients.

Reference	Stage of disease	No of patients/ lymphadenec-tomy performed	Positive lymph nodes (%)	Variable measured	Lymphadenectomy		p-value
					Yes	No	
Non-randomized studies							
Chan et al. 2007	III-IV	13918/4260	60 %	5-year DSS	35.2-47.8 %*	26,1 %	<0.001
Chan et al. 2007	I	6686/2862	-	5-year survival	92.6 % (+/- 0.6)	87.0% (+/-0.6)	<0.001
Aletti et al. 2006	IIIc-IV	219/93	68 %	OS, RR (95 % CI)	0.479 (0.348-0.654)	1	<0.001/0.705**
Saygili et al. 2002	III	61/29	59 %	RR (95 % CI)	1	1.23 (0.44-3.42)	0.69**
Scarabelli et al. 1995	IIIc-IV	53/30	76.6 %	4-year survival	22 %	0 %	<0.001
Randomized studies							
Panici et al. 2005	IIIb-IV	427/216	42-70 %	OS, HR (95 % CI)	0.97 (0.74-1.29)	1	0.85**
Maggioni et al. 2006	I-II	268/138	-	OS, HR (95 % CI)	0.85 (0.49-1.47)	1	0.56**

* 5-year disease-specific survival based on the extent of lymphadenectomy (1 - > 20 nodes removed)
**Multivariate analysis
CI= Confidence intervals, DSS= Disease-specific survival, HR=hazard ratio, OS=overall survival, RR=Relative risk

2.2.3 Cytoreductive surgery

In 1975, Griffiths reported that the duration of survival was directly related to the diameter of the largest residual tumor after cytoreductive surgery. The study included 102 patients with stage II and III epithelial ovarian cancers, and it indicated that if the size of the residual tumor exceeded 1.5 cm, prognosis was poor. Since this landmark study, many other authors have confirmed that surgical cytoreduction gives a survival advantage (Bristow et al 2002, DiSaia et al. 2001, Chi et al. 2006, du Bois et al. 2006, Eisenkop et al. 2003 and 2006, Hoskins et al. 1994, Le et al. 1997, Tilgulstad et al. 2003, Trimble et al. 1999). Virtually all studies indicate that the amount of residual disease after primary surgery is one of the most important prognostic factors of patients treated for advanced ovarian cancer (Bristow et al. 1999 and 2002, Chi et al. 2006, Eisenkop et al. 2003 and 2006, Griffiths 1975, Hoskins et al. 1994, Junor et al. 1994, Le et al. 1997).

Surgery for ovarian cancer does not follow the general principles of tumor surgery in the sense that radical resections are undertaken even in patients for whom the likelihood of complete macroscopic removal of tumor is small. Still the balance of benefit and morbidity has to be considered carefully (Covens 2000). In patients who have a poor performance status, diffuse carcinomatosis or liver metastasis, the benefits of aggressive surgical cytoreduction is not convincing (Covens 2000). According to a recent randomized study from Germany the probability of complete debulking is significantly decreased in these patients (Wimberger et al. 2007). The benefit of cytoreduction has been suggested to be based on the factors presented in below (Hacker 1989, Covens 2000), but individual, patient-related factors in this hypothesis are difficult to study in the clinical setting and confirmatory data is not available.

- Removal of poorly vascularized tumor reduces the volume of tumors inaccessible by cytostatics.
- The small residual tumor mass has a higher growth fraction since it is better perfused, which favors an increased cell kill with cytotoxic therapy.
- Small tumor masses require fewer cycles of chemotherapy and, less opportunity induced drug resistance.
- Drug-resistant clonogenic cells are removed.
- The patient´s immunocompetence is enhanced by the removal of large tumor bulk.

The definition of "optimal" debulking surgery has varied over time. The accuracy of tumor measurements is dubious, as no calibrated instrument or standardized techniques are available. It is also unlikely that the prognosis of patients with diffuse carcinomatosis is similar to the prognosis of patients with a few tumor nodules of the same size. Originally, optimal cytoreduction was defined as < 2cm diameter of the largest remaining cancer nodule (Griffits 1975, Piver et al. 1988, Wharton et al. 1981). Currently only complete debulking to no macroscopic residual tumor is considered optimal debulking in many recent publications (Chi et al 2006, du Bois et al. 2006, Eisenkop et al. 2006). The available literature does not clarify whether the survival advantage for patients who have had maximal cytoreductive surgery is related to the surgeon's skills or to some favourable biological characteristics of the tumor which in themselves enhance the possibilities for successful cytoreductive surgery. The operability of ovarian cancer is probably dependent on both the operative skills of the physician and on the biological characteristics of the tumor (Eisenkop et al. 2001).

Surgery with the intent of maximal cytoreduction before primary chemotherapy is the current standard of treatment. Interval debulking after three courses of chemotherapy is an option for patients in whom surgery with maximal effort is not possible at primary diagnosis. The concept of interval debulking may provide a benefit for some patients. The study by van der Burg was the first one to show significant impact of interval surgery on survival (van der Burg. et al. 1995). In contrast to the EORTC trial (van der Burg. et al. 1995), treatment of advanced ovarian cancer after maximal cytoreductive surgery, chemotherapy plus aggressive secondary surgery improved neither progression-free nor overall survival as compared to chemotherapy alone (Rose et al. 2004).

2.2.4 Conservative surgery

A small subset of ovarian cancer patients are young and preservation of fertility needs to be considered. Between 2001 and 2005, 5 % of the women with ovarian cancer were less than 40 years of age in Finland (www.cancerregistry.fi). Especially stage I ovarian cancer and borderline tumors can be diagnosed in women of childbearing age for whom preservation of the reproductive function is important (Tropé et al. 2006). Conservative surgery is feasible only in young patients with borderline tumors, or endometrioid, mucinous, or serous Stage IA, grade I ovarian cancer (Benedet et al. 2000, Suh-Burgmann 2006, Tropé et al. 2006, Zanetta et al. 1998). However, staging of the tumor should be performed according to the same principles as in definite surgery with the exception that the uterus and the other ovary are left situ (Benedet et al. 2000).

2.2.5 Surgery of recurrent ovarian cancer

Surgery followed by chemotherapy is the standard approach of treatment of primary epithelial ovarian cancer. About 70 % of patients with advanced ovarian cancer with no clinical evidence of disease after primary therapy will ultimately develop recurrent disease (Heinz et al. 2006). Cytoreductive surgery for recurrence is defined as an operation performed on patients with recurrent disease who have completed primary treatment and have had a period with no evidence of disease (du Bois et al. 2006). The role of cytoreductive surgery in relapsed ovarian cancer has not been established. Selected patients with recurrent ovarian cancer who undergo macroscopically complete surgical cytoreduction have prolonged survival (Güngör et al. 2005, Harter et al. 2006). Still there is no level A/B evidence supporting cytoreductive surgery in recurrent ovarian cancer (du Bois et al. 2006). The possibilities of cytoreduction have to be evaluated carefully by imaging techniques when surgery for recurrent ovarian cancer is considered.

2.3 Chemotherapy

The current standard chemotherapy for ovarian cancer consists of combination of platinum and taxane (McGuire et al. 1996, Piccart et al. 2000, Vasey et al. 2004, du Bois et al. 2005). Two randomized, controlled trials of first-line cisplatin-based dual therapy have showed additional clinical benefit from replacing cyclophosphamide with paclitaxel (McGuire at al. 1996, Piccart et al. 2000). The Gynecologic Oncology Group 111 trial studied 386 women with stage III suboptimally debulked or stage IV disease who received cisplatin combined with either paclitaxel or cyclophosphamide for a six cycles (McGuire et al. 1996). The results were confirmed in European-Canadian study (Piccart et al. 2000). The efficacy of cisplatin + paclitaxel versus carboplatin + paclitaxel has been compared in two studies. Survival rates were similar for both treatments, but carboplatin + paclitaxel was easier to administer and had better side effect and safety profile (du Bois et al. 2003, Ozols et al. 2003).

Treatment with docetaxel + carboplatin may be an alternative combination. In a randomized controlled trial comparing docetaxel + carboplatin with paclitaxel + carboplatin both groups had similar progression-free survival times (median of 15 months for both groups) and overall 2-year survival rates (64 % and 69 %). Docetaxel + carboplatin treatment was associated with more myelosuppression but with statistically significantly less neurotoxicity than paclitaxel + carboplatin treatment (Vasey et al. 2004).

A high proportion of patients (60 – 80 %) with advanced epithelial ovarian cancer responds to first-line chemotherapy and will achieve complete clinical remission (Högberg et al. 2001). Unfortunately, most patients will relapse and eventually die of their disease (Heintz e al. 2006). For patients who have responded well to primary chemotherapy and who develop recurrence more than six months after the end of primary treatment, a platinum + taxane combination is the recommended treatment modality (Parmar et al. 2003). For patients who experience early recurrence, further chemotherapy with a number of agents may be used. The response rates are low and the literature provides no unequivocal guidance for the choice of treatment. Pegylated liposomal doxorubicin and topotecan may be considered for second line treatment (Gordon et al. 2001 and 2004). Single-agent gemcitabine is an acceptable alternative to pegylated liposomal doxorubicin for patients with platinum resistant ovarian cancer (Mutch et al. 2007).

Usually the ovarian cancer has spread beyond the ovary at the time of diagnosis. Consequently, the peritoneal cavity is the major site of recurrence and peritoneal spread is related to the high death rate from ovarian cancer. Many chemotherapeutic agents can be administered directly into the peritoneal cavity. Intraperitoneal chemotherapy refers to the local instillation of drug into the tumor-containing peritoneal cavity to increase the ratio of drug exposure for the tumor relative to that for other parts of the body. There are three, large randomized GOG studies which demonstrate the survival advantage of intraperitoneal versus intravenous therapy over intravenous therapy (Armstrong et al. 2006, Markman et al. 2001, Walker et al. 2006). There is some controversy relating to increased toxicity and catheter-related complications of intraperitoneal treatment which has limited the enthusiasm, especially in Europe, for using this treatment modality. In North-America it has gained more widespread acceptance as first-line treatment of optimally-debulked, advanced ovarian cancer during the last few years. The National Cancer Institute (NCI) in the USA has released a formal Clinical Announcement on intraperitoneal chemotherapy (NCI 2006).

2.4 Radiotherapy

Ovarian cancer does not typically recur as a solitary focus, and therefore radiation therapy has a very limited role in the treatment of ovarian cancer. The results of a randomized Swedish-Norwegian study suggest that radiotherapy covering the whole abdominal area may be an option for consolidation therapy in patients with complete pathologic remission after chemotherapy (Sorbe et al. 2003). However, serious treatment-related adverse events were more frequent in the radiotherapy

group. In a recent study postoperative whole abdominal radiotherapy was given to 106 stage III ovarian cancer patients who had minimal residual disease at second-look laparotomy. Radiation was discontinued because of acute toxicity in 11 patients and 30 of the 106 patients experienced severe intestinal toxicity (Petit et al. 2007). Understandably, radiotherapy is no longer considered to be a serious option in the treatment of ovarian cancer, because the beneficial effect is modest but toxicity considerable (Heintz et al. 2006).

2.5 Prognostic factors

A definition of a prognostic factor is a situation or condition, or a characteristic of a patient that can be used to estimate the probability of recovery from a disease or the probability of the disease recurring. Clinically, prognostic factors may help in individualizing treatment for patients. A predictive factor is a variable that can account for differences in the response to a given treatment and may be useful in the selection of patients likely to benefit from a specific therapy. Epithelial ovarian cancer is a heterogeneous disease and many biological and molecular factors are involved in the development and progression of the disease (Baekelandt et al. 1999 and 2000, Sillanpää et al. 2003, Skirnisdottir et al. 2001). Known prognostic factors for ovarian cancer include age, FIGO stage and grade, and the amount of tumor remaining after surgery (Griffiths 1975, Heinz et al. 2006, Krag et al. 1989, Pectasides et al. 2007, Skirnisdottir et al. 2007, Tingulstad et al. 2003, Winter et al. 2007).

2.5.1 Age

Age is an important prognostic factor for patients with ovarian cancer. Older patients have often medical comorbidities and usually only patients with a good performance status are operable. In series of 28,165 patients diagnosed with epithelial ovarian cancer, younger age was a significant positive prognostic factor for survival. Across all stages, very young women (< 30 years) had a significant survival advantage - their 5-year disease specific survival was 78.8 %, compared to 58.8 % for women under 60 years of age and 35.3 % for women over 60 years of age ($p < 0.0001$). Younger patients had more often early stage and lower grade disease. Even after controlling for ethnicity, stage, grade, and surgical treatment, the younger group still had a better prognosis (Chan et al. 2006). A similar conclusion was made in a retrospective study of 1748 epithelial ovarian cancer patients (Pectasides et al. 2007), but contradictory results suggesting that the survival advantage of the younger patients may be attributed to the increased frequency of early-stage, lower

grade disease, and borderline tumors have also been reported (Duska et al. 1999, Massi et al. 1996). In a study by Bruchim and co-workers, elderly patients (≥ 70 years, n = 46) were less likely to undergo definitive surgery than younger patients (< 70 years of age, n = 97) (73.9 % vs. 91.8 %, p = 0.004), but age was not a limiting factor in achieving optimal debulking in the group of patients who did undergo surgery (older 53 %, younger 54 %) (Bruchim et al. 2002).

2.5.2 Stage

The FIGO stage is based on the macroscopic spread of the tumor and on the histology of the tumor samples taken for staging. In women with low-risk stage I epithelial ovarian cancer, 5-year survival rates can be as high as 90 %. As the disease become more advanced, survival declines and is only 18 % for women with stage IV ovarian cancer (Heintz et al. 2006). The tumor stage at diagnosis is considered to be the most important prognostic factor for survival of ovarian cancer patients (Heintz et al. 2006).

2.5.3 Grade

There are highly significant relationships between histological grade, tumor stage and survival, especially in early stage disease. Poorly differentiated cancers prevail in advanced stages, and vice versa - most grade I cancers are of early stage. In two studies totaling 1896 stage I epithelial ovarian cancer patients, the tumor grade was the most powerful prognostic indicator of disease-free survival (Zanetta et al. 1998, Vergote et al. 2001).

The prognostic value of tumor differentiation is controversial in advanced ovarian carcinoma. In a retrospective study of 112 patients with stage III epithelial ovarian cancer, there was a significant survival disadvantage for patients with high-grade tumors, even after debulking to tumor size below 0.5 cm in diameter (Farias-Eisner et al. 1994). In contrast, in a large retrospective review of 1895 patients with advanced epithelial ovarian cancer, grade was not an independent predictor of outcome (Winter et al. 2007).

2.5.4 Residual tumor

Postoperative residual tumor is one of the most important independent prognostic factors for survival (Bristow et al. 2002, Eisenkop et al. 2003, Griffits 1975, Heintz 2006, Wimberger et al.

2007, Winter et al. 2007). In addition, surgical outcome is one of the few prognostic factors that can be influenced by treatment. In a meta-analysis including 6885 patients there was a statistically significant positive correlation between percentage of maximal cytoreduction and median survival after controlling for other variables (Bristow et al. 2002).

The importance of tumor load before cytoreduction is controversial. Not only is the residual tumor but also the initial metastatic tumor load of prognostic significance. Hacker and co-workers were the first to report that patients with extensive metastatic disease prior to cytoreduction or with clinical ascites had a poor prognosis even if the disease was cytoreducted to an optimal status (Hacker et al. 1983). In a study by the Gynecologic Oncology Group involving 349 patients with residual cancer of 1 cm or less, multivariate analysis showed that the presence of 20 or more residual lesions was an independent unfavorable prognostic variable (Hoskins et al. 1992), while cytoreduction to macroscopically disease-free status may have a more significant influence on survival than the extent of metastatic disease before surgery (Eisenkop et al. 2003).

What is the impact of the biological behavior of the tumor or is it surgical intervention alone that has an independent effect on patient survival (Covens 2000)? Several factors influencing surgical outcome have been described: therapist-related factors: e.g. surgical training and experience (Giede et al. 2005, Vernooij et al. 2007), patient related factors like performance status and comorbidity, and disease-related factors like growth pattern and extension of disease (Eisenkop et al. 2001). There is some experimental evidence indicating that the immune system may be involved in ovarian tumor progression and clinical outcome. The presence of intratumoral T-cells correlates reportedly with improved clinical outcome in a study with 102 patients with advanced epithelial ovarian cancer (Zhang et al. 2003).

2.5.5 Operating surgeon

A relationship between sub-specialty training in gynecological oncology and survival of patients with ovarian cancer has been suggested. Several studies have shown that patients who have undergone surgery by a gynecologist had better survival than patients who underwent surgery by a general surgeon (Earle et al. 2006, Engelen et al. 2006, Kehoe et al. 1994, Nguyen et al. 1993, Woodman et al. 1997). According to two recent reviews on the relationship between surgical specialty and survival of patients with ovarian cancer the outcome is better when treatment is

provided by a gynecological oncologist (Giede et al. 2005, Vernooij et al. 2007). One of these reviews claims that patients with advanced or early stage ovarian epithelial cancer should be operated on by gynecological oncologists (Giede et al. 2005) and the other (based largely on different studies that the previous one) demonstrated a better outcome for patients treated by gynecological oncologists or whose treatment was provided in specialized hospitals (Vernooij et al. 2007). However, although survival was better after treatment in specialized hospitals, the influence of the treating physician on survival did differ between subgroups of patients (Vernooij et al. 2007). Table 5 summarizes the results from five studies on the relationship between specialty of the operating surgeon and survival of ovarian cancer patients.

Table 5. Training of surgeon and survival of patients with ovarian cancer

Reference	Surgeon	Stage of disease	Number of patients	Survival
				Hazard ratio (95 % CI)
Earle et al. 2006	General surgeon Gynecologist Gynecological oncologist	I-IV	3067	1.00* 0.86 (0.78-0.96)* 0.85 (0.76-0.95)*
Engelen et al. 2006	Gynecologist Gynecological oncologist	III	680	1.00* 0.71 (0.54-0.94)*
Paulsen et al. 2006 **	General surgeon Gynecologist Gynecological oncologist	III	198	3.08 (1.26-7.52)* 2.11 (1.13-3.95)* 1.00*
Junor et al. 1999	General surgeon Gynecologist Gynecological oncologist	III	830	1.32 (1.07-1.63)* 1.00* 0.75 (0.62-0.92)*
Woodman et al. 1997	General surgeon Gynecologist	I-IV	351	1.58 (1.19-2.10) 1.00

*Multivariate analysis
**Prospective study

2.5.6 Hospital operative volume

Compelling evidence from multiple studies suggest that ovarian cancer patients who are operated on hospitals with high case volumes have a better outcomes than patients treated in hospitals with fewer patients (Hillner et al. 2000, Oberaigner et al. 2006, Tingulstad et al. 2003, Ioka et al. 2004, Goff et al. 2007). Not all studies, however, agree on this. In two large population-based cohort

studies, the volume of operations was not a strong predictor of survival of ovarian cancer patients aged 65 years or more (Earle et al. 2006, Goff et al. 2007, Schrag et al. 2006). In addition to volume, the number of patients operated on by an individual surgeon has been taken into account in recent reports (Earle et al. 2006, Bristow et al. 2004, Paulsen et al. 2006). The two recent articles may be the first population-based studies were both surgeon and hospital procedure volumes have been taken into account (Earle et al. 2006, Paulsen et al. 2006).

2.6 Borderline tumors

2.6.1 Epidemiology

Borderline tumors are a specific entity of ovarian tumors and account for 15 % of all epithelial ovarian cancers (Auranen et al. 1996, Disaia et al. 2002, Benedet et al. 2000). Compared to obviously malignant neoplasms, borderline tumors tend to affect a younger population (Auranen et al. 1996) and nearly 75 % are confined to ovaries at the time of diagnosis (Benedet et al. 2000). About 20 % of the newly diagnosed women with a borderline tumor are less than 40 years old (www.cancerregistry.fi). In 2004, 113 new cases and 5 deaths from borderline tumors were reported in Finland (Cancer statistics for Finland 2005).

2.6.2 Survival

Despite some histological features suggestive of malignancy, borderline tumors carry on excellent prognosis of the patients compared to patients with invasive ovarian cancer. Five-year survival rates range from 79 % to 100 % (Bjorge et al. 1998, Burger et al. 2000, Prat et al. 2002, Sherman et al. 2004, Heintz et al. 2006), the mean survival rate being 87 % for all stages (Heintz et al. 2006). The overall 5-year survival of patients with borderline tumors has not changed since 1982 when the survival improved from 77 % to 89 % (Heinz et al. 2006). The reason for this improvement is not known, but may be due to more accurate diagnosis of borderline tumors.

2.6.3 Histology

Ovarian tumors range from benign tumors without nuclear atypia or stromal invasion to cancers with both characteristics. An intermediate group of tumors can be distinguished, referred to as borderline tumors or tumors with low malignant potential. Borderline ovarian tumors were first

described in 1929 (Taylor 1929). However, it was not until 1971 that the category of borderline tumor was introduced by FIGO. Borderline tumors have mostly a serous or mucinous histology, display mitotic and nuclear abnormalities, show cellular multilayering, and are capable of metastasis, but lack stromal invasion (Riman et al. 2001). Some 30 – 60 % of serous borderline tumors are bilateral, compared to mucinous tumors which are usually unilateral (Gershenson 1999, Hart 2005).

Histopathological analysis is essential for diagnosis and planning of adequate therapy for patients with an ovarian neoplasm. During the operation, frozen sections are taken to separate benign, borderline and malignant lesions, to discriminate primary from metastatic tumors and to identify unusual neoplasms. The accuracy of frozen section diagnosis varies from 33.3 % to 78.6 % for borderline tumors and from 90.4 % to 98.5 % for invasive ovarian cancer (Boriboonhirunsarn et al. 2004, Pinto et al. 2001).

2.6.4 Operative treatment

According to the FIGO guidelines treatment of borderline tumors is as follows. For patients with Stage I disease who still desire to have children, conservative surgery with unilateral oophorectomy can be considered after intra-operative inspection of the contra lateral ovary to exclude involvement. However, for fertile patients with only one ovary, or with bilateral cystic ovaries, a partial oophorectomy can be considered in the interest of retaining fertility. For all other patients, total hysterectomy and bilateral salpingo-oophorectomy, are recommended, with maximal cytoreduction if the disease has metastasized. Additionally, appendectomy in patients with mucinous tumors is recommended (Benedet et al. 2000). Currently, lymph node sampling is not indicated routinely for staging, but any enlarged nodes should be resected for histology (Wong et al. 2007). Staging is seldom adequate in patients with borderline tumors (Desfeux et al. 2005, Fauvet et al. 2004, Lin et al. 1999). However, surgical staging is important to identify invasive extraovarian implants that carry an adverse prognosis (Wong et al. 2007).

2.6.5 Chemotherapy

Optimally cytoreduced patients in all stages of borderline tumors should receive only expectant management and no adjuvant chemotherapy, provided that no invasive implants are detected (Benedet et al. 2000). The current literature does not support the use on chemotherapy for

borderline tumors (Benedet et al. 2000, Lackman et al. 2003 Tropé et al. 2000). Only a small subset of patients with advanced stage borderline tumors with invasive extraovarian implants may benefit from adjuvant therapy (Gilks et al. 2003).

3. AIMS OF THE STUDY

The general aim of the present study was to evaluate how primary operative treatment of ovarian cancer and borderline tumors is performed in different hospital categories in Finland. In addition, we studied the effect of the operative volume of these hospitals and the training of the operating surgeons on the survival of patients with ovarian cancer.

The individual papers had the following specific aims:

1) To assess the 5-year relative survival rates of all operated ovarian cancer patients in Finland between 1983 and 1994 and to examine the outcome in different hospital categories.

2) To obtain accurate and detailed information about the quality and extent of primary operative treatment of ovarian cancer in Finland in different hospital categories.

3) To study how hospital operative volume and the differences in the operative treatment are reflected in progression-free survival and 5-year cancer-specific survival of ovarian cancer patients.

4) To evaluate the extent of staging and operative treatment of patients with ovarian borderline tumors operated in different hospital categories in 1999 in Finland. Also the 5-year survival data of these patients were reported.

4. PATIENTS, MATERIALS AND METHODS

4.1 Finnish health care system

In Finland, five university hospitals are tertiary referral centers for the total population of 5.2 million people. In addition, there are 16 central hospitals, which do not necessarily have all the specialist services, e.g. radiotherapy units, and may provide the services of gynecological oncologists only occasionally. The third hospital category consists of smaller city and district hospitals and other miscellaneous units. Health care services are financed primarily out of tax revenue. The service is complemented by the private section health care.

Either gynecological oncologists or general gynecologists are responsible for ovarian cancer treatment in Finland. Further chemotherapy and follow-up of primary treated patients may be carried out in smaller units following accepted treatment policies.

4.2 Finnish Cancer Registry

The population-based, nationwide Finnish Cancer Registry (FCR) was founded in 1952. All physicians, hospitals and other institutions in the country are obliged to send a notification to the Finnish Cancer Registry of all cancer cases that come to their attention. The coded data include information on patient characteristics; date of diagnosis, site of malignancy, histological type and simple stage of the tumor (local, advanced); treatment (e.g., chemotherapy, surgery and radiation therapy) as well as the date of and vital status (alive or deceased) at the end of follow-up. There is also information on the hospitals where specific treatments are given. In a quality control exercise, the FCR covered over 99 % of all solid tumors diagnosed in Finland from 1985 to 1988 (Teppo et al. 1994).

4.3 Participating hospitals

In the retrospective study we recognized 86 hospitals in which patients were operated on for ovarian cancer between 1983 and 1994. All five university hospitals, 17 central hospitals and 64 other hospitals participated in the study.

Finland is divided into 20 hospital districts, and there is, in addition, the semi-autonomous province of Ahvenanmaa that forms its own district. Each municipality refers patients to a particular hospital district, each of which contains a central and regional hospital. Of the central hospitals, five are university hospitals that provide specialized treatment. At the time of our retrospective study, the hospital district of Helsinki and of Uusimaa were separate areas, and this explains the higher number of central hospitals in our first study.

In the prospective study performed in 1999 the number of hospitals had decreased to 41 because less small hospitals operated ovarian cancer patients. All five university hospitals and 15 out of 16 central hospitals and 21 other hospitals participated in the prospective part of the study.

In the follow-up study, all five university hospitals, 15 central hospitals, and 12 other hospitals participated in the follow-up of the ovarian cancer patients who had been operated in 1999.

4.4 Patients

A summary is presented in Table 6.

Table 6. Patients

Study	Number of patients	Coverage	Study period	Source of material
I	3851 ovarian cancer patients	99 %	1983-1994	FCR* data Retrospective study
II	307 ovarian cancer patients	88 %	1999	Questionnaires filled in by physicians. Linked with FCR* data. Prospective study
III	275 invasive epithelial ovarian cancer patients	79 %	1999-2005	Questionnaires filled in by physicians. Linked with FCR* data. Prospective study
IV	65 borderline tumor patients	78 %	1999-2005	Questionnaires filled in by physicians. Linked with FCR* data. Prospective study

*FCR= Finnish Cancer Registry

Study I

Between 1983 and 1994, 5950 patients with ovarian neoplasms were diagnosed in Finland. In case of any inconsistency with the coded data, all registry notifications were manually searched and examined. Of the 5950 patients, 2099 were ineligible for the study and were excluded for the following reasons**:** 618 cases were based on autopsy or were not operated on; in 530 patients ovarian cancer was not the first malignancy; data on the operating hospital or the date of the operation were missing of 173 cases; 14 were excluded for miscellaneous other reasons (e.g., operation outside Finland) and 764 neoplasms were borderline tumors. The final patient population in study I consisted of 3851 patients operated on for invasive ovarian cancer.

Study II and IV

Detailed data on the clinical characteristics of the patients and their surgical treatment were collected using a specific questionnaire. The translated version of the questionnaire is presented in Appendix 1. The questionnaire was sent to 54 hospitals or units where ovarian cancer patients were known to have been operated. In addition to the questionnaire filled in by the operating physicians or other physicians at the unit, copies of the surgical reports, histopathology reports and cytology reports were collected. Thus, the size of the primary tumor, the extent of the operation, the (FIGO) stage, histology and residual tumor could be confirmed from two sources.

Questionnaires were returned on 401 patients including both borderline and invasive cancers. After checking the data, 19 patients were excluded because of one of the following reasons: primary origin of the tumor was uncertain (6 cases), recurrent ovarian cancer (6 cases) and synchronous second primary tumors (7 cases). Ten patients with granulosa cell tumor were excluded from the borderline tumor category. The final study population consisted of 307 patients with invasive ovarian cancer and 65 patients with an epithelial borderline tumor.

Study III

The study population consisted of 307 invasive ovarian cancer patients, operated in 1999. The follow-up data was collected by another specific questionnaire including questions on the date of progression, the detection method, treatment received, and the date and status of the patient when last seen. A translated version of the questionnaire is presented in Appendix 2. The inquiry form

was returned covering 296 patients with a malignant ovarian neoplasm. Twenty patients had non-epithelial ovarian cancer and were excluded from the follow-up study: 10 patients had a sex cord stromal tumor, 5 patients had a germ cell tumor, 4 patients had a sarcoma or some other non-epithelial ovarian tumor, and 1 patient had peritoneal carcinoma of uncertain origin. Additionally one patient was excluded because the primary ovarian cancer operation was performed in 1998. Eleven patients were lost from follow-up. The final study population consisted thus of 275 patients with epithelial ovarian cancer operated primarily in 1999.

4.5 Coverage

Study I

The Finnish Cancer Registry obtains data on all cancer cases diagnosed in Finland, and the coverage of this registry is 99 % for solid tumors.

Study II

In 1999, the number of invasive ovarian cancers reported to the Finnish Cancer Registry was 426. This figure includes 35 patients who had not been operated, 11 patients with ovarian cancer diagnosed at autopsy, 5 patients who had not been operated in 1999, and 28 patients with tumors of the Fallopian tubes. After manual checking of the data of all the patients not reported in the current study, there were 40 patients who had been operated on for invasive ovarian cancer but for whom questionnaires had not been filled in. Thus, Study II covered 88 % of the patients who had undergone surgical treatment for invasive ovarian cancer in Finland in 1999.

Study III

The follow-up data was obtained of 296 patients and covered 96 % of the operated invasive ovarian cancer patients reported in 1999. Only epithelial ovarian cancer patients were included in the current study, i.e. the results are based on 275 patients who cover 79 % of the epithelial ovarian cancer patients operated in Finland in 1999.

Study IV

109 borderline ovarian tumors were reported to the Finnish Cancer Registry. Four patients were reported only in the current survey and three patients were reported in 2000 to the FCR. Thirty three patients reported to Finnish Cancer Registry were not operated on for a borderline tumor in 1999; twenty-six patients had granulosa cell tumor, in two the tumor was found at autopsy, one patient was not operated, one was operated in 2000, and three had synchronous second primary tumors. After checking manually the data of all patients who were not reported to the current survey, there were 18 patients who had been operated on for a borderline ovarian tumor in 1999 but had not been reported to the study. The coverage of borderline tumor patients operated in 1999 in Finland was 78 %.

4.6 Follow-up

Study I

The follow-up of the patients was started on the date of the first operation for primary ovarian cancer. No other information on further operations or other treatments was collected for the survey. The last date of follow-up was set to December 31, 1998, or on the date of death, which ever came earlier. Using the unique personal identification number given to everyone residing in Finland, we were able to link all patients with the files of the Central Population Register with complete death and emigration information. Thus, no patients were lost from follow-up.

Study III

The 5-year follow-up of the patients operated on in 1999 was started on the date of the primary operation and ended to the date of last contact (before May 15, 2005) or death, which ever came first. Information on the status of the disease, further operations or other treatments was collected using specific questionnaire shown in Appendix 2. Eleven patients were lost from follow-up.

4.7 Analysis of demographic and operative data

Studies II and IV

Data analysis was mainly performed using Microsoft Excel. Difference in the proportions of patients with no postoperative macroscopic tumor between operations performed by gynecological oncologists and general gynecologists was analysed using Fisher´s exact test. Differences between preoperative and postoperative findings were evaluated using McNemar´s test (Study II).

4.8 Survival analysis

Study I

A life-table proportional hazards model based on the annual relative survival rates (RSR) for the first five follow-up years was used with GLIM statistical software (Hakulinen et al. 1987, Payne 1986). This was done to obtain the best estimates of the relative excess risk of death (RR) between the patient categories operated on in the different hospital categories. To control for confounding factors a model was constructed before fitting the hospital category variable (the three types of hospitals and the quartiles by hospital volume, respectively). All variables were categorical. The model included all available prognostic factors (stage, age at first operation, period of diagnosis, type of operation and follow-up year) and their significant interaction terms. Age at operation was grouped into 0-49, 50-64 and 65-99 years. There were two periods of diagnosis (1983-88, 1989-94). Type of operation had three categories: curative, palliative or unknown. The three tumor stage categories were localized, non-localized and unknown.

Study III

Annual hospital case volume was defined as the number of reported patients with primary ovarian cancer, and ranged from 1 to 47 operations in 1999. Department volume was divided into three categories by number of operations per year (<10, 10-20, or >20). The effect of hospital volume on the outcome was analyzed both by category and as a continuous variable.

Cox regression was used to analyze the time from operation to death due to ovarian cancer (CSS). If the patient was alive after 5-years from operation she was censored and the censoring time was counted from surgery to the last known date when patient was alive or to the end of follow-up (the maximum was set at 5 years).

Cox regression was also used to analyze DFS. The time was calculated from the operation day to the day of reported recurrence or until May 15, 2005 if the patient remained disease free (maximum was set at 5 years). If the disease did not relapse, the patient was marked as censored. If the patient had refractory disease (no disease-free time), the event-time was set at zero. Both response types were analyzed using several explanatory variables and these were adjusted for the age-group (0-49, 50-69 and over 70 years) and FIGO stage. Results from the Cox regression were expressed by hazard ratios (HR), with 95 % confidence intervals (CI) and p-values. A p-value of less than 0.05 was considered statistically significant. The statistical analyses were carried out using the SAS/STAT(r) software, Version 9.1.3 SP4 of the SAS System for Windows.

5. RESULTS

The main results are shown in the accompanying tables and are briefly presented in the text. Details are given in the separate original publications.

5.1 Study I

A population-based survival analysis was performed covering 3851 ovarian cancer patients operated on in Finland between 1983 and 1994. The patients operated on in hospitals with the highest volume of operations had the highest RSR compared with the patients operated on at hospitals with fewer operations. The age and stage distribution of the patients by the type of hospital is shown in Table 7. The relative excess risk of death in the first five years of follow-up among ovarian cancer patients, by volume of the first operating hospital (quartile 1 with the highest volume) and period of time is shown in Table 8.

Over the study period, the hospitals in the second quartile were able to improve their results significantly. From having the highest RR of 1.32 (1.12–1.56) in the first half of the study period, second quartile hospitals improved their results and brought these hospitals to the same level with the largest hospitals to a RR of 1.00 (0.85–1.18) in the latter half of the study period.

Table 7. Distribution of patients by prognostic factors in different hospital categories for ovarian cancer patients operated on in 1983-1994 in Finland

	University hospitals (N = 1393)	Central hospitals (N = 1470)	Other hospitals (N = 988)
Age group, years (%)			
0–49	25	20	20
50–64	38	39	36
≥ 65	37	40	44
Stage (%)			
Localized	24	23	29
Non-localized	66	68	64
Unknown	10	10	8

Table 8. Relative risk of excess death during the first 5-years of follow-up by hospital category for ovarian cancer patients operated on in 1983-1994 in Finland

Prognostic factor	RR	95 % CI	p-value
Type of Hospital			
University	1 (reference)		
Central	1.11	1.00–1.22	0.043
Other	1.06	0.95–1.18	0.325
Surgical volume			
Quartile 1 (largest)	1 (reference)		
Quartile 2	1.16	1.03–1.31	0.013
Quartile 3	1.06	0.94–1.20	0.309
Quartile 4	1.13	1.00–1.28	0.046

5.2 Study II

The prospective nation-wide study included 307 ovarian cancer patients operated on in different hospital categories in Finland. Half of the patients were operated on in university hospitals, where 72 % of the operations were performed by gynecological oncologists. In contrast, only 4 % and 19 %, respectively, of the patients were operated on by gynecological oncologist in central and other hospitals. Outside the university hospitals adequate surgical staging was performed only in a minority of the patients. Pelvic lymphadenectomy was performed in 88 %, and para-aortic lymphadenectomy in 73 % of the patients with stage I disease operated in university hospitals. The corresponding figures ranged from 11 % to 21 % in the central and district hospitals. The extent of operation by hospital category is presented in Table 9.

Table 9. Extent of surgery in different hospital categories by malignancy of the tumor for ovarian cancer patients operated in 1999 in Finland

	University hospitals (N = 156)	Other hospitals (N = 151)	All hospitals (N = 307)
Operations:			
Uni/bilat oophorectomy	136+5 (90 %)	129+2 (87 %)	272 (89 %)
Hysterectomy	114+5 (76 %)	93+3 (64 %)	215 (70 %)
Omentectomy	121+10 (84 %)	98+3 (67 %)	232 (76 %)
Peritoneal biopsy/biopsies	65+6 (46 %)	28+2 (20 %)	101 (33 %)
Para-aortic lymphadenectomy	70+9 (51 %)	6+2 (5 %)	87 (28 %)
Pelvic lymphadenectomy			
-unilateral	4 (3 %)	1 (1 %)	5 (2 %)
-bilateral	77+11 (56 %)	13+2 (10 %)	103 (34 %)
Bowel resection	2+1 (2%)	13 (12%)	16 (5 %)
Appendectomy	45+4 (31 %)	19+2 (14 %)	70 (23 %)

+ = Number of procedures performed at re-operation on the 16 re-operated invasive ovarian cancer patients

No macroscopic residual tumor was left in 47 % of the patients. For stage III patients operated on by gynecological oncologists, the estimated odds ratio for no macroscopic tumor was 3.0 times higher (95 % CI 1.2-7.5) than for those operated on by general gynecologists. The change in the amount of macroscopic pre- and postoperative extra ovarian tumor in stage III ovarian cancer patients is shown in Table 10. The information is presented in histogram form in original Study II.

Table 10. Change in amount of pre- and postoperative extra ovarian tumor in stage III ovarian cancer patients operated on in 1999 in Finland

	University	Central	District	Gyn.oncologist	Gynecologist
No macroscopic .					
preoperative	7 (11 %)	1 (2 %)	2 (10 %)	6 (11 %)	4 (4 %)
postoperative	22 (33 %)	6 (10 %)	4 (19 %)	19 (35 %)	13 (14 %)
	+ 22 %	+ 8 %	+ 9 %	+ 24 %	+ 10 %
>2cm					
preoperative	39 (60 %)	46 (78 %)	16 (76 %)	33 (62 %)	68 (73 %)
postoperative	27 (41 %)	32 (54 %)	11 (52 %)	23 (43 %)	47 (51 %)
	- 19 %	- 24 %	- 24 %	- 19 %	- 22 %

5.3 Study III

The prospective, five-year follow-up study included 275 patients operated on for epithelial ovarian cancer in 1999 in Finland. High hospital operative volume was a significant beneficial prognostic factor for disease-free (HR = 0.988, p = 0.048) and cancer-specific survival (HR = 0.986, p = 0.036).

The overall 5-year CSS was 56 % in the whole study population. Older age, advanced stage and larger residual tumor were significant unfavorable prognostic survival factors. Multivariate analyses of CSS and DSF, adjusted for age and stage of the disease, are shown in Table 11.

The median follow-up time was 43 months (range 0-61) and the disease-free interval had a median of 33 months (range, 0-61 months). By the end of the 5-year follow-up, 101 (37 %) patients had a recurrence of the tumor, 60 (22 %) patients had persistent disease, and 114 (41 %) patients had complete response to primary treatment and had remained disease free. All 60 patients with persistent disease died from ovarian cancer. Additionally, 121 patients (44 %) died from ovarian cancer although the disease had not persisted, while 9 (3 %) patients died from causes unrelated to

ovarian cancer. After cytoreduction, 81 % of the patients received platinum-based chemotherapy within an average of 20 days after the primary operations. The percentage was same in all hospital categories. Chemotherapy with a platinum + taxane combination was given to 63 % of the patients in the university and in 49 % in the other hospitals ($p = 0.0763$).

Table 11. Multivariate analysis of prognostic survival factors of ovarian cancer operated in 1999 in Finland. Adjusted for age and disease stage.

Variable	Disease-free survival			5-year cancer-specific mortality		
	Hazard ratio	95 % Confidence interval	p-value	Hazard ratio	95 % Confidence interval	p-value
Hospital volume						
As continuous variable	0.988	0.976-1.000	0.048	0.986	0.973-0.999	0.036
As categorical variable			0.019			0.188
>20 operations/year	1 (reference)			1 (reference)		
10-20 operations/year	1.481	1.031-2.126		1.359	0.900-2.052	
0-10 operations/year	1.789	1.158-2.763		1.367	0.828-2.257	
Hospital category			0.062			0.188
University	1 (reference)			1 (reference)		
Other	1.357	0.984-1.872		1.280	0.886-1.849	
Operating surgeon			0.503			0.081
General gynecologist	1 (reference)			1 (reference)		
Gynecological oncologist	0.894	0.644-1.241		0.712	0.486-1.043	
Residual disease			< 0.0001			< 0.001
Left with residual	1 (reference)			1 (reference)		
No macroscopic	0.207	0.124-0.345		0.186	0.096-0.358	

Preoperative CA 125 value was available for 256 patients. Low CA 125 level was seen more frequently in patients with early stage disease or with no macroscopic tumor. Patients with favorable outcome had more often low CA 125 levels. The data is presented in Table 12.

Table 12. Percentage and outcome of patients in different categories by preoperative CA 125 value

	CA 125 < 35 U/ml	CA 125 35-100 U/ml	CA 125 100-1000 U/ml	CA 125 > 1000 U/ml
Number of patients	28	46	120	62
FIGO Stage				
Stage I-II	22 (79%)	31 (67%)	38 (32%)	9 (15%)
Stage III-IV	6 (21%)	15 (33%)	82 (68%)	53 (85%)
Histology				
Serous	9 (32%)	19 (41%)	61 (51%)	38 (61%)
Mucinous	8 (29%)	11 (24%)	16 (13%)	1 (2%)
Other	11 (39%)	16 (35%)	43 (36%)	23 (37%)
Ascites				
no ascites	15 (54%)	22 (48%)	32 (27%)	5 (8%)
<200ml	13 (46%)	14 (30%)	48 (40%)	11 (18%)
200-1000ml	1 (4%)	5 (11%)	14 (12%)	13 (21%)
>1000ml	0	5 (11%)	26 (22%)	33 (53%)
Residual disease				
No macroscopic	23 (82%)	31 (67%)	53 (44%)	12 (19%)
Macroscopic	5 (18%)	15 (33%)	67 (56%)	50 (81%)
Tumor recurrence	8 (29%)	16 (35%)	72 (60%)	52 (84%)
Died from ovarian cancer	4 (14%)	10 (22%)	56 (47%)	42 (68%)

5.4 Study IV

The results are based on 65 borderline ovarian cancer patients operated on in Finland in 1999. In the study group 37 (57 %) of the tumors were of serous histology, 27 (42 %) mucinous and 1 (1%) mixed epithelial. More than half of the patients were operated on in outside the university hospitals. Borderline tumor patients were younger, had lower level preoperative CA 125 concentrations, and their tumor was usually confined to the ovaries. Adequate staging including omentectomy, and peritoneal biopsies were taken only in a minority of patients. There were no obvious differences in the extent of operative treatment between the different hospital categories. Comparison of the characteristics of patients with borderline tumor or invasive ovarian cancer is presented in Table 13.

Table 13. Comparison of characteristics of patients and histology with borderline tumor (Study IV) and invasive ovarian cancer (Study II) operated on in 1999 in Finland.

	Borderline tumors (N = 65)	**Invasive ovarian cancers** (N = 307)
Patients:		
- Age years	52 (21-89)	60 (16-93)
- Age < 40 years	16 (25 %)	27 (9 %)
- BMI (body mass index)	26 (19-39)	25 (16-44)
- CA 125 U/l	46 (1-401)	1052 (3-40100)
- CA 125 < 35 U/l	31 (48 %)	53 (17 %)
- CA 125 missing	11 (17 %)	20 (7 %)
- Ascites ml	74 (5-300)	1853 (5-13000)
- No ascites	39 (60 %)	79 (26 %)
- Tumor macroscopically confined to ovary	60 (92 %)	111 (36 %)
- Microscopic extra ovarian spread	7 (11 %)	222 (72 %)
Histology		
-Serous	37 (57 %)	139 (45 %)
-Mucinous	27 (42 %)	35 (11 %)
-Endometrioid	-	40 (13 %)
-Clear cell	-	6 (2 %)
-Other*	1 (1 %)	55 (18 %)
-Non-epithelial	-	20 (7 %)
-Unknown	-	12 (4 %)

* Other category includes mixed, undifferentiated, unclassified and Brenner tumors

The extent of surgery of borderline tumors in each hospital category is presented in Table 14. Most patients underwent bilateral salpingo-oophorectomy and hysterectomy. Lymphadenectomy, omentectomy and multiple peritoneal biopsies were more often taken in the university hospitals than in the other hospitals. Ten patients (15 %) were operated on primarily by laparoscopy, and eight of these patients had stage I disease.

Table 14. Extent of surgery of borderline tumors operated in 1999 in Finland, by hospital category

	University (N = 28)	**Other** (N = 37)	**All** (N = 65)
Operations:			
Unilat. oophorectomy	8 (29 %)	13 (35 %)	21 (32 %)
Bilat. oophorectomy	20 (71 %)	23 (66 %)	43 (66 %)
Hysterectomy	15 (54 %)	23 (62 %)	38 (58 %)
Omentectomy	15 (54 %)	7 (19 %)	22 (34 %)
Peritoneal biopsy/biopsies	6 (21 %)	10 (27 %)	16 (25 %)
-multiple (5-21) biopsies	6/6	2/10	8/16
Para-aortic lymphadenectomy	2 (7 %)	0	2 (3%)
Pelvic lymphadenectomy			
-unilateral	1 (4 %)	1 (3 %)	2 (3 %)
-bilateral	6 (21 %)	1 (3 %)	7 (11 %)
Appendicectomy			
-mucinous tumors	3/10 (30 %)	5/17 (29 %)	8/27 (30 %)
-serous	3/18 (17 %)	2/19 (11 %)	5/37 (14 %)
Frozen section	14 (50 %)	19 (51 %)	33 (51 %)

6. DISCUSSION

6.1 Clinical characteristics of the patients

Surgical treatment is the cornerstone of ovarian cancer treatment. In this survey various factors contributing to the extent and outcome of primary surgery have been evaluated. We have focused on hospital category, hospital operative volume and training of the operating surgeon. Also the effect of these factors on patient outcome was evaluated.

6.1.1 Retrospective study (Study I)

The retrospective, population-based survey consisted of 3851 patients operated between 1983 and 1994 in Finland for invasive ovarian cancer. The study was based on Finnish Cancer Registry data and included information on the date of diagnosis, site of malignancy, histological type and division to either a local or advanced tumor. The treatment modality (e.g. surgery, radiation therapy and chemotherapy) and the status at follow-up was also given.

The strengths of the study is large sample size, population based analysis, and completeness of data and follow-up. For solid tumors, the coverage of the Finnish Cancer Registry is over 99 % (Teppo et al. 1994). A weakness is the lack of detailed data on surgical treatment and chemotherapy.

A higher proportion of patients operated on in the non-university hospitals had localized tumors. The reason may be the well known difficulties to differentiate between early stage ovarian cancer and benign ovarian tumor. On the other hand, a higher proportion of younger patients were operated on at the university hospitals, which may indicate a low threshold of referring young patients to bigger units. The statistical model was designed to control for possible bias due to differences in age and FIGO stage. The model analyzed the data by age group and then combined the results.

According to registry data, 71 % of the patients in our series received chemotherapy. The use of chemotherapy was slightly more common in university hospitals (74 %) and central hospitals (74 %) than in other hospitals (62 %). Detailed information concerning chemotherapy was not available from registry data. However, during the study period platinum based combination was commonly used as first-line chemotherapy to treat ovarian cancer in Finland. Therefore, the mostly

obviously different factor between the hospital categories and quartiles was the primary operative treatment.

6.1.2 Prospective studies (Studies II-IV)

In the prospective baseline study (Study II), the patients operated on in the university hospitals had higher mean CA 125 values, more ascites, and more often stage IV disease than patients operated on in the other hospital categories. On the other hand, more stage I patients and young patients with stage I disease were operated on in university hospitals. The age variation between university and other hospital was statistically significant ($p = 0.0001$), unlike the stage variation ($p = 0.144$). However, the multivariate analysis (Study III) was adjusted for age and stage of the disease.

The definition of the hospital responsible of the first-line treatment was not always clear. For patients treated by one department only, this definition was not problematic, but in some cases, more than one department was involved in the initial treatment. The percentage of patients treated by more than one department was only 5 % according to the prospective study. In these cases, the department which was responsible for the operation was defined as having had the primary responsibility for the treatment.

Strengths of the prospective study are completeness of the data and follow-up, and a uniformly evaluated surgical database. The coverage of the prospective baseline evaluation was checked from the population-based, nation-wide Finnish Cancer Registry, and was 88 % of the patients who had undergone surgical treatment for invasive ovarian cancer in Finland in 1999. In the 5-year follow-up study, the response rate to the survey was no less than 96 %. Additionally, it was possible to complete and verify death notifications from the data of the Finnish Cancer Registry. The study does not cover the possible preoperative decision making regarding patient selection between the different hospital categories.

The amount of residual tumor is a subjective assessment. To minimize the data error, copies of the surgical reports, histopathology reports and cytology reports were collected and analyzed. A central review of the histopathological samples taken at primary surgery was not performed, and information on histology was obtained from the hospital records. On the other hand, histology is not centrally reviewed in clinical setting, either.

After cytoreduction, 81 % of the patients received platinum-based first-line chemotherapy. The percentage was the same in university and other hospitals. The number of patients treated with a platinum + taxane combination was higher in university hospitals, 63 % compared to 49 % in other hospitals but the difference was not statistically significant (p = 0.0763). Also 11 % of the patients treated in the university hospitals and 18 % in the other hospitals received less than six cycles of chemotherapy due to early stage disease, side effects, or poor general condition (p = 0.0733). Therefore, it is unlikely that the difference in survival would be explained by chemotherapy effect. It is worth notice that the patients were treated in 1999 and that the randomized study by McGuire and co-workers showing superiority of paclitaxel + cisplatin over cyclophosphamide + cisplatin was published in 1996 (McGuire et al. 1996). Taxanes were not yet in nation-wide use in Finland in 1999 and apparently university hospitals (and gynecological oncologists) accepted the new drug earlier than other hospitals. In some survival studies that have examined the association between hospital volume and outcome of ovarian cancer patients, the use of postoperative chemotherapy were not taken into account in the statistical analyses (Elit et al. 2002, Ioka et al. 2004, Oberaigner et al. 2006). The effect of chemotherapy on survival is a contentious issue. In several studies, platinum-based chemotherapy is carried out with better adherence in higher volume cancer centers (Junor et al. 1994, Schrag et al. 2006), but also adverse effects were seen (Tingulstad et al. 2003 and 2003). When the type of chemotherapy is taken into account, patients receive paclitaxel combination therapy more often in higher volume units, and this improves the treatment results (Oksefjell et al. 2006, Paulsen et al. 2006).

The duration of disease-free survival can be based on physical examination, symptoms, imaging studies and tumor markers. All these factors are used clinically. RECIST criteria (Response Evaluation Criteria in Solid Tumors, Jaffe 2006, Therasse et al. 2000) were not implemented yet in 1999 and could not be used in the 5-year follow-up study. Therefore modified criteria which were feasible for a nationwide study were used and this may be regarded as another weakness of the current study.

6.2 Extent of operative treatment

6.2.1 Lymphadenectomy

Lymphadenectomy is part of the surgical staging procedure of ovarian cancer, but the data on its effect on survival is controversial. The extent of the operation could be evaluated in the prospective study performed in 1999 (Study II). Pelvic lymphadenectomy was performed in 58 % and para-aortic lymphadenectomy in 46 % of the patients who had macroscopic tumor confined to the ovaries. Most of lymphadenectomies were performed in the university hospitals by gynecological oncologists. Based on surgical staging, 26 patients (8 %) had tumor outside the ovaries according to pathology reports and were upstaged and one of the 13 re-operated patients with macroscopic tumor confined to ovaries was upstaged to stage IIIC. A number of reports have documented that up to one-third of all patients with disease apparently confined to the ovaries or pelvis will have occult disease in the upper abdomen, retroperitoneal lymph nodes, or beyond (Le et al. 2002, Hoskins et al. 1993, Winter et al. 2002). The low percentage of upstaged patients in the current study may be explained by the relatively low number of lymphadenectomies performed on patients with clinical stage I disease. It is well established that systematic lymphadenectomy gives better information on the disease spread and is of utmost importance for patients with clinical stage I disease (Buchsbaum et al. 1989, Burghardt et al. 1991, di Re et al. 2000, Pereira et al. 2007, Suzuki et al. 2000). The lack of lymphadenectomy and peritoneal biopsies imply suboptimal staging and probably, suboptimal treatment.

Retrospective, non-randomized, studies suggest that thorough staging and debulking of the retroperitoneal lymph nodes improves patient outcome (Aletti et al. 2006, Bristow et al. 2002, Chan et al. 2007, Scarabelli et al. 1995). In 2005, Panici and co-workers reported the first randomized prospective study of systematic lymphadenectomy of the pelvic- and para-aortic region versus removal of bulky nodes only for stage IIIb – IV- patients with residual disease ≤ 1cm (Panici et al. 2005). A total of 427 patients were randomized into two groups and were well matched with respect to age, stage, residual disease, tumor grade and cell type. Although systematic lymphadenectomy improved progression-free survival by 5 - 7 -months, there was no significant benefit in overall survival. In addition, patients who underwent systematic lymphadenectomy had a longer operation time and more complications. However, the survival comparison was based on 191 events in only 44.2 % of all recruited patients and thus the final results may be biased. Two-thirds of the included patients had intra-abdominal residual cancer tissue with a size of up to 1cm. Lymphadenectomy

would not alter their tumor status and they still had small volume disease intra-abdominally even if small lymph node metastases had been removed.

In the other randomized study in 2006, Maggioni and co-workers examined the value of systemic lymphadenectomy for the treatment of patients with epithelial ovarian cancer confined to the pelvis. With 268 patients randomized, there was no significant benefit in terms of progression-free survival or overall survival at a median follow-up of 87.8 months (Maggioni et al. 2006).

In the present study the number of lymphadenectomies was higher in the university hospitals than the other hospitals, regardless disease stage. However, it is not possible to draw any conclusions on the association between lymphadenectomy and survival. On the basis of the above mentioned studies, it would seem reasonable to conclude that patients with macroscopic residual intraperitoneal disease do not benefit from systematic lymphadenectomy. Patients with advanced disease, who are cytoreduced to no macroscopic tumor, might benefit from lymphadenectomy. For these patients complete debulking should be the ultimate aim of surgery before primary chemotherapy.

6.2.2 Cytoreductive surgery

Primary cytoreductive surgery remains the standard care in the treatment of advanced ovarian cancer (Benedet et al. 2000). Cytoreductive surgery for advanced ovarian cancer was first introduced by Meigs in 1934. In 1975 Griffiths re-established the concept of cytoreductive surgery and showed an inverse relationship between residual tumor diameter and survival (Griffith et al. 1975). Since this landmark study, these findings have been confirmed by many other authors (Bristow et al. 2002, DiSaia et al. 2001, Chi et al. 2006, du Bois et al. 2006, Eisenkop et al. 2003 and 2006, Hoskins et al. 1994, Le et al. 1997, Tingulstad et al. 2003, Trimble et al. 1999, Wimberger et al. 2007). This finding has led to the concept of "optimal residual disease" which has been defined differently over time. Different authors have used ≤ 2cm, ≤ 1cm, or no residual tumor as the criteria for optimally debulked ovarian cancer. In recent publications no residual tumor is considered to be optimal result of cytoreductive surgery (Chi et al. 2006, du Bois et al. 2006, Eisenkop et al. 2006).

The amount of residual tumor is dependent on many factors. Factors that are often considered include comparison of general gynecologists vs gynecological oncologists, teaching hospitals vs

non-teaching hospitals and hospital operative volume. The present study (Study III) shows that sufficient training of the surgeon, the use of a multidisciplinary team, and better primary debulking have a favourable influence of outcome. In stage III patients operated on by gynecological oncologist the estimated odds ratio for no macroscopic tumor was three times higher than for general gynecologists. This indicates that it is important to have patients operated on by physicians specialized in this field of cancer surgery and that the surgeons perform a sufficient number of operations. In a study by Hacker and co-workers, even in patients with advanced ovarian cancer who are initially thought to be unresectable by less experienced surgeons, an optimal cytoreductive debulking (defined as largest residual tumor mass 1.5 cm or less in diameter) was achieved in 71 % by gynecological oncologists (Hacker et al. 1983).

According to our prospective survey (Study II), the number of patients with no macroscopic disease increased after primary surgery most in the university hospitals (14 %), compared with 8 %, and 5 % in central and district hospitals, respectively. The percentage of stage III patients with no macroscopic residual tumor was the highest in the university hospitals and when the surgeon was a gynecological oncologist. Apparently the training of surgical skills and the hospital operative volume go hand in hand. Thus, the present data are in line with studies indicating that better operative outcomes can be achieved in larger units.

6.3 Survival by hospital categories

6.3.1 Disease-free survival

In spite of the initial high response rates to primary treatment, most patients with advanced disease will ultimately relapse. In our prospective study on patients operated in 1999 (Study III), 41 % of the patients remained disease-free during the 5-year follow-up. A statistically significant association between the hospital operative volume and DFS was identified in favor of high operative volume hospitals ($p = 0.019$). The four largest university hospitals operated 44 % of all ovarian cancer patients in 1999. However, the differences between university and other hospitals, was not statistically significant ($p = 0.062$). It may be justified to state that the figures suggest a trend of better DFS for patients operated in the university hospitals. The reason might be related to one university hospital operating less than 20 patients per year which may be a confounding factor.

Adequate staging is considered to be important when deciding on postoperative chemotherapy. Comprehensive surgery can separate patients with true stage I disease from patients with microscopic stage III disease in their lymph nodes. In clinical practice, almost all patients with ovarian cancer (with the exception of stage IA grade I) are treated with postoperative chemotherapy. Although platinum-based chemotherapy was used equally often in the different hospital categories, patients treated in university hospitals did receive more often platinum + taxane combination therapy than patients treated in other hospitals but the difference was not statistically significant.

Estimating an accurate date of progression is difficult. Recurrence of ovarian cancer does not usually produce symptoms and is diagnosed clinically by increasing CA 125 levels or by imaging studies. Progression can be defined by a doubling of the CA 125 levels from the upper limit of the reference range or from the nadir level, if levels are persistently elevated (Rustin et al. 2001). When an elevated CA 125 value is detected, it needs to be confirmed by other samples and imaging. The date of progression is dependent on the timing of the follow-up and defining the exact date of recurrence is impossible. In a randomized trial of 556 relapsed epithelial ovarian cancer patients, whose disease progression was determined by clinical or radiological methods were compared with 389 patients whose disease progression was determined by the CA 125 definition. The specifity of CA 125 to define progression was 95 %, and the magnitude of the therapeutic benefit was similar between the two trial arms (Rustin et al. 2006). In this nation-wide study, the RECIST criteria or CA 125 criteria could not be used, and the date of progression was defined by the physician responsible for the follow-up. The main outcome, overall survival, was a more reliable definitive end point.

In a retrospective analysis of 1895 patients with stage III epithelial ovarian cancer, 1505 recurrences were identified during a median follow up of 43 months. Overall median progression-free survival was 17.1 months (95 % CI, 16.4 to 17.8 months), and the independent predictors of prognosis were age, performance status, tumor histology, and residual tumor (Winter et al. 2007). The results of a Norwegian study that was based on patient records and Cancer Registry information of 776 stage IIIC ovarian cancer patients were similar as the current study: the more radical the primary operation had been and the higher the level of the hospital, the better the overall survival and the progression-free survival (Oksefjell et al. 2006). A drawback of the study is that it was retrospective.

6.3.2 Cancer-specific survival

According to the Finnish Cancer Registry data, the overall 5-year RSR of ovarian cancer in Finland in 1985 – 94 was 37 %. In 2001 - 2003 the survival was 49 %. The cancer-specific 5-year survival was higher (56 %) in our follow-up study (Study III). Only operated ovarian cancer patients were included in the survey, which excluded patients with the poorest prognosis. The study population covered 79 % of all operated epithelial ovarian cancer patients in 1999 in Finland. The percentage of included patients was the highest in the university hospitals. These factors explain together the higher than expected cancer specific 5-year survival in the current survey.

The effect of hospital volume on survival has been discussed in recent articles (Engelen et al. 2006, Ioka et al. 2004, Junor et al. 1994, Paulsen et al. 2006, Tingulstad et al. 2003). In a study from Japan the number of patients with ovarian cancer treated at the respective hospitals was directly related to survival (Ioka et al. 2004). Another study reported a significantly poorer survival for ovarian cancer patients who had been operated on in low operative volume departments (Oberaigner et al. 2006). Both of these studies were based on cancer registry data, which limits the information on confounding factors.

The above results are in line with the current study showing that patients operated on in the highest volume university hospitals had the best prognosis when compared to patients operated on in smaller hospitals. The results showed relative risk of 1.06 for other hospitals as compared to university hospitals ($p = 0.325$) and a relative risk of 1.13 for the smallest compared to the largest hospitals by quartiles ($p = 0.046$). In the prospective study (Study III) a statistically significant association between hospital operative volume as a continuous variable and better CSS by multivariate analysis was detected ($p = 0.036$).

Treatment in teaching hospitals has been reported to improve survival. Population-based studies from England (Olaitan et al. 2001) and Norway (Paulsen et al. 2006, Tingulstad et al.2003) report better survival rates of patients treated in teaching hospitals compared with non-teaching hospitals due to more successful debulking surgery. In the present study, the increase in the risk of dying of patients operated on in non-university hospitals was 28 %, which was not statistically significant in comparison to university hospitals ($p = 0.188$). As discussed above, the highest volume hospital category consists of four out of the five university hospitals in Finland. The number of operated epithelial ovarian cancer patients per study year varied between 17 and 47 in the university

hospitals. More stage III and IV patients were operated on in the smallest university hospital compared to the largest one (65 % versus 53 %) reflecting differences in referral policy between these hospital districts. Cytoreduction to macroscopic disease-free state was achieved in 57 % of the patients in highest operative volume university hospital, compared to 41 % in the lowest, which goes together with the higher number of advanced stage patients in the small volume university hospital.

6.4 Prognostic factors

Numerous studies evaluating the value of different prognostic variables on survival of patients with ovarian cancer have been published. The well established prognostic factors of ovarian cancer are FIGO stage, age, histology and residual tumor. The most consistent, statistically significant prognostic factors in the literature are FIGO stage and size of residual tumor (Bristow et al. 2002, Chi et al. 2006, Skírnisdóttir et al. 2007). In a retrospective gynecologic oncology group study of 1895 stage III epithelial ovarian cancer patients who had been treated with primary cytoreduction and intravenous platinum + paclitaxel chemotherapy; advanced age, impaired performance status, mucinous or clear-cell histology, and gross residual disease were independent predictors of decreased progression-free and overall survival (Winter et al. 2007). In addition to these factors based on demographic and histological data, a number of molecular markers have been evaluated (Baekelandt et al. 1999 and 2000, Sillanpää et al. 2003, Skirnisdottir et al. 2001). The clinical significance and use of these markers is still limited. In the current prospective study (Study II-III) FIGO stage, age and residual tumor were strong prognostic factors and a high preoperative CA 125 concentration in the blood was associated with advanced disease.

6.4.1 Age

The mean age of nearly all industrialized populations is increasing, due to a lower birth rate and increased life expectancy. Ovarian cancer is diagnosed mainly in postmenopausal women. Since calendar age does not equal to biological age, and older patients have a longer life expectancy than before, we raised the age cut-off point defining elderly from 65 years in retrospective study to 70 years in the prospective study. Persons above 65 years constitute 44 % of the retrospective study population and above 70 years 29 % of the prospective study population.

The aging population makes outcome monitoring among elderly cancer patients particularly important. Some reports have indicated that younger age is not an independent prognostic survival factor suggesting that the survival advantage of the younger patients may be attributed to the increased frequency of early-stage, lower grade disease, and borderline tumors (Duska et al. 1999, Massi et al. 1996). However, other studies have reported age as a significant prognostic factor (Chan et al. 2007, Pectasides et al. 2007, Winter et al. 2007). Maybe differences in tumor biology, immune response, and co morbidities explain the increased risk of recurrence and death in elderly patients (Winter et al. 2007).

In this study older age was a significant prognostic factor for inferior survival. This was the case in the retrospective and the prospective survey (p values < 0.0001 to 0.0004). In the prospective study, less staging procedures were performed for the women aged 70 years and older. The results are in line with recent studies showing that older women are likely to be treated surgically more conservatively than their younger counterparts (Bruchim et al. 2002, Maas et al. 2005, Uyar et al. 2005). Recent studies indicated that the younger the patient, the higher was the probability of successful complete resection (Goff et al. 2007, Wimberger et al. 2007). Older patients often have multiple medical comorbidities, and often only the patients with a good performance status are selected for invasive staging and therapy. Young women with ovarian cancer need to be treated aggressively, because their young age does not confer an improved prognosis. Clinical management should be based on the medical circumstances and biological age rather than calendar age.

6.4.2 Stage

A number of prognostic factors related to patients with early stage ovarian cancer are not included in the FIGO staging system, which is based on the findings at surgical exploration and histopathologic analysis. The FIGO nomenclature (Rio de Janeiro 1988) includes features such as tumor capsule rupture and positive cytology. However, this classification does not take into account the degree of differentiation, or the amount of residual disease, which are known to be significant and independent prognostic factors (Vergote et al. 2001, Zanetta et al. 1998, Griffiths et al. 1975, Eisenkop et al. 2003, Heintz et al. 2006, Wimberger et al. 2006).

Despite its limitations, the FIGO stage is an established prognostic factor, and carried prognostic information also in the current study. Excluding a few low risk stage I patients, all ovarian cancer

patients were treated with postoperative chemotherapy. Detection of metastatic lymph nodes in a women with clinical stage I disease plays an important role in decision making.

6.4.3 Grade

In a number of studies including all stages (Heintz et al. 2006, Engelen et al. 2006, Junor et al. 1994, Woodman et al. 1997), tumor grade was considered to be a significant prognostic factor. In studies including only early ovarian cancer, the grade was more often the most important prognostic factor (Chan et al. 2007, Vergote et al. 2001, Zanetta et al. 1998).

In our analysis, age, FIGO stage and residual tumor were strong predictors of survival. Tumor differentiation was not, however, a significant determinant of outcome ($p = 0.210$), probably because of the high percentage of patients with advanced disease. All FIGO stages I-IV tumors were included in the patient population and only 28 % of the patients had stage I disease, where tumor grade is regarded as the most powerful prognostic factor. We did not analyze stage I patients separately, since they were too few.

6.4.4 Residual tumor

Appropriate staging and maximal cytoreduction are the two goals of the primary surgery of ovarian cancer. Surgical outcome is one of the few prognostic factors which can be influenced by treatment. In a large meta-analysis of 53 studies, 81 cohorts, and 6885 patients with stage III or IV ovarian cancer, the proportion of maximal cytoreductive surgery was the most powerful independent determinant of cohort survival (Bristow et al. 2002). All patients received platinum-based chemotherapy, and neither the platinum dose-intensity nor the cumulative platinum dose was significantly associated with the median survival time. Maximal cytoreductive surgery was defined according to the largest diameter of residual disease, which ranged from 0.5 cm to 2 cm. Ninety-five percent of the studies used either 1 or 2 cm as the discriminating criterion, and no evaluation of potential effect of median survival and the diameter of residual disease was done (Bristow et al. 2002). In a multivariate analysis patients with no residual disease had the best prognosis. Patients with residual disease $\leq$ 2cm or $>$ 2cm only differ slightly from each other (Heintz et al. 2006). These results are strong arguments in favor of a policy of optimal primary or interval debulking surgery. The strength of the amount of residual tumor as a prognostic factor was seen also in the current survey (Study II-III). The percentage of patients with no macroscopic tumor increased the

most in university hospitals and when operated by gynecological oncologist. Survival among completely debulked patients was significantly better: complete debulking reduced the risk of dying by 81 % compared to patients with residual tumor after surgery ($p < 0.001$).

The relationship between aggressive tumor biology and the extent of the disease has been studied. Indirect evidence is available suggesting that inherent tumor biology relates to resectability (Eisenkop et al. 2006). The consistent effect of the surgeon's specialty on survival argues against tumor biology as the sole determinant of both surgical outcome and survival. Surgical outcome depends on both biology of the patient and the disease, surgical skills and infrastructure of the hospital (Wimberger et al. 2007). Table 15 summarizes the results of seven studies evaluating the effect of the residual disease on survival of ovarian cancer patients.

Table 15. Effect of size of residual disease on survival of ovarian cancer patients

Reference	Stage of disease	Number of patients	Residual macroscopic disease (Number of patients, %)	Survival rate	p-value
Present study	I-IV	275	No macroscopic residual (126, 46 %) Left with residual tumor (149, 54 %)	0.186 (0.096-0.358) HR (95 % CI), reference	< 0.001*
Chi et al. 2006	IIIc	465	No gross residual (67, 15 %) Gross residual ≤ 1 cm (169, 36 %) Gross residual > 1cm (229, 49 %)	HR (95 % CI), reference 2.07 (1.23-3.46) 3.70 (2.27-6.04)	 0.006* < 0.001*
Winberger et al. 2006	IIb-IV	761	No macroscopic tumor (227, 29.8 %) Residual tumor ≤ 1 cm (32.5 %) Residual tumor >1 cm (37.7 %)	Mean OS 4.7 years Mean OS 3.5 years Mean OS 3.0 years	< 0.0001
Eisenkop et al. 2003	IIIc	408	No gross residual (351, 86 %) Gross residual ≤ 1cm (41, 10 %) Gross residual > 1cm (16, 4 %)	RR (95 % CI), reference 2.32 (1.20-5.37) 2.98 (1.74-5.23)	0.001*
Bristow et al. 1999	IV	84	Gross residual ≤ 1cm (25, 30 %) Gross residual > 1cm (59, 70 %)	MST (mo) 38.4 MST (mo) 10.3	0.0004, significance retained in multivariate analysis
Junor et al. 1994	I-IV	406	Gross residual < 2cm (184, 45%) Gross residual >2cm (222, 55 %)	0.50 (0.37-0.66) HR (95%CI), reference	< 0.001*
Griffiths et al. 1975	II-III	102	No gross residual (29) Gross residual 0-0.5 cm (28) Gross residual 0.6-1.5 cm (16) Gross residual > 1.5 cm (29)	MST (mo) 39 MST (mo) 29 MST (mo) 18 MST (mo) 11	

*Multivariate analysis
CI=Confidence intervals, HR=Hazard ratio, MST= Median survival time in months, OS=Overall survival

6.4.5 Training of surgeon

In the past two decades, interest has grown regarding the relationship between surgical specialty and outcome of cancer treatment. In ovarian cancer, there may be a relationship between sub-specialty training and survival (Earle et al. 2006, Engelen et al. 2006, Giede et al. 2005, Kehoe et al. 1994, Hillner et al. 2000, Nguyn et al. 1993, Vernooij et al. 2007, Woodman et al. 1997). In general a gynecological oncologist is defined as a gynecologist who has formal training and experience in gynecological oncology. In the United States, fewer than 50 % of ovarian cancer patients had the benefit of having their initial surgery performed by a qualified gynecological oncologist (Carney et al. 2002, Bristow et al. 2004).

An evidence-based review evaluated the relationship between surgical specialty and survival of operated ovarian cancer patients. The data demonstrated a 6 - to 9 - month median survival benefit for patients operated on by gynecological oncologists (p values 0.009 to 0.001). It was significantly more likely that gynecological oncologists performed optimal staging in early stage patients and optimal cytoreductive surgery in advanced stage patients than general gynecologists (Giede et al. 2005). Similar conclusions were drawn in another systematic review of 12 differing studies from the total of 19 retrieved articles (Vernooij et al. 2007). The selection criteria varied slightly between the reviews and were less restrictive in the latter study which also included only studies in which patients were diagnosed after 1990. The latter study included also articles published after 2005. The authors concluded that there is an effect of gynecological oncologists on survival in subgroups of patients, but other factors, e.g. chemotherapy, also explain the better results obtained in specialized hospitals (Vernooij et al. 2007). In another recent study, chemotherapy for ovarian cancer patients given by medical oncologists and gynecological oncologists was significantly different in terms of treatment time. Patients treated by medical oncologists received chemotherapy longer and had more chemotherapy-associated adverse events. However, the survival of matched patient groups was virtually identical (Silber et al. 2007).

In the current study (Study II) 72 % of all operations were performed by gynecological oncologists, compared with only 4 % - 19 % in other hospitals. Patients operated on in the highest operative volume hospitals, where gynecological oncologist were responsible for the operations, had significantly better cancer-specific and disease-free survival relative to patients operated in other hospitals, where mainly general gynecologists operated. Gynecological oncologists followed surgical guidelines more closely and removed more often all macroscopic tumor. For stage III

patients operated on by gynecological oncologists, the estimated odds ratio for no postoperative macroscopic tumor in Fisher's exact test was 3.0 times higher (95 % CI 1.2-7.5) than for those operated on by general gynecologists. Furthermore, lymphadenectomies were mainly performed by gynecological oncologist. This indicates that most of the general gynecologists were not trained to perform comprehensive staging of ovarian cancer.

The results of the current study (Study III) imply that surgery by a gynecological oncologist has a positive effect on survival and reduces the risk of dying by 29 %. Our results are in line with a population-based study, where gynecological oncologists were substantially more likely to do necessary staging, resulting in a more accurate assignment of disease stage and administration of the appropriate adjuvant treatment (Engelen et al. 2006). The result of the current survey (Study III) did not reach statistical significance ($p = 0.081$), probably due to the relatively low number of cases. The hospital category and the surgeon's specialty might have been too weak to be independent prognostic factors when the stronger factors, e.g. residual disease and hospital volume, were taken into account in multivariate analysis. The experience of an individual surgeon was not evaluated in the current study.

The surgical treatment of ovarian cancer was more heterogeneous in Finland in 1999 than today. Every fourth patient undergoing surgery for ovarian cancer even in university hospitals was operated on by a general gynecologist. Since then, the number of gynecological oncologists has increased in Finland and currently only a small minority of the patients with gynecological cancer treated in university hospitals is operated on by general gynecologists. With increasing awareness of the recommendations on tumor surgery, the clinical practices are changing. Further centralization can be achieved through frictionless collaboration and an effective referral policy, and accurate preoperative evaluation of pelvic tumors, e.g. by using the risk of malignancy index (Andersen et al. 2002, Tingulstad et al. 1996).

6.4.6 Hospital operative volume

A higher hospital operative volume was a significant prognostic factor associated with improved CSS (HR 0.986, $p = 0.036$) and DFS (HR 0.988, $p = 0.048$) in the prospective part of this study (Study III). Recent retrospective studies report a positive volume-outcome relationship in initial cancer surgery (Hillner et al. 2000, Ioka et al. 2004, Oberaigner et al. 2006). In contrast, in two large population-based cohort studies, the hospital operative volume was not a strong predictor of

survival for ovarian cancer among women aged 65 years or older (Earle et al. 2006, Schrag et al. 2006). Both studies focused on the approximately 3000 patients who had surgery for primary epithelial ovarian cancer and were identified through the SEER-Medicare database which covers 14 % of the U.S. population. Higher hospital operative volume was associated with lower 2-year mortality and higher overall survival. These figures were unaffected by case-mix adjustment, but the relationship lost statistical significance when the surgeon's operative volume was added into the equation (Schrag et al. 2006). However, Schrag and co-workers study included limitations due to the nature of the SEER-Medicare database. Because of incomplete data on ovarian cancer 24 % of the patients were excluded. This may have caused bias. Furthermore, there was no information on residual disease after primary surgery. Only overall mortality was considered rather than disease-specific outcomes such as DFS or cancer-specific mortality, as a result of the data not having been reliably captured from the SEER-Medicare data. The database included only patients aged 65 years or older. It is a well known fact that the patient's age at diagnosis and advanced clinical stage are among the strongest determinants of a poor outcome (Chan et al. 2006, Gershenson et al. 1993) a fact also observed in the analysis by Schrag and co-workers. Table 16 summarizes the effect of hospital operative volume on survival of ovarian cancer patients.

Table 16. Survival of ovarian cancer patients by hospital operative volume

Reference	Number of patients	FIGO stage	Hospital category	Outcome parameters	survival	p-value
The present study	275	I-IV	Volume as continuous variable	Hazard ratio (95 % CI)	0.986 (0.973-0.999)	0.036*
			Volume > 20pat/year	Hazard ratio (95 % CI)	1 (reference)	0.188*
			Volume 10-20 pat/year		1.359 (0.900-2.052)	
			Volume < 10 pat/year		1.367 (0.828-2.257)	
Oberaigner et al. 2006	453	I-IV	Volume 24-35 pat/year	Hazard ratio (95 % CI)	1.78 (1.50-2.12)*	
			Volume ≤ 11 pat/year		1.00*	
Schrag et al. 2006	2952	I-IV	Volume 29-93 pat/8-years	2-year mortality rate,	40.4 (38.5-42.3)	0.011
			Volume 13-28 pat/8-years	% (95 % CI)	41.1 (39.7-43.6)	
			Volume 1-12 pat/8 years		45.2 (43.2-46.9)	
Ioka et al. 2004	2132	I-IV	Volume 9 pat/year	5-year survival rate	57.4 % (2.1)	< 0.01
			Volume 4 pat/year	(standard error)	50.2 % (2.5)	
			Volume 2 pat/year		38.2 % (2.0)	
			Volume < 1 pat/year		28.7 % (2.2)	
Tingulstad et al. 2003	23	III-IV	Teaching hospitals	5-year survival rate	n=6 (26 %)	0.01
	46		Community hospitals		n=2 (4 %)	

*Multivariate analysis
CI=Confidence intervals

6.5 Operative treatment of borderline tumors

Borderline ovarian tumors are different from invasive ovarian cancer as shown in the current study (Table 11). Borderline tumors affect a younger age group than does invasive ovarian cancer, and future fertility is important for many of these women. The mean age of the patients with borderline tumor was 52 years, which is almost 10 years less than among the patients with invasive ovarian cancer. There were also differences in CA 125 levels and in the amount of ascites.

Surgical resection is the mainstay of treatment of borderline tumors and adequate surgical staging is important in for the identification of invasive, extra-ovarian implants that predict an adverse prognosis. The same FIGO staging system is used for borderline tumors as for invasive ovarian cancer with the exception of lymphadenectomy, which is excluded for the latter diagnoses. In early-stage disease, unilateral salpingo-oophorectomy is adequate, if fertility is desired (Benedet et al. 2000). For stage I borderline tumors, laparoscopic management may be considered, if the tumor is less than 10 cm in diameter (Ødegaard et al 2007). In the present study hysterectomy and bilateral salpingo-oophorectomy were the most frequently performed surgical procedures (Study IV). Ten out of 16 women who were under 40 years of age at the time of the operation underwent conservative surgery.

Since 1995, systematic pelvic and para-aortic lymphadenectomy have not been required for staging of this tumor type (Gershenson 1999), still any enlarged nodes should be removed. In the current, lymphadenectomy was performed in connection with the primary surgery on seven patients (11 %) with early stage disease and two patients (3 %) with macroscopically advanced stage disease. In these cases there was a strong clinical suspicion of invasive ovarian cancer in spite of a non malignant histology according to frozen section examination. None of these patients had lymph node metastases.

The data on the need for comprehensive staging of borderline tumors is still controversial. Staging is recommended by FIGO guidelines but the published literature does not support the effectivity of the procedure on survival. In a retrospective review of 247 patients with epithelial borderline tumors there were no significant differences in outcome measures of recurrence and mortality after staging versus unstaging procedures. Staging procedures comprising at least laparotomy, peritoneal washings, adnexectomy, peritoneal biopsies, and omental biopsy were performed on 164 (66 %) of the patients, and 39 patients in this group also underwent lymph node dissection. The authors

conclude that surgical resection is the mainstay of treatment, and conservative surgery where fertility is desired. Once the desired number of offspring has been obtained the remaining ovarian tissue should be removed. Patients treated by cystectomy only were reported to have three times higher recurrence rates than those treated by oophorectomy (Suh-Burgmann 2006). Furthermore 38 (15 %) of 249 women with a borderline ovarian tumor underwent fertility-sparing surgery. Six of these 38 patients had a recurrence after a median follow-up of 26 months, but none of the women died from disease (Rao et al. 2005).

The benefit of complete surgical staging has not been demonstrated in early disease, but the contralateral ovary should be carefully evaluated macroscopically at operation and by imaging pre- and postoperatively for evidence of bilateral disease. There has been no profound discussion on how this evaluation should be performed (Wong et al. 2007). In the cohort study of 93 patients with borderline tumor, 48 women had surgical staging including hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node sampling, omental biopsy, peritoneal biopsies, and cytologic washings. Eight (17 %) of these staged patients were upstaged on the basis of surgery, but only in 6 % of them was this due to retroperitoneal involvement. Survival and recurrence rates were not significantly different between staged (n=48) and unstaged (n=45) patients with an average follow-up of 6.5 years (Winter et al. 2002). The number of upstaged patients was higher in a study of Lin and co-workers. With accurate surgical staging, 41 % of the patients were upstaged because of microscopic extra ovarian disease (Lin et al. 1999). In the present study, one-fourth of the patients underwent recommended surgical staging with omentectomy and peritoneal biopsies. Only one biopsied patient had advanced stage disease. Appendectomy was performed for 8 out of 27 patients with mucinous borderline tumor. The percentage of patients who underwent omentectomy, lymphadenectomy and multiple peritoneal biopsies was somewhat higher in university hospitals than in the other hospital categories, but there were no clear differences (Table 14).

In the present study samples for frozen section examination were taken in half of the patients and the percentage was same in different hospital categories. The histological diagnosis according to frozen section examination remained unchanged in 72 % of the cases, and changed in 11 patients with a large tumor. For six patients reported in this survey (Study IV), a diagnosis of low malignant potential tumor by frozen section was changed to invasive cancer and these patients were excluded from the borderline study. In five additional cases the primary frozen section indicated a benign tumor while the final diagnosis after examination of samples from paraffin blocks revealed a

borderline tumor. In all instances of misdiagnosis, the tumor was large and contained 5 – 11 liters of cyst fluid at surgery. The reason for the relatively low number of frozen sections taken is not clear. It can not be explained simply by availability or lack of services, because in the university hospitals which have pathological services, also only half of the operated patients with a borderline tumor had frozen section taken.

The long term prognosis of borderline tumors is good. The reported rates of recurrence vary between 2.4 % - 25 % (Lackman et al. 2003, Longacre et al. 2005, Prat et al 2002, Suh-Burgmann 2006, Winter et al. 2002, Wong et al. 2007). According to a review of 247 ovarian borderline tumor patients, only six had recurrent disease (2.4 %) (Wong et al. 2007). However, the rate of recurrence was higher in the long-term follow up (mean 6.9 years) of 193 borderline tumor patients, with 11 % of women treated with conservative surgery experiencing a recurrence. Half of these recurrences were successfully managed by repeated conservative surgery, with only 6 % of the patients needing ultimately complete removal of the ovaries for recurrence (Suh-Burgmann 2006). In the current study during a relatively short follow-up only one patient who was suboptimally operated with macroscopic residual disease at primary operation had recurrent borderline tumor and was successfully re-operated.

In the current study, the overall 5-year survival rate was no less than 96 %, and there were no deaths attributable to borderline tumor (Study IV). However, the clinical follow-up time was a median of 41 months (range 1 to 67 months) and detailed 5-year follow-up data was obtained only on a minority of the patients, since the hospitals showed great variability in their follow-up schedules ranging from none to 65 months of follow-up. So it is possible that accurate recurrence rates could have been higher with more reliable follow-up information. The survival rate can be considered reliable, because it was obtained from the Finnish Cancer Registry.

Our results agree with a recent report according to which complete staging is infrequently performed in patients with early borderline tumor (Desfeux et al. 2005). Still the overall 5-year survival and recurrence rates were similar with and without staging (Winter et al. 2002). Although the lack of data showing a survival benefit was associated with surgical staging, this diagnostic procedure has been advocated in order to provide the patient with more accurate prognostic information.

7. SUMMARY

During the years 1983 - 1994 surgical treatment of ovarian cancer was decentralized and performed in over 80 units, including all health care categories from small district hospitals to university hospitals. In 1999 half of the ovarian cancer patients were operated on in university hospitals, but 20 % were still operated on in small units with less than 10 patients per year. In addition, even in the university hospitals every fourth patient with ovarian cancer was operated on by general gynecologists. Available literature from other countries suggests that the larger hospital operative volume and the subspecialty training in gynecological oncology would improve survival of ovarian cancer. Hence, studying the association between hospital operative volume and survival was of special public health interest. The purpose of the current study was to evaluate the extent and outcome of operative treatment of ovarian cancer in different hospital categories in Finland and how these possible differences are reflected in disease-free survival and 5-year cancer specific survival. We performed a larger retrospective registry survey of 3851 patients and a smaller, prospective nationwide study of 372 patients operated in 1999 in Finland.

According to retrospective, population-based study, centralization of the surgical treatment of ovarian cancer improves survival rates on a population level. The results are in line with our prospective study demonstrating that ovarian cancer patients operated in the highest operative volume university hospitals (> 20 patients/year) were more frequently optimally debulked and had significantly better cancer-specific survival than patients operated in the other hospitals. Only a minority of patients with borderline tumor was staged according to the recommendations and the result was seen in all hospital categories. The data indicates that the optimal results from the treatment of ovarian cancer will be achieved if primary surgery is centralized to multidisciplinary units where the number of treated patients is sufficient to guarantee adequate training and maintenance of surgical skills and where the treatment is performed by physicians specialized in ovarian cancer surgery and chemotherapy.

8. CONCLUSIONS

Based on the results of the current study the following conclusions can be drawn:

1. The 5-year RSRs of ovarian cancer were the best in hospitals with the highest operative volumes during the study period 1983-1994. The results of the study indicate that centralization of the treatment of ovarian cancer improves the survival rate on a population level.

2. Operative treatment of ovarian cancer varied in different hospital categories. More lymphadenectomies and staging biopsies were performed in university hospitals. Consequently a clinically significant number of clinical stage I patients were upstaged to surgical stage III in university hospitals.

3. The majority of gynecological oncologists worked in university hospitals. For stage III patients operated by gynecological oncologists, the estimated odds ratio for no macroscopic residual tumor was 3.0 times higher (95 % CI 1.2-7.5) than for those operated by general gynecologists.

4. Multivariate analysis showed that FIGO stage, patient age, residual tumor, and hospital operative volume were independent prognostic factors for 5-year survival. In addition, higher hospital operative volume was a significant prognostic factor for improved cancer-specific survival ($p = 0.036$) and disease-free survival ($p = 0.048$).

5. Only a minority of the patients with a borderline tumor were staged according to the recommendations. Multiple peritoneal biopsies and omentectomy were the most frequently neglected procedures. More attention should be paid on adequate staging of borderline tumors in all hospital categories.

6. The results of the current study are in favor of centralization of primary operative treatment of ovarian cancer.

9. APPENDIX

Appendix 1.

Questionnaire 1. The questionnaire used in the survey performed in 1999 contained detailed information on demographic patient characteristics as well as on the extent of the surgical treatment.

Ovarian cancer operations in Finland in 1999

Social security number: _____

Anamnesis

		Yes	No	Year
1.	Prior hysterectomy	1	2	_____
2.	Prior omentectomy	1	2	_____
3.	Prior ovarian cystectomy	1	2	_____

Present disease

4. Weight (kg) _____
5. Height (cm) _____
6. Preop. CA 125 _____
7. Preop. TATI _____
8. Day of the procedure _____
9. Hospital category 1 = University hospital 2 = Central hospital 3 = Other hospital
10. Name of the hospital _____
11. Operating physician 1= Gyn. oncol. 2 = Assistant physician 3 = Specialist 4 = Other
12. Operation 1= Elective 2 = Emergency
13. Category of the operation 1= Laparotomy 2 = Laparoscopy 3 = Laparoscopy prior laparotomy

Distribution of the tumor		**Yes**	**No**
14.	Tumor detected in one ovary	1	2
15.	Tumor detected in both ovaries	1	2
16.	Tumor detected in tube	1	2
17.	Tumor detected in uterus	1	2
18.	Tumor detected in other part of the pelvic area	1	2
19.	Tumor detected on bladder	1	2
20.	Tumor detected on intestine	1	2
21.	Tumor detected in fossa Douglas	1	2
22.	Tumor detected in omentum	1	2
23.	Tumor detected in diaphragm	1	2
24.	Tumor detected on liver	1	2
25.	Amount of ascites	_____ml	
26.	Was the tumor ruptured?	1	2
27.	Did the tumor rupture during the operation?	1	2

28. Largest tumor (ovaries not included) in the abdominal cavity
    1= no macroscopic, 2 = < 1 cm, 3 = 1 – 2 cm, 4 = 1-5 cm, 5 = > 5 cm

Extent of the operation	**Yes**	**No**
29. Inoperable	1	2
30. S-O-ectomy l.dx	1	2
31. S-O-ectomy l.sin	1	2
32. Hysterectomy	1	2
33. Amputatio uteri	1	2
34. Pelvic lymphadenectomy l. dx	1	2
35. Pelvic lymphadenectomy 1. sin	1	2
Amount of lymph nodes:_____pcs		
36. Para-aortic lymhadenectomy (above)	1	2
37. Para-aortic lymphadenectomy (below)	1	2
Amount of lymph nodes:_____pcs		
38. Omentectomy	1	2
39. Palliative bowel resection	1	2
40. Resection of the bladder	1	2
41. Stageing biopsies	1	2
Amount of biopsies:_____pcs		
42. Was the operation macroscopically radical	1	2

Residual disease

43. Size of the largest macroscopic tumor
    1 = no macroscopic, 2 = < 1 cm, 3 = 1 – 2 cm, 4 = 1-5 cm, 5 = > 5 cm

Histology and cytology

44. Patient was diagnosed 1= borderline tumor, 2= invasive carcinoma

FIGO stage 1= Ia, 2 = Ib, 3 = Ic, 4 = IIa, 5 = IIb, 6 = IIc, 7 = IIIa, 8 = IIIb, 9 = IIIc, 10 = IV

If stage IV disease, determine the location of metastases: _____

COPY OF THE PAD AND CYTOLOGY REPORTS SHOULD BE ALSO INCLUDED.

Appendix 2.

Questionnaire 2. The questionnaire used in the follow-up survey conducted in 2005 contained questions i.a. progression of the disease and management of the patient. Questionnaires were send to the hospitals where the patients had been operated in 1999.

Social security number: _____

No follow-up information, because of:
1 = follow-up carried out in an other hospital, name of the hospital _____
2 = the reason for no follow-up _____

Hospital category, name and type of the hospital_____
1 = university hospital 2 = central hospital 3 = distinct hospital 4 = other

Disease recurrence
1 = yes 2 = no If yes, 0-6months _____, >6months _____after primary therapy

Day of the recurrence _____

Relapse noticed
1 = Physical examination
2 = symptoms; beginning _____ months from primary operation
3 = ultrasound
4 = CT, MRI
5 = ascites
6 = CA 125 value _____
7 = laparotomy
8 = laparoscopy
9 = fossa Douglas cytology
10 = biopsies of metastases
11 = autopsy
12 = other method , define _____

Primary chemotherapy:
1 = carboplatin 2 = cisplatin 3 = paclitaxel 4 = taksotere 5 = liposomal doxorubicin
6 = topotecan 7 = gemcitabine 8 = etoposide 9= other _____

Number of primary chemotherapy cycles: _____
The reason if less than six cycles: _____

Chemotherapy used at first recurrence:
1 = carboplatin 2 = cisplatin 3 = paclitaxel 4 = docetaxel 5 = liposomal doxorubicin
6 = topotecan 7 = gemcitabine 8 = etoposide 9= other _____

Chemotherapy not used, because of
1 = patients refused 2 = poor general condition 3 = other reason_____

Hormonal therapy 1 = yes 2 = no used medication: _____
Radiation therapy 1 = yes 2= no

Surgical treatment after primary operation
- Day of operation _____
- Operative hospital _____
- Procedure _____

Last day of follow-up _____
Survival status
-Alive 1 = disease free 2 = alive with disease
-Died from 3 = ovarian cancer 4 = other reason
-Day of death _____

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