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DISSERTATION

ROLE OF AGE IN EPITHELIAL OVARIAN CANCER

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ZUSAMMENFASSUNG

Ziel der Studie:

Das Ziel der hier vorgelegten Dissertation ist die systematische Analyse klinisch-pathologischer Prognosefaktoren sowie perioperativer Morbiditäts- und Mortalitätsraten nach ausgedehnten Ovarialkarzinom-Operationen bei älteren Frauen (> 65 Jahre) im Vergleich zu jüngeren Frauen (≤ 65 Jahre). Nur wenige Studien hatten sich bisher mit dieser klinisch-relevanten Thematik befasst.

Material und Methoden:

Die Studienkohorte schloss insgesamt 446 Frauen, die konsekutiv zwischen September 2000 und April 2006 in der Klinik für Gynäkologie, Campus Virchow-Klinikum, Charité Berlin, wegen einem histologisch gesicherten Ovarialkarzinom behandelt wurden. Alle klinischen Daten stammen aus der prospektiven Tumorbank Ovarialkarzinom (TOC). Insgesamt wurden 269 (60,3%) Patientinnen mit primärem Ovarialkarzinom (POC) und 177 (39.7%) Patientinnen mit erstem Ovarialkarzinom-Rezidiv (FROC) in diese eingeschlossen. Ein systematisches und validiertes Instrument zur chirurgischen und histopathologischen Tumordokumentation, (Intraoperatives Mapping von Ovarialkarzinomen (IMO)), wurde zur detailliertes Dokumentation und Charakterisierung der Tumorausbreitung und eingesetzter chirurgischer Methoden verwendet.

Ergebnisse:

Der Überlebensunterschied zwischen jungen und älteren Frauen zeigte statistisch signifikante Unterschiede in Abhängigkeit vom Tumorrest. Patientinnen ohne Resttumor und jünger als 65 Jahre hatten ein 5-Jahresüberleben von 60,7%, die Älteren über 65 Jahre von 51,6%. Der Resttumor verschlechterte die Überlebenswahrscheinlichkeit deutlich: 19,8% bei unter 65 Jahre bzw. 10,2% in der Gruppe über 65 Jahre.

Das Alter war ein statistisch signifikanter Risikofaktor für das Gesamtüberleben bei Patientinnen mit primärem Ovarilkarzinom, älter als 65 Jahre (HR 4), FIGO-

Stadium III/IV (HR 1,7 bzw. 3,4), seröse Histologie (HR 2,3), Level II und III Tumorinfiltration (HR 1,9 bzw. 2,2), Peritonelkarzinose (HR 2,1) und Resttumor (HR 1,7). Beim krankheitsfreien Überleben beeinflusste das Alter das FIGO-Stadium (HR 4), Level II (HR1,6) und Peritonealinfiltration (HR 1,6) signifikant.
Ältere Patientinnen mit rezidiviertem Ovarialkarzinom zeigten ein ungünstiges Gesamtüberleben insbesondere bei Level II Tumorbefall (HR 2) und postoperatives Tumorrest (HR 2,3). Das krankheitsfreie Intervall wurde signifikatn durch den Tumorrest beeinflusst.
Die multivariat Analyse ermittelte das Alter als nicht signifikanter Prognosefaktor für das Gesamtüberleben (HR 0,9, p=0,7), allerdings zeigte sich als deutliche Tendenz des negativen Einflusses des postoperativen Tumorrests auf das Überleben. Ausgedehnte operative Eingriffe (z.B. mit Dünn-/Dickdarmresektionen), nicht platin-haltige Chemotherapie in der Adjuvanz oder ein platin-resistentes Rezidiv waren ebenfalls mit einer signifikant höheren Mortalität assoziiert. Das krankheitsfreie Überleben wurde von dem FIGO-Stadium (III/IV vs. I/II) sowie von dem Tumorrest (>1cm vs. ≤1cm) signifikant negativ beeinflusst.
Das Gesamtüberleben von Patientinnen mit platinresistentem Ovarialkarzinomrezidiv war durch eine signifikant höhere Mortalität gekennzeichnet im Vergleichzu Frauen mit platin-sensitivem Rezidiv. Der Tumorrest, der Aszites und eine ausgedehnte Darmtumorchirurgie waren ebenfalls mit einem ungünstigen Überlebenseffekt assoziiert. Das progressionsfreie Überleben war signifikant von dem Tumorrest als auch von der Aszitesmenge beeinflusst.

Schlussfolgerung:

Die vorliegende Studie stellt einer der bisher grössten Analyse zu dieser Thematik dar. Die Ergebnisse zeigen eindrucksvoll, dass auch „ältere“ Patientinnen mit kompletter Tumorresektion beim primären- und rezidivierten Ovarialkarzinom ein signifikant verlängertes Gesamtüberleben zeigen. Unsere Studie demonstriert , dass der postoperative Tumorrest auch bei der älteren

Patientin mit Ovarialkarzinom den wichtigsten Prognosefaktor darstellt. Die Präsenz von Aszites und die Platinsensibilität beeinflussen ebenfalls signifikant das Gesamtüberleben und progressionsfreie Überleben. Diese Aussagen treffen sowohl für die Primärsituation als auch der Rezidivsituation zu.

Frauen ab dem 65. Lebensjahr ohne relevante Komorbiditäten sollten demnach ausgedehnten zytoreduktiven Operationen ebenso wie jüngere Frauen zugeführt werden. Hierbei ist aber ein abgestimmtes interdisziplinäres und interprofessionelles Vorgehen die Grundvoraussetzung. Weitere Studien zu diesem klinisch so relevanten Thema sind notwendig um das Kollektiv mit dem besten Langzeitergebnissen noch besser charakterisieren zu können.

ABSTRACT

Purpose of the study:

Because of increasing life expectancy in the general population and limiting data, the primary aim of the present study was to analyze the impact of age on clinical outcome and survival of patients with epithelial ovarian cancer.

Method(s):

The study cohort consisted of 446 women treated between September 2000 and April 2006 in the clinic for Gynecology, Campus Virchow-Klinikum, Charité Berlin. All clinical data were provided by the Tumor Bank Ovarian Cancer (TOC). We enrolled 269 (60.3%) patients with primary ovarian cancer (POC) and 177 (39.7%) patients with first recurrency of ovarian cancer (FROC).

A systematic and validated surgical and histo-pathological tumor documentation instrument, IMO (Intraoperative Mapping of Ovarian Cancer) was used for the documentation of the tumor spread and surgical methods. Kaplan-Meier curves were calculated for overall survival (OS) and disease free survival (DFS). The Cox regression analysis was performed to identify independent predictors of mortality.

Result(s):

In patients with POC, 77.3% were ≤65 years, 12.6% between 66 and 70 and 10% >70 years. FIGO stage III was the most common tumor stage, 55.8% ≤65, 55.9% 66-70 and 63% >70 years at primary diagnose. A complete tumor resection was achieved in 70.7% ≤65, 47.1% 66-70 and 40.7% >70 years. The OS was worse for elderly patients with residual tumor, peritoneum and level II and III tumor spread, and FIGO III and IV. In patients with FROC, 87% were ≤65 years, 8.5% between 66 and 70 and 4.5% >70 years. FIGO stage III was the most common tumor stage, 71.3% ≤65, 69.2% 66-70 and 50% >70 years at primary diagnose. A complete tumor resection was achieved in 43.5% ≤65, 60% 66-70 and 37.5% >70 years. The OS was worse for elderly patients with residual tumor and level II tumor spread.

In POC is documented the mortality rate as 41.3% in patients >65 years and in FROC 64.4% >65 years. In case of Follow up, patients with POC the median was 31.3 months and patients with FROC the median was 15.9 months with range 0-100 and 0-90 months, correspondingly.

The multivariable analysis showed that only stomy, residual tumor and platinum resistance patients with POC affected negatively OS, but not age. DFS were significantly worse for patients with FIGO stage III and IV and residual tumor. In patients with FROC, presence of ascites, stomy, residual tumor, and platinum resistance affected negatively OS, but not age. For DFS, patients with presence of ascites, residual tumor or platinum resistance, had significantly worse results.

Conclusion(s):

The results demonstrate that patients with complete tumor resection have the best OS rates in primary and in first recidive ovarian cancer. Our study demonstrates the important role of residual mass. Also presence of ascites and platinum response influence significantly OS and DFS in patients with FROC. Women older than 65 years without significant comorbidity can undergo extensive cytoreductive surgery as well as younger women younger than 65 years, suggesting that the same therapy protocols should be applied to all ovarian cancer patients independent from the chronologic age. Nevertheless, the increased postoperative morbidity must be considered, and specially the high requirement for special interdisciplinary postoperative management in this collective.

1. INTRODUCTION

1.1. Ovarian Cancer

1.1.1. Epidemiology

Epithelial ovarian cancer (EOC) is the fourth leading cause of cancer death among women in Europe [1] and it is considered to be the most frequent fatal gynecologic malignancies [2]. More than half of the patients die from the disease within 5 years of their diagnosis [3]. The lifetime risk of developing ovarian cancer in the general population is 1–2%. For patients with a family history of ovarian cancer, their lifetime risk of developing this disease increases to 4 to 5% with one first degree relative and to 7% when 2 first-degree relatives are affected [4] [5].

The deficient of established population-based screening programmes and early diagnosis of the disease, absence of specific symptoms and signs of ovarian cancer in early stage and it tends to present at an late stage, which is characterized by widespread peritoneal dissemination and ascites, are possible explanation for the overall poor prognosis and high mortality rate [6]. Early stage of ovarian cancer (stage I, International Federation of Gynecology and Obstetrics (FIGO) has an excellent survival rate at 5 years with over than 85% of patients, but about 70% of newly diagnosed women are in advanced stage (stage III and IV) with extra-ovarian disease. In spite of improvement in surgical management, stage III and IV disease are frequently not totally resecable and still associated with a long-term survival rate of less than 20%. All established therapies reveal a poor efficiency in the advanced stage of the disease, especially in older patients which are treated often less aggressively, and though therapies have been further optimized in the last decade, the mortality rate due to ovarian cancer is still to high. [7]. Consequently, new therapeutic strategies for ovarian cancer treatment are urgently needed.

1.1.2. Aetiology and Risk Factors

Risks of developing an ovarian cancer appear to be reproductive and hormonal factors. It is observed by several studies that women with few children, infertility and later age of menopause have high incidence rates. Quite the opposite, women with elevated parity, oral contraceptive use, prophylactic hysterectomy or oophorectomy seem to have protective effects [8]. A tubal ligation or hysterectomy with ovarian conservation is also associated with a decreased risk of ovarian cancer, as is prophylactic oophorectomy for patients who have a deleterious mutation in the *BRAC1* or *BRCA2* genes [9] [10].
The environmental factors like diet (a high intake of saturated fat, low intake of vegetables) [11] [12] [13], smoking, use of talcum powder [14] [15] on the perineum, psychotropic medication, the mumps virus and high level physical activity seem to be also a risk factors. Postmenopausal use of hormone replacement therapy (also called hormone therapy [HT]) [16] [17], and between women who have used fertility drugs [14-18].

1.1.2.1. Pathogenesis

The probable histopathologic precursors of the ovarian or of the fallopian tube cancer appear to be:

- Epithelial dysplasia of the surface epithelium or germinal inclusions
- Benign proliferative lesion such as endometriosis
- Benign neoplasms, that is, cystadenomas and cystadenofibromas.

Ovarian cancers pathogenesis is remains unclear. The carcinomas could also result directly from the surface epithelium without an intermediate precursor lesion. Numerous theories have been proposed to explain the epidemiology of ovarian cancer. Fathalla's theory of "incessant ovulation" [19] suggests that repetitive ovulation traumatizes the ovarian epithelium, rising the likelihood of

errors occurring during DNA repair and the exposure of the epithelial cells to the estrogen-rich follicular fluid that is present during ovulation, so making the ovarian cells more susceptible to malignant change. The decreased risk of ovarian cancer associated with pregnancy, multiparity, lactation and the oral contraceptive pill support Fathalla's theory, and propose preventing ovulation can protect against ovarian tumor [20]. Constant increase of gonadotropins has also been proposed as an underlying mechanism leading to ovarian cancer [21]. The ovarian epithelium constantly invaginates all through life to form clefts and inclusion cysts, leading to a theory that under extreme stimulation by gonadotropins (FSH and LH) and estrogen and its precursors, the ovarian epithelium may undergo malignant transformation. This theory would explain the decreased risk of ovarian tumor associated with pregnancy and oral contraceptive use.

A third theory is that factors associated with excess androgenic stimulation of ovarian epithelial cells may be decreased by factors related to greater progesterone stimulation [22]. This theory is supported by the findings that elevated levels of androstenedione and dehydroepiandrostenedione (DHEA) were associated with an augmented risk of ovarian cancer and that an augmented risk was also seen among women with polycystic ovary (PCO) syndrome [23].

One method of considering the pathogenesis of ovarian cancer is by dividing them into epithelial and non-epithelial ovarian carcinoma.
The epithelial types represent 60% of all ovarian neoplasms and for 80% to 90% of ovarian malignancies. They arise from the surface epithelium or serosa of the ovary and appear to develop de novo (serous carcinomas). Non-epithelial tumors account around 7-10% of all malignant ovarian tumors. They arise from ovarian germ cells or stromal cells and appear to develop from benign and atypical proliferative precursor lesions (mucinous, endometrioid and clear cell carcinomas) [24].

Some recent studies have challenged the dogma that the ovary is the main source of high- grade ovarian cancer. Most ovarian cancer researches are based on the hypothesis that high-grade serous ovarian carcinoma develops from ovarian surface epithelial cells. However, recent studies suggest that >50% of high-grade serous carcinomas relating the ovary likely arise from fallopian tube epithelium. The researchers observed that when early cancer were found, it was located in the fallopian tube rather than on the ovarian surface. The theory is that early cancer start in the fallopian tube, cancer cells break away and are deposited on the ovarian surface where they start to grow. Consequently, ovarian cancer does start on the surface, not from within. Therefore that salpingectomy in high-risk populations could therefore prevent and promise to significantly impact ovarian cancer incidence and outcomes [100].

1.1.2.2 Genetic Factors

Family history is the most important risk factor for ovarian cancer of a first-degree relative (e.g., mother, daughter, or sister) with the disease. The maximum risk appears in women with 2 or more first-degree relatives with ovarian cancer [25]. The risk is slightly lower for women with one first-degree and one second-degree relative (grandmother or aunt) with ovarian cancer. The majority of ovarian cancers are sporadic and only 5 -10% of the cancers seem to be the result of an autosomal-dominant susceptibility factor with high penetrance [26].

The cell is regulated by many genes and their respective proteins in a complex interrelated series of events. In the development of ovarian cancers from normal epithelium though adenomas or benign tumors to carcinomas, the steps have been paralleled by detection of some genetic loci which are mutated as the tumor develops. Neoplastic conversion is the product of an accumulation of genetic events, such as a genetic predisposition, exposure to carcinogenic agents, leading to activation of oncogenes and loss of tumor suppressor genes.

Alterations in tumor suppressor genes such as P53, RB1, ARH1 (NOEY2), BRCA1 and BRCA2 are implicated in ovarian carcinogenesis. P53 mutations happen in about 50-80% of tumors when analysed by complete gene sequencing. Functional wild-type P53 is necessary for chemo- and radio-sensitivity due to its role in apoptosis. The mutation of P53 is followed by loss of the wild-type consequence in resistance to therapy. 90% of ovarian cancers with P53 expression have mutations of P53 which increases the half-life of the P53 protein. Advanced ovarian cancers have in 50% overexpressed or mutant P53 which correlates with late grade and poor survival, but not with chemoresponsiveness [27, 28].

Some recent studies propose by analysis of P53 mutations patterns, dual pathways of serous carcinogenesis. They suggest that serous borderline tumors are the precursor of low-grade serous carcinomas and a high-grade serous carcinoma is developed from in situ alterations. The similar frequency of P53 mutation was detected in serous borderline tumors and low-grade invasive serous carcinomas in contrast to the significantly higher frequency of P53 mutations in high-grade serous carcinomas [29].

About 10% of ovarian epithelial cancers thought to have a hereditary component, 90% are allied with breast-ovarian syndrome. This syndrome is associated with BRCA1 and BRCA2 which are involved in DNA repair and transcription regulation. Mutations are distributed all through the entire coding regions of BRCA1 and BRCA2, and most result in truncation of the protein. [25,26-28,30-34]**.**

1.1.3. Tumor dissemination

About 75% of epithelial carcinomas at the time of diagnosis are high grade and extensively disseminated throughout the peritoneum after exfoliation of malignant cells from the surface of the ovary. The omentum often attracts these malignant cells and is consequently a frequent location of metastasis. The main volume of the tumor is generally outside the ovary and it disseminate frequently

via the lymphatics. About 10% of woman with ovarian cancer have metastases to pelvic and paraaortic lymph nodes. A basis of drainage follows the ovarian blood provide in the infundibulopelvic ligament to lymph nodes around the aorta and vena cava to the level of the renal vessels. In addition, there is lymphatic drainage throughout the broad ligament and parametrial channels; thus, pelvic sidewall lymphatics, including the external iliac, obturator, and hypogastric chains, are also habitually involved. Infrequently, spread to the round ligament, resulting in participation of inguinal lymph nodes [35].

Exceptional are hematogenous metastases to extraabdominal sites, including brain or bone metastasis. In addition, there can be direct extension of the tumor to involve the adjacent peritoneal surfaces of the bladder, rectosigmoid, and pelvic peritoneum.

1.1.4. Histological Classification

Around 90% of all ovarian cancers are epithelial, i.e., derived from relatively pluripotent cells of the celomic epithelium or “modified mesothelium.” These cells can undergo metaplasia.
Approximately 10% to 20% of epithelial ovarian neoplasms are borderline or low malignant potential tumors. Of the invasive epithelial ovarian cancers, about 75% to 80% are serous, 10% are mucinous, and 10% are endometrioid. Less frequent types include clear cell, Brenner, small cell, and undifferentiated carcinoma. Non-epithelial types of ovarian cancer include the sex cord-stromal (6% of ovarian cancers), germcell (3%), and indeterminate tumors (1%) [36].

Table 1.1 World Health Organization histological classification of ovarian tumors: Surface epithelial-stromal tumors [36]

Histology type	**Frequency in %** [37]
Serous tumors	50
Mucinous tumors, endocervical-like and intestinal types	10-15
Endometrioid tumors	10-25
Clear cell tumors	5
Transitional cell tumors: -Brenner tumor, -Borderline malignancy (proliferating) -Malignant Brenner tumor -Transitional cell carcinoma (non Brenner type)	<1
Undifferentiated	5-10

Histopathology grades (G) of ovarian tumors:

GX: Grade cannot be assessed

G1: Well-differentiated cancer

G2: Moderately differentiated cancer

G3: Poorly differentiated or undifferentiated cancer

1.1.5.Stage Classifications

1.1.5.1. FIGO Classifications

The Federation Internationale de Gynecologie et d'Obstetrique (FIGO) and the American Joint Committee on Cancer (AJCC) have standardized the staging of gynaecologic cancers [38, 39].

Table 1.2 Definitions of the FIGO classification for Staging Primary Ovarian Carcinoma [38, 39]

STAGE	DEFINITION
Stage I	Growth limited to ovaries
Stage Ia	Growth limited to one ovary, no ascites, no tumor on external surface, capsule intact
Stage Ib	Growth limited to both ovaries, no ascites, no tumor on external surface, capsule intact
Stage Ic	Tumor either stage Ia or Ib, but with tumor on one or both ovaries, with capsule ruptured, with ascites present containing malignant cells, or with positive peritoneal washings
Stage II	Growth involving one or both ovaries with pelvic extension
Stage IIa	Extension and/or metastases to the uterus and/or tubes
Stage IIb	Extension to other pelvic tissues
Stage IIc	Tumor either stage IIa or IIb, with tumor on the surface of one or both ovaries, but with capsule(s) ruptured, with ascites present containing malignant cells, or with positive peritoneal washings
Stage III	Tumor involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or inguinal nodes. Superficial liver metastases equal stage III. Tumor limited to the true pelvis but with histological proven malignant extension to small bowel or omentum
Stage IIIa	Tumor grossly limited to the true pelvis with negative nodes but with histological confirmed microscopic seeding of abdominal peritoneal surfaces.
Stage IIIb	Tumor involving one or both ovaries with histological confirmed implants of abdominal peritoneal surfaces, none exceeding 2cm in diameter. Nodes are negative.
Stage IIIc	Abdominal implants >2cm in diameter and/or positive retroperitoneal or inguinal nodes.
Stage IV	Growth involving one or both ovaries with distant metastases.

1.1.5.2. TNM Classification

The primary tumor (T), regional lymph nodes (N) and the state of metastasis (M) are classified according to the following categories:

Table 1.3 TNM Staging-Tumors [38]:

T1:	**Tumor is limited to one or both ovaries.**
T1a:	Tumor is limited to one ovary. The capsule, or outer wall of the tumor, is intact, there is no tumor on the ovarian surface, and there are no cancer cells in ascites (abdominal fluid build-up) or peritoneal lavage ("washings" from the abdominal cavity).
T1b:	Tumor is limited to both ovaries. The capsule is intact, there is no tumor on the ovarian surface, and there are no cancer cells in ascites or peritoneal lavage.
T1c:	Tumor is limited to one or both ovaries with any of the following: ruptured capsule (burst outer wall of the tumor), tumor on ovarian surface, or cancer cells in the ascites or peritoneal lavage.
T2:	**Tumor involves one or both ovaries with spread into the pelvis.**
T2a:	Tumor has spread and/or attaches to the uterus and/or fallopian tubes. There are no cancer cells in ascites or peritoneal lavage.
T2b:	Tumor has spread to other pelvic tissues. There are no cancer cells in ascites or peritoneal lavage.
T2c:	Tumor has spread to pelvic tissues, with cancer cells in ascites or peritoneal lavage.
T3:	**Tumor involves one or both ovaries, with microscopically confirmed peritoneal metastasis outside the pelvis and/or metastasis to regional (nearby) lymph node(s).**
T3a:	Microscopic peritoneal metastasis beyond the pelvis.
T3b:	Macroscopic (visible to the naked eye) peritoneal metastasis beyond the pelvis, 2 cm or less in greatest dimension.
T3c:	Peritoneal metastasis beyond the pelvis, more than 2 cm in greatest dimension.
N0:	Regional lymph nodes contain no metastases.
N1:	Evidence of lymph node metastasis.
M0:	No distant metastases are found (this excludes peritoneal metastasis).
M1:	Distant metastases are present

The TNM system places ovarian cancer growth at a particular stage:

Table 1.4 TNM Staging-Stage Grouping [38]:

Stage 1a:	T1a, N0, M0
Stage 1b:	T1b, N0, M0
Stage 1c:	T1c, N0, M0
Stage 2a:	T2a, N0, M0
Stage 2b:	T2b, N0, M0
Stage 2c:	T2c, N0, M0
Stage 3a:	T3a, N0, M0
Stage 3b:	T3b, N0, M0
Stage 3c:	T3c, N0, M0 or T(any), N1, M0
Stage 4:	T(any), N(any), M1

1.1.6.Clinical aspects

The symptoms of ovarian cancer are non-specific and there is no efficient screening tool. As a result, ovarian tumors, until they are advanced in stage or size, are usually difficult to detect, as the symptoms are vague and manifest over time. The main symptoms consist of: shortness of breath, fatigue, increased abdominal girth, non-productive cough, bloating, and amenorrhea for premenopausal women, menstrual irregularity and weight loss. Most ovarian cancers origin symptoms by exerting pressure on contiguous structures, resulting in augmented urinary frequency, pelvic discomfort and constipation. Abdominal distension results from enlargement of the tumor. Ascites or abdominal metastases cause nausea, heartburn, bloating, anorexia and weight loss. Most women present one or more nonspecific symptoms, but only in advanced stage. It is estimated that only 15% of patients have the disease limited to the ovary at the time of diagnosis [40, 41].

Women are usually diagnosed with advanced stage. The 5-year survival rates are around 27% and 16% for FIGO III and IV respectively [42-44]. Early detection of ovarian cancer should decrease mortality and morbidity from the disease.

1.1.7. Screening and Diagnosis

The time interval for progression from stage I to IV ovarian cancer remains to be defined and the duration of preclinical invasive disease in ovarian cancer is unclear. If it is short, it will not to be possible to introduce a screening program with a satisfactorily short screening interval. Ovarian palpation, radiology diagnostic, serum CA 125 determinations and other existing screening techniques are not sufficiently precise to recommend general population screening and all are limited by insufficient sensitivity and specificity. One effective screening test should be sensitive and specific, with high positive predictive value (PPV) and a high negative predictive value. The incidence of ovarian cancer increases with age and the highest risk occurs in women with BRCA1 and BRCA2 mutations. Therefore, most trials are concentrated on screening woman over 50 years and young woman, over 25 years, with family history of ovarian cancer [45, 46]. Potential screening tests for ovarian cancer enclose bimanual pelvic and rectovaginal examination, transvaginal ultrasound (TVS), and CA 125 antigen as a tumor marker. The measurement of CA 125 levels, habitually in combination with other modalities such as bimanual pelvic examination and transvaginal ultrasonography [47, 48], has been proposed as a method for the early detection of ovarian cancer. Nevertheless, numerous other conditions can be associated with an elevated CA 125 level, including cirrhosis, pelvic inflammatory disease, peritonitis, pancreatitis, endometriosis, uterine leiomyomata and benign ovarian cysts. Therefore, though CA 125 is a useful marker to monitor an ovarian cancer patient’s disease status, it is not an effective biomarker for early detection. Serum CA 125 levels correlate with progression/remission of ovarian cancer and has been used clinically to monitor patients with epithelial ovarian carcinomas but one current study shows no

evidence of a survival benefit with early treatment of relapse on the basis of a raised CA125 concentration alone, therefore the value of regular measurement of CA125 in the follow-up is not proven [49].

Recent study compared multimodal screening (MMS group) considering CA 125 levels measurement and transvaginal ultrasound scan as a second-line test and annual screening with transvaginal ultrasound alone (UUS group). [50].This study shows that both screenings strategies are viable. In cooperation, on the initial screening, approximately half of the patients were detected in stage I/II in both groups. Specificity was higher in the MMS group and also less overdiagnosis of borderline tumors was found. Sensitivity was not statistically significant.

Some other recent studies describe a dual pathway in low-grade and high-grade cancer. They suggest that serous borderline tumors are the precursor of low-grade serous carcinomas and a high-grade serous carcinoma is developed from in situ alterations (“de novo”).

There are a lot of new candidate biomarkers being studied (over 200 candidate in ovarian cancer), but currently no validated to predict response or progression of ovarian cancer [29, 51, 52]. One of new tumor markers is a human epididymal secretory protein E4 (HE4). Some studies showed that if CA125 was combined with HE4, the prediction rate was higher, showing sensitivity for detecting malignant disease of 76.4% at a specificity of 95%. In other multicentre prospective study patients were classified as being at a high or low risk for ovarian cancer with a specificity of 75.0% and a sensitivity of 92.3% for post-menopausal patients, and a specificity and sensitivity of 74.8 and 76.5%, respectively, for pre-menopausal patients. Serum HE4 levels are a more potent tool than CA125 assay to differentiate EOC from ovarian endometriosis and pelvic inflammatory disease. The serum concentration of HE4 adds valuable information to CA125 in classifying patients with EOC versus other benign pelvic disease [101-103].

1.1.8. Therapy

The treatment options are based on radical and optimal debulking surgery [53] followed by a platinum-based combination chemotherapy [54, 55]. In ovarian cancer the prognosis is better when there is a minimal postoperative residual tumor mass [56] and this therapeutic management we tied to applies to every age, always under consideration of the comorbidities and the individual characteristics of each patient.

Surgery should consist of total abdominal hysterectomy and bilateral salpingo-oophorectomy with omentectomy and debulking of as much gross tumor as can carefully be executed. As primary cytoreductive surgery may not correct for biologic characteristics of the tumor, significant evidence indicates that the volume of disease left at the completion of the primary surgical procedure is associated to patient survival and prognosis. An advanced FIGO stage is frequently presented in elderly patients. Radical surgery with maximal tumor resection is associated with better survival also in elderly patients, but as well with several risk factors for higher perioperative morbility and mortality [56, 57]. Also in recidive ovarian cancer, an optimal debulking surgery showed better survival [58].

The options for intraperitoneal (IP) regimens are less likely to apply both practically (as far as inserting an IP catheter at the outset) and theoretically (aimed towards destroying microscopic disease in the peritoneal cavity). Some recent studies compared therapy with intravenous paclitaxel plus cisplatin with intraperitoneal treatment with cisplatin plus paclitaxel in patients with stage III ovarian cancer and no residual mass upper than 1 cm. They observed an improve progression-free and overall survival for IP chemotherapy but significantly worse quality of life [59].

The current gold-standard accepted chemotherapy for ovarian cancer is a platinum-taxane combination. The standard therapy for platinum sensitive patients is: Carboplatin AUC 6 and Paclitaxel 175mg/m2, 6 cycles.

American Gynecologic Oncology Group (GOG) in ASCO (American Society of Clinical Oncology) 2010 presented Phase III study GOG-218 results for Bevacizumab (vascular endothelial growth factor inhibitor) like a first line chemotherapy for ovarian cancer. Bevacizumab, added to carboplatin and paclitaxel therapy, like a first line therapy for ovarian cancer, improved progression free survival. In AGO-Ovar 11 (ICON7) and ASCO 2011 also was presented the randomized phase III study with Bevacizumab, where added to carboplatin and paclitaxel standard therapy improved progression free survival and both, progression free but not overall survival, in patients with high risk for disease progression [52, 60]. For platinum resistant patients (relapse before 6 months after chemotherapy with paclitaxel and carboplatin) the standard therapy is with Topotecan or pegylated liposomal Doxorubicin or Gemcitabin or Paclitaxel weekly, all of them with similar efficiency.

1.2. ROLE OF ADVANCED AGE IN OVARIAN CANCER

The risk of developing ovarian cancer increases exponentially with age and the incidence rates increases from less than 3 /100.000 in women under age 30, 15 to 16 /100.000 in the 40- to 44- year- old age group to a peak rate of 57 /100.000 in the 70- to 74-year-old age group [35]. Incidence of ovarian cancer rises in a linear mode from age 30 years to age 50 years and continues to increase, although at a slower rate, thereafter. The risk of developing epithelial ovarian cancer before age 30 years is remote; even in hereditary cancer families [45].

Gynecologic malignancies occur often among elderly women. Most ovarian cancers develop after menopause and the overall risk of malignancy of an adnexal mass is estimated to be 29 to 35% [61]. Half of all ovarian cancers are found in women above the age of 63 [62]. At any age, surgery is the principal treatment for these patients. Today, life expectancy has expanded and as a result, several risk factors for postoperative morbility and mortality are present in elderly patients [63]. Though, the physical and emotional stress that is required for surgical treatment is limited by patients' functional reserve,

decreasing with age and further deteriorating due to chronic illnesses. There is, consequently, reason to believe that perioperative morbidity and mortality rates may be increased in elderly patients. As a result, there is frequently reluctance to perform major surgical procedures in these patients [64].

The tumor residuals and stage after radical surgery are the most significant prognostic factors in patients with ovarian cancer [65].Today due to new developments in surgical techniques, anesthesiology and perioperative care the exclusion criteria for surgery in elderly patients has been reduced and the operative security has been increased [65]. Age and the surgeon's expertise are factors that influence the quality of surgical treatment of ovarian cancer. Because the incidence of ovarian cancer is highest in elderly women, and mostly in advanced stages, radical surgery is necessary in this population.

Numerous studies demand that elderly women with gynecologic malignancies are treated less aggressively than younger patients [66-68]. Alternatively, recent data demonstrates that elderly women, who do undergo radical pelvic surgery, tolerate it quite well [69-71]. Chronological age by itself should not be a contraindication for the treatment of elderly women with gynecological malignancy. Important prolongation of human life span has been achieved in industrial countries over the past half decade for patients with advanced ovarian cancer. Therefore, age distribution of the general population has undergone a dramatic shift, with an increase in the number of elderly people [65]. Nerveless, data about role of age in elderly patients are very limited due the fact that in most trials elderly patients are excluded for analysis.

The objective of this study was to analyzed the role of age on the therapy management and prognosis in patients with primary ovarian cancer (POC) and first recurrent ovarian cancer (FROC). Furthermore, we compared the complication rate, relapse rate, postoperative morbidity and mortality rates of elderly (≥65 years) and younger (<65 years) patients. We further investigated if elderly age is an independent prognostic factor for survival and if older patients (≥65 years) had other prognosis with the same tumor characteristics POC and FROC and the same applied operations methods than younger patients (≤65 years).

2. MATERIALS AND METHODS

In our study we separated the surgeries collective in two groups, primary situation and recurrence situation (in both curative and palliative aims were included). We studied the influence of age on the surgical and clinical outcome.

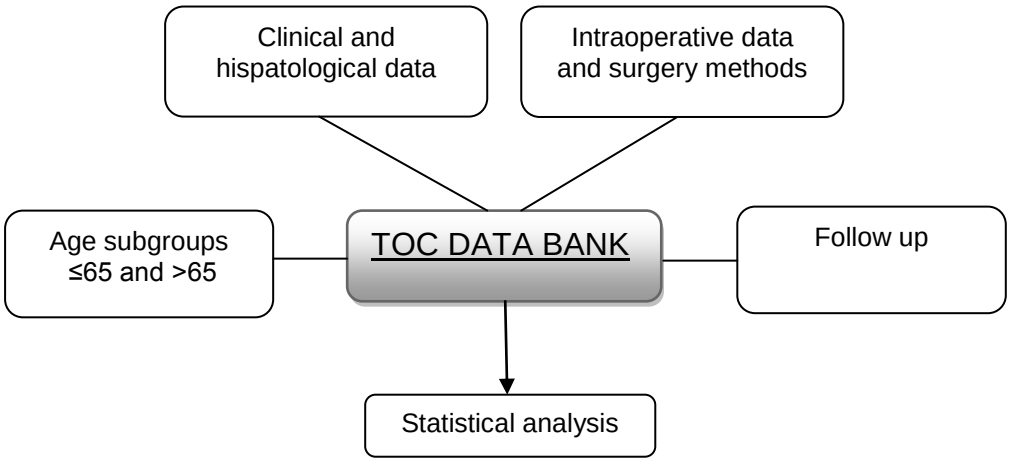

Fig. 1: Study design

1.3. PATIENTS SELECTION

The aim of the current study was to compare the rates of perioperative morbidity and mortality between elderly (>65 years of age) and younger (≤65 years of age) women, undergoing surgery due to either POC or FROC.

The study cohort consisted of 446 consecutive women between September 2000 and April 2006 year undergoing different operations methods (optimal versus nonoptimal debulking) due to POC and FROC realized in the clinic for Gynecology, Campus Virchow-Klinikum, Charité Berlin University.

Patients were divided to 269 (60.31%) patients with POC and 177 (39.69%) patients with FROC. Women having POC were further subdivided to those ≤65

years of age (208 women) and those >65 years of age (61 women). Women with FROC were subdivided to those ≤65 years of age (154 women) and those >65 years of age (23 women).

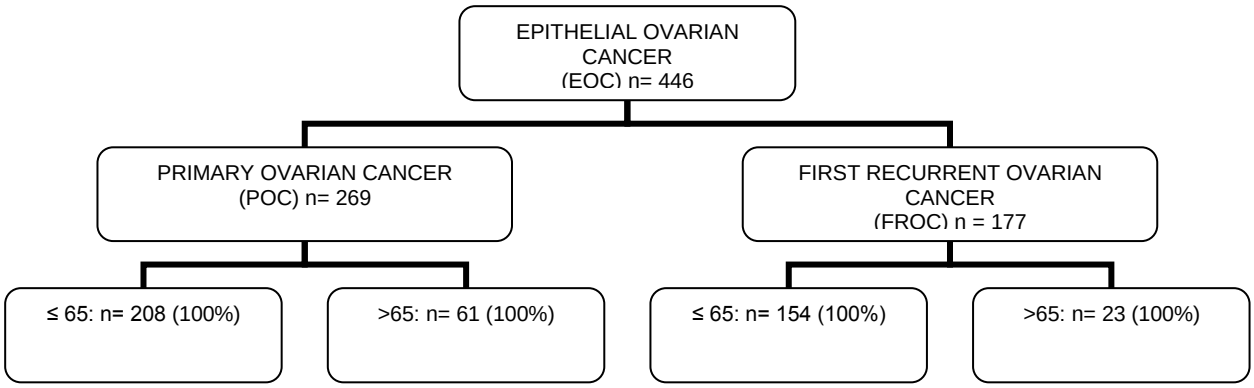

Fig. 2: Patients flow characteristics

1.4. COLLECT OF THE DATA

The approval of ethics commission of the Charité was present at the beginning of the study. All patients were informed on the day before the planned operation and gave their written agreement.

The criteria for inclusion were:

1. Written informed consent, which must be filled out before the therapeutic procedure
2. Patients with verified histopathological ovarian cancer, Fallopian tube cancer or peritoneal carcinoma.
3. Age greater than or equal to 18 years.

1.4.1. „IMO" (Intra operative Mapping of Ovarian Cancer) [72]

In the „One-Step-Documentation", the surgeon documents the tumor spread and the surgical methods executed in an operation procedure list. All the macroscopic spread of the organs should be described in this list as well as the volume of the operative ascites (if presence), the diameter of the post operative

tumor mass, the percent of the tumor debulking and a detailed description of the peritoneal carcinosis.
As well, in a documentation sheet which is an abdomen schema representation, all the tumor spread location at the time of the surgical procedure, the location of largest tumor mass as well as the location of the post operative tumor mass are noted.
The distribution of the tumor site in the schema in 9 fields (A1-3, B1-3, and C1-3) and in 3 levels respectively takes out an anatomical and topographical orientation criteria and it is used for the statistic coding of the above mentioned data.
The combined anatomical and topographical location of the wide spread disease is divided into the levels below:

- Level I: A1, B1, C1 small bowel (douglas, vagina, uterus, bladder /ureter, rectum, sigma)
- Level II: A2, B2, C2 intestine/mesentery (small and large intestine)
- Level III: A3, B3, C3 omentum majus, bursa omentalis, diaphragm, liver, spleen, gastric
- Retroperitoneal: Level IV: lymph nodes (pelvic und para aortal)
- As well as diffuse peritoneal carcinosis (gastric wall and pelvis wall)

There are three types of widespread:

1. localized type (2 levels and individual fields)
2. central type (3 levels and predominant in B1-3)
3. diffuse type (3 levels and ≥ 3 fields)

The location of tumor widespread, largest disease and postoperative tumor residual mass as well as tumor reduction of patients with primary or relapse ovarian cancer were at real time documented within an interview with the surgeon for about 5-10 minutes at the end of every surgery [72] and based on online-documentation tool.

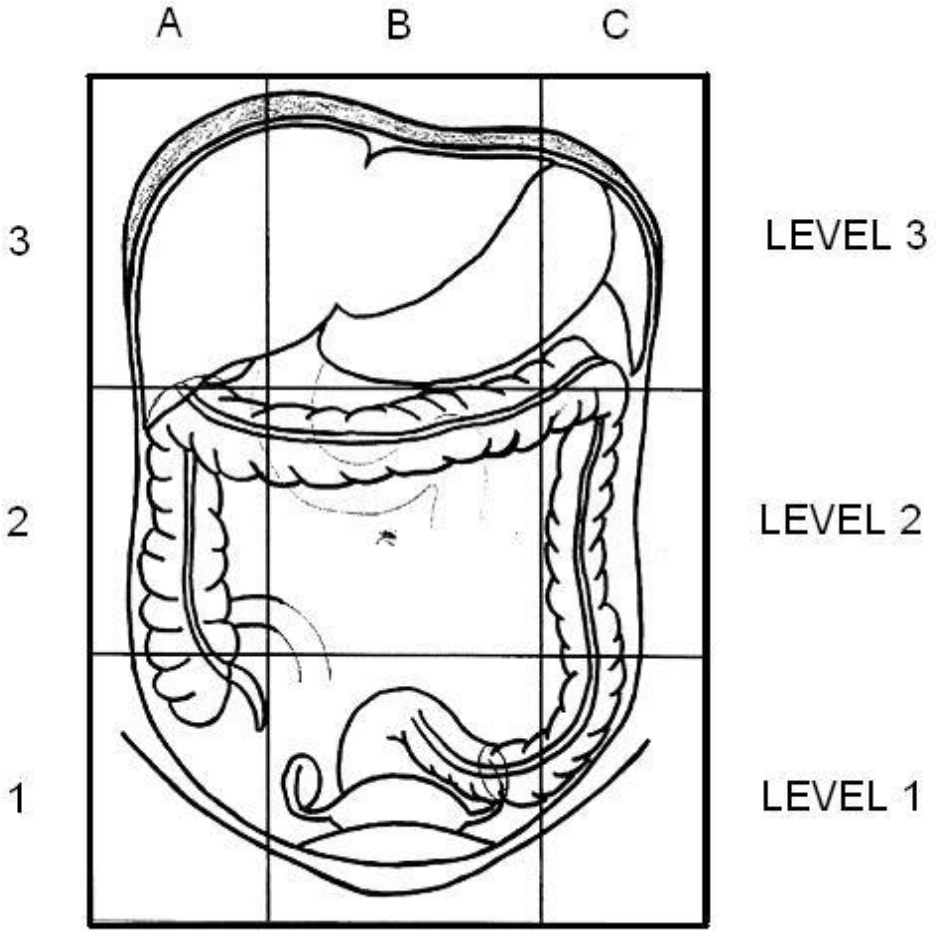

Fig 3: Documentation sheet

The data are processing and evaluating anonymously using the statistic programme SPSS (Version 16.0, SPSS Inc., Chicago, IL).The alternative answers is in dichotomies or in cordierites labels transformed and the open answers are categorised. In the table are coded all the extracted intra operative data, histo-pathological and clinical relevant information for individual patient.

Table 2.1 Intraoperative data: (at the time of surgical procedures)

1. Surgery date and place
2. Presence or absence of ascites (any, <500ml, >500ml)
3. Macroscopic tumor spread in levels: Level 1, Level 2, Level 3
4. Duration of surgery
5. Diffuse peritoneal carcinosis
6. Diameter of residual disease (residual tumor): macroscopically no residual tumor versus <1cm residual mass versus ≥1cm residual mass
7. Surgery procedures:

Hysterectomy	Partially Lung resection
Adnectomy	Partially gastric resection
Omentectomy	Splenectomy
Para-aortic +/- pelvic lymphadenectomy	Diaphragm resection
Appendectomy	Peritonectomy
Intestine resection (small and large)	Infrared contact coagulation
Partially pancreas resection	Bladder and ureter resection
Partially liver (±capsula) resection	Colostomy-Ileostomy

Table 2.2 Clinical and histo-pathological data

1. Age at first diagnostic
2. FIGO Stage
3. Grade of differentiation
4. Tumor histology
5. Second malignancy
6. Response or resistance to platinum chemotherapy (without specifying regimens or schedules)
7. Follow up (last contact April 2009)
8. Disease free survival
9. Postoperative overall survival

All follow-up information was obtained directly from the patient's medical records (MedVision), family members, or referring physician during a period of 100 months for POC and 90 months for FROC.
Surgical morbidity was defined as any potentially serious untoward event and surgical mortality as any death occurring within the first 30 postoperative days. 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 visit for all surviving patients to assure equivalent starting points from which the subsequent survival of patients could be compared. Disease free interval was also calculated in months from the date of surgery to the date of next relapse. Sensitivity to platinum-containing cytotoxic agents was according to international criteria (clinical, radiographic, and serologic disease free interval of at least 6 months after last cycle of primary adjuvant platinum-based chemotherapy, GOG).

1.5. DATA DOCUMENTATION: SPSS-DATE BANK

The most important purpose of our study is to analyze the influence of age on operative radicality, overall and disease free survival in patients with ovarian cancer, for these aim, and to collect all the possible information about the operative procedure itself, we developed a systematic surgical and histo-pathological tumor documentation instrument, the IMO (Intraoperative Mapping of Ovarian Cancer) [72]. It is a new instrument for a detailed and objective documentation of surgical and pathological results of patients with ovarian cancer and helps provide a more precise staging. Potentially this prospective documentation supports the development of SOP's (Standard Operating Procedures) and could be an efficient instrument of quality management.

1.6. STATISTICAL ANALYSIS

The results of the upraised operative and therapy data should be statistically analyzed, in relation to the age and in cohesion with the clinical prognostic factors as FIGO, grading, TNM-Stage, tumor rest etc.

For the data acquisition and statistic analysis SPSS for Windows software release was used 16, 0 (SPSS Inc., Chicago, IL, the USA, 2001). The following statistic analysis methods were used:

a) For the analysis of associations between age group and nominal scaled variables Chi Square tests and the Fisher´s exact test were used, for ordinal variables Kendall´s tau b and for continuous variables the U-Test of Mann-Whitney.

b) For the predictors of tumor removal odds ratios (OR) and 95% confidence intervals (95% CI) were computed using multivariate logistic regression analysis.

c) For progression free and overall survival, Cox regression analyses were performed. Primary the age groups were taken into account and additionally several other prognostic factors.

d) A p-value of < 0.05 was considered as statistically significant for all analyses.

1.7. STUDIES GROUPS

A total of 446 women meeting the study selection criteria were identified. Patients were divided as it's shown in Fig. 3 into patients with primary cancer 269 (60.31%) and patients with FROC 177 (39.69%). Age of the patients is the main factor to take into account in this study. Owing to this, both groups are subdivided in younger patients (≤65 years) and elderly patients (>65 years) to analysis if age is a prognostic factor in woman with ovarian cancer.

Percentage results shown in this study are referred to the four described subgroups. In this way, each one of the four subgroups is considered the 100%.

2. RESULTS

2.1. DESCRIPTIVE CROSS SECTIONAL ANALYSIS: PATIENT AND TUMOR CHARACTERISTICS

In Cross sectional descriptive analysis, we observed frequency and characteristics of the specific studies groups.

In the table 3.1 and 3.2 we can observe the patient´s characteristics which only at this table will be divided into 3 subgroups: ≤65 years, between 65 and 70 years and >70 years just for more detailed information.

In POC is documented the mortality rate as 41.3% in patients >65 years and in FROC 64.4% >65 years. In case of Follow up, patients with POC the median was 31.3 months and patients with FROC the median was 15.9 months with range 0-100 and 0-90 months, correspondingly.

We observed that there was no statistically significant difference between younger and elderly patients in the two groups, POC and FROC, regarding FIGO stage, histological type, grade, second malignancy and family history of ovarian cancer. In this cross sectional analysis, for patients with POC, tumor spread level II and III, ascites and relapse were significant. For a patients with FROC, only tumor spread level II was significant.

Table 3.1 Patient's characteristics

Primary ovarian cancer (POC) n=269

Age	**≤ 65 years** **66 – 70 years** **> 70 years**	**n=208 (77.3%)** **n=34 (12.6%)** **n=27 (10.0%)**		
		≤65 (100%)	**66-70 (100%)**	**>70 (100%)**
Grading				
	G1	18 (8.8)	3 (8.8)	4 (15.4)
	G2	75 (36.6)	16 (47.1)	10 (38.5)
	G3	112 (54.6)	15 (44.1)	12 (46.2)
		p=0.19		
FIGO stage				
	I	32 (15.4)	6 (17.6)	3 (11.1)
	II	12 (5.8)	1 (2.9)	1 (3.7)
	III	116 (55.8)	19 (55.9)	17 (63.0)
	IV	31 (14.9)	6 (17.6)	4 (14.8)
		p=0.99		
Histology				
	Serous	165 (80.1)	26 (78.8)	23 (88.5)
	Mucinous	10 (4.9)	3 (9.1)	1 (3.8)
	Endometrioid	17 (8.3)	1 (3.0)	2 (7.7)
	Clear Cell	5 (2.4)	1 (3.0)	0
	Unclassified tumors	2 (1.0)	0	0
	Unknown/other	7 (3.4)	2 (6.1)	0
		p=0.89		
Second malignancy				
	No second malignancy	181 (87.0)	31 (91.2)	19 (70.4)
	Breast cancer	11 (5.3)	1 (2.9)	5 (18.5)
	Endometrial cancer	6 (2.9)	1 (2.9)	1 (3.7)
	Colon cancer	2 (1.0)	0	1 (3.7)
	Cervix cancer	2 (1.0)	0	0
		p=0.36		
Tumor spread				
	Peritoneum	146 (70.2)	26 (76.5)	20 (74.1)
	Level I	202 (98.1)	34 (100)	26 (96.3)
		p=0.99		
	Level II	134 (65.0)	28 (82.4)	20 (74.1)
		p=0.04		
	Level III	85 (41.3)	20 (58.8)	15 (55.6)
		p=0.03		
Residual tumor				
	Tumor free	147 (70.7)	16 (47.1)	11 (40.7)
	≤1cm	38 (18.3)	10 (29.4)	10 (37)
	>1cm	23 (11.1)	8 (23.5)	6 (22.2)
		p>0.001		
Ascites				
	None	56 (27.3)	5 (14.8)	5 (18.5)
	≤500ml	92 (44.7)	13(38.2)	10 (37.0)
	>500ml	58 (28.3)	16 (47.1)	12 (44.4)
		p=0.01		
Relapse				
		112 (53.8)	16 (47.1)	8 (29.6)
		p=0.03		

Table 3.2 Patient's characteristics

First recidive ovarian cancer (FROC) n=177

Age	**≤ 65 years** **66 – 70 years** **> 70 years**	**n=154 (87.0%)** **n=15 (8.5%)** **n= 8 (4.5%)**		
		≤65 (100%)	**66-70 (100%)**	**>70 (100%)**
Grading				
	G1	9 (6.1)	0	0
	G2	44 (29.7)	6 (46.2)	3 (37.5)
	G3	95 (64.2)	7 (53.8)	5 (62.5)
		p=0.71		
FIGO stage				
	I	19 (12.7)	1 (7.7)	0
	II	5 (3.3)	0	1 (12.5)
	III	107 (71.3)	9 (69.2)	4 (50.0)
	IV	16 (10.7)	1(7.7)	2 (25.0)
		p=0.09		
Histology				
	Serous	128 (87.1)	14 (100)	7 (87.5)
	Mucinous	2 (1.4)	0	1 (12.5)
	Endometrioid	8 (5.4)	0	0
	Clear Cell	4 (2.7)	0	0
	Unclassified tumors	4 (2.7)	0	0
	Unknown/other	1 (0.7)	0	0
		p=0.59		
Second malignancy				
	No second malignancy	137 (89.0)	13 (86.7)	6 (75.0)
	Breast cancer	7 (4.5)	1 (6.7)	1 (12.5)
	Endometrial cancer	6 (3.9)	1 (6.7)	0
	Colon cancer	1 (0.6)	0	0
	Cervix cancer	1 (0.6)	0	0
		p=0.63		
Tumor spread				
	Peritoneum	126 (81.8)	10 (66.7)	6 (75.0)
	Level I	133 (87.5)	11 (78.6)	6 (75.0)
		p=0.27		
	Level II	123 (80.9)	8 (57.1)	8 (100)
		p=0.04		
	Level III	97 (63.8)	10 (71.4)	6 (75.0)
		p=0.38		
Residual tumor				
	Tumor free	67 (43.5)	9 (60)	3 (37.5)
	≤1cm	42 (27.3)	2 (13.3)	2 (25)
	>1cm	45 (29.2)	4 (26.7)	3 (37.5)
		p=0.70		
Ascites				
	None	71 (47.0)	5 (33.3)	5 (62.5)
	≤500ml	49 (32.5)	4 (26.7)	3 (37.5)
	>500ml	31 (20.5)	6 (40.0)	0
		p=0.24		
Relapse		75 (48.7)	7 (46.7)	2 (25.0)
		p=0.35		

Considering the tumor metastasis, “IMO” [72] results between tumor spread and age variable, the results were:

Table 3.3 Tumor spread POC

Tumor metastasis	**≤65 (%)**	**>65 (%)**	***p*-value**
pelvis	73 (35.1)	22 (36.1)	0.88
ovarium/uterus	177 (85.1)	53 (86.9)	0.84
bursa omentalis/pancreas	21 (10.1)	14 (23)	**0.02**
liver	25 (12.1)	8 (13.6)	0.82
gastric	12 (5.8)	5 (8.2)	0.55
diaphragm	67 (32.2)	25 (41)	0.22
small-large intestine	105 (50.5)	39 (63.9)	0.08
lung	1 (0.5)	1 (1.7)	0.39
spleen	10 (4.8)	7 (11.5)	0.07
mesentery	62 (29.8)	26 (42.6)	0.06

Table 3.4 Tumor spread FROC

Tumor metastasis	**≤65 (%)**	**>65 (%)**	***p*-value**
pelvis	79 (51.3)	7 (30.4)	0.07
ovarium/uterus	10 (6.5)	3 (13)	0.38
bursa omentalis/pancreas	32 (20.8)	5 (21.7)	1.0
liver	43 (28.9)	5 (21.7)	0.62
gastric	20 (13)	6 (26.1)	0.11
diaphragm	58 (37.7)	9 (39.1)	1.0
small-large intestine	115 (74.7)	15 (65.2)	0.32
lung	1 (0.7)	0 (0)	1.00
spleen	16 (10.4)	3 (13)	0.71
mesentery	79 (51.3)	11 (47.8)	0.82

The most frequent surgical procedures in patients with POC are also underwent in this study. 88.9% patients ≤65 years and 88.5% >65 years had adnectomies, 75.5% and 68.9% hysterectomies, omentectomies 94.7% and 86.9%, in that order.

As frequent surgery procedures in patients with FROC, but without significant difference, we have documented deperitonealisation and infrared coagulation: 58.0% ≤65 years and 43.5% >65 years, 66.7% ≤65 and 60.9% >65 years correspondingly.

Table 3.5 Operation procedure POC

OP procedure	**≤65 (%)**	**>65 (%)**	***p*-value**
hysterectomy	157 (75.5)	42 (68.9)	0.32
adnectomy	185 (88.9)	54 (88.5)	1.0
omentectomy	197 (94.7)	53 (86.9)	**0.047**
pelvic lymphadenectomy	164 (78.8)	26 (42.6)	**<0.001**
paraaortic lymphadenectomy	155 (74.5)	25 (41)	**<0.001**
appendectomy	104 (50)	28 (45.9)	0.66
bowel resection	66 (31.7)	24 (39.3)	0.28
colostoma or ileostoma	8 (3.9)	9 (15.3)	**<0.001**
liver part resection	2 (1)	1 (1.7)	0.53
gastric part resection	4 (1.9)	1 (1.7)	1.00
splenectomy	7 (3.4)	1 (1.7)	0.69
diaphragm part resection	12 (5.8)	0	0.07
bladder part resection	4 (1.9)	0	0.57
pancreas part resection	1 (0.5)	0	1.0
peritonectomy	111 (53.9)	27 (45.8)	0.46
infrared contact coagulation	99 (48.1)	27 (45.8)	0.77
curative	192 (92.3)	51 (83.6)	0.05

Table 3.6 Operation procedure FROC

OP procedure	**≤65 (%)**	**>65 (%)**	***p*-value**
hysterectomy	5 (3.2)	1 (4.3)	0.57
adnectomy	5 (3.2)	2 (8.7)	0.22
omentectomy	52 (33.8)	7 (30.4)	0.81
pelvic lymphadenectomy	31 (20.1)	5 (21.7)	0.79
paraaortic lymphadenectomy	33 (21.4)	6 (26.1)	0.59
appendectomy	21 (13.6)	2 (8.7)	0.74
bowel resection	86 (55.8)	11 (47.8)	0.51
Colostoma or ileostoma	21 (14)	21 (17.4)	0.74
liver part resection	6 (4)	0	1.0
gastric part resection	4 (2.7)	4 (17.4)	**0.01**
splenectomy	5 (3.3)	1 (4.3)	0.58
diaphragm part resection	8 (5.3)	1 (4.3)	1.0
bladder part resection	5 (3.3)	0	1.0
pancreas part resection	4 (2.7)	0	1.0
peritonectomy	87 (58)	10 (43.5)	0.26
infrared contact coagulation	100 (66.7)	14 (60.9)	0.64
curative	117 (76)	14 (60.9)	0.13

The influence of age on a time of surgery was not significant. In POC, patients under 65 years had median time of surgery of 240 minutes (95% confidence interval (CI) of 45 and 545 minutes). Patients over 65 years had a median time of surgery of 237 minutes (95% CI of 60 and 570 minutes). For patients with FROC under 65 years, median duration of surgery was 256 minutes and for patients over 65 years, 188 minutes (95% CI of 23 - 719 and 52 - 440 minutes correspondingly).

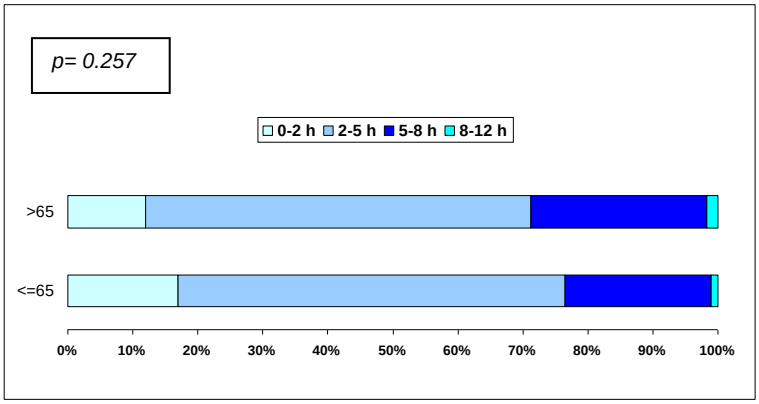

Fig. 3a: POC Duration time of surgery

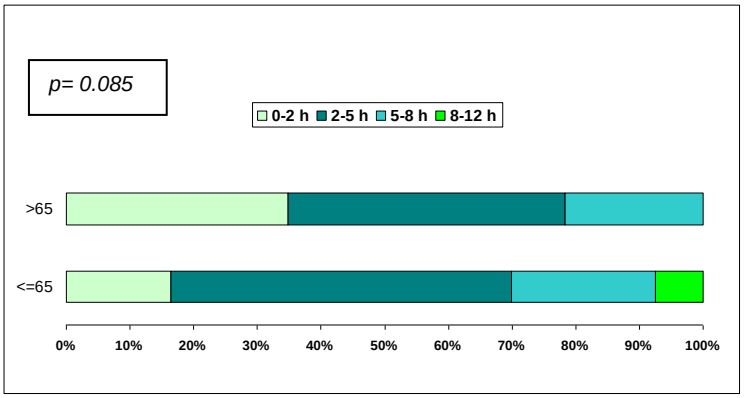

Fig. 3b: FROC Duration time of surgery

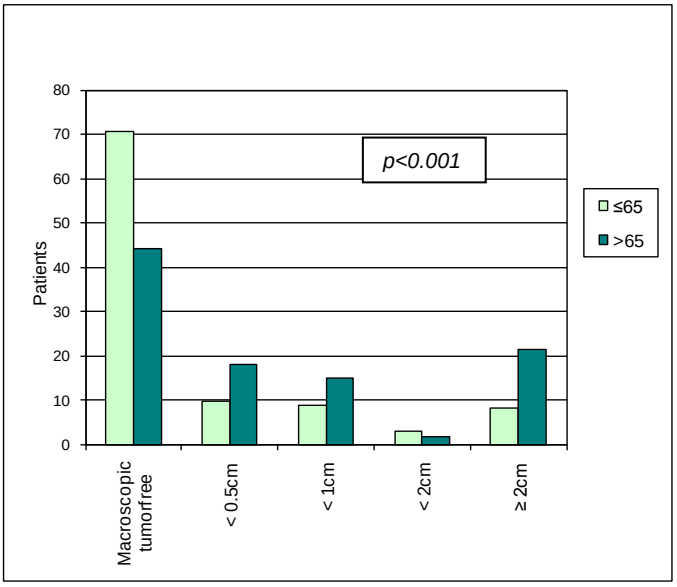

Fig 4a: POC Residual tumor

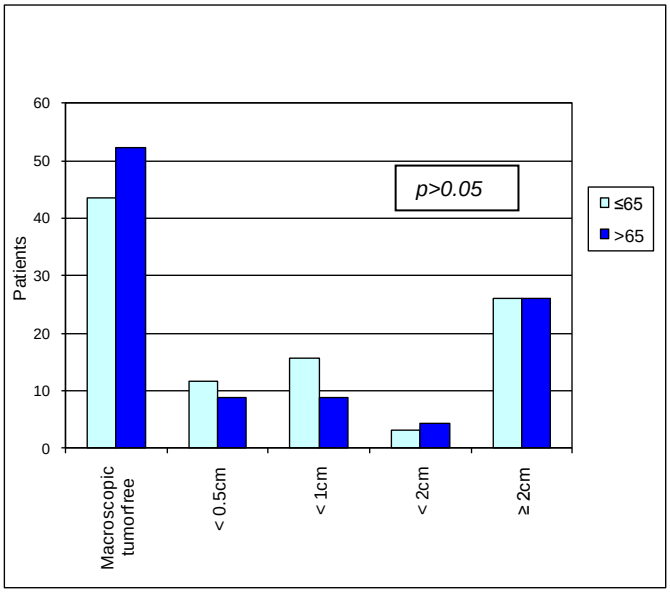

Fig 4b: FROC Residual tumor

Table 3.7 Postoperative complications POC

COMPLICATION	**≤65 (%)**	**>65 (%)**	***p*-value**
lung edema	0	2 (3.3)	**0.04**
pleural effusion	13 (6.3)	4 (6.7)	1.0
pneumothorax	2 (1)	0	1.0
neurological deficiency	9 (4.3)	4 (6.7)	0.49
hemorrhage	4 (1.9)	0	0.57
arrhythmia	3 (1.4)	3 (5)	0.12
multiorgan failure	2 (1)	5 (8.3)	**0.01**
fistula	7 (3.4)	7 (11.7)	**0.02**
Ileus	4 (1.9)	3 (5)	0.19
sepsis	3 (1.4)	3 (5)	0.12
infections	18 (8.7)	9 (15)	0.15
tromboemboly	10 (4.8)	1 (1.7)	0.46

Table 3.8 Postoperative complications FROC

COMPLICATION	**≤65 (%)**	**>65 (%)**	***p*-value**
lung edema	1 (0.7)	0	1.0
pleural effusion	9 (6)	3 (14.3)	0.16
pneumothorax	1 (0.7)	0	1.0
neurological deficiency	4 (2.6)	2 (9.5)	0.15
hemorrhage	5 (3.3)	1 (4.8)	0.54
arrhythmia	2 (1.3)	0	1.0
multiorgan failure	3 (2)	1 (4.8)	0.41
fistula	14 (9.3)	1 (4.8)	0.69
ileus	2 (1.3)	0	1.0
sepsis	5 (3.3)	0	1.0
infections	15 (9.9)	5 (23.8)	0.07
tromboemboly	10 (6.6)	1 (4.8)	1.0

There was only some significant difference in the rate of postoperative complications comparing the younger and the older patients with POC: lung edema, *p=0.049* (OR was not possible to calculate because a risk was of 3.3% for older patients in relation to risk of 0% for younger, multiorgan failure, *p=0.007* with OR 8.62 for elderly patients, and fistula, *p=0.019* with OR of 3.45 for older patients).

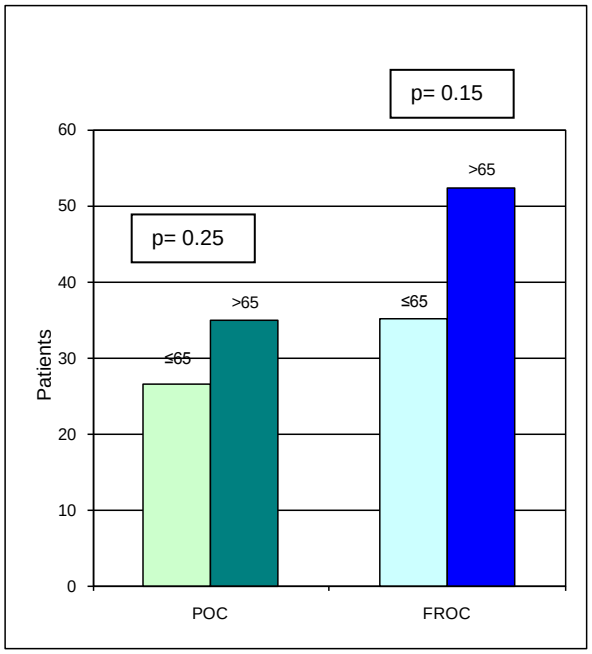

Fig. 5: Postoperative complications

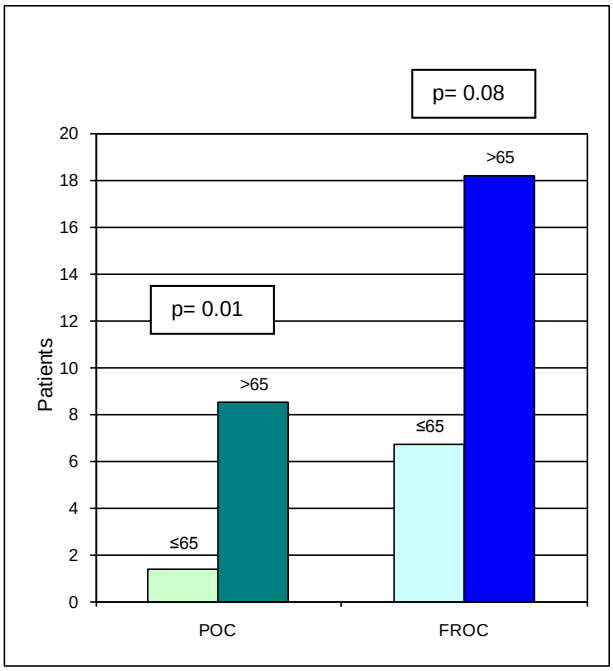

Fig. 6: Died due postoperative complications

Patients with POC ≤65 years, 26.6% experienced complications and >65 years, 35%. They died due this complications in 1.4% <65 years and in 8.5% >65 years. For patients with FROC, 35.1% experienced some complications ≤65 years and 52.4% >65 years, where 6.7% ≤65 and 18.2% >65 died (Fig 5 and 6).

There was a significant difference between both subgroups regardless to the platinum sensitive patients, *p=0.02*. The platinum sensitive patients by POC

were 78.6% and 59.5% in patients ≤65 and >65 years respectively. On the other hand, the platinum resistant patients were observed in 21.4% and 40.5% in patients ≤65 and >65 years in that order. In patients with FROC we didn´t find significant difference respect to the platinum sensitivity between elderly and younger patients, *p=1.0.* The platinum sensitive were 71.1% and 70.0% and platinum resistant 28.9% and 30% for patients ≤65 and >65 years correspondingly.

2.2. KAPLAN MEIER ANALYSIS: OVERALL AND DISEASE FREE SURVIVAL

The median follow up period in the present study was in patients with POC 31.3 months and patients with FROC the median was 15.9 months with a range 0-100 and 0-90 months, respectively.

In the bivariate survival analyses, cumulative survival curves were calculated according to the Kaplan-Meier method. We analyzed established prognostic predictors of patient survival to verify the representatively of our patient collective.

Estimated 5-years survival rates for POC:

For patients without residual tumor ≤65 years was of 60.7% and >65 years of 51.6% and for patients with residual tumor ≤65 years was of 19.8% and >65 years of 10.2%.

Estimated 3-years survival rates for FROC:

For patients without residual tumor ≤65 years was of 58.3% and >65 years of 40.7%. Patients with residual tumor ≤65 years, the 3-years survival rate was of 17.6% and >65 years was 0%.

2.2.1. POC Overall survival (OS) analysis

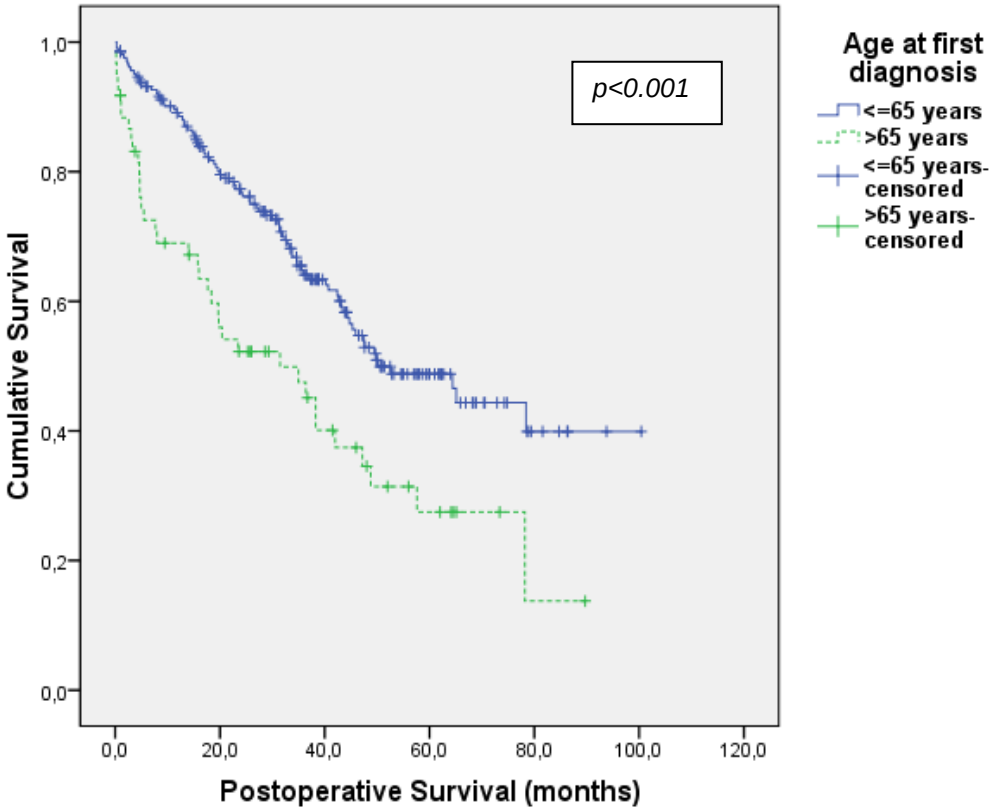

Fig. 7: POC postoperative survival- age at first diagnosis

Table 3.9 POC Overall survival (OS)

		Median	95% CI	*p*-value
age at first diagnosis 65	≤65	50.1	35.5-64.7	<0.001
	>65	31.5	15.9-47	
	total	47.5	40.8-54.2	

For elderly patients we had significant higher HR 1.99 with *p<0.001*.

Kaplan-Meier stratified survival analysis demonstrated a significant impact of clinicopathological prognostic parameters such as patient age (p<0.001), FIGO stage (p<0.001), tumor reduction (p<0.001) and postoperative residual mass (p<0.001) on patient survival with POC.

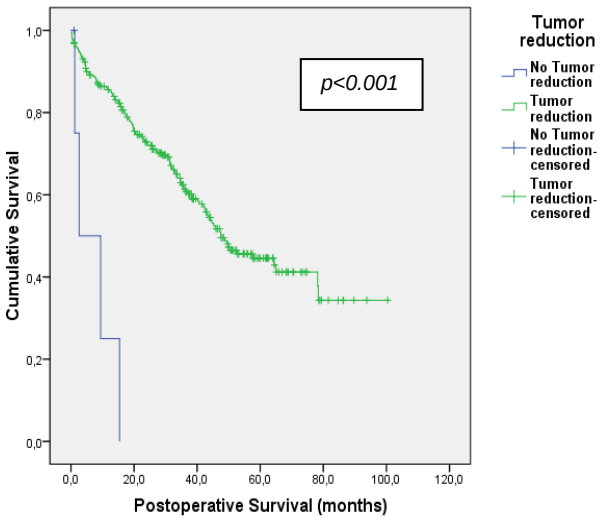

Fig 8: POC postoperative survival – tumor reduction vs.no tumor reduction

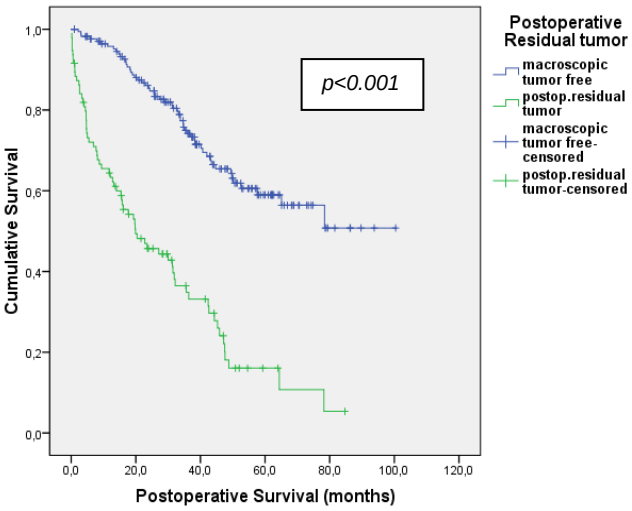

Fig 9: POC postoperative survival – macroscopic tumor free vs. postoperative residual tumor

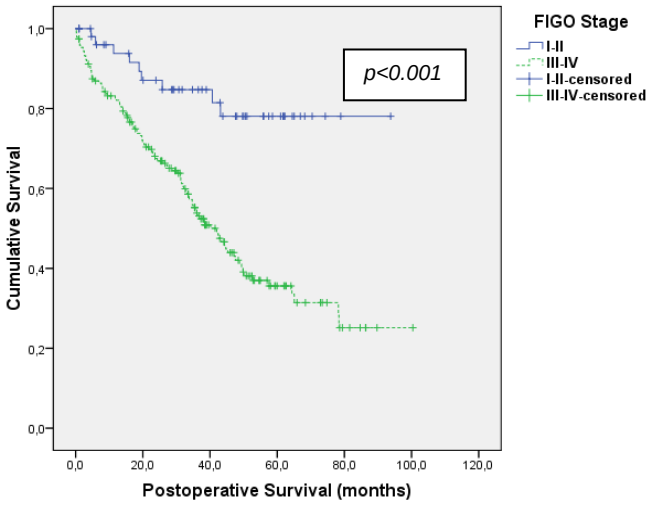

Fig 10: POC postoperative survival – FIGO stage

In detailed analysis of each group in function of age as a prognostic factor, we found a statistically significant difference between elderly and younger patients with POC upon to FIGO stage. For FIGO stage III and IV, higher age is one risk factor. Patients ≤65 years with FIGO III had a median survival of 49.8 months and >65 years 38.3 months, p=0.02. Also in FIGO IV stage, the median survival

was worses for elderly patients with only 3.3 months and 15.4 months for younger ones, $p<0.001$.

For serous tumors elderly age was also significant with median survival of only 31.5 months in comparison with 52.6 months for younger patients with serous tumors, $p<0.001$.

The median survival for elderly patients with level II affection was only 20.4 months and for younger 44.3 months, $p<0.001$. Regardless to level III affection, the NO affection of level III was significant for elderly patients with median survival of 78.2 months, $p=0.02$.

Patients with affection of the peritoneum, the median survival was worse for elderly patients with 19.8 months compared with 44.7 months for younger patients, $p<0.001$.

We noticed that elderly patients with residual tumor after surgery had a significant poor median survival of 14 months compared to younger with a median survival of 31.3 months, $p=0.03$. In patients with POC and platinum sensitive or resistant, age was not a significant risk factor, $p=0.3$ and $p=0.5$, respectively.

Table 4.1 POC Overall survival (OS)- HR age >65 in next variables:

	HR	95% CI	*p*-value
age >65 years	**2**	1.3-2.9	**<0.001**
FIGO I+II	1.3	0.2-6.5	0.71
FIGO III	**1.7**	1.1-2.9	**0.02**
FIGO IV	**3.4**	1.5-7.6	**0.002**
serous tumors	**2.3**	1.5-3.6	**<0.001**
other no-serous	0.9	0.3-2.8	0.92
level II- YES	**1.9**	1.3-3	**0.001**
level II- NO	0.9	0.2-3.2	0.94
level III- YES	1.5	0.9-2.4	0.08
level III- NO	**2.2**	1.1-4.2	**0.02**
peritoneal carcinomatosis-YES	**2.1**	1.4-3.1	**0.001**
peritoneal carcinomatosis-NO	1.1	0.3-3.7	0.91
ascites none	2.7	0.9-8.2	0.09
ascites ≤500ml	**1.9**	1.01-3.5	**0.047**
ascites >500ml	1.5	0.8-2.6	0.16
tumor free (macroscopic)	1.1	0.6-2.4	0.68
residual tumor	**1.7**	1-2.7	**0.03**
platinum sensitive	1.4	0.7-2.8	0.31
platinum resistant	1.2	0.6-2.4	0.52

For patients with FIGO stage III and IV regardless to residual tumor, we observed next results:

Table 4.2 POC Overall survival (OS) FIGO stage III and IV regardless to residual tumor

		FIGO III			FIGO IV		
>65 years		HR	95% CI	*p*-value	HR	95% CI	*p*-value
tumor free		1.3	0.6-2.8	0.52	-	-	-
residual tumor		1.6	0.8-3.1	0.17	1.5	0.6-3.4	0.34
		OS months	95% CI	*p*-value	OS months	95% CI	*p*-value
tumor free	≤65	65.1	40.4-89.8	0.52	-	-	-
	>65	42	12.6-71.4				
residual tumor	≤65	42.4	27.1-57.7	0.17	4.6	0-10.2	0.33
	>65	23.5	3.3-43.7		3.3	0-8.4	

The median survival for elderly patients with FIGO stage III and tumor free surgery was 42 months and for younger 65.1 months. Patients >65 years with residual tumor after surgery had 23.5 months of OS and ≤65 years 42.4 months. In case of FIGO stage IV, none patients were free operated. OS for elderly patients with residual tumor was 3.3 months and younger 4.6 months. We found no statistically significant differences between age's groups.

2.2.2. POC Disease free survival (DFS) analysis

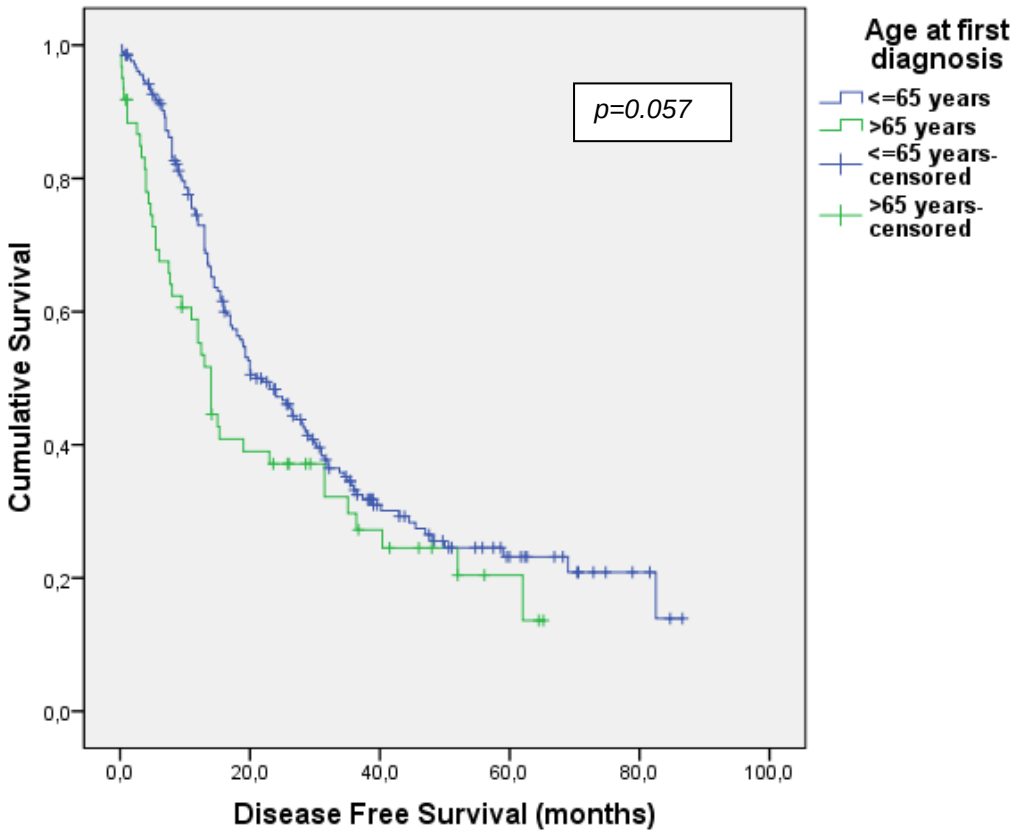

Fig. 11: POC disease free survival- age at first diagnosis

Table 4.3 POC Disease free survival

		Median	95% CI	*p*-value
age at first diagnosis 65	<=65	21.0	16.1-25.9	0.06
	>65	14.0	11.6-16.4	
	total	19.3	14.8-23.8	

Table 4.4 POC Disease free survival (DFS)- HR age >65 in next variables:

	HR	95% CI	*p*-value
age >65 years	1.4	0.9-1.9	0.06
FIGO I+II	0.7	0.1-3.1	0.63
FIGO III	1.4	0.9-2.1	0.14
FIGO IV	**4**	1.8-9.1	**0.001**
serous tumors	**1.6**	1.1-2.3	**0.01**
other no-serous	0.7	0.2-2.1	0.56
level II- YES	**1.6**	1.1-2.2	**0.02**
level II- NO	0.4	0.1-1.4	0.17
level III- YES	1.1	0.7-1.6	0.75
level III- NO	1.3	0.7-2.4	0.33
ascites none	1.05	0.4-2.7	0.91
ascites ≤500ml	1.3	0.7-2.4	0.31
ascites >500ml	1.1	0.7-1.9	0.65
peritoneal carcinomatosis-YES	**1.6**	1.1-2.3	**0.01**
peritoneal carcinomatosis-NO	0.6	0.2-1.8	0.37
tumor free (macroscopic)	0.8	0.5-1.5	0.57
residual tumor	1.3	0.8-2.1	0.22

Only for patients with FIGO stage IV, elderly age was a significant risk factor with median DSF of 3.3 months and for younger patients were 11 months. The results were similar for serous tumors, were elderly patients had significantly worse DFS 12.5 months respect to younger patients who had 20.1 months.

Elderly age seems to be a significant risk factor also in level II tumor spread with DFS of 12 months where younger patients presented 17 months of DFS and 12 and 17.3 months for elderly and younger patients, correspondingly, with peritoneal carcinomatosis. Age was not significant risk factor in patients with residual tumor or macroscopic tumor free surgery.

Table 4.5 POC Disease free survival (DFS) FIGO stage III and IV regardless to residual tumor

		FIGO III			**FIGO IV**		
>65 years		HR	95% CI	*p*-value	HR	95% CI	*p*-value
tumor free		1.2	0.6-2.2	0.58	-	-	-
residual tumor		1.1	0.6-2.1	0.64	1.9	0.8-4.4	0.15
		DFS months	95% CI	*p*-value	DFS months	95% CI	*p*-value
tumor free	≤65	23.1	14.6-31.6	0.58	16	0-37.2	-
	>65	31.5	8.6-54.3		-	-	
residual tumor	≤65	17	12.6-21.3	0.64	4.6	2.2-6.9	0.14
	>65	12.5	6.9-18		3.3	0-8.4	

We didn´t found patients >65 years and FIGO stage IV without residual tumor. We found no statistically significant differences between age's groups.

2.2.3. FROC Overall survival (OS) analysis

In contrast to POC, for FROC age was not significant risk factor for overall survival.

Elderly age was a significant risk factor in patients with level II tumor spread and patients with residual tumor. Patients with level II tumor spread had 7.7 months of OS in comparison with younger patients with 18.9 months. Similar results we found in elderly patients with residual tumor with only 3.4 months of OS in comparison with 12.4 months for younger patients.

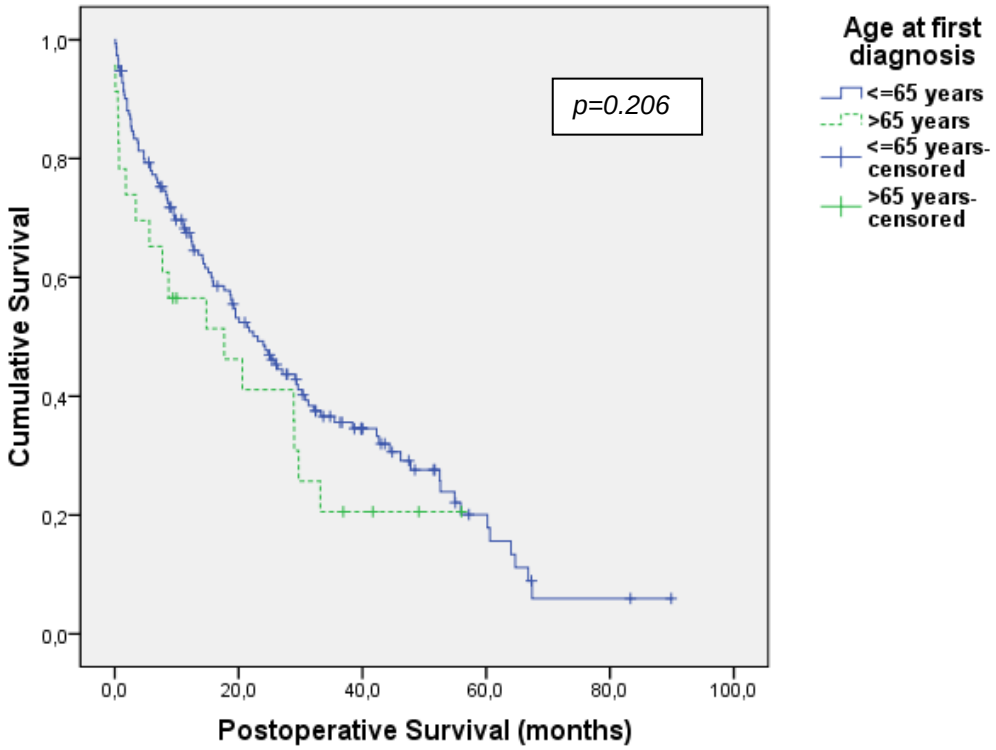

Fig. 12: FROC postoperative survival-age at first diagnosis

Table 4.6 FROC Overall survival (OS)- HR age >65 in next variables:

	HR	95% CI	*p*-value
age >65 years	1.4	0.8-2.3	0.21
serous tumors	1.2	0.7-2.1	0.52
other no-serous	Only 1 patient >65 years had no serous histology type		
level II- YES	**2**	1.1-3.5	**0.02**
level II- NO	0.6	0.1-2.7	0.52
level III- YES	1.6	0.9-2.9	0.11
level III- NO	0.7	0.2-2.2	0.49
ascites none	1.9	0.8-4.6	0.14
ascites ≤500ml	0.95	0.4-2.5	0.92
ascites >500ml	0.8	0.3-2	0.56
peritoneal carcinomatosis- YES	1.7	0.9-3	0.08
peritoneal carcinomatosis- NO	1.3	0.4-4.2	0.59
tumor free (macroscopic)	1.2	0.5-3	0.61
residual tumor	**2.3**	1.2-4.5	**0.01**
platinum sensitive	1.3	0.6-2.7	0.44
platinum resistant	1.9	0.8-4.7	0.13

Table 4.7 FROC Overall survival (OS) according to diagnosis of first recidive and platinum response

Time interval from first diagnosis to first relapse		**N**	**OS months**	**95% CI**	***p*-value**
≤6 months	≤65	7	5.8	3.2-8.4	**0.01**
	>65	1	0	-	
6-12 months	≤65	27	9.5	4-14.9	0.59
	>65	7	8.7	6.1-11.3	
≥12 months	≤65	119	27.1	21.5-32.7	0.45
	>65	15	20.6	2.4-38.8	

Platinum response		**N**	**OS months**	**95% CI**	***p*-value**
platinum sensitive	≤65	106	30.8	20.8-40.8	0.44
	>65	14	29	10.8-47.2	
platinum resistant	≤65	42	8.8	7.3-10.3	0.12
	>65	6	3.4	0-9.5	
no platinum based	≤65	4	1.6	0.3-2.9	0.65
chemo *	>65	3	0.6	0-1.4	

*no platinum based chemotherapy was administered

Table 4.8 FROC Overall survival (OS) according to platinum response regardless to residual tumor

		Platinum sensitive			**Platinum resistant**		
		OS months	95% CI	*p*-value	OS months	95% CI	*p*-value
tumor free	≤65	46.2	31.2-61.2	0.27	23.1	0-37.2	-
	>65	29.7	11.6-47.8		-	-	
residual tumor	≤65	19.5	13.4-25.6	0.16	8.3	4.1-12.4	0.44
	>65	8.7	0-21.5		3.4	0-9.5	

	Platinum sensitive			**Platinum resistant**		
>65 years	HR	95% CI	*p*-value	HR	95% CI	*p*-value
tumor free	1.6	0.7-4.05	0.27	-	-	-
residual tumor	2.3	0.7-7.5	0.17	1.4	0.6-3.5	0.45

2.2.4.FROC Disease free survival analysis

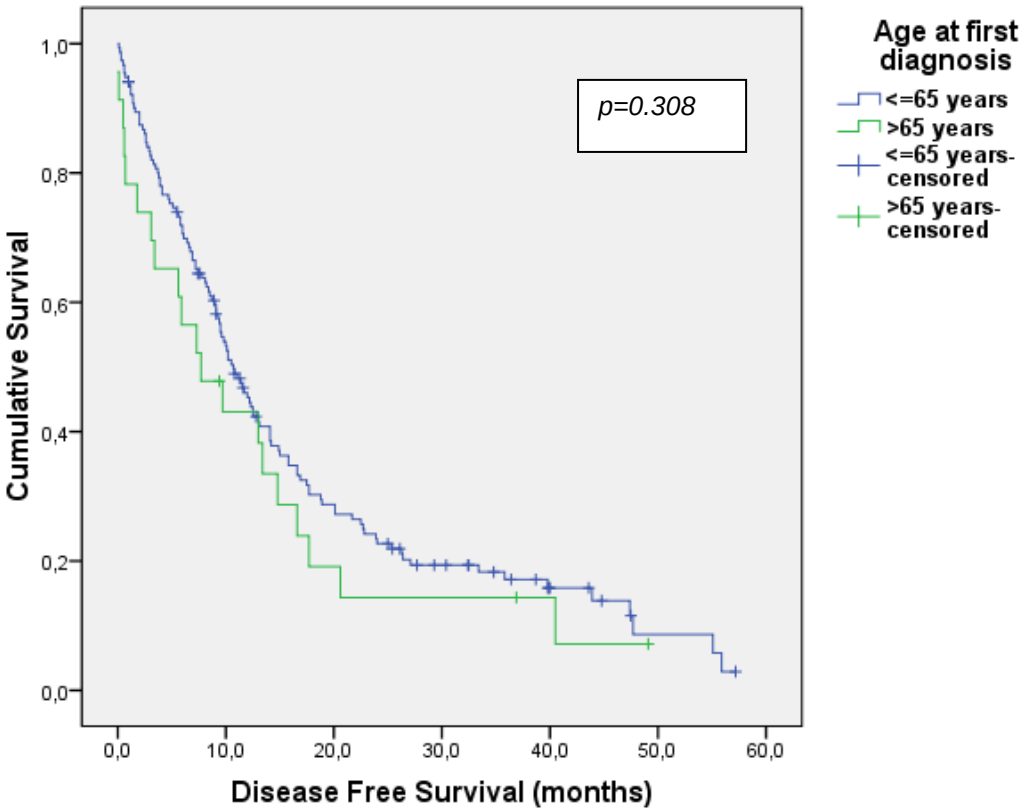

Fig. 13: FROC disease free survival- age at first diagnosis

Table 4.9 FROC Disease free survival

		Median		95% CI	*p*-value
age at first diagnosis 65	≤65	10.7	8.669	12.731	0.31
	>65	7.7	1.944	13.456	
	total	10.5	8.618	12.382	

Table 5.1 FROC Disease free survival (DFS)- HR age >65 in next variables:

	HR	95% CI	*p*-value
age >65 years	1.3	0.8-2	0.31
serous tumors	1.2	0.7-1.9	0.50
other no-serous	Only 1 patient >65 years had no serous histology type		
level II- YES	1.5	0.9-2.7	0.11
level II- NO	0.8	0.2-2.4	0.70
level III- YES	1.6	0.9-2.9	0.08
level III- NO	0.8	0.3-2	0.62
ascites none	1.5	0.7-3.1	0.32
ascites ≤500ml	0.98	0.4-2.3	0.97
ascites >500ml	1.1	0.5-2.8	0.76
peritoneal carcinomatosis- YES	1.4	0.8-2.4	0.21
peritoneal carcinomatosis- NO	1.3	0.5-3.7	0.55
tumor free (macroscopic)	1.1	0.5-2.2	0.85
residual tumor	**2.7**	1.4-5.1	**0.003**
platinum sensitive	1.2	0.6-2.2	0.58
platinum resistant	2.2	0.9-5.3	0.08

Only for residual tumor significant association was found regardless to the age. Elderly patients had only 3.4 months of DFS in comparison to the younger patients with 8.2 months.

Table 5.2 FROC Disease free survival (DFS) according to diagnosis of first recidive and platinum response

Time interval from first diagnosis to first relapse		**N**	**DFS months**	**95% CI**	***p*-value**
≤6 months	≤65	7	5.8	3.2-8.4	**0.01**
	>65	1	0	-	
6-12 months	≤65	27	6.7	3.5-9.9	0.97
	>65	7	7.3	3.7-10.9	
≥12 months	≤65	119	12.5	10-14.95	0.47
	>65	15	13.4	0-30.6	

Platinum response		**N**	**DFS months**	**95% CI**	***p*-value**
platinum sensitive	≤65	105	14.1	11.6-16.6	0.58
	>65	14	13.4	10.3-16.5	
platinum resistant	≤65	43	5.8	4.5-7.1	0.08
	>65	6	3.4	0-9.5	
no platinum based chemo *	≤65	4	1.6	0.3-2.9	0.65
	>65	3	0.6	0-1.4	

* no platinum based chemotherapy was administered

Table 5.3 FROC Disease free survival (DFS) according to platinum response regardless to residual tumor

		Platinum sensitive			**Platinum resistant**		
		DFS months	95% CI	*p*-value	DFS months	95% CI	*p*-value
tumor free	≤65	17.5	10.3-24.6	0.55	11.5	0-34.8	-
	>65	16.6	11.2-21.9		-	-	
residual tumor	≤65	12.2	9.2-15.2	0.15	5.8	4.4-7.1	0.15
	>65	7.3	0-17.9		3.4	0-9.5	

	Platinum sensitive			**Platinum resistant**		
>65 years	HR	95% CI	*p*-value	HR	95% CI	*p*-value
tumor free	1.2	0.6-2.6	0.55	-	-	-
residual tumor	2.3	0.7-7.8	0.16	1.9	0.8-4.6	0.16

2.3. MULTIVARIATE ANALYSIS FOR OVERALL AND DISEASE FREE SURVIVAL

In order to evaluate all factors that were significant in the bivariable analysis, to confirm the Kaplan-Meier analysis and to adjust for confounding factors, we further analyzed the data using the Cox proportional hazards regression. A multivariate progression analysis based on the Cox proportional hazard model was performed to test the independent value of each parameter predicting overall survival and disease free survival.

Table 5.4 Cox Regression Variable

Variable	Reference Category
Age 65 (Age at first diagnosis 65)	≤65
Small-or Large intestinal metastasis	No
Perit (Peritoneal carcinosis)	No
Level II (spread Level II: extra pelvic)	No
Level III (spread Level III :extra pelvic)	No
Ascites	No ascites
Figo groups (FIGO Stage Groups)	I-II
Histology groups	Serous
Stoma (anus preater or ileostomy or jejunostomy)	No
Residual tumor	Macroscopic free
Respond (Platinum sensitive)	Platinum sensitve

The variable level I was excluded because only 3 patients with POC showed no tumor widespread to level I.

2.3.1. POC POSTOPERATIVE OVERALL SURVIVAL ANALYSIS

Table 5.5 POC Overall survival (OS)

	HR	95% CI	*p*-value
age >65	2.01	1.3-3.05	**0.001**

The variable age appears to be a risk factor for OS. After progression analysis and after adjusting for confounding factors, independent significance of each parameter predicting overall survival was as follows:

	HR	95% CI	*p*-value
age >65	0.9	0.6-1.5	0.69
small-or large intestinal metastasis	0.7	0.4-1.2	0.25
peritoneal carcinomatosis	1.1	0.4-2.6	0.86
level II affection	1.1	0.5-2.1	0.84
level III affection	1.2	0.7-2	0.43
ascites			0.53
ascites ≤500ml	0.98	0.5-1.8	0.96
ascites >500ml	1.3	0.6-2.5	0.45
FIGO III-IV	1.9	0.7-5.3	0.18
histology no serous	1.2	0.7-2.1	0.49
colostomy or ileostomy	**3.4**	1.7-6.7	**<0.001**
residual tumor			**<0.001**
residual tumor ≤1cm	**2.3**	1.3-3.9	**0.003**
residual tumor >1cm	**6.7**	3.6-12.5	**<0.001**
platinum response			**<0.001**
platinum resistant	**4.5**	2.8-7.4	**<0.001**
no platinum based chemo*	**6.1**	3.3-11.1	**<0.001**

*no platinum based chemotherapy was administered

After adjusting all significant variables, Cox analysis shows, in table 5.5, that age is not a significant prognostic factor (HR 0.9, p=0.7). But we saw a significant increased risk of dying for patients with residual tumor compared with patients with complete tumor reduction. Colo/ileostomy and platinum resistant

patients or no platinum based chemotherapy applied had also statistically significant higher risk for dying. All other variables were not statistically significant. These effects are independent of all other recorded variables.

2.3.2. POC DISEASE FREE SURVIVAL ANALYSIS

Table 5.6 POC Disease free survival

	HR	95% CI	*p*-value
age >65	1.5	1.03-2.1	**0.03**

After adjusting all significant variables:

	HR	95% CI	*p*-value
age >65	1.01	0.7-1.5	0.92
small-or large intestinal metastasis	0.9	0.6-1.4	0.67
peritoneal carcinomatosis	1.4	0.8-2.6	0.22
level II affection	1.1	0.7-1.8	0.68
level III affection	1.3	0.9-2.02	0.16
ascites			0.05
ascites ≤500ml	0.6	0.4-1	0.52
ascites >500ml	0.96	0.6-1.6	0.87
FIGO III-IV	**2.2**	1.1-4.4	**0.02**
histology no serous	0.9	0.5-1.5	0.67
colostomy or ileostomy	1.6	0.9-2.8	0.12
residual tumor			**<0.001**
residual tumor ≤1cm	**1.6**	1.05-2.5	**0.03**
residual tumor >1cm	**3.3**	1.9-5-5	**<0.001**

We observed that FIGO stage III-IV had much higher risk of relapse compared with patients with FIGO stage I-II. As well patients with residual tumor ≤1cm or >1cm had an increased risk of recurrence.

2.3.3. FROC POSTOPERATIVE SURVIVAL ANALYSIS

Table 5.7 FROC Overall survival

	HR	95% CI	*p*-value
age >65	1.2	0.7-2.2	0.53

After adjusting all significant variables:

	HR	95% CI	*p*-value
age >65	1.7	0.8-3.5	0.14
small-or large intestinal metastasis	0.9	0.5-1.6	0.75
peritoneal carcinomatosis	1.6	0.7-3.7	0.29
level I affection	**0.4****	0.2-0.9	**0.03**
level II affection	1.4	0.6-2.9	0.42
level III affection	**0.5****	0.2-0.9	**0.02**
ascites			**<0.001**
ascites ≤500ml	**2.9**	1.7-5.05	**<0.001**
ascites >500ml	**4.6**	2.3-8.9	**<0.001**
FIGO III-IV	0.8	0.4-1.6	0.47
histology no serous	1.1	0.5-2.4	0.81
colostomy or ileostomy	**2.1**	1.1-3.9	**0.02**
residual tumor			**0.001**
residual tumor ≤1cm	**2.5**	1.4-4.4	**0.002**
residual tumor >1cm	**2.8**	1.5-5.1	**0.001**
platinum response			**<0.001**
platinum resistant	**2.6**	1.6-4.1	**<0.001**
no platinum based chemo*	**6.1**	1.6-23.2	**0.01**

*no platinum based chemotherapy was administered
**statistically significant protective factor

After inclusion of all significant variables in table 5.7, similar effects remain significant in patients with FROC. Patients with platinum resistant or no platinum based chemotherapy are associated with an increased risk of dying compared to patients with platinum response. Also patients with residual tumor, ascites or colo/ileostomy had a significantly increased risk of dying in the next moment. In

addition, patients with level I and III affection had a significantly lower risk of dying. The effects are independent of all other recorded variables.

2.3.4. FROC DISEASE FREE SURVIVAL ANALYSIS

Table 5.8 FROC Disease free survival

	HR	95% CI	*p*-value
age >65	1.3	0.7-2.2	0.38

After adjusting all significant variables:

	HR	95% CI	*p*-value
age >65	1.6	0.9-3.1	0.13
small-or large intestinal metastasis	0.6	0.4-1.2	0.14
peritoneal carcinomatosis	1.4	0.7-2.9	0.35
level I affection	0.8	0.4-1.6	0.53
level II affection	1.3	0.7-2.4	0.44
level III affection	0.9	0.5-1.4	0.58
ascites			**0.003**
ascites ≤500ml	**2**	1.2-3.2	**0.004**
ascites >500ml	**2.4**	1.3-4.3	**0.003**
FIGO III-IV	1.4	0.7-2.7	0.38
histology no serous	1.1	0.5-2.1	0.86
colostomy or ileostomy	1.6	0.9-2.8	0.13
residual tumor			**0.04**
residual tumor ≤1cm	**2**	1.1-3.4	**0.01**
residual tumor >1cm	1.6	0.9-2.7	0.14
platinum response			**<0.001**
platinum resistant	**2.3**	1.5-3.5	**<0.001**
no platinum based chemo*	**6.8**	1.8-24.8	**0.004**

*no platinum based chemotherapy was administered

Variable ascites is significantly associated with disease free survival. Patients with ascites >500ml had a fast two and half fold risk to relapse and patients with ascites <500 ml double risk compared to patients without ascites. Patients with incomplete tumor reduction (residual tumor ≤1cm) had also an increased risk of recurrence.

3. DISCUSSION AND CONCLUSION

Epithelial ovarian cancer (EOC) is principally a disease in postmenopausal women with peak incidences in the sixth to seventh decades of life. The median age at diagnosis is 63 [73] and about half of all ovarian cancers occur in women over the age of 65 [74-76]. The incidence in the younger woman is low, only 3-17% of all EOC patients are <40 years [77-81]. Because of the inevitable aging of the women population, EOC affects older women. The gynecological oncologists are increasingly called upon to provide optimal cancer management in elderly patients comparable to the care provided for younger women [82].

The aim of the present study was to analyze the clinical-pathologic prognostic factors, perioperative morbidity and mortality rates after ovarian cancer surgery in elderly women (>65 years) comparing with the younger ones (≤65 years). This study examines parameters such as FIGO stage, histology, tumor spread, postoperative residual tumor and platinum response in relation with postoperative morbidity and mortality in elderly as compared to younger women undergoing ovarian cancer surgery in POC and FROC.

Some studies evalued the implications of aging in surgical oncology, speak of prejudice and discrimination on the part of health care providers to any person who has attained a chronological age that the social group defines as “old” [82]. Then, we face an ethical dilemma presents in the clinical day when a physician is called to reach a labile counterbalance between chronogical and biological age [83] and between overtreatment and undertreatment in elderly EOC patients.

We tried to determine if age is an independent prognostic factor for survival and patient’s aptitude to tolerate the same surgical treatment under the same conditions of disease (eg. histology, FIGO stage). In our analysis on POC and FROC we made two subgroups, younger woman ≤65 years and elderly woman >65 years.

It is essential to remark that our results showed that age by itself is a poor predicting factor for surgical risk and there is no statistically significant

increasing risk for worse OS and DFS with increasing age. We didn't observe more incidence in elderly patients regardless to postoperative complications, but we observed significantly more died due complications in patients over 65 years with POC.

The prognostic significance of age has been investigated in EOC [45, 62, 67, 68, 70, 71, 81, 84, 85, 86, 99]. There have been data sets suggesting that older age is a negative prognostic factor and that in general, younger patients have been diagnosed with lower grade and earlier stage tumors [57, 87, 88]. The younger patients have also been treated more aggressively and have carried better prognosis in comparison to the older patients [57, 68, 84, 85]. We can observe more frequent residual tumor in elderly patients than in younger ones, probably because of higher stage at diagnosis and comorbid frequent conditions. Also in our study, patients over 65 years had more incidences of colostomy and ileostomy because of frequent anastomosis insufficiency. We saw in multivariable survival analysis that colo- / ileostomy is a significant risk factor for OS in patients with POC and FROC, but not for DFS. Some studies reported that younger age is an important prognostic factor for improved survival independent of age-associated determinants such as performance status [70] and that increasing age independently predicted morbidity and mortality, it was significantly associated with both [99]. It was also reported that younger patients should be treated more aggressively, particularly at time of recurrence because their young age confers an improved prognosis. A probable justification for this result may rely upon the preexisting belief that perioperative morbidity and mortality rates are higher in elderly, and that the presumed life expectancy of such elderly women is limited. However, it is common that elderly patients are simply diagnosed with more aggressive tumors, later stage tumors and receive less aggressive surgery/palliative surgery and less frequently chemotherapy than younger, further increasing the negative effect on prognosis [71, 86].

Other studies have shown that younger age is not an independent prognostic factor for better survival [81, 84, 89]. Some of those studies report that women older than 65 years of age responded as well as those who were younger [89,

90]. Age-associated clinical determinants such as tendency for clinicians to treat younger patients more intensively and a performance status may contribute to explain some differences but not all [71].

Today, OC survival has significantly improved and this improvement is in general attributed to optimal surgical treatment (cytoreduction) and to the use of more effective new chemotherapy drugs [51, 52, 53, 54, 55]. Both cytoreductive surgery and chemotherapy require good physiologic capacities and because elderly patients are more likely to have comorbid conditions, they are less likely to receive optimal surgery and chemotherapy [62]. Two retrospective population-based studies have shown that older patients with advanced ovarian cancer were less apt than younger to receive chemotherapy, to be treated by oncology specialists and to undergo adequate primary cytoreductive surgery [92, 93]. Some studies have established a survival advantage for patients who underwent “optimal” vs “suboptimal” primary surgical cytoreduction [94, 95, 96] and recent studies have demonstrated that the intraoperative tumor dissemination pattern and the post-operative residual tumor, therefore, primary radical surgery are decisive for prognosis in epithelial ovarian cancer [91, 97, 98]. Consequently, we can ask if the poorer outcome of the elderly patients is simply due to a less aggressive medical management than what is received by their younger counterparts. The reported prognostic significance of age in woman cancers has been inconsistent, table 5.9.

In conclusion, POC in women older than 65 years presents in most cases at an advanced FIGO stage, with rates higher than those in younger women. Radical surgery aiming maximal tumor reduction that significantly affects survival also in the elderly women is, though, related with a higher perioperative morbidity and mortality than in younger patients. Our results demonstrated that patients with residual tumor had a significantly increased risk of dying compared with patients without it, independent of patient’s age or other variables. Patients with POC and FROC and residual tumor had worse OS and DFS. In the other hand, chronologic age is not an independent prognostic factor for overall survival or disease free survival of EOC but we saw the importance of primary radical

surgery in EOC and that woman >65 years without significant comorbidity can support extensive cytoreductive surgery as well as women ≤65 years. Also patients with POC platinum resistant or treated with no platinum based chemotherapy had worse OS and for patients with FROC, OS and DFS were both significantly lower. FIGO stage was important factor for DFS in both cases, POC and FROC, and presence of ascites was significant factor in patients with FROC for OS and DFS.

In conclusion, our study suggests that the same therapy protocols that are used to treat younger women (≤65) should be applied to elderly patients (>65) as well. These procedures have the potential to improve significantly survival of women with EOC. Chronologic age by itself should not be a contraindication to the surgical treatment of elderly women with EOC.

Regardless of the methodical limitation of our study, our data indicate the value of surgical radicality in elderly patients. In addition, further perioperative studies are warranted to identify parameters predicting perioperative morbidity and long-term survival in elderly patients with EOC [70].

At last, table 5.9 resume outcomes of five important studies we wanted to remark and together with this study should motivate further research and help increase knowledge of ovarian cancer and its treatments.

Table 5.9 Summary of important studies

	Age at diagnosis	Age as an independent progn.fact.	FIGO stage	Surgery	Residual tumor (RT)after OP	Overall survival (median)	Disease free survival (median)	Chemotherapy
Satge III and IV invasive EOC in younger vs older women. What prognostic factors are important? Chan, JK	≤45 vs >45 years and older vs younger had HR 1.82	yes	III-IV. FIGO stage IV vs III had HR 3.	Optimal (<1cm after initial surgery) 69% for ≤45 and 67% for >45 years, p=0.8. Suboptimal vs optimal debulking: HR1.62	RT >1cm in 31% of younger patients and 33% of older patients, p >0.05	54 months for ≤45 and 34 months for patients >45, p=0.003. Optimal surgey: 66 months for patients ≤45 and 21 months for patients >45, p=0.003	31 months in younger and 18 months for older patients, p>0.06	Not statistic differences between ages groups.
Poorer survival of eldery patients with ovarian cancer. Petignat, P	>70 years (older) vs ≤70 years (youger) HR 1.8	yes	I-II: 31.9% for younger and 18.6% for older pat., p= 0.001 III-IV: 62.3% for younger and 76.1% for older pat., p= 0.001	Optimal (**) 43.2% for younger and 20.4% for older patients, p= 0.000	Suboptimal surgery (**): 80% for older patients and 57% for younger.	53% of younger patients had 5-years specific survival and 18% of older patients, p<0.05	*	Older patients had less frequently chemotherapy, 52% vs 73%, p<0.001
Ovarian cancer (OC) in younger vs older women. Chan, JK	<30 vs 30-60 vs >60 years, HR 1.2, p<0.001.	yes	I-II:65.3% for <30, 40.2% for 30-60 and 22.5% for >60 years, p<0.001 III-IV: 34.8% for <30, 59.8% for 30-60 and 77.5% for >60 years, p<0.001. Stage I vs II vs III vs IV HR 1.93, p<0.001.	Uterus sparing[1]: 52% <30, 13.4% for 30-60 and 15.6% for >60 years. standard[2]:44.5% <30, 79.7% for 30-60 and 57.4% for >60 years, p<0.001. No surgery vs any surgery HR 0.69, p<0.001.	*	Overall 5-years specific survival for <30 years, 78.8%, 30-60 years, 58.8% >60 years, 35.3% p<0.001.	*	*
Impact of age on outcome in patients with advanced OC treated within a prospectively randomized phase III study (AGO-OVAR). Wimberger P.	<50 vs 50-65 vs >65	yes	IIB-IIIA: 27.3% <50, 11.5% 50-65 and 12.8% >65 years. p<0.00 IIIB-IV: 72.7% <50years, 88.5% 50-65 years and 87.2% >65 years	<50 (IIB-IIIA): Optimal surgery in 100% and >65% in 84.2%, p=0.02. <50 (IIIB-IV): Optimal surgery in 90.2% and >65 in 71.3%, p<0.00	No RT <50 years 45.1%, 50-65 years 25.7% and >65 years 24.5%, p<0.00. No RT in FIGO IIB-IIIA 75.2% vs. FIGO IIIB-IV 21.5%, p<0.00	<50 years, 60.7 months 50-65, 41.3 and >65 years, 33.2 months, p<0.00. with RT: <50 years 39.1 months and >65 years 29.2 months, p=0.038.	In patients without RT <50 years, 25.3, 50-65 years 16.8 and >65 years, 16 months, p<0.00. In patients with RT, no significant difference in the age groups.	For OS and DFS, number of cycles was a significant factor in age groups 50-65 and >65 years but not in patients <50 years.
EOC in the reproductive age group. Duska, LR	≤ 40 years (Border line tumot and carcinoma)	no	Only carcinoma: FIGO I-II: 37%, p=0.012 FIGO III-IV:63%, p=0.012	Patients with carcinoma: 13% conservative surgery and borderline: 54.3%	Only carcinoma: ≤2 cm 82.6% and >2cm 17.4%, p=0.05	Overall 5-years survival for border line and carcinoma: ≤30 years 95% 31-40years,68%,p=0.0014	*	*
Epitehlial ovarian tumors in the reproductive age group: age in not an independent prognostic factor. Massi, D.	≤40 years	no	FIGO I-II: 45.95%, FIGO III-IV: 54.05%, p<0.001	Conservative':≤30 47% and 31-40 32.5%; radical":44.1%≤30 and 57.5% 31-40;palliative ≤30 2.9% and 30-40 10%.p=0.3	≤2 cm 14.86% and >2 cm 35.13%, absent 50%, p<0.001	≤30 years 71.3% and 31-40 years 47.1%.p=0.009 Patients with RT≤2cm 80.8% and >2cm 11.5%. p<0.05	*	*
Primary Radical Surgery in Elderly Patients with EOC. Fotopoulou, C.	>70 years	no	FIGO III-IV: 86.1%	Complete tumor resection in 44.6% of patients	9.9% had residual tumor <5mm, 6.9% had TR between 5 and 10mm, 17.8% between 1-2cm and 15.8% >2cm.	OS 47.29 months. 5-years OS, 40%. Patients with no RT, 5-years OS was 70% respect to 13% in patients with any RT.	DFS 49.54 months	No chemotherapy affect negatively OS in eldary patients.
Current study	≤65 (young) vs >65 (old)	no	POC: FIGO I-II: 21.2% for ≤65 and 18.1% for >65, p >0.05; FIGO III-IV: 70.7% for ≤65 and 75.5% for >65, p >0.05	Curative aim (defined in our study) was passible in 92.3% patients ≤65 and 83.6% for >65 years with POC, p=0.051	POC.tumor free in 70.7% of patients ≤65 and 44.3% in >65; FROC: tumor free % ≤65 and % >65; *p<0.001*	OS in POC was worse in patients >65 years and with residual tumor, 14 months respect to 31.3 months in patients ≤65 years,p=0.03	DFS was worse in patients >65 years with FIGO IV, 3.3 months respect to 11 months for ≤65 years, p=0.00	In POC and FROC not significant for OS but significant independent factor in multivariate analysis.

* Absent data.

** Optimal surgery: peritoneal washing, total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy ± regional lymph node removal without remaining macroscopic residual disease. Non optimal surgery: incomplete surgery with remaning macroscopic or bulky disease.

[1] Uterus sparing surgeries: minimal surgery or surgeries that did not include a hysterectomy; [2] Standard: surgeries including a hysterectomy and/or debulking.

'Conservative surgery: only adnexa; ''Radical: total abdominal hysterectomy, bilateral salpingo-oophorectomy and debulking.

RT: Residual tumor

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5. EIDESSTATTLICHE ERKLÄRUNG

,, Ich, Dunja Kozo Abramovic, erkläre, dass ich die vorgelegte Dissertation mit dem Thema: Role of age in epithelial ovarian cancer, 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 24.01.2013
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Dedicated to my parents...

7. CURRICULUM VITAE

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