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DISSERTATION

Role of the operative tumor reduction in patients with epithelial ovarian cancer and suboptimal debulking

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1. Introduction

1.1. Epidemiology

Ovarian cancer is the fourth most common malignant disease among European women. It is the fifth most frequent cause of death in women (Bristow and Berek 2006) and related to the number of patients affected, the most common cause of death from gynecological malignancies. Worldwide there are 204,449 new cases of ovarian cancer diagnosed annually (accounting for 4% of female cancers) with an estimated 124,869 disease-related deaths.

In Europe (UE-25) there are 40,600 new cases annually (3.9% of female cancers) with 28,500 disease-related deaths (5.6% of female cancer-related deaths) (Ferlay, Autier et al 2007). Ovarian cancer seems to have a north-south gradient in UE-25, with the highest rate in the Czech Republic, Denmark and Sweden and the lowest rate in Southern European countries such as Portugal, Greece and Italy. Germany stands in the upper-middle of European rates. According to the latest results of the Robert Koch Institute based on the cancer registration data up to 2004, in Germany approx. 9,660 women develop cancer of the ovaries every year. The disease thus accounts for 4.7% of all malignant neoplasms in women. This incidence has been constant over the last 20 to 30 years. Nevertheless, due to a worse prognosis mortality, at almost 5,500 cases per annum, ovarian cancer is responsible for 5.6% of all cancer-related deaths. The survival prospects of patients with ovarian cancer have improved slightly over time. The relative 5-year survival rate in Germany is currently about 47% (data from the report “Cancer in Germany 2003 – 2004 Incidence and Trends”, published by the Robert Koch Institute and the Association of Population-based Cancer Registries in Germany, Sixth edition, 2008).

1.2 Ovarian cancer etiology

The etiology of ovarian cancer is still unknown.The carcinogenesis seems to be influenced multifactorially by genetic, endocrine and other determinants. The most accepted models of ovarian carcinogenesis are:

Incessant ovulations hypothesis

In 1971 MF Fathalla published his “Incessant Ovulation Hypothesis” in Lancet. He postulated a possible relationship between the repeated involvement of the ovarian surface epithelium in the process of ovulation and the frequency of the development of the common ovarian neoplasm from this epithelium. In this context, spontaneous mutations and the defective repairing process could lead to malignant transformations.

Excessive gonadotropin stimulation hypothesis

Years later, entrapment of surface epithelium within the ovarian stroma was proposed as initial event in the pathogenesis of ovarian cancer. Subsequent eventual malignant transformation of the entrapped epithelium was seen as a consequence of stimulation by estrogen or estrogen precursors (Cramer and Welch 1983; Stadel 1975).

Mullerian origin

Previous hypothesis failed to explain the resemblance of ovarian cancers to structures of Müllerian origin such as fallopian tubes, endometrium and endocervix. In recent studies, epidemiological data support a Müllerian origin of epithelial ovarian cancer and make for the hypothesis that primary ovarian epithelial tumours, fallopian tube carcinomas and primary peritoneal carcinomas are all Müllerian in nature and could therefore be regarded as a single disease entity (Dubeau 2008). This points to the possibility that the cell of origin for cancer initiation originates from outside the ovary (Widschwendter et al. 2009).

1.3. Risk and protective factors

Epidemiologic and molecular-genetic studies identify numerous risk and protective factors:

Age

Age is a risk factor for cancer due to the duration of carcinogenesis, the vulnerability of aging tissues to environmental carcinogens, and other bodily changes that favor the development and growth of cancer.

The average age at the point of diagnosis of the disease is between 67 and 68, and incidence increases with the age setting: the highest incidence rate (62-65 per 100,000

women) is found in the eight life decade (at an age of about 75 years) (data from the report “Cancer in Germany 2003 – 2004 Incidence and Trends”, published by the Robert Koch Institute and the Association of Population-based Cancer Registries in Germany, Sixth edition, 2008).

Socio-demographic

With regard to the components of diagnostic delay (total, patient and primary care, referral, secondary care) none of the socio-demographic factors seems to have a relationship (Allgar, Neal et al. 2006). Some studies reported a higher risk of disease in the upper socio-cultural class (Booth, Beral et al. 1989) but that effect may be attributed to the small number of births. On the other hand, authors such as Purdie have postulated that education beyond secondary school is associated with a significant reduction in risk {Odds Ratio (OR)=0.77, CI 0,62-0.95 in Purdie, Green et al. 1995}.

Ethnic origin

Worldwide, the highest incidence rate of ovarian cancer is to be found in the industrialized countries of Europe and North America and the lowest in Asia and Africa. The role of the ethnic origin still remains unclear.

In 2002, McGuire et al. included 38,012 women that between 1973 and 1997 were diagnosed with primary invasive epithelial ovarian cancer in the Surveillance, Epidemiology and End Results Program of the National Cancer Institute. After adjusting for age at diagnosis, stage of disease at diagnosis and cancer histology, they found that, compared to women of European descent, death rates were significantly elevated among African-Americans and significantly reduced among Hispanics and Filipinas (McGuire, Jesser et al. 2002). Other studies show that African, Asian and Hispanic women have a lower incidence rate than American women of European descent (Weiss and Peterson 1978). Similarly, women of African and Caribbean descent have a lower rate than British women of European origin (McCredie, Coates et al. 1994).

Genetic predisposition

The majority of cases of ovarian cancer are known to be sporadic, and only 5% to 10% of ovarian cancers are familial (Holschneider and Berek 2000).

The incidence of family predisposition to ovarian cancer has been demonstrated in a large number of epidemiological studies. Over the last 20 years, several genetic factors in relationship with the inherited ovarian cancer have been identified.

About 90% of all hereditary ovarian cancer is believed to be attributable to the BRCA genes. Inherited mutations in BRCA1 (Breast Cancer) or BRCA2 confer a strong predisposition to ovarian cancer as well as to breast cancer. Generally, the risk of breast cancer is probably higher than that of ovarian cancer in BRCA heterozygotes. Estimates of the lifetime ovarian cancer risk associated with BRCA mutation are variable and depend on the population studies, ranging from 15% to 60% (Boyd 2001; Chen, Iversen et al. 2006).

The remaining 10% of hereditary ovarian cancer cases are attributable to other mutations like the mutation in the “Hereditary Non-Polyposis Colon Cancer” (HNPCC) gene which inherits the colon cancer (Lynch II-Syndrom) (Marra and Boland 1995).

Age at menarche and age at natural menopause

Effects of ovulation at different ages and of the various exposures or events that suppress ovulation have not been established. Most of the large studies stated that there was no significant extra risk for women with an early menarche and a late menopause. Only weak trends were found (Whittemore, Harris et al. 1992; Hankinson, Colditz et al. 1995; Purdie, Green et al. 1995). But in 2003, Purdie et al. published a new study of 791 ovarian cancer cases and 853 controls to examine the effect of ovulation on ovarian cancer risk. An increase of 1 year’s worth of ovulation was associated with a 6% increase in risk of ovarian cancer (95% CI 4-8) (Purdie, Bain et al. 2003).

Height and weight

In The Netherlands Cohort Study on Diet and Cancer, initiated in 1986, data support a positive association between height (and to a lesser extent body mass) and ovarian cancer risk in a population of postmenopausal women. Multivariate analysis yielded a rate ratio of 2.17 of ovarian cancer for women with an adult height of more than 175 cm, compared with those with a height of less than 160 cm. The rate ratio for women with a body mass index of more than 30 was 1.69 compared with women with a Quetelet index of less than 25 (Schouten, Goldbohm et al. 2003). Furthermore, findings support the

hypothesis that obesity is an important risk factor for ovarian cancer among women of African and European descent (Hoyo, Berchuck et al. 2005).

Parity and breast feeding

In multiple studies, multiparous women have been observed to have lower risk than do nulli-parous women. Population data of the collaborative analysis of 12 US case-control studies from the Collaborative Ovarian Cancer Group strongly support a model according to which each additional pregnancy after the first confers the same percent risk reduction, estimated to be 14%.This reduction is smaller than the 40% reduction associated with the first term pregnancy (Whittemore, Harris et al. 1992). Data from seven case-control studies (1,122 cases and 5,359 controls) relate the incidence rate and probability of developing ovarian cancer with the number of term pregnancies. Among women with no family history of ovarian cancer, the risk at age 65 varied from 0.3% to 1.6% depending on the number of pregnancies (0 pregnancies: RR=2.4,95% CI 2.0-2.9; 1-2 pregnancies: RR=1.6,95%CI 1.4-1.9; >2 pregnancies: RR=1 in Hartge, Whittemore et al. 1994) . These findings were similar to the results of a pooled analysis of three European case-control studies of epithelial ovarian cancer (Negri, Franceschi et al. 1991) and with other prospective studies (Hankinson, Colditz et al. 1995).

Whittemore et al. found that breast feeding (and also pregnancy) may protect against ovarian cancer by suppressing ovulation (OR=0.8, 95% CI 0.68-0.95). Each month of breast feeding was associated with an overall risk reduction of 0.99 (Whittemore, Harris et al. 1992). The effect of abortions was considered unclear.

Exogenous estrogens

The effect of oral contraceptives in ovarian cancer was evaluated in several epidemiological studies. Overall, these studies showed that women who had used oral contraceptives had a lower risk for invasive epithelial ovarian cancer than did non-users. Among ever-users, risk decreased with increasing years of use (Whittemore, Harris et al. 1992; Hartge, Whittemore et al. 1994; Hankinson, Colditz et al. 1995; Chiaffarino, Pelucchi et al. 2001;Vessey, Painter et al. 2003; Rodriguez, Walmer et al. 1998).

Hormone therapy

The epidemiological evidence regarding hormone therapy and ovarian cancer risk has had different results over time. Early studies did not show an increase in risk associated

with estrogen therapy (Whittemore, Harris et al. 1992). In 2000, Coughlin et al. conducted a meta-analysis. The estimated RR of ovarian cancer among women who had used estrogen therapy was 1.1 (95% CI 0.9-1.3) in comparison to women who had never used estrogen therapy (Coughlin, Giustozzi et al. 2000).

Recently, a review and meta-analysis of data published between 1966 and 2006 concluded that the current use of postmenopausal hormone therapy increased the risk of ovarian cancer by 30% compared to the absence of it. It suggested that ovarian cancer risk with estrogen therapy alone was higher than the risk associated with estrogen plus progestin therapy (Greiser et al.2007, Danforth et al. 2007). However, the Million Women Study published in Lancet 2007 comprising 948,576 women and 2,273 incident cases of ovarian cancer found an increased risk of ovarian cancer but not a significant differential effect of estrogen therapy and estrogen plus progestin therapy (Beral et al. 2007). Finally, a Danish study published in 2010 comprehending 909,946 women concluded that regardless of the duration of use, the formulation, estrogen dose, regimen, progestin type, and route of administration, hormone therapy was associated with an increased risk of ovarian cancer (Steinrud and LØkkrgaard et al. 2009).

Infertility

Increased ovarian cancer risk among nulliparous women could reflect an association between ovarian cancer and infertility, as suggested in the study of Whittemore et al. (1992). The differentiation between infertile and fertile but nulliparous women is important for the interpretation of studies´ results and characterizes the methodological difficulties in those studies. However, those women who attributed their infertility to ovulatory disorders did not show a significant increase in risk of ovarian cancer (pooled analysis of data from the USA: OR=2.1 95% CI 0.90-4.7 in Whittemore, Harris et al. 1992 and OR=0.80 95% CI 0.54-1.18 in Ness, Cramer et al. 2002). This is biologically plausible if fewer ovulatory cycles and/or lower peaks of estrogen and progesterone levels reduce ovarian cancer risk. Fallopian tube dysfunction was also shown not to be a significant factor for an increased risk (OR=1.3 95% CI 0.63-2.8). Women with other or unspecified types of infertility showed no increased risk (OR=0.77 95% CI 0.55-1.1 in Whittemore, Harris et al. 1992). In this study, there were no consistent or statistically significant differences in risk between nulliparous women who had been pregnant and those who had not. The absence of a relation between ovarian cancer risk and gravidity and marital status among nulliparous women suggests that their elevated risk may be

largely, if not entirely, attributable to deprivation of some direct benefit associated with pregnancy.

Fertility drugs

In several trials, comparisons within the general population did not show a statistically significant increase in ovarian cancer incidence with users of fertility drugs (Rossing, Daling et al. 1994; Modan, Ron et al. 1998; Potashnik, Lerner-Geva et al. 1999; Shelley, Venn et al. 1999). The pooled re-analysis of case-control studies reported by Whittemore et al. (Whittemore, Harris et al. 1992) and Ness et al. (2002) provide important data on the risk of ovarian cancer among women who were treated with fertility drugs. The report from Whittemore et al. included cases that were diagnosed between 1977 and 1981. Those women were most likely exposed to fertility treatment in the 1950s and 1960s. For all women with ovarian cancer, the OR associated with exposure to fertility drugs was 2.8 (95% CI 1.3-1.6). An analysis of subgroups yielded an OR=27.0 for nulligravid women treated with fertility drugs (95% CI 2.3-315.6) and an OR=1.4 for gravid women (95% CI 0.5-3.6). Such an increased risk has not been found in subsequent studies, including the re-analysis of case-control studies reported by Ness et al (2002). Studies re-analysed by Ness et al. included cases diagnosed between 1980 and 1999 where women had probably been exposed to fertility drugs in the 1970s or later. The results showed no association between the use of fertility drugs and the overall risk of ovarian cancer (OR=0.97 95% CI 0.76-1.25). In addition, an increase in the duration of fertility drug use (Clomiphene citrate and human menopausal gonodotropin) was not associated with an increased risk. Separate analyses of cancer in nulligravid and gravid women showed a non-significant increase in the OR for nulligravid women exposed to fertility drugs (OR=1.60 95% CI 0.9-2.87 in Venn, Healy et al. 2003).

1.4. Histological classification and grading

The ovary surface presents a simple cuboid epithelium (really a modified mesothelium). In histology as well as in immunohistochemistry, the ovary surface is similar to the peritoneum because both tissues develop from the Müller-epithelium. Malignant lesions of the ovaries include primary lesions arising from the ovary and secondary lesions from cancers arising elsewhere in the body. Primary lesions include epithelial ovarian

carcinoma (70% of all ovarian malignancies), germ-cell tumors, sex-cord stromal tumors, and other more rare types. Metastases to the ovaries are relatively frequent, mostly from the endometrium, breast, colon, stomach, and cervix.

The histological classification of ovarian tumors by the World Health Organization (WHO) is based on histogenetic principles and this classification categorizes ovarian tumors with regard to their derivation from coelomic surface epithelial cells, germ cells, and mesenchyme. Epithelial ovarian tumors are further grouped according to histological types such as: serous, mucinous, endometrioid, clear cell, transitional cell tumors (Brenner tumors), carcinosarcoma, mixed epithelial tumor, undifferentiated carcinoma, and others (Table 1 from Kaku et al. 2003).

Table 1: WHO histological classification of ovarian tumors: surface epithelial-stromal tumors

1. Serous tumors

(1) Benign
1. Cystadenoma and papillary cystadenoma
2. Surface papilloma
3 Adenofibroma and cystadenofibroma

(2) Of borderline malignancy (of low malignant potential)
1. Cystic tumor and papillary cystic tumor
2. Surface papillary tumor
3. Adenofibroma and cystadenofibroma

(3) Malignant
1. Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
2. Surface papillary adenocarcinoma
3. Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

2. Mucinous tumors, endocervical-like and intestinal types

(1) Benign
1. Cystadenoma
2. Adenofibroma and cystadenofibroma

(2) Of borderline malignancy (of low malignant potential)
1. Cystic tumor
2. Adenofibroma and cystadenofibroma

(3) Malignant
1. Adenocarcinoma and cystadenocarcinoma
2. Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

3. Endometrioid tumors

(1) Benign
1. Cystadenoma
2. Cystadenoma with squamous differentiation
3. Adenofibroma and cystadenofibroma
4. Adenofibroma and cystadenofibroma with squamous differentiation

(2) Of borderline malignancy (of low malignant potential)
1. Cystic tumor
2. Cystic tumor with with squamous differentiation
3. Adenofibroma and cystadenofibroma
4. Adenofibroma and cystadenofibroma with squamous differentiation

(3) Malignant
1. Adenocarcinoma and cystadenocarcinoma
2. Adenocarcinoma and cystadenocarcinoma with squamous differentiation
3. Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)
4. Adenocarcinofibroma and cystadenocarcinofibroma with squamous differentiation (malignant adenofibroma and cystadenofibroma with squamous differentiation)

(4) Epithelial-stromal and stromal
1. Adenosarcoma, homologous and heterologous
2. Mesodermal (Müllerian) mixed tumor (carcinosarcoma), homologous and heterologous
3. Stromal sarcoma

4. Clear cell tumors

(1) Benign
1. Cystadenoma
2. Adenofibroma and cystadenofibroma

(2) Of borderline malignancy (of low malignant potential)
1. Cystic tumor
2. Adenofibroma and cystadenofibroma

(3) Malignant
1. Adenocarcinoma
2. Adenocarcinofibroma and cystadenocarcinofibroma (malignant adenofibroma and cystadenofibroma)

5. Transitional cell tumors

(1) Brenner tumor
(2) Brenner tumor of borderline malignancy (proliferating)
(3) Malignant Brenner tumor
(4) Transitional cell carcinoma (non-Brenner type)

6. Squamous cell tumors

7. Mixed epithelial tumors (specific types)

(1) Benign
(2) Of borderline malignancy (of low malignant potential)
(3) Malignancy

8. Undifferentiated carcinoma

Histopathological grades

Tumor malignancy potential is graded on a three-tier scale; well-differentiated (Grade 1), moderately-differentiated (Grade 2) and poorly-differentiated (Grade 3). Well-differentiated tumors have a better prognosis than poorly-differentiated tumors.

1.5. Tumor spread pattern

Ovarian carcinoma can spread by local extension, lymphatic invasion, intraperitoneal implantation, haematogenous dissemination and transdiaphragmatic passage. Intraperitoneal dissemination is the most common and recognized type of tumor spread of ovarian cancer. Malignant cells can settle anywhere in the peritoneal cavity but are

more likely to implant in sites of stasis along the peritoneal fluid circulation. Cells implant on the lining of the abdominal cavity (peritoneum) and may grow on the surface of the liver, omentum, small and large bowel, bladder, and diaphragm. These cells can start growing into new tumours before cancer is even diagnosed.

Disease on the diaphragm can result in an impaired drainage of fluid from the abdominal cavity, leading, for some women, to a large collection of abdominal fluid (known as ascites). The cancer cells spread to the surface of the lungs and chest cavity, leading to a pleural effusion. However, an early haematogenous spread is clinically unusual, although it is not infrequent in patients with advanced disease. Ovarian cancer may also spread through lymphatic channels. The first and most common pathway of lymphatic spread follows the ovarian vessels to retroperitoneal nodes (para aortal) near the renal hila. The second pathway passes laterally in the broad ligament to the internal iliac and obturator nodes along the pelvic sidewall. The third passes with the round ligament to the external iliac and inguinal nodes. Extra-abdominal nodal metastases are rare at presentation although they do occur in recurrent disease (Dauplat, Hacker et al. 1987; Rose, Piver et al. 1989; Cormio, Rossi et al. 2003). The most common sites of metastases are the pleural cavity, liver and lung. Sites of parenchymal metastasis are similar to those of other carcinomas. The presence of lymphatic and vascular invasion in the primary tumour is predictive of such involvement.

1.6 Tumor stage

Stage is a powerful predictor of prognosis for ovarian cancer (Heintz, Odicino et al. 2001). The stages of ovarian cancer have been classified by the American Joint Committee on Cancer (AJCC) (histopathological TNM classification) and the Fédération Internationale de Gynécologie et d'Obstétrique (clinical FIGO classification, also called the International Federation of Gynecology and Obstetrics).

In the latter AJCC classification, primary peritoneal carcinoma was also included (the original source for this material is the AJCC Cancer Staging Manual, seventh edition (2010) published by Springer-Verlag New York, Inc.).

Primary Tumor: (FIGO stage in parentheses)

- T1 (I) - limited to one or both ovaries
  - T1a (IA) - involves one ovary; capsule intact; no tumor on ovarian surface; no malignant cells in ascites or peritoneal washings
  - T1b (IB) - involves both ovaries; capsule intact; no tumor on ovarian surface; negative washings
  - T1c (IC) - tumor limited to ovaries with any of the following: capsule ruptured, tumor on ovarian surface, positive washings
- T2 (II) - pelvic extension or implants
  - T2a (IIA) - extension or implants onto uterus or fallopian tube; negative washings
  - T2b (IIB) - extension or implants onto other pelvic structures; negative washings
  - T2c (IIC) - pelvic extension or implants (T2a or T2b) with positive peritoneal washings
- T3 (III) - microscopic peritoneal implants outside of the pelvis
  - T3a (IIIA) - microscopic peritoneal metastases beyond pelvis
  - T3b (IIIB) - macroscopic peritoneal metastases beyond pelvis less than 2cm in size
  - T3c (IIIC) - peritoneal metastases beyond pelvis > 2 cm. (lymph node metastasis is also IIIC for FIGO)

Regional Lymph Nodes: includes pelvic, para-aortic, inguinal, retroperitoneal

- N0 - no
- N1 (IIIC) - yes

Distant Metastases:

- M0 - no
- M1 (IV) – yes

Note: primary peritoneal tumors are usually either Stage III or IV

Note: seeding of the liver capsule is Stage III but liver parenchymal metastases are Stage IV.

1.7 Screening and diagnosis

Pelvic examination in the annual gynaecologic examination has been the primary method for detection of ovarian carcinoma. Unfortunately, it is not helpful for the detection of early disease, so most women show disease beyond the pelvis (Stages III and IV) at the time of first diagnosis. Detection of an early stage disease may therefore offer an opportunity to reduce mortality. So far no screening protocol for ovarian cancer

has been shown to achieve this aim (Jacobs and Menon 2004; Rosenthal, Menon et al. 2006).

The tumor marker CA 125 (ovarian cancer-associated antigen) is a glycoprotein antigen expressed on an ovarian cancer cell line. CA125 was first identified in 1981 and is one of the most extensively studied and useful molecular markers in ovarian cancer. At an upper limit normal cutoff of 35 U/ml, CA 125 achieves a sensitivity of 78.3% and a specificity of 82%. The test is not absolutely specific: elevations have been reported with pregnancy, endometriosis, menstruation, benign ovarian tumors, and with cancers of the breast, colon, pancreas, lung, stomach, and liver. Employing an upper cutoff limit of 65 U/ml in postmenopausal women, sensitivity decreases to 71.7% and specificity increases to about 95% (Maggino et al. 1994). Other markers have been investigated, including lysophosphatidic acid, tumour-associated glycoprotein 72 (TAG 72), OVX1, and macrophage colony-stimulating factor (Rosenthal, Menon et al. 2006). A recent study examining a panel of serum biomarkers for detecting malignancy in women with a pelvic mass demonstrated that the addition of HE4 to CA125 improved the sensitivity and specificity over that of CA125 alone. The HE4 gene is part of a family of protease inhibitors and has been shown to be overexpressed by epithelial ovarian cancer tumors.The study suggests that through an algorithm using HE4 and CA125, patients could be successfully assigned to high and low risk groups with 93.8% of epithelial ovarian cancer correctly classified as high risk (Moore et al. 2009).

Transvaginal ultrasound (TVUS) provides higher resolving power for ovarian abnormalities than transabdominal ultrasound or physical examination. CA 125 and TVUS may be complementary (Kramer, Gohagan et al. 1993). Although screening of the general population was shown to be impaired by low incidence rates and high rates of false positive results, it may, however, be beneficial for patients at risk due to the higher incidence rates (e.g. in female carriers of a mutation in the BRCA1 or BRCA2 gene). Screening for ovarian cancer by TVUS and CA 125 in women with a familial predisposition aims at the diagnosis of early stage tumors with a favorable prognosis (Jacobs, Skates et al. 1999; Bosse, Rhiem et al. 2006).

There has been considerable interest regarding the characterization of computer-analyzed protein patterns in the blood as a way of improving screening for ovarian cancer. Such methods are currently undergoing intensive research and clinical validation (Rosenthal, Menon et al. 2006).

1.8. Treatment

Treatment of ovarian cancer is undertaken after consideration of many factors, including the extent of disease spread, symptoms, and patients' wishes and fitness to undergo treatment.

Surgery in primary treatment

Surgery is the initial treatment of choice. The aim of surgery is to confirm diagnosis (define the extent of disease) and resect all visible tumor.

Possible benefits of surgery include: (1) removal of poorly vascularised tumor whereupon pharmacologic sanctuaries are eliminated; (2) a higher growth fraction in the better perfused small residual tumor masses, which favors an increased cell death with chemotherapy; (3) small tumor masses require fewer cycles of chemotherapy so there is less opportunity for induced drug resistance; (4) removal of drug-resistant clonogenic cells; and (5) host immunocompetence enhanced by the removal of large tumor bulk (Covens 2000).

The incision for surgery should be midline abdominal. In young women with early-stage disease, a transverse incision may be considered. Careful inspection and/or palpation of the abdominal contents should be performed, including all peritoneal surfaces, the liver, large and small bowel and mesentery, stomach, appendix, kidneys, spleen, retroperitoneal spaces, and all pelvic structures.

Appropriate surgery, depending on whether or not disease is visible outside the ovaries, is described below. It is essential that, even if there is no visible disease outside the ovaries, patients should be adequately surgically staged (noteworthy incidence of microscopic metastases).

- No visible disease outside of the ovary
    - Aspirate ascitic fluid for cytology studies.
    - Perform peritoneal washings for cytology if ascites is not present.
    - Remove the ovary and ovarian tumor intact.
    - Perform diaphragmatic scraping for cytology studies.
    - Obtain peritoneal biopsy specimens.
    - Perform a subcolic omentectomy.

  - Obtain bilateral para-aortic and pelvic node samples. The incidence of positive para-aortic and pelvic lymph nodes is 24% in stage I, 50% in stage II, 74% in stage III, and 73% in stage IV *.
  - Obtain biopsy samples of adhesions or other suspicious areas.
  - If the patient does not desire future fertility, perform a total abdominal hysterectomy and excise the opposite ovary.
  - Remove the appendix if mucinous tumor is present.
- Macroscopic disease outside of the ovary
  - All visible tumor should be removed. This may require extensive surgery, including small-bowel-resection, colon resection, colostomy, ileostomy, ileum-pouch, splenectomy, pelvic floor-covering, peritoneal removal and infrared contact coagulation. Radical multivisceral surgery is feasible, safe and efficient in primary situation of advanced ovarian cancer (Eisenkop, Friedman et al. 1998; Lichtenegger, Sehouli et al. 1998; Eisenkop, Friedman et al. 2000).

*There is some debate about the definition of complete debulking regarding systematic lymphadenectomy. While some authors argue that systematic lymphadenectomy should always be included, others postulate that it may be enough to remove palpable enlarged lymph nodes. Thus the role of lymphadenectomy still remains a cornerstone of staging in early ovarian cancer and should be discussed with ovarian cancer patients with respect to the side-effects and possible benefits (Panici, Maggioni et al. 2005; du Bois and Harter 2006).

Surgery for patients with stage IV disease should be performed in a customized way, particularly if the disease is in the liver and above the diaphragm. Patients who are in stage IV because of small-volume disease in the liver, abdominal wall, or lung should undergo cytoreductive surgery if medically fit (Burghardt, Girardi et al. 1991).

Surgery with maximal effort of cytoreduction before starting primary chemotherapy remains the standard of care. However, interval debulking after two or three courses of systemic therapy is an option for patients in whom surgery with maximal effort is not possible at the point of primary diagnosis (e.g. poor performance status, co-morbidity which might improve or technical reasons). Overall, the concept of interval debulking may provide a benefit for a small subgroup of patients; however, the study by van der Burg was the first to show any significant impact of this type of surgery on the survival rate (van der Burg, van Lent et al. 1995).

Cytoreductive surgery in recurrent ovarian cancer

Cytoreductive surgery for recurrence is defined as an operation performed in patients with recurrent disease after the completion of primary treatment (surgery with or without chemotherapy) and a period without any evidence of disease. This excludes surgery for diagnostic purposes (e.g. second-look operations), secondary debulking (i.e. an operation performed in patients after chemotherapy with an attempt to remove any remaining tumour which could not be removed by chemotherapy) and surgery for progressive ovarian cancer. When feasible, it is performed with the purpose of removing as much of the tumour as possible (Eisenkop, Friedman et al. 1998; Lichtenegger, Sehouli et al. 1998; Eisenkop, Friedman et al. 2000).

Until today, only few publications have focused on selection criteria for cytoreductive surgery (CS) in recurrent ovarian cancer. In 1998, the 2nd International Ovarian Cancer Consensus Conference suggested the following criteria for optimal candidates for secondary CS (Harter, Bois et al. 2006): (1) disease-free interval > 12 months, (2) response to first-line therapy, (3) potential for complete resection based on preoperative evaluation (without diffuse carcinomatosis), (4) good performance status, and (5) younger age (Berek, Bertelsen et al. 1999; Vergote 2004).

Chemotherapy

Epithelial ovarian cancer is considered to be a chemo-sensitive neoplasm, with initial overall response rates to systemic therapy exceeding 80% when combined with cytoreductive surgery.

However, among women with advanced-stage disease at the point of first diagnosis, the probability of long-term survival remains poor due to eventual tumor recurrence and emergence of drug-resistant disease. Primary chemotherapy has evolved from single alkylating agents to cisplatin and cisplatin-based combinations, followed by the incorporation of paclitaxel and substitution of carboplatin for cisplatin. After more than 25 years of investigation, platinum still remains the most important conventional cytotoxic agent used in the treatment of EOC, and it is generally accepted that carboplatin is at least as effective as cisplatin in this setting. Today, the international community has largely adopted carboplatin at either AUC 5 or 6, depending on the regimen and method of dose calculation, to maximize the delivery of six cycles of primary therapy on a 3-week schedule without dose-limiting toxicity (Bookman 2005).The second most important class of cytotoxic agents are the taxanes. Most

clinical experience has been based on paclitaxel. It has been evaluated as a single agent using a variety of doses, schedules, and infusion durations. Within a safely tolerated range, there is no evidence that clinical outcomes are improved using doses above 175 mg/m^2 every 3 weeks (Omura, Brady et al. 2003).

Considering the central role of platinum, there has been particular interest in the incorporation of agents that might accentuate the platinum response. In the Gynecologic Cancer Intergroup trial (GOG-0182–ICON5), four experimental arms were included to evaluate the addition of three new drugs (topotecan, gemcitabine, and polyethylene–glycosylated liposomal doxorubicin) using two different strategies for drug administration (sequential doublet and triplet combinations). For the regimens evaluated, there was no evidence that adding a third active cytotoxic agent prolongs progression-free survival in EOC. More studies have been carried out, but thus far, there are not sufficient data to recommend any regimen over a combination of paclitaxel 175 mg/m² and carboplatin AUC5 in a three-week schedule in the front-line setting as a gold standard (Sehouli, Stengel et al. 2002; Bookman 2005; Scarfone and Bolis 2006).

Recently, the GOG-0218 study has reported a progression-free survival gain of 3.8 months with carboplatin-paclitaxel plus concomitant and maintenance bevacizumab (Avastin, humanized monoclonal antibody directed against vascular endothelial growth factor) compared with carboplatin-paclitaxel alone (14.1 months compared with 10.3 months, respectively; hazard ratio [HR] = 0.717; $p < 0.0001$) with no unexpected adverse events observed (data from Abstract LBA1, ASCO 2010).

Chemotherapy in recurrent disease

Although ovarian cancer is very responsive to multiple chemotherapeutic agents, with objective response rates of up to 80% with standard platinum and taxane doublets, 75% of patients relapse within 2 years of primary therapy and become candidates for treatment of recurrent disease (Tummala and McGuire 2005). Classically, patients have been treated based upon the interval from last platinum administration during front-line therapy until the time of recurrence (Herzog 2006). Patients with recurrent ovarian carcinoma are considered either platinum-sensitive or platinum-resistant, depending on whether the response duration was less or greater than 6 months from prior therapy with a platinum-based agent. In platinum-sensitive patients with relapsed ovarian cancer, a platinum-based combination represents the standard second-line chemotherapy (Colombo, Van Gorp et al. 2006). Combinations such as

carboplatin/caelyx (CALYPSO-Study), carboplatin/alimta or carboplatin/topotecan (HECTOR-Study) versus standard therapy have been studied.
In platinum-resistant patients with ovarian cancer, chemotherapy is highly palliative. The response rate and progression-free survival are limited. Several chemotherapies as topotecan, gemcitabine and caelyx can be applied, however normally as mono-therapies (Pecorelli, Pasinetti et al. 2006; Bookman 2005).

1.8 Prognostic factors for survival

In the practical experience, treatment decisions of the physician (e. g. surgery, chemotherapy) are based on individual prognostic factors that can be attributed to the patient with ovarian cancer. Prognostic factors identified in literature are age, stage, histology, grade, volume of ascites, performance status, molecular marker CA-125, postoperative tumor mass, lymph node status and newer molecular biological factors as Her-2-status, PAI-1, MMP, VEGF and CD24 (Sehouli, Mustea et al. 2004).

Stage

Ovarian cancer is staged using the International Federation of Gynecology and Obstetrics staging system. Approximately 20%, 5%, 58%, and 17% of women present stage I, II, III, and IV respectively. Survival is highly dependent on the stage of disease: 5-year survival in patients with an early stage is 80-90% compared to 25% for patients with advanced-stage disease (Colombo, Van Gorp et al. 2006). Despite this, the 5-year survival rate for ovarian cancer has improved significantly in the last 20 years. The overall survival rate in 1975 was 37%, compared to 50% in 1995.

Table 2: Survival rate for ovarian cancer. Numbers below are based on patients diagnosed from 1995 to 1998. These numbers come from the American College of Surgeons, National Cancer Data Base.

Stage	Relative 5-Years Survival Rate
IA	92.7%
IB	85.4%
IC	84.7%
IIA	78.6%
IIB	72.4%
IIC	64.4%
IIIA	50.8%
IIIB	42.4%
IIIC	31.5%
IV	17.5%

Histology

The histology type is not widely accepted as a prognostic factor except for clear cell and mucinous epithelial ovarian cancers, which have been associated with a poorer response to platinum-based first-line chemotherapy when compared with patients with other histologic subtypes of EOC. Their survival has also been reported to be worse (Hoskins, Bundy et al. 1992; Holschneider and Berek 2000; Fujita, Enomoto et al. 2003; Hess, A'Hern et al. 2004).

Grade

The histopathological grade of EOC has generally been found to be a prognostic factor, although the grading system used has varied among published reports. The major proposed grading system was the FIGO grading system until a new system was proposed by Shimizu/Silverberg (Silverberg 2000). The architectural grade, nuclear grade, and mitotic count in the Shimizu study were independent variables both in stage I/II and stage III/IV disease. Each of them correlated with survival for most combinations of histology type and stage (Shimizu, Kamoi et al. 1998). Years later, a tumour grade based on the M. D. Anderson two-tier system for grading ovarian serous carcinoma was found to be another statistically significant independent prognostic factor. However,

there is a strong correlation between the two-tier grading system and the Shimizu/Silverberg and the FIGO grading systems. (Malpica, Deavers et al. 2004).

Age

Young age has been reported to be a favourable prognostic factor in ovarian cancer. Patients older than 69 years exhibited a significantly lower survival rate (30%) than younger patients (64%), even after correction for stage, residual disease, and performance status (Thigpen, Brady et al. 1993). Although radical surgery for primary EOC obtaining complete tumor resection is associated with a significantly prolonged overall survival in elderly patients (≥70 years), the increased postoperative morbidity must be considered (Fotopoulou et al. 2010).

Performance status

Patients with a Karnofsky index (KI) <70 have a significantly shorter survival than those with a KI>70 (Thigpen, Brady et al. 1993; Holschneider and Berek 2000).

Lymph node status

The role of systematic aortic and pelvic lymphadenectomy in patients with optimally debulked advanced ovarian cancer is unclear (Burghardt, Girardi et al. 1991). According to a new study, the addition of systematic para-aortic and pelvic lymphadenectomy to cytoreductive surgery prolonged progression-free survival. It may have an important impact on the quality of life of patients with advanced ovarian cancer, however no prolonged overall survival was addressed (Panici, Maggioni et al. 2005). More studies need to be done in this field.

Ascites

The presence of ascites on preoperative physical examination or imaging study is highly predictive of ovarian malignancy in women with a pelvic mass. The absence of ascites may not always predict benign disease since nearly half of borderline tumours and 83% of early stage malignant ovarian tumours do not produce ascites. A progressive relationship between stage of malignancy and incidence as well as the volume of ascites has been observed (Shen-Gunther and Mannel 2002). Ascites were identified as an independent prognostic factor in several studies (Makar, Baekelandt et al. 1995; Chi, Liao et al. 2001; Shen-Gunther and Mannel 2002).

Molecular marker CA-125

CA125 is expressed by over 80% of ovarian cancers, and levels at presentation correlate with the risk of malignancy, stage of disease and histology. In addition, changes in CA125 levels can be used to predict response to chemotherapy, while changes during follow-up can predict relapse with a lead time of approximately 60 days. It is therefore not surprising that various CA125 indices have been extensively analysed for their prognostic ability. These include CA125 levels at presentation, following initial debulking surgery, prior to the second or third cycle of chemotherapy, half-life during chemotherapy, at the end of chemotherapy, and at relapse (Meyer and Rustin 2000). In most laboratories the normal range of CA 125 in serum goes to 35 U/ml, but serum CA 125 is not specific for ovarian cancer. High levels can also be found in patients with non-ovarian gynaecological and non-gynaecological tumours as well as patients with benign diseases and even in apparently healthy persons (van der Burg, Lammes et al. 1992). A concentration of CA125 > 35U/ml should indicate a repeated test after a short period of time. Two consecutively elevated CA 125 values strongly suggest progressive disease (van der Burg, Lammes et al. 1990).

New molecular biological factors

A multitude of new molecular biological prognostic factors has been described for ovarian cancer. Their significance as independent prognostic parameters is still unclear, and more multivariate analyses have to be carried out. Among the parameters are the estrogen and progesterone receptor status (Geisler, Wiemann et al. 1996), the expression of latent matrix metalloproteinase 9 (Lengyel, Schmalfeldt et al. 2001), the surface protein CD24 (Kristiansen, Denkert et al. 2002; Choi, Kim et al. 2005), abnormalities of the nuclear DNA and DNA-ploidy (Pfisterer, Kommoss et al. 1994; Ozalp, Yalcin et al. 2001), Mib-1 (Marx, Meden et al. 1997), interleukin-6 (Scambia, Testa et al. 1995) and interleukin-12 (Zeimet, Widschwendter et al. 1998), p53 and c-erbB3 expression (Terauchi et al. 2005; Wen, Reles et al. 1999; Tanner, Hasenclever et al. 2006), expression of cyclooxygenase 2 (Denkert, Kobel et al. 2002), the “Vascular-Endothelial-Grow Factor” VEGF (Tempfer, Obermair et al. 1998; Ueda, Terai et al. 2005; Rudlowski, Pickart et al. 2006) and the urokinase (uPA) and its inhibitor PAI-1 (Kuhn, Schmalfeldt et al. 1999).

Quality of care

A significant percentage of women with ovarian cancer do not receive the recommended surgical procedures. Almost 50% of women with early stage disease are not adequately staged and in women with advanced disease, the percentage who have additional surgical procedures such as bowel resections is much lower than in institutions that report high optimal cytoreduction rates (Goff, Matthews et al. 2006). Participation in clinical studies is the only transparent hospital characteristic with significant impact on the prognosis of ovarian cancer. Participation in studies as criterion for quality of care should be included in counseling ovarian cancer patients and should help guiding selection of hospitals for primary therapy (du Bois, Rochon et al. 2005).

Post-operative tumor mass

In 1934, Meigs was a pioneer in promoting cytoreductive surgery in advanced ovarian cancer to enhance the effects of postoperative radiation therapy. The concept of primary cytoreduction was supported when Griffiths showed that survival depends on residual disease. Ever since, residual disease after surgery has been one of the most powerful independent prognostic factors described in the literature for primary ovarian cancer (Hoskins, Bundy et al. 1992; Kikkawa, Kawai et al. 1994; Eisenkop, Friedman et al. 1998; Lichtenegger, Sehouli et al. 1998; Parazzini, Valsecchi et al. 1999; Eisenkop, Friedman et al. 2000; Bristow, Tomacruz et al. 2002; du Bois and Harter 2006).

According to the Gynecologic Oncology Group (GOG), depending on the post-operative tumor mass volume, debulking surgery can be referred to as optimal (≤1 cm.) or suboptimal (>1 cm.) corresponding to improvement in survival. However, various authors recommend defining as optimal patients without any residual disease (Chi, Eisenhauer et al. 2006; du Bois et al. 2009)

In a recurrent situation, cytoreductive surgery aims at the prolongation of survival and its practice follows similar rules as the primary surgery for advanced disease. Some authors defined secondary optimal debulking as the removal of all visible tumor while others reported small residuals disease with varying dimensions of maximum diameters (0.5-2 cm). However, the concept of optimal debulking has not been very well established in cytoreductive surgery for recurrent disease.

1.9 Objectives of the study

Primary

The purpose of this study is to evaluate the role of postoperative tumor residual and tumor reduction in patients with ovarian cancer (at primary situation and recurrent ovarian cancer) with survival (overall and progression-free) as the primary endpoint.

Secondary

The study tries to establish the meaning of cytoreductive surgery in the outcome of ovarian cancer (as an independent factor) with special regard to suboptimal situations.

2 Material and methods

2.1 Study site and population

All women with histopathologically documented primary or first recurrent epithelial ovarian cancer (or peritoneal carcinoma) who underwent tumor debulking surgery between September 2000 and April 2006 in the Department of Gynecology at the Charité Campus-Virchow-Klinikum were asked to be included in our prospective study. Patients fulfilling all the inclusion criteria and none of the patients fulfilling the exclusion criteria were included in the study.

Inclusion criteria

- female over 18 years old
- documented primary or first recurrent EOC or peritoneal carcinoma
- curative (aiming maximal tumor resection) or palliative (aiming alleviate symptoms) surgery
- documented informed consent

Exclusion criteria

- documented borderline tumor
- in recurrence situation: ascites and/or diffuse tumor dissemination in imaging modalities and without symptoms which made an operative intervention inevitable
- patients who decline an operative approach
- presence of medical contraindications to an extensive surgical procedure

2.2 Data collection

In every patient, the detailed tumor pattern was intraoperatively assessed by an independent trained person as based on the surgical procedures performed and by systematic interview of the surgical team. Postoperatively all histological findings and collected data were entered into a validated histopathological documentation system

(IMO: “Intraoperative Mapping of Ovarian Cancer”), especially developed for ovarian neoplasms. Data were analyzed within TOC databank (Tumor bank Ovarian Cancer).

Intraoperative Mapping of Ovarian Cancer (IMO)

IMO represents an instrument for a detailed and objective documentation of surgical and pathological results of patients with ovarian cancer and helps provide a more precise staging (Sehouli, Konsgen et al. 2003). In the „One-Step-Documentation“, the surgeon documents the tumor spread and the surgical procedures performed in an operation procedure list. All the macroscopic spread in the organs should be described in this list as well as the volume of the intraoperative ascites (if present), diameter of the postoperative tumor rest, percentage of tumor reduction and a detailed description of the peritoneal carcinomatosis. Pelvic und para aortal palpable lymph nodes will also be documented. Additionally, in a documentation sheet (see example Fig. 1), tumor spread location at the time of surgery (X), location of the largest tumor mass (O) as well as the location of the postoperative tumor rest (^) are illustrated.

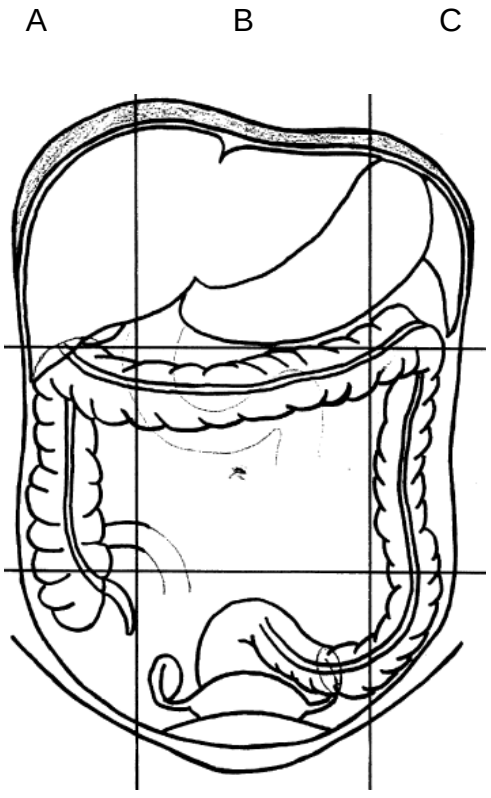


Fig. 1: Documentation IMO sheet

Three “IMO-levels” divide the abdomen into three spaces according to anatomical and topographical criteria:

Level I (lower abdomen): pelvis (Douglas, ovaries, vagina, uterus, bladder/ureter, rectum, sigma)
Level II (middle abdomen): small and large bowel
Level III (upper abdomen): omentum majus, bursa omentalis, diaphragm, liver, spleen and stomach

After surgery a specific online documentation is performed within the “Tumor bank Ovarian Cancer” databank (www.TOC-Network.de), a clinical, multicentric and prospective tumor databank for ovarian cancer. In the databank intraoperative, histo-pathological and clinically relevant information for each patient was included. All relevant data of a patient including history, follow-up and survival data were abstracted from the patient´s records (MedVision). Survival data of the patients were updated based on patients´ files and/or responses from their physicians or insurance companies. The following standardized data collection was performed:

Intraoperative data: (at the time of surgery)
Date and place of surgery
Presence or absence of ascites: none vs ≤ 500ml vs >500ml
Macroscopic tumor spread in levels:

* Levels:
    - Level 1: lower abdomen
    - Level 2: middle abdomen
    - Level 3: upper abdomen
* Specific organs:

omentum majus/mesentery	diaphragm
ovary/uterus	abdominal wall
bladder/ureter	small bowel
bursa omentalis/pancreas	large bowel
liver	pleura
stomach	spleen

Operation time: in minutes

Surgical procedures performed:

- hysterectomy
- bilateral salpingo-oophorectomy
- omentectomy
- para-aortic+/-pelvic lymphadenectomy
- appendectomy
- bowel resection (small and large)
- pancreas resection
- partial stomach resection
- partial liver resection
- cholecystectomy
- splenectomy
- diaphragm resection
- contact coagulation
- bladder and ureter resection
- colostoma
- ileostoma

Diffuse peritoneal carcinomatosis: defined as tumor nodules diffusely covering the majority of the surfaces of bowel serosa and the parietal peritoneum of the abdomen and pelvis

Diameter of residual tumor: macroscopic tumor-free/ ≤0.5 cm / ≤1.0 cm / ≤2 cm / >2.0 cm

Tumor reduction: defined in this study as the percentage of initial tumor mass removed in the surgery and categorized as 1/5, 2/5, 3/5, 4/5, or 5/5 (macroscopic tumor-free)

Postoperative complications: Postoperative complication was defined as any potentially serious untoward event occurring within the first 30 postoperative days.

* Surgical:
  - Fistula
  - Ileus
  - Bowel perforation
  - Anastomosis insufficiency
  - Wound dehiscence
  - Hemorrhage
  - Pneumothorax
  - Sepsis
  - Short-bowel syndrome
* Non-surgical:
  - Thomboembolia
  - Infection
  - Pleural effusion
  - Bowel obstruction
  - Organ malfunction
  - Heart rhythm disorder
  - Neurological disorder
  - Postoperative ascites
  - Icterus
  - Pulmonary edema

Postoperative mortality: defined as any death occurring within the first 30 postoperative days.

Clinical and histo-pathological data:

Age at first diagnosis: ≤ 60 vs >60 years old

Tumor stage (following FIGO, 1989)

Grading: I vs II vs III

Histology: documented by the Institute of Pathology, Charité

Serous/ mucinous/ endometrioid/ clear cell/ undifferentiated/ mixed/ other

Second malignancy: none/ breast cancer/ endometrium cancer/ colon cancer/ cervix cancer/ other

Chemotherapy received: paclitaxel/carboplatin vs platinum-based systemic combination therapy vs carboplatin or cisplatin mono vs paclitaxel mono vs treosulfan mono vs other chemotherapy vs no therapy

Response to platinum-based therapy: Sensitivity to platinum-containing cytotoxic agents was defined according to international criteria (clinical, radiographic, and serologic disease-free interval of at least 6 months after primary adjuvant platinum-based chemotherapy, GOG).

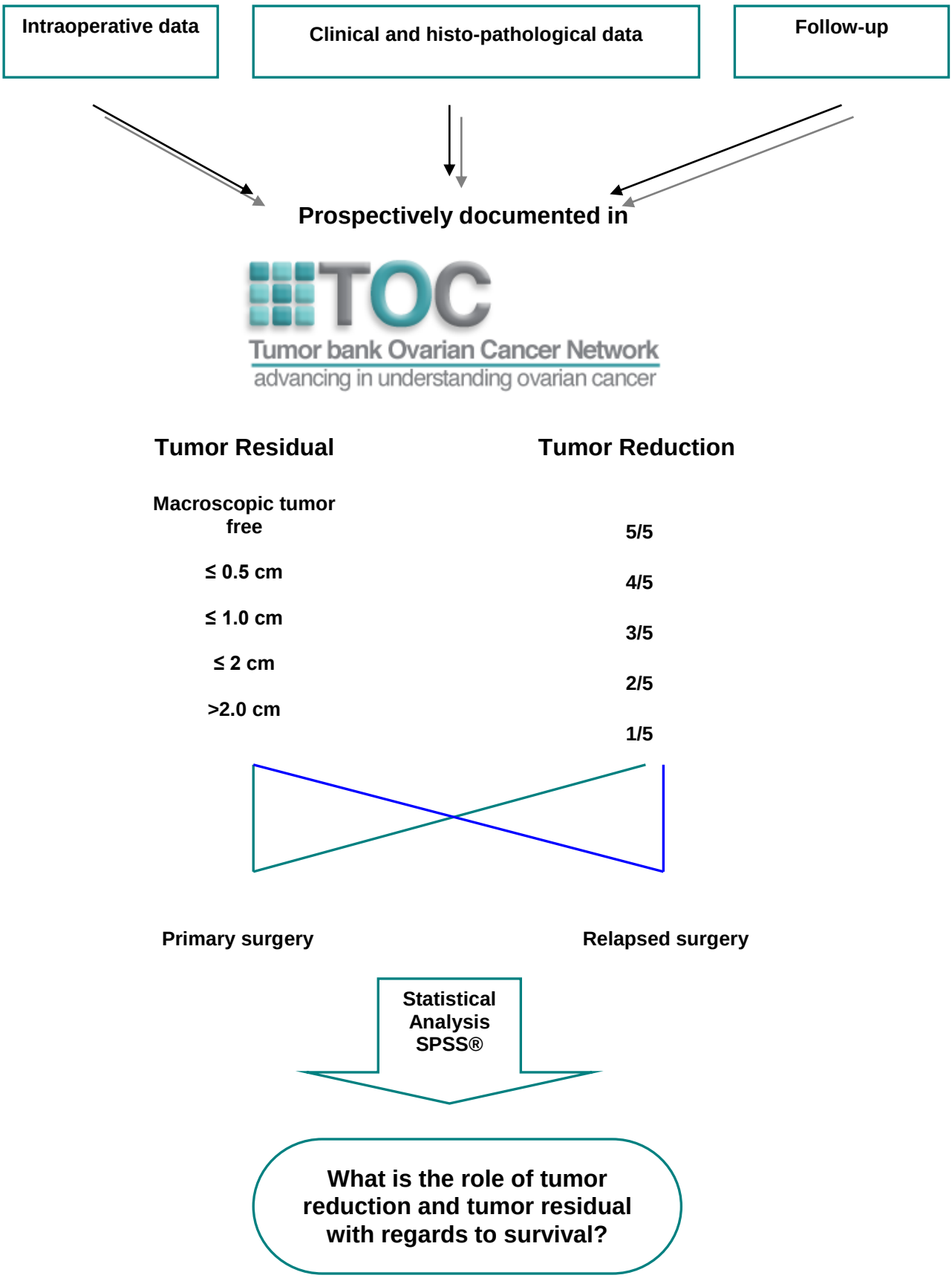
Disease-free interval (in months): Survival data were calculated in months from the date of surgery to either the date of death or to the date of last follow-up for surviving patients to assure equivalent starting points to which the subsequent survival of patients could be compared.

Postoperative survival (in months): Postoperative survival was also calculated in months from the date of surgery to the date of death or to the date of last follow-up.

Time of follow-up (in months)

2.3 Study flowchart

The design of the study is illustrated in the following flowchart:



2.4 Statistical data analysis

Statistical analysis was performed using SPSS statistical software for Windows version 17.0 and 18.0 (SPSS Inc., Chicago, IL, USA).

The following methods were used:

- Cross-classified tables (contingency tables) were used to relate particular variables.
- Chi Square test after Pearson, Fisher´s exact test and Kendall´s tau b were used to analyse correlations between variables and to calculate *p*-values and correlation coefficients.
- Survival curves were estimated according to the Kaplan-Meier method and log-rank tests were used for univariate statistical comparisons. Median survival times that could not be determined were not reported.
- The Cox proportional hazards regression model was used to identify the relative importance of variables as independent predictors of overall and progression-free survival.
- Multivariable logistic regression was used to calculate predictive factors for complete tumor reduction.
- Threshold analysis of residual tumor size was performed using the log-rank-test.
- Graphics were created with SPSS (bar, pie charts, Kaplan Meier curves, Histograms) and Microsoft Excel (threshold analysis) from Office 2007
- All *p*- values less than or equal to 0.05 were considered significant.

3 Results

A total of 446 operations - 269 on patients with primary ovarian cancer and 177 on patients with relapsed ovarian cancer - were included in the analysis. Primary ovarian cancer and recurrent cancer were analysed separately.

3.1 Primary ovarian cancer

3.1.1 Descriptive analysis

Two hundred sixty-nine patients with primary ovarian cancer who underwent tumor reduction surgery at our ward were enrolled in our study. The median age at first diagnosis in primary ovarian cancer was 59 years (range: 22-92 years) as can be seen in figure 2. Off these 269 operations performed, 243 (90.3%) aimed to be curative and 26 (9.7%) palliative.

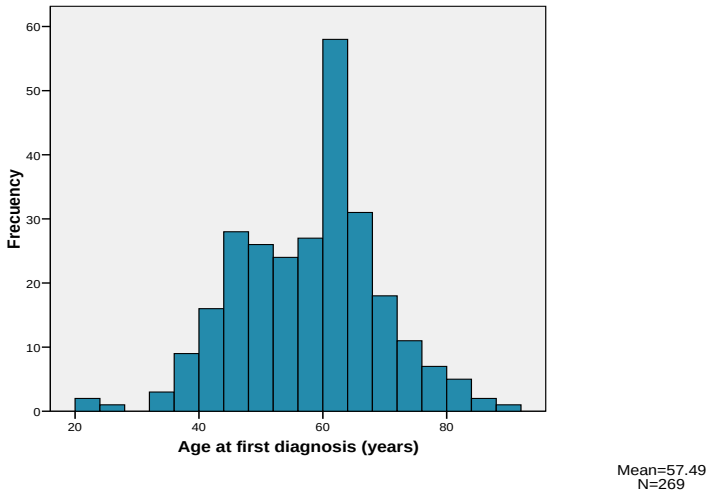


Fig. 2: Histogram. Age at first diagnosis in primary ovarian cancer

The characteristics of patients are outlined in table 3. Most patients (92.3%) had primary ovarian cancer and 7.7% had primary peritoneal carcinoma. The histology and tumour grade were confirmed by a pathologist and were mostly serous (214, 80.8%), followed by endometrioid (20, 7.5%) and mucinous (14, 5.3%). Thirty-eight patients (14.1%) had a second malignancy, most of them, breast cancer (17, 6.3%).

Macroscopic tumor spread was present in 98.1% (262) in level 1, in 68.2% (182) in level 2 and in 44.9% (120) in level 3 (Figure 3). Primary disease was located in 230 cases (85.5%) in the ovaries and uterus and in 95 (35.3%) in the pelvic wall. Eighty-eight (32.7%) had a tumour spread in the mesentery, 164 (61.0%) in the omentum, 36 (13.4%) in the bladder and ureters, 17(6.3%) in the spleen, 126 (46.8%) and 80 (29.7%) in the large and small bowel respectively, 92 (34.2%) in the diaphragm, 52 (19.3%) in the abdominal wall, around 10% each in the stomach, liver and pancreas and 2 (0.8%) in the pleura. Hundred ninety-two patients (71.4%) had diffuse peritoneal carcinomatosis. Sixty-six cases (24.8%) had no ascites at the time of surgery, 200 (75.2%) showed intraoperative ascites [≥500ml (32.3%) and <500ml (42.9%)].

Table 3: Patient characteristics in primary situation.

Patient Characteristics in primary situation (N=269)

Characteristics	Results
Age (yrs), median (range)	57.4 (22-92)
Tumor stage (FIGO)	
I	41 (15.2%)
II	14 (5.2%)
III	152 (56.5%)
IV	41 (15.2%)
Peritoneal cancer	21 (7.8%)
Grading	
I	25 (9.4%)
II	1041(38.1%)
III	139 (52.5%)
Histology	
Serous	214 (80.8%)
Mucinous	14 (5.3%)
Endometrioid	20 (7.5%)
Clear Cell	6 (2.3%)
Undifferentiated	2 (0.8%)

Mixed	7 (2.6%)
Others	2 (0.8%)
Ascites	
No ascites	66 (24.8%)
<500ml	114 (42.9%)
≥500ml	86 (32.3%)
Second malignancy	
None	231 (85.9%)
Breast Cancer	17 (6.3%)
Endometrial Cancer	8 (3.0%)
Colon Cancer	3 (1.1%)
Cervical Cancer	2 (0.7%)
Others	8 (3.0%)
Location of primary disease	
Ovary and Uterus	230 (85.5%)
Pelvic wall	95 (35.3%)
Mesentery	88 (32.7%)
Omentum	164 (61.0%)
Bladder/ureter	36 (13.4%)
Spleen	17 (6.3%)
Large bowel	126 (46.8%)
Small bowel	80 (29.7%)
Diaphragm	92 (34.2%)
Abdominal wall	52 (19.3%)
Stomach	17 (6.3%)
Liver	33 (12.4%)
Pancreas	35 (13.0%)
Pleura	2 (0.8%)
Peritoneal carcinomatosis	192 (71.4%)

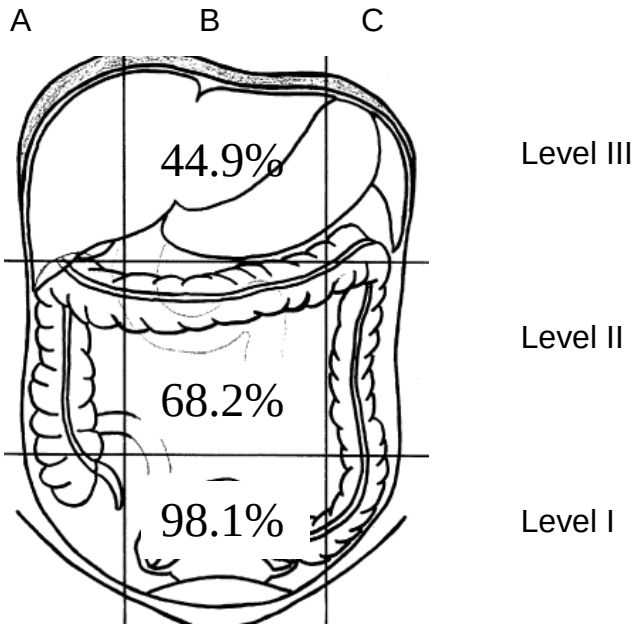


Fig. 3: Tumor spread in primary ovarian cancer in IMO sheet

The surgical procedures performed are summarized in table 4; tumor residual and tumor reduction are shown in table 5 and in figures 6 and 7. The median operation time was 240 minutes (range, 45-570 minutes). In 40 cases (14.9%) small bowel resections and in 83 (30.9%) large bowel resections had to be performed (see figures below 4 and 5).

Table 4: Surgical procedures performed in primary situation (*N* = 269)

Surgical procedures	**No. patients**	**Percent**
Bilateral salpingo-oophorectomy	239	88.8
Hysterectomy	199	74.0
Omentectomy	250	92.9
Pelvic lymphadenectomy	190	70.6
Para-aortic lymphadenectomy	180	66.9
Large bowel resection	83	30.9
Small bowel resection	40	14.9
Deperitonealisation	138	52.1
Appendectomy	132	49.1
Diaphragm resection	12	4.5
Contact coagulation	126	47.5
Splenectomy	8	3.0

Surgical procedures	No. patients	Percent
Distal pancreatectomy	1	0.4
Partial liver resection	3	1.1
Cholecystectomy	5	1.9
Bladder partial resection	4	1.5
Partial stomach resection	5	1.9
Ileostomy	7	2.6
Colostomy	12	4.5

162 (60.2%) patients received systematic lymphadenectomy (pelvic and para-aortic), 25 (9.3%) only pelvic lymphadenectomy and 5 (1.9%) only para-aortic lymphadenectomy.

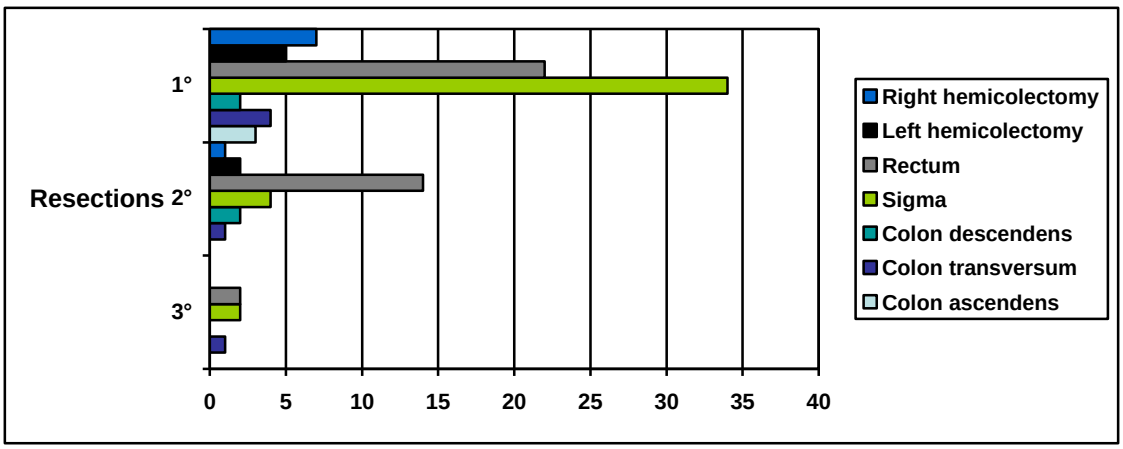


Fig. 4: Large bowel resections performed in primary ovarian cancer N= 83 (30.9%)

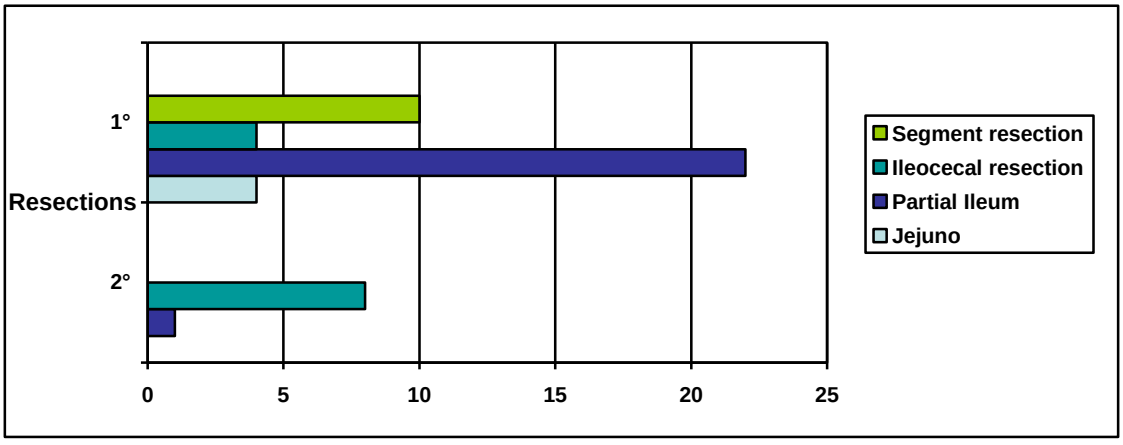


Fig. 5: Small bowel resections performed in primary ovarian cancer n=40 (14.9%)

Table 5: Tumor Residual and Tumor reduction in primary ovarian cancer

Tumor residual and Tumor reduction

Diameter tumor residual	Patients
Tumor free	174 (64.7%)
≤0.5cm	31 (11.5%)
≤1cm	27 (10.0%)
≤2cm	7 (2.6%)
>2cm	30 (11.2%)

Tumor reduction	Patients
5/5	174 (64.7%)
4/5	70 (26.0%)
3/5	11 (4.1%)
2/5	5 (1.9%)
1/5	4 (1.5%)
No tumor reduction	5 (1.9%)

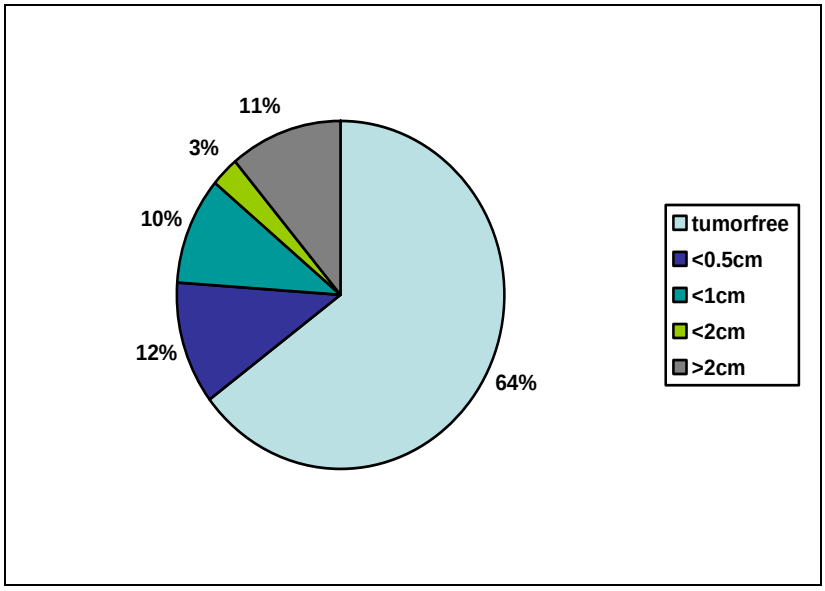


Fig. 6: Diagram with tumor residual in primary ovarian cancer

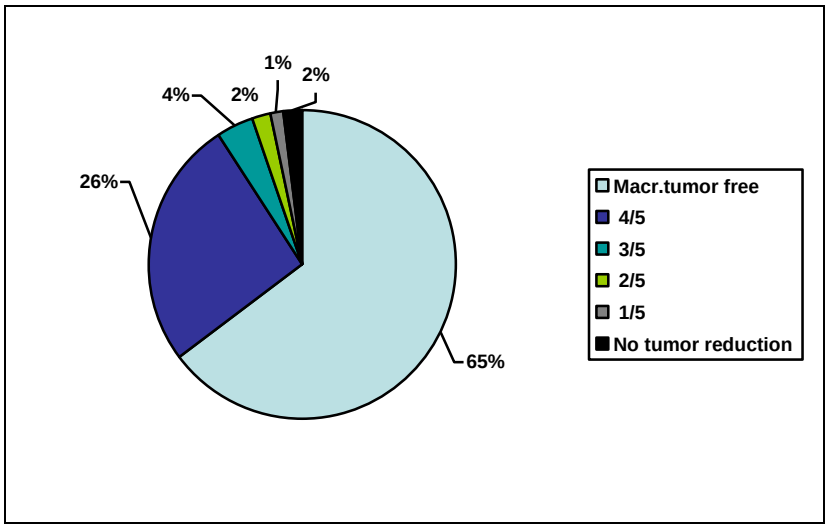


Fig. 7: Diagram with tumor reduction in primary ovarian cancer

Overall, 174 (64.7%) patients were operated on to become macroscopically tumor-free, 65 (24.2%) had residual disease ≤ 2cm, and 30 (11.2%) had > 2 cm intra abdominal residual disease.

In 70 (26.0%) patients 4/5 of the tumor were removed, in 11 (4.1%) patients 3/5, in 5 (1.9%) patients 2/5 and in 4 (1.5%) cases a 1/5 reduction was achieved.

Five cases (1.9%) - all of which with stage T3c M1 (3 with malignant pleura effusion, 1 with metastasis in the liver and spleen and 1 with metastasis in the lung), with wide spread - underwent surgery with palliative aim and were seen at surgery time to have unresected disease (index as >2cm tumor residual-no tumor reduction).

Postoperative complications are described in table 6 and indicate a postoperative morbidity rate of 28.5%. 76 patients experienced non-surgical and surgical postoperative complications such as infections (27 patients; 10%) and neurological disorders (13 patients; 4.8%). Among those patients with potentially serious morbidity, 6 (2.2%) had sepsis related to the surgical site or central venous catheter; 4 (1.5%) had a fistula or hemorrhage; 7 (2.6%) suffered ileus or an organ malfunction; and 3 (1.1%) had an anastomosis insufficiency (figures 8 and 9). Eight patients died within 30 days of surgery (perioperative mortality rate 3.0%). Five of them died because of infection and sepsis, two of them due to an organ malfunction and one patient because of a previous disease that was not related to the surgery.

Table 6: Postoperative complications in primary ovarian cancer (*N* = 76, 28.5%)

Surgical complications	**No. patients**	**Percent**
Fistula	4	1.5
Ileus	7	2.6
Bowel perforation	6	2.2
Anastomosis insufficiency	3	1.1
Wound dehiscence	4	1.5
Hemorrhage	4	1.5
Pneumothorax	2	0.7
Sepsis	6	2.2
Non-surgical complications		
Thomboembolia	11	4.1
Infection	27	10
Pleural effusion	17	6.3
Bowel obstruction	1	0.4
Organ malfunction	7	2.6
Heart rhythm disorder	6	2.2
Neurological disorder	13	4.8
Postoperative ascites	1	0.4
Pulmonary edema	2	0.7
Post operative deaths	8	3.0

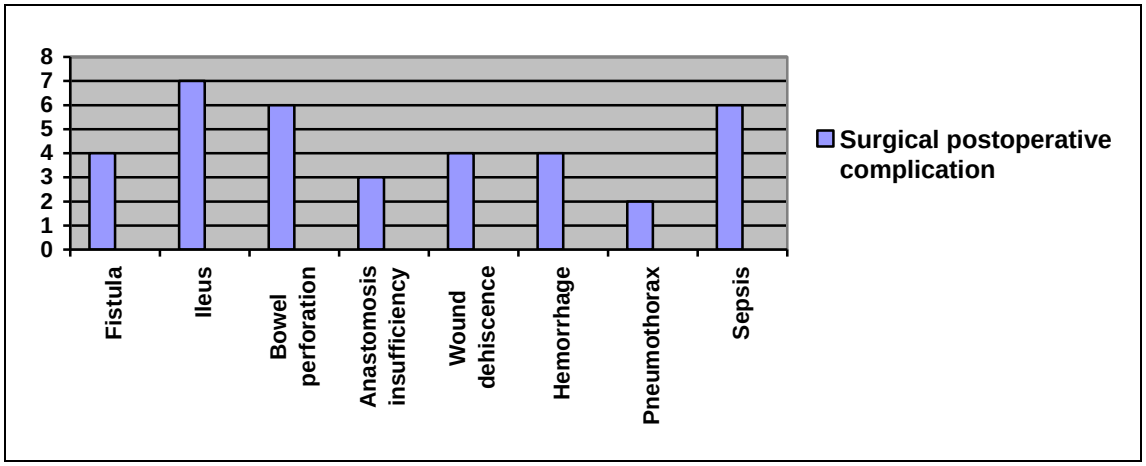


Fig. 8: Surgical postoperative complications in primary ovarian cancer

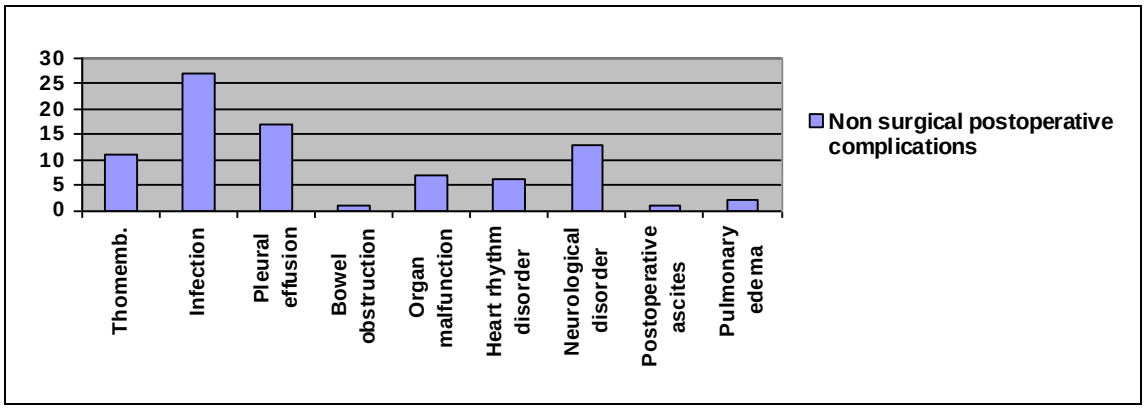


Fig. 9:Non-surgical postoperative complications in primary ovarian cancer

Adjuvant therapy

203 patients (75.5%) received intravenous paclitaxel/carboplatin therapy after surgery; 31 (11.5%) were treated with another platinum-based systemic combination therapy; 6 (2.2%) were treated with carboplatin or cisplatin mono; 2 (0.7%) were treated with treosulfan mono and 1 (0.4%) was treated with paclitaxel mono or other chemotherapy. 21 (7.8%) patients did not receive any therapy because of early-stage or refusal. The median of number of cycles was 6.0 with a range of 1-18.

At the time of the last follow-up (December 2006) 189 patients (70.3%) were alive, 77 (28.6%) had died and 3 (1.1%) could not be followed up. The median follow-up time was 18.4 months (range 0.1-74.5 months).

3.1.1.1. Descriptive analysis for suboptimally debulked primary OC

We carried out a descriptive analysis of suboptimally debulked primary ovarian cancer in order to compare the patients' characteristics from this cohort to those in the main group.

Table 7: Characteristics of suboptimally debulked patients with primary ovarian cancer

Characteristics of suboptimally debulked patients with primary ovarian cancer (N=95)

Characteristics	Results
Age (yrs), median (range)	62.0 (26-92)
Tumor stage (FIGO)	
II	2 (2.1%)
III	53 (55.8%)
IV	26 (27.4%)
Peritoneal cancer	14 (14.7%)
Grading	
I	4 (4.3%)
II	36 (38.7%)
III	53 (57.0%)
Histology	
Serous	83 (90.2%)
Mucinous	2 (2.2%)
Endometrioid	3 (3.3%)
Undifferentiated	1 (1.1%)
Mixed	1 (1.1%)
Others	2 (2.2%)
Ascites	
No ascites	7 (7.4%)
<500ml	35 (36.8%)
≥500ml	53 (55.8%)
Second malignancy	
None	81 (85.3%)
Breast Cancer	6 (6.3%)
Endometrial Cancer	2 (2.1%)
Colon Cancer	1 (1.1%)
Others	5 (5.3%)
Location of primary disease	
Level 1	94 (100%)
Level 2	89 (94.7%)
Level 3	72 (76.6%)

The patients' characteristics in table 7 were observed to have some statistical differences when compared to table 3 (characteristics of the main cohort). The suboptimally debulked group of patients was older (p=0.003 Fisher exact test) and in a significantly higher FIGO stage (p<0.001 Fischer exact test). Moreover, their tumor histology was more likely to be serous than in the main cohort (p=0.009 Fisher exact test). A higher percentage of peritoneal cancer was also prevalent with these patients (14.7% versus 7.8%), the same applies to the presence of ascites at first diagnosis (p<0.001 tau b) and the spread of the disease (p<0.001 Fisher exact test in both extra pelvic levels 2 and 3). Grading, second malignancy and other characteristics were not significantly different between both cohorts.

In a total of 95 patients with primary ovarian cancer, complete debulking could not be achieved. Off these operations, 26 were palliative and 69 curative. The median operation time was 270 minutes (range, 50-570 minutes), thirty minutes longer than in the main cohort (median 4 hours, 240 minutes). In 24 operations (25.3%) small bowel resections and 45 (47.4%) large bowel resections were performed, both percentages higher than in the main cohort. In contrast to this, less systematic lymphadenectomies were performed than in the main collective. In the suboptimal group, there were 37 (38.9%) systematic lymphadenectomies (pelvic and para-aortic), 9 (9.5%) pelvic- and 1 (1.1%) para-aortic lymphadenectomies (table 8).

Table 8: Surgical procedures performed in suboptimally debulked patients (*N* = 95)

Surgical procedures	**No. patients**	**Percent**
Bilateral salpingo-oophorectomy	84	88.4
Hysterectomy	63	66.3
Omentectomy	87	91.6
Pelvic lymphadenectomy	48	50.5
Para-aortic lymphadenectomy	44	46.3
Bowel resection(s)	50	52.6
Deperitonealisation	59	63.4
Appendectomy	35	36.8
Diaphragm resection	3	3.2
Contact coagulation	63	67.7
Splenectomy	3	3.2
Partial liver resection	1	1.1

Surgical procedures	No. patients	Percent
Cholecystectomy	2	2.1
Bladder partial resection	2	2.1
Partial stomach resection	3	3.2
Ileostomy	5	5.3
Colostomy	10	10.6

Thirty-five patients (36.8%) had non-surgical and surgical postoperative complications. Among those patients with potentially serious morbidity, eight died within 30 days of surgery, which were same patients that were in the main group. Therefore, all patients who died in the postoperative period were suboptimally debulked.

After recovering from suboptimal surgery 67 patients (70.5%) received intravenous paclitaxel/carboplatin therapy; 10 (10.5%) were treated with another platinum-based systemic combination therapy; 2 (2.1%) were treated with carboplatin or cisplatin mono; 1 (1.1%) was treated with paclitaxel mono or treosulfan mono or with another chemotherapy. Eleven (11.6%) patients did not receive any therapy. The median number of cycles was again 6.0 with a range of 1-18.

At the time of last follow-up, 45 patients (47.4%) were alive and 49 (51.6%) had died. A higher percentage of patients with suboptimal debulking died compared to those in the main cohort. The median follow-up was 14.6 months (range 0.1-64.0 months).

3.1.2. Correlation analysis

We analysed the correlation between tumor residual/tumor reduction and clinical and physiopathological factors (see table 9). The factors are shown in the list of the variables that were used in the descriptive analysis.

Tumor reduction (1/5, 2/5, 3/5, 4/5 and 5/5- Column **III**) significantly correlated with the age at first diagnosis, FIGO, ascites, tumor localization (levels 2 and 3 and in all organs besides ovary and uterus), operation time period, procedures such as bilateral salpingo-oophorectomy, hysterectomy, omentectomy, lymphadenectomy, bowel resections, deperitonealisation, contact coagulation, appendectomy and colostomy, postoperative morbidity and mortality and platinum-based chemotherapy sensitivity and tumor residual.

Tumor residual (macroscopic tumor-free, ≤2cm, >2cm- Column **II**) significantly correlated with the age at first diagnosis, FIGO, histology, presence of ascites, tumor localization (besides level I), time period of operation, procedures such as hysterectomy, lymphadenectomy, bowel resections, deperitonealisation, contact coagulation, appendectomy and colostomy, postoperative morbidity and mortality and platinum-based chemotherapy sensitivity and tumor reduction.

The same variables significantly correlated with tumor residual (macroscopic tumor-free, <0.5cm, ≤1cm, ≤2cm.>2cm.-Column **I**), and histology and postoperative complications. Grading, second malignancy and many of the abdominal procedures did not bear any relation.

Table 9: Variables associated with tumor residual and tumor reduction in primary ovarian cancer

Column I- Relating to tumor residual (tumor free, <0.5cm, ≤1cm, ≤2cm,>2cm.)

Column II- Relating to tumor residual (tumor free, ≤2cm, >2cm.)

Column III- Relating to tumor reduction (1/5, 2/5, 3/5, 4/5, 5/5, no tumor reduction).

Variables associated with tumor residual and tumor reduction in primary ovarian cancer

Variables	**I.*p*.value**	**II.*p*.value**	**III.*p*.value**
Age (yrs)[a]	0.012	0.007	0.015
	0.003	*0.001*	*0.002*
FIGO[b]	p<0.001	p<0.001	p<0.001
Grading	N.S.	N.S.	N.S.
	0.081	*0.099*	
Histology[c]	N.S.	p<0.042	N.S.
serous/another	*0.013*	*0.010*	*0.005*
Ascites	p<0.001	p<0.001	p<0.001
Second malignancy	N.S.	N.S.	N.S.
Tumor localization			
Level I	N.S.	N.S.	0.731
	0.024	*0.024*	*0.024*
Level II	p<0.001	p<0.001	p<0.001
Level III	p<0.001	p<0.001	p<0.001
Ovary and Uterus	0.048	0.025	0.217

	0.271	*0.304*	*0.210*
Pelvic wall	p<0.001	p<0.001	p<0.001
Mesentery	p<0.001	p<0.001	p<0.001
Omentum	p<0.001	p<0.001	p<0.001
Bladder/ureter	p<0.004 *0.003*	p<0.002 *0.002*	0.001 *0.003*
Spleen	p<0.0001 *0.002*	p<0.0001 *0.002*	p<0.001 *0.002*
Large bowel	p<0.001	p<0.001	p<0.001
Small bowel	p<0.001	p<0.001	p<0.001
Diaphragm	p<0.001	p<0.001	p<0.001
Abdominal wall	p<0.001	p<0.001	p<0.001
Stomach	p<0.001	p<0.001	p<0.001
Liver	p<0.0001 *0.009*	p<0.0001 *0.010*	p<0.0001 *0.012*
Pancreas	p<0.0001	p<0.0001	p<0.0001
Pleura	p<0.0001 *0.156*	0.047 *0.155*	0.034 *0.163*
Peritoneal carcinomatosis	p<0.001	p<0.001	p<0.001
Surgical procedures			
Bilateral salpingo-oophorectomy	N.S.	N.S.	0.015 *0.636*
Hysterectomy	0.001 *0.010*	p<0.001 *0.012*	0.005 *0.015*
Omentectomy	N.S.	N.S.	p<0.027 *0.324*
Pelvic Lymphadenectomy	P<0.001	P<0.001	p<0.001
Para-aortic Lymphadenectomy	p<0.001	p<0.001	p<0.001
Large bowel resection(s)	p<0.001	p<0.001	p<0.001
Small bowel resection(s)	0.001 *0.002*	p<0.001 *0.002*	p<0.001 *0.002*
Deperitonealisation	p<0.0001 *0.034*	p<0.0001 *<0.050*	0.003 *0.027*
Contact coagulation	p<0.001	p<0.001	p<0.001
Appendectomy	p<0.041	p<0.007	p<0.003

	0.001	*0.001*	*<0.001*
Diaphragm resection	p<0.018 *0.798*	N.S.	N.S.
Splenectomy	N.S.	N.S.	N.S.
Distal pancreatectomy	N.S.	N.S.	N.S.
Partial liver resection	0.018 *0.916*	N.S.	N.S.
Cholecystectomy	N.S.	N.S.	N.S.
Bladder partial resection	N.S.	N.S.	N.S.
Partial stomach resection	N.S.	N.S.	N.S.
Colostomy	0.008 *0.007*	0.002 *0.005*	0.004 *0.006*
Operation time	p<0.025 *0.038*	0.001 *0.038*	0.003 *0.036*
Postoperative complications	N.S. *0.017*	0.042 *0.017*	0.013 *0.020*
Postoperative mortality	p<0.001 *0.003*	p<0.001 *0.002*	p<0.001 *0.002*
Tumour residual (0cm,<0.5cm,≤1cm,≤2cm,>2cm)			p<0.001
Tumour residual (≤2cm.,>2cm.)			p<0.001
Tumor reduction (1/5,2/5,3/5,4/5,5/5)	p<0.001	p<0.001	

NS: not significant, p>0.005

Analysis according to the Chi square test by Pearson

Tau b of Kendall in cursive.

[a] Age: at first diagnosis ≤ 60 vs. >60 years.

[b] FIGO: early stadium (I-II) vs. advanced stadium (III-IV).

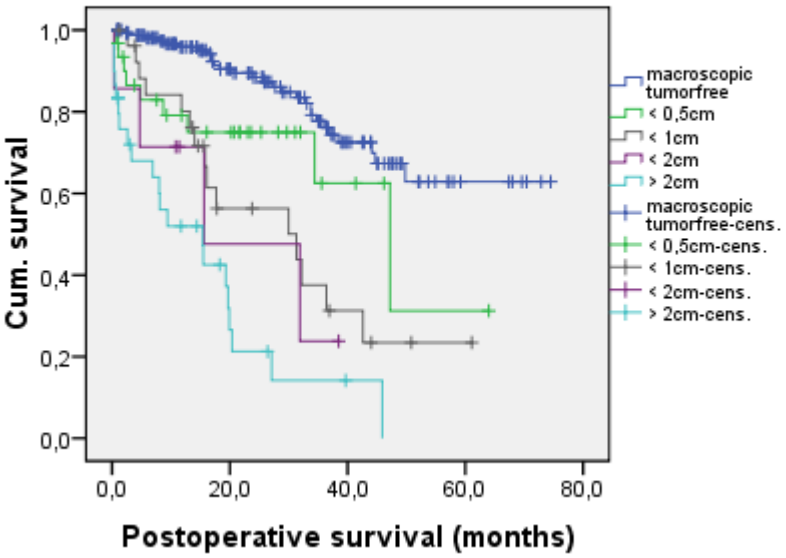
[c] Histology: WHO groups.

3.1.3. Survival analysis

The role of tumor residual and tumor reduction on survival (overall and progression-free) was further evaluated by univariate analysis. The analysis was conducted for primary ovarian cancer and again for suboptimal debulked situations.

3.1.3.1 Overall and progression-free survival in primary ovarian cancer

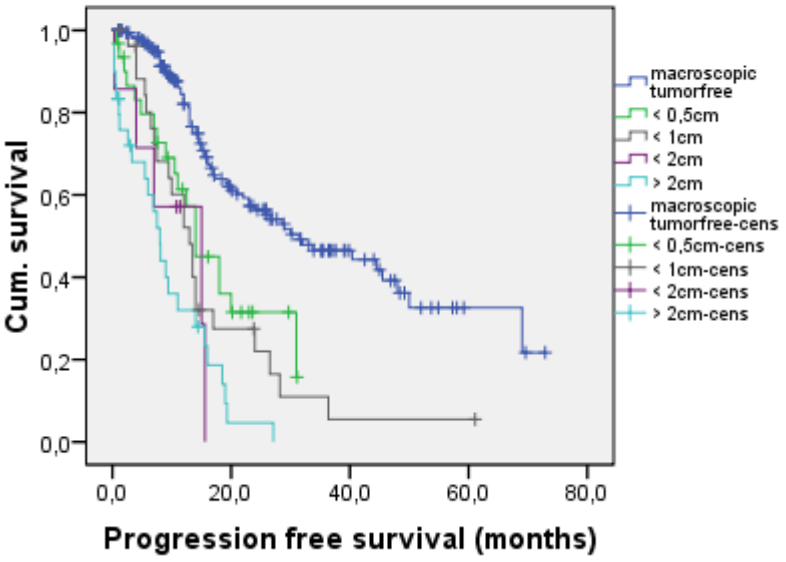
The median disease-free interval after primary surgery was 13.0 months (range 0.1-72.9 months). Postoperative survival could not be reached. Variables tumor residual and tumor reduction in different splits had an effect on the overall survival and progression-free survival in primary ovarian cancer (see tables 10 to 17 and figures 10 to 17).



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	-	-
<0.5cm.	47.2	28.6-65.7
≤1cm.	31.3	7.0-55.5
≤2cm.	15.6	0.0-40.8
>2cm.	15.4	4.6-26.1

***p*<0.001**

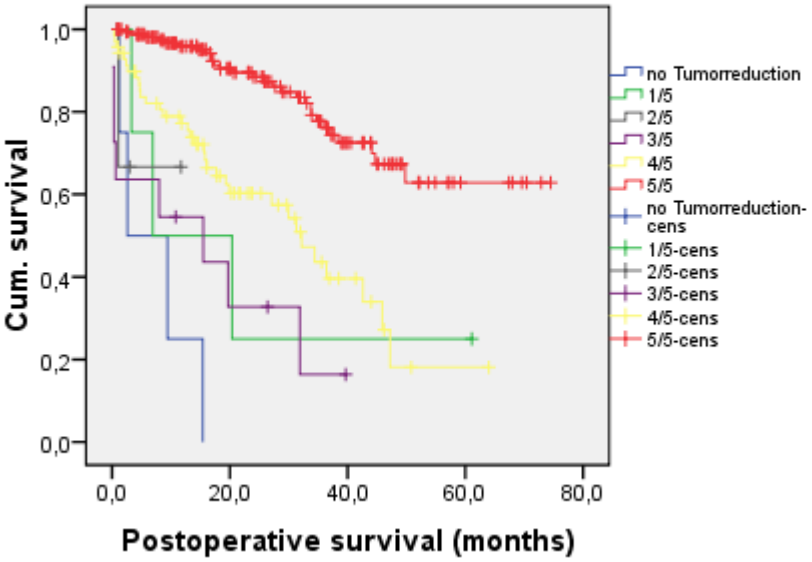
Fig. 10 and table 10: Postoperative survival for tumor residual (tumor free, <0.5cm. ≤1cm, ≤2cm,>2cm) in primary ovarian cancer.



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	31.5	19.1-43.8
<0.5cm.	14	11.6-16.3
≤1cm.	13	9.5-16.4
≤2cm.	15	2.7-27.2
>2cm.	8	6.0-9.9

***p*<0.001**

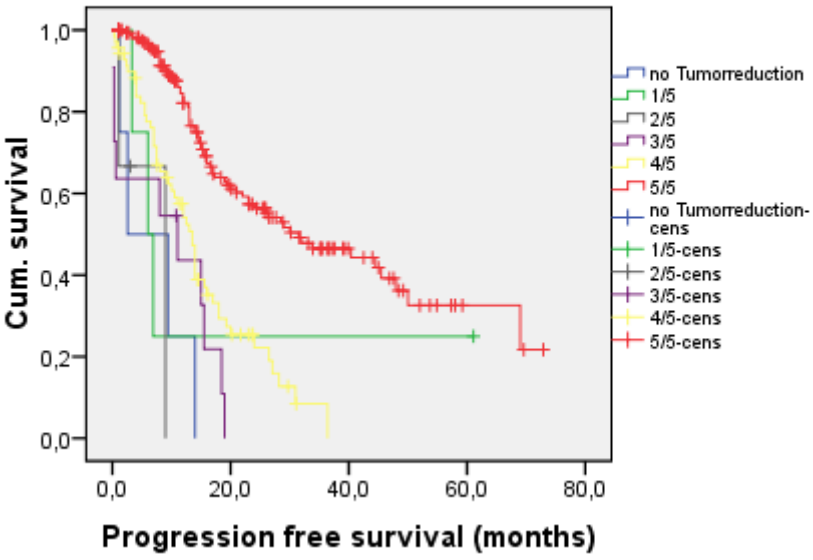
Fig. 11 and table 11: Progression-free survival for tumor residual (tumor free, <0.5cm. ≤1cm, ≤2cm, >2cm) in primary ovarian cancer.



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0-10.6
1/5	6.9	0-23.6
2/5	-	-
3/5	15.5	0-38.1
4/5	32.2	24.2-40.1
5/5	-	-

***p*<0.001**

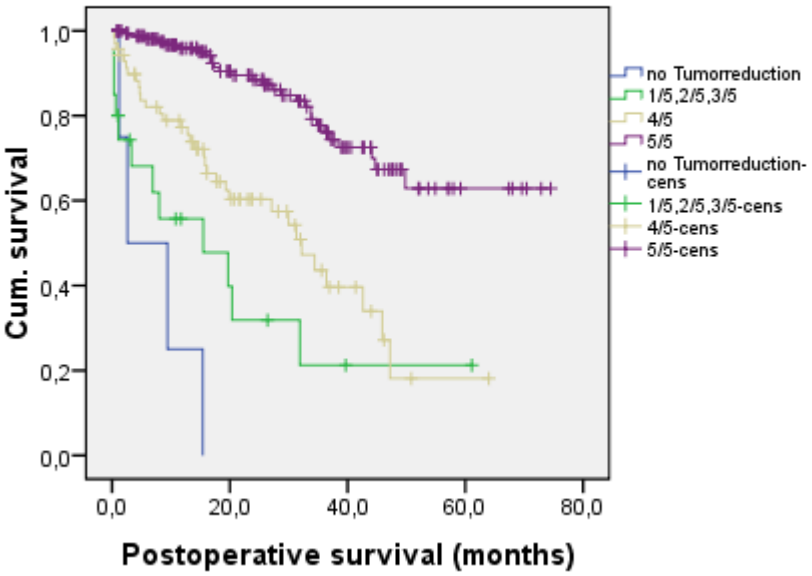
Fig. 12 and table 12: Postoperative survival for tumor reduction (no tumor reduction,1/5, 2/5, 3/5, 4/5 and 5/5) in primary ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5	6.0	2.4-9.5
2/5	9	-
3/5	11	0.0-26.7
4/5	13.5	11.5-15.4
5/5	31.5	19.1-43.8

***p*<0.001**

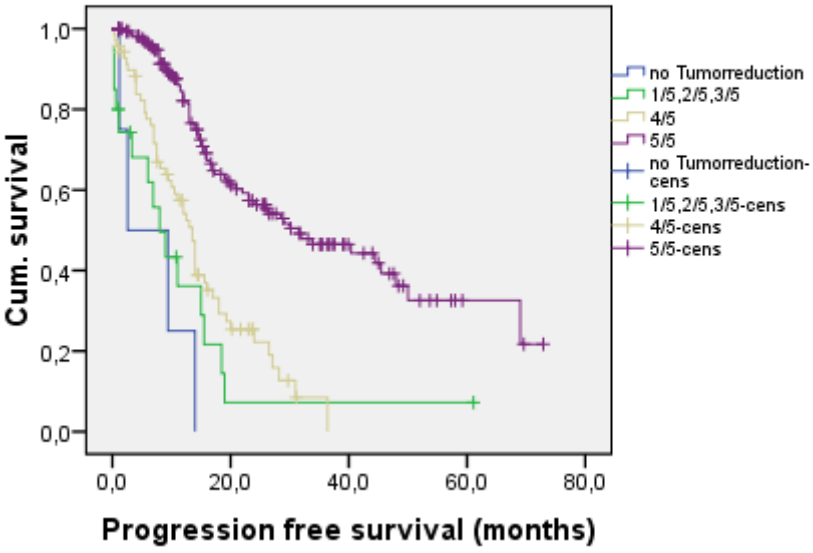
Fig. 13 and table 13: Progression-free survival for tumor reduction (no tumor reduction, 1/5, 2/5, 3/5, 4/5 and 5/5) in primary ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5,2/5,3/5	15.5	0.0-33.6
4/5	32.2	24.2-40.1
5/5	-	-

***p*<0.001**

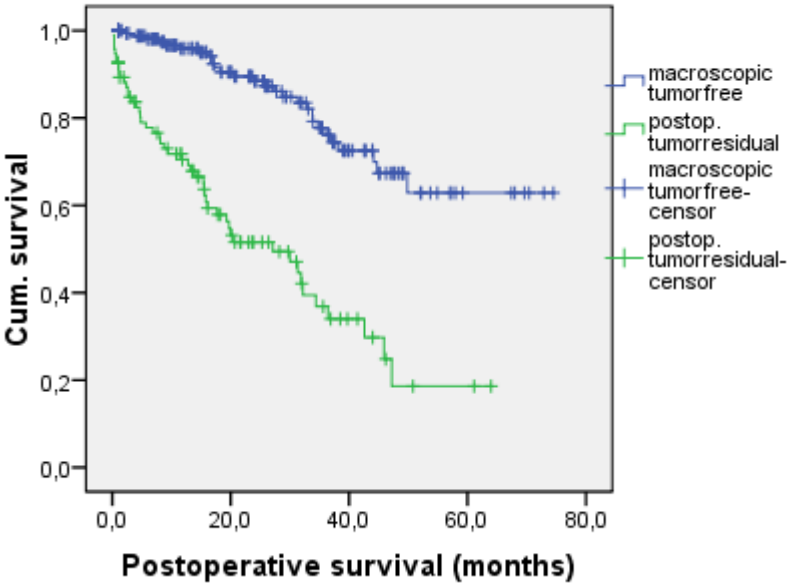
Fig. 14 and table 14: Postoperative survival for tumor reduction (no tumor reduction vs. 1/5, 2/5, 3/5, vs. 4/5 vs. 5/5) in primary ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5,2/5,3/5	8	3.9-12.0
4/5	13.5	11.5-15.4
5/5	31.5	19.1-43.8

***p*<0.001**

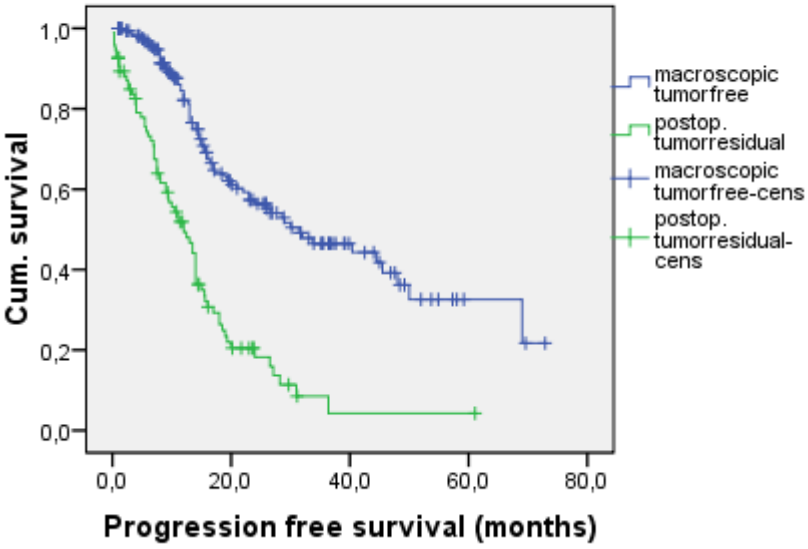
Fig. 15 and table 15: Progression-free survival for tumor reduction (no tumor reduction vs. 1/5, 2/5, 3/5, vs. 4/5 vs. 5/5) in primary ovarian cancer



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	-	-
Tumor residual	27.1	15.2-38.9

***p*<0.001**

Fig. 16 and table 16: Postoperative survival for tumor residual (yes vs. no) in primary ovarian cancer.



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	31.5	19.1-43.8
Tumor residual	12.0	8.7-15.2

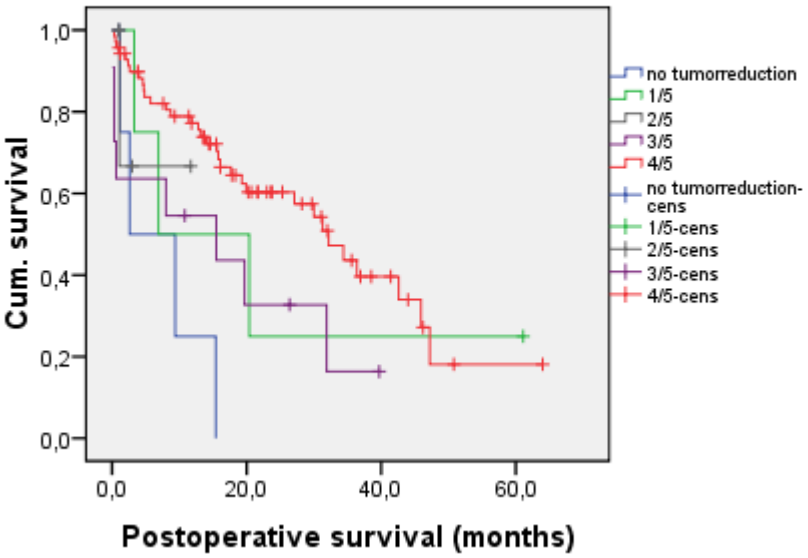
***p*<0.001**

Fig. 17 and table 17: Progression-free survival for tumor residual (yes vs. no) in primary ovarian cancer

Other variables found to have a statistically significant effect in univariate analysis on postoperative survival in primary ovarian cancer were age, FIGO stage, histology, presence of ascites, location of the tumor mass (infestation in levels 2 and 3, pelvic wall, mesentery, omentum, bladder and ureter, spleen, large bowel, small bowel, diaphragm, abdominal wall, stomach, liver and pancreas), presence of peritoneal carcinomatosis, some procedures (as lymphadenectomy, hysterectomy, omentectomy, big bowel resection, contact coagulation, partial stomach resection and colostomy) and postoperative complications. Statistically significant factors on progression-free survival were FIGO stage, presence of ascites, location of the tumor mass (levels 2 and 3, pelvic wall, mesentery, omentum, bladder and ureter, spleen, large bowel, small bowel, diaphragm, abdominal wall, stomach, liver and pancreas), peritoneal carcinomatosis, some procedures (lymphadenectomy, omentectomy, big bowel resection, small bowel resection, deperitonealisation, contact coagulation and colostomy) and postoperative complications.

3.1.3.2. Postoperative and progression-free survival in suboptimally debulked primary ovarian cancer.

In the current univariate analysis, not all macroscopic tumor-free disease patients (5/5) were included. The aim was to see if a relative tumor reduction has an effect on postoperative and progression-free survival. As shown in figure 18 and table 18, the relative tumor reduction did have a statistically significant effect on postoperative survival (p=0.01) although not on progression-free survival (p=0.12).



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5	6.9	0.0-23.6
2/5	-	-
3/5	15.5	0.0-38.9
4/5	32.2	24.2-40.1

***p*=0.01**

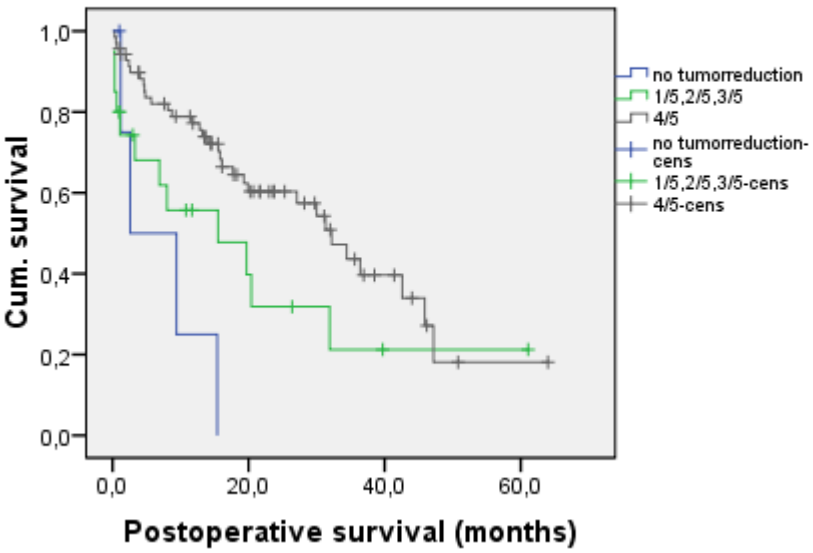
Fig. 18 table 18: Postoperative survival for relative tumor reduction (1/5, 2/5, 3/5, 4/5 and no tumor reduction) in primary ovarian cancer.

Table 19: Progression-free survival for relative tumor reduction (1/5, 2/5, 3/5, 4/5 and no tumor reduction) in primary ovarian cancer.

Parameter	**Median**	**95%CI**
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5	6	2.4-9.5
2/5	9	-
3/5	11	0.0-26.7
4/5	13.5	11.5-15.4

***p*=0.12**

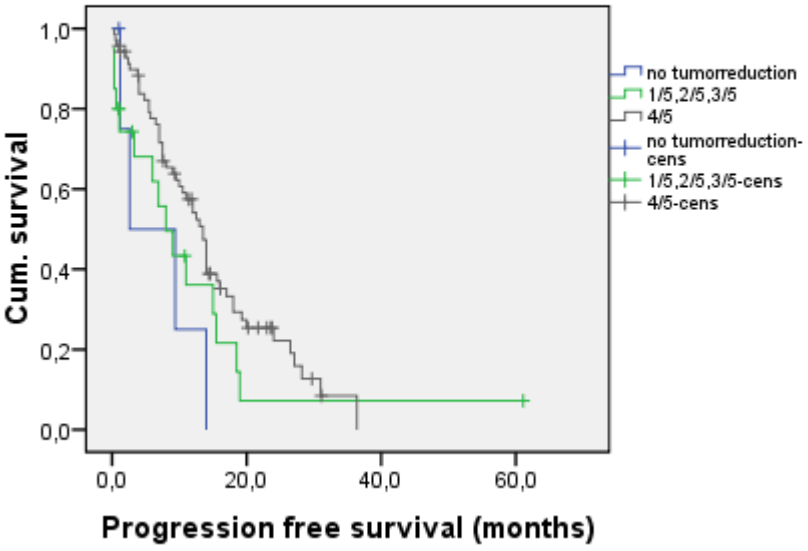
A statistically significant effect on postoperative and progression-free survival was observed when regrouping relative tumor reduction 4/5 vs. any other relative tumor reduction vs. no tumor reduction (see figures 19 and 20 and tables 20 and 21).



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5,2/5,3/5	15.5	0.0-33.6
4/5	32.2	24.2-40.1

***p*=0.002**

Fig. 19 table 20: Postoperative survival for relative tumor reduction (1/5, 2/5, 3/5 vs. 4/5 vs. no tumor reduction) in primary ovarian cancer.



Parameter	Median	95%CI
Tumor reduction		
No reduction	2.6	0.0-10.6
1/5,2/5,3/5	8	3.9-12.0
4/5	13.5	11.5-15.4

***p*=0.04**

Fig. 20 table 21: Progression-free survival for relative tumor reduction (1/5, 2/5, 3/5 vs. 4/5 vs. no tumor reduction) in primary ovarian cancer

3.1.4. Multivariate analysis

The variables age (>60 vs. ≤60), ascites (< 500m vs. ≥500ml vs. no ascites), small bowel and big bowel metastasis (yes vs. no), peritoneal carcinomatosis (yes vs. no), tumor localization in levels 1, 2 and 3 (yes vs. no), tumor FIGO stage (I-II vs. III-IV), tumor grade (I vs. II vs. III), histology (serous vs. others) and tumor reduction (no reduction vs. 1/5,2/5,3/5 vs. 4/5 vs. 5/5) and tumor residual, which mostly showed to have an effect on survival in univariate analysis, were included in the multivariate model. The Cox-Regression model was employed stepwise to evaluate the prognostic significance of these variables on postoperative and progression-free survival in primary ovarian cancer.

Variables used (in the following order):

Variable	Category of reference
Age (Age at first diagnosis 60)	>60
Bowel metastasis (small or large)	No
Peritoneum carcinomatosis	No
Level 2	No
Level 3	No
Ascites	No ascites
Grade	III
FIGO Stage	I-II
Histology	serous
LN affection	N0
Tumor reduction	5/5
Tumor residual	>1 cm

Variable tumor spread in level 1 was not taken into consideration because only 3 patients were not affected in this abdominal level.

3.1.4.1 Postoperative survival

Table 22: Multivariate analysis for postoperative survival in primary OC.

	HR	**p**
Age >60	1.081	.782
Bowel mtx	1.907	.080
Peritoneum carcinomatosis	.734	.583
Level 2	1.024	.961
Level 3	.613	.157
Ascites		.230
<500ml	.860	.746
≥500ml	1.539	.403
FIGO III-IV	3.272	.079
Grade		.128
grading I	.430	.306
grading II	1.529	.141
Histology	2.790	**.002**
LN affection		.005
N1	1.193	.648
Nx	3.106	**.005**
Tumor reduction		**.001**
no Tumor reduction	10.627	**.001**
1/5, 2/5, 3/5	4.516	**.002**
4/5	5.471	**.002**
Tumor residual		.070
<1cm	.428	.070

Introducing variables Tumor reduction and Tumor residual, no variable besides histology and unknown lymph node affection remained significant.

Tumor reduction had a significant and independent effect on survival. Patients without tumor reduction or without macroscopic tumor-free disease had a higher risk of dying compared to those who were macroscopically tumor-free following surgery. In addition, patients with tumor residual < 1cm had a lower risk of dying compared to those patients with tumor residual ≥ 1 cm. This figure is not statistically significant, however.

Tumor histology other than serous was also observed to have a higher statistically significant HR compared to patients with serous tumor histology. Unknown lymph node

affection had a significant HR of 3.1 (p<0.005). Outcomes of these variables were all independent from others variables that were included in the analysis.

3.1.4.2 Progression-free survival

Table 23: Multivariate analysis for progression-free survival in primary ovarian cancer.

	HR	**p**
Age >60	1.227	.315
Bowel mtx	.836	.458
Peritoneum carcinomatosis	1.049	.893
Level 2	1.063	.840
Level 3	1.277	.321
Ascites		.187
≤500ml	.783	.388
>500ml	1.224	.541
FIGO III-IV	3.342	**.006**
Grade		.271
grading I	.732	.576
grading II	1.336	.170
Histology	1.127	.672
LN affection		.129
N1	1.016	.949
Nx	1.683	.081
Tumor reduction		**.014**
no Tumor reduction	3.780	**.025**
1/5, 2/5, 3/5	2.928	**.004**
4/5	2.142	.061
Tumor residual		.195
< 1cm	.614	.195

Tumor reduction had an independent effect on progression-free survival. Patients without tumor reduction or with tumor reduction (1/5 to 3/5) had a significantly higher HR for progression disease. Patients with a 4/5 reduction did not have a significantly higher HR compared to patients with complete tumor reduction but had a lower risk than those with other tumor reduction or no tumor reduction. Patients with tumor residual < 1cm had a low, not significant risk for progression disease compared to those with tumor

residual >1cm. Besides that, only FIGO stadium III-IV had an independent significantly higher HR.

3.1.5. Predictive factors for complete tumor reduction in primary ovarian cancer

Predictive factors for complete tumor reduction in primary ovarian cancer were identified by logistic regression following the Cox-Regression Model. Following variables were included in the stepwise model through four blocks:

Block one: age

Block two: block one + tumor preoperative characteristics; age, ascites, small bowel and big bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3

Block three: block two +tumor postoperative characteristics; age, ascites, small bowel and large bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3, FIGO, grade and histology

Block four: block three +lymphadenectomy; age, ascites, small bowel and big bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3, FIGO, grade, histology and systematic lymphadenectomy.

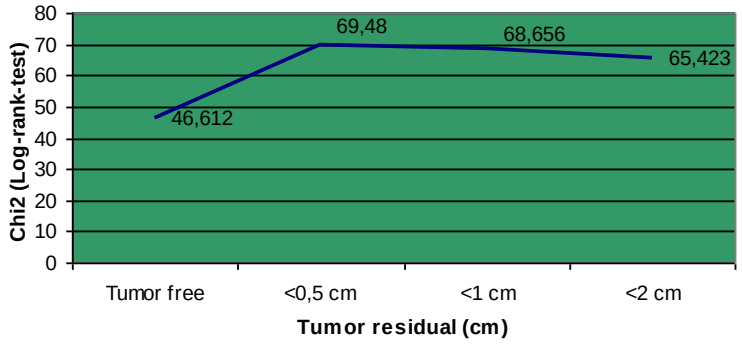
	Regression coef.B	Standard error	Wald	df	Sig.	Exp(B)	95% IC for EXP(B)	
							Lower	Upper
Age >60	-.832	.398	4.382	1	**.036**	.435	.200	.948
Ascites			.899	2	.638			
<500ml	-.486	.629	.597	1	.440	.615	.179	2.111
>500ml	-.638	.674	.894	1	.344	.529	.141	1.982
S. bowel	-1.295	.433	8.931	1	**.003**	.274	.117	.640
L.bowel	-.525	.443	1.402	1	.236	.592	.248	1.410
Peritoneal	-1.097	.922	1.417	1	.234	.334	.055	2.032
Level 2	-.524	.649	.652	1	.419	.592	.166	2.112
Level 3	-1.076	.444	5.880	1	**.015**	.341	.143	.814
Figo III-IV	-.177	1.094	.026	1	.871	.837	.098	7.143
Grading			5.326	2	.070			
grading	-2.835	1.347	4.433	1	.035	.059	.004	.822
Histology	-.099	.627	.025	1	.875	.906	.265	3.098
LymphaDN	1.859	.474	15.406	1	**.000**	6.416	2.536	16.231
Constant	5.357	1.588	11.381	1	.001	211.998		

Variables such as age (>60 years) (OR=0,36 ; 95%CI 0,2-0,94 p<0.05), small bowel metastasis (OR=0,27; 95% CI 0,17-0,64 p<0.05), tumor spread in upper abdomen (OR=0,34; 95% CI 0,14-0,81 p<0.05) and systematic lymphadenectomy (OR 6.4 CI 95% 2.5-16.2 p<0.001) were identified as significant predictive factors for complete tumor reduction in primary ovarian cancer.

3.1.6. Threshold value analysis for primary OC

Using threshold analysis for tumor residual and tumor reduction, we were able to determine the value of the variable where survival the KM graph diverges.

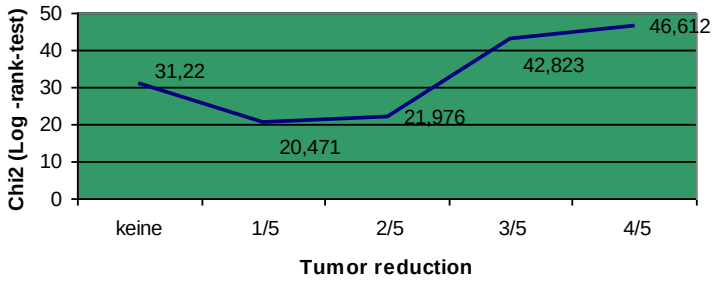
The tumor residual threshold analysis is shown in figure 21. It shows a point between a tumor residual diameter of 0.5cm and 1cm, where the maximal difference between a good and a worse prognosis in primary situation was found.



		Chi² Log Rank Test
Tumor free	Tumor residual	46,612
< 0,5 cm	≥ 0,5	69,480
< 1 cm	≥ 1 cm	68,656
< 2 cm	≥ 2 cm	65,423

Fig. 21 and table 24: Threshold analysis of tumor residual in primary ovarian cancer.

In fig 30 for tumor reduction, there is no clear value where the Kaplan-Meier survival graphic diverges.



		Chi² Log Rank Test
No tumor reduction	1/5 till 5/5	31,220
≤ 1/5	≥ 1/5	20,471
≤ 2/5	≥ 2/5	21,976
≤ 3/5	≥ 3/5	42,823
≤ 4/5	5/5	46,612

Fig. 22 and table 25: Threshold analysis of tumor reduction in primary ovarian cancer.

3.2. Relapsed ovarian cancer

3.2.1 Descriptive analysis

Between September 2000 and April 2006, a total of 177 operations on patients with first relapsed ovarian cancer were performed in Virchow Klinikum. 131 operations (74.0%) were intended to be curative and 46 (26.0%) palliative. The median age at first diagnosis of these patients with relapsed ovarian cancer was 55 years (range, 23-83 years) as seen in figure 23.

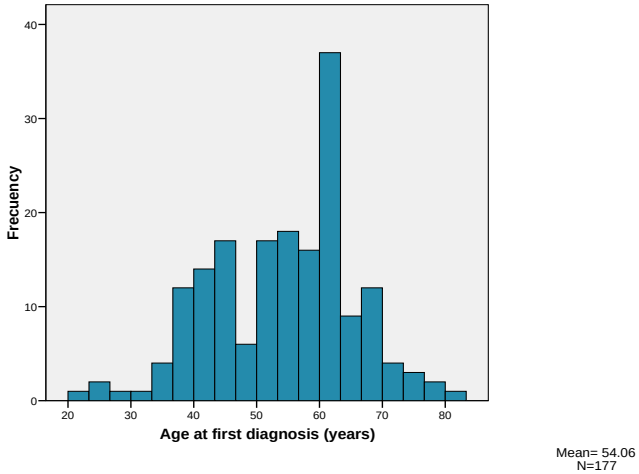


Fig. 23: Histogram. Age at first diagnosis in relapsed ovarian cancer patients

Continuous and categorical descriptive variables of relapsed ovarian cancer patients are summarized in Table 9. FIGO classification is according to the first diagnosis. Six patients (3.5%) had relapsed peritoneal carcinoma. The main histological type was, as in primary ovarian cancer, serous (n=149, 88.2%), followed by endometrioid (n=8, 4.7%) and clear cell (n=4, 2.4%). Twenty-one patients (11.9%) had a second malignancy; most of them had breast cancer (n=9, 5.1%).

Macroscopic tumor spread was present in 86.2% (150) in Level 1, in 79.9% (139) in Level 2 and in 64.9% (113) in Level 3 (figure 24). Compared to those with primary ovarian cancer, in patients with relapsed ovarian cancer, the tumor was more widely spread in the upper abdomen (Level 3). Recurrent disease was located in 13 cases (7.3%) in the ovaries and uterus, in 86 (48.6%) in the pelvic wall, ninety (50.8%) had tumor spread in the mesentery, 68 (38.4%) in the omentum, 49 (27.7%) in the bladder and ureter, 19 (10.7%) in the spleen, 124 (70.1%) and 96 (54.2%) in the large and small bowel, 67 (37.9%) in the diaphragm, 58 (32.8%) in the abdominal wall, around 20%

each in the liver and pancreas, 26 (14.7%) in the stomach and 1 (0.6%) in the pleura. 142 patients (80.2%) had diffuse peritoneal carcinomatosis. Eighty-one patients (46.6%) had no ascites at the time of surgery, 37 had equal or more than 500ml (21.3%) and 56 patients < 500ml (32.2%).

Table 26: Patient characteristics in relapsed ovarian cancer

Patient Characteristics at relapsed ovarian cancer (n=177)

Characteristics	Results
Age (yrs), median (range)	55.0 (23-83)
Tumor stage (FIGO)	
I	20 (11.3%)
II	6 (3.4%)
III	119 (67.2%)
IV	19 (10.7%)
Peritoneal cancer	6 (3.4%)
Missing data	7 (3.9%)
Grading	
I	9 (5.3%)
II	53 (31.4%)
III	107 (63.3%)
Histology	
Serous	149 (88.2%)
Mucinous	3 (1.8%)
Endometrioid	8 (4.7%)
Clear Cell	4 (2.4%)
Undifferentiated	4 (2.4%)
Mixed	1 (0.6%)
Ascites	
No ascites	81(46.6%)
< 500ml	56 (32.2%)
≥ 500ml	37 (21.3%)

Second malignancy	
None	156 (88.1%)
Breast Cancer	9 (5.1%)
Endometrial Cancer	7 (4.0%)
Colon Cancer	1 (0.6%)
Cervical Cancer	1 (0.6%)
Others	3 (1.7%)
Location of relapsed disease	
Ovary and Uterus	13 (7.3%)
Pelvic wall	86 (48.6%)
Mesentery	90 (50.8%)
Omentum	68 (38.%)
Bladder/ureter	49 (27.7%)
Spleen	19 (10.7%)
Large bowel	124 (70.1%)
Small bowel	96 (54.2 %)
Diaphragm	67 (37.9%)
Abdominal wall	58 (32.8%)
Partial stomach	26 (14.7%)
Liver	48 (27.9%)
Pancreas	37 (20.9%)
Pleura	1 (0.6%)
Peritoneal carcinomatosis	142 (80.2%)

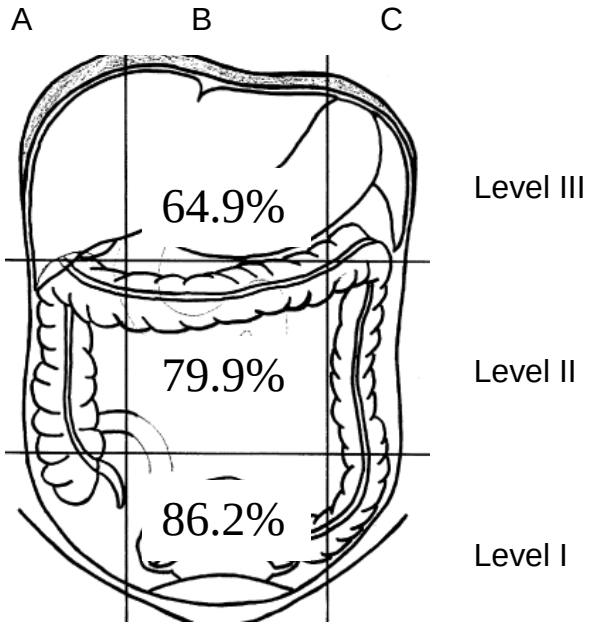


Fig. 24 Tumor spread in relapsed ovarian cancer in IMO Sheet.

At the time of relapsed ovarian cancer surgery; hysterectomy was performed in 6 (3.4%) patients; in 7 (4.0%) bilateral salpingo-oophorectomy; in 59 (33.3%) excision of retained omental tissue; 23 (13.0%) received systematic lymphadenectomy (para-aortic and pelvic), 10 (5.6%) pelvic lymph node dissection and 12 (6.8%) para-aortic lymph node dissection; 97 (54.8%) underwent bowel resections, among which 62 (35.2%) received small bowel resection and 75 (42.4%) large bowel resection (see graphic below, fig.18 and 19). In 23 patients (13.0%) appendectomy was performed; 97 (56.1%) received deperitonealisation; 9 (5.2%) received diaphragm resection and 8 (4.6%) partial stomach resection; 6 (3.5%) received partial liver resection or splenectomy; 4 (2.3%) received distal pancreatectomy; 5 (2.9%) cholecystectomy; 114 (65.9%) contact coagulation; 5 (2.9%) bladder partial resection and 14 (8.1%) received colostomy, and 11 (6.4%) ileostomy. All surgical procedures are summarized in table 10. The median operation time was 250 minutes (range, 23-719 minutes).

Table 27: Surgical procedures performed in relapsed ovarian cancer (N=177)

Surgical procedures	No. patients	Percent
Bilateral salpingo-oophorectomy	7	4.0
Hysterectomy	6	3.4
Omentectomy	59	33.3
Pelvic lymphadenectomy	36	20.3
Para-aortic lymphadenectomy	39	22.0
Small bowel resection	62	35.2
Large bowel resection	75	42.4
Deperitonealisation	97	56.1
Appendectomy	23	13.0
Contact coagulation	114	65.9
Diaphragm stripping/resection	9	5.2
Splenectomy	6	3.5
Distal pancreatectomy	4	2.3
Partial liver resection	6	3.5
Cholecystectomy	5	2.9
Bladder partial resection	5	2.9
Partial stomach resection	8	4.6
Ileostomy	11	6.4
Colostomy	14	8.1

Among patients with bulky resected disease, 79 (44.6%) had a macroscopic disease-free surgery, in 56 (31.6%) 4/5 of the tumor were removed, in 13 (7.3%) 3/5 and in 7 (4.0%) each 2/5 and 1/5 tumor reduction was achieved. Fifteen patients (8.5%) who underwent palliative operation to alleviate symptoms due to ovarian cancer relapse were considered to have unresectable disease. Six of them had previously been resistant to platinum-based chemotherapy and in one patient, sensitivity was not applicable. Six had metastasis (in the spleen, skin, lungs, kidney capsule and two intrahepatics) and two of them died from postoperative complications.

Forty-six (26.0%) patients had residual disease < 1 cm, and 52 (29.4%) had ≥ 1 cm intra-abdominal residual disease (table 11).

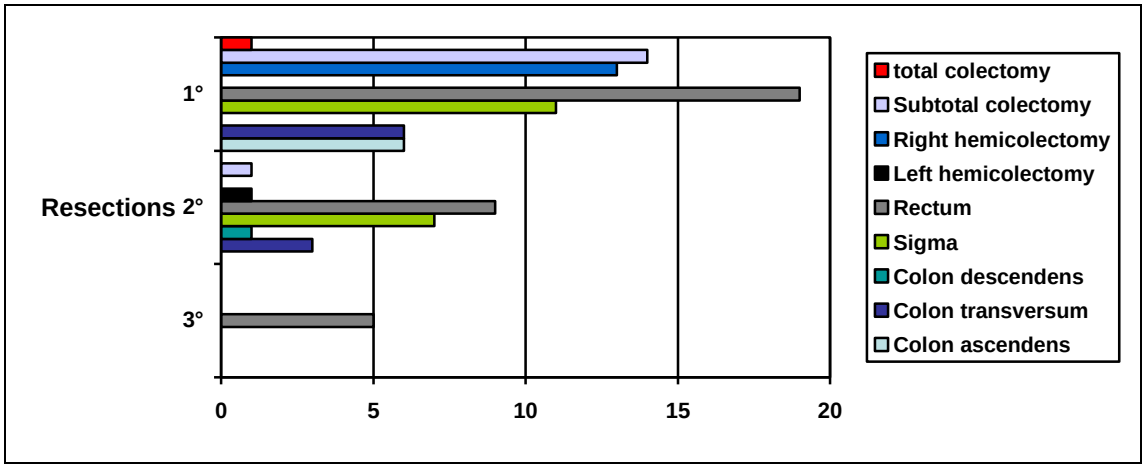


Fig. 25: Large bowel resections performed in relapsed ovarian cancer (N=75)

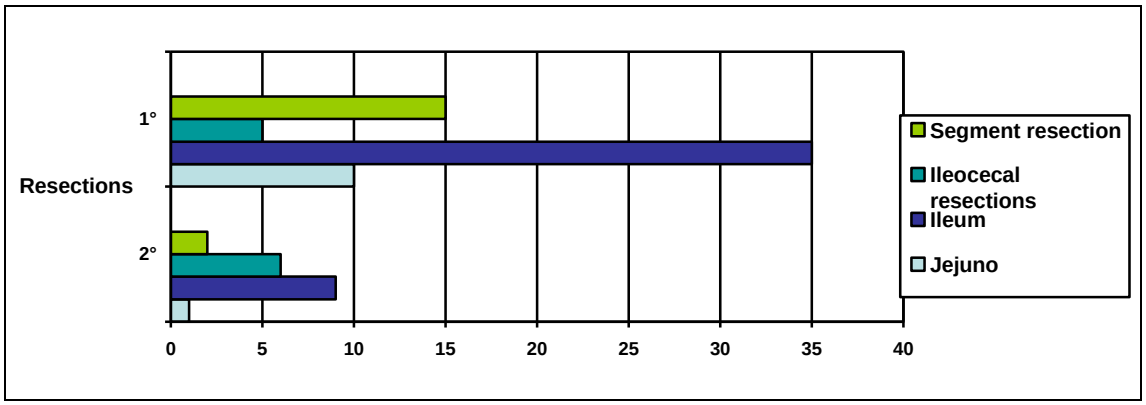


Fig. 26: Small bowel resections performed in relapsed ovarian cancer (N=62)

Table 28: Tumor residual and tumor reduction in relapsed ovarian cancer

Tumor residual and Tumor reduction

Diameter tumor residual	patients
Tumor free	79 (44.6%)
≤0.5cm	20 (11.3%)
≤1cm	26 (14.7%)
≤2cm	6 (3.4%)
>2cm	46 (26.0%)
Tumor free	79 (44.6%)
<1cm	46 (26.0%)
≥1cm	52 (29.4%)
Tumor reduction	patients
5/5	79 (44.6%)
4/5	56 (31.6%)
3/5	13 (7.3%)
2/5	7 (4.0%)
1/5	7 (4.0%)
No tumor reduction	15 (8.5%)

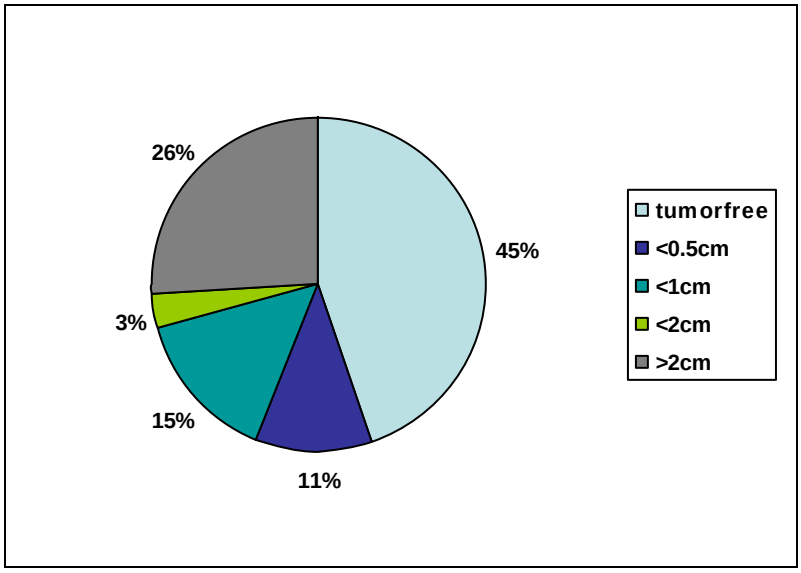


Fig. 27: Diagram with tumor residual in relapsed ovarian cancer

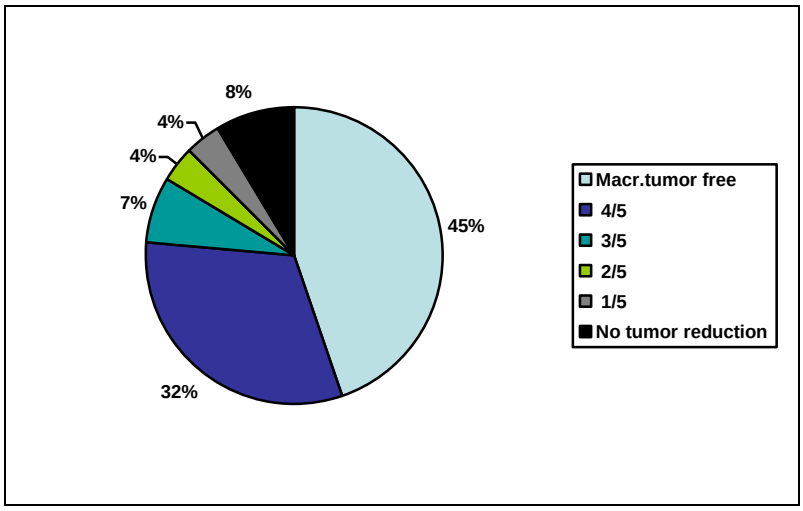


Fig. 28: Diagram with tumor reduction in relapsed ovarian cancer

Sixty-four patients experienced non-surgical and surgical postoperative complications (postoperative morbidity rate of 37.2%) which are described in table 29. Twenty patients (11.6%) had an infection; 12 (7%) had pleura effusion; 11 (6.4%) had thromboembolia; 7(4.0%) had short-bowel syndrome; around 5 each suffered sepsis, fistula, bowel perforation, anastomosis insufficiency, hemorrhage, organ malfunction or neurological disorders; 2 (1.2%) each had ileus, wound dehiscence, heart rhythm disorder or postoperative ascites. Fourteen patients died within 30 days of surgery (perioperative mortality 8.2%). Two of them died because of postoperative hemorrhage, three because of sepsis, one because of thromboembolia, six because of organ malfunction and two of them because of a previous disease.

Table 29: Postoperative complications in second surgery (N=64, 37.2%)

Surgical complications	**No. patients**	**Percent**
Fistula	5	2.9
Ileus	2	1.2
Bowel perforation	6	3.5
Anastomosis insufficiency	4	2.3
Wound dehiscence	2	1.2
Hemorrhage	6	3.5
Pneumothorax	1	0.6
Short-bowel syndr.	7	4.0
Sepsis	5	2.9
Non-surgical complications		
Thomboembolia	11	6.4
Infection	20	11.6
Pleural effusion	12	7.0
Organ malfunction	4	2.3
Heart rhythm disorder	2	1.2
Neurological disorder	6	3.5
Postoperative ascites	2	1.2
Icterus	1	0.6
Pulmonary edema	1	0.6
Post operative deaths	14	8.2

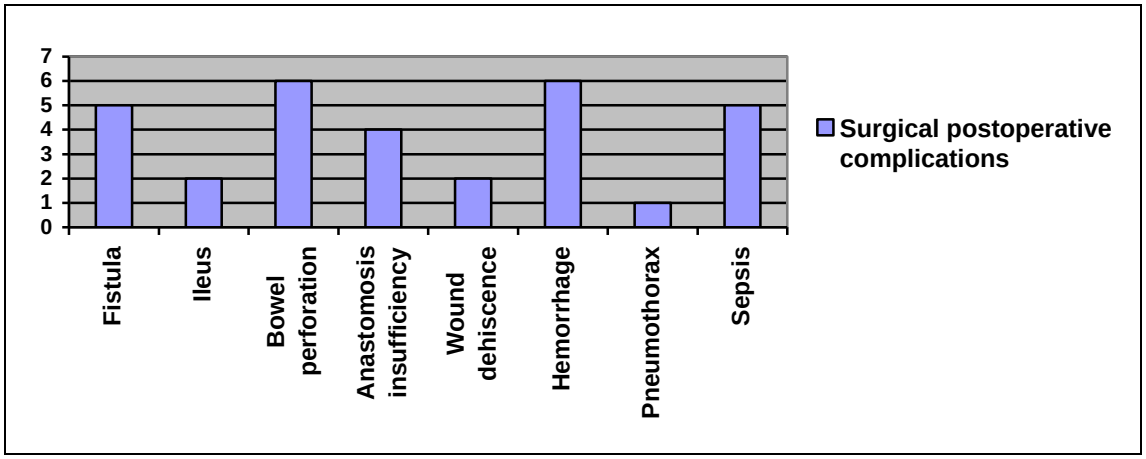


Fig. 29: Surgical postoperative complications in relapsed ovarian cancer

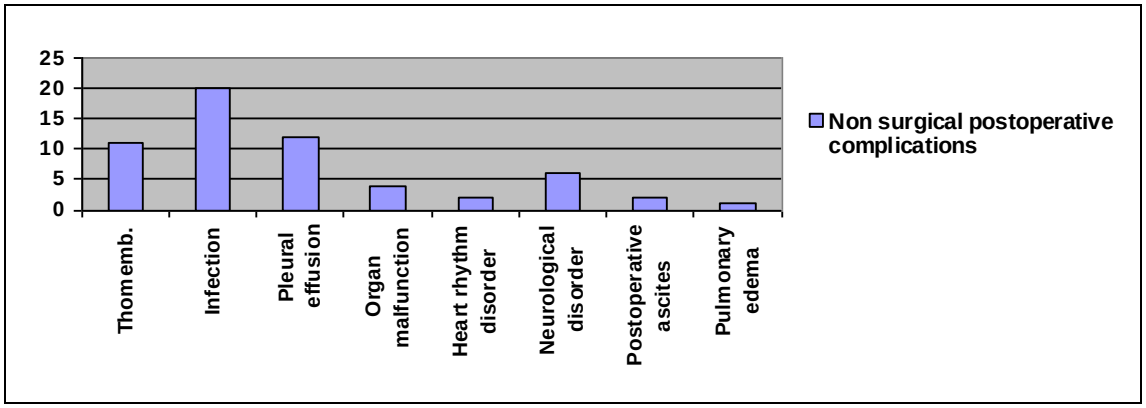


Fig. 30: Non-surgical postoperative complications in relapsed ovarian cancer

Adjuvant therapy

In 173 patients (98.9%), relapsed ovarian cancer surgery was performed after treatment with some sort of chemotherapy. 127 (72.6%) received intravenous paclitaxel/carboplatin as first chemotherapy; 39 (22.3%) were treated with other platinum-based systemic combination therapy; 3 (1.7%) were treated with carboplatin or cisplatin mono; 1 (0.6%) was treated with paclitaxel mono and 3 (1.7%) were treated with another chemotherapy. The median of number of cycles was 6.0 with a range of 2-18. Among the patients treated with previous chemotherapy, 49 (28.2%) had disease that progressed or failed to respond to the treatment with platinum-containing cytotoxic agents and therefore were considered platinum-resistant following GOG criteria. 118 (67.8%) treated patients were platinum-sensitive (fig. 25). In 7 (4%) patients the platinum-sensitivity was not applicable because of previous non-platinum therapy or no therapy.

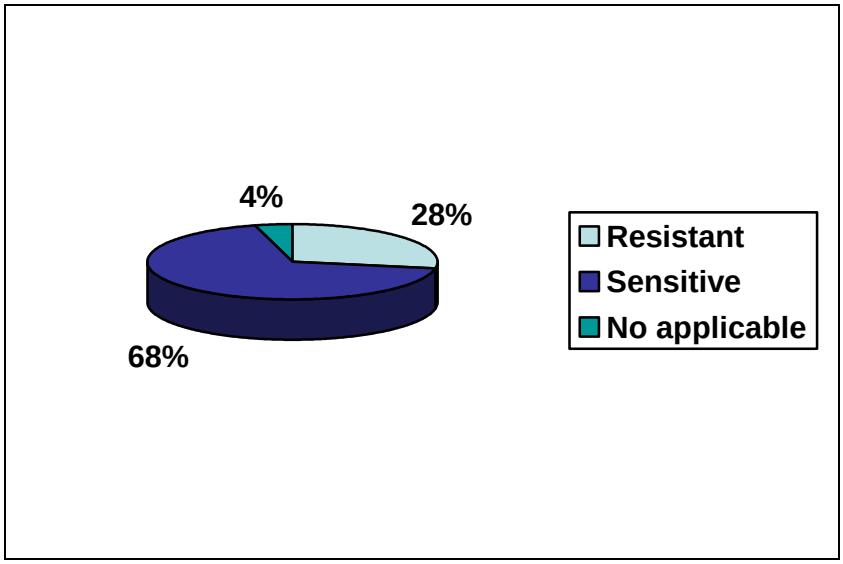


Fig 31: Previous platinum-based chemotherapy response in relapsed ovarian cancer

159 patients received chemotherapy for second time based on the initial treatment, response to prior treatment, disease-free interval, surgical findings, surgical outcome and anticipated ability to tolerate side effects. Eighteen patients (9.7% of those) received intravenous paclitaxel/carboplatin therapy as second course of chemotherapy; 22 (13.8%) were treated with other platinum-based systemic combination therapy; 7 (4.4%) with carboplatin or cisplatin mono; 4 (2.5%) were treated with paclitaxel mono and 2 (1.3%) with treosulfan mono; 46 (28.9%) with topotecan; 10 (6.3%) with caelyx and 50 (31.4%) were treated with another chemotherapy. The median of number of cycles in second course of chemotherapy again was 6.0 with a range of 1-40 cycles.

At the time of last follow-up, 91 patients (51.4%) were alive, 84 (47.5%) had died and 2 (1.1%) were lost to follow-up. The median follow-up time was 10.8 months (range 0.0-65.0 months).

3.2.1.1 Descriptive analysis for suboptimally debulked recurrent ovarian cancer

In 98 patients with relapsed ovarian cancer, tumor-free reduction could not be achieved. A descriptive analysis of this cohort was carried out (table 30) in order to compare it to the main cohort of patients with relapsed ovarian cancer.

Table 30: Characteristics of suboptimally debulked patients with relapsed ovarian cancer

Characteristics of suboptimally debulked patients with relapsed ovarian cancer (N=98)	
Characteristics	**Results**
Age (yrs), median (range)	57.0 (26-79)
Tumor stage (FIGO)	
I	7 (7.1%)
II	4 (4.1%)
III	69 (70.4%)
IV	10 (10.2%)
Peritoneal cancer	5 (5.1%)
Grading	
I	4 (4.2%)
II	35 (36.8%)
III	56 (58.9%)
Histology	
Serous	89 (91.8%)
Mucinous	2 (2.1%)
Endometrioid	1 (1.0%)
Clear Cell	3 (3.1%)
Undifferentiated	2 (2.1%)
Ascites	
No ascites	27 (28.1%)
<500ml	37 (38.5%)
≥500ml	32 (33.3%)
Second malignancy	

None	83 (84.7%)
Breast Cancer	6 (6. %)
Endometrial Cancer	5 (5.1%)
Colon Cancer	1 (1.0%)
Cervical Cancer	1 (1.0%)
Others	2 (2.0%)
Location of relapsed disease	
Level 1	86 (89.6%)
Level 2	91 (94.8%)
Level 3	78 (81.2%)

Some differences between the main and the suboptimally debulked cohorts were statistically significant. Patients who underwent suboptimal recurrence surgery had at the time of recurrence diagnosis more ascites: a higher percentage of them had more than 500ml ($p<0.001$ tau b) compared to those patients in the main group. The spread was more pronounced ($p<0.001$ Fishers exact test for level 2 and 3) in the suboptimal group. FIGO, histology, age at first diagnosis, grading and second malignancy were not significantly different between both cohorts.

Overall, in 98 patients with relapsed ovarian cancer, complete debulking was not achieved. 43 of these operations (43.9%) were intended to be palliative and 55 (56.1%) to be curative. The median operation time was 260 minutes (range 30-719 minutes).

Some procedures (table 31) such as small bowel resections (performed in 46 patients, 46.9%) and large bowel resections (in 50 patients, 51.0%) were required significantly more often than in patients who underwent complete debulking ($p<0.001$ and $p=0.014$ Fisher exact test respectively). Pelvic and para aortic lymphadenectomies were significantly less frequent ($p=0.004$, $p=0.006$ Fishers exact test). Twelve (12.2%) pelvic lymphadenectomies and 14 (14.3%) para-aortic lymphadenectomies were performed. There were significant differences between colostomy percentages for the two groups ($p=0.022$ Fisher exact test).

Table 31: Surgical procedures performed in suboptimally debulked relapsed ovarian cancer (N=98)

Surgical procedures	No. patients	Percent
Bilateral salpingo-oophorectomy	3	3.1
Hysterectomy	3	3.1
Omentectomy	28	28.6
Pelvic lymphadenectomy	12	12.2
Para-aortic lymphadenectomy	14	14.3
Bowel resection(s)	64	65.3
Deperitonealisation	56	58.9
Appendectomy	11	11.2
Contact coagulation	66	69.5
Diaphragm resection	4	4.2
Splenectomy	3	3.2
Distal pancreatectomy	4	4.2
Partial liver resection	4	4.2
Cholecystectomy	2	2.1
Partial bladder resection	5	5.3
Partial stomach resection	6	6.3
Ileostomy	9	9.5
Colostomy	12	12.6

Thirty-eight patients (40.0%) had non-surgical and surgical postoperative complications. Among those patients with potentially serious morbidity, twelve died within 30 days of surgery (mortality rate 12.8%).

Of these suboptimally debulked patients, 52 (54.7%) had previously been platinum-sensitive and 39 (41.1%) were platinum-resistant while to 4 patients (4.2%) sensitivity was not applicable (figure 32). These are significantly different values compared to the main recurrent ovarian cancer group ($p<0.001$ chi^2 test).

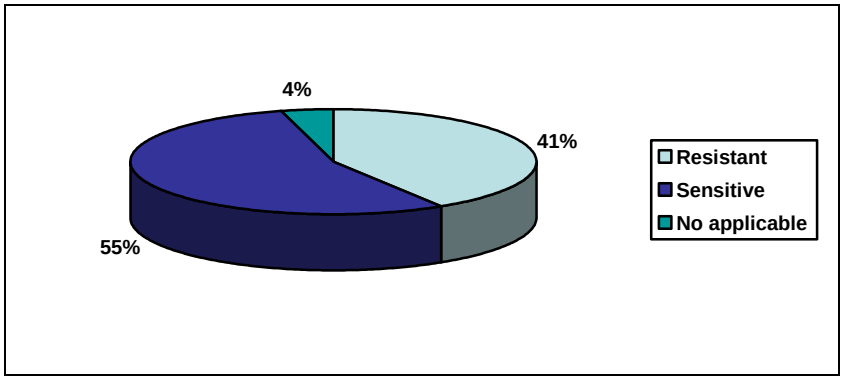


Fig. 32: Previous platinum-based chemotherapy response in suboptimally debulked ROC

After suboptimal debulking, 7 (8.0%) received intravenous paclitaxel/carboplatin therapy as second course of chemotherapy; 9 (10.3%) were treated with an other platinum-based systemic combination therapy; 4 (4.6%) were treated with carboplatin or cisplatin mono; 3 (3.4%) were treated with paclitaxel mono and 1 (1.1%) was treated with treosulfan mono;25 (28.7%) were treated with topotecan; 9 (10.3%) were treated with caelyx and 29 (33.3%) with another chemotherapy. The median number of cycles again was 6.0 (range 1-40 cycles).

At the time of last follow-up, 35 patients (35.7%) were alive and 61 (62.2%) had died. A higher percentage of patients with suboptimal debulking died compared to those in the main cohort.

3.2.2. Correlation analysis for relapsed ovarian cancer

In relapsed ovarian cancer surgery, tumor reduction (1/5, 2/5, 3/5, 4/5 and 5/5- Column **III**) significantly correlated with the presence of ascites, tumor localization (level 2 and 3), disease localization (mesentery, bowel, diaphragm, abdominal wall, stomach, pancreas, pleura and peritoneal carcinosis), operation time period, procedures such as omentectomy, lymphadenectomy, bowel resections, deperitonealisation, contact coagulation and partial stomach resection, platinum-based chemotherapy sensitivity and tumor residual.

Tumor residual (macroscopic tumor free, ≤2cm and >2cm- Column **II**) significantly correlated with the presence of ascites, tumor localization (besides ovary and uterus localization, omentum, spleen and pleura), operation time period, procedures as omectectomy, lymphadenectomy, bowel resections, deperitonealisation, contact

coagulation, appendectomy, partial bladder resection and colostomy, previous platinum-based chemotherapy sensitivity and tumor reduction.

The same variables significantly correlated with tumor residual (macroscopic tumor free, <0.5cm, ≤1cm, ≤2cm. and >2cm.-Column **I**) besides tumor localization in level I and liver and colostomy. There was no correlation with age at first diagnosis, FIGO, grading, histology, second malignancy, disease localization in ovary and uterus, omentum and spleen, many abdominal procedures (bilateral salpingo-oophorectomy, hysterectomy, diaphragm resection, splenectomy, distal pancreatectomy, partial liver resection and cholecystectomy) and postoperative morbidity and mortality (Table 32).

Table 32: Correlating variables with tumor residual and tumor reduction in relapsed ovarian cancer
Column I- Relating to tumor residual (tumor-free, <0.5cm, ≤1cm, ≤2cm,>2cm.)
Column II- Relating to tumor residual (tumor-free, ≤2cm, >2cm.)
Column III- Relating to tumor reduction (1/5, 2/5, 3/5, 4/5, 5/5, no tumor reduction).

Variables associated with tumor residual and tumor reduction in relapsed ovarian cancer

Variables	**I.*p*.value**	**II.*p*.value**	**III.*p*.value**
Age (yrs)[a]	N.S.	N.S.	N.S.
FIGO[b]	N.S.	N.S.	N.S.
Grading	N.S.	N.S.	N.S.
Histology[c]	N.S.	N.S.	N.S.
Ascites	p<0.001	p<0.001	p<0.001
Second malignancy	N.S.	N.S.	N.S.
Tumor localization			
Level I	N.S.	p<0.05 *0.625*	N.S.
Level II	p<0.001	p<0.001	p<0.001
Level III	p<0.001	p<0.001	p<0.001
Ovary and Uterus	N.S.	N.S.	N.S.
Pelvic wall	0.014 *0.460*	p<0.027 *0.680*	N.S.
Mesentery	p<0.001	p<0.001	p<0.001
Omentum	N.S.	N.S.	N.S.

Bladder/ureter	0.011 *0.023*	p<0.004 *0.030*	N.S. *0.014*
Spleen	N.S.	N.S.	N.S.
Large bowel	p<0.001	p<0.001	p<0.001
Small bowel	p<0.001	p<0.001	p<0.001
Diaphragm	0.018 *0.341*	0.009 *0.280*	0.027 *0.246*
Abdominal wall	p<0.001	p<0.001	p<0.001
Stomach	p<0.004 *<0.001*	p<0.001	p<0.033 *0.002*
Liver	N.S. *0.025*	0.012 *0.020*	N.S. *0.040*
Pancreas	p<0.001	p<0.001	p<0.001
Pleura	N.S.	N.S.	p<0.001 *0.314*
Peritoneal Carcinomatosis	p<0.001	p<0.001	p<0.001
Surgical procedures			
Bilateral salpingo-oophorectomy	N.S.	N.S.	N.S.
Hysterectomy	N.S.	N.S.	N.S.
Omentectomy	0.024 *0.010*	0.012 *0.009*	0.045 *0.004*
Pelvic Lymphadenectomy	0.006 *<0.001*	0.002 *<0.001*	0.007 *<0.001*
Para-aortic Lymphadenectomy	0.015 *0.013*	0.014 *0.005*	0.048 *0.002*
Large bowel resection(s)	p<0.001 *0.512*	p<0.001 *0.568*	p<0.001 *0.730*
Small bowel resection(s)	p<0.001 *0.019*	p<0.001 *0.029*	p<0.001 *0.086*
Deperitonealisation	0.002 *0.441*	p<0.001 *0.445*	p<0.001 *0.418*
Contact coagulation	0.003 *0.579*	p<0.001 *0.706*	p<0.001 *0.432*
Appendectomy	0.007	0.030	N.S.

	0.076	*<0.050*	*0.063*
Diaphragm resection	N.S.	N.S.	N.S.
Splenectomy	N.S.	N.S.	N.S.
Distal pancreatectomy	N.S.	N.S.	N.S.
Partial liver resection	N.S.	N.S.	N.S.
Cholecystectomy	N.S.	N.S.	N.S.
Bladder partial resection	0.006	0.007	N.S.
	0.106	*0.083*	*0.072*
Partial stomach resection	N.S.	N.S.	p<0.001
			0.220
Colostomy	N.S.	0.049	N.S.
	0.019	*0.017*	*0.016*
Operation time[d]	p<0.004	p<0.001	0.001
	0.669	*0.569*	*0.459*
Postoperative complications	N.S.	N.S.	N.S.
Postoperative mortality	N.S.	N.S.	N.S.
	0.063	*0.037*	*0.032*
Chemotherapy			
Platinum Sensitivity[e]	0.004	p<0.0001	0.01
Tumor residual (0,≤0.5,≤1,≤2,>2)			p<0.001
Tumor residual (0cm, ≤2cm.>2cm.)			p<0.001
Tumor reduction (1/5,2/5,3/5,4/5,5/5)	p<0.001	p<0.001	

NS: not significant, p>0.005

Analysis by Chi square test by Pearson.

Tau b of Kendall in cursive.

[a] Age: at first diagnosis ≤ 60 vs. > 60 years.

[b] FIGO: early stadium (I-II) vs. advanced stadium (III-IV).

[c] Histology: WHO groups.

[d] Operation time interval: 0-2hr., 2-5hr., 5-8hr., 8-12hr.

[e] Platinum sensitivity: response to platinum-based chemotherapy with a disease free interval ≥ 6 months.

Figure 33 shows the correlation between tumor reduction (no tumor reduction, 1/5, 2/5, 3/5, 4/5 and 5/5) and tumor residual (tumor-free, <0.5cm, ≤1cm, ≤2cm,>2cm.)

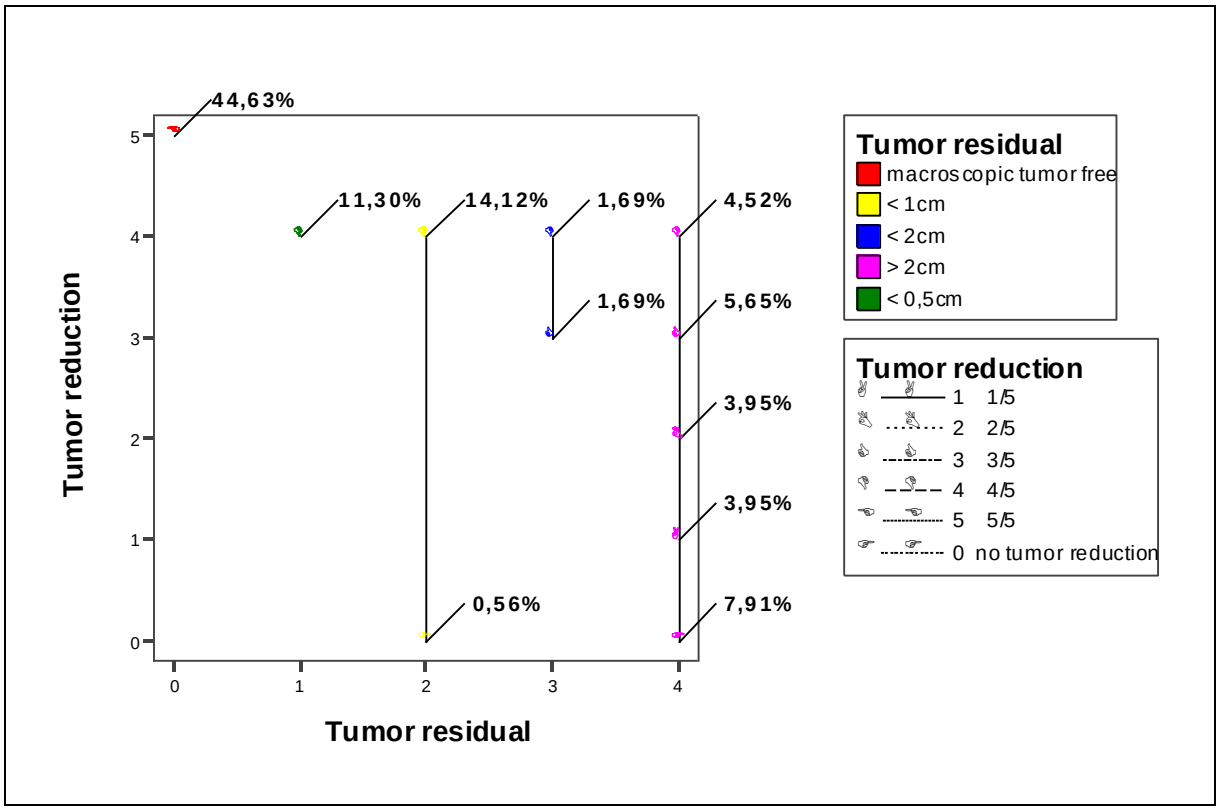


Fig.33: Correlation graphic for tumor reduction and tumor residual in ROC.

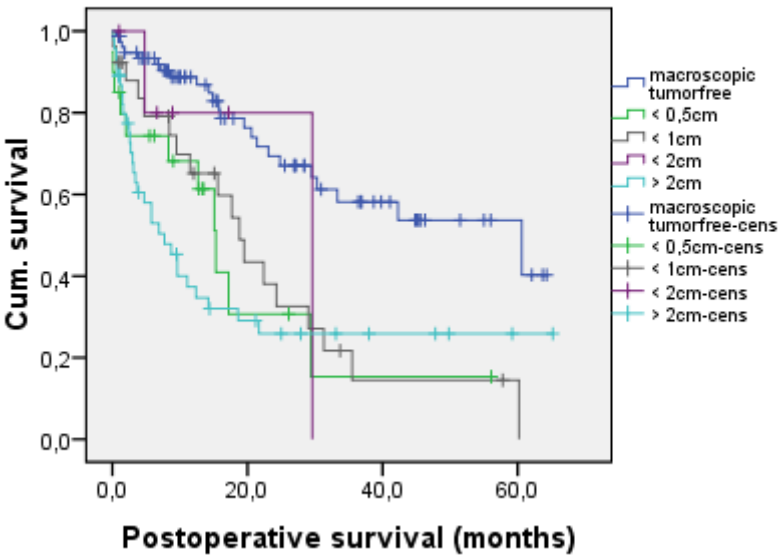
3.2.3. Survival analysis

The role of tumor residual and tumor reduction for survival (overall and progression-free) was further evaluated by univariate analysis. The analysis was carried out for recurrent ovarian cancer as well as for a suboptimal debulked situation.

3.2.3.1 Overall and disease-free survival in relapsed ovarian cancer

The median disease-free interval was 8.4 months (range 0.0-55 months). The median overall survival was 22.4 months (95%CI 14.7-30.62).

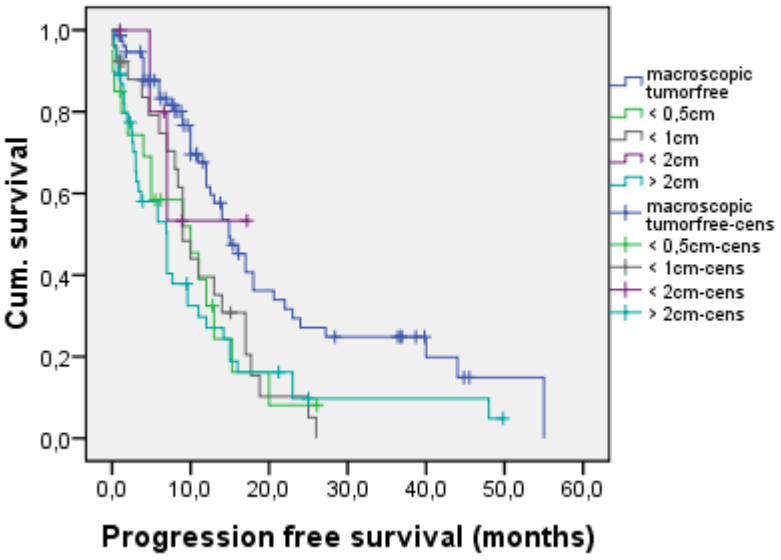
The variables tumor residual in different splits and tumor reduction (also in different splits) were found to be highly significant for overall and progression survival in first relapsed ovarian cancer (figures 34 to 43 and tables 33 to 42).



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	60.6	21.3-99.86
<0.5cm.	15.3	11.7-18.8
≤1cm.	18.8	13.5-24.0
≤2cm.	29.6	-
>2cm.	7.7	3.5-11.8

***p*<0.001**

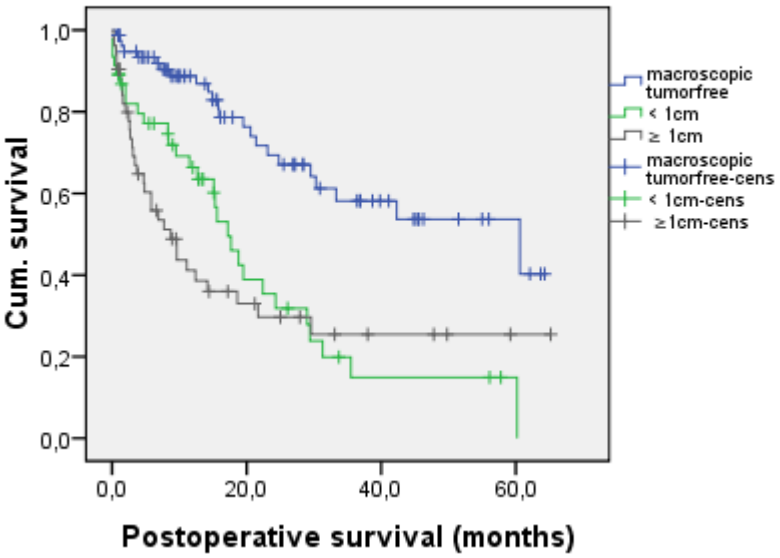
Fig. 34 and table 33: Postoperative survival for tumor residual (tumor free, <0.5cm, ≤1cm, ≤2cm, >2cm) in relapsed ovarian cancer.



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	14.9	11.7-18.0
<0.5cm.	10	2.7-17.2
≤1cm.	9	7.1-10.8
≤2cm.	-	-
>2cm.	7	4.1-9.8

***p*<0.001**

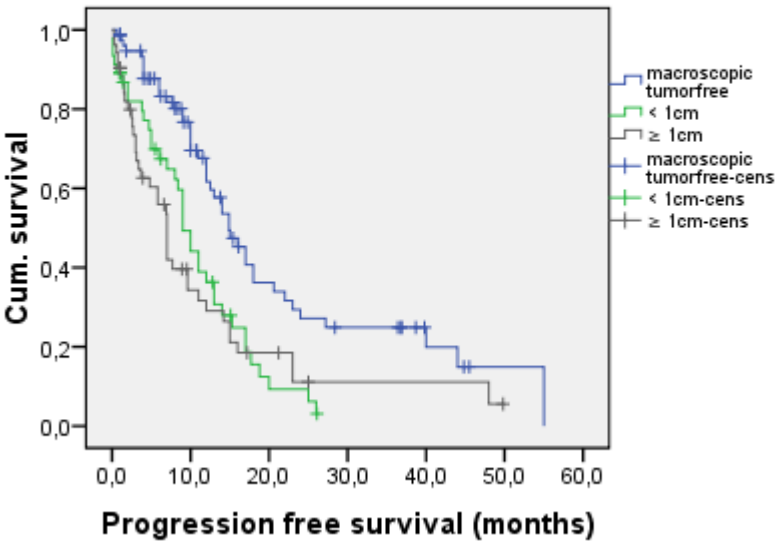
Fig. 35 table 34: Progression-free survival for tumor residual (tumor-free, <0.5cm. ≤1cm, ≤2cm,>2cm) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumour		
Residual		
Macrosc.free	60.6	21.3-99.8
<1cm.	17.2	13.0-21.3
≥1 cm.	8.7	4.1-13.2

***p*<0.001**

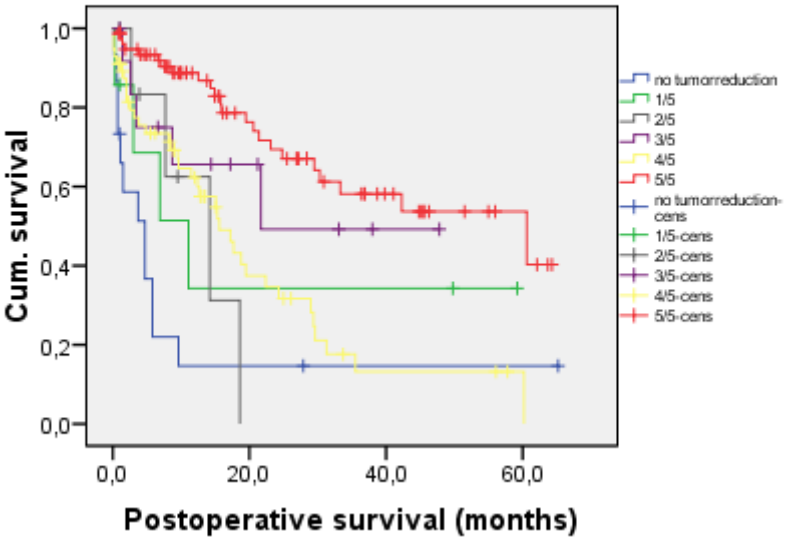
Fig. 36 and table 35: Postoperative survival for tumor residual (tumor free, <1cm, ≥1 cm) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumour		
Residual		
Macrosc.free	14.9	11.7-18.0
<1cm.	9	7.4-10.5
≥1cm.	7	5.7-8.2

***p*<0.001**

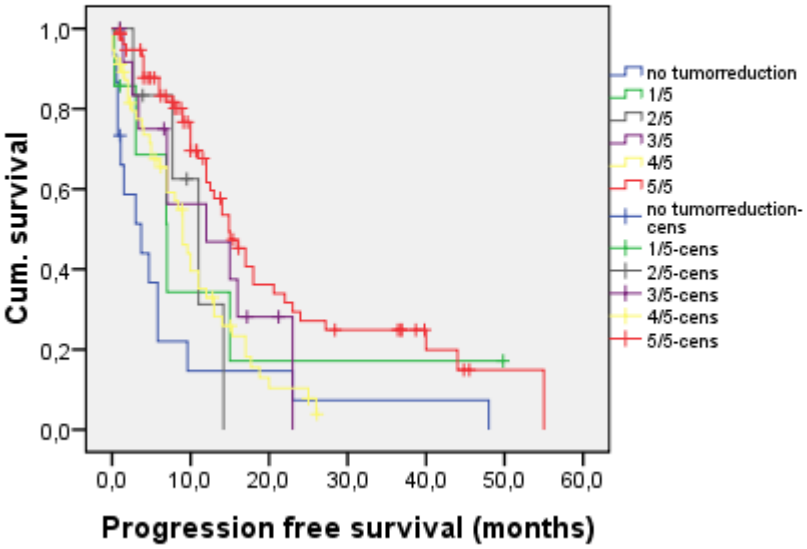
Fig. 37 and table 36: Progression-free survival for tumor residual (tumor free, <1cm, ≥1cm) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	4.7	1.0-8.3
1/5	11.1	2.0-20.1
2/5	14.2	4.1-24.2
3/5	21.7	-
4/5	15.6	10.3-20.8
5/5	60.6	21.3-99.8

***p*<0.001**

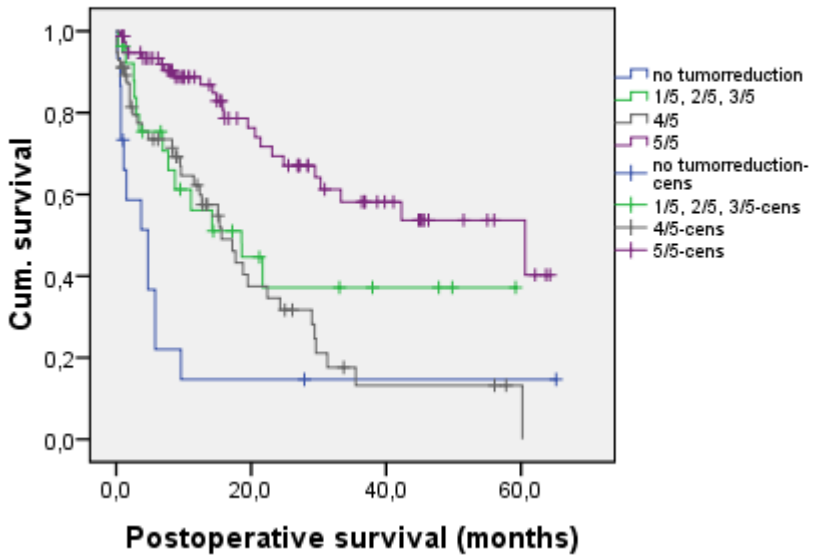
Fig. 38 and table 37: Postoperative survival for tumor reduction (no tumor reduction, 1/5, 2/5, 3/5, 4/5 and 5/5) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	3.7	0-7.6
1/5	7	2.5-11.4
2/5	11	5.9-16
3/5	12	0-24.5
4/5	9	7.2-10.7
5/5	14.9	11.7-18

***p*<0.001**

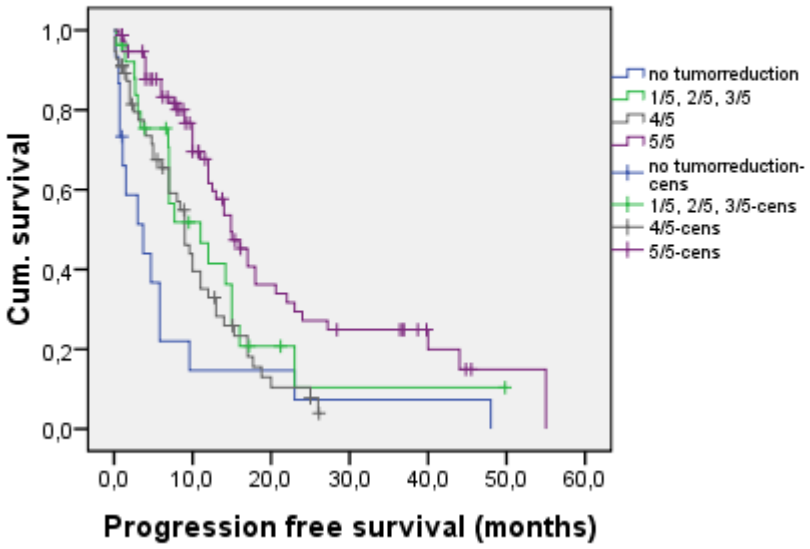
Fig. 39 and table 38: Progression-free survival for tumor reduction (no tumor reduction, 1/5, 2/5, 3/5, 4/5, and 5/5) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	4.7	1.0-8.3
1/5,2/5,3/5	18.6	4.3-32.8
4/5	15.6	10.3-20.8
5/5	60.6	21.3-99.8

***p*<0.001**

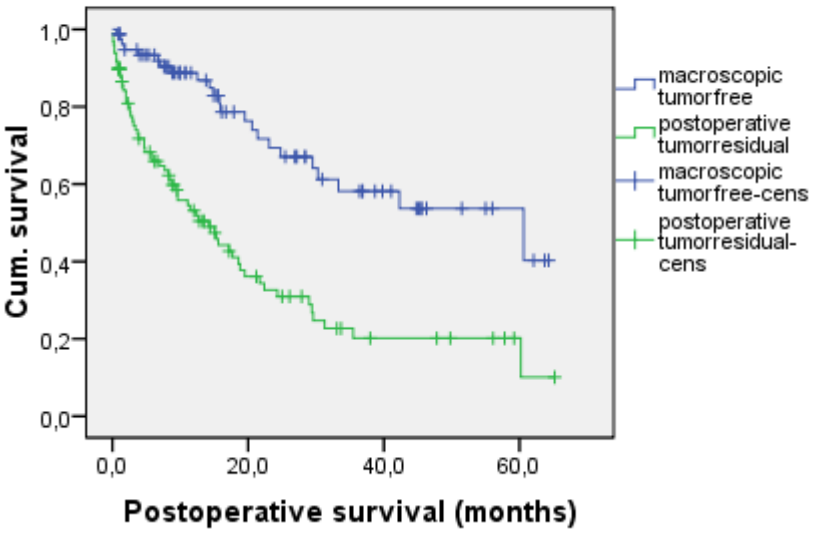
Fig. 40 and table 39: Postoperative survival tumor reduction (1/5, 2/5, 3/5 vs. 4/5 vs. 5/5 vs. no tumor reduction) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumor reduction		
No reduction	3.7	0.0-7.6
1/5,2/5,3/5	11	4.0-17.9
4/5	9	7.2-10.7
5/5	14.9	11.7-18.0

***p*<0.001**

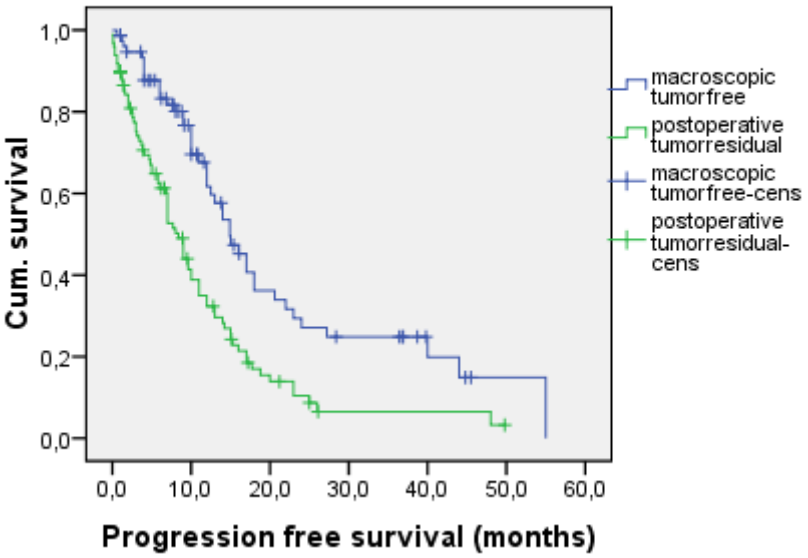
Fig. 41 and table 40: Progression-free survival for tumor reduction (1/5, 2/5, 3/5 vs. 4/5 vs. 5/5 vs. no tumor reduction) in relapsed ovarian cancer



Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	60.6	21.3-99.8
Tumor residual	14.2	8.5-19.8

***p*<0.001**

Fig. 42 and table 41: Postoperative survival tumor residual (yes vs. no) in relapsed ovarian cancer

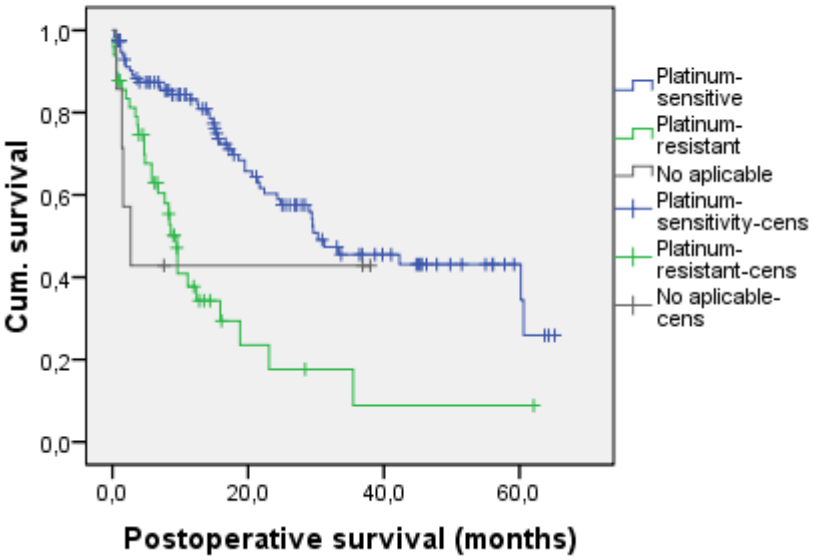


Parameter	Median	95%CI
Tumor Residual		
Macrosc.free	14.9	11.7-18.6
Tumor residual	8.4	7.0-9.7

***p*<0.001**

Fig. 43 and table 42: Progression-free survival for tumor residual (yes vs. no) in relapsed ovarian cancer

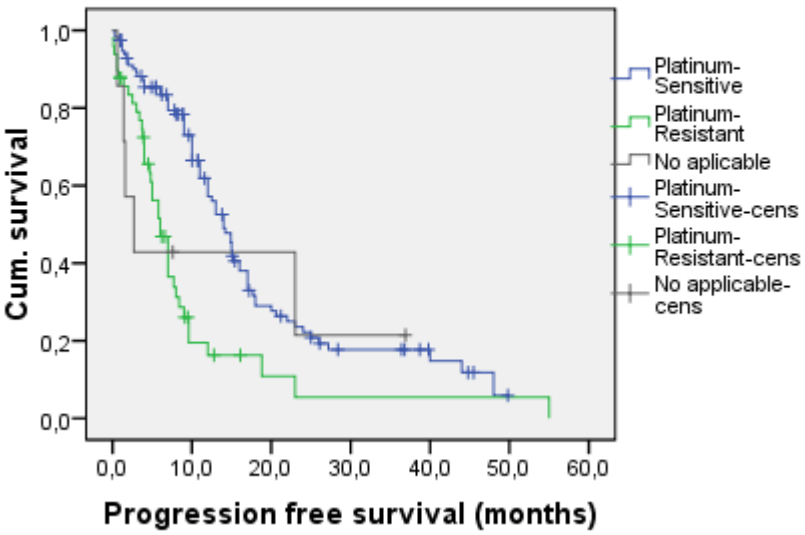
Figures 44 and 45 and tables 43 and 44 show a statistically significant effect of sensitivity to platinum-based chemotherapy on postoperative and progression-free survival in relapsed ovarian cancer.



Parameter	Median	95%CI
Platinum sensitivity		
Platinum sensitive	30.3	18.4-42.1
Platinum resistant	9.5	8.1-10.8
No applicable	2.7	0.0-5.5

***p*<0.001**

Fig. 44 and table 43: Postoperative survival with platinum-sensitivity in relapsed ovarian cancer.



Parameter	Median	95%CI
Platinum sensitivity		
Platinum sensitive	14	12.2-15.7
Platinum resistant	6	4.5-7.4
No applicable	2.7	0.0-5.5

***p*<0.001**

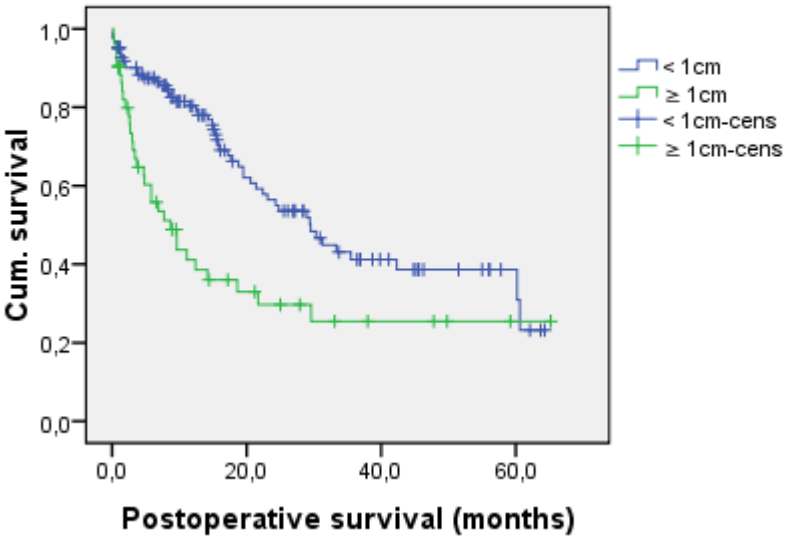
Fig. 45 and table 44: Progression-free survival with platinum-sensitivity in relapsed ovarian cancer.

When patients who were platinum sensitive were analyzed separately from those who were platinum resistant, the effect of tumor reduction (no tumor reduction, 1/5, 2/5, 3/5, 4/5, 5/5) and tumor residual (tumor free, <1cm, ≥1cm) on overall and progression-free survival in both groups remained statistically significant.

Other variables that in univariate analysis were found to have a significant effect on postoperative survival in relapsed ovarian cancer were the presence of ascites, some tumor locations (infestation in level 2, mesentery, small bowel, abdominal wall and stomach), colostomy procedure and postoperative complications. Progression-free survival was significantly affected by the presence of ascites, location of the tumor mass (level 2, small bowel abdominal wall and stomach) and procedure colostomy.

3.2.3.2. Postoperative and progression-free survival in suboptimally debulked relapsed ovarian cancer

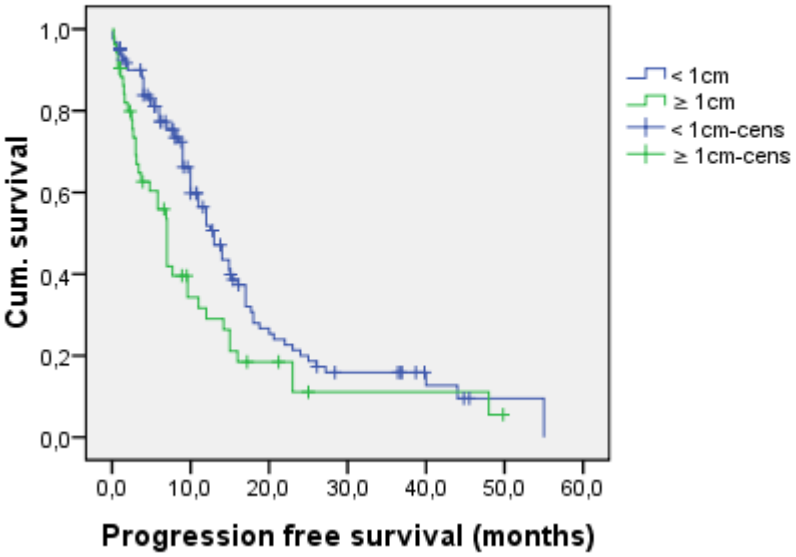
In this analysis we did not include any patient who were macroscopic free disease after surgery(5/5 tumor reduction). The goal was to see if relative tumor reduction had a significant effect on postoperative and progression-free survival in patients who underwent surgery at first relapsed ovarian cancer. We performed the same analysis as with the primary suboptimal situation but no significant effect was found with the exception of the effect of tumor residual (<1cm vs. ≥1cm) on progression-free and postoperative survival (see figures 46 and 47 and tables 43 and 44).



Parameter	Median	95%CI
Tumour Residual		
<1cm.	29.5	21.6-37.3
≥1 cm.	8.7	4.1-13.2

***p*<0.001**

Fig. 46 table 43: Postoperative survival for suboptimal tumor residual (<1cm, ≥1cm) in ROC



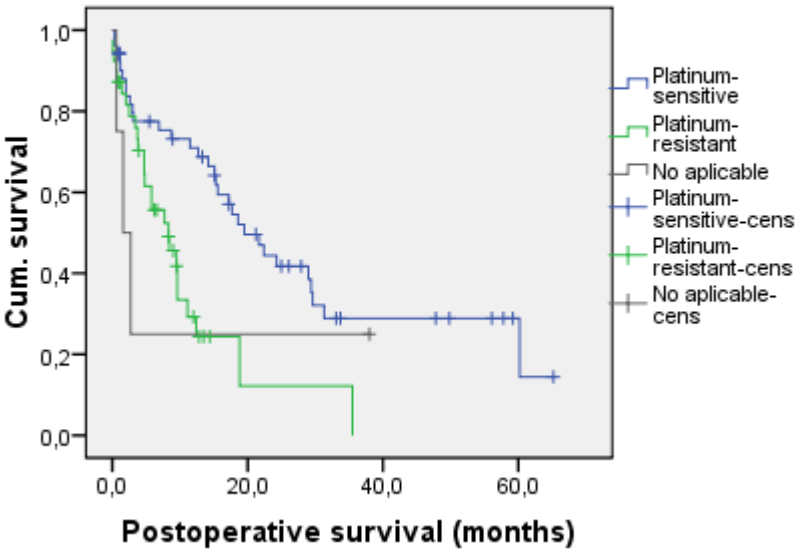
Parameter	Median	95%CI
Tumour Residual		
<1cm.	13.0	10.6-15.3
≥1 cm.	7	5.7-8.2

***p*=0.009**

Fig. 47 and table 44: Progression-free survival for suboptimal tumor residual (<1cm, ≥1cm) in ROC.

Figures 48 and 49 and tables 45 and 46 show the effect of platinum-based chemotherapy sensitivity on postoperative and progression-free survival when a

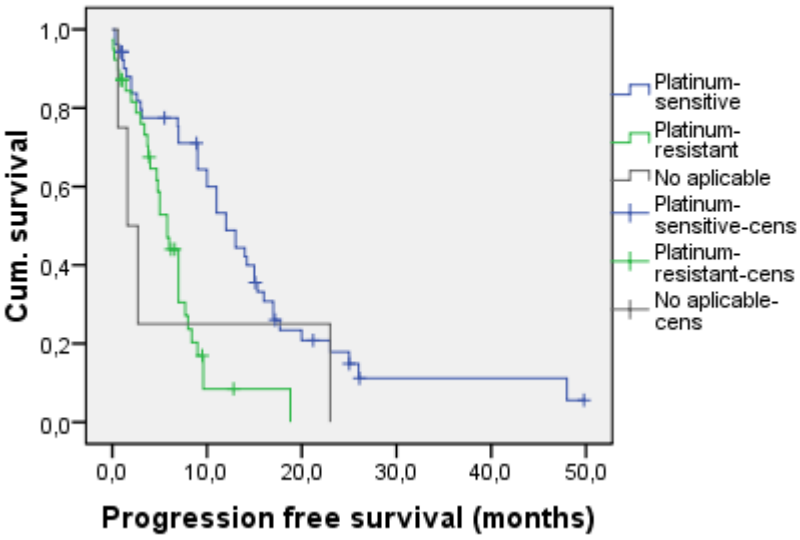
macroscopic tumor-free state could not be achieve in first relapsed ovarian cancer surgery.



Parameter	Median	95%CI
Platinum sensitivity		
Platinum sensitive	19.5	13.4-25.5
Platinum resistant	8.3	3.8-12.7
No applicable	1.6	0.0-3.6

***p*=0.005**

Fig. 48 and table 45: Postoperative survival for platinum sensitivity in suboptimally debulked ROC.



Parameter	Median	95%CI
Platinum sensitivity		
Platinum sensitive	12	9.2-14.7
Platinum resistant	5.8	4.4-7.1
No applicable	1.6	0.0-3.6

***p*<0.001**

Fig. 49 and table 46: Progression-free survival for platinum sensitivity in suboptimally debulked ROC.

3.2.4. Multivariate analysis in relapsed ovarian cancer

Variables that had an effect on survival in univariate analysis were also included in the multivariate model. The Cox-Regression model was employed stepwise to evaluate the prognostic significance and independence of these variables for postoperative and progression-free survival in relapsed ovarian cancer.

Variables used in relapsed ovarian cancer analysis in order of appearance:

Variable	Category of reference
Age (Age at first diagnosis 60)	>60
Bowel metastasis (small or large)	No
Peritoneum carcinomatosis	No
Level 1	No
Level 2	No
Level 3	No
Ascites	No ascites
Grade	III
FIGO Stage	I-II
Histology	serous
Tumor reduction	5/5
Tumor residual	>1 cm
Platinum sensitivity	Platinum sensitive

3.2.4.1. Postoperative survival

Table 47: Multivariate analysis for postoperative survival in ROC.

	HR	**p**
age >60	1.438	.224
Bowel mtx	1.329	.433
Peritoneum carcinomatosis	1.187	.714
Level 1	.296	**.006**
Level 2	1.352	.521
Level 3	.313	**.001**
Ascites		**.000**
<500ml	2.828	**.003**
≥500ml	4.755	**.000**
FIGO III-IV	.740	.461

Grade		.130
grading I	.398	.222
grading II	.608	.082
Histology	1.356	.500
Tumor reduction		**.001**
no tumor reduction	4.784	**.002**
1/5, 2/5, 3/5	1.772	.244
4/5	6.770	**.000**
Tumor residual		**.038**
<1cm	.389	**.038**
Sensitivity		**.001**
Platinum resistant	2.754	**.001**
no applicable	4.895	**.021**

Variables for tumor location in levels 1 and 3, ascites, platinum-based chemotherapy sensitivity, tumor reduction and tumor residual were independent predictors for the overall survival in relapsed ovarian cancer. Patients with ≥500ml ascites had an almost fivefold risk (HR=4.7) and those with <500 ml ascites an almost threefold risk (HR=2.8) of dying compared to patients with no ascites. A macroscopically tumor-free state after secondary cytoreduction significantly correlated with overall survival (p<0.001). Patients with a tumor residual <1cm had a significantly lower risk of dying compared to patients that had a residual of ≥ 1cm (HR 0, 3 p<0,005). Platinum-resistant patients and those with no appreciable response had a significantly higher morbidity ratio when compared to platinum-sensitive patients. The results of these variables were all independent from each other and from other variables included in the analysis.

3.2.4.2. Progression-free survival

Table 48: Multivariate analysis for progression-free survival in ROC.

	HR	**p**
Age >60	1.866	.018
Bowel mtx	.819	.525
Peritoneum carcinomatosis	1.122	.779
Level 1	.698	.357
Level 2	1.581	.221
Level 3	.641	.104

Ascites		**.001**
<500ml	2.565	**.001**
≥500ml	2.657	**.002**
FIGO III-IV	1.251	.551
Grade		.120
grading I	.373	.080
grading II	.717	.170
Histology	1.021	.958
Tumor reduction		**.028**
no tumor reduction	1.795	.156
1/5, 2/5, 3/5	.730	.438
4/5	2.812	**.026**
Tumor residual		.205
< 1cm	.583	.205
Response		**.000**
platin resistant	2.690	**.000**
no applicable	3.444	**.049**

Variables such as age, ascites and platinum-based chemotherapy response significantly correlated with progression-free survival in relapsed ovarian cancer. The hazard ratio of patients over 60 was almost twice as high as that of patients under 60. Patients with less than 500ml or ≥500ml ascites had a twofold risk of having a recurrence compared to patients without ascites. A macroscopic tumor-free state significantly correlated with progression-free survival: a 4/5 tumor reduction showed a HR of 2.8 ($p<0.026$). Platinum-resistant patients (HR 2.6) and those with no applicable response (HR 3.4) had a significantly higher morbidity ratio than platinum-sensitive patients. The results of these variables were all independent from other variables that were included in the analysis.

3.2.5. Predictive factors in relapsed ovarian cancer for complete tumor reduction

Predictive factors for a complete tumor reduction in relapsed ovarian cancer were again identified through logistic regression following the Cox-Regression Model. Variables were examined in four blocks (step-by-step model)

Block one: patient characteristics

Block two: block one + tumor preoperative characteristics; age, ascites, small bowel and big bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3

Block three: block two + tumor postoperative characteristics; age, ascites, small bowel and large bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3, FIGO, grade and histology

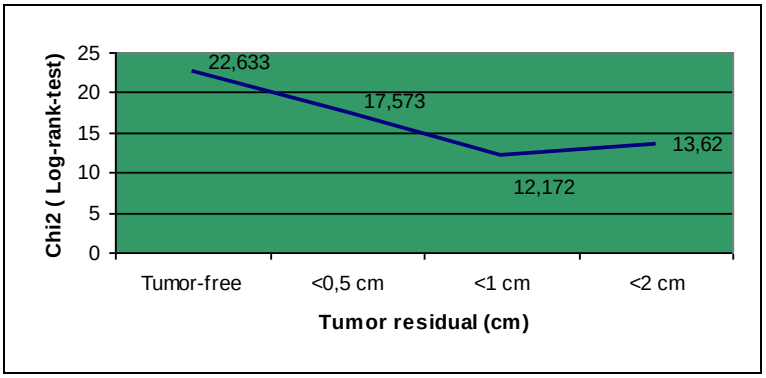
Block four: block three + LDN and platinum sensivity; age, ascites, small bowel and big bowel metastasis, peritoneal carcinomatosis, tumor localization in levels 2 and 3, FIGO, grade, histology, platinum-based chemotherapy response/sensitivity and systematic lymphadenectomy.

	Regression coef.B	Standard error	Wald	df	Sig.	Exp(B)	95% IC for EXP(B)	
							Lower	Upper
Age >60	.203	.518	.153	1	.695	1.225	.443	3.384
Ascites			5.127	2	.077			
<500ml	-1.171	.536	4.769	1	**.029**	.310	.108	.887
>500ml	-.959	.713	1.811	1	.178	.383	.095	1.549
S. bowel	-1.480	.583	6.443	1	**.011**	.228	.073	.714
L.bowel	.511	.639	.639	1	.424	1.667	.476	5.835
Peritoneal	-.343	.831	.170	1	.680	.710	.139	3.619
Level 1	-.415	.774	.288	1	.592	.660	.145	3.010
Level 2	-1.085	.786	1.905	1	.167	.338	.072	1.577
Level 3	-1.087	.550	3.898	1	**.048**	.337	.115	.992
Figo III-IV	.293	.719	.167	1	.683	1.341	.328	5.486
Grading			5.008	2	.082			
grading	-1.452	1.088	1.781	1	.182	.234	.028	1.975
Histology	1.773	.797	4.950	1	**.026**	5.891	1.235	28.101
Sensitivity			8.510	2	**.014**			
Platinresistant	-1.672	.582	8.266	1	**.004**	.188	.060	.587
no applicable	-1.036	1.353	.586	1	.444	.355	.025	5.032
LDN	.822	.540	2.314	1	.128	2.274	.789	6.556
Constant	3.343	1.629	4.212	1	.040	28.296		

Variables such as ascites less than 500ml (OR=0.3; 95% CI 0.1-0.8 p<0.05), small bowel metastasis (OR=0.22; 95% CI 0.07-0.71 p<0.05), tumor spread in upper abdomen (OR 0.33 CI 95% 0.1-0.9 p <0.005), serous tumor histology (OR 5.8 95% CI 1.2-28.1) and platinum-sensitivity (platinum-resistant OR 0.1 95% CI 0.06-0.5 p< 0.01) were identified as significant predictive factors. Age was not significant.

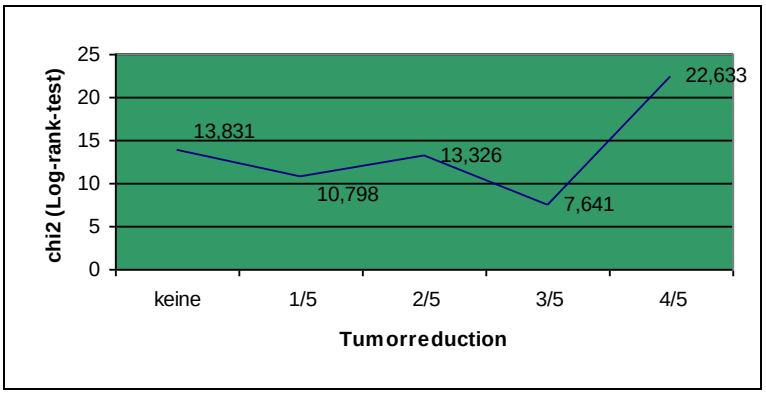
3.2.6 Threshold value analysis for ROC

Threshold analysis in recurrent ovarian cancer did not result in a clear value where the Kaplan-Meier survival graph diverges. A longer survival was mostly related to a bigger tumor reduction and less tumor residual (figures 50 and 51).



		Chi² Log Rank Test
Tumor-free	Tumor residual	22,633
< 0,5 cm	≥ 0,5	17,573
< 1 cm	≥ 1 cm	12,172
< 2 cm	≥ 2 cm	13,620

Fig. 50 and table 49: Threshold analysis of tumor residual in relapsed ovarian cancer



		Chi² Log Rank Test
No tumor reduction	1/5 till 5/5	13,831
≤ 1/5	≥ 1/5	10,798
≤ 2/5	≥ 2/5	13,326
≤ 3/5	≥ 3/5	7,641
≤ 4/5	5/5	22,633

Fig. 51 and table 50: Threshold analysis of tumor reduction in relapsed ovarian cancer.

4 Discussion

4.1. Impact of cytoreduction on postoperative and progression-free survival in patients with ovarian cancer

The role of cytoreductive surgery will be discussed for different categories of disease.

4.1.1. Primary cytoreductive surgery

The survival data calculated in this study support the hypothesis that the removal of all macroscopic tumor in primary surgery is one of the most relevant prognostic survival factors for patients with primary ovarian cancer (see table 22).

According to our results, macroscopically tumor-free surgery clearly improves patients' postoperative and progression-free survival. In our study, 174 women (64.7%) underwent macroscopic disease-free tumor resection at primary surgery. The median survival rate with regard to progression-free survival was improved by 20 months when compared to those patients that still had some tumor residual (*p<0 .001*). At the time of analysis, the median for postoperative survival could not be determined in the group of patients that were macroscopically disease free. In patients with a residual tumor, an improvement in survival was achieved by decreasing tumor residual (*p<0 .001)*.

The importance of cytoreduction or tumor debulking was first promoted by Meigs in 1934. In his work, Meigs emphasised the benefit of primary cytoreductive surgery for advanced ovarian carcinoma in order to improve postoperative radiation therapy (Bristow, Tomacruz et al. 2002). The decisive work by Griffiths in 1975 confirmed an inverse relationship between residual tumor diameter and patient survival. In his study of 102 patients with stages II and III epithelial ovarian carcinomas, Griffiths discovered that a residual tumor of more than 1.5 cm was a significant indicator for a negative prognosis. Since this landmark study, numerous other authors and two meta-analyses have confirmed the benefits of surgical cytoreduction for survival (Hoskins, Bundy et al. 1992; Hoskins 1993; Eisenkop, Friedman et al. 1998; Lichtenegger, Sehouli et al. 1998; Bristow, Tomacruz et al. 2002; Chi, Eisenhauer et al. 2006; du Bois and Harter 2006).

In the large meta-analysis of Bristow and colleagues, published in 2002, 53 studies analyzing this issue (published in medical literature between 1989 and 1998 involving

6,885 patients with ovarian carcinoma) were evaluated. Maximal cytoreduction was found to be the most significant predictor for survival. The authors evaluated the relative effect of percentages of maximal cytoreductive surgery on survival among cohorts of patients with advanced-stage ovarian cancer that were treated with platinum-based chemotherapy. There was a statistically significant positive correlation between the percentage of maximal cytoreduction and log median survival time. This correlation remained significant after controlling for all other variables ($p < 0.001$) as it did in our analysis. Every 10% increase in maximal cytoreduction (defined in Bristow analysis as ≤ 3cm maximal tumor diameter) was associated with a 5.5% increase in the median survival time. When the actuarial survival was calculated, cohorts with a maximal cytoreduction of ≤ 25% had a mean weighted median survival time of 22.7 months, whereas cohorts with a maximal cytoreduction of more than 75% had a mean weighted median survival time of 33.9 months. This is an increase of almost 50 percent (Bristow, Tomacruz et al. 2002).

Even though the magnitude of surgical cytoreduction in advanced ovarian cancer has become well recognized in OS as well as in PFS, the definition of “optimal” versus “suboptimal” primary cytoreduction remains controversial.

In the 1970s, the traditional definition of optimal residual disease was ≤2 cm (Bristow, Tomacruz et al. 2002). In the 1980s, GOG Protocol 47 described optimal residual disease as <3 cm (Omura, Blessing et al. 1986). This definition was subsequently revised by the GOG, and in Protocol 97 (from 1986) the definition was lowered to ≤1 cm (Omura, Brady et al. 1991). The definition of optimal cytoreduction has remained ≤1 cm in all subsequent GOG protocols.

However, our results suggest that the definition of optimal cytoreduction for advanced EOC should be changed from the current Gynecologic Oncology Group threshold of ≤1 cm residual disease to no gross residual disease at all. This is due to the improved survival of patients that were operated on to become macroscopically disease-free. These data are supported by recent studies such as the one published by du Bois et al in 2005 and Chi et al. in 2006. This last study analysed the median overall survival in relation to the 5 residual disease categories: no gross residual; gross ≤0.5 cm; 0.6–1.0 cm; 1–2 cm and >2 cm. A statistical comparison between the 5 residual disease categories revealed just 3 distinct groups with significantly different survival rates ($p < 0.01$). Those 3 groups were: no gross residual; gross ≤1 cm residual and >1 cm residual. Although the difference in survival did not reach statistical significance, within

the gross ≤1 cm residual group there was a trend toward longer survival in patients that were left with a smaller volume ≤0.5 cm residual when compared with those with a 0.6–1.0 cm residual (p = 0.06).The authors of the study concluded that if complete gross resection is not feasible, a maximal removal of the residual tumor should be the focus of cytoreductive efforts. Each incremental decrease in residual disease below 1 cm may be associated with an incremental improvement in overall survival (Chi, Eisenhauer et al. 2006).

When in our study we analyzed the group of patients with an incomplete tumor resection but tumor residual <1cm, the threshold analysis illustrated a point between 0.5 and 1cm of tumor residual where the Kaplan-Meier postoperative survival graph diverges. This may mean that within this narrow rank a good prognosis turns into a poor one. In a publication by Utler et al. from 2005, the threshold was found to be at a tumor residual diameter of 9mm. The median overall survival was 60 months for the group with a residual tumor of ≤9mm. Thus a tumor residual of ≤1cm (i.e. "optimal" cytoreduction) may not represent an optimal survival prognosis but the threshold between a good and a poor survival prognosis.

The predictive factors for a complete tumor reduction identified in our analysis were age, small bowel metastasis, tumor spread in upper abdomen and systematic lymphadenectomy. Patients aged over 60, with metastasis in the small bowel and tumor in the upper abdomen were less likely to be macroscopically tumor-free and therefore did not enjoy the same survival benefits from surgery.

It should be noted that the postoperative mortality rate in our report (3%) was in line with population-based studies on postoperative mortality after primary cytoreductive surgery for EOC. In these studies the rate was 3.7% on average (Cornelis et al. 2009).

4.1.2. Relapsed cytoreductive surgery

The role of primary cytoreduction in patients with epithelial ovarian cancer has been studied extensively, and its impact on survival has been clearly validated as can be seen in literature on the meta-analysis, published by Bristow et al. in 2002 (Bristow, Tomacruz et al. 2002).

To our knowledge, the role and potential benefits of secondary cytoreductive surgery are currently some of the most debated issues. Skepticism regarding secondary cytoreduction may arise because of the less favorable prognosis for recurrent ovarian

carcinoma, the technical difficulties, the development of chemotherapy, and heterogeneous data concerning this surgical approach. Although several authors reported a survival benefit for patients who underwent secondary cytoreduction, it remains uncertain which patients with recurrent ovarian cancer are suitable for further surgery.

It is difficult to standardize this second-line surgical approach because of the heterogeneity of the patients that were included in studies dealing with secondary cytoreduction.

The first study to describe the value of secondary cytoreduction for recurrent ovarian cancer was published by Berek and colleagues more than 20 years ago. These authors demonstrated that patients who underwent optimal debulking (defined as residual disease ≤1.5 cm) at the time of secondary cytoreduction had a median survival time of 20 months compared with 5 months for patients who had been debulked suboptimally. They also reported that the duration of therapy, symptoms, ascites, and the initial tumor mass before secondary resection were important prognostic factors for survival (Berek, Hacker et al. 1983). Later, Morris et al. studied 30 patients with recurrent ovarian cancer and using a cut-off size of 2 cm for optimal debulking found no survival benefit for secondary cytoreduction (Morris, Gershenson et al. 1989). In a follow-up study of 25 patients, Munkarah et al. again found no statistically significant benefit of secondary cytoreduction (Munkarah, Levenback et al. 2001).

Several new studies as well as our own analysis suggest that procedures which have been described for primary cytoreduction are also applicable to secondary surgery. A careful follow-up and early detection of recurrences may facilitate a complete cytoreduction with a surgical effort that is far less extensive than what might be required during primary cytoreductive surgery (Harter, Bois et al. 2006;Eisenkop, Friedman et al. 2000; Scarabelli, Gallo et al. 2001; Zang, Li et al. 2004; Lichtenegger, Sehouli et al. 1998).

In the present study, 44.6% of women who underwent second surgery were rendered visibly disease-free and had a median overall survival of 5 years from the time of surgery (60.0 months, 95% CI 21.3-99.8), 44 months more than patients left which some tumor rests and 56 months more than patients who did not undergo any tumor reduction (*p<0.001)*. There is an inverse correlation between the diameter of tumor residual and postoperative as well as progression-free survival (*p<0.001*).

As the significance of cytoreductive surgery in relapsed ovarian cancer is not yet clearly defined, the selection of patients remains arbitrary and depends on the center's preference rather than on established selection criteria. Until now, few publications have focused on selection criteria for cytoreductive surgery in recurrent ovarian cancer. In 1998, the 2nd International Ovarian Cancer Consensus Conference suggested the following criteria for optimal candidates to undergo secondary cytoreduction surgery: (1) disease-free interval > 12 months, (2) response to first-line therapy, (3) potential for complete resection based on preoperative evaluation, (4) good performance status, and (5) young age. However, these criteria were based on experts' opinions rather than on valid data (Berek, J. S., K. Bertelsen, et al. 1999).

The Descriptive Evaluation of Preoperative Selection Criteria for Operability in recurrent OVARian cancer trial (DESKTOP OVAR) was carried out to form a hypothesis for a set of criteria that can be used for the selection of patients who might benefit from surgery in relapsed ovarian cancer (Harter, Bois et al. 2006). The DESKTOP I trial was an exploratory study based on data from a retrospective analysis of hospital records. Twenty-five member institutions of the *Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Committee* (AGO OC) and AGO-OVAR boards collected data on their patients with cytoreductive surgery for relapsed invasive epithelial ovarian cancer performed between 2000 and 2003. 267 patients were included. The median follow-up time after cytoreductive surgery for recurrence was 19 months (95% CI 16.3-22.7). Complete resection was associated with a statistically significant longer survival when compared to surgery leaving any postoperative residuals (median 45.2 vs. 19.7 months; hazard ratio 3.71; 95% CI 2.27-6.05; $p < 0.001$). Variables associated with complete resection were: performance status [Eastern Cooperative Oncology Group (ECOG) 0 vs. > 0; $p < 0.001$], FIGO stage at initial diagnosis (FIGO I/II vs. III/IV, $p = 0.036$), residual tumor after primary surgery (none vs. present, $p < 0.001$) and absence of ascites > 500 ml ($p < 0.001$). The three factors which were independent from complete resection were combined to form a predictive score called "AGO score". A backward analysis was applied to the whole population. The score was believed to achieve positive results if a patient (a) had a good performance status (ECOG 0), (b) had no residual tumor after initial surgery (or , if unknown, had FIGO stage I/II disease initially), and (c) had a clinical diagnosis of less than 500 ml ascites. A combination of performance status, early initial FIGO stage or no residual tumor after first surgery, and the absence of ascites could predict a complete resection in 79% of patients. The predictive score

developed in the DESKTOP I study has been prospectively evaluated in the new trial DESKTOP II study (AGO-OVAR OP.2). The study cohort consisted of patients with platinum-sensitive recurrent ovarian cancer with a positive AGO-score (PE ECOG 0, no residual tumor after primary surgery and ascites <500ml), who underwent surgery with the aim of achieving maximal cytoreduction. The goal of the study was to determine in a prospective multicentric setting if the newly developed AGO-score had predictive validity.

At the IGCS biennial meeting, the scientists presented their results for the prospective validation of the AGO score system. In the trial AGO-DESKTOP 2, 412 patients with a first relapse of platinum-sensitive recurrent ovarian cancer were screened. Out of 193 patients who were eligible for surgery (AGO score positive), 127 patients underwent surgery and complete resection was achieved in 76% of patients. These findings suggest the usefulness of the AGO score (Harter and Sehouli et al. 2008). A randomized trial based on the AGO score system is already planned (DESKTOP III). Here the application of the AGO score serves as an inclusion criterion for eligible patients in whom a formal comparison of the role of secondary debulking of relapsed ovarian cancer could be performed.

The analysis included 177 women with recurrence of invasive epithelial ovarian or peritoneal cancer of any initial stage who had relapsed after a tumor-free interval after completion of first-line therapy and who underwent surgery in our center. In 79 of them (44.6%) complete debulking was achieved. This rate of complete resection is in line with the rate reported by Harter et al. (Harter, Bois et al. 2006).

Significant predictive factors identified in our study for complete tumor debulking in relapsed ovarian cancer included the absence of ascites <500ml (HR 0.3), no tumor in the upper abdomen (HR 0.3), no small bowel metastases (HR 0.2), serous tumor histology (HR 5.8) and sensitivity to platinum-based chemotherapy (platinum-resistant HR 0.1).

The median overall survival (OS) in our study was 22.4 months (95%CI 14.7-30.6), falling between the median OS described in the recent and large prospective trials ICON4/AGO-OVAR 2.2 (Gonzalez-Martin 2005) and the Gynecologic Cancer Intergroup (GCIG) study AGO-OVAR 2.5. These studies had a median survival of 18 and 29 months, respectively. In most of the studies regarding cytoreductive surgery for recurrent ovarian cancer, the median survival is not much higher than the ICON4/AGO-OVAR2.2 results (Scarabelli, Gallo et al. 2001;Zang, Li et al. 2004). On average,

however, series with more completely debulked patients exceed these results (Eisenkop, Friedman et al. 2000;Harter, Bois et al. 2006). The median postoperative survival of 60.6 months (95% CI 21.3-99.8) for patients that had no gross residual in our study is one of the longest reported for patients with recurrent ovarian cancer to date. In a new study published by Benedetti Panici et al., the median survival time was also 61 months for patients who achieved optimal residual disease. The definition of optimal here was ≤ 1cm residual tumor (Benedetti Panici, De Vivo et al. 2007). However, the lack of randomized trials makes it impossible to conclude whether a more favorable outcome in series with high rates of complete debulking could be attributed to biology (selection bias) or to surgical efforts.

In our multivariate analysis, complete tumor resection in recurrence surgery was one of the independent prognostic factors in overall survival and progression-free survival for relapsed ovarian cancer. Other independent variables associated with survival included the presence of ascites, sensitivity to platinum-based chemotherapy and age (the last variable being relevant only to progression-free survival). It is remarkable that HRs between ≤500ml ascites and >500ml ascites were alike.

Consequently, in the present analysis we were able to show that high complete tumor resection rates are possible in ROC surgery and are associated with a prolonged survival time. We agree with the fact that the aim of ROC surgery should be the complete tumor resection. Therefore, the selection criteria for patients remain the cornerstone of recurrent surgery. According to our study, patients with ascites, platinum resistance and/or a wide-spread tumor in relapsed situation would not entirely benefit from surgery and may be candidates for other therapies.

4.2. The impact of relative tumor reduction (or suboptimal debulking) on postoperative and progression-free survival in patients with ovarian cancer

4.2.1. Primary ovarian cancer surgery

Many previous studies tried to confirm the hypothesis that surgical cytoreduction independently correlates with extended survival. Their authors argue that the perceived benefit may represent a smaller initial tumor burden, indicating less advanced or less biologically aggressive disease (Eisenkop, Spirtos et al. 2003; Eisenkop and Spirtos

2001;Hoskins, Bundy et al. 1992). In 1992, Hoskins et al. completed in the Gynecologic Oncology Group Protocol 52, a randomized trial of cisplatin and cyclophosphamide with or without doxorubicin in "optimal" Stage III epithelial ovarian cancer to demonstrate a significant difference in the outcome of 349 patients. The aim was to determine the influence of cytoreductive surgery on survival. Since eligibility for the study was the presence of residual disease of 1 cm or less, the influence of cytoreductive surgery could be evaluated by comparing the results of patients with large-volume extrapelvic disease who were cytoreduced to small-volume disease with patients who had an initial disease of ≤ 1 cm. The volume of initial extrapelvic disease remained significant when gross disease was present in the omentum and in other extrapelvic sites. According to univariate analysis, however, patients with an extrapelvic disease of 1 cm or less had a better recurrence-free interval and survival rate than patients with large-volume disease who were cytoreduced to a disease of 1 cm or less (Hoskins, Bundy et al. 1992).

A study by Eisenkop et al. that included 213 patients with Stage IIIC epithelial ovarian cancer concluded that the need to remove a large number of peritoneal implants correlated with the biological aggressiveness and diminished survival but the figures were not statistically significant to preclude long-term survival or justify abbreviation of the operative effort (Eisenkop and Spirtos 2001). Few years later, in 2003, Eisenkop and colleagues carried out another study with 408 patients who had also been diagnosed with stage IIIC epithelial ovarian cancer. A ranking system was devised to prospectively quantify the extent of disease. Survival was analyzed on the basis of the rankings of anatomic regions, the sum of intraabdominal rankings, and the cytoreductive outcome. Survival was more strongly influenced by the completeness of cytoreduction than the volume of metastatic disease present before surgery (Eisenkop, Spirtos et al. 2003).

All the three studies mentioned above failed to prove the hypothesis that initial cytoreductive surgery would allow a patient with a large volume ovarian cancer to have the same chance of survival as a patient found to have small-volume disease.

Our working hypothesis addressed the following question: Does the initial tumor volume in terms of percentage of tumor debulking have an effect on survival rates?

In our study, we evaluated 95 patients with primary ovarian cancer who had been operated on without becoming tumor-free. Depending on the results of surgery, they were categorized into: no-debulking; 1/5 tumor removed; 2/5 tumor removed; 3/5 tumor removed and 4/5 tumor removed. With these 95 patients, a relationship between

survival and relative tumor reduction (1/5 vs.2/5 vs.3/5 vs.4/5 vs. no tumor reduction) could be shown in univariate analysis (*p=0.01)*. Furthermore, patients who underwent a 4/5 tumor reduction were found to have a survival benefit of 15 months (32.2 months, 95% CI 24.2-40.1) compared to patients who underwent a 1/5, 2/5 or 3/5 tumor reduction (15.5 months 95%CI 0.0-33.6) (*p* =0.002). A benefit of 5 months was also established in univariate analysis regarding progression-free survival (4/5 13.5 months, 95%CI 11.5-15.4 vs. 1/5, 2/5, 3/5 8 months, 95%CI 3.9-12.0, p<0.05). Multivariate analysis confirmed that the tumor reduction independently influenced survival, although relative tumor reductions showed very similar HR, and variable tumor residual was not found to be an independent factor when added after tumor reduction. However, tumor residual of less than 1 cm did lead to a better prognosis than tumor residual of ≥1 cm on overall survival in both univariate and multivariate analysis, although it did not reach significance in multivariate analysis (p=0.07). We should note that the group “no tumor reduction” should not be used as control group because as the patients were not randomized but unresectable.

Our results support the premise that operative efforts should not be abbreviated (Eisenkop, Spirtos et al. 2003) while better survival is reported with a higher percentage of tumor debulked even if it does not achieve complete tumor resection. More trials should be carried out in order to evaluate the role of initial tumor gross and relative tumor reduction.

4.2.2. Recurrent ovarian cancer surgery

This brings us back to the question as to what could be an appropriate surgical endpoint in secondary cytoreduction. In literature numerous reports have focused on the survival benefit of secondary cytoreductive surgery for patients with recurrent ovarian cancer. However, it remains controversial which patients would most benefit from this procedure and what size of residual disease would lead to the greatest advantage in terms of survival. Do patients only have a survival benefit from complete tumor resection, or do patients with so-called optimal debulking have a survival benefit as suggested for primary surgery?

To our knowledge, five more studies on recurrent ovarian cancer surgery including more than 100 patients have been published (Eisenkop, Friedman et al. 2000; Harter, Bois et

al. 2006; Scarabelli, Gallo et al. 2001; Zang, Li et al. 2004; Chi, McCaughty et al. 2006). They delivered controversial findings.

In the Harter et al. trial, only complete resection was associated with prolonged survival in recurrent ovarian cancer (Harter, Bois et al. 2006). This observation confirmed results from Eisenkop et al. from the year 2000, which equally showed a survival benefit for completely debulked patients only.

In our study, univariate analysis revealed a statistically significant effect of tumor residual <1cm vs. ≥1cm on postoperative and progression-free survival ($p<0.001$ and $p=0.009$, respectively). When this association was subjected to multivariate analysis, the relationship remained statistically significant as an independent prognostic factor for overall survival (HR 0.38 for <1cm against ≥1cm tumor residual $p=0.038$). Patients with a tumor residual of <1cm have a better survival value (independent from others factors) as reported by Zang et al. (2004), Scarabelli et al. (2001), Chi et al. (2006) and more recently by Benedetti Panici et al. in 2007. Therefore, an improvement to survival could also be achieved by decreasing tumor residuals to an “optimal” size of <1cm.

This analysis may bear interesting results as far as it may suggest that not only complete tumor resection but also “optimal” cytoreduction to tumor residuals of <1cm seem to contribute to a prognostic benefit in recurrent surgery. In light of this perspective, one has to consider that even in cases where complete tumor resection appears unlikely and ROC surgery is performed due to otherwise non-treatable symptoms, maximal efforts should be undertaken in order to obtain maximum tumor resection (always considering the associated morbidity, of course). The value of <1cm tumor residual in ROC surgery, however, should be prospectively evaluated in future trials.

4.3. Strengths and weakness of the study

A strength of this study is in the large number of patients who were treated at the same institution in a uniform fashion and were prospectively documented in the TOC-Databank. A weakness may lie in the fact that our results are based on a monocentric experience of a high-volume university hospital with a constantly high surgical quality that serves as a reference center for gynecologic oncology and therefore the results may not be extended to other centers. Despite the limitations we hope that this study provides further insight and supports surgeons in their daily work.

5 Summary and Conclusions

Background and objectives: Ovarian cancer (OC) is the main cause of mortality related to gynaecologic cancer worldwide. Surgical cytoreduction is the cornerstone of current treatment in patients with advanced primary disease. In contrast, the value of surgery in recurrent ovarian cancer (ROC) remains unclear. In the present study, we evaluate the role of postoperative tumor residual and tumor reduction in primary and recurrent ovarian cancer with survival as primary goal.

Methods: All consecutive patients with primary or first relapsed OC who underwent tumor-debulking surgery at our institution were systematically analyzed with the help of an intraoperative documentation tool. We evaluated the tumor characteristics as well as the operative and clinical outcomes. Then we performed univariate and multivariate analyses to identify independent predictors for mortality and disease progression as well as predictors for complete tumor resection in both situations.

Results: A total of 446 operations performed between 09/2000 and 04/2006 were included in the analysis (269 on patients with primary OC and 177 on patients with ROC). The median age at first diagnosis for the primary situation was 59 years. 71.7% of patients had tumor FIGO stage III-IV. Overall, 64.7% of patients were operated to be macroscopically tumor-free, 21.5% had residual disease ≤ 1cm, and 13.8% had >1 cm intra abdominal residual disease. In 26.0%, 4/5 of the tumor was removed, in 7.5 % less than 4/5 of the tumour was removed and 1.9% were considered to have unresectable disease. The postoperative morbidity rate was 28.5%, while the perioperative mortality rate was 3.0%. 75.5% of patients received adjuvant paclitaxel/carboplatin therapy. The median follow-up time was 18.4 months (range 0.1-74.5 months). In multivariate analysis, no tumor resection (HR 10.6), 4/5 tumor reduction (HR 5.4) and other tumor histology than serous (HR 2.7) were the most significant factors for mortality. The postoperative median survival (OS) could not be calculated and the median progression-free survival (PFS) was 13.0 months (range 0.1-72.9 months). Median OS was 32.2 months (95%CI 24.2-40.1), 15.5 months (95%CI 0.1-33.6) and 2.6 months (95 %CI 0.1-10.6) for patients with 4/5 tumor resection, less than 4/5 tumor resection and no tumor resection, respectively (*p*-value=0.002). For patients left with tumor residual of any size, OS was 27.1 months (95%CI 15.2-38.9). Threshold analysis illustrated a point between 0.5 and 1cm tumor residual where the survival KM graph diverges. Variables

such as age (>60 years) (OR=0,36; 95%CI 0,2-0,94), small bowel metastasis (OR=0,27; 95% CI 0,17-0,64), tumor spread in the upper abdomen (OR=0,34; 95% CI 0,14-0,81) and systematic lymphadenectomy (OR 6.4 CI 95% 2.5-16.2) were identified as significant predictive factors for complete tumor reduction in primary OC.

In ROC, 67.8% of patients were platinum-sensitive and 28.2% platinum-resistant. In 44.6%, a complete tumor resection was achieved; in another 26.0% postoperative tumor residuals were <1 cm. In 31.6%, 4/5 of the tumour was removed. The postoperative morbidity rate was 37.2% while the perioperative mortality rate was 8.2%. The median follow-up was 10.8 months (range 0.0-65.0 months). Median PFS was 8.4 months (range 0.0-55 months). In multivariate analysis, ascites (≥500ml HR 4.7 and <500 ml. HR 2.8 compared with no ascites), no tumor reduction (HR 4.7 compared with macroscopic tumor-free), tumor residual <1cm (HR 0.3 compared with tumor residual >1cm) and platinum-resistance (HR 2.7) were independent predictors for OS. Median OS for patients with complete tumor resection was 60.6 months (95%CI 21.3-99.8). Among patients with a tumor residual of any size, median OS was 29.5 (21.6-37.3) and 8.7 (4.1-13.2) for patients with residual of <1cm and ≥1cm, respectively (*p* value <0.001). Variables such as ascites less than 500ml (OR=0.3; 95% CI 0.1-0.8 p<0.05), small bowel metastasis (OR=0.22; 95% CI 0.07-0.71 p<0.05), tumor spread in the upper abdomen (OR 0.33 CI 95% 0.1-0.9 p <0.05), serous tumor histology (OR 5.8 95% CI 1.2-28.1 p<0.05) and platinum-sensitivity (platinum-resistance OR 0.1 95% CI 0.06-0.5 p< 0.01) were identified as significant predictive factors for complete tumor reduction. Age was not significant.

Conclusion: Complete debulking to achieve no visible tumor residual must be considered the ultimate goal of primary ovarian cancer surgery. In patients with any residual tumor, improved survival was achieved by ascending tumor reduction percentages. Tumor residual ≤1cm (“optimal” cytoreduction) may not represent the best survival prognosis, but the threshold between a good and a poor survival prognosis.

Procedures which have been described in recent years for primary cytoreduction may be also be applicable to secondary surgery. Complete tumor resection should also be the aim of ROC surgery, as it is associated with a prolonged survival. However, not only complete tumor resection but also “optimal” cytoreduction to tumor residuals of <1cm seem to contribute to a prognostic benefit. Therefore, operative efforts should be carried out fully in order to obtain maximum tumor resection, always considering the associated morbidity of course.

6 Zusammenfassung und Schlussfolgerungen

Hindergrund und Ziele: Das Ovarialkarzinom ist weltweit die führende Ursache der Mortalität gynäkologischer Malignome. Die chirurgische Zytoreduktion ist der Eckpfeiler in der heutigen Behandlung von Patienten in fortgeschrittenem Stadium des primären Ovarialkarzinoms. Im Gegensatz hierzu ist der Stellenwert der chirurgischen Therapie bei rezidiviertem Ovarialkarzinom unklar. In der vorliegenden Untersuchung untersuchen wir die Rolle des postoperativen Tumorrests sowie der Tumorreduktion bei primärem und rezidiviertem Ovarialkarzinom, hierbei gilt als primärer Endpunkt das Überleben.

Methoden: Sämtliche Patienten mit Primär- oder Erstrezidiv-Ovarialkarzinom, die in unserer Klinik einer Tumor-Debulking-Operation unterzogen wurden, wurden systematisch auf der Basis eines intraoperativen Dokumentations-Verfahrens untersucht. Hierbei wurden Tumorcharakteristik, Muster der Tumor-Disseminierung und operatives und klinisches Outcome untersucht. Uni- und multivariate Analysen wurden duchgeführt, um unabhängige Prädiktivfaktoren für Mortalität und Progression sowie Prädiktoren einer kompletten Tumor-Resektion in beiden klinischen Situationen zu identifizieren.

Ergebnisse: Zwischen 09/2000 und 04/2006 wurden insgesamt 446 Operationen in die Analyse eingeschlossen, 269 davon in Patienten mit primaerem Ovarialkarzinom und 177 in Rezidivsituation. Bei primaerem Ovarialkarzinom lag der Altersmedian bei 59 Jahren. 71,7% der Patienten hatten Tumorstadium FIGO III-IV. Insgesamt konnten 64,7% der Patienten makroskopisch tumorfrei operiert werden, 21,5% hatten einen Tumorrest ≤ 1 cm und 13,8% wiesen einen >1 cm intraabdominalen Tumorrest auf. In 26% wurden 4/5, in 7,5% weniger als 4/5 des Tumors entfernt und in 1,9% war der Tumor nicht resektabel. Die postoperative Morbidität lag bei 28,5% und die perioperative Mortalität bei 3%. 75,5% erhielten eine adjuvante Paclitaxel/Carboplatin-Therapie. Die mediane Nachbeobachtungszeit lag bei 18,4 Monaten (0,1-74,5 Monate). In der multivariaten Analyse zeigten sich als Faktoren mit höchster Signifikanz für erhöhte Mortalität: keine Tumorresektion (Hazard-Ratio (HR) 10,6), 4/5 Tumor-Reduktion (HR 5,4) und nicht-seröse Tumor- Histologie (HR 2,7). Das postoperative mediane Überleben konnte nicht berechnet werden und das mediane progressionsfreie Intervall (PFS) lag bei 13 Monaten (0,1- 72,9 Monate). Das mediane Gesamtüberleben

lag bei 32,2 Monaten (95% KI 24,2- 40,1),15,5 Monaten (95% KI 0,1- 33,6) und 2,6 Monaten (95% KI 0,1- 10,6) für Patienten mit 4/5 Tumorresektion, weniger als 4/5 Tumorresektion und Patienten ohne erzielte Tumorresektion (p-Wert= 0,002). Für Patienten mit Residualtumor jedweder Größe lag das Gesamtüberleben bei 27,1 Monaten (95% KI 15,2-38,9). Eine Schwellenwert- Analyse zeigte für einen Wert zwischen 0,5cm und 1cm Tumorrest einen Unterschied in der Kaplan-Meier-Überlebenskurve. Variablen wie Alter (> 60 Jahre) (Odds Ratio (OR)= 0,36; 95% KI 0,2-0,94), Dünndarmmetastasierung (OR=0,27; 95% KI 0,17-0,64), Tumorausbreitung im oberen Abdomen (OR= 0,34; 95% KI 0,14- 0,81) und systematische Lymphadenektomie (OR 6,4; 95% KI 2,5- 16,2) wurden als signifikante Prädiktivfaktoren einer kompletten Tumorentfernung im primärem Ovarialkarzinom identifiziert.

Beim rezidivierten Ovarialkarzinom zeigten sich 67,8% der Patienten Platin- sensibel und 28,2% Platin- resistent. In 44,6% konnte eine komplette Tumor-Resektion erreicht werden; in weiteren 26% war der postoperative Tumorrest < 1cm. In 31,6% konnten 4/5 des Tumors entfernt werden. Die postoperative Morbidität lag bei 37,2%, die perioperative Mortalität bei 8,2%. Die mediane Nachbeobachtungsdauer waren 10,8 Monate (0,0- 65 Monate). Das mediane PFS lag bei 8,4 Monaten (0- 55 Monate). In der multivariaten Analyse waren unabhängige Faktoren des Gesamtüberlebens: Aszites (≥500ml HR 4,7 und <500ml HR 2,8 verglichen mit keinem Aszites), nicht erreichte Tumorreduktion (HR 4,7 verglichen mit makroskopischer Tumorfreiheit), Tumorrest < 1cm (HR 0,3 verglichen mit Tumorrest >1cm) und Platin-Resistenz (HR 2,7). Das mediane Gesamtüberleben von Patienten mit kompletter Tumorresektion lag bei 60,6 Monaten (95% KI 21,3- 99,8). Für Patienten mit Tumorrest jedweder Größe lag das mediane Gesamtüberleben bei 29,5 (21,6- 37,3) Monaten für Tumorrest < 1cm und bei 8,7 (4,1- 13,2) Monaten für Tumorrest ≥ 1cm (p-Wert < 0,001). Variablen wie Aszitesmenge <500ml (OR=0,3; 95% KI 0,1-0,8; p<0,05), Dünndarmmetastasierung (OR=0,22; 95% KI 0,07-0,71), Tumorausbreitung im oberen Abdomen (OR 0,33 KI95% 0,1-0,9; p<0,005), seröse Tumorhistologie (OR 5,8; 95%KI 1,2.-28,1) und Platin-Sensibilität (Platin-Resistenz OR 0,1 95%KI 0,06-0,5; p<0,01) konnten als signifikante Prädiktivfaktoren einer kompletten Tumorreduktion identifiziert werden. Alter war nicht signifikant.

Schlussfolderung: Das komplette „Debulking“ mit Erreichen eines makroskopisch nicht sichtbaren Tumorrestes muss als absolutes Ziel in der Operation des primären Ovarialkarzinoms angesehen werden. In Patienten mit Tumorrest jedweder Größe

wurde eine Verlängerung des Überlebens in Korrelation mit erhöhten Prozentzahlen der Tumorreduktion erzielt. Ein Tumorrest ≤1cm („optimale“ Zytoreduktion) bedeutet nicht die beste Prognose, sicher aber einen Schwellenwert zwischen guter und schlechter Überlebens-Prognose.

Traditionell für die primäre Zytoreduktion beschriebene (operative) Verfahren können ebenso in Situationen einer sekundären Operation angewandt werden. Eine komplette Tumorresektion sollte auch in der Chirurgie des rezidivierten Ovarialkarzinoms angestrebt werden, da sie mit verlängertem Überleben assoziiert ist. Nicht nur die komplette Tumorresektion sondern ebenso eine „optimale“ Zytoreduktion mit Tumorresten < 1cm scheinen einen prognostischen Nutzen zu haben. Deshalb sollte das operative Bemühen immer auf die maximal erreichbare Tumorreduktion abzielen, wobei die perioperative Morbidität berücksichtigt werden muss.

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8 Abbreviations

BRCA	Breast Cancer
CA125	Ovarian cancer-associated antigen
CS	Cytoreductive surgery
DFI	Disease Free Interval
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelium ovarian cancer
FIGO	International Federation of Gynecology and Obstetrics
GCIG	Gynecologic Cancer Intergroup
GOG	Gynecologic Oncology Group
HR	Hazard ratio
IP	Intraperitoneal chemotherapy
KI	Karnofsky index
OC	Ovarian cancer
OS	Overall survival
PFS	Progression-free survival
PET	Positron emission tomography
POM	Postoperative mortality
PPV	Positive predictive value
PS	Performance status
ROC	Recurrent ovarian cancer
TVUS	Transvaginal ultrasound

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Berlin, August 2010 Blanca Gil Ibáñez

10 Erklärung

Ich, Blanca Gil Ibáñez, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: ‚Bedeutung der operativen Tumorreduktion bei Patientinnen mit Ovarialkarzinom und suboptimalem Debulking' selbst verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel benutzt, ohne die (unzulässige) Hilfe Dritter verfasst und auch in Teilen keine Kopien anderer Arbeiten dargestellt habe.

Datum Unterschrift

11 Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.