

Progressive epithelial ovarian carcinoma

Prognostic factors and clinical management

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1. INTRODUCTION

Epithelial ovarian cancer is the fifth most common cancer in Danish women, exceeded only by breast, skin, lung, and colon cancer (3). In Denmark, epithelial ovarian cancer is diagnosed in about 600 new cases annually resulting in an age-standardized incidence rate of 14 pr. 100.000/year (3). The incidence rate of epithelial ovarian cancer varies geographically, and the Danish incidence rate is among the highest in the world (73). The age-standardized incidence rate in Denmark has decreased slightly during the last three decades (3), as in the US population where the age-standardized incidence rate has declined at a rate of 0.7% per year in the period 1989-2000 (2). The incidence rate increases with age and in Danish women the maximum is reached in the age group 60-70 years (3). In Denmark, the 5-year relative survival (all stages) has been unchanged from the period 1986-90 (32%) to 1991-95 (32%) (155), in contrast to e.g. the USA where the relative 5-year survival (all stages) increased from 40% (1983-85) to 52% (1992-99) (85). The different survival between ovarian cancer patients from different countries have been explained by differences in demography, co-morbid conditions, tumour-specific factors, or therapy level (25, 73).

The first-line treatment of primary epithelial ovarian cancer is standardized according to FIGO (International Federation of Gynaecology and Obstetrics; www.igo.org) and consists of a combined approach of maximum surgical tumour removal at the initial staging operation followed by adjuvant chemotherapy in patients with FIGO stage II to IV (12, 73). The identification of which subgroups of patients with FIGO stage Ia-c that benefits of adjuvant first-line chemotherapy is still debated (163). The content of the first-line chemotherapy has changed considerably over time from single oral alkylating agents in the 70ties to platinum-based regimens in the 80ties, most often cisplatin combined with cyclophosphamide. Based on the results from three randomised trials in the 1990ties, carboplatin has displaced cisplatin as the platinum-component (53, 116, 123). The introduction of paclitaxel in the first-line chemotherapy was supported by two randomised trials in which platinum+paclitaxel proved superior to platinum+cyclophosphamide in terms of progression-free and overall survival (107, 131). At present, the standard first-line chemotherapy is internationally agreed to be 6 cycles of combination chemotherapy consisting of carboplatin (AUC (area under the curve) 5-7.5) plus paclitaxel (175 mg/m² over 3 hours) (12, 73). Paclitaxel might be substituted with docetaxel (75 mg/m² over 1 hour) (73). The addition of a third agent (topotecan, liposomal doxorubicin, epirubicin, or gemcitabin) to

the present paclitaxel+carboplatin doublet is presently under investigation in several large multicenter trials, and for the time being two of these trials have proven no benefit of the addition of epirubicin in relation to progression-free survival (ASCO (American Society of Clinical Oncology; www.asco.org) abstracts no. 5003 and 5005, 2004).

Despite initial high response rate to the first-line treatment, the majority of patients with advanced disease will ultimately develop progression (122). Some patients experience progression during the first-line chemotherapy (primary progression), and other experience progression after a disease-free interval, which might last from months to years (secondary progression). The definitions of primary, and secondary progression, respectively, are further discussed in chapter 3.1. The optimal follow-up schedule after the end of first-line chemotherapy is controversial. Most often patients are seen every few months for physical examination, measurement of the tumour marker Cancer Antigen 125 (CA125) in serum, and occasionally also evaluation by tumour imaging techniques. The value of routine CA125 measurements is disputed, and concern has been expressed that routine monitoring of serum CA125 levels is associated with unnecessary emotional stress without any evidence that acting upon an elevated CA125 level improves survival or quality of life (109). The benefit of early chemotherapy based on increased CA125 levels alone versus delayed chemotherapy based on conventional clinical indicators for relapsed ovarian cancer, is currently under investigation in a randomised trial (EORTC (European Organisation for Research and Treatment of Cancer; www.eortc.be) protocol 55955). In contrast to the first-line treatment, there is at present no agreed standard second-line treatment for patients with primary/secondary progression (122). The second-line treatment modalities include surgery, chemotherapy, anti-hormonal agents, molecular-targeted therapy, and external radiation (12, 13, 73, 122). A number of randomised trials comparing different cytotoxic/anti-hormonal/molecular-targeted agents have been performed in the second-line clinical setting (chapters 5.2-5.4), but still there is no overall consensus on the preferred treatment regimens. Guidelines are few (12, 13, 34), and it is realised that the present guidelines for the second-line therapy are based on data from patients who did not receive the actual paclitaxel+platinum containing standard first-line regimen and therefore need to be re-evaluated. Hence, there is a need to develop new strategies for the clinical management of patients with progressive epithelial ovarian carcinoma.

2. AIMS

The aims of this thesis were in patients with progressive epithelial ovarian carcinoma:

- To optimise the clinical management of patients based on an analysis of the present treatment strategies.
- To determine the efficacy and the feasibility of novel cytotoxic regimens.
- To clarify prognostic factors for survival in different patients categories.
- To elucidate whether the procurement of prognostic factors may be useful in the monitoring of second-line chemotherapy.
- To investigate the potential of serological tumour markers to signal tumour response and the prognosis of the patients.

3. PATIENTS AND METHODS

3.1 DEFINITION OF PROGRESSIVE OVARIAN CARCINOMA

The term "Progressive ovarian carcinoma" (POC) is a clinical definition based on the clinical impact of cytotoxic and surgical treatment of the ovarian tumour, and it is classified as (A) primary progression or (B) secondary progression.

A. Primary progression is defined as initial progression during first-line treatment (refractory disease).

B. Secondary progression is defined as progression following initial stabilization, or response, to first-line treatment. Secondary progression thus encompasses clinical entities such as persistent disease, early relapse or late relapse.

Tumour "relapse" is often, alternatively, called "recurrence" or "recurrent disease". The GCIg (The Gynecologic Cancer Intergroup; www.ctep.cancer.gov/resources/gcig/index), an international collaboration of 12 cooperative cancer research groups and the National Cancer Institute, has considered a six-category clinical classification of ovarian carcinoma relapse as follows (www.ctep.cancer.gov/resources/gcig/classrecomm.html).

1. Progression during (first-line) treatment
2. Progression after partial response or stable disease
3. Recurrence < 3 months after complete response
4. Recurrence ≥ 3 months and < 12 months after complete response
5. Recurrence > 12 months after complete response
6. Recurrence after (primary) surgical resection alone

The above classification of POC in primary (GCIg category 1) and secondary progression (GCIg categories 2-6) thus represents a simplification of the six-category GCIg classification.

In general, patients with *primary* epithelial ovarian cancer are offered *first-line treatment* consisting of *primary surgery* and *first-line chemotherapy*. Patients with *POC* are offered *second-line treatment* consisting of *secondary surgery* (chapter 4) and *second-line chemotherapy* (chapters 5 and 6).

3.2 INVESTIGATED POPULATION

Since August 1994, when paclitaxel+platinum was introduced as standard first-line chemotherapy for epithelial ovarian carcinoma at Rigshospitalet, Copenhagen, Denmark, all patients with epithelial ovarian tumours referred to Rigshospitalet have been consecutively registered (name and civil registration number) at the Clinical Research Unit (Klinisk Forskningsenhed), Department of Oncology, Finsen Centre, Rigshospitalet.

3.2.1 Treatment

The initial tumour staging operation in the majority of patients was performed at local peripheral hospitals and the patients were staged according to FIGO guidelines (12). The histological type of the tumour was categorized according to WHO (World Health Organization; www.who.int/en/) guidelines (1). The tumours were classified according to the degree of differentiation as (grade 1) well, (grade 2) moderately, or (grade 3) poorly differentiated tumours, combining structural and cellular features. Hereafter, patients with FIGO stage Ic-IV were referred to Rigshospitalet for first-line chemotherapy and, if possible, interval cytoreductive surgery.

First-line chemotherapy was paclitaxel (175 mg/m² over 3 hours) followed by either carboplatin (AUC 5) or cisplatin (75 mg/m²) repeated every 3 weeks (116). The carboplatin dose was calculated according to Calvert (31), using a glomerular filtration rate estimate by EDTA clearance. After the end of first-line chemotherapy, the patients were followed in the outpatient clinic with monthly CA125 values and tri-monthly clinical examinations and ultrasonography (abdominal and endovaginal).

Patients with primary or secondary POC were generally offered second-line chemotherapy. Selected patients with secondary POC were also considered for secondary cytoreductive surgery. The choice of agents for second-line chemotherapy depended on a calculation of the treatment-free interval and followed departmental guidelines, as follows. The treatment-free interval was defined as the time interval from the end of first-line treatment to the first day of second-line chemotherapy. Since March 1997, standard second-line chemotherapy for patients with treatment-free interval more than 6 months was paclitaxel+carboplatin using a schedule similar to the

first-line regimen. Before March 1997, these patients were treated with either carboplatin or paclitaxel as mono-regimens, or platinum+taxane. The second-line chemotherapy for patients with treatment-free interval ≤ 6 months has also changed over time. From March 1997 to June 2001, standard second-line chemotherapy was topotecan (1.0 mg/m², day 1-5 every 3 weeks) intravenously. From June 2001, standard treatment was liposomal doxorubicin (Caelyx[®]) (50 mg/m², day 1 every 4 weeks). Before March 1997 there was no standard treatment for these patients. Other second-line regimens have included some phase I-II studies with topotecan plus oral etoposide, oral topotecan, topotecan (1.2 mg/m²), or smaller pilot studies with ifosfamide, topotecan-doxorubicin, or mainly for elderly patients, oral melfalan. Furthermore, some patients with secondary POC had no second-line chemotherapy following complete tumour resection in relation to secondary cytoreductive surgery and some other patients refused treatment.

The impact of the treatment was assessed by imaging techniques (abdominal and endovaginal ultrasonography and/or CT (computed tomography)-scans, and chest X-ray) after every two courses of chemotherapy. Ultrasonography rather than CT-scans was employed in the majority of patients because of local expertise in ultrasonographic examinations at the Rigshospitalet. The imaging techniques and the imaging-based tumour response criteria are outlined in chapter 3.5. Duration of treatment was dependent on evaluation of response and followed departmental guidelines for standard second-line therapy. In patients obtaining a complete response (CR), chemotherapy was continued for two cycles after a complete response was achieved. In patients with partial response (PR) or stable disease (SD), antineoplastic treatment was continued until tumour progression. Patients with progression of the disease (PD) or unacceptable toxicity were offered several different regimens (third-line treatment) including supportive care, endocrine therapy or inclusion in phase I-II protocols with investigational new agents. Before each cycle of first-line and second-line chemotherapy, serum samples have been prospectively collected and stored in aliquots at -20°C at Statens Serum Institute (Copenhagen, Denmark).

In the period August 1994 to December 2001, 577 consecutive patients with primary ovarian carcinoma treated with paclitaxel+platinum as first-line chemotherapy were registered at the Clinical Research Unit (Klinisk Forskningsenhed). Of these, 306 patients (53%) had primary ovarian cancer without progression, and 271 patients (47%) subsequently experienced POC (observation until October 2002).

3.2.2 The CODOVA database

Included in the CODOVA (Copenhagen Database for Ovarian Carcinoma; The Danish Data Protection Agency No. 2000-41-0126) were the 271 patients that experienced POC. The database was established in January 2000. The patient files, surgical and histopathological reports, tumour imaging reports and laboratory data were retrospectively examined (1994-2000), and the clinical parameters were recorded in the CODOVA. From January 2000 to October 2002, the clinical data from newly referred patients presenting with POC were prospectively recorded in the CODOVA.

The second-line chemotherapy of the CODOVA patients is outlined in **Table 1**. The second-line chemotherapy was started in the period August 1995 to October 2002.

In patients treated with standardized second-line chemotherapy regimens (paclitaxel+carboplatin, or topotecan, or liposomal doxorubicin), the survival of the patients is summarized in **Table 2**. All patients died from ovarian cancer verified by review of the patient files. No patients were lost to follow-up. The minimum and maximum follow-up time of living patients were 4.1 and 10.8 years, respectively. In the four patients alive with a survival more than 10 years after the initial diagnosis, the FIGO stage was Ic, IIIa, IIIb, IIIc, respectively.

The quality of the clinical data in the CODOVA has been checked

Table 1. CODOVA: Second-line chemotherapy regimens (1995-2001) in patients pre-treated with paclitaxel+platinum (1994-2001).

Regimen	Agents	No.
Standard regimens	Carboplatin+Paclitaxel	85
	Topotecan (1.0 mg/m ²)	72
	Liposomal doxorubicin	17
Other regimens	Paclitaxel	24
	Topotecan-Etoposide orally	15
	Melfalan orally	14
	Ifosfamide	11
	Topotecan orally	6
	Topotecan+Doxorubicin	5
	Topotecan (1.2 mg/m ²)	4
	Carboplatin	4
	Cisplatin+Paclitaxel	4
	No treatment	10
Total		271

No treatment: complete tumour resection in relation to secondary cytoreductive surgery, or refusal for any reason.

Table 2. CODOVA: Overall survival proportions in patients with POC.

Survival	From initial diagnosis	From diagnosis of POC
1 year	91% (87-96%)	61% (54-68%)
2 year	66% (59-74%)	39% (31-46%)
5 year	28% (21-34%)	19% (13-25%)

The table only includes patients ($n = 174$) treated with standard second-line chemotherapy regimens (carboplatin+paclitaxel, or topotecan, or liposomal doxorubicin). The table is constructed by Kaplan-Meier estimates of survival probabilities. Survival proportions with 95% confidence intervals. Survival by May 1st 2005.

and improved by several means. (A) If data sheets were absent in the patient files, data were obtained from the referring hospital (surgical and histo-pathological reports) or Statens Serum Institute (CA125). (B) In case of conflicting data registration between patient files and clinical parameter reports, the data were evaluated by two physicians (BG, SAE). (C) All data inputs in the CODOVA were subjected to double-checks and spot checks. A revision of the tumour histological type and the tumour grade was not performed, because both parameters are characterized by a subjective method of assignment, which results in considerable inter-observer and intra-observer variability (8, 16, 154). Furthermore, no generally accepted tumour grading classification existed in the study period. Accordingly, the results from the histological typing and grading from the referring hospital were maintained. Despite standardized patient consultation check schemes, some clinical data (e.g. non-haematological toxicity, or performance status) were not recorded in the patient files. Due to the retrospective nature of the database, these data were not obtainable, and they were handled as missing values in the statistical analyses. The frequency of missing data in all variables ranged from 0-14%.

3.3 TUMOUR MARKERS

A tumour marker is defined as a molecule either produced by the cancer cells or released by the host as various epiphenomena of metabolic changes caused by the presence of malignancy (55). Tumour markers can be classified according to different criteria, such as serological markers, tissue markers (immunohistochemical), and molecular biological markers (105). This thesis focuses on the clinical use of serological tumour markers because tissue markers and usually also molecular biological markers require tissue specimens, which, most often are not easily available in POC patients due to diffuse carcinosis. In the 1980'ies, the monoclonal antibody technology led to the identification of a number of ovarian cancer-associated antigens, whose serum measurement (serological markers) could offer a biochemical tool in the clinical management of the disease. A comprehensive review of tumour markers in ovarian cancer is found elsewhere (55, 164).

The serological tumour markers investigated in this thesis are

CA125, Cancer-associated serum antigen (CASA), tetranectin, and YKL-40. CA125 is the golden standard tumour marker in ovarian cancer (109). CA125 expression is related to histological type and under expressed in tumours with mucinous (61%) and clear-cell (57%) histology (164). CASA was selected to act as a supplement for the potential use in CA125 negative patients. Some ovarian cancer markers may not be tumour-derived products but epiphenomena of metabolic changes caused by the presence of ovarian cancer cells. To reflect the patient host microenvironment, we selected the markers tetranectin and YKL-40.

The clinical uses of tumour markers have been investigated in relation to the following clinical scenarios (A) in monitoring response to second-line treatment (II-V, VII, VIII), and (B) as prognostic factors of survival (IX, X).

3.3.1 CA125

The CA125 compound was first characterized by Bast et al using the monoclonal antibody OC125 (10). It is a membrane glycoprotein expressed by epithelial cells of different origin and of unknown function (88). Serum levels of CA125 were determined using a commercial CA125 enzyme immunoassay kit (Abbott CA125 EIA, Abbott Laboratories, Chicago, IL, USA). In this assay the monoclonal antibodies OC125 and M-11 act as tracer and catcher, respectively. They both belong to a large group of at least 26 monoclonal antibodies that bind to different domains on the protein part of the glycoprotein CA125 (171).

3.3.2 CASA

The detection of the CASA epitope was originally reported by McGuckin et al (106). Several epitopes on the polymorphic epithelial mucin MUC1 constitute a family of tumour markers. The role of mucins are not yet fully understood but presumed functions are in membrane protection and cell adhesion (66, 136). Serum CASA was measured by a commercial sandwich CASA-ELISA (enzyme-linked immunosorbent assay) kit (Medical Innovations, Labrador, Queensland, Australia). This kit utilizes the monoclonal antibody BC2 to capture antigen and the monoclonal antibody BC3 as tracer. Both monoclonal antibodies recognize a repeated amino-acid sequence on the MUC1 protein core (106).

3.3.3 Tetranectin

Tetranectin was first isolated, purified, and characterized by Clemmensen et al (39). Tetranectin, a protein present in a variety of mesenchymal, epithelial, and endocrine cells, enhances the activity of plasminogen by tissue-type plasminogen activator (t-PA) (39), and might be a regulator of local proteolysis (43, 174). Serum tetranectin was quantified by an ELISA based on the polyclonal rabbit antihuman tetranectin antibody A-371 (DAKO A/S, Glostrup, Denmark) (76).

3.3.4 YKL-40

The term, YKL-40, originates from the one-letter code of its three N-terminal amino acids and the molecular weight (40 kDa), and it was first identified and described by Price et al (86). YKL-40 is a glycoprotein expressed by several types of cancer (46). YKL-40 is a growth factor for connective tissue cells and probably has a function in the remodelling of the extra cellular matrix (86, 137). YKL-40 has also been revealed as a potent migration factor for endothelial cells and it may play a role in angiogenesis (98). YKL-40 levels were determined by a commercial YKL-40 sandwich ELISA kit (Quidel Corporation, Santa Clara, CA, USA) (72).

The serological tumour markers CA125, CASA, and tetranectin were all analysed at Statens Serum Institute (Copenhagen, Denmark), whereas YKL-40 was analysed at Herlev Hospital (Copenhagen, Denmark).

3.4 TUMOUR MARKER RESPONSE

In the monitoring of second-line chemotherapy of POC, only the

Table 3. Comparison between different CA125 response classifications.

	A Rustin criteria	B GCIG criteria	C Ratio criteria
Pre-treatment samples required (n)	1 or 2	1 ^a	1
Moment of response evaluation	Variable	Variable	Fixed ^b
Confirmation sample required	+	+	-
Studies	II, III, V	IV, VII, VIII	VII
References	(148)	(149)	(44)

GCIG: The Gynecologic Cancer Intergroup. a) Only one pre-treatment sample required in the latest version of the GCIG criteria. b) After 1, 2, 3 ... M cycles of second-line chemotherapy.

tumour marker, CA125, has previously been evaluated and validated (109). In this thesis, the longitudinal measurement of CA125 was further studied, and alterations in CA125 levels were classified by CA125-based response criteria (chapter 3.4.1).

3.4.1 CA125-based response criteria

A CA125 response definition needs to take into account the natural intra-individual biological variations in serum CA125 levels. In a study of 25 ovarian cancer patients with clinically stable disease during first-line chemotherapy, Tuxen et al found an intra- and inter-individual coefficient of variation of serum CA125 of 24% and 43%, respectively (165). The analytical imprecision of the assay (Cobas Core, EIA, Roche, Switzerland) was 12%. In order to define critical differences between successive CA125 values, several models for CA125 alterations in the monitoring of ovarian carcinoma treatment have been proposed. These include single measurement of CA125 values at selected time intervals (44), a CA125 ratio at selected time intervals (44, 45), relative percentage reduction in the CA125 level (32, 51, 56, 108, 145, 147, 148), exponential regression analysis of the CA125 levels (45, 129, 175), and time to normalization of the CA125 level (61).

In this thesis, the following CA125 response algorithms were used (A) the Rustin CA125 response criteria, (B) the GCIG CA125 response criteria, and (C) the CA125 ratio criteria. The differences between the three CA125 response classifications are summarized in Table 3. Whereas the Rustin criteria and the GCIG criteria are based on alterations in numeric values of CA125, the ratio criteria also include a time factor thus reflecting the rate of decline in CA125 levels.

A. Rustin criteria

In the last decade, most widely used in clinical trials have been the Rustin criteria (148). The original Rustin CA125 response criteria are combination criteria depending on whether at least two, or only one elevated pre-treatment CA125 sample (≥ 70 U/L) are present. If two or more samples exist, a response has occurred if there is at least a 50% decrease in CA125 levels that is confirmed by a fourth sample (four samples are required for evaluable disease). If only one sample exists, a response has occurred if there has been a serial decrease in CA125 levels of more than 75% over three samples (three samples are required for evaluable disease). A response has occurred if either of the above criteria is fulfilled.

B. GCIG criteria

Recently, the GCIG has developed simplified CA125 response criteria (149). One pre-treatment sample at least twice (≥ 70 U/L) above the upper cut-off of normal values (> 35 U/L) and at least two additional samples after start of treatment are required to define evaluable disease. A response has occurred if there is at least a 50% decrease in the CA125 level confirmed by a fourth sample.

In this thesis, the original version of the GCIG criteria were applied (142), which differs slightly from that finally agreed upon by GCIG (149). The original GCIG criteria (compared to the revised criteria) required two pre-treatment CA125 samples (instead of one) before start of therapy, and that the response is maintained at least 21 days (instead of 28 days).

C. Ratio criteria

The CA125 ratio criteria represent another simplified CA125 re-

sponse algorithm (44). Only one pre-treatment elevated sample (≥ 70 U/L) is required to define evaluable disease. A CA125 ratio is calculated after every series of second-line chemotherapy by dividing the actual CA125 level following treatment, by the pre-treatment CA125 value directly prior to start of second-line treatment. A confirmatory sample is not mandatory. Three response categories are defined:

Response (CR + PR): ratio ≤ 0.5 .
 SD: ratio > 0.5 and < 2.0 .
 PD: ratio ≥ 2.0

3.5 IMAGING-BASED TUMOUR RESPONSE

The ability of different imaging techniques to visualize ovarian cancer disease has been compared in several studies. In a prospective study of 280 women suspected for ovarian cancer, ultrasonography (abdominal and endovaginal), CT-scans and magnetic resonance imaging (MR), all had approximately equal accuracy (0.91) for the overall diagnosis of malignancy (92). In differentiation of disease confined to the pelvis (stage I and II) from abdominal spread (stage III and IV), the specificity of ultrasonography (96%) was higher than that of CT (89%) and also significantly higher than that of MR (88%; $P = 0.018$), whereas the sensitivities of MR (98%; $P = 0.003$) and CT (92%; $P = 0.014$) were significantly higher than that of ultrasonography (75%). The ability of the imaging techniques to visualize POC has been addressed by Prayer et al (134). The effectiveness of pre-operative CT, MR, and clinical palpation combined with CA125 measurement, respectively, was compared in 24 pre-treated ovarian cancer patients whose tumours were subsequently verified by surgical exploration. The accuracy of the palpation/CA125, CT and MR were 96%, 83%, and 88%, respectively.

Changes in the tumour load during second-line chemotherapy can be visualized by conventional imaging-based techniques such as ultrasonography, CT, or chest radiography (62, 92, 158). Changes in tumour load can also be visualized using other imaging techniques such as MR (138) or FDG-PET (positron emission tomography) (27), but these technical modalities were not the standard imaging techniques in the CODOVA patient series. In the last two decades, ultrasonography rather than CT has been the preferred imaging modality in many malignant and non-malignant diseases in Denmark due to the pioneering work by Holm and co-workers (79, 80) and the presence of a Danish manufacturer of ultrasonography hard- and software (B&K, Copenhagen, Denmark). Therefore, the imaging-based technique utilised in the majority of POC patients included in the CODOVA was ultrasonography.

3.5.1 Imaging techniques

A. Ultrasonography

State-of-the-art commercially available ultrasonography equipment was used. The systems used were the Elegra (Siemens, Germany) or Acuson type 128 or Sequoia (Acuson, Mountain View, Calif. USA) platforms. All machines had transabdominal and endovaginal frequencies of 2-5 MHz and 5-7 MHz, respectively. In the mid-1990'ties, some ultrasonographies were performed with the B&K 2102 Hawk platform (B&K, Copenhagen, Denmark).

Patients were evaluated both by abdominal and by endovaginal ultrasonography. The abdominal cavity including retro peritoneum and the pelvic region were examined. All tumour lesions were de-

scribed in relation to shape, size, and localisation, and the findings were reported in the patient files. In general, larger tumours were measured bi-dimensionally. The ultrasonographic images were documented electronically (from 1999) or in print (before 1999). Senior staff consultants at the Department of Radiology, Rigshospitalet, performed the ultrasonographic examinations and measurements.

B. CT-scan

The CT scanner was the Prospeed SX (GE Medical Systems, Milwaukee, USA). The scanners were used in a dynamic or a spiral mode. After opacification of the gastro-intestinal tract with oral contrast material, the pelvis was examined during peak venous enhancement after intravenous injection of contrast material. The pelvis was scanned with 10-mm collimation. Spiral CT was performed with a 10 mm per second table speed and 10 mm reconstruction thickness, and incremental CT was performed with contiguous scans obtained at 1 scan per second.

3.5.2 Imaging-based response criteria

For two decades, imaging-based tumour response has been evaluated by the WHO response criteria (110). This set of criteria has been used in trials as well as in daily practice to evaluate the efficacy of chemotherapy.

A. WHO response criteria

All measurable tumour lesions are recorded, and the product of the perpendicular diameters (area) of all lesions is calculated (110).

- CR: complete disappearance of all tumour disease sustained for at least 4 weeks.
- PR: a decrease of at least 50% in the total area of all measurable lesions.
- SD: a reduction in the total tumour area of 50% or less, or an increase of less than 25% in one or more measurable lesions.
- PD: an increase of at least 25% in the area of existing lesions or the identification of new lesions.

In the WHO criteria, all measurable lesions are regarded as target lesions. To avoid exhaustive measurement of all lesions, a number of different modifications of the criteria have been used over the years, resulting in a situation where the response criteria were no longer comparable between research groups. For this, and other reasons, the RECIST (Response Evaluation Criteria in Solid Tumours) criteria were developed (161).

B. RECIST response criteria

Measurable disease is defined as uni-dimensional disease assessed by conventional imaging techniques (≥ 20 mm), or by spiral CT (≥ 10 mm). All measurable and non-measurable lesions are recorded at baseline. From the measurable lesions, a number of target lesions (max. 10) are selected and the sum of the longest diameter of all target lesions is recorded (The baseline sum longest diameter).

- CR: complete disappearance of all tumour disease sustained for at least 4 weeks.
- PR: a decrease of at least 30% in the baseline sum longest diameter.
- SD: any condition not meeting the other criteria.
- PD: an increase of at least 20% in the longest diameter taking as reference the smallest sum longest diameter since the start of the treatment or the appearance of one or more new lesions.

It is realised that ultrasonography is generally discouraged as imaging technique in the RECIST guidelines, and it is stated that "ultrasound should not be used to measure tumour lesions that are clinically not easily accessible" (161). However, most POC tumours are located in the pelvic region, and the top of the vagina easily located by endovaginal ultrasonography may act as an anatomic landmark.

Table 4. Mathematical equivalent changes for uni- bi- and three-dimensional products in a spherical tumour.

	Change in diameter (uni-dimensional)	Change in area (bi-dimensional)	Change in volume (three-dimensional)
Decrease	30%	50%	65%
	50%	75%	87%
Increase	12%	25% ^b	40%
	20% ^a	44%	73%
	30%	70%	120%

Ex. In a sphere, a 50% decrease in diameter equals a 75% decrease in the area which equals a 87% decrease in volume. a) RECIST: PD. b) WHO: PD.

Therefore, the RECIST criteria were applied for response evaluation both in patients monitored by CT-scans and by ultrasonography (abdominal and endovaginal).

Because the recommended imaging-based response criterion was changed from the WHO to the RECIST criteria in the study period, this thesis contains papers in which either the WHO (II, III, V-VII) or the RECIST (IV, VIII, IX) criteria have been used. A major difference between the WHO (bi-dimensional) and the RECIST criteria (uni-dimensional) is in relation to the measured dimensions of the tumours. The mathematical relationship between linear dimension (uni-dimensional), area (bi-dimensional) and volume (three-dimensional) is depicted in Table 4. The definitions of CR by the two response classifications are essentially the same. Regarding PR, the classifications are almost equivalent if one assumes a spherical tumour and that the longest diameter and the diameter perpendicular to the longest diameter both decrease by at least 30%. The response classifications differ with respect to PD. A 20% in diameter (to obtain a PD by RECIST) do not equal a 25% decrease in area (to obtain a PD by WHO) (Table 4). Assuming spherical tumours, the application of the RECIST alternative to WHO criteria in a patient study group, will expand the group of SD with some of the patients that previously were assigned a PD using WHO criteria. The concordance between the WHO and the RECIST classifications has been evaluated in a retrospective study of 554 ovarian cancer patients finding similar response rates of 23% and 24%, respectively (161). The WHO and the RECIST criteria have been compared in most other solid tumours and, overall, the studies demonstrate concordant results (>90%) between the two response classifications (124, 161).

The measurement of tumour size and response by imaging methods is influenced by the intra- and inter-observer variability. The ultrasonographic examination and measurements were performed by a few highly experienced radiologists, which might have limited the intra- and inter-observer variability. Response evaluation by imaging-based methods is subject to a number of potential biases including classification bias. All patients with difficult response evaluation were classified by two physicians (BG, SAE) in agreement. Furthermore, all CR and PR were confirmed by another response evaluation after at least 4 weeks, thus limiting the risk of classifying non-responders as responders.

3.6 STATISTICAL METHODS: RESPONSE AND SURVIVAL

In many observational studies, survival as function of response has usually been examined by separating patients in groups of responders and non-responders, and the difference in survival distribution has been tested statistically by log-rank testing (the usual method). By this method, the length of the survival itself will influence the chance of a patient to be classified into one group or the other, because patients who become responders must live long enough to obtain a response. This so-called guarantee time is at least as long as the time to a response is recorded. No such guarantee time is required for the non-responding group. In fact, patients who die before the first response evaluation are automatically included in the non-responding group, which represents a bias. The guarantee-time bias by the usual method can be eliminated by using one of two

other methods (A) the time-dependent co-variate method, or (B) the landmark method. The methods have been outlined in detail by Anderson et al (4), and by Buyse et al (30), respectively. Neither of the methods provides a test for the efficacy of the treatment in improving survival because this can only be provided in a randomised trial. This is further discussed in the chapters 6.3-6.5.

3.6.1 Time-dependent covariate method

All patients begin at start of treatment in a 'no response' state. Those patients who eventually respond enter the 'response' state at the time where the response is first recorded and remain there until death or censoring. At each time of death, the number of patients in each response state is used to estimate the risk of death for each response category. This method assesses whether the risk of death is higher for patients who had not previously attained a response relative to those patients who had. As tumour response is a co-variate which can change over time, this method allows patients to accrue times at risk of death to the appropriate response category. An advantage of this method is that it is a powerful test of the hypothesis of equal death rates for each response category versus the alternative that the death rates for the two response states differ by the same proportion over time (proportional hazards). A disadvantage is that it does not produce meaningful survival curves.

3.6.2 Landmark method

In the landmark method, a fixed time after the start of second-line chemotherapy is a priori set as a landmark for conducting the analysis of survival. Those patients still receiving treatment at the landmark time are separated into two categories according to whether they have responded or not, and regardless of any subsequent changes in response status. Patients are followed from the landmark time onwards, and their survival is related to the response classification as assessed at the landmark. Patients that expire before the landmark are excluded from the analysis. An advantage of this method is, that estimates of survival probabilities as functions of response are available. In addition, a correct statistical significance test for differences in survival by response can be conducted. A disadvantage is, that the results depend on an arbitrary landmark time, and conclusions may differ depending on which landmark is chosen. If the landmark period is chosen too short, many responses are ignored; if it chosen too long many early deaths are not accounted for.

4. SECONDARY SURGERY

The classification of surgery applied in epithelial ovarian cancer (Table 5) is based on a previous consensus report and relates to different phases of the tumour as the disease evolves over time (13). The phases differ in regard to tumour cell kinetics, chemo sensitivity (chapter 5.1), and goals of treatment (chapter 6.1). According to the definition of POC (chapter 3.1), the category "secondary POC" encompasses both patients with persistent disease following first-line chemotherapy (Table 5, category C), and patients with early or late relapse (Table 5, category E). For the sake of convenience, the terms "persistent disease" and "relapse" are used instead of the POC classification throughout chapter 4.

Table 5. Surgery in epithelial ovarian carcinoma.

Surgery	Time
A Primary surgery	At initial staging operation
B Early interval surgery	After 3 cycles of first-line chemotherapy
C Late interval surgery (persistent disease)	After more than 3 cycles of first-line chemotherapy
D Second-look surgery	After end of first-line chemotherapy
E Secondary surgery (early or late relapse)	Following a disease-free interval after the end of first-line chemotherapy
F Acute palliative surgery	Any time

Cytoreductive surgery: A, B, C, E. Diagnostic procedure: D. Salvage surgery: F.

In epithelial ovarian cancer, the benefit from cytoreductive surgery on survival was first reported by Griffiths (69). In ovarian cancer patients with a residual disease less than 1.5 cm (maximum diameter) after primary surgery, survival improved significantly as the residual tumour size decreased. Since then, maximum surgical tumour removal (debulking) in relation to the initial staging operation has been the mainstay in the primary surgical treatment of ovarian cancer (12, 73). Although a prospective randomised study regarding the impact of primary cytoreductive surgery has never been performed, multiple studies in Danish (15) and in international (28, 82) patient populations have provided consistent evidence that survival is inversely proportional to the residual tumour size. In a Danish multicenter study in patients with advanced disease, Bertelsen et al showed that optimal primary cytoreduction (< 1 cm) indicated improved survival whereas sub optimal cytoreduction implied poorer prognosis (15). In a recent meta-analysis including 81 cohorts of patients with advanced disease (stage III or IV) treated with platinum-based first-line chemotherapy ($n = 6885$), there was a statistically significant positive correlation between percent maximal cytoreduction following primary surgery and log median survival time (28). Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time.

Despite initial high response rates to first-line treatment, the majority of patients with advanced disease will ultimately relapse (122). It is tempting to extrapolate the survival benefit of the primary cytoreductive surgery to a secondary cytoreductive surgical approach in relapsing disease.

4.1 RESECTABILITY

The ability to achieve complete surgical cytoreduction (no macroscopic visible disease) in relapsing disease reflects the unusual biology of epithelial ovarian cancer to remain confined to the peritoneal cavity without deep-tissue infiltration of abdominal organs and distant metastases. In several studies of secondary surgery, multiple clinical parameters have been demonstrated to be associated with the resectability of tumour relapse in univariate analyses (38, 153). These parameters may be interrelated and only few studies have examined this issue by using multivariate regression models (Table 6).

In the study by Grønlund et al [I] of 38 patients who underwent secondary surgery, the clinical parameters that increased the probability of a complete tumour resection were evaluated. In a multivariate logistic regression analysis the parameters, solitary relapse tumour (solitary vs. multiple tumour sites; $P = 0.01$) and absence of broad base adhesion of the largest tumour node (no vs. yes; $P = 0.03$), were found to be independently associated with complete tumour resection. However, an analysis of the residuals suggested that it was questionable to enter the latter parameter (broad base adhesion of the largest tumour node) in the regression model, thus only the parameter, number of relapse tumour sites (solitary vs. multiple; OR: 0.12; 95% CI: 0.03-0.59; $P = 0.009$) was found to be independently associated with complete tumour resection. In the study by Grønlund et al [I], the classification of patients with respect to residual disease following secondary surgery was based on a review of the patient files, which may be due to inter-observer variation, and thus represent a bias. All surgical reports were evaluated by two physicians (BG, LL) in agreement, which may have reduced this bias.

Previously, patients with (A) long disease-free interval (> 12

Table 6. Clinical variables increasing the probability of complete tumour resection in secondary cytoreductive surgery.

Variable	Study (ref.)	Year
Tumour size less than 10 cm	Eisenkop et al (58)	1998
Favorable performance status	Eisenkop et al (58)	1998
No prior second-line chemotherapy		
before surgery	Eisenkop et al (58)	1998
Solitary tumour	Grønlund et al [I]	2005

The table only includes clinical parameters identified from multivariate analyses.

months), (B) younger age, and (C) favourable performance status has been identified as optimal candidates for secondary surgery in a consensus report (14). There is a discrepancy between the recommendations from the consensus report and the results from the abovementioned studies (Table 6), because the guidelines include clinical parameters (disease-free interval, age) that are not consistently identified by multivariate analysis. The parameter, disease-free interval, is a well-known prognostic factor for survival (57), but its role as a criterion for the selection of surgical candidates is questionable. Patients with late relapses (long disease-free interval) often present with solitary tumours, which might easily be resectable, but this does not infer that patients with early relapse should be excluded from secondary surgery. The same arguments apply to the parameter, younger age. The parameter, age, has never been revealed as an independent factor for complete tumour resection in a mature study of the impact of secondary surgical cytoreduction. Hence, the selection criteria for an optimal candidate for secondary surgery should be re-evaluated, and preferably include the parameters listed in Table 6.

Conclusion

* POC patients with (A) solitary tumour, (B) tumour size less than 10 cm, (C) favourable performance status, and (D) no prior second-line chemotherapy before surgery, have increased probability for complete cytoreduction by secondary surgery.

4.2 SURVIVAL

The attempt to analyse the impact of secondary surgery on survival has been limited by heterogeneous patient populations, different second-line chemotherapy regimens, and vague inclusion criteria in previous studies (96, 114). Several recent studies of secondary surgery (150, 177) also included patients with persistent disease (Table

5, category C), which is considered as another clinical entity than patients with a relapse following complete response to first-line treatment and a disease-free interval (Table 5, category E). Studies on secondary surgery of first relapse (Table 5, category E) are listed in Table 7. The studies differ in relation to patient inclusion criteria, design, definition of optimal cytoreduction and the applied statistical methods. Overall, the studies suggest that patients left with no macroscopic residual disease following secondary surgery seem to benefit in terms of prolonged survival in the range of 29-52 months. However, only a part of the studies included an informative multivariate analysis of survival, and there is no general consensus on which clinical parameters that should properly be included in the multivariate analysis, which may impact the results, because many clinical parameters seem to act as each other's proxies.

The impact of secondary cytoreductive surgery on survival in patients treated with no other first-line chemotherapy than paclitaxel+platinum was first reported by Grønlund et al [1]. In a univariate analysis, a significant difference in survival was found for the three variables: residual tumour size (no macroscopic vs. macroscopic visible residual disease; HR: 0.32; 95% CI: 0.13-0.76; $P = 0.009$), disease-free interval (≤ 12 months vs. > 2 months; HR, 2.4; 95% CI, 1.1-5.3; $P = 0.03$), and number of relapse tumour sites (solitary vs. multiple; HR, 0.28; 95% CI, 0.10-0.73; $P = 0.01$). In the multivariate analyses of survival, two Cox models were examined for the stepwise analyses of the statistically significant variables from the univariate analyses (Table 8). Including only the parameters, residual tumour size and disease-free interval in the model, residual tumour size was found significantly inversely correlated with survival (Table 8; Cox model A; $P = 0.02$). However, including also the parameter, number of relapse tumour sites, in the model, the parameter, residual tumour size, no longer appeared to be significantly associated with survival, probably attributable to the association be-

Table 7. Clinical series on secondary cytoreductive surgery.

Study (ref.)	Year	Design	No.	Optimal cytoreduction criteria (cm)	Survival		
					Median (months)	Multivariate analysis performed	"No. of tumour sites" included in multivariate analysis
<i>Morris et al (112)</i>	1989	R	30	<2.0 >2.0	18 13	-	-
<i>Jänicke et al (84)</i>	1992	R	30	0 >0	29 9	+	-
<i>Vacarello et al (166)</i>	1995	R	38	<0.5 >0.5	>41 23	+	-
<i>Kuhn et al (91)</i>	1998	P	96	a	38 12	-	-
<i>Cormio et al (41)</i>	1999	R	21	0 >0	32 9	-	-
<i>Gaducci et al (63)</i>	2000	R	30	0 >0	37 19	-	-
<i>Eisenkop et al (58)</i>	2000	P	106	0 >0	44 19	+	-
<i>Munkarah et al (113)</i>	2001	R	25	<2 >2	57 25	+	-
<i>Tay et al (157)</i>	2002	R	46	0 >0	38 15	+	-
<i>Zang et al (176)</i>	2004	P	117	<1 >1	26 15	+	+
<i>Güngör et al (70)</i>	2005	R	44	0 >0	19 9	-	-
<i>Grønlund et al [1]</i>	2005	R	38	0 >0	52 20	+	+
<i>Onda et al (118)</i>	2005	R	44	0 >0	52 22	+	+

P: Prospective, R: Retrospective, a) Not reported (surgery vs. non-surgery).

Table 8. Survival following secondary cytoreductive surgery: multivariate analysis ($n = 38$).

Cox model	Variables included in the model	HR	95% CI	P value
A	Residual tumour size	0.36	0.15-0.88	0.02
	Disease-free interval	1.9	0.9-4.2	0.11
B	Residual tumour size	0.55	0.21-1.42	0.22
	Disease-free interval	2.3	1.0-5.3	0.05
	Number of tumour sites	0.31	0.11-0.89	0.03

Residual tumour size (no macroscopic visible residual disease vs. macroscopic visible residual disease). Disease-free interval (≤ 12 vs. > 12 months). Number of tumour sites (solitary vs. multiple). Reproduced from (1) with permission from Elsevier, copyright (2005).

tween the two parameters (Table 8; Cox model B; $P = 0.22$). These results question the prognostic impact of secondary cytoreductive surgery in ovarian cancer patients. Other factors than the surgery-related amount of residual disease after the secondary surgery appear to be more important in determining how the patients fare.

The number of relapse tumour sites is a well-known prognostic factor for survival (57). It is speculated that a solitary tumour relapse is a distinct biological entity with limited metastatic potential, and on the other hand that multiple relapsing tumours may be related to the presence of occult metastasis thus worsening the prognosis of these patients. In the study by Eisenkop et al including 106 patients, complete tumour resection was possible in a significantly larger proportion of patients with a solitary relapse than in patients with multiple disease sites ($P = 0.03$) (58). However, the parameter number of relapse tumour sites was not included in the multivariate analysis of survival (Table 7). Also in the study by Grønlund et al [1], complete tumour resection was observed in a significantly larger proportion of patients with a solitary relapse than in patients with multiple disease sites ($P = 0.01$). It is possible that patients who have a tumour that can be cytoreduced are a selected group with less aggressive disease because of different biological tumour characteristics independent of the cytoreductive surgery. It is also possible that the positive impact of secondary surgery observed in previous studies (58, 63, 157, 166) may be partially explained by a selection bias, and that the prognosis is primarily determined by the inherent biology of the tumour.

None of the studies in which a prognostic impact of complete surgical cytoreduction have been found, have included the parameter, number of relapse tumours, in the multivariate analysis of survival (58, 63, 157, 166). In the study by Zang et al, complete cytoreduction was found to be independently associated with prolonged survival also after including the parameter, number of relapse sites, in the multivariate analysis of survival (176). However, complete cytoreduction was defined as residual tumour less than 1 cm, and the study did not include data regarding the resectability of the explored relapses. In a recent study by Onda et al, the parameter, number of relapse sites, was also included in the multivariate analyses of survival (118). However, the important parameter, residual tumour size following the secondary surgical approach (complete vs. non-complete cytoreduction), was not included in the analyses.

The role of secondary cytoreductive surgery thus remains uncertain. Whether or not the improved survival in patients with small residual tumour is associated with the secondary surgical cytoreduction or the biology of easily resectable and less aggressive tumours cannot be answered from the non-randomised studies performed so far (Table 7). The benefits of secondary cytoreduction are best established from a randomised trial comparing patients randomised to surgery versus no surgery, and equivalent chemotherapy. In 2000, such a randomised study was initiated randomising between second-line chemotherapy plus secondary surgery versus second-line chemotherapy alone, in patients with disease-free interval more than 12 months after end of first-line treatment (Larocson EORTC 55963). Unfortunately, this study was recently closed because only 32 patients were included over 30 months.

Conclusion

* Secondary cytoreductive surgery in ovarian cancer patients has dubious impact on survival, and other parameters related to the biology of the disease appear to be more important in determining the prognosis.

4.3 SURGICAL STRATEGIES

In the study by Grønlund et al [1], the pre-operative finding of a solitary tumour (versus multiple tumours) was positively associated with the probability of complete tumour resection, in agreement with others (58). Nevertheless, complete tumour resection was only obtained in a modest proportion (27%) of patients presenting with multiple intraabdominal/pelvic relapse. Non-solitary disease was often caused by the presence of carcinosis, and relapse debulking was abandoned perioperatively in 7 cases (18%) because of the presence of massive carcinosis. All patients in the series of Grønlund [1] were pre-operatively evaluated by imaging methods (CT-scans or ultrasonography), to exclude massive presence of peritoneal carcinosis, but it is well known that carcinosis may be difficult to evaluate by conventional imaging techniques. It is therefore possible that other imaging methods such as MR (138) or PET (27) will provide better results and possibly replace CT-scans in the future. Otherwise, these findings suggest that any secondary surgical effort should be preceded by a laparoscopic peritoneoscopy of the patient. The finding of massive carcinosis may thus abort further secondary cytoreductive attempts. A laparoscopy may also avoid the morbidity related to a large abdominal incision in patients where further secondary surgical efforts seem futile.

Although a standard technique for secondary cytoreductive surgery has been suggested by Chen et al. (38), there is at present no general agreement on what a secondary surgical procedure should encompass. Carcinosis located in the pelvis may be removable by modified posterior pelvic exenteration using a retroperitoneal approach, as described by Eisenkop (59). Large areas of carcinosis may also be subject to destruction with the argon beam coagulator, but the willingness to utilize all technical modalities to accomplish complete tumour resection in secondary surgery is, at present, not a standard procedure in Denmark. The impact of centralized surgery versus surgery performed at the local hospital is a matter of debate. In a study of primary cytoreductive surgery in ovarian cancer patients by Tingulstad et al, the effect of centralized (teaching hospitals) versus local (community hospitals) surgery was examined (162). For patients with advanced disease, patients operated on centralized hospitals had significantly better outcome than the controls (5-year survival: 26% vs. 4%; median survival: 21 vs. 12 months; $P = 0.01$). Whether this concept also applies to secondary surgery remains to be elucidated.

5. SECOND-LINE CHEMOTHERAPY: AGENTS

5.1 CONCEPT OF PLATINUM-SENSITIVITY

The selection of chemotherapeutic agents for the second-line treatment has generally been guided by a characterization of the platinum-sensitivity of the relapsing tumour. Based on the observation by Blackledge et al of an increasing response rate of cisplatin with the length of the time from the end of first-line treatment (18),

Table 9. Connection between the classification of POC (primary and secondary progression) and the concept of platinum-sensitivity (platinum-resistant and platinum-sensitive disease).

	Primary progression	Secondary progression		
	Refractory disease	Persistent disease	Early relapse	Late relapse
Platinum-resistant disease	+	+	+	
Platinum-sensitive disease				+

Markman et al were the first to introduce the concept of platinum-sensitivity, which predicts the expected response rate to platinum in the second-line treatment (103, 104).

Platinum-sensitive disease, defined as a late relapse in a patient who has previously achieved a documented response to first-line platinum-based treatment and has been off therapy for an extended period of time (the treatment-free interval), has a favourable expected response rate (>30%) to platinum re-treatment, and platinum-containing second-line treatment is therefore advocated (35).

Platinum-resistant disease, defined as relapse within a relatively short period of time following the completion of first-line treatment (the treatment-free interval), has a considerably lower expected response rate (0-30%) to platinum re-treatment. Thus, other agents than platinum are warranted (35).

To discriminate between platinum-sensitive and platinum-resistant disease, several cut-offs of 4 (13), 6 (35, 89), 12 (13, 144), or 24 months (104), respectively, for the treatment-free interval have been suggested, but a precise definition of the minimal required duration of the treatment-free interval to determine the platinum-resistance versus potential platinum-sensitivity has never been established. The connection between the classification of primary and secondary progression, respectively, and the concept of platinum-sensitivity is outlined in Table 9.

The concept of platinum-sensitivity is particularly useful with regard to platinum-based therapy, but it does also apply to chemotherapy in general (120). It is realized that the cut-off is not a distinct discrimination value but rather a continuum of treatment-free intervals into which the probability of a response induced by a second-line chemotherapeutic agent increases with the treatment-free interval. Hence, patients with a long treatment-free interval (chemo-sensitive tumours) are expected to have a higher response rate to second-line chemotherapy than patients with a short treatment-free interval (chemo-resistant tumours).

5.2 REVIEW OF AGENTS

In phase II studies, a variety of single agents have demonstrated activity in POC (Table 10), and a wide range in response rates has been observed (40). A review of agents or combinations of agents

Table 10. Summary of active agents in platinum-pretreated ovarian cancer patients.

Drug class	Agent
Platinum compounds	Cisplatin Carboplatin Oxaliplatin
Vinca alkaloids	Vinorelbine
Alcylating agents	Cyclophosphamide Hexamethylmelamine Ifosfamide Melfalan Treoosulfan
Topoisomerase inhibitors	Etoposide Irinotecan Lurtotecan Topotecan
Antibiotics	Doxorubicin Epirubicin Liposomal doxorubicin
Antimetabolites	Capecitabine Gemcitabine Pyrizoloacridine
Taxanes	Paclitaxel Docetaxel
Endocrine	Goserelin Leuprorelin Letrozole Megestrole Medroxyprogesteron Tamoxifen

employed in phase III trials of POC is provided in Table 11 (platinum-sensitive disease) and Table 12 (platinum-resistant disease). Studies comparing different schedules of the same agent are not included in the tables.

Recent clinical studies have also explored the impact of new non-cytotoxic pathway-targeted agents that interfere with tumour growth factors, cellular receptors, angiogenesis, signal transduction, apoptosis, or cell-cycle regulation in patients with solid tumours (121, 152). In POC patients, both monoclonal antibodies (trastuzumab, Herceptin[®]; cetuximab, Erbitux[®]; bevacizumab, Avastin[®]), small molecule weight inhibitors (gefitinib, Iressa[®]; erlotinib, Tarceva[®]; bortezomib, Velcade[®]) and CA125 binding molecules (oregovomab, Ovarex[®]) have been evaluated in phase I-II trials (152). This new generation of novel compounds act on biological processes distinct from chemotherapy but may also act synergistically with cytotoxic drugs. At present, the impact of the combination of conventional cytotoxic agents and the newer "biologicals" is planned elucidated in randomised trials.

5.3 PLATINUM-SENSITIVE DISEASE

Ovarian cancer is one of the most chemo-sensitive of all solid tumours, and responses are reported in almost 80% of patients who receive the standard first-line paclitaxel+carboplatin combination (35). A re-treatment regimen using the same agents as in the first-line chemotherapy therefore seems an attractive treatment option in patients with platinum-sensitive disease. Single platinum treatment, usually carboplatin, has long been advocated as the standard chemotherapy regimen in patients with platinum-sensitive disease because of its easy administration (30 min. infusion) and favourable toxicity profile (no alopecia, limited nausea and manageable haematological toxicity) (33, 35, 89, 100). An important question is, whether platinum should be combined with another agent.

In a recent trial by Pfisterer et al (130), carboplatin+gemcitabine proved favourable to single carboplatin in terms of response and progression free survival (Table 11). The study was not adequately powered to demonstrate a difference in overall survival. In the study by Parmar et al (ICON4 (International Collaborative Ovarian Neoplasm 4), 802 patients were randomly assigned paclitaxel+platinum or conventional platinum-based chemotherapy, which included single carboplatin (71%) or other platinum-based combinations (29%) (126). The authors found a statistical significant difference in overall survival in favour of paclitaxel+platinum ($P = 0.02$), corresponding to an absolute difference in 2-year survival of 7%.

Additional exposure to paclitaxel in patients pre-treated with paclitaxel may potentially cause cumulated neurotoxicity. In the study by Parmar et al (126), neurotoxicity (grade 2-4) was reported in 20% of the patients in the paclitaxel+platinum arm. Unfortunately, there was no distinction between grade 2 and grade 3-4 neurotoxicity. Moreover, the patient group was somewhat heterogeneous also including patients with more than one line of previous chemotherapy, and patients that were taxane-naïve, which might affect the frequency of neuropathy in the second-line clinical setting. The toxicity of paclitaxel+carboplatin re-treatment in patients pre-treated with paclitaxel+platinum has been elucidated in three retrospective studies (Table 13). The main differences between the studies are with respect to the paclitaxel dose and infusion time and the treatment-free interval. Furthermore, in the study by Dizon, 24% of the patients did not receive paclitaxel in the first-line chemotherapy combination (52). The low frequency of grade 3-4 neurotoxicity (2% of patients) in the study by Grønlund et al. [II] is in agreement with the other studies (Table 13). However, all three studies are limited by the retrospective design, which might have inferred an underestimation of the rate of neuropathy. In comparison, in the three prospective randomised trials comparing cisplatin+paclitaxel versus carboplatin+paclitaxel in the first-line treatment, the frequency of grade 3-4 neuropathy in the carboplatin+paclitaxel arms ranged 3-7% (53, 116, 123).

Table 11. Randomised studies in patients with platinum-sensitive disease.

Study (ref.)	Year	No.	Regimens	Response rate		Overall survival		Comments
				%	P value	Median (months)	P value	
Bokkel <i>et al</i> (20)	1997	107	Topotecan Paclitaxel	29 20	0.21	14 ^a 10 ^a	0.51	PFS: <i>P</i> = 0.002
Gordon <i>et al</i> (68)	2001	220	Topotecan Liposomal doxorubicin	29 28	0.96	16 25	0.008	
Bolis <i>et al</i> (22)	2001	190	Carboplatin Carboplatin+Epirubicin	55 58	0.67	24 28	ND	
Cantu <i>et al</i> (36)	2002	97	Paclitaxel CAP	45 55	0.06	26 35	0.04	TFI >12 months
Parmar <i>et al</i> (126)	2003	802	Platinum + Platinum+Paclitaxel	54 66	0.06	24 29	0.02	ICON4
Gonzales <i>et al</i> (67)	2005	81	Carboplatin Carboplatin+Paclitaxel	50 76	0.02	ND	ND	
Pfisterer <i>et al</i> (130)	2005	356	Carboplatin Carboplatin+Gemcitabine	31 47	0.002	17 18	NS	PFS: <i>P</i> = 0.003

Ongoing studies (May 1st 2005) are not included. ASCO: American Society of Clinical Oncology. CAP: Cyclophosphamide-doxorubicin-cisplatin. ICON: International Collaborative Ovarian Neoplasm (Study Group). ND: no data. NS: not significant. PFS: progression-free survival. TFI: treatment-free interval. a) Platinum-resistant and platinum-sensitive patients combined.

Table 12. Randomised studies in patients with platinum-resistant disease.

Study (ref.)	Year	No.	Regimens	Response rate		Overall survival		Comments
				%	P value	Median (months)	P value	
Pater <i>et al</i> (127)	1987	205	Melfalan orally Melfalan+Hexamethylmelamine	0 1	ND	4 15	NS	
Bokkel <i>et al</i> (20)	1997	119	Topotecan Paclitaxel	13 7	0.30	14 ^a 10 ^a	0.51	PFS: <i>P</i> = 0.002
Bolis <i>et al</i> (21)	1999	81	Paclitaxel Paclitaxel+Epirubicin	17 34	0.10	14 9	ND	
Piccart <i>et al</i> (132)	2000	86	Paclitaxel Oxaliplatin	17 16	ND	9 11	ND	Analysed as two phase II trials
Gordon <i>et al</i> (68)	2001	254	Topotecan Liposomal doxorubicin	7 12	0.12	10 8	0.46	Long-term follow-up results 2004
Du Bois <i>et al</i> (54)	2002	78	Treosulfan Leuprorelin	0 0	ND	8 7	ND	PFS: <i>P</i> = 0.04
O'Byrne <i>et al</i> (ASCO abstract 808)	2002	213	Liposomal doxorubicin Paclitaxel	19 24	NS	13 11	NS	
Meier <i>et al</i> (ASCO abstract 1810)	2003	357	Topotecan Treosulfan	ND	ND	ND	ND	PFS: <i>P</i> < 0.0001
Buda <i>et al</i> (29)	2004	234	Paclitaxel Paclitaxel+Epidoxorubicin	47 37	0.17	14 12	0.33	TFI < 12 months

Ongoing studies (May 1st 2005) are not included. ASCO: American Society of Clinical Oncology. ND: No data. NS: Not significant. PFS: Progression-free survival. TFI: Treatment-free interval. a) Platinum-resistant and platinum-sensitive patients combined.

At present, the elucidation of which agent that should be combined with carboplatin in patients with platinum-sensitive disease is under evaluation in several international trials including the 6-arms randomised GOG (Gynecologic Oncology Group; www.gog.org) study (protocol 213) comparing topotecan, liposomal doxorubicin, gemcitabine, docetaxel, paclitaxel, and sequential paclitaxel, respectively. The abundance of accumulating data will help to identify subgroups of patients who would benefit preferentially from combination second-line chemotherapy.

Conclusions

- * In platinum-sensitive disease, combination chemotherapy has proved favourable to single-agent therapy in terms of increased progression-free and overall survival. Which agent that should be combined with carboplatin is presently under evaluation in several randomised trials.
- * In three retrospective studies of the re-treatment regimen (paclitaxel+carboplatin), cumulative neurotoxicity was not found,

but the frequency of neurotoxicity is probably underestimated due to the design of the studies and needs to be further elucidated.

5.4 PLATINUM-RESISTANT DISEASE

The efficacy of various chemotherapeutic agents, or combination of agents, in platinum-resistant disease has been compared in several randomised trials, in which no regimen was found superior to another regimen in terms of response rate and overall survival (Table 12). The data from the randomised studies demonstrate the poor prognosis of patients with platinum-resistant disease having a median overall survival of 4-14 months (Table 12).

5.4.1 Low-dose topotecan

Topotecan, a water-soluble semi-synthetic analogue of the plant alkaloid camptothecin from the tree, *Camptotheca acuminata*, has been examined in two randomised trials. In the study by Bokkel *et al* (20), the U.S. Food and Drug Administration (FDA; www.fda.gov)-

Table 13. Response and toxicity of re-treatment with the paclitaxel+carboplatin combination (platinum-sensitive disease).

Study (ref.)	Year	No.		Doses		TFI (months)	Response Rate	Toxicity			
		Total	Measurable disease	Paclitaxel (mg/m ²)	Carboplatin (AUC)			Neutropenia (Grade 4)	Sepsis	Neurotoxicity (Grade 1-2) (Grade 3-4)	
Rose et al (140)	1998	25	11	135, 24 hour	5-6	10 (6-30)	91%	ND	16%	4%	0%
Grønlund et al [II]	2001	43	23	175, 3 hour	5	16 (6-42)	78%	9%	4%	30%	2%
Dizon et al (52)	2002	84	58	135-188 ^a	5-6	22 (7-86)	67%	ND	1%	ND	1%

Toxicity events in % of patients. AUC: Area under the curve. ND: no data. TFI: treatment-free interval. a) Infusion time not disclosed. Some other patients were treated with weekly paclitaxel 60-80 mg/m².

approved dose of topotecan (1.5 mg/m², days 1-5 every 3 weeks) was compared with paclitaxel (175 mg/m² every 3 weeks), and in the study by Gordon et al (68), topotecan (1.5 mg/m², days 1-5 every 3 weeks) was compared with liposomal doxorubicin (50 mg/m² every 4 weeks). In both trials, neutropenia was significantly more frequent in the topotecan arm than in the other treatment arm, and treatment with topotecan was more likely to be associated with dose modification, growth factor or blood product utilization, sepsis and treatment related death (20, 68).

In order to reduce the haematological toxicity of topotecan, a number of alternative dosing options have been considered including lower dose, shorter schedule, or continuous long-time infusion (74). The efficacy and toxicity of second-line treatment with a low-dose topotecan regimen (1.0 mg/m², days 1-5 every 3 weeks) have been reported by Grønlund et al [III] and by Rodriguez et al (139). The efficacy and haematological toxicity of pivotal studies of single topotecan is summarized in Table 14. Informal comparison of toxicity frequencies in a non-randomised setting should be made with caution, but both the study by Grønlund et al [III] and the study by Rodriguez et al (139) indicate a more favourable toxicity profile of low-dose topotecan (1.0 mg/m²) compared to the full-dose (1.5 mg/m²) regimen. It is well known that response rates in retrospective studies tend to be higher than in prospective phase II and III trials using the same regimen. However, the data from the two retrospective studies [III](139) indicate that the dose of topotecan may be reduced without apparent loss of efficacy. However, an improved therapeutic index of low-dose topotecan (1.0 mg/m²) in POC patients should be confirmed in other studies to support the hypothesis of similar efficacy and reduced toxicity compared to the FDA-approved regimen. Interestingly, a recommendation of a reduced-dose regimen (1.0 or 1.25 mg/m²) has recently been incorporated in dosing guidelines for patients having risk factors for developing haematological toxicity which included high number of prior treatment lines, prior platinum, greater age, impaired renal function and prior radiation therapy (6).

Conclusion

* The therapeutic index of topotecan may be improved using a low-dose regimen (1.0 mg/m² days 1-5 every 3 weeks) compared to the full-dose regimen. A randomised trial is required before a definitive conclusion can be made regarding the comparative efficacies and safety profiles of the low-dose regimen and the standard FDA-approved regimen of topotecan.

5.4.2 Combination chemotherapy

In platinum-resistant disease, many single cytotoxic agents have

documented activity in phase II studies (Table 10), but often response rates are low and of short duration because of the growth of tumour clones resistant to the mono-drug regimen (49). The combination of several anticancer drugs may circumvent drug-resistance and halt progression (170). In patients with platinum-resistant disease, the efficacy of combination versus single-agent treatment has been compared in very few studies (Table 12). In the study by Bolis et al (21), patients were randomised to paclitaxel+epirubicin versus paclitaxel alone. Response rates (34% vs. 17%; *P* = 0.10), median survival (14 vs. 9 months; *P* no data), and 2-year survival proportion (18% vs. 10%; *P* = 0.33), respectively, were similar between the groups. Moreover, higher frequencies of leukopenia grade 3-4 (*P* = 0.05) and thrombocytopenia grade 3-4 (*P* = 0.003) were observed in the combination arm. In a recent study by Buda et al (29), patients were randomised between paclitaxel or paclitaxel+epidoxorubicin, and no differences in neither response rate nor overall survival were observed. Also in this study, neutropenia grade 3-4 was significantly more common in the combination arm (37% vs. 18%; *P* = 0.01). The study included patients with a treatment-free interval of 6-12 months.

In the study by Grønlund et al [IV], a Scandinavian, multicenter phase I-II study was undertaken to determine the maximum tolerable dose, toxicity, efficacy and the feasibility of a sequential regimen of fixed-dose topotecan (1.00 mg/m², days 1-5) and increasing doses of oral etoposide (50, 75, 100 mg; days 6-12/19) in patients pre-treated with paclitaxel+platinum. The general principles for the design of clinical phase I and II trials are outlined elsewhere (19, 48). Using a conventional dose-finding phase I design, the maximum tolerable dose could not be settled because of unpredictable toxicity, as dose-limiting toxicity was found at all dose levels except the starting dose level. The main dose-limiting toxicities were neutropenia grade 4 (more than one week), and neutropenic fever/sepsis. Overall, neutropenia grade 4 and neutropenic fever/sepsis were noticed in 3% and 2% of cycles (*n* = 155), respectively, and these events were observed at every dose level. More than half of the incidents of neutropenia grade 4 or neutropenic fever/sepsis occurred during the first cycle of treatment. The neutropenia grade 4 was non-cumulative and not dose-dependent, and the main clinical problem was that the events of neutropenia grade 4 were unpredictable and not related to the dose level. Non-haematological toxicity was generally mild.

Although the planned phase II trial in the study by Grønlund et al [IV] was not initiated, the patients from the phase I trial were followed onwards in the outpatient clinic and were thus assessable for response evaluation. The overall response was 32% (95% CI 16-52%). In other phase II trials of platinum-resistant disease, encour-

Table 14. Response and haematologic toxicity of topotecan in second-line chemotherapy (platinum-resistant disease).

Study (ref.)	Year	No.	Design	Topotecan dose (mg/m ² /day)	Response rate	Grade 4		Neutropenic Fever	Sepsis related death
						Neutrophils	Platelets		
Bokkel et al (20)	1997	119	P	1.5	13%	79%	25%	25%	+
Gordon et al (68)	2001	254	P	1.5	7%	77% ^a	34% ^a	4%	+
Rodriguez et al (139)	2001	36	R	1.0	22%	49%	5%	14%	-
Grønlund et al [III]	2002	43	R	1.0	12%	32%	13%	0.5%	-

Toxicity frequencies in % of patients. P: Prospective. R: Retrospective. a) Grade 3 and 4 toxicity.

aging response rates (26-29%) of the combination of oral etoposide and other agents have been reported. The combinations included, as the other agent, liposomal doxorubicin (141), or ifosfamide (5). It is well-known that etoposide is leukaemogenic by increasing the risk of acute myeloid leukaemia (71), which also was registered in the study by Grønlund et al [IV]. Therefore, a combination regimen including other agents than oral etoposide might be preferable. Recently, the concept of platinum-sensitivity (chapter 5.1) has been challenged by some phase II studies of weekly cisplatin and oral etoposide in patients with platinum-resistant disease. In a study of 28 patients with treatment-free interval less than 4 months, weekly cisplatin plus oral daily etoposide resulted in a response rate of 46%, median progression-free interval of 5 months and overall survival of 13 months (168). However, the regimen appeared somewhat toxic reporting grade 3-4 myelotoxicity in 45-58% of patients. In a similar study by Meyer et al, the response rate in patients with treatment-free interval less than 6 months was 46% (108).

Conclusions

- * In platinum-resistant disease, a number of agents have demonstrated activity. Since the efficacies (response rates, survival) of the drugs are the same, the selection of agent should be based on toxicity and convenience of administration.
- * No advantage of combination chemotherapy versus single-agent therapy has been revealed in the randomised studies yet performed.
- * A sequential regimen of iv. topotecan and oral etoposide is not recommended for future trials in patients with POC because of unpredictable haematological toxicity. However, the attractive response rate highlights the potential additive effect of topoisomerase I and II inhibitors.
- * The high response rates reported in recent phase II trials of other combination chemotherapy regimens should be unravelled in randomised trials.

5.5 CHEMOTHERAPY IN THE ELDERLY

Despite the overall improvement in survival of ovarian cancer patients, Oriel et al has demonstrated marked changes over time in the mortality by age (119). The authors used data from the American Centre for Disease Control and Prevention, and demonstrated that the age-adjusted mortality rate had decreased for younger women (≤ 65 years) whereas the mortality rate for elderly patients (> 65 years) has increased from the periods 1979-83 to 1991-95 (119). The higher mortality rate in the elderly patients might be influenced by an impaired treatment because of their chronological age. Observational studies of ovarian cancer patients have demonstrated that the elderly are subjected to (A) time delay in diagnosis, probably due to doctor's delay, which may be responsible for the increased frequency of advanced stage, as the disease develops over time, (B) less referral to cancer centres, (C) exclusion from trials based only on chronological age, (D) less aggressive surgery and larger amount of residual disease following the initial staging operation, and (E) lower doses of chemotherapy due to fear of toxicity (133, 160, 169). Accordingly, there is a need to reveal whether elderly patients with POC in fact experience increased toxicity in the administration of second-line chemotherapy.

In the study by Grønlund et al [V], the outcome in 102 consecu-

tive POC patients treated with modern up-to date intravenous second-line chemotherapy was examined. Chemotherapy was either topotecan for platinum-resistant disease, or paclitaxel+carboplatin for patients with platinum-sensitive disease. All patients started full dose schedules irrespective of age. No differences in the rate of postponement of treatment, neutropenia grade 4, thrombocytopenia grade 3-4, nadir fever, nor hypersensitivity reaction to either cytotoxic regimen between older (≥ 65 years) and younger patients (< 65 years) were noticed ($P > 0.05$). Moreover, the overall response rate in patients aged less than 65 years was similar to the response rate in patients aged more than 65 years (50% vs. 44%; $P = 0.29$).

The practice of administration of lower doses of chemotherapy due to fear of toxicity in the elderly might be based from the well-known physiological changes in the immune system and pharmacokinetics in the elderly. It has been demonstrated that both the haemopoietic reserve capacity (94) and the glomerular filtration rate (9) are decreased in the elderly. However, none of the studies including a comparison between elderly and younger POC patients have provided any evidence that neither frequencies of degree of haematological toxicity nor response rates differed with respect to age (Table 15). The studies are limited by the low number of patients (17, 93) and the retrospective design (17, 42). Moreover, the patient cohorts may have been exposed to a potential selection bias if patients with high risk of toxicity are not included in the study groups. At least the study by Grønlund et al [V] consisted of consecutively treated patients, which may have limited a selection bias.

Overall, the relative role of the extrinsic factors related to treatment, and the intrinsic factors related to the ageing process, in determining the outcome of the treatment of elderly patients is controversial (133, 160, 169). Nevertheless, a study by Hightower et al. concluded that the impaired treatment of the elderly might have been contributory for the decreased survival in the elderly (75). The critical question is whether the survival would be improved if elderly ovarian cancer patients were treated as aggressively as their younger counterparts. For ethical reasons this question cannot be answered from randomised studies. Until more results from prospective studies emerge, scientific efforts should focus on defining better criteria for selection of patients at high risk of toxicity with the aim of developing the best treatment plan for the individual patient.

Conclusions

- * The choice of second-line chemotherapy in patients with POC should be based on other parameters than the chronological age. An individual therapeutic plan should be based on a multifactorial geriatric evaluation.
- * More studies are needed to reveal to what degree the applied treatment strategies represent appropriate clinical judgment and to what degree other factors play a role.

6. SECOND-LINE CHEMOTHERAPY: MONITORING

6.1 GOALS OF SECOND-LINE TREATMENT

In primary ovarian cancer, long-term follow-up studies have found that cure following optimal surgical debulking and first-line chemotherapy is observed in 26% of Danish patients (all stages) (155). Whereas cure is possible in primary disease, POC is generally considered as incurable with few long-time survivors (122). It is well-described that some patients might respond multiple times to

Table 15. Second-line chemotherapy in the elderly: differences in haematological toxicity and response rate with respect to age.

Study (ref.)	Year	No.	Design	Age cut-off (years)	Agents	Hematological toxicity	Response rate
Cornelison et al (42)	1993	93	R	60	Carboplatin	-	NS
Bicher et al (17)	1993	48	R	60	Paclitaxel	NS	-
Lichtman et al (93)	1996	50	P	65	Paclitaxel	NS	-
Bookman et al (24)	1998	139	P	65	Topotecan	-	NS
Grønlund et al [V]	2002	102	R	65	Topotecan Carboplatin+Paclitaxel	NS NS	NS ^a

NS: Not significant. R: Retrospective. P: Prospective. a) Treatment groups combined.

multi-line treatment (101). These observations have led to a paradigm shift in the treatment concept of POC, which should be considered more like a chronic disease, like hypertension and type I diabetes in which the basal pathogenetic mechanisms cannot be altered, but the disease-related symptoms and survival of the patients can be improved by proper management (11, 156, 172). In the palliative clinical setting of POC, extension of survival and improvement of cancer-related symptoms are generally considered as the main therapeutic goals (122).

Central issues in the treatment of patients with POC are: (A) should second-line chemotherapy be administered or not, and (B) how to monitor the efficacy of the cytotoxic treatment, and (C) for how long should the second-line chemotherapy be continued?

(A). At present, there are no randomised trials in which patients with POC have been randomised between antineoplastic treatment versus supportive care. Based on the favourable response rates observed in many Phase II and III trials and in observational studies, most authors advocate the initiation of cytotoxic treatment in patients with POC (12, 13, 73).

(B). Generally, the clinical decision of continuing the present cytotoxic treatment (in preference to supportive care) has been guided by intermediate end-points, such as tumour response evaluation, assuming a correlation between a tumour response and the prolongation of survival and impairment of symptoms (99). Whether this holds true for patients with POC is a matter of debate (chapters 6.2-6.4). Proper monitoring criteria are important as a tool to establish whether to continue or discontinue an on-going treatment. The choice of monitoring criteria is the issue in chapter 6.5.

(C). No randomised trials have elucidated the optimal number of cycles in the second-line clinical setting leaving the decision to be based on an overall clinical judgement of the benefits of treatment. This decision should be based on a number of factors including patient symptoms, previous toxicity, quality of life, clinical and laboratory findings, and also patient preference and cost of treatment (23, 99). The realistic goals of the second-line treatment should thus be determined in close cooperation with the individual patient, and it should be realized that the treatment goals differ from patient to patient. Regarding the question of how long second-line chemotherapy should be continued, the answer is that treatment should be continued until the individualised treatment goals have been fulfilled.

6.2 RESPONSE AND SURVIVAL: A MODEL

In daily clinical practice, an intermediate endpoint is accepted as a 'surrogate' for a true endpoint if it can be used in lieu of the true endpoint to assess treatment benefit. A clinical definition of a surrogate end-point is provided by Temple as a "laboratory measurement or a clinical sign used as a substitute for a clinical meaningful endpoint that measures directly how the patient feels, functions or survives" (159). However, in statistical theories the term 'surrogate endpoint' means somewhat different and more extensive than 'intermediate endpoint'. Prentice was the first to present a formal statistical definition of a surrogate end-point (135). Using a triplet model illustrating the relationship between (A) the specific treatment, (B) the surrogate endpoint, and (C) the true endpoint, Prentice outlined how potential surrogate endpoints could be validated. The validation criteria, including multiple significance tests and estimation of appropriate parameters, have been much debated leading to modifications in the validation process (60).

However, the triplet model is useful also to explain the relationship between an 'intermediate' and a true endpoint. The question is, what intermediate measures (short-term outcome) are plausible in providing 'surrogate' estimates of the efficacy of second-line chemotherapy in terms of prolonging survival (long-term outcome). In the papers by Grønlund et al [VI, VIII] the intermediate endpoint is 'response' and the true endpoint is 'survival'. Although the achievement of a response may be correlated with prolonged survival, there

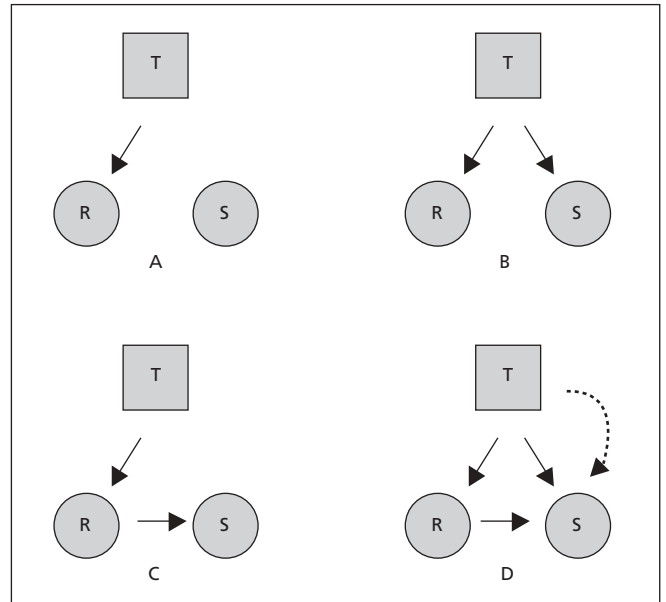


Figure 1. A triplet model to explain the relationships between an intermediate (response) and a true endpoint (survival). T: Treatment; R: Response; S: Survival. (A) The treatment might affect disease pathways, which only affect response, and not the patho-physiological processes that ultimately influence survival. (B) The treatment might affect both disease pathways causally related to survival and also some other pathways that only affect response. (C). The treatment may affect only disease pathways affecting survival mediated through response. (D). The treatment might also affect survival by unintended mechanisms of action that are independent of the disease process, or the effects of the treatment might be mediated through intended mechanisms, which could be substantially offset by unintended, unanticipated, or unrecognised mechanisms.

are several explanations why response might not be a valid surrogate of survival (Figure 1). In summary, the relationship between a response and the patient's ultimate outcome, survival, is complicated. However, in the second-line treatment of POC, tumour response has widely been used as an intermediate endpoint assuming a relationship between treatment-induced response and survival.

6.3 IMAGING-BASED RESPONSE CRITERIA

During the administration of second-line chemotherapy, important questions are: What is the prognostic impact of a response by imaging-based methods on survival? Does a tumour response add to the known prognostic factors for survival? Has tumour response a prognostic value over and above that of the prognostic factors at the time of start of the second-line treatment, in other words, is response an independent prognostic factor for survival?

The relation between tumour response and survival in most solid tumours is unclear (128). At present, there are no studies on second-line treatment of POC that clearly demonstrate the impact of a tumour response on overall survival.

6.3.1 Response and survival

The prognostic impact of an imaging-based tumour response and survival has been examined in two studies by Grønlund et al [VI, VIII]. In a study of 100 consecutive POC patients with solid tumour (measurable disease), the impact on survival of the response categories, CR and PR (WHO response classification), to second-line chemotherapy with topotecan (platinum-resistant disease) or paclitaxel +carboplatin (platinum-sensitive disease) was studied [VI]. The survival of patients from the response categories (CR, PR) was expressed in relation to the survival of the patients with PD, including the parameter, WHO response, as a time-dependent co-variate (chapter 3.6.1). The prognostic impact of an imaging-based tumour response is depicted in Table 16. The results of the Cox regression analyses A-B were included in the study by Grønlund (VI) whereas the results of the analyses C-D have not previously been published.

Table 16. Prognostic impact of an imaging-based tumour response (WHO criteria) during second-line chemotherapy.

Cox analyses	Variables	Hazard ratio	95% CI	P value
A	CR vs. PD	0.07	0.02-0.24	<0.0001
B	PR vs. PD	0.20	0.06-0.62	0.006
C	CR+PR vs. PD	0.11	0.04-0.32	<0.0001
D	CR+PR vs. SD+PD	0.27	0.13-0.53	0.0002

CR: Complete response. PR: Partial response. SD: Stable disease. PD: Progression of disease.

The results demonstrate, that an imaging-based response is an independent prognostic impact for survival in the second-line treatment of patients with POC. The results indicate that a CR, and also a PR, are relevant treatment outcomes in the second-line chemotherapy of POC.

In another study by Grønlund et al [VIII] of POC patients characterized by both solid tumour and elevated levels of CA125 (>70 U/ml), the prognostic impact of a RECIST response (responders vs. non-responders) on survival was retrospectively analysed by the landmark method (chapter 3.6.2). In univariate analysis, survival after the landmark time was significantly longer in patients with a response according to RECIST compared with non-responders ($P = 0.035$). Median survival of responders and non-responders was 20.2 months (range: 0.8-39.3 months) and 9.2 months (range: 1.7-37.0 months), respectively (Figure 2). However, in a multivariate Cox regression analysis of survival to adjust for the confounding from other clinical parameters, the parameter RECIST response had non-significant prognostic impact ($P = 0.62$). The studies by Grønlund et al [VI, VIII] differ in relation to inclusion criteria, number of included patients, response classifications (WHO vs. RECIST), and applied statistical methods (time-dependent analysis vs. the landmark method), which makes comparison difficult. It is realised that in a spherical tumour, the discrimination between responders and non-responders by the two response classifications (WHO, RECIST) is almost equal (Table 4). Although many patients from the CODOVA were included in both patient series, the target tumours selected for the response evaluation were somewhat different between the studies.

In a retrospective study including patients ($n = 506$) from five multicenter trials, Cesano et al (37) found an independent prognostic value of the response categories CR, and PR, respectively, following second-line treatment consisting of topotecan or paclitaxel. The prognostic impact of an overall response (CR+PR) was not evaluated in the study. Furthermore, the patient group was very heterogeneous including taxane-naïve patients and also patients treated with external radiation.

The retrospective studies by Grønlund [VI] and Cesano (37) do not prove a causal relation between response and survival, and the studies have not answered if the survival benefit the patients derived from cytotoxic treatment is merely due to the presence of unknown prognostic factors.

Conclusion

* A reduction in tumour size during second-line chemotherapy measured by imaging techniques is an independent prognostic factor for survival, and thus it adds to the known prognostic factors for survival in POC patients.

6.3.2 Stable disease and survival

In second-line chemotherapy, POC patients demonstrating shrinkage in the tumour size by imaging techniques have generally been continued on the present treatment, whereas patients with increasing of tumour load have been referred to third-line investigational treatment or supportive care. For patients with stable tumour size without a demonstrable response to second-line chemotherapy, the impact of continued cytotoxic treatment is unclear.

The prognostic value of a stabilization of the tumour size during

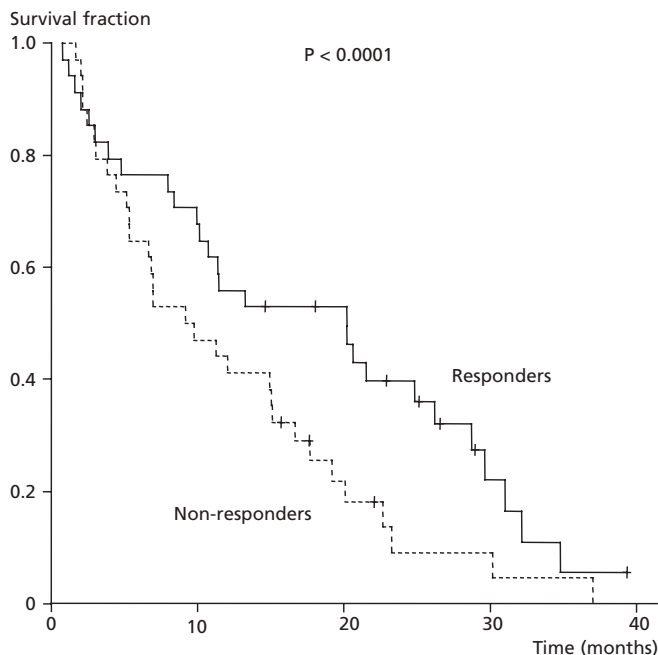


Figure 2. Survival according to response category by imaging-based tumour response criteria (RECIST). Reproduced from (VIII) with permission from the American Society of Clinical Oncology, copyright (2004).

second-line chemotherapy in POC patients was evaluated by Grønlund et al [VI]. In 100 consecutive patients with solid tumour (measurable disease), the patients were retrospectively assigned a best response (WHO response classification) following the start of second-line treatment (CR>PR>SD>PD). Patients with PD were treated mainly with supportive care or endocrine therapy, and patients from the other response categories (CR, PR, SD) were treated with cytotoxic regimens (topotecan or paclitaxel+carboplatin). In a multivariate Cox regression analysis including the parameter, WHO response, as a time-dependent variable (chapter 3.6.1) patients with SD had a survival benefit compared to the PD patients with a risk of death of only 37% of the PD group (Table 17). Patients with SD thus enjoy a 63% reduction in death hazard rate compared to patients with PD and the increment in survival was statistically significant ($P = 0.02$). These findings demonstrate that SD is an independent prognostic indicator for survival in second-line treatment of ovarian carcinoma.

In heterogeneous tumours including a mix of chemosensitive and chemoresistant tumour cells, a cytotoxic agent which kills small but rapidly dividing tumour cell clones may only have a marginal short-term impact on the overall tumour size but a solid long-term influence on the rate of the total tumour growth. SD may thus represent a clinically relevant therapeutic efficacy parameter, which cannot be adequately assessed using conventional imaging techniques, but may prove to have a favourable prognostic impact on survival. However, without knowing the values of the inherent tumour cell kinetic parameters in the tumour, it remains uncertain whether the SD category represents a direct antineoplastic effect of the second-line chemotherapy in fast-growing tumour cells, or simply reflects slowly growing tumour cells resistant to chemotherapy.

In antineoplastic treatment, a reduction in tumour size as documented by a PR, probably reflects the result of a direct cytotoxic ef-

Table 17. Prognostic impact of stable disease (WHO criteria) during second-line chemotherapy.

Cox analysis	Variables	Hazard ratio	95% CI	P value
A	SD vs. CR	4.76	1.96-12.5	0.0004
B	SD vs. PR	1.75	0.68-4.55	0.09
C	SD vs. PD	0.37	0.16-0.86	0.02

CR: Complete response. PR: Partial response. SD: Stable disease. PD: Progression of disease.

fect in the tumour cells. In the study by Grønlund et al [VI], there was no statistically significant difference in survival ($P = 0.09$) between patients with SD and PR (Table 17). As the study group comprised consecutively treated patients, this finding suggests that SD was due more to a biological effect of the second-line chemotherapy rather than a crude observation of the natural history of the disease.

The prognostic impact of a stabilization of the disease has also been studied by Cesano et al (37). The study group included 506 platinum-pretreated patients and the antineoplastic treatment was either topotecan or paclitaxel. In a retrospective analysis, the prognostic impact of SD was examined by Cox regression with the parameter, response to treatment, included as a time-dependent covariate. The risk ratio of SD lasting at least 8 weeks was 0.47 (topotecan; SD vs. PD; 95% CI: 0.34-0.64; $P < 0.001$) and 0.40 (paclitaxel; SD vs. PD; 95% CI: 0.24-0.66; $P < 0.001$), respectively.

Both the study by Grønlund et al [VI], and the study by Cesano (37) compared the survival of patients with SD (cytotoxic treatment) to patients with PD (non-cytotoxic treatment) in a non-randomised design. Although the results may justify continued therapy in patients demonstrating SD to cytotoxic treatment, the question of either (A) further cytotoxic treatment regimens or (B) alternative non-cytotoxic regimens/supportive care, in non-responding patients should preferably be addressed in a randomised study.

In a recent study by du Bois et al (54), 78 pre-treated ovarian cancer patients were randomised to either Treosulfan intravenously or endocrine treatment (Leuprorelin). The study was stopped early because of suspected lack of efficacy. The analysis demonstrated a statistically significant advantage of Treosulfan with respect to progression-free survival ($P = 0.035$), but no difference in overall survival ($P = 0.87$). The impact of cytotoxic treatment versus endocrine therapy is compared in another on-going randomised study (NSGO (Nordic Society Gynecological Oncology; www.nsgo.org) protocol 9905). Included are POC patients with ovarian cancer refractory or resistant to platinum and taxane. Treatment arm A is chemotherapy (weekly paclitaxel, or liposomal doxorubicin), and treatment B is tamoxifen. At present, there are no studies in which POC patients are randomised to cytotoxic treatment versus supportive care, and such a randomised study will possibly never be initiated because it would be unethical to enrol patients in studies with untreated controls.

It is important to recognize a potential benefit of stable disease using antineoplastic agents, in order to justify further treatment of this patient segment in preference to supportive care. Although the study by Grønlund [VI] and Cesano (37), respectively, do not provide final proof of the prognostic impact of stable disease on survival, because this can only be obtained from a randomised trial ideally including quality of life data, the findings give support to the concept of achieving stabilization of the tumour burden in the monitoring of second-line chemotherapy of ovarian cancer. Since POC is considered as an incurable disease, it is suggested that stabilization of the tumour burden should be considered as a reasonable treatment outcome in the salvage clinical setting.

Conclusion

* Stabilization of the tumour size during second-line chemotherapy of POC is associated with a survival benefit compared to patients with PD.

6.4 TUMOUR MARKER-BASED RESPONSE CRITERIA

At the time of start of second-line chemotherapy, many POC patients have non-measurable disease because of complete cytoreduction in relation to secondary surgery (chapter 4), or because of peritoneal carcinosis or other ill-defined tumours. In these patients the impact of chemotherapy cannot be adequately monitored by conventional imaging techniques. Alterations in the serum level of a tumour marker may present an alternative tool to monitor the efficacy of the chemotherapeutic treatment. The value of tumour markers as prognostic indicators of survival has been explored both

as single sample determination before start of chemotherapy, and as serial measurements during chemotherapy. The prognostic impact of pre-treatment tumour marker determination is discussed in chapter 7. The prognostic impact of serial measurements of tumour markers is discussed in the present chapter.

6.4.1 Response and survival

In first-line chemotherapy, several studies have demonstrated that the CA125 concentration after one, two or three cycles of first-line chemotherapy was the most important prognostic factor for survival (109, 164). Mogensen et al found that a useful separation between long and short time survivors can be obtained by measuring the CA125 level one month after the third cycle of chemotherapy (111). In patients with a low CA125 level (11-100 U/ml), the median survival was 22 months compared with a median survival of 7 months in patients with elevated CA125 levels (>100 U/ml) ($P < 0.0001$). Furthermore, the apparent half-life of CA125 has also been found to independently correlate to overall survival in many studies of first-line chemotherapy (111, 167).

In the second-line treatment of POC many studies have correlated CA125 alterations with changes in tumour size measured by imaging techniques (chapter 3.5.1), but very few studies have examined the alteration in CA125 levels as a prognostic factor for survival. In a study of 68 POC patients with pre-treatment elevated levels of CA125 (>70 U/ml) by Grønlund et al [VIII], the prognostic impact of a serial CA125 response during second-line chemotherapy was examined. In a univariate analysis, the survival of CA125 responders at landmark time following four cycles of second-line chemotherapy was significantly longer compared with non-responders ($P < 0.0001$). Median survival of CA125 responders and non-responders was 20.4 months (range: 1.2-39.3 months) and 5.3 months (range: 0.8-23.3 months), respectively (Figure 3). In a multivariate Cox regression analysis including other potential prognostic parameters, CA125 response (responders vs. non-responders: HR: 0.21; 95% CI: 0.11-0.38; $P < 0.001$) was identified as an independent prognostic factor for survival. This means, that patients who obtain a 50% reduction in CA125 levels (equal to a GCIG CA125 response) have a death hazard rate of 21% of patients with stable or increasing CA125 levels after completion of the 4th cycle of second-line chemotherapy. The prognostic impact of a CA125 response was also present in the subgroups of patients ($n = 31$) treated with mono-

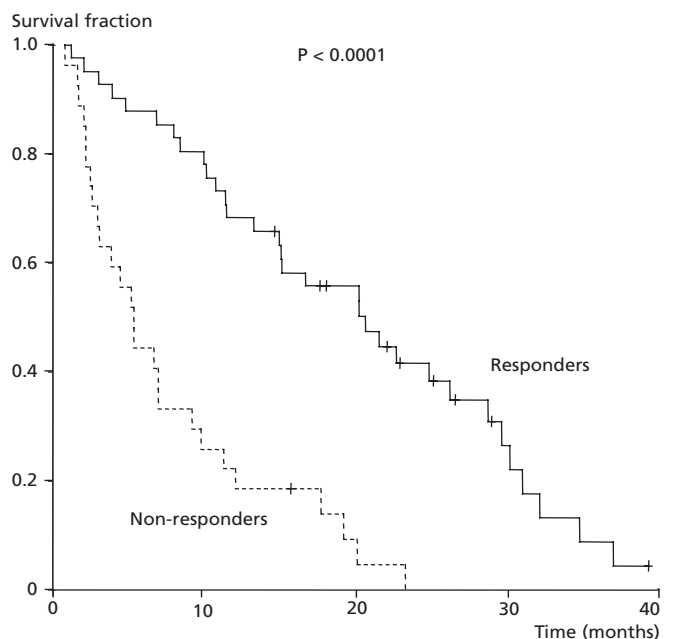


Figure 3. Survival according to response category by CA125-based tumour response criteria (GCIG CA125 criteria). Reproduced from (VIII) with permission from the American Society of Clinical Oncology, copyright (2004).

therapy (topotecan) (HR: 0.47; 95% CI: 0.29-0.76; $P = 0.002$) and in patients ($n = 37$) treated with combination therapy (paclitaxel+carboplatin) (HR: 0.55; 95% CI: 0.33-0.91; $P = 0.022$).

In another study of 66 pre-treated ovarian cancer patients undergoing salvage chemotherapy with paclitaxel, Pearl et al (129) examined the alterations in CA125 levels by exponential regression analyses and found that the rate of regression was not correlated with survival (Spearman rank correlation; $P = 0.92$). Davelaar et al evaluated the prognostic value of a CA125 ratio after 4 cycles of paclitaxel (44). In 77 pre-treated ovarian cancer patients, the survival between responders and patients with progression differed significantly ($P = 0.001$). Generally, studies of the prognostic impact on survival of serial tumour marker measurements other than CA125 have been very limited (109, 164).

Conclusion

- * A halving of the pre-treatment CA125 level after the 4th cycle of second-line chemotherapy is independently associated with prolonged survival in patients with POC.

6.5 COMPARISON OF IMAGING-BASED AND TUMOUR MARKER-BASED RESPONSE CRITERIA

The correlation between changes in the tumour load and alterations in CA125 levels during first-line chemotherapy has been extensively studied (109, 146). The correlation has also been studied for other tumour markers (CASA, CA15-3, CA72-4, CA19-9, CA50, TPA, TPS, tetranectin, and TATI, but generally the number of studies are few, and a wide range in concordance is observed (95, 164). Overall, the studies have demonstrated that the combined evaluation of several tumour markers was not superior to serum CA125 alone in prediction of the course of the disease (response/progression) (95). In a review by Tuxen, including data from 15 clinical series of first-line treatment, the CA125 level changed in accordance with the response/progression designation in more than 74% of the matched events (164). The measurement of CA125 has as such an established role in the monitoring of the efficacy of first-line chemotherapy in both clinical trials and in the individual patient (109, 142).

Contrary, the correlation between changes in the tumour load and alterations in CA125 levels during second-line chemotherapy is disputed (chapter 6.5.1), and the clinical use of CA125 in the monitoring of second-line treatment is controversial (chapter 6.5.2).

6.5.1 Response

Several studies have compared changes in CA125 levels (CA125 response criteria) with changes in the tumour load (WHO tumour response criteria) in pre-treated ovarian carcinoma patients receiving second-line chemotherapy, finding a concordance in the range of 30-85% (Table 18). Concordance means that the designations of response, or non-response, following second-line treatment were similar using CA125 and WHO tumour response criteria. Concordance is calculable only in patients with both measurable disease (imaging-based response criteria) and evaluable disease (CA125-based response criteria). The results from the different studies have thus been conflicting which may partly be explained by differences in CA125 assays, CA125 cut-off levels, imaging techniques, and different second-line regimens. In a recent meta-analysis of 19 phase II

trials including 14 different drugs, Rustin et al. found that the CA125 criteria and the WHO criteria were concordant in 20 of 25 groups, but overall the CA125 response rates were slightly higher than the WHO response rates by a factor 1.11 (145).

It is important to rely on accurate response criteria in order to decide whether or not to continue a second-line chemotherapy that is considered as palliative. If, theoretically, a CA125 response definition overestimates a true therapeutic benefit as reflected by a response by WHO criteria, patients with chemo-resistant disease may continue an anti-neoplastic treatment without benefit in terms of tumour shrinkage but with the potential risk of developing chemotherapy-induced toxicity. Similarly, if the WHO response criteria underestimate a true benefit of an antineoplastic regimen in terms of a reduction in the number of CA125 expressing cancer cells as reflected by a CA125 response, a potential active regimen may be prematurely withdrawn in preference to supportive care.

The performance of two different CA125 response classifications (chapter 3.4.1) to depict a response measured by conventional imaging methods (WHO criteria) was examined by Grønlund et al [VII]. The accuracy of the GCIG CA125 criteria (79%) was numerically favourable to the CA125 ratio criteria (66-75%). The performance characteristics of the Rustin CA125 response criterion (chapter 3.4.1) were not evaluated in the study by Grønlund [VII]. Therefore, it was calculated as follows. The sensitivity, specificity, and accuracy of the Rustin criteria were 97%, 69%, and 81%, respectively. Using the Rustin CA125 criteria on the patient population in the study by Grønlund [VII], the response rate of the WHO criteria (60%) and the Rustin CA125 criteria (42.5%) were similar ($P = 0.057$).

Over the years, several definitions of CA125 response have emerged, and it has been demonstrated that CA125 response rates can vary considerably in the same trial if different CA125 response classifications are used (142). This was confirmed in the study by Grønlund [VII], and from the abovementioned results from the application of the Rustin criterion. Hence, the accuracy of CA125-based criteria ranged 66-81% in the same patient population depending on which CA125 response criterion (Table 3) was selected.

Conclusions

- * A discrepancy exists, because the GCIG CA125 criteria overestimate a tumour response measured by WHO criteria in monitoring the efficacy of second-line chemotherapy. A more interesting question is whether, imaging-based response criteria or CA125-based response criteria best reflect the efficacy of second-line chemotherapy as related to survival.
- * The concordance between CA125-based response criteria and imaging-based response criteria is highly dependent on the applied CA125 response algorithm.

6.5.2 Survival

In POC patients, it is not clear whether tumour marker-guided response criteria or imaging-based response criteria best reflect the outcome of the second-line chemotherapy in terms of survival. This is an important question with implications both for trials and in the management of the individual patient. At present, regulatory authorities such as the FDA do not accept studies in which the efficacy of ovarian cancer agents have been documented solely by

Table 18. Concordance between CA125 response criteria and the WHO tumour response criteria in pre-treated ovarian cancer patients.

Study (ref.)	Year	No.	Agents	Concordance
Davelaar et al (44)	1996	77	Paclitaxel	30%
Rustin et al (147)	1997	72	Altretamine orally	85%
Bridgewater et al (26)	1999	214	Paclitaxel	80%
Dieras et al (51)	2002	27	Oxaliplatin	78%
Grønlund et al [VII]	2004	124	Paclitaxel+Carboplatin Topotecan	79% ^a

Concordance means that the designations of response, or non-response, were similar by using CA125-based response criteria and the WHO tumour response criteria. a) Treatment groups combined in the analysis. Reproduced from (VIII) with permission from Nature publishing Group, copyright (2004).

CA125-based response criteria, rather than imaging-based techniques (RECIST), in the drug approval process (87). Concern has been raised, because many ovarian cancer patients are not assessable by RECIST, and they are therefore excluded from trials when survival is not the end-point (102, 125, 144). It has been estimated, that acceptance of CA125-based criteria would double the number of patients eligible for clinical trials (144).

The comparison of the prognostic value of a response by CA125-based response criteria with a response by imaging-based response criteria on survival was first reported by Grønlund et al [VIII]. From the CODOVA, 68 selected patients with both solid tumour and elevated levels of CA125 (> 70 U/ml) were identified. All patients were treated with topotecan (platinum-resistant disease) or paclitaxel + carboplatin (platinum-sensitive disease). The prognostic impact of a RECIST response (responders versus non-responders) (chapter 3.5.2) and a GCIG CA125 response (responders versus non-responders) (chapter 3.4.1) on survival were analysed by the landmark method. The landmark was arbitrarily defined as the day of the first clinical evaluation following 4 cycles of second-line chemotherapy. The response rates by the RECIST and the GCIG CA125 criteria after 4 cycles of second-line chemotherapy (landmark time) are depicted in Table 19.

The results from the Cox analyses are summarized in Table 20. The GCIG CA125 response criteria was found to be two to three times [(1/0.23)/(1/0.57)] better than the RECIST at disclosing survival (Table 20; Cox analyses A and B). A more refined estimate takes the responder-to-non-responder ratio into account (Table 19) and forms the ratio of the two prognostic efficacies, as follow: $[\ln 0.23 \sqrt{(41/68)} (27/68) / \ln 0.57 \sqrt{(34/68)} (34/68)] = 2.6/1$. In a multivariate Cox analysis (Table 20; Cox analysis D) with inclusion of potential prognostic parameters, CA125 response (HR: 0.21; $P < 0.001$) and number of tumour sites (solitary versus multiple; HR: 0.47; $P = 0.020$) were identified as contributory prognostic factors for survival, whereas the parameter RECIST, as well as the remaining variables, had non-significant prognostic impact.

Table 19. Response by the RECIST and the GCIG CA125 tumour response criteria after four cycles of second-line chemotherapy (landmark time).

CA125 criteria	RECIST		Total
	Responders	Non-responders	
Responders	31	10	41
Non-responders	3	24	27
Total	34	34	68

The patients had both measurable disease (RECIST criteria) and evaluable disease (GCIG CA125 response criteria) ($n = 68$). The table depicts number of patients for each response constellation. RECIST: Response Evaluation Criteria in Solid Tumours. GCIG: Gynecologic Cancer Intergroup. Reproduced from (VIII) with permission from the American Society of Clinical Oncology, copyright (2004).

Table 20. Comparison of the prognostic impact of an imaging-based response (RECIST) and a CA125-based response (GCIG criteria).

Cox analysis	Variable	Hazard ratio	95% CI	P value
A	RECIST response	0.57	0.33-0.97	0.037
B	CA125 response	0.23	0.13-0.42	<0.001
C ^a	RECIST response	1.66	0.70-3.92	0.25
	CA125 response	0.16	0.06-0.39	<0.001
D ^b	RECIST response	—	—	—
	CA125 response	0.21	0.11-0.38	<0.001
	No. of tumour sites	0.47	0.25-0.88	0.020

RECIST and GCIG CA125 response: (responders vs. non-responders). No. of tumour sites (solitary vs. multiple). a) Both response classifications included in the regression model b) No independent prognostic value was found for any of the following co-variables: FIGO stage; histology; residual disease after staging operation; initial performance status; response to first-line treatment; treatment-free interval (6 months); age; performance status at time of second-line treatment. Reproduced from (VIII) with permission from the American Society of Clinical Oncology, copyright (2004).

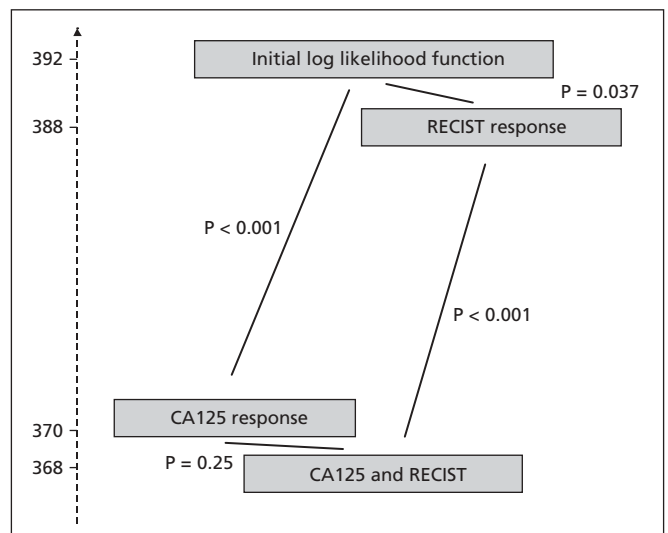


Figure 4. A hierarchy of survival prediction models (Cox regression applied to survival after landmark date). Ordinate axis shows the value of the minus 2 log likelihood function.

The changes in the log likelihood function by including RECIST and CA125 response parameters, respectively, in the set of predictor variables in the regression model are illustrated in Figure 4. The diagram shows that the RECIST classification is less informative than the GCIG CA125 criteria, and, in particular, held no significant information once CA125 response was taken into account. Hence, CA125-based response criteria should be preferred to imaging-based response criteria for prognostication during second-line chemotherapy of ovarian cancer. Noteworthy, the findings are valid only for patients treated with either topotecan or paclitaxel + carboplatin. Other agents, or combinations of agents, may potentially act differently and other findings of the impact of CA125 criteria and RECIST may be observed. The impact of the CA125 criteria and the RECIST in prognosticating survival should thus be examined for every single agent or combinations.

A central question is, whether the findings have any implication for how to monitor second-line chemotherapy in trials, and in the management of the individual POC patient?

Regarding trials, the data suggests, that the GCIG response criteria incorporating CA125 kinetics should be accepted by regulatory authorities in the approval process of ovarian cancer drugs. The use of the GCIG CA125 response criteria should enable positive or negative decisions on further development of new drugs to be made more quickly, leading to both cost savings and the reduction in the exposure of patients to inactive drugs. In the drug approval process, the GCIG criteria should be used to support so-called go/no-go decisions for further development of drugs in phase II trials (143).

Regarding the palliative second-line treatment of the individual patient, prolongation of survival is a major goal among other goals, which also include the palliation of symptoms and increasing the quality of life (chapter 6.1). As the CA125 criteria better than the RECIST prognosticate survival, CA125-based response criteria are preferable to imaging-based response criteria in the monitoring of salvage chemotherapy.

The study by Grønlund et al [VIII] was commented in an editorial by G. Rustin in the *J Clin Oncol* (143). The author stressed the importance to determine if the RECIST or the CA125 criteria is the more reliable method for predicting survival. It was concluded that the increased confidence in the GCIG CA125 criteria following the study by Grønlund et al [VIII] "should lead to a cheaper and, in some cases, more accurate method for monitoring ovarian carcinoma therapy than standard radiographic criteria." The author emphasized, that the GCIG response definition was applicable in many circumstances including retrospective analyses, and in the individual patient management.

Table 21. Prognostic factors for survival in patients with POC (CODOVA database).

Variable	Patients		Univariate analysis P value	Multivariate analysis		
	No.	%		HR	95% CI	P value
<i>At initial diagnosis</i>						
Tumour stage (FIGO)			0.006	–	–	NS
I-II	32	17				
III	129	68				
IV	28	15				
Tumour histology			0.28	a	a	a
Serous	108	57				
Mucinous	13	7				
Endometrioid	16	8				
Clear cell	12	6				
Undifferentiated	3	2				
Adenocarcinoma without specification	37	20				
Tumour grade ^b			0.13	a	a	a
G1	11	7				
G2	55	34				
G3	97	60				
Residual disease (cm) ^b			0.01	–	–	NS
≤1	64	34				
>1	124	66				
Age (years)			0.94	a	a	a
≤65	134	71				
>65	55	29				
Performance status ^b			<0.0001	–	–	NS
0	123	69				
1-2	56	31				
CA125 (U/ml) ^b			0.09	a	a	a
≤35	42	23				
>35	137	77				
<i>During first-line treatment</i>						
Interval operation			0.001	–	–	NS
Yes	76	40				
No	113	60				
Response			0.01	–	–	NS
CR+PR	129	68				
SD+PD	24	13				
Non-assessable	36	19				
<i>At primary or secondary progression</i>						
Treatment-free interval (months)			<0.0001			
≤6	74	39		1		<0.0001
6-12	50	26		0.39	0.26-0.60	<0.0001
>12	65	34		0.36	0.19-0.68	0.002
Time to relapse/progression (months)			<0.0001			
≤18	126	67		1		0.05
18-24	31	16		0.97	0.53-1.8	0.92
>24	32	17		0.43	0.20-0.92	0.03
Size of tumour (cm)			0.46	a	a	a
≤5	135	71				
>5	54	29				
No. of disease sites			0.05	a	a	a
Solitary	45	24				
Multiple	144	76				
Sites of relapse			0.79	a	a	a
Pelvic	136	72				
Extra-pelvic	53	28				
Sites of relapse			0.001	–	–	NS
Liver	19	10				
Non-liver	170	90				
Sites of relapse			0.008	–	–	NS
Pulmonal	11	6				
Non-pulmonal	178	94				
CA125 (U/ml)			0.001			
≤35	32	17		1		0.001
35-120	63	33		1.84	1.06-3.18	0.03
120-339	48	25		2.96	1.65-5.30	<0.0001
>339	46	24		2.84	1.62-4.96	<0.0001

Continued next page

Table 21. Continued.

Variable	Patients		Univariate analysis P value	Multivariate analysis		
	No.	%		HR	95% CI	P value
Age (years)			0.77	a	a	a
≤65	122	65				
>65	67	35				
Performance status			<0.0001			
0	110	58		1		
1-2	79	42		2.50	1.76-3.55	<0.0001

No. of patients = 189, No. of death (1.9.2004) = 152 (80%). The table includes consecutive patients subsequently treated with one of the following second-line regimens: paclitaxel+carboplatin (n = 85), topotecan (1.0 mg/m²)(n = 72), liposomal doxorubicin (n = 17) or topotecan-orally etoposide (n = 15). Treatment-free interval: the time interval from the end of first-line treatment to the first day of second-line chemotherapy. Time to relapse/ progression: the time interval from the initial diagnosis to the diagnosis of the first relapse or primary progression during first-line chemotherapy. a) Not included in the multivariate analyses. b) Some missing values

Conclusions

- * Tumour response by CA125 criteria is more accurate than response evaluation by RECIST criteria in prognosticating survival in the second-line chemotherapy of POC patients.
- * The prognostic favourable impact of a response (CA125 criteria) is specific for patients receiving either topotecan or paclitaxel+carboplatin combination but possibly also for other second-line chemotherapy regimens.
- * CA125-based response criteria should be accepted by regulatory authorities in the drug approval process of new agents in the treatment of ovarian cancer.
- * As prolongation of survival is a major goal in second-line treatment, CA125-based response criteria should be preferred to imaging-based response criteria in the monitoring of second-line chemotherapy in the individual patient.

**7. PROGNOSTIC FACTORS FOR SURVIVAL:
PRE-TREATMENT PARAMETERS**

A prognostic factor may be defined as a factor at a given time point that forecast the subsequent clinical outcome (survival) (25). In ovarian cancer patients, multiple prospective and retrospective studies have reported various clinico-pathological, biochemical and molecular biological parameters as prognostic factors for survival (57, 151). A comprehensive review of prognostic factors in ovarian cancer has been published by Bösze (25), and by Eisenhauer et al (57). The present chapter focuses on the pre-treatment prognostic factors that are available prior to the onset of the second-line treatment. The prognostic factors related to the surgical treatment (chapter 4) and the antineoplastic treatment (chapter 6) have previously been discussed.

7.1 CLINICAL PARAMETERS

The prognostic factors for survival in 189 Danish patients with POC are depicted in Table 21. The patient data were retracted from the CODOVA database (chapter 3.2.2). The chosen time point for prognostication was after the diagnosis of POC before the start of second-line treatment. The results from the uni- and multivariate analyses of survival have not previously been published, albeit the patient cohort was identical to the validation cohort in the study by Grønlund [X].

The clinical parameters, treatment-free interval, time to relapse/progression, and performance status at time of diagnosis of POC, were all identified to have independent prognostic information on survival (Table 21). The parameters, treatment-free interval and performance status at time of POC, are both well-known prognostic factors for survival (25, 57), and the analyses thus confirm these parameters as important prognostic factors for survival. The parameter, time to relapse/progression, is rarely used in clinical studies of ovarian cancer, albeit used in an important study of prognostic factors by Hoskins (81). Noteworthy, in patients where the chemotherapy is initiated shortly after diagnosis of POC, the length of the time to relapse/primary progression is almost equal to the duration of the first-line chemotherapy plus the treatment-free in-

terval. Other well-established prognostic factors such as FIGO stage, residual disease following initial staging surgery, initial performance status were all found to be statistically significant in the univariate analyses of survival, but of no independent prognostic value in the multivariate analyses probably due the number of patients (n = 189). The prognostic power of a factor in a statistical model is dependent on the applied statistical model used to capture its power and with the other factors included in the model (25). In this analysis, only significant variables from the univariate analyses were included in the multivariate analysis.

Conclusion

- * The clinical parameters, treatment-free interval, time to relapse/progression, and performance status at time of diagnosis of POC, are confirmed as independent prognostic factors for survival.

7.2 TUMOUR MARKERS

The pre-treatment determination of serological tumour marker levels before start of second-line treatment may provide prognostic information that is independent from the abovementioned conventional clinical parameters.

7.2.1 CA125

In the present homogeneous Danish patient cohort (X), the pre-treatment CA125 level was found to be an independent prognostic factor for survival (Table 21). A high pre-treatment level of CA125 was associated with worsened prognosis. The potential prognostic value of CA125 in patients with POC has been examined in three other studies (Table 22). In a prospective study by Grønlund et al [IX] of a cohort of POC patients not included in the CODOVA, the parameter, pre-treatment CA125 level, was not found to be significantly associated with survival by any of the cut-offs (35, 65, 132 U/ml). In a retrospective study of 135 pre-treated ovarian cancer patients by Makar et al (97), independent prognostic factors for survival were, histological type (clear cell vs. other; P <0.0001), and pre-treatment CA125 level (≤35 U/ml vs. >35 U/ml; P <0.01). In another retrospective study of 60 pre-treated ovarian cancer patients by Gaducci et al (64), survival was significantly related to time to re-

Table 22. Prognostic value of pre-treatment determination of serological tumour markers in patients with POC.

Tumour marker	Prognostic value	No.	Study (ref.)	Year
CA125	+	135	Makar et al (97)	1993
	-	60	Gaducci et al (64)	1997
	-	70	Grønlund et al [IX]	2005
	+	189	Grønlund et al [X]	2005
CASA	+	70	Grønlund et al [IX]	2005
Tetranectin	+	70	Deng et al (47)	2000
YKL-40	+	70	Dehn et al (46)	2003

The table only includes results from multivariate analyses.

lapse (≤ 12 vs. > 12 months; $P < 0.001$), but not to the pre-treatment CA125 level before start of second-line chemotherapy at any of the examined CA125 cut-offs (35, 76, 178, 339 U/ml). The different findings in the studies (Table 22) might be explained by heterogeneous patient populations and different first-line chemotherapy regimens.

In primary ovarian cancer, several other studies have examined the prognostic value of single measurement of the CA125 level before the start of first-line chemotherapy. Overall, the results have been contradictory (78, 97, 111, 115), because only some of the studies were able to demonstrate that CA125 supplied independent prognostic information.

7.2.2 CASA

In a prospective study by Grønlund et al, the prognostic value of the pre-treatment CASA level was examined [IX]. Serum levels of CASA were prospectively determined in 70 consecutive patients with POC before the start of second-line chemotherapy. Median level of serum CASA was 6.5 U/ml (range: 0.2–1437 U/ml). Univariate analysis showed, that patients with a CASA level more than 10.0 U/ml had significantly shorter survival compared to patients with CASA level less than, or equal with 10.0 U/ml ($P = 0.002$). Using different CASA cut-off levels (6.0, 6.5, 10.0 U/ml), multivariate Cox analyses identified CASA as an independent prognostic factor for survival at every cut-off level. A strong prognostic function for CASA was found at a cut-off level of 10.0 U/ml (> 10 U/ml vs. ≤ 10 U/ml; HR: 2.7; 95% CI: 1.6–4.7; $P < 0.001$).

In primary ovarian cancer, an adverse prognostic impact of an elevated pre-treatment CASA level has been reported in several studies (50, 77, 83, 90, 117, 173), whereas the prognostic value of CASA determination in patients with POC has only been reported by Grønlund et al [IX].

7.2.3 Other tumour markers

Studies on the prognostic value of the pre-treatment level of other tumour markers in patients with POC are few (Table 22). The studies have demonstrated an adverse prognostic impact of low tetranectin levels (< 9.3 vs. > 9.3 mg/l; HR: 2.1; $P = 0.005$) (47) and high levels of YKL-40 (> 160 vs. < 160 mg/ml; HR: 2.3; $P = 0.006$) (46).

In a preliminary study, the prognostic value of a panel of serological tumour markers (tetranectin, YKL-40, CASA, and CA125) was evaluated. In 82 consecutive POC patients from the CODOVA database, stored serum samples were analysed and pre-treatment serum levels of the tumour markers were correlated with overall survival. The results suggest that tetranectin might be a better prognosticator than CA125, CASA and YKL-40 (unpublished data).

Most studies of the prognostic value of serological tumour marker measurement in ovarian cancer have been performed in patients with primary disease. The results from the many studies are reviewed elsewhere (105, 164). Åvall-Lundqvist evaluated the prognostic value of several tumour markers (CA125, TPA, neopterin, CRP, SCC, TK, CEA), and found poor prognosis related to elevated levels of TPA, followed by neopterin and CRP (7). However, the clinical use of prognostic tumour markers in primary disease is limited, because all patients with advanced disease are offered standardized first-line chemotherapy irrespective of the appearance of adverse tumour markers (12, 73). Contrary, POC represents another clinical setting in which the decision to onset a palliative second-line chemotherapy should be balanced toward many parameters not least the presence of adverse prognostic tumour markers.

In primary ovarian cancer, recent studies have examined the prognostic impact of newer molecular biological markers and immuno-histochemical markers (65, 105). These marker analyses might require tumour specimen, which is easily obtainable from the cytoreductive surgery in relation to the initial staging operation (primary surgery). Contrary, in patients with POC, secondary cyto-

reductive surgery (chapter 4) is not standard procedure and usually tissue samples are not available for molecular biological marker analyses in these patients. As the goal of treatment in patients with POC is palliation, it is questionable if tissue-based marker analyses will be useful in the clinical management outside investigational protocols. This fact highlights the feasibility of serological tumour marker measurement.

Conclusions

- * High levels of CA125 and CASA, respectively, before start of second-line treatment is independently associated with poor prognosis.
- * Serum measurements of CA125 and CASA may thus serve as additional clinical tools in the selection of therapy options in the treatment of patients with POC.
- * The results from a preliminary study of a panel of tumour markers (tetranectin, YKL-40, CASA, and CA125) suggest that tetranectin might be a better prognosticator than CA125, CASA and YKL-40.

7.3 THE COPENHAGEN INDEX

The combination of several prognostic factors in an index may provide additional prognostic information compared to the use of a single prognostic factor. In POC patients, only Hoskins et al has combined several prognostic factors (The Canadian prognostic index) in an index for the use of prognostication (81). The authors suggested a three-covariate prognostic index (tumour grade at diagnosis, initial performance status, and time to relapse/progression (TRP)). Three prognostic groups are defined: (I) *good prognosis group* consisted of patients with either TRP more than 18 months and a grade 1-2 tumour, or TRP more than 24 months and a grade 3 tumour (II) *intermediate prognosis group* included either patients with TRP 18-24 months and a grade 3 tumour, or TRP less than 18 months and an initial performance status of 2 or better, and (III) *poor prognosis group* of patients with TRP less than 18 months and an initial performance status of 3 (81).

The validation of the Canadian index in a European patient population was first conducted by Grønlund et al [X]. Despite differences in patient characteristics, the Canadian index validated in the Danish patient population revealed a statistical significant difference in survival between the prognostic groups *good* and *intermediate* ($P < 0.0001$), whereas there was no significant difference in survival between the prognostic groups *intermediate* and *poor* ($P = 0.51$) (Figure 5). The accuracy of the Canadian index could thus not be overall confirmed in the Danish validation group, because the index failed to discriminate between the risk groups *intermediate* and *poor*. The Canadian index is weakened by the fact that the index lacks detailed information of the clinical picture at time of relapse/progression. In order to improve the performance of the Canadian index, an updated prognostic model (The Copenhagen index) was constructed by Grønlund et al [X]. The final model was: 0.8 (performance status) + $0.33 \log$ (CA125) – $1.31 \log$ (treatment-free interval). The improved model was a good predictor of one-year survival (AUC 0.85; logistic regression; $P < 0.0001$). The median survival (with 95% CI) of the four prognostic groups (A-D) was 50.6 (34.0- not available), 25.0 (22.1-33.6), 11.3 (8.5-12.9), and 5.2 (3.5-6.3) months, respectively (Figure 6).

The overall credibility of the Copenhagen index was emphasized by using clear definitions (treatment-free interval, TRP), well-established tumour marker assays (CA125), and internationally recognized classification systems (tumour stage (FIGO), tumour histology (WHO), performance status (WHO)) for the variables included in the multivariate survival analyses underlying the model. The transportability of the Copenhagen index remains to be evaluated. The four-groups Copenhagen index, as well as other prognostic indices, was constructed to obtain the largest discrimination possible in the present population. Therefore, a validation in independent

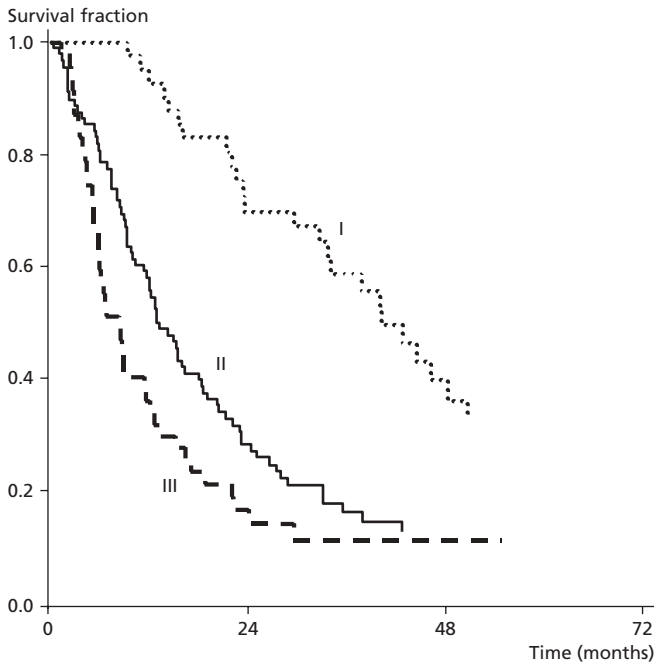


Figure 5. Survival: Canadian prognostic index evaluated in Danish patients. I: Good prognosis. II: Intermediate prognosis. III: Poor prognosis. Reproduced from (X) with permission from Elsevier, copyright (2005).

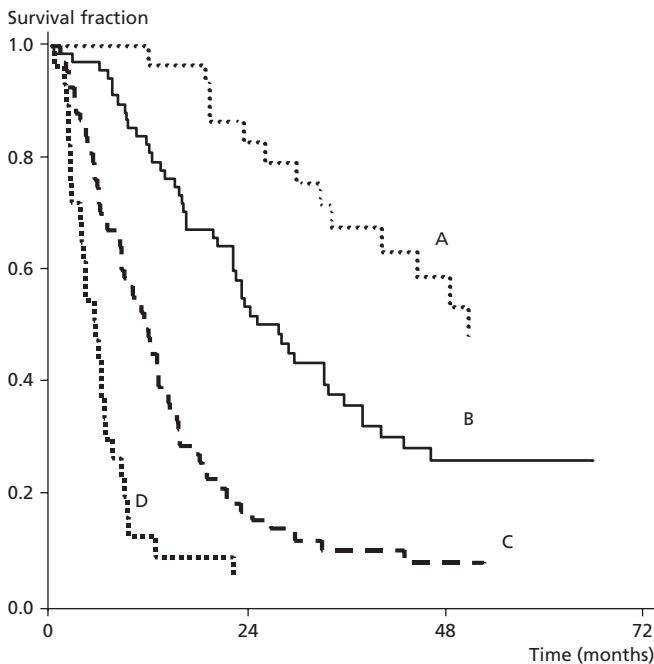


Figure 6. The Copenhagen prognostic index. A: Excellent prognosis. B: Good prognosis. C: Fair prognosis. D: Poor prognosis. Reproduced from (X) with permission from Elsevier, copyright (2005).

data sets is needed. The Copenhagen prognostic index may have potential application both in trials and in clinical practice.

Conclusions

- * The Copenhagen index is a novel three-covariate model (CA125, performance status, treatment-free interval) for the use of prognostication in patients with POC.
- * In trials, the Copenhagen index may be used to adjust for imbalances between patient groups in the design and analysis of studies. Moreover, the index may be used to control for confounding factors in observational studies of treatment efficacies.
- * In clinical practice, the Copenhagen index might be used to identify risk groups that may benefit from alternative treatment strategies. Furthermore, the index may serve as a guide for the

clinician to balance the probability of a favorable outcome toward the toxicity of the treatment.

8. SUMMARY AND FUTURE ASPECTS

In the absence of preventable etiological factors and with inadequate screening techniques for epithelial ovarian cancer patients, improved clinical management is the strategic challenge. Whereas the surgical and the cytotoxic treatment of patients with primary ovarian cancer is standardized and internationally agreed, the optimal management of patients with POC is presently not settled. Based on the clinical data from a large cohort of POC patients (The CODOVA database), recent treatment strategies have been challenged and new hypotheses generated. This thesis reviews the results from these studies and discusses the clinical application of the results.

It was demonstrated that POC patients with a solitary tumour had increased probability for complete secondary cytoreduction. The selection criteria for an optimal candidate for secondary surgery should be re-evaluated and include the parameters: solitary tumour, tumour size less than 10 cm, favourable performance status, and no prior second-line chemotherapy before surgery. We found that secondary surgical cytoreduction in POC patients has dubious impact on survival. The application of secondary surgery should be based on evidence from randomised trials. Unfortunately, such a trial comparing patients randomised to surgery versus no surgery, and equivalent chemotherapy (Larocson EORTC 55963) has recently been discontinued which limits the probability that level I evidence will ever prevail in this clinical setting.

The optimal cytotoxic regimen in POC patients is presently elucidated in multiple randomised trials. In POC patients with platinum-sensitive disease, the combination of two cytotoxic agents has proven favourable to single-agent therapy (carboplatin) in terms of prolonged survival. Regarding the potential of increased toxicity by combination chemotherapy, we found no evidence of increased neurotoxicity by using a re-treatment regimen of paclitaxel+carboplatin in paclitaxel+platinum pre-treated patients. Which agent that should be combined with carboplatin, and whether the other agent should be administered as combination chemotherapy or sequentially, is presently under evaluation.

In POC patients with platinum-resistant disease, the combination of two agents compared with single-agent treatment has, so far, added nothing but increased toxicity. In a Scandinavian, multi-centre phase I-II study, we found unpredictable toxicity by a sequential regimen of topotecan (iv) and oral etoposide. Moreover, it was found that the therapeutic index of single-agent topotecan might be improved by using a low-dose regimen (1.0 mg/m² days 1-5 every 3 weeks) compared to the full-dose FDA-approved regimen (1.5 mg/m² days 1-5 every 3 weeks). We demonstrated no difference in haematological toxicity between older (≥65 years) and younger (<65 years) patients, and the choice of second-line antineoplastic treatment in patients with POC should thus be based on other parameters than the chronological age. The high response rates reported in recent phase II trials of platinum-based combination chemotherapy in patients with "platinum-resistant" disease challenges the concept of platinum-sensitivity as a treatment guide in patients with POC. Thus, there is a need to reveal more accurate clinical predictors of the efficacy of the second-line treatment.

In the last decade, clinical studies have explored the impact of newer pathway-targeted agents directed against growth factors, cellular receptors, angiogenesis, signal transduction, apoptosis, and cell-cycle regulation in patients with solid tumours. In ovarian cancer patients, the impact of the combination of conventional cytotoxic agents and the newer "biologicals" is presently planned elucidated in randomised trials (e.g. ICON7). Furthermore, gene therapy, immunotherapy and matrix metallo-proteinase inhibitors may have a potential application in the treatment of POC.

We demonstrated that stable disease during second-line chemotherapy of POC is associated with a survival benefit compared to pa-

tients with PD. Stabilization of the tumour burden should thus be considered as a reasonable treatment outcome, because POC is considered as an incurable disease and extension of survival is among the main therapeutic goals. Recently, a new treatment concept, treatment beyond disease progression, has emerged. Conventional oncological practice suggests that if tumour progression occurs during therapy further treatment with the same agent is not indicated. Whether this holds true also for the novel biological agents with minimal toxicity and distinct non-cytotoxic effects remains to be determined.

Contrary to primary ovarian cancer, tumour tissue is rarely available in POC patients outside clinical trials. This fact highlights the utility of serological tumour markers in the clinical management of the disease. We found that tumour marker based response evaluation (CA125) was more accurate than classical imaging-based response evaluation in prognosticating survival in the second-line chemotherapy. CA125-based response criteria should thus be accepted by regulatory authorities in the drug approval process of new agents in the treatment of ovarian cancer. In the individual patient management, CA125-based response criteria should be preferred to imaging-based response criteria in the monitoring of second-line chemotherapy.

We found the serological tumour markers CA125 and CASA, respectively, to be prognostic factors for survival in patients with POC. The tumour marker, CA125, was included in a novel three-covariate prognostic index (The Copenhagen Index) with potential use both in trials and in the individual patient management. The transportability of the Copenhagen Index should be validated in another data set. Preliminary data from a study of the prognostic impact of a panel of serological tumour markers (tetranectin, YKL-40, CA125, CASA) suggest that tetranectin might be a better prognosticator than the other markers. Future studies should reveal if the combination of several serological tumour markers in an index gives added prognostic information. Overall, the findings in the thesis infer an increased confidence in the use of serological tumour markers in the clinical management of patients with POC.

The technological advances in genomic and proteomic technologies have boosted the discovery of numerous novel molecular markers, but their use and validation in the clinical management of ovarian cancer remains largely to be studied. The identification of distinct classes of POC patients using microarray chips will probably facilitate the identification of patients that will benefit from pathway-targeted therapy. Moreover, the molecular markers will increase our knowledge of the biology of malignant epithelial ovarian tumours, and the differences between primary ovarian cancer and POC.

Improved clinical management in patients with POC may result from new therapies, but, as the treatment goal of POC patients for a while remains palliation, major improvements may also come from individualised treatment based on an overall evaluation including the patient symptoms, previous toxicity, quality of life, and also patient preference and cost of treatment.

THE THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

- I. Grønlund B, Lundvall L, Christensen IJ, Knudsen JB, Hogdall C. Surgical cytoreduction in recurrent ovarian carcinoma in patients with complete response to paclitaxel-platinum. *Eur J Surg Oncol* 2005; 31(1): 67-73.
- II. Grønlund B, Hogdall C, Hansen HH, Engelholm SA. Results of reinduction therapy with paclitaxel and carboplatin in recurrent epithelial ovarian cancer. *Gynecologic Oncology* 2001; 83(1): 128-34.
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- IV. Grønlund B, Engelholm SA, Horvath G, Mäenpää J, Ridderheim M. Sequential topotecan and oral etoposide in recurrent ovarian carcinoma pretreated with platinum-taxane. Results from a multicenter phase I/II study. *CANCER* 2005; 103(7): 1388-96.
- V. Grønlund B, Hogdall C, Hansen HH, Engelholm SA. Performance status rather than age is the key prognostic factor in second-line treatment of elderly patients with epithelial ovarian carcinoma. *CANCER* 2002; 94(7): 1961-67
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- IX. Grønlund B, Dehn H, Hogdall C, Engelholm SA, Jørgensen M, Nørgaard-Pedersen B, Hogdall EVS. Cancer-associated serum antigen (CASA) level: a novel prognostic indicator for survival in patients with recurrent ovarian carcinoma. *Int J Gynecol Cancer* 2005; 15 (5): 836-43.
- X. Grønlund B, Christensen IJ, Bülow-Lehnsby AL, Engelholm SA, Hansen HH, Hogdall C. Recurrent epithelial ovarian cancer: validation and improvement of an established prognostic index. *Eur J Obstet Gyn Rep Biol* 2005; 123 (1): 98-106.

The publications are referred to in the text by their Roman numerals.

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