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Positron Emission Tomography using F-18 Fluorodeoxyglucose for Monitoring Neoadjuvant Chemotherapy in Advanced Stage Ovarian Cancer

Stefanie Sassen

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ABBREVIATIONS

Bq	Becquerel
β^+	Positron
cm	Centimeter
CA125	Cancer Antigen 125
CT	Computed Tomography
CTx	Chemotherapy
d	Days
e^-	Electron
FBP	Filtered Backprojection
FDG	Fluorodeoxyglucose
FDG-PET	Positron Emission Tomography using FDG
FIGO	International Federation of Gynecologic Oncology
FWHM	Full Width at Half Maximum
g	Gram
GLUT	Glucose Transport Protein
l	Liter
MBq	Megabecquerel
mCi	Millicurie
min	Minute
ml	Milliliter
mm	Millimeter
MR	Magnetic Resonance
NPV	Negative Predictive Value
n	Neutron
n	Number
ns	Nanosecond
ν	Neutrino
p	Proton
PPV	Positive Predictive Value
sec	Second
SUV	Standardized Uptake Value
SUVav	SUV for average activity values
SUVav-glc	SUVav normalized to blood glucose
SUVmax	SUV for maximum activity values
SUVmax-glc	SUVmax normalized to blood glucose
SUVmean	Mean SUV of all metastatic tumor lesions per patient
$t_{1/2}$	Physical Half-life
U/ml	Units per Milliliter

1 Introduction

Ovarian cancer is the fifth most common cancer in women in Western Europe and the United States and the most common cause of death among women with gynecologic malignancies [43, 139]. One of every 55 women will develop ovarian cancer during her lifetime resulting in approximately 9500 new cases and 6000 deaths in Germany annually [13, 87].

The majority of ovarian cancer (approximately 90%) is of epithelial origin arising from the ovarian surface epithelium and occurring predominantly in patients between ages of 40 and 65 [105]. Epithelial ovarian cancer is comprised of four histological subtypes: approximately 65-70% are serous, 10-15% endometrioid, 10% mucinous, and 6% clear cell carcinoma [91, 105]. Germ cell malignancies account for up to 5% of all primary ovarian malignancies and occur most commonly in women younger than 30 years [105]. Rare malignancies include lipoid cell tumors, sarcomas or metastases from breast or colorectal cancer. Approximately 10% of all ovarian malignancies and 60-70% in women <40 years of age are borderline tumors. These tumors exhibit low malignant potential and carry a good prognosis with a 5-year survival of 96-99% when diagnosed in early stages [106, 126].

The pathogenesis of ovarian malignancies is still unknown. Genetic mutations related to ovarian carcinogenesis have been identified in multiple genes. Mutations with the largest effect on ovarian cancer risk are within the breast cancer genes, BRCA1 and BRCA2 [119]. In addition B-raf and K-ras mutations are found in low-grade serous carcinomas [14, 20], K-ras mutations in mucinous carcinomas [21], and β-catenin and PTEN mutations and microsatellite instability are frequently observed in endometrioid carcinomas [109]. High-grade serous carcinomas are often associated with p53 mutations [14, 60], amplification and overexpression of HER-2/neu and AKT-2 oncogenes [109, 113], as well as altered expression of proteins involved in adhesion, invasion, and angiogenesis [49, 57, 109]. Tumor cell surface-associated proteolytic enzyme systems such as the urokinase-type plasminogen activator (uPA) and its inhibitor (PAI-1) have been shown to play an important role in tumor invasion and the development of metastases [2, 62].

No reliable screening modalities for ovarian cancer have been established to date. As patients are generally asymptomatic when the disease is confined to the ovary, about 70% of women with ovarian cancer have advanced stage of disease at initial diagnosis. Considering all stages, the overall 5-year survival rate is about 40% in patients <50 years of age at diagnosis and 15%

for patients >50 years of age at diagnosis [79]. In advanced stages, ascites is a frequent finding in symptomatic patients.

Most patients with ovarian cancer present with an adnexal or pelvic mass; however, the majority of patients with adnexal or pelvic masses (70-95%) do not have malignancy [16]. Besides physical examination, ultrasonography (transvaginal or abdominal) is the most common imaging procedure for characterization of adnexal masses. Although not routinely used in the preoperative evaluation, computed tomography (CT) and magnetic resonance (MR) imaging are frequently helpful in determining the extension, size, and origin of a pelvic mass. However, malignant and non-malignant findings cannot be differentiated reliably by routine diagnostic imaging procedures. Invasive procedures are necessary to establish the diagnosis in patients suspected of having ovarian cancer; either laparoscopy or laparotomy, with removal and histologic examination of the suspicious mass. The stage of ovarian cancer is defined according to the FIGO (International Federation of Gynecology and Obstetrics) classification, based on findings at surgical exploration (see Annex 2).

Cancer antigen 125 (CA125) is a high-molecular weight glycoprotein expressed on the surface of most serous ovarian carcinomas, as well as adult pleura, pericardium and peritoneum [136]. CA125 surface antigen is partly released into the serum and detectable by a monoclonal antibody assay. The use of the CA125 serum tumor marker for initial diagnosis of ovarian cancer is limited. While CA125 is elevated in up to 80% of women with stage III and IV ovarian cancer, only 40-60% of women with stage I disease have elevated levels [91]. Furthermore, its specificity for ovarian cancer is low as CA125 levels may also be elevated in benign ovarian tumors and malignancies of the uterus, cervix, pancreas, liver, colon, breast, lung, and digestive tract. Non-cancerous conditions including endometriosis, uterine adenomyosis, pelvic inflammatory disease, peritonitis, pleuritis, pancreatitis, liver disease, heart and renal failure, menstruation and pregnancy may also be associated with elevated CA125 levels [136].

Management of advanced ovarian cancer consists of tumor debulking surgery followed by chemotherapy [102]. The combination of paclitaxel with a platinum compound is currently the standard chemotherapy [83]. This regimen results in a high overall initial response rate of about 60-70% with a clinical complete remission rate of approximately 50% [18, 25, 72, 86]. In advanced-stage patients who achieve a complete remission after six cycles of chemotherapy, approximately 25% to 30% will have no evidence of disease at second-look laparotomy [79]. However, despite clinical complete remission the median time to progression in these patients

remains less than 2 years [15]. In patients not responding to paclitaxel/platinum based chemotherapy, second-line chemotherapeutic agents such as anthracyclines or gemcitabine are available [69].

The most important prognostic factor in patients with ovarian cancer is the extent of residual disease after cytoreductive surgery. Several studies have shown improved survival for patients with minimal (<1-2 cm) or no residual tumor after surgical resection [26, 36, 46, 66]. Two meta-analyses demonstrated an increase in median survival of 20-22 months [6] or 6.3% for each 10% increase in cytoreduction [10]. However, optimal cytoreductive surgery can only be achieved in 35-50% of women with advanced ovarian cancer [6, 51].

Neoadjuvant chemotherapy refers to the administration of cytotoxic chemotherapy prior to surgery. Several studies showed that optimal surgical cytoreduction (<1 cm residual tumor) can be achieved significantly more often in advanced-stage patients who underwent neoadjuvant chemotherapy. Several retrospective studies reported equivalent overall survival in patients treated with neoadjuvant chemotherapy, while operating time, intraoperative blood loss, and postoperative hospital stay were statistically reduced in this group [29, 53, 63, 75, 80, 83, 103, 104, 121, 129].
At our university hospital, neoadjuvant chemotherapy has been applied within clinical treatment protocols for more than 10 years. Thorough selection of candidates for neoadjuvant chemotherapy is critical. A retrospective analysis of patients with FIGO stage IIIC and IV ovarian cancer revealed large ascites volume to be highly predictive of primary nonresectable advanced ovarian cancer [63]. Improvement in survival of patients treated with neoadjuvant chemotherapy was demonstrated in a prospective nonrandomized Phase II study, consisting of 63 patients with FIGO stage IIIC and IV ovarian cancer and large ascites volumes >500 ml. Median overall survival was 42 months in patients treated with neoadjuvant chemotherapy, compared to 23 months in conventionally treated patients [63]. The only randomized prospective trial to date that directly compares neoadjuvant chemotherapy followed by cytoreductive surgery with the conventional approach of initial surgery followed by postoperative chemotherapy is still ongoing [27].

The increasing use of neoadjuvant chemotherapy in solid tumors necessitates methods for accurate staging as well as modalities to accurately predict and assess response to treatment. Patients not responding to chemotherapy may benefit from immediate surgery or second-line chemotherapy. The current endpoint for assessing response to therapy in solid tumors is by measuring the change in tumor size. According to the newly defined RECIST criteria (response evaluation criteria in solid tumors), response is defined as a decrease of the maximum tumor

diameter by at least 30% [122]. Frequently, changes in tumor size are measured by CT imaging. However, in ovarian cancer the accuracy of CT imaging to assess changes in tumor volume is limited by the difficulty to precisely determine the extent of disease in the peritoneal cavity [59]. Changes in the serum levels of the tumor marker CA125 are often used in addition to standard response criteria. The Gynecologic Cancer Intergroup (GCIG), consisting of representatives from the major gynecologic cancer trial groups around the world, recently defined CA125 response as a decrease from baseline of at least 50% [96]. However, only a few studies addressed the role of CA125 in the setting of neoadjuvant chemotherapy, and no study has been published to date that prospectively demonstrated a correlation between response according to CA125 or RECIST criteria and patient outcome.

The assessment of changes in tumor metabolism instead of changes in tumor size offers an alternative for visualizing therapeutic effects. Positron emission tomography (PET) is a functional imaging modality that allows noninvasive assessment of biological tissue characteristics by using specific radiolabeled probes. Biologic molecules, such as metabolic substrates, receptor ligands, antibodies, drugs, neurotransmitters, and others are labeled with positron emitters. Ideally, the labeling process results in a high specific activity and does not change the physical or biochemical characteristics of the biologic molecule. The radiotracer should follow the same pathway within the human body as the non-labeled physiologic counterpart. PET is measuring the concentration of positron emitting radionuclides and provides a series of cross-sectional images representing the radiotracer distribution within the body. The “tracer principle” was first established by George de Hevesy who applied the radiotracer method to medical science by studying the physiologic course of radioactive phosphorus [40]. George de Hevesy was later awarded the Nobel Prize in Chemistry for the discovery of the radiotracer principle [76].

The current PET instrumentation provides very high sensitivity and enables the detection of positron emitting radiotracers in the nano- and picomolar range. The ability to perform accurate attenuation correction by taking the photon absorption within the body into account allows translating measured count rates into absolute tracer concentrations (Becquerel/voxel). First introduced in the early 1970s, PET studies initially focused on imaging functions of the brain and heart [23, 123]. With the development of whole body PET scanners, PET has gained widespread use for oncological applications.

The radiolabeled glucose analogue F-18 fluorodeoxyglucose (FDG) is currently the most commonly used PET tracer. Gallagher et al. [34] and Ido et al. [52] first described the synthesis and

biodistribution of FDG. FDG is stable in blood, crosses the cell membrane through facilitated transport via glucose transport proteins (GLUT), and is then phosphorylated by intracellular hexokinases similar to glucose. FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase. Subsequently, FDG-6-phosphate accumulates in cells since it can no longer pass the cell membrane and the enzyme level of glucose-6-phosphatase is generally low in most cells. The use of FDG for oncological applications is based on the elevated glucose metabolism of tumor cells, which was first described by Warburg [132]. The increased FDG uptake in cancer depends on numerous factors, including the expression of glucose transport proteins, hexokinase levels, oxygen tension, blood glucose and insulin levels, cell-cycle status, adenosine triphosphate levels, receptor status, and others [3].

Various methods are used to describe the FDG uptake into tissue. Sokoloff et al. introduced a three-compartment model for the autoradiographic measurement of local cerebral glucose utilization using C-14 2-deoxy-D-glucose [115]. Subsequent reports have described the kinetics of radiolabeled deoxyglucose and fluorodeoxyglucose (FDG) *in vivo* [47, 85, 115]. The Patlak-Gjedde analysis, one of the most common tracer kinetic models for FDG, estimates the tracer tissue influx rate by relating radioactivity concentrations in the tissue over time (output function) with radioactivity concentrations in the blood over time (arterial input function) [84]. Standardized uptake values (SUV) are semiquantitative measures of FDG uptake and reflect the tracer accumulation in tissue at a single time point. SUVs are based on the assumption that the integrated tracer concentration in plasma and tissue is proportional to the injected dose of the radiotracer and inversely proportional to body weight [120]. SUVs represent the most common approach for quantification of FDG uptake in tumors and provide a stable and highly reproducible measure in oncological PET imaging [73, 88, 135].

FDG-PET provides accurate characterization of tumors and detection of tumor infiltrated lymph nodes and distant metastasis [88]. Currently, FDG-PET is used for the diagnosis and staging of various types of tumors in many countries. However, its utility in the diagnosis of primary ovarian cancer is limited. Hübner et al. were the first to evaluate FDG-PET for the diagnosis of primary and recurrent ovarian cancer in a small group of patients [48]. Subsequent larger series by Grab et al. and Fenchel et al. showed a low specificity of FDG-PET in differentiating malignancy from benign inflammatory lesions in patients suspected of having ovarian cancer [31, 35]. Inflammatory processes are the most common differential diagnosis in asymptomatic adnexal masses. A study at our university hospital by Römer et al. also found a low specificity of FDG-PET for the diagnosis of primary ovarian cancer, with false-positive

results in 4 patients with benign inflammatory lesions and in 2 of 7 patients with non-inflammatory benign lesions [89]. In addition, FDG-PET was limited in the primary evaluation of asymptomatic adnexal masses by the low FDG uptake of borderline tumors and early stage ovarian cancer.

In contrast, the same study demonstrated FDG-PET to be highly sensitive and specific in detecting recurrent ovarian cancer where inflammatory processes play a minor role in the differential diagnosis. FDG-PET correctly identified and localized recurrence in 4 of 5 patients with elevated CA125 levels after cytoreductive surgery [89]. While rising CA125 levels are a highly sensitive indicator of recurrent disease, it is often difficult to localize the disease by standard imaging procedures [55, 59]. FDG-PET allowed differentiating post-treatment fibrotic tissue and viable tumor, which frequently display similar radiographic appearance. Therefore, FDG-PET provided accurate diagnosis of recurrent ovarian cancer [55, 77, 88, 124, 140, 141].

PET/CT is a new imaging modality that allows the acquisition of spatially registered PET and CT data in one imaging procedure [125]. Using a combined PET/CT scanner may improve anatomic localization of lesions and may help to distinguish physiologic tracer uptake, e.g. in the bowel or urinary tract, from disease processes. The use of PET/CT for the diagnosis of primary and recurrent ovarian cancer has only been described in case reports thus far [68, 82, 112].

Sequential FDG-PET imaging performed at baseline and after completion of chemotherapy allows assessment of changes in tumor glucose metabolism. The decrease in tumor FDG uptake after completion of therapy correlates with the reduction of viable tumor cells and reflects the effectiveness of anti-tumor treatment. Numerous studies in various types of tumors have successfully used FDG-PET for assessment of response after completion of chemotherapy (for recent review see [4]).

Sequential FDG-PET imaging was also used for prediction of response early after initiation of therapy based on the concept that a decrease in tumor glucose metabolism (FDG uptake) correlates with the effectiveness of treatment. Studies in malignant lymphoma, osteosarcoma, breast and esophageal cancer found a significant correlation between early changes in FDG uptake during chemotherapy or radiotherapy and subsequent histopathologic tumor regression and patient survival [12, 42, 54, 81, 99, 100, 131, 134]. A potential clinical application of predicting response early in the course of therapy by sequential FDG-PET imaging is to avoid ineffective chemotherapy and to assist in patient stratification for individualized therapy [4].

No studies are available so far describing changes in FDG uptake in patients with advanced stage ovarian cancer undergoing neoadjuvant chemotherapy. This thesis prospectively evaluated the hypothesis that early changes in tumor glucose utilization assessed by sequential FDG-PET predict the effectiveness of chemotherapy and subsequent patient outcome.

1.1 Aim of the study

The overall goal of this thesis was to evaluate changes in tumor glucose utilization assessed by sequential FDG-PET as surrogate endpoint to determine response to neoadjuvant chemotherapy in patients with advanced stage (FIGO IIIC and IV) ovarian cancer.

In an interdisciplinary collaboration between the department of nuclear medicine, the department of obstetrics and gynecology, and the institute of pathology at the Technische Universität München, patients undergoing neoadjuvant chemotherapy for advanced ovarian cancer were studied with sequential FDG-PET. The relative decrease in FDG uptake between baseline and after the first and third cycle of chemotherapy was compared with clinical and histopathologic response. The overall survival served as reference.

Specific aims of the study:

I. Evaluation of sequential FDG-PET for prediction of treatment response after the first and third cycle of chemotherapy.

   a) To evaluate metabolic response after the first cycle of chemotherapy by using a previously defined threshold of 20% decrease in FDG uptake.

   b) To retrospectively determine the optimal threshold for differentiation between metabolic responders and non-responders after the first and third cycle of chemotherapy by survival analysis.

   c) To assess the correlation between metabolic response after the first and third cycle of chemotherapy.

II. Comparison of different methods for normalization of standardized uptake values (SUV) with regard to their ability to predict response to therapy.

III. Comparison of FDG-PET (metabolic response) with clinical criteria, changes in tumor marker CA125, and histopathologic criteria with regard to their ability to predict response to chemotherapy.

2 Patients and Methods

2.1 Patients

Study patients were recruited from the Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Munich. Patients who presented with newly diagnosed advanced ovarian cancer FIGO stage IIIC or IV and large ascites volumes >500ml, and participated in a prospective neoadjuvant treatment protocol, were eligible for this study. Histological diagnosis was confirmed by diagnostic laparoscopy in all patients prior to inclusion. Exclusion criteria were known diabetes, pregnancy and <18 years of age. Patients with a second malignancy or chemotherapy or radiotherapy within the last six months were also excluded. A physician explained details of the study and written informed consent was obtained in all patients. The Institutional Review Board of the Technische Universität München approved the study protocol.

Between 1998 and 2001, a total of 37 patients undergoing neoadjuvant chemotherapy followed by tumor debulking surgery and postoperative chemotherapy were enrolled in the study, of which 4 were excluded because they did not undergo surgery (n=2), had a secondary malignancy discovered at surgery (n=1) or did not complete FDG-PET imaging (n=1). Thirty-three patients were available for therapy monitoring and follow-up. Standard neoadjuvant chemotherapy consisted of three cycles of carboplatin area under the curve (AUC) 5mg/ml/min plus paclitaxel 175mg/m² body surface area (BSA), administered at intervals of three weeks. For patients considered by the treating gynecologist to be in poor general state of health, single-agent carboplatin was administered alternatively. Twenty-two (66.7%) of thirty-three patients received the standard combination of carboplatin plus paclitaxel and eleven (33.3%) of thirty-three patients received single-agent carboplatin due to a poor performance status. Following neoadjuvant chemotherapy, all patients underwent standard debulking surgery, including bilateral adnectomy, high resection of ovarian blood vessels, hysterectomy, infragastric omentectomy, appendectomy, and pelvic and para-aortal lymphadenectomy. Additional abdominal surgery was performed according to tumor spread, such as resection of the small or large intestine, deperitonization of the pelvis, paracolic gutters and infradiaphragmatic area, as well as upper abdominal surgery, including pancreas resection, splenectomy and partial liver resection. The goal of all surgical procedures was to obtain tumor free status or macroscopically minimal residual tumor of less than 1cm. Standard postoperative chemotherapy consisted of another three cycles of carboplatin plus paclitaxel at the same doses

and was administered in twenty-seven (81.8%) of thirty-three patients. Adjustments in the chemotherapeutic regimen were undertaken in six (18.2%) of thirty-three patients, due to severe drug toxicity or supposed drug resistance, according to clinical judgment by the treating gynecologists. Five patients received single-agent treosulfan, topotecan, or fluoruracil, respectively. One patient received single-agent carboplatin due to a poor performance status.

Table 1 shows the characteristics of all thirty-three patients entered into the study. According to the inclusion criteria, all patients presented with FIGO stage IIIC or IV disease and large ascites volumes (>500ml) at initial diagnosis. Median age was 60 years, ranging from 34 to 76 years. Among the thirty-three tumors, histological diagnosis revealed 29 serous, 2 mucinous, 1 endometrioid, and 1 Müllerian tumor. Most tumors were poorly differentiated WHO-grade three to four. Median follow-up time was 48.8 months (range 38.3-70.6 months).

Patients [n = 33]	
Age, [years]	
Median	60
Range	34-76
Stage, [n]	
FIGO IIIC	23
FIGO IV	10
Histological Subtype, [n]	
Serous	29
Endometrioid	1
Müllerian (clear cell carcinoma)	1
Mucinous	2
Grade, [n]	
G2	3
G3	27
G3-4	3
Nodal Status, [n]	
N0	10
N1	12
NX	11
Ascites Volume, [n]	
>500ml	33

Neoadjuvant Chemotherapy, [n]	
Carboplatin plus Paclitaxel	22
Single-agent Carboplatin	11
Follow-up, [months]	
Median	49
Range	38-71

Table 1. Patient characteristics.

2.2 Principles of positron emission tomography (PET)

Positron emission tomography (PET) is a functional imaging modality that allows measuring the concentration of positron emitting radionuclides within the body. By using specific radiolabeled probes, PET imaging is able to provide *in vivo* noninvasive assessment of metabolic pathways and biologic tissue characteristics. The radiolabeled glucose analogue F-18 fluorodeoxyglucose (FDG) is currently the most commonly used PET tracer.

Various nuclear reactions can be used to produce F-18. The major route is to derive F-18 from an oxygen-18 (O-18) enriched water target in a cyclotron (particle accelerator). For this study, F-18 was produced with an 11-MeV self-shielded cyclotron (RDS 112, CTI/Siemens, Knoxville, TN, USA) by accelerating protons (p) onto an O-18 water target and initiating the following nuclear reaction: **O-18 (8p,10n) + p → F-18 (9p,9n) + n.** A proton entered the oxygen-nucleus by emitting a neutron and thereby generating the instable fluorine isotope F-18.

F-18 has a physical half-life of 109.8 minutes. Its unstable proton-rich and neutron-deficient nucleus converts into a more stable energetic state by radioactive decay, which is 97% positron decay and 3% decay by electron capture that can be disregarded. Positron or beta-plus decay is described by the following reaction: **F-18 (9p,9n) → O-18 (8p,10n) + β^+ + ν**. A proton is converted into a neutron and the resulting energy is passed on to the emitted positron (β^+) and a neutrino (ν). The surrounding electrons decelerate the positively charged positron. After passing few millimeters in surrounding tissue, the positron is recombined with an electron. During this annihilation process the masses of both particles are transferred into photomagnetic energy. According to the conservation of energy and momentum ($E=mc^2$) this

process results in two gamma quanta with an energy of 511keV each that are emitted back-to-back under an angle of ~180°.

The two gamma quanta from an annihilation event are simultaneously registered in scintillation crystal detectors that are arranged in rings within the PET scanner (ECAT EXACT 47, CTI/Siemens, Knoxville, TN, USA). The simultaneous registration of gamma quanta in two opposing detectors within a very short coincidence-timing window of 15-20ns allows to localize the annihilation event along the line connecting the two detectors (coincidence line). The colinearity of the two gamma quanta is thereby used for "electronic collimation", resulting in a higher sensitivity of PET compared to conventional gamma cameras where mechanical collimation is needed.

The coincidence count rate of each pair of detectors is corrected for random and scattered (so called 'false') coincidences. Mathematical algorithms are used to correct for a falsely low count rate due to the dead time of single detector units and the dead time of the system. Attenuation correction takes into account photon absorption within the body and allows translating measured count rates into absolute tracer concentrations (absolute image quantification). A transmission scan e.g. with germanium-68 rod sources ($t_{1/2}$ = 288d) rotating around the patient allows to calculate the ratio of true compared to measured activity (attenuation coefficient) for different body regions. The resulting attenuation map provides attenuation correction factors that were used in the final image reconstruction.

The corrected emission data were reconstructed by using the technique of "filtered backprojection" with a Hanning filter (cutoff frequency 0.4 cycles/ bin). Image reconstruction resulted in a series of 47 contiguous cross sectional images, each spaced 3.4mm apart, representing the spatial distribution of the measured radioactivity in a pixel (or voxel) matrix. The resulting transaxial in-plane resolution was approximately 6mm full width half maximum (FWHM) and axial resolution was approximately 5mm FWHM [138].

2.3 F-18 fluorodeoxyglucose

F-18 fluorodeoxyglucose (FDG) was produced by a technique similar to that described by Hamacher et al. [39]. Starting from tetra-acetyl-triflyl-D-mannose, nucleophilic substitution with F-18 produces tetraacetyl-2-(F-18)-fluor-2-deoxy-D-glucose, and hydrolysis with hydrochloric acid then produces 2-(F-18)-fluor-2-deoxy-D-glucose. After neutralization and purification, an

injectable isotonic solution is produced by sterile filtration. One hour of proton irradiation with a current of 20 μA, resulting in approximately 500 mCi or 18-20 GBq of F-18, and a further 1.5 hours of radiochemical synthesis with an average yield of 40% results in approximately 200 mCi or 7.5 GBq of F-18-FDG.

The glucose analogue F-18-FDG is stable in blood and crosses the cell membrane through facilitated transport via glucose transport proteins (GLUT), especially GLUT-1. FDG is then phosphorylated by intracellular hexokinases similar to glucose, and since FDG-6-phosphate is not a suitable substrate for glucose-6-phosphate isomerase, the glycolytic metabolization of FDG ends at this point. Subsequently, FDG-6-phosphate accumulates in cells since it can no longer pass the cell membrane and the enzyme level of glucose-6-phosphatase, responsible for dephosphorylation, is generally low in most human cells (except liver parenchyma) [65]. The metabolism of FDG is largely irreversible to this point and FDG accumulates in the tissue over time after tracer administration.

2.4 Quantitative analysis of FDG-PET

Quantitative measurements of FDG uptake were derived from attenuation corrected PET images. Count rates of each pixel (or voxel) were calibrated to activity-concentrations in Becquerel per milliliter (Bq/ml). Decay-correction was performed using the time of tracer injection as a reference. Regional activity concentrations in Becquerel per gram tissue were determined by using the "region of interest" technique. On the PET monitor, circular regions of interest (ROI) of 1.5 cm diameter were placed computer assisted over the tumor lesions. Activity concentrations (Bq/g) were measured as mean activity concentration within the ROI as well as the maximum activity concentration of one voxel within the ROI. A standardization of regional activity concentrations within the body can be accomplished by various techniques of different complexity. One of the most widely used approaches in oncological applications is the calculation of "standardized uptake values" (SUV). Therefore, the measured radioactivity concentrations are normalized to the injected activity of F18-FDG and the patient's total body weight by the following formula:

SUV = measured activity concentration (Bq/g) × body weight (g) / injected activity (Bq).

The equation results in a semiquantitative nondimensional measure that represents FDG accumulation in tissue at a given time point. Since FDG uptake into tissue and blood glucose

levels show an inverse relationship, SUVs can additionally be normalized to blood glucose by assuming a linear correlation:

SUV (glc) = SUV × blood glucose concentration / 100 mg/ml

To ensure reproducibility of SUVs in intraindividual analysis, a constant time interval between FDG injection and data acquisition was maintained to take into account the increasing FDG uptake into tissue over time. Depending on tumor size, SUVs tend to be underestimated in lesions with a diameter smaller than twice the scanner resolution at full width half maximum (FWHM). This "partial volume effect" was corrected by using appropriate correction factors. Spherical phantoms of different size but equal activity were imaged, and by assessing the ratio of true to measured activity concentration a recovery coefficient was defined for different diameters.

2.5 PET protocol

FDG-PET was performed before initiation of treatment and after the first and third cycle of chemotherapy. All 33 patients underwent a baseline PET scan within 5±3.8 days before initiation of neoadjuvant chemotherapy and a final FDG-PET after the third cycle of chemotherapy, at an average of 23±10 days after completion of chemotherapy. A subgroup of 26 patients was additionally examined after the first cycle of chemotherapy at an average of 16±4.7 days (range 8-24 days) after initiation of chemotherapy. A total of 92 FDG-PET scans were performed.

PET scans of the abdomen and pelvis were obtained using 3-4 bed positions. Patients were fasted for at least 6 hours prior to PET imaging to ensure standardized glucose metabolism. Blood glucose level was measured before each PET examination by photometric analysis with glucose reagent strips (Glucometer II and Glucostix, Bayer Diagnostics, Munich). A bolus of 320–380MBq (approximately 10mCi) F-18-FDG, depending on the available activity, was injected through an intravenous catheter. To reduce tracer retention in the urinary system and to minimize the FDG uptake in the bowel, 20mg of furosemide and 20mg N-butyl-scopolamine were administered concurrently [118]. Patients rested in quiet room for 60 minutes to allow FDG uptake into tissue. After positioning the patient in the scanner, emission scans (2D-mode) of 10 minutes duration each were performed for 3-4 bed positions, starting at 60 minutes post injection. Following the three 10-minute frames, a 10-minute transmission scan with a Ge-68 rod source was obtained for attenuation correction. Emission data corrected for random events,

dead time and attenuation were reconstructed with filtered back-projection (Hanning filter with cutoff frequency of 0.4 cycles per bin). The image pixel counts were calibrated to activity-concentration (Bq/ml) and decay corrected using the time of tracer injection as a reference.

Regions of interest (ROI) were placed semi-automatically over the tumor lesions in attenuation corrected images. The slice with the highest radioactivity concentration within a tumor lesion was identified and a circular ROI with a diameter of 1.5 cm was placed in this area as well as in the adjacent slices. The diameters of all tumor lesions were substantially larger than the size of the ROI. This method was chosen to reduce partial volume effects, which play a substantial role if a ROI is placed around the entire tumor and tumor size changes after the baseline study. Standardized uptake values (SUV) were calculated for average and maximum activity values within the ROIs of 3 adjacent slices, normalized to injected dose and patient's body weight, with and without normalization to blood glucose levels (SUVav, SUVmax, SUVav-glc, SUVmax-glc).

2.6 Assessment of therapy response

2.6.1 Metabolic response

Evaluation of metabolic response was accomplished regarding relative changes in tumoral FDG uptake. FDG uptake in ovarian cancer (SUV) from follow-up studies after the 1st and 3rd cycle of chemotherapy was compared with the baseline study. If multiple metastatic tumor lesions were present in one patient, the lesion with the lowest change in FDG uptake was used for analysis based on the rationale that the metastatic tumor with the worst response would ultimately determine survival. For methodological comparison, the mean of all metastatic tumor lesions per patient was analyzed similarly.

Metabolic response after the first cycle of chemotherapy was prospectively defined as a decrease in SUV of more than two times the standard deviation of spontaneous changes, which is 20% or more for the standardized uptake value (SUV) approach [134, 135]. In addition, the best threshold for prediction of response after the third cycle of chemotherapy was determined retrospectively by survival analysis. Survival in patients with and without a metabolic response was compared for increasing thresholds, starting with a decrease in SUV of 20%. The threshold that produced the most significant difference in overall survival of metabolic responders and non-responders was identified.

Since no standard exists to date to define the exact method for calculation of standardized uptake values, SUVs calculated for maximum and average activity within a tumor ROI, with or without normalization to blood glucose (SUVav, SUVmax, SUVav-glc, SUVmax-glc) were compared with regard to their ability to predict response to chemotherapy.

2.6.2 Clinical response

Clinical evaluation of therapy response was accomplished at the time of tumor debulking surgery after the third cycle of neoadjuvant chemotherapy. Three criteria were assessed, including intraoperative tumor extension compared to initial tumor extension at diagnostic laparoscopy, regression of peritoneal carcinomatosis, and change in CA125 tumor marker levels. All patients had presented with bulky tumors larger than 4cm and extensive peritoneal carcinomatosis at initial diagnosis. Patients were classified as clinical responders when at least 2 of the following 3 criteria were present: intraoperative residual tumor less than 4cm, regression of peritoneal carcinomatosis from widespread to small and single standing implants, and a decrease of 75% or more from baseline or a complete normalization (<35 U/ml) of CA125 tumor marker levels. CT imaging was not included in this study because of the inherent limitation to accurately determine the extent of disease in the peritoneal cavity [59].

CA125 tumor marker response:

CA125 response criteria were either a decrease of 75% or more from baseline [95] or a complete normalization of CA125 levels (<35 U/ml) [32] after the 3rd cycle of chemotherapy.

Decrease in ascites:

Decrease in ascites has been suggested for clinical assessment of response to postoperative or palliative chemotherapy. Response to treatment was assumed when ascites had decreased below the limit of detection on physical examination.

2.6.3 Histopathologic response

Histopathologic assessment of therapy response was performed after three cycles of neoadjuvant chemotherapy on specimens from tumor debulking surgery. For assessment of histopathologic response, specimens were cut in slices measuring 0.5 cm and evaluated for the presence or absence of macroscopic tumor. Specimens were fixed according to standard

procedures in 4% neutral buffered formaldehyde and embedded in paraffin. Sections of 5µm thickness were prepared and stained with hematoxylin and eosin (H&E staining), as well as with periodic acid-schiff (PAS staining) on selected sections. All sections were studied microscopically by an experienced pathologist (J.N.) for signs of tumor regression, such as marked necrosis, apoptosis, and stromal fibrosis or reactive inflammation. Specimens with no detectable residual tumor, residual tumor of ≤1 cm and marked signs of regression, or scattered foci of microscopic tumor were classified as histopathologic responders. Specimens with residual tumor greater than 1 cm or diffuse extensive infiltration on microscopic examination and no signs of regression were classified as non-responders in histopathology.

2.7 Statistical analysis

For comparison of FDG uptake in ovarian cancer between baseline and follow-up after the first and third cycle of chemotherapy, relative changes in SUV were calculated. Survival time was measured from the date of surgery, and cumulative overall survival and survival probability were estimated by the Kaplan Meier method. Patients who are still alive are integrated in Kaplan Meier analysis as “censored events”, counting the time period from the date of surgery until the date of statistical analysis. One patient who died three months after surgery from a cause unrelated to her cancer history was also integrated as a censored event. Metabolic response was prospectively defined by a threshold of 20% or more decrease in SUV. In addition, the best threshold for metabolic response after the 3rd cycle of chemotherapy was determined retrospectively by survival analysis. Survival of patients with and without a metabolic response was compared by the log-rank test and differences with $p<0.05$ were considered significant. Increasing thresholds were used to define metabolic response and the cutoff value that produced the most significant difference in overall survival of metabolic responders and non-responders was identified.

Metabolic response as assessed by FDG-PET was compared with tumor response according to clinical and histopathologic criteria. The Mann-Whitney *U* test was used for comparison of SUVs between groups of histopathologic or clinical responders and non-responders. Fisher’s exact test was used to test for a correlation between metabolic response and clinical or histopathologic response. Overall survival of clinical and histopathologic responders and non-responders was compared with the Kaplan Meier method and log-rank test.

Multivariate analysis was performed for various combinations of FDG-PET (metabolic response) with other response criteria and other parameters potentially influencing patient outcome by estimating overall survival with the Cox regression model.

Linear regression and Spearman's rank correlation coefficient (rho) were used to describe the correlation between SUV calculated for maximum and average activity values within a tumor ROI, with or without normalization to blood glucose (SUVav, SUVav-glc, SUVmax, SUVmax-glc). All quantitative parameters are expressed as mean value ± one standard deviation (SD). All statistical tests were performed two-sided at a 5% level of significance. Statistical analysis was performed using SPSS software package (Statistical Package for the Social Sciences; SPSS for Windows, Version 12.0, SPSS Inc., Chicago, IL, USA) and StatView software package (Version 5.0, SAS Institute, Cary, NC, USA).

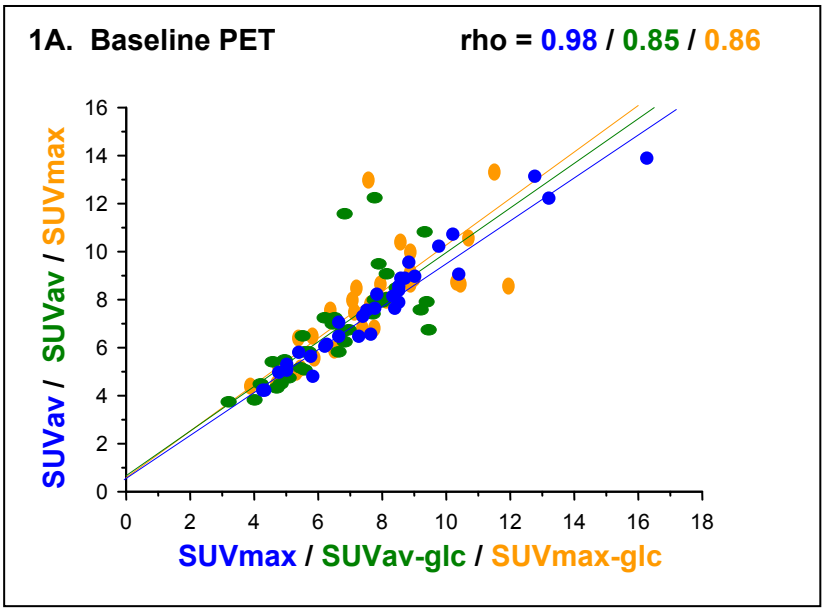
3 Results

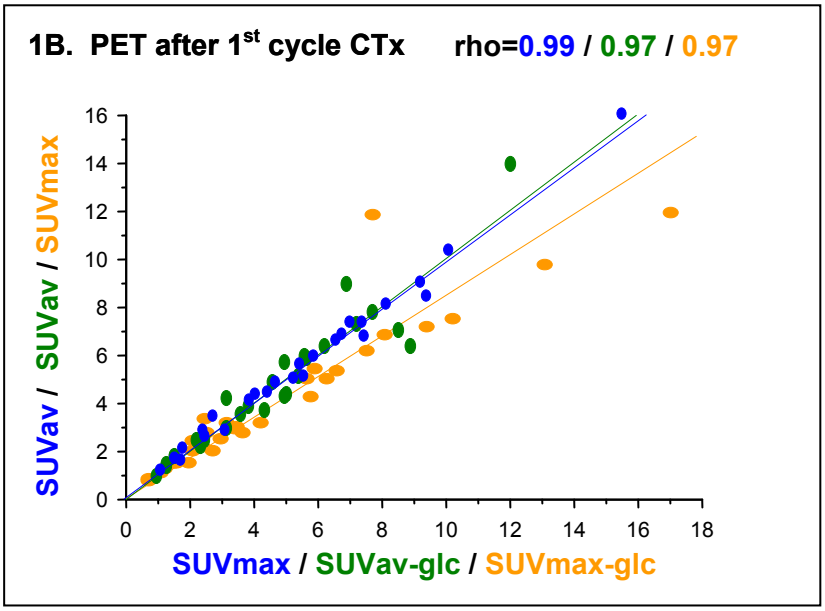
3.1 Patients

A total of 37 patients were enrolled in this study of which 4 were excluded because they did not undergo surgery (n=2), had a secondary malignancy discovered at the time of surgery (n=1) or did not complete FDG-PET imaging (n=1). In 33 patients the baseline FDG-PET was within 5±3.8 days before initiation of neoadjuvant chemotherapy. Twenty-six patients had FDG-PET after the first cycle of chemotherapy at a mean interval of 16±4.7 days (range 8–24 days) after initiation of chemotherapy and all 33 patients were studied after the third cycle at a mean of 23±10 days after completion of chemotherapy. Blood glucose levels at the first, second and third FDG-PET scan were 99.3±15.9 mg/dl, 100.6±12.7 mg/dl and 107±20.7 mg/dl, respectively. In 33 patients, 73 metastatic lesions were analyzed. A total of 92 FDG-PET scans were performed.

3.2 FDG-PET monitoring of therapy response

Evaluation of metabolic response was accomplished regarding relative changes in tumoral FDG uptake (SUV). SUVs were calculated for average activity concentrations within a tumor ROI, in accordance with the analyses in previous studies at our university hospital [134, 137]. For methodological comparison, SUV calculated for average and maximum activity concentrations, with and without normalization to blood glucose (SUVav, SUVav-glc, SUVmax, SUVmax-glc) were compared, and showed a good correlation at baseline and after the first and third cycle of chemotherapy (rho values between 0.99 and 0.85; $p<0.01$; **Figure 1A, B, and C**).


1A. Baseline PET
rho = 0.98 / 0.85 / 0.86
SUVav / SUVav / SUVmax
SUVmax / SUVav-glc / SUVmax-glc
0
2
4
6
8
10
12
14
16
18


1B. PET after 1st cycle CTx
rho=0.99 / 0.97 / 0.97
SUVav / SUVav / SUVmax
SUVmax / SUVav-glc / SUVmax-glc
0
2
4
6
8
10
12
14
16
18

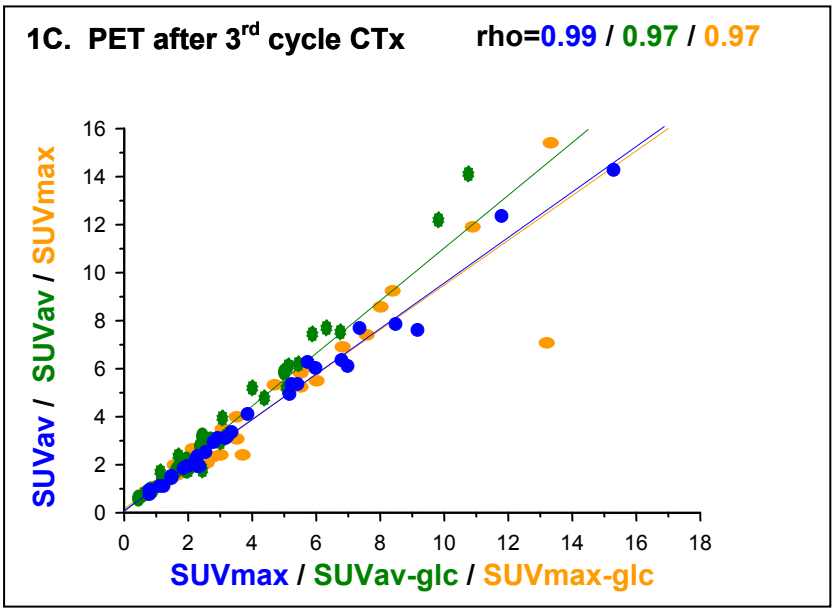


Figure 1. Correlation between SUVmax and SUVav, SUVav and SUVav-glc, and SUVmax and SUVmax-glc, at baseline (**A**) and after the 1st (**B**) and 3rd (**C**) cycle of chemotherapy.

In 33 patients, all metastatic tumors showed high FDG uptake at baseline with a mean SUV of 6.8±2.1. After the first cycle of chemotherapy the mean SUV decreased to 4.9±2.8 (n=26) and decreased further to 3.5±2.8 (n=33) after the third cycle of chemotherapy.

Between one and four lesions per patient were identified on baseline FDG-PET. The criterion was a distinct area of increased FDG uptake. Every lesion was measured in the baseline and both follow-up PET scans. The variability in decrease in FDG uptake (metabolic response) of different tumor lesions within the same patient was generally low (±10%). The metabolic response was used for selection of one reference lesion per patient. The lesion with the lowest decrease in FDG uptake was used for subsequent analysis in this study based on the rationale that these tumor deposits would determine survival.

By using a previously defined threshold of 20% decrease in SUV after the first cycle of chemotherapy, 15 (57.7%) out of 26 patients were classified as metabolic responders and had a mean decrease in SUV of 49.5±19.0%. Eleven (42.3%) metabolic non-responders (change in SUV <20%) had a mean decrease of 4.0±13.3% (**Figure 2A**). After the third cycle of chemotherapy a threshold of 55% decrease in SUV was found to optimally differentiate between metabolic responders and non-responders. Eighteen (54.5%) out of 33 patients were classified as metabolic responders and had a mean decrease in SUV of 74.4±9.1% compared to a mean decrease in SUV of 23.9±17.9% in 15 (45.5%) non-responders (**Figure 2B**).

For methodological comparison, the mean of all metastatic tumor lesions per patient (SUVmean) was analyzed likewise. The rate of metabolic responders increased to 18 (69.2%) of 26 patients after the first cycle and 19 (57.6%) of 33 patients after the third cycle of chemotherapy when regarding changes in SUVmean.

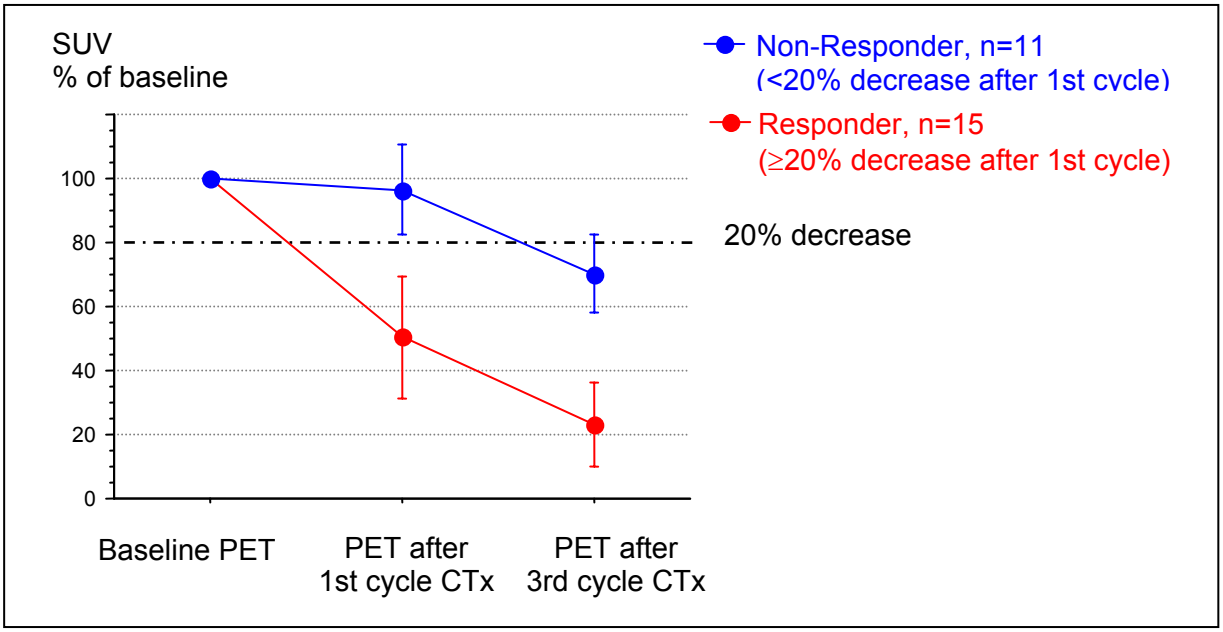


Figure 2A. Changes in FDG uptake (SUV) in metabolic responders and non-responders, defined by a decrease in SUV of ≥20% after the 1st cycle of chemotherapy.

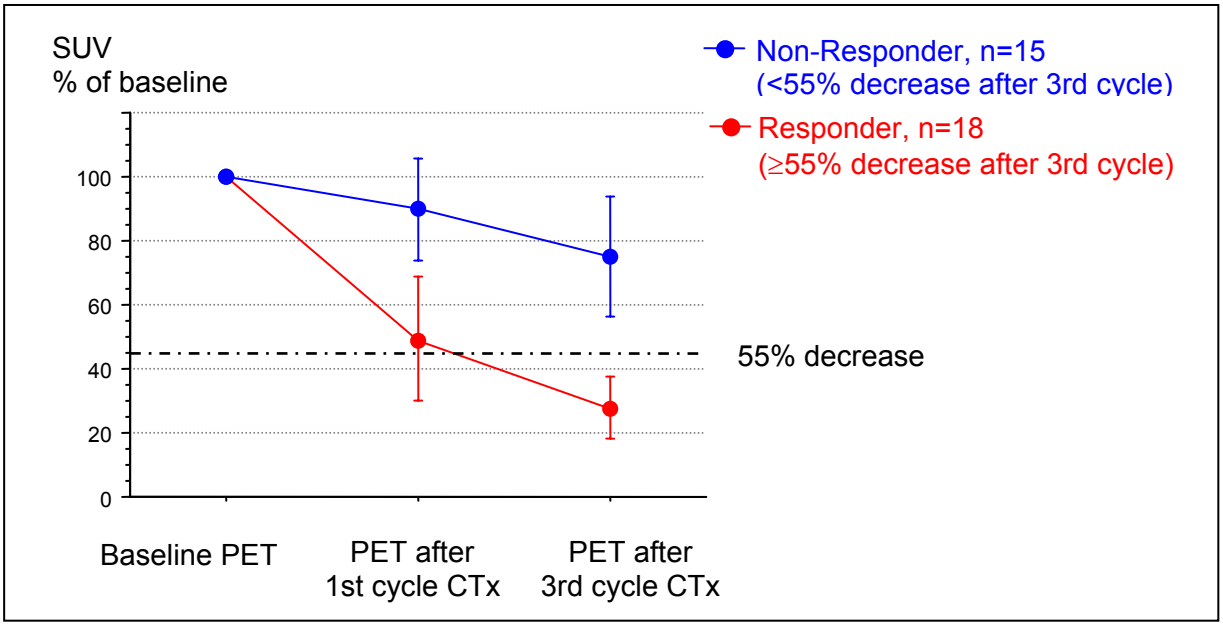


Figure 2B. Changes in FDG uptake (SUV) in metabolic responders and non-responders, defined by a decrease in SUV of ≥55% after the 3rd cycle of chemotherapy.

3.2.1 Correlation between FDG-PET after first and third cycle of chemotherapy

Changes in FDG uptake (SUV) after the first and third cycle of chemotherapy showed a close correlation (rho=0.81, p<0.01; **Figure 3**). FDG-PET was discordant regarding the metabolic response classification in only two out of 26 patients who had three FDG-PET scans. These 2 patients were classified as non-responders after the third cycle but had a decrease in SUV of more than 20% after the first cycle. More important, no responder after the third cycle has been erroneously classified as non-responder after the first cycle.

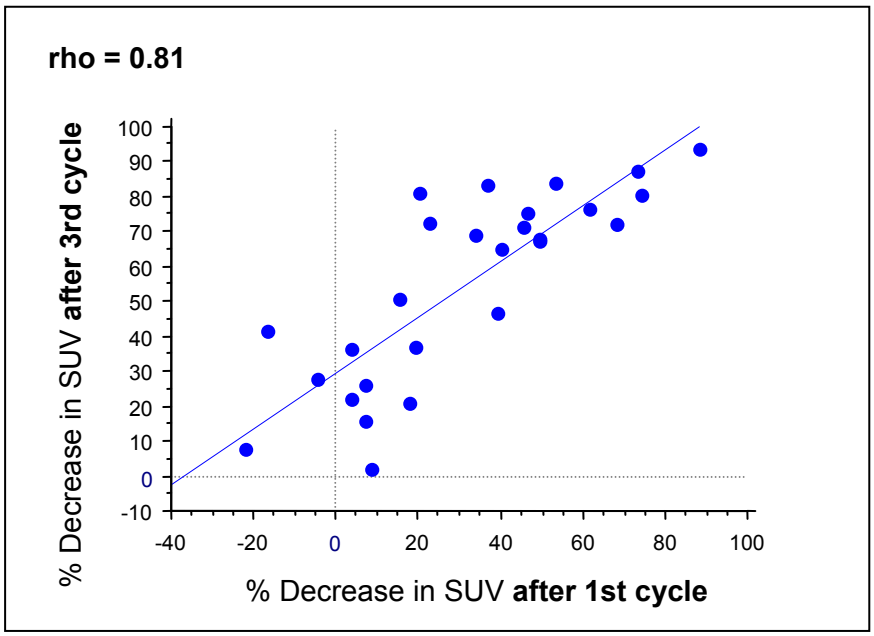


Figure 3. The relative decrease in FDG uptake (SUV) after the first and third cycle of chemotherapy showed a close correlation (rho=0.81).

In a comparative analysis, relative changes in SUVav-glc, SUVmax, and SUVmax-glc after the first and third cycle of chemotherapy were also closely correlated (rho=0.86, 0.84, and 0.79, respectively). By using SUVmax-glc or SUVav-glc one patient with metabolic response after the third cycle had less than 20% decrease after the first cycle and would have been erroneously classified as non-responder after the first cycle. For SUVmax, two patients with metabolic response after the third cycle would have been erroneously classified as non-responder after the first cycle.

In 26 patients who had 3 FDG-PET scans, the overall decrease in SUV in metabolic responders (defined by ≥55% decrease after 3rd cycle; n=14) was 50.1% after the first cycle and 76.2% after the third cycle of chemotherapy. Thus, in metabolic responders 65.7% of the metabolic changes occurred within the first two weeks (16±4.7 days) after initiation of chemotherapy. In

contrast, in metabolic non-responders (n=12) SUV decreased by 7.0% after the first cycle and 27.3% after the third cycle. In metabolic non-responders, 25.6% of the metabolic changes occurred within the first two weeks (**Figure 4**).

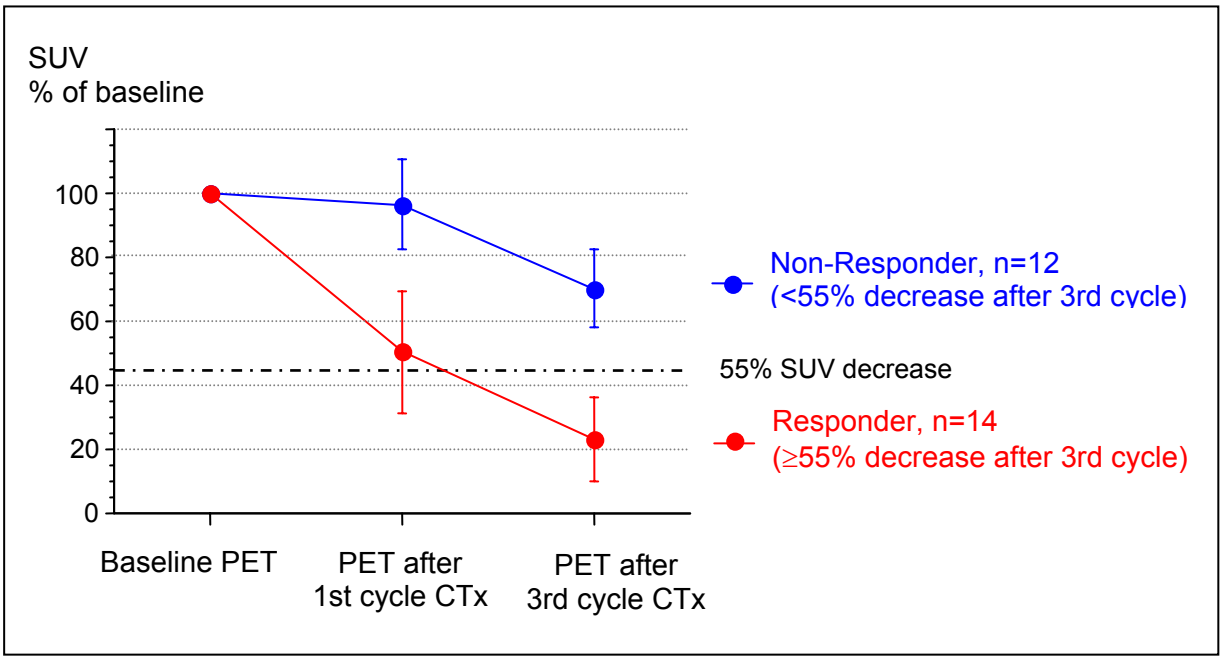


Figure 4. Metabolic response in FDG-PET defined by a decrease in SUV of ≥55% after the 3rd cycle of chemotherapy. In metabolic responders, 65.7% of the overall decrease in SUV occurred within 2 weeks after initiation of chemotherapy.

In a comparative analysis, this finding was similar for SUVav-glc, SUVmax, and SUVmax-glc. In metabolic responders, about two thirds (65.9%, 65.5%, and 67.6%, respectively) of the metabolic effect of chemotherapy occurred within the first two weeks after initiation of chemotherapy. In metabolic non-responders only one quarter to one third (33.8%, 25.6%, and 24.3%, respectively) of the metabolic effect of chemotherapy occurred within the first two weeks.

3.2.2 Patient follow-up and survival

Median follow-up time was 48.8 months (range 38.3-70.6 months). During this period, 23 out of 33 patients have died. Median overall survival was 25.6 months. The overall 2-year and 3-year survival rates were 57.6% and 42.4%, respectively. Nineteen patients have died in a subset of 26 patients who had an FDG-PET scan after the first cycle of chemotherapy.

3.3 Metabolic response and survival

There was a significant correlation between metabolic response in FDG-PET after the first (p=0.008) and after the third (p=0.005) cycle of chemotherapy respectively, and overall survival. Starting with a threshold of 20% decrease in SUV, which is more than two times the standard deviation of spontaneous changes, increasing thresholds were used to define metabolic response. Survival of metabolic responders and non-responders was compared by Kaplan Meier analysis and the log-rank test and the threshold that optimally differentiated between responders and non-responders was identified. Since there is currently no consensus whether to calculate SUV for maximum or average activity values within a tumor ROI, and whether normalization to blood glucose should be performed, these approaches were compared with regard to their ability to predict response and their correlation with overall survival.

3.3.1 Metabolic response after the first cycle and survival

Using a prospectively defined threshold of 20% decrease in SUV from baseline after the first cycle of chemotherapy, median survival was 38.3 months in metabolic responders compared to 23.1 months in metabolic non-responders (p=0.008; **Figure 5**). The corresponding 2-year survival rates were 73.3% and 45.5% in metabolic responders and non-responders, respectively.

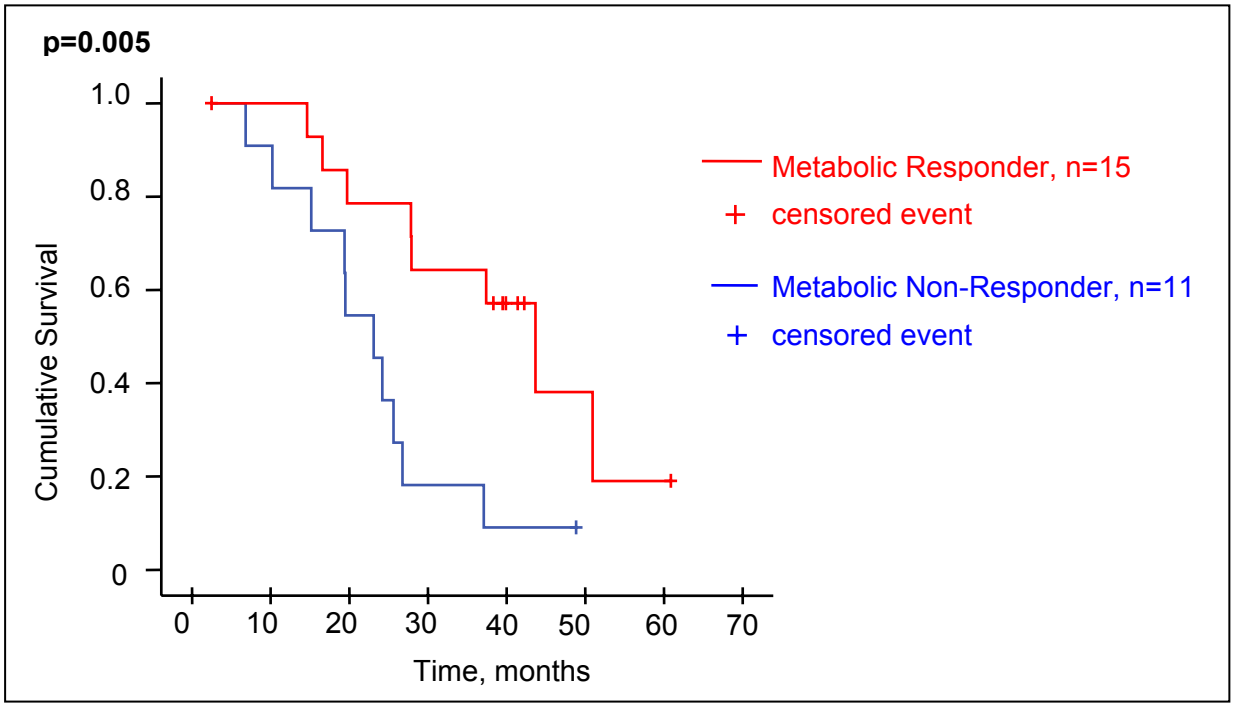


Figure 5. Survival of metabolic responders and non-responders, defined by a decrease in SUV of ≥20% (prospective threshold) after the 1st cycle of chemotherapy.

In a comparative analysis, when using SUVav-glc, SUVmax, and SUVmax-glc, respectively and a threshold of 20% decrease in SUV, the difference in overall survival of metabolic responders and non-responders remained significant (p=0.02, 0.03, and 0.004, respectively). Using increasing thresholds from 20% to 40% decrease from baseline after the first cycle of chemotherapy, in increments of 5%, also showed significant difference in the overall survival of metabolic responders and non-responders when applied to SUVav, SUVav-glc, SUVmax, and SUVmax-glc, respectively. The highest significance level was reached for a threshold of 20% decrease in SUVmax-glc (p=0.004).

3.3.2 Metabolic response after the third cycle and survival

After the third cycle of chemotherapy, a threshold of 55% decrease in SUV was found to optimally differentiate between metabolic responders and non-responders. Using this criterion, median survival was 38.9 months in metabolic responders compared to 19.7 months in metabolic non-responders (p=0.005; **Figure 6**). The corresponding 2-year survival rates were 72.2% and 40.0% in metabolic responders and non-responders, respectively.

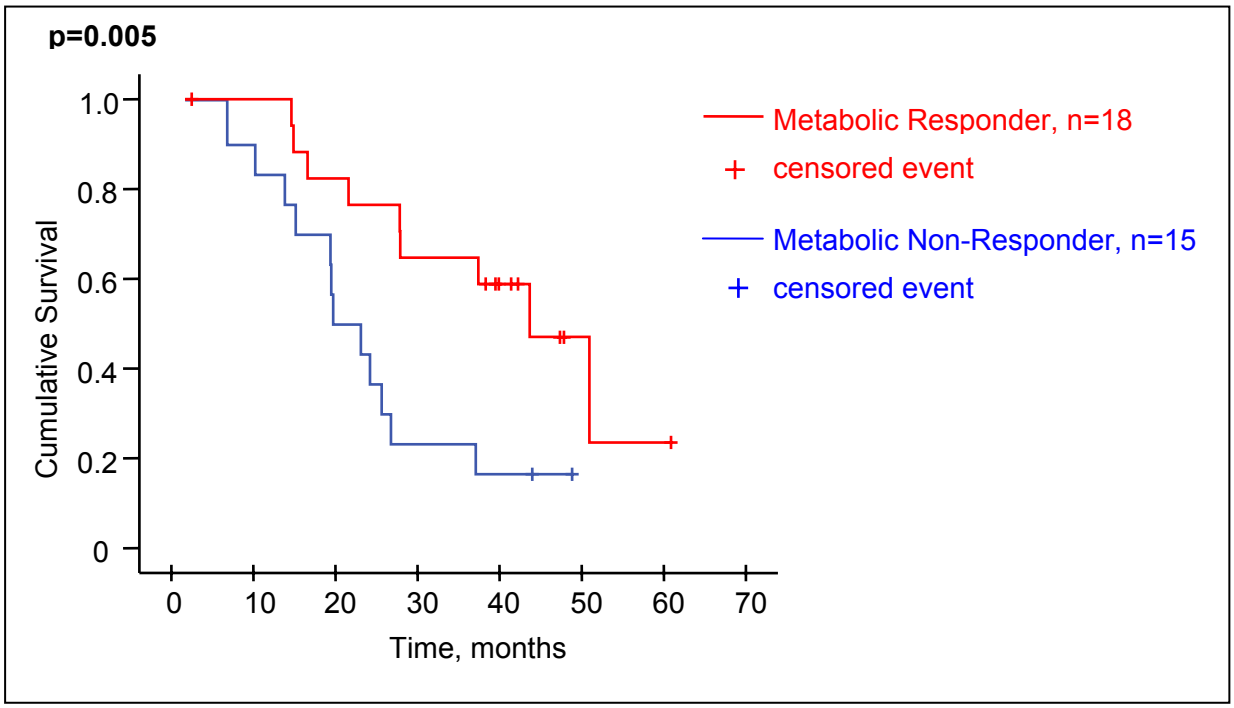


Figure 6. Survival of metabolic responders and non-responders, defined by a decrease in SUV of ≥55% after 3rd cycle of chemotherapy.

A threshold of 20% decrease after the 3rd cycle of chemotherapy was not found to be significant. In contrast, a significant difference in overall survival of metabolic responders and non-responders was found for thresholds between 35% and 55% decrease in SUVav, SUVav-glc, SUVmax, and SUVmax-glc. The highest significance was reached for a threshold of 55% decrease in SUVmax-glc ($p<0.001$).

3.3.3 Metabolic response in patients with multiple metastatic tumor lesions

If multiple metastatic tumor lesions were present within one patient, the lesion with the lowest change in FDG uptake was used for analysis based on the rationale that the metastatic tumor with the worst response would determine survival. For methodological comparison, the mean of all metastatic tumor lesions per patient was analyzed likewise (SUVmean).

In 33 patients a total of 73 metastatic tumor lesions were analyzed (mean 2.2±1.0 lesions per patient). By regarding the lesion with the worst response, 15 (57.7%) of 26 patients showed a metabolic response after the first cycle of chemotherapy and 18 (54.5%) of 33 patients showed a metabolic response after the third cycle. Regarding the mean of all metastatic tumor lesions per patient, the rate of metabolic responders increased to 18 (69.2%) of 26 patients after the first cycle and 19 (57.6%) of 33 patients after the third cycle of chemotherapy. Using a threshold of 20% decrease in SUVmean after the first cycle of chemotherapy, metabolic responders (n=18) had a median survival of 32.7 months compared to 21.3 months in metabolic non-responders (n=8; p=0.06). Using a threshold of 55% decrease in SUVmean after the third cycle of chemotherapy, metabolic responders (n=19) had a median survival of 38.3 months compared to 19.6 months in metabolic non-responders (n=14; p=0.007).

3.4 Clinical and histopathologic response

Clinical response after chemotherapy was defined as response in at least 2 of the following 3 criteria: intraoperative residual tumor less than 4 cm, regression of peritoneal carcinomatosis from widespread to small and single standing implants, and a decrease ≥75% from baseline or a complete normalization (<35 U/ml) of CA125 tumor marker levels. Twenty-one (63.6%) out of 33 patients were classified as clinical responders and 12 (36.4%) patients were classified as non-responders. CA125 response was defined as a decrease of ≥75% or a complete normalization (<35 U/ml). Thirty-three patients showed a mean baseline CA125 serum level of

2912±7404 U/ml (range 94–42160 U/ml) and a mean post-chemotherapy level of 135±255 U/ml (range 15-1120 U/ml). After chemotherapy, CA125 had decreased by 75% or more in 29 (84.8%) patients and in 13 (39.4%) patients CA125 levels were normal (<35 U/ml). Out of 33 patients with large ascites volumes (>500ml) before chemotherapy, 31 had no detectable ascites on physical examination after the third cycle of chemotherapy and 2 patients had persistent ascites.

Histopathologic response criteria were based on the amount of residual viable tumor (≤ or > 1cm) and histomorphologic signs of regression. After 3 cycles of chemotherapy, 6 (18.2%) out of 33 patients showed histopathologic response and 27 (81.8%) out of 33 patients had no response in histopathology.

3.4.1 Clinical response and changes in FDG uptake

There was a significantly greater decrease in SUV in clinical responders compared to non-responders. After the first cycle of chemotherapy, SUV decreased by 39.9±26.1% in clinical responders (n=18) compared to 8.4±20.2% in non-responders (n=8; p=0.01). After the third cycle of chemotherapy the decrease in SUV was 62.8±21.6% in clinical responders (n=21) compared to 31.5%±30.2 % in clinical non-responders (n=12; p=0.007). Accordingly, there was a significant correlation between metabolic response after the first (p=0.04) and third (p=0.01) cycle of chemotherapy and clinical response (**Table 2A and B**). Fifteen out of 18 metabolic responders after the third cycle of chemotherapy were subsequently classified as clinical responders. Only 6 out of 15 metabolic non-responders were classified as clinical responders. The resulting sensitivity and specificity were 72.2% and 75.0%, respectively. Of note, 8 out of 18 metabolic responders achieved a complete clinical response in all 3 clinical response criteria (see above *3.4*), whereas none out of 15 metabolic non-responders achieved a complete clinical response in all 3 criteria.

2A.

After 1st cycle	Clinical			**p=0.04**
	Responder	Non-Responder		
Metabolic				
Responder	13	2	15	PPV 87% (13 of 15)
Non-Responder	5	6	11	NPV 55% (6 of 11)
	18	8	26	
	Sens. 72% (13 of 18)	Spec. 75% (6 of 8)		

2B.

After 3rd cycle	Clinical			**p=0.01**
	Responder	Non-Responder		
Metabolic				
Responder	15	3	18	PPV 83% (15 of 18)
Non-Responder	6	9	15	NPV 60% (9 of 15)
	21	12	33	
	Sens. 71% (15 of 21)	Spec. 75% (9 of 12)		

Table 2. Correlation between FDG-PET (metabolic response) after 1st (**A**) and 3rd cycle (**B**) of chemotherapy and clinical response. (NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity)

A weak correlation was found between metabolic response after the first (p=0.07) and third (p=0.03) cycle of chemotherapy and ≥75% decrease in CA125 levels. No correlation was found between metabolic response and normalization of CA125 levels (p=0.7 and p=0.2 after first and third cycle, respectively). A multivariate analysis is described in chapter 3.6.

3.4.2 Histopathologic response and changes in FDG uptake

Comparing changes in FDG uptake (SUV) with histopathology, there was a more pronounced decrease in SUV in histopathologic responders compared to non-responders. After the first cycle of chemotherapy, SUV decreased by 48.9±4.2% in histopathologically responding tumors (n=3) compared to 27.8±29.2% in non-responding tumors (n=23; p=0.1). After the third cycle of chemotherapy the decrease in SUV in histopathologically responding tumors (n=6)

was 71.6±9.4% compared to 47.0%±30.0 % in non-responding tumors (n=27; p=0.06). There was a significant correlation between FDG-PET response classification after the third cycle of chemotherapy and histopathologic response classification (p=0.02; **Table 3B**). Metabolic response after the first and third cycle of chemotherapy was a highly sensitive predictor for subsequent histopathologic response. Six out of 6 histopathologic responders were classified as metabolic responders after the third cycle of chemotherapy (**Table 3B**). In a subset of 3 histopathologic responders who had FDG-PET after the first cycle of chemotherapy, 3 out of 3 were classified as metabolic responders (**Table 3A**). No metabolic non-responder (n=15 and n=18, after first and third cycle respectively) achieved a response in histopathology, resulting in a negative predictive value of 100%. In contrast, specificity was low (47.8% and 55.6% after first and third cycle respectively) as not all histopathologic non-responders were identified (**Table 3**).

3A.

After 1st cycle	Histopathologic			**p=0.23**
	Responder	Non-Responder		
Metabolic				
Responder	3	12	15	PPV 20% (3 of 15)
Non-Responder	0	11	11	NPV 100% (11 of 11)
	3	23	26	
	Sens. 100% (3 of 3)	Spec. 48% (11 of 23)		

3B.

After 3rd cycle	Histopathologic			**p=0.02**
	Responder	Non-Responder		
Metabolic				
Responder	6	12	18	PPV 33% (6 of 18)
Non-Responder	0	15	15	NPV 100% (15 of 15)
	6	27	33	
	Sens. 100% (6 of 6)	Spec. 56% (15 of 27)		

Table 3. Correlation between FDG-PET (metabolic response) after 1st (**A**) and 3rd cycle (**B**) of chemotherapy and histopathologic response. All histopathologic responders were correctly identified by FDG-PET (sensitivity 100%). (NPV, negative predictive value; PPV, positive predictive value; Sens., sensitivity; Spec., specificity)

3.4.3 Clinical and histopathologic response and survival

Clinical response criteria (p=0.7) and CA125 criteria (p=0.5) did not correlate with overall survival, and histopathologic response criteria showed only a weak correlation (p=0.09) with overall survival. Median overall survival was 27.8 months in clinical responders (n=21) and 22.5 months in clinical non-responders (n=12; **Figure 7**). Patients with normal CA125 levels after chemotherapy had a median overall survival of 27.8 months (n=13) compared to 24.4 in patients with elevated CA125 (n=20; p=0.4). Patients with a decrease in CA125 of 75% or more (n=29) had a median overall survival of 27.8 months compared to 22.5 months (p=0.5) in patients with a decrease in CA125 of <75% (n=4; **Figure 8**).

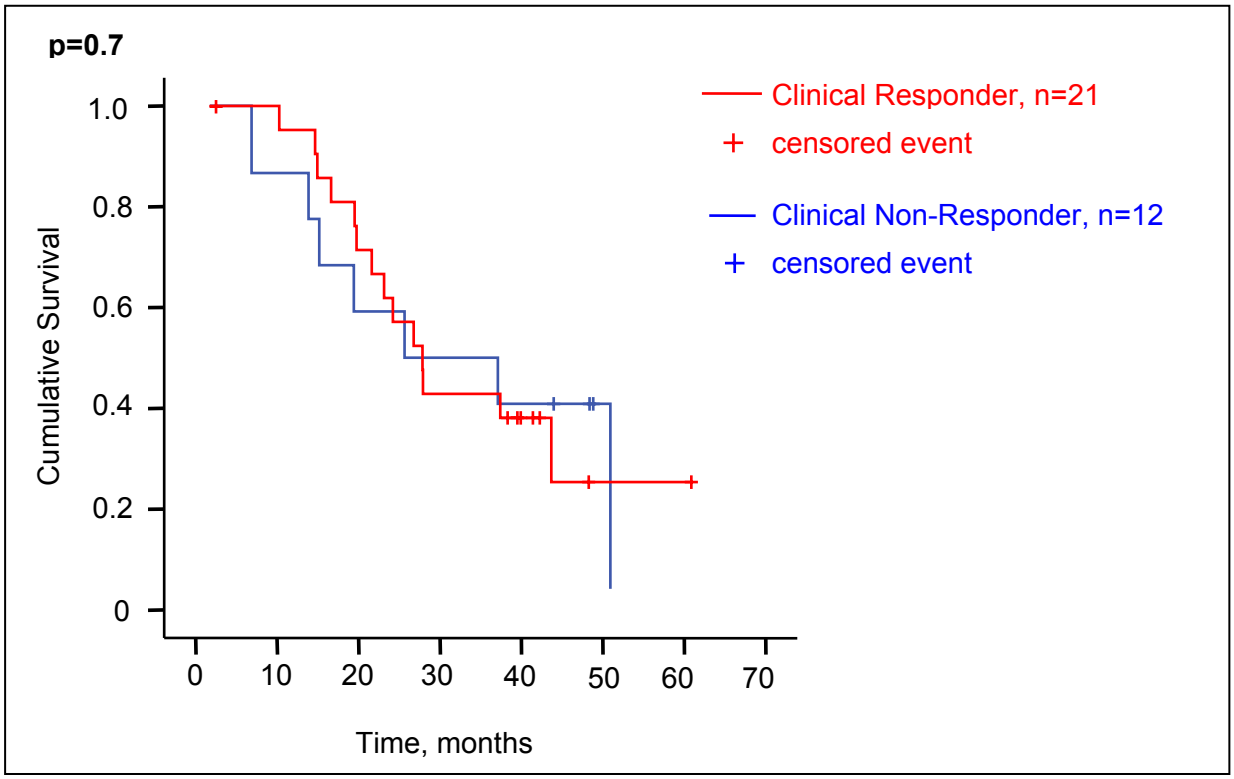


Figure 7. Overall survival of clinical responders and non-responders did not show a significant difference.

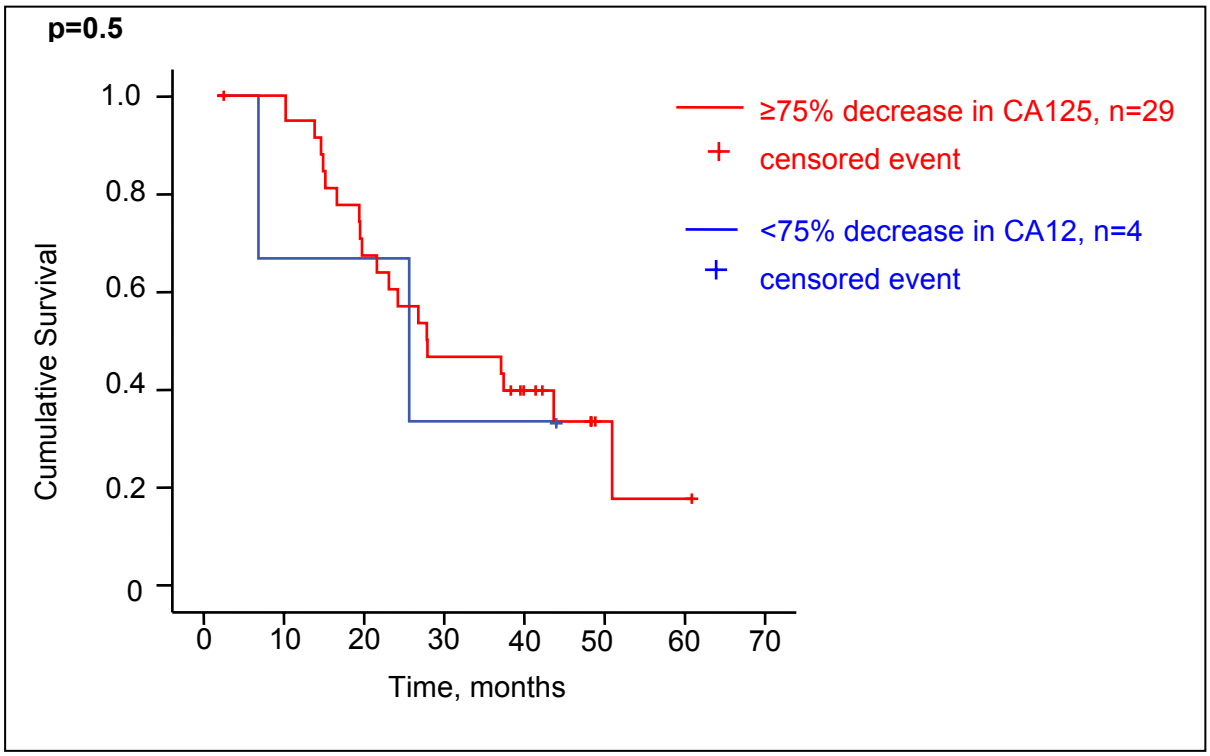


Figure 8A. Survival of patients with and without a decrease in CA125 levels of 75% or more after 3 cycles of chemotherapy did not show a significant difference.

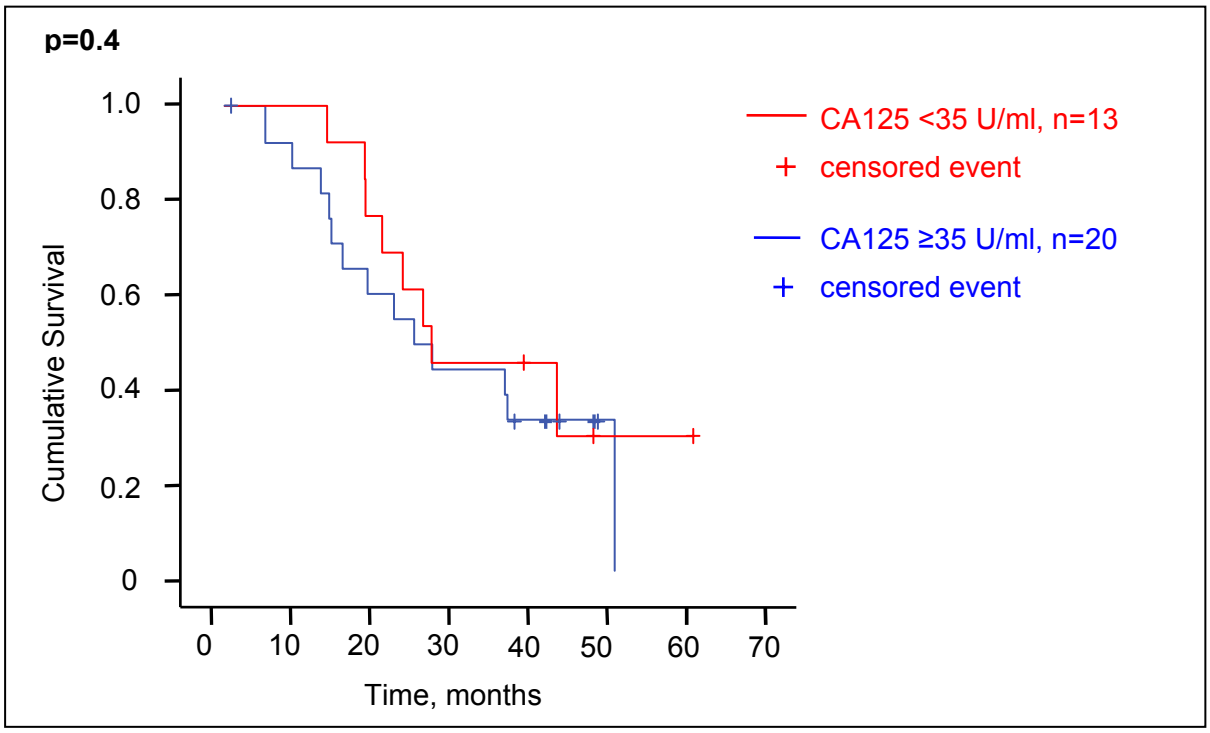


Figure 8B. Survival of patients with and without a normalization (<35 U7ml) of CA125 levels after 3 cycles of chemotherapy did not show a significant difference.

To take into account the high baseline levels in CA125 and the pronounced decrease in CA125 in the selected patient group, a decrease of 80% or more was also tested, but did not show correlation with overall survival. The complete resolution of ascites in almost all (31 out of 33) patients after the third cycle of chemotherapy did not allow valid statistical analysis of decrease in ascites as a single prognostic criterion.

Patients who achieved a histopathologic response had a median overall survival of 43.3 months (n=6) compared to 25.6 months (p=0.09) in patients with no histopathologic response (n=27) after the 3rd cycle of chemotherapy (**Figure 9**).

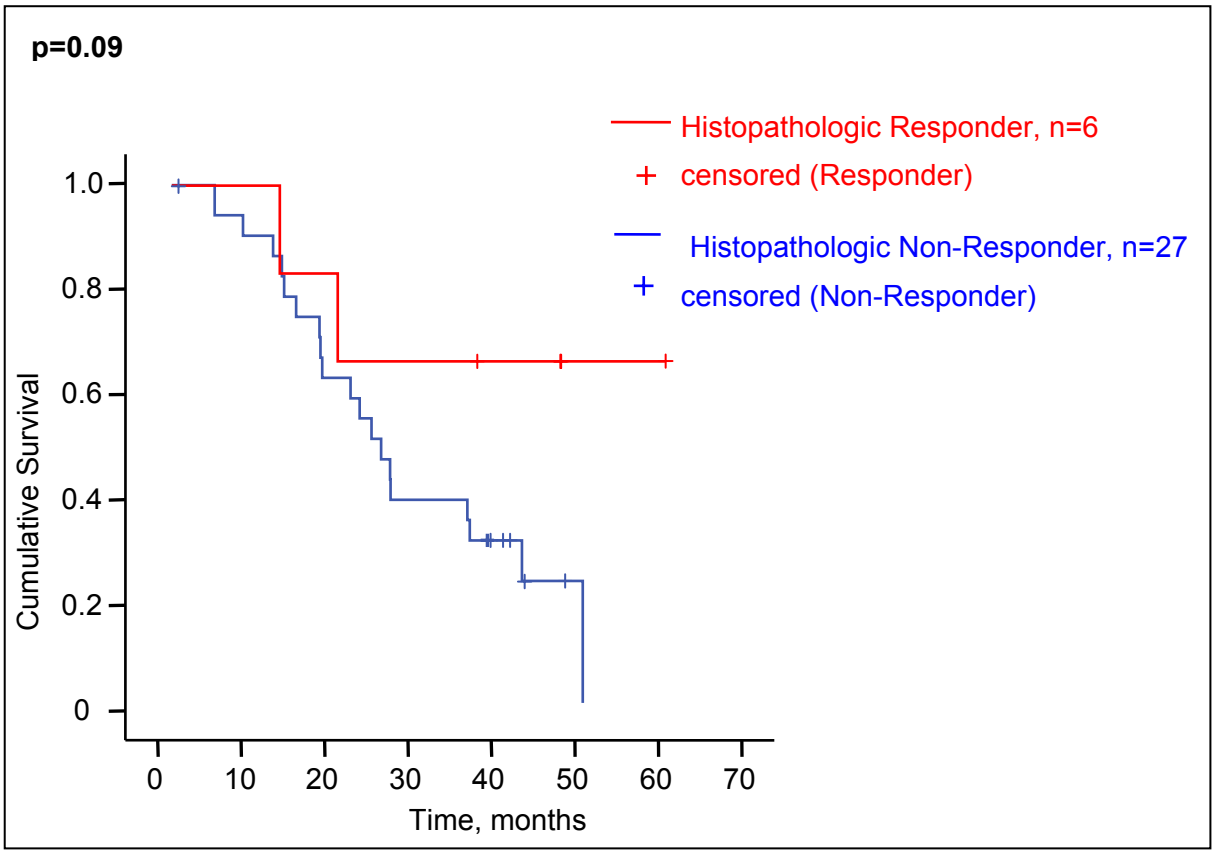


Figure 9. Survival of histopathologic responders and non-responders as assessed after 3rd cycle of chemotherapy.

Clinical parameters known to be important prognostic factors at initial diagnosis include tumor stage and grade. FIGO stage at diagnosis significantly correlated with overall survival (p=0.03). Patients with FIGO stage IIIC (n=23) had a median survival of 27.9 months compared to 15.9 months in patients with FIGO stage IV (n=10). The homogenous patient

population in the current study, with 30 of 33 patients showing WHO grade 3 tumors, did not allow statistical analysis of tumor grade as a single prognostic factor.

The type of chemotherapeutic regimen (single-agent versus combination chemotherapy) did not significantly correlate with patients' overall survival (p=0.8 in univariate and multivariate analysis, respectively). Median overall survival was 26.8 months in patients who received combination chemotherapy (n=22), and 37.4 months in patients who received the single-agent regimen (n=11).

3.5 Residual tumor after surgery and survival

It is generally accepted that optimal cytoreductive surgery is defined by residual tumor masses smaller than 1 cm in largest diameter. Out of 33 patients 11 had residual tumor masses ≥1 cm and 22 patients had tumor masses smaller than 1 cm. Optimal cytoreductive surgery was achieved in 15 (83.3%) out of 18 metabolic responders and in 7 (46.6%) out of 15 metabolic non-responders. Macroscopically tumor free surgery was achieved in 6 (33.3%) out of 18 metabolic responders compared to only 1 (6.7%) out of 15 metabolic non-responders. In patients with optimal cytoreductive surgery median overall survival was 37.9 months compared to 15.2 months in patients with residual tumor masses larger than 1 cm after surgery (p=0.002; **Figure 10**). No significant difference in survival was found between patients with residual tumor masses smaller than 2cm (n=30; median 27.3 months) and patients with residual tumor ≥2 cm (n=3; median 25.6 months; p=0.5). Macroscopically tumor free patients (n=7) showed a significantly better median overall survival of 39.9 months compared to 24.2 months in patients with residual tumor (n=26; p=0.03) after surgery.

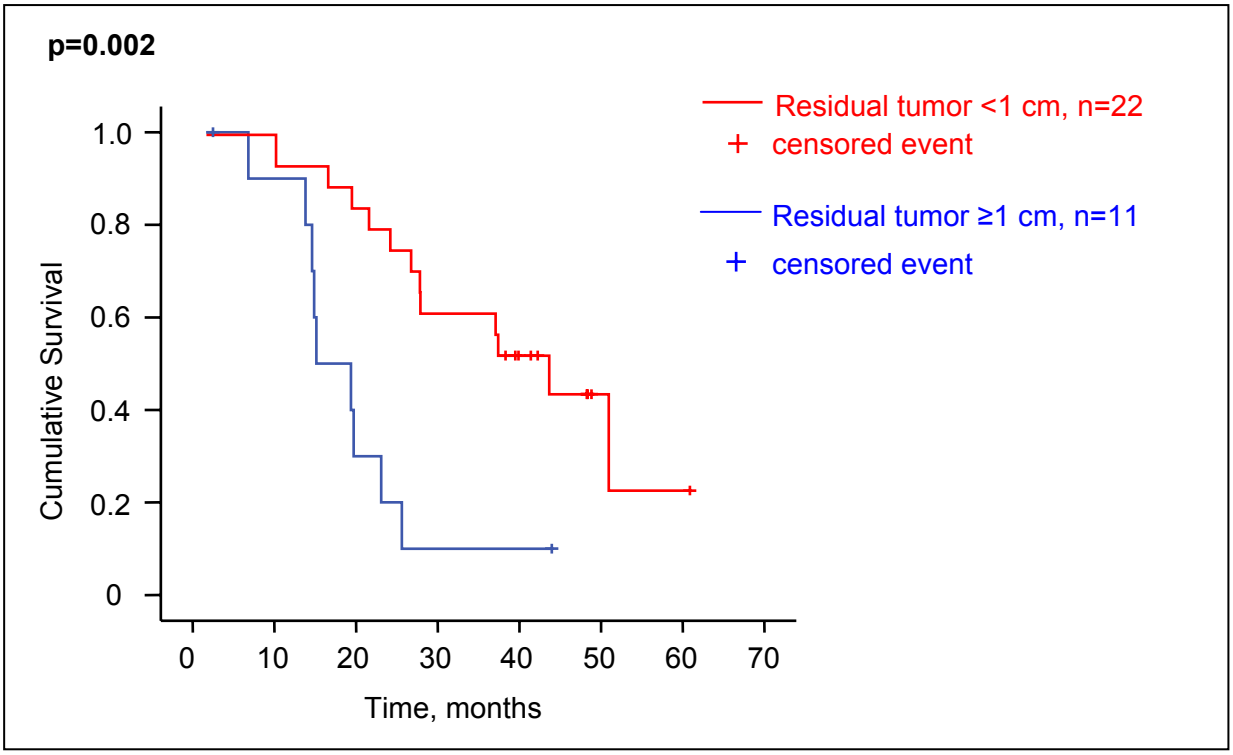


Figure 10. Survival of patients with optimal debulking (residual tumor <1 cm) and those with subobtimal debulking (residual tumor ≥1 cm) after surgery.

3.6 Multivariate analysis of response criteria

Combinations of FDG-PET (metabolic response), clinical, and histopathologic criteria were evaluated with regard to their ability to predict response to chemotherapy. Multivariate analysis was limited to a maximum combination of two parameters, due to the relatively small number of patients investigated and the accordingly small number of events for survival analysis (n=23 patient deaths).

In univariate analysis, metabolic response as assessed by FDG-PET and the size of residual tumor after surgery best predicted patient outcome. Further, histopathologic response showed the highest potential to provide relevant prognostic information. Patients who achieved a histopathologic response showed a longer median overall survival (43.3 months) than non-responders (25.6 months), although this difference was not statistically significant (p=0.09). **Table 4** summarizes the different response criteria evaluated in univariate analysis, with regard to the difference in overall survival of responders and non-responders.

Response criteria	Median overall survival (months) Responder		Non-Responder		Signif.
Clinical	(n=21)	28	(n=12)	23	p=0.7
CA125					
decrease ≥75%	(n=29)	28	(n=4)	23	p=0.5
normalization <35 U/ml	(n=13)	28	(n=20)	24	p=0.4
Histopathology	(n=6)	43	(n=27)	26	p=0.09
FDG-PET					
after 1st cycle ≥20%	**(n=15)**	**38**	**(n=11)**	**23**	**p=0.008**
after 3rd cycle ≥55%	**(n=18)**	**39**	**(n=15)**	**20**	**p=0.005**
Residual tumor					
<1 cm	(n=22)	38	(n=11)	15	p=0.002
Tumor free	(n=7)	40	(n=26)	24	p=0.03

Table 4. Comparison of response criteria with regard to their ability to predict overall survival.

≥20%, relative decrease in SUV (threshold for metabolic response after 1st cycle of CTx); ≥55%, relative decrease in SUV (threshold for metabolic response after 3rd cycle of CTx); Residual tumor, size of residual tumor after debulking surgery; Signif., significance

Combination of FDG-PET with histopathologic criteria:

To test the combination of metabolic and histopathologic response criteria, patients were divided into three groups (A, B, and C). The relatively large group of histopathologic non-responders (27 of 33 patients) was therefore further classified according to their result in FDG-PET after the 1st cycle:

Group A. Patients who achieved a histopathologic response (n=6)

Group B. Patients who achieved no histopathologic response, but showed a metabolic response in FDG-PET after the 1st cycle of chemotherapy (n=12)

Group C. Patients who showed no histopathologic and no metabolic response after 1st cycle of chemotherapy (n=11).

Patients in group A showed the highest survival probability, while survival probability was worst for patients in group C (p=0.01; **Figure 11**). Median overall survival was 43.3 months for group A, 43.7 months for group B, and 23.3 months for group C.

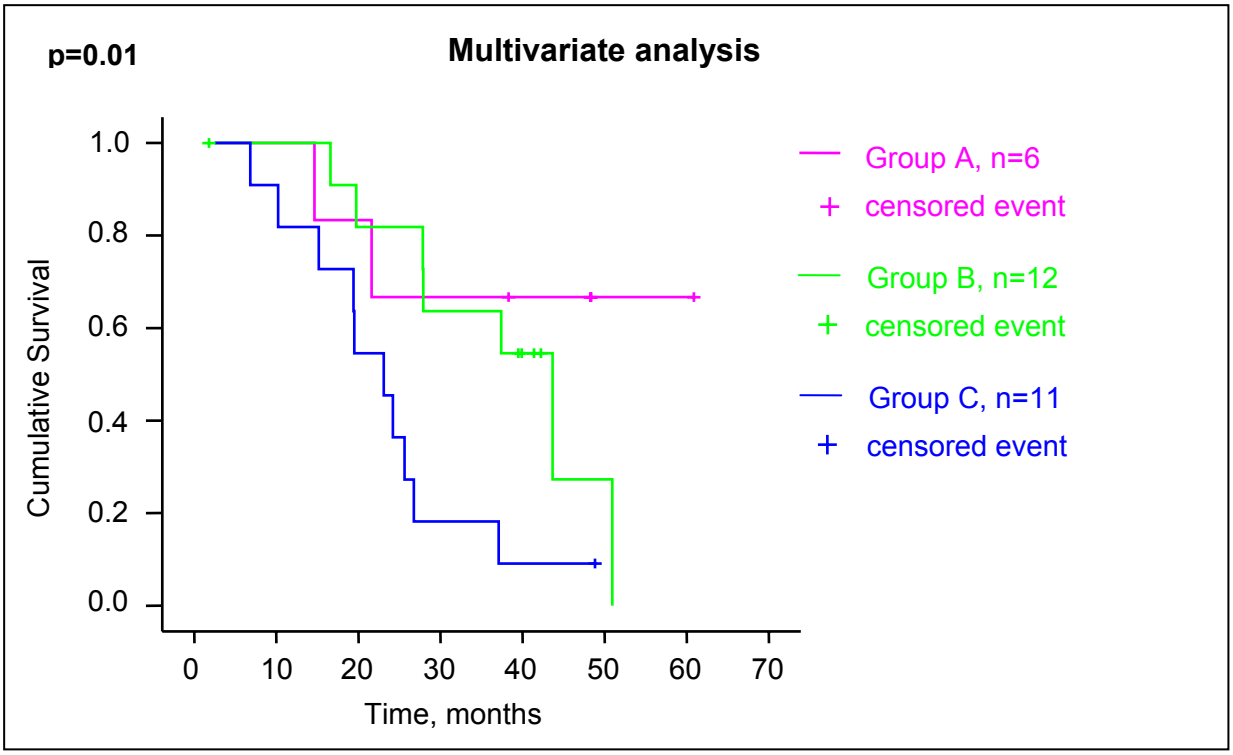


Figure 11. Multivariate analysis, combining metabolic and histopathologic response criteria. Patients with no histopathologic and no metabolic response (group C) showed the poorest prognosis and significantly shorter overall survival.

The most significant difference (p=0.004) in overall survival of responders and non-responders in multivariate analysis was reached when comparing patients with no histopathologic and no metabolic response (group C; median overall survival 23.1 months) to patients who either achieved a histopathologic or a metabolic response (group A+B; median overall survival 43.7 months; **Figure 12**).

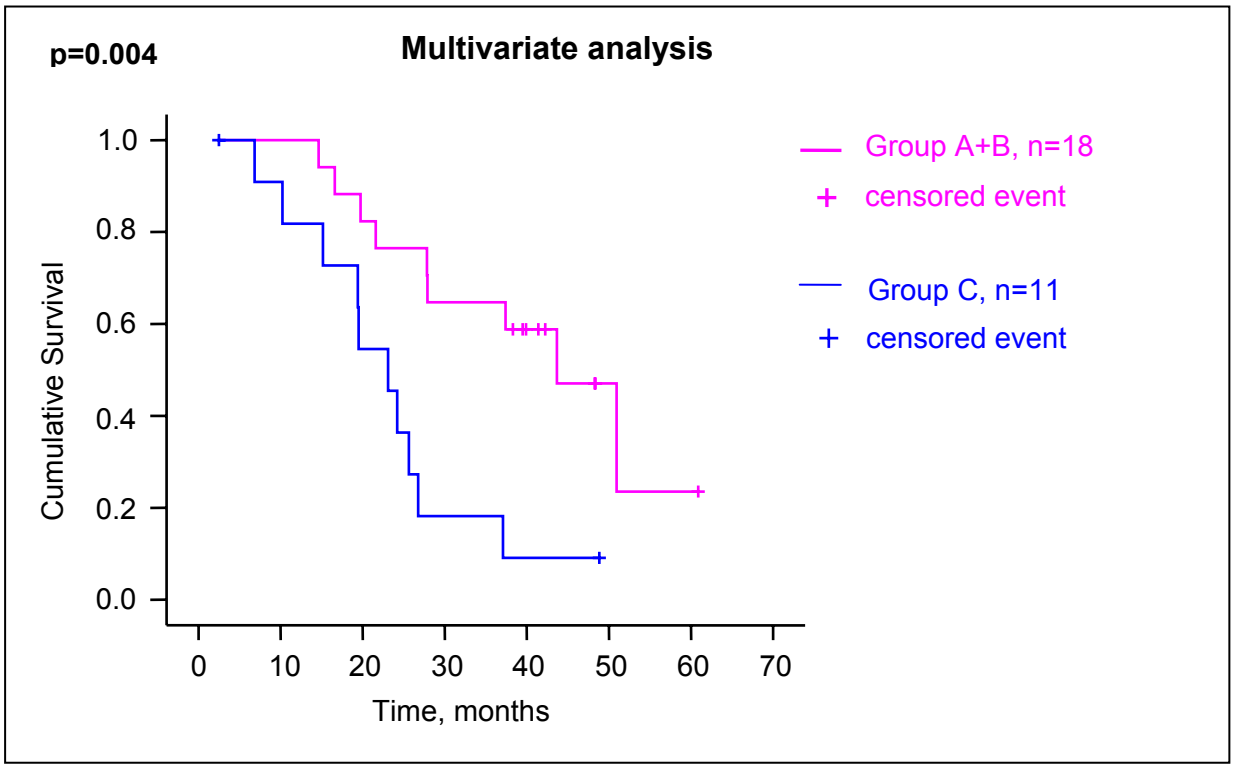


Figure 12. Multivariate analysis, combining metabolic and histopathologic response criteria. Patients with no histopathologic and no metabolic response (group C) showed the poorest prognosis and significantly shorter overall survival.

FDG-PET in multivariate analysis:

Prediction of response by FDG-PET after the 1st and 3rd cycle of chemotherapy remained significant in multivariate analysis, when combined with clinical (p=0.009 and p=0.005 after 1st and 3rd cycle, respectively), CA125 (p=0.02 and p=0.005) or histopathologic response criteria (p=0.02 and p=0.03). FDG-PET remained significant (p=0.008) when tested in combination with the type of neoadjuvant chemotherapy, which was carboplatin plus paclitaxel in 22 patients, and single-agent carboplatin in 11 patients. The type of chemotherapeutic regimen (single-agent versus combination chemotherapy) did not significantly correlate with patients' overall survival (p=0.8 in univariate and multivariate analysis, respectively). When combining FDG-PET (metabolic response) and residual tumor after surgery in multivariate analysis, the combination was highly significant (p=0.004) but each single criterion did not remain significant (p=0.16 and p=0.15, respectively). This is in accordance with the fact that metabolic response clearly correlated with a higher rate of optimal cytoreduction (residual tumor <1 cm) and macroscopic tumor free status after surgery.

4 Discussion

This study prospectively evaluated the hypothesis that early changes in tumor glucose utilization, as assessed by FDG-PET, allow prediction of the effectiveness of chemotherapy and subsequent patient outcome. Patients undergoing neoadjuvant chemotherapy for advanced stage ovarian cancer were studied with FDG-PET at baseline and after the first and third cycle of chemotherapy. FDG uptake was assessed semiquantitatively by calculating standardized uptake values (SUV). Relative changes in SUV between baseline and follow-up PET scans were determined for each patient. A significant correlation was found between a decrease in FDG uptake in ovarian cancer (metabolic response) and subsequent overall survival.

Currently, changes in tumor size are used as endpoint for assessment of response to treatment in solid tumors. The RECIST criteria (response evaluation criteria in solid tumors) define tumor response by a decrease of the maximum tumor diameter by at least 30% [122]. Tumor size is frequently determined by consecutive CT imaging. However, in ovarian cancer RECIST criteria have not been prospectively validated and are not widely accepted [96]. CT imaging, although a valuable assessment parameter in other cancers, was not included in this study because of the inherent limitation to accurately determine the extent of disease in the peritoneal cavity [38, 59].

An important limitation of tumor size measurements for assessment of treatment response is the observation that several cycles of chemotherapy are necessary before tumor shrinkage can be expected. In contrast, metabolic changes may precede changes in tumor size during chemotherapy. One of the first studies using sequential FDG-PET imaging for monitoring treatment response was in breast cancer in the early 1990s [131]. Eleven patients underwent neoadjuvant chemohormonotherapy for locally advanced breast cancer and were studied with FDG-PET at baseline and during the first three cycles of treatment. A close correlation was observed between the decrease in FDG uptake and subsequent histopathologic tumor response. Of note, the tumor size did not significantly change during the first three cycles of treatment [131].

In the current study, the FDG uptake decreased by 50.1% after the first cycle and 76.2% after the third cycle of chemotherapy in ovarian cancer patients responding to treatment (metabolic response). In these patients, 65.7% of the overall metabolic changes occurred within the first two weeks after initiation of chemotherapy. Similar observations were reported in successfully treated non-Hodgkin's lymphoma [90]. The FDG uptake decreased by 60-67% from baseline to

the first week after initiation of chemotherapy. Two thirds of the overall metabolic effect of chemotherapy occurred within the first week of treatment [90]. In contrast, FDG uptake in non-responding ovarian cancer patients in the current study decreased by 7.0% after the first cycle and 27.3% after the third cycle. Only 25.6% of the overall metabolic changes occurred within the first two weeks of treatment.

4.1 Prediction of response after the first cycle

Several studies evaluated the correlation between changes in FDG uptake and subsequent tumor response. In 30 patients treated with neoadjuvant chemotherapy for locally advanced breast cancers the mean reduction in FDG uptake after the first cycle of chemotherapy was significantly higher in lesions with partial, complete macroscopic or complete microscopic histopathologic response [114]. Schelling et al. [99] compared the FDG uptake in 22 breast cancer patients after the first and second cycle of neoadjuvant chemotherapy to baseline PET. Patients classified as responders by histopathology had a significantly more pronounced decrease in FDG uptake than non-responding patients. All responders were correctly identified after the first cycle of chemotherapy (specificity 85%) [99]. Weber et al. [133] studied 40 patients with locally advanced adenocarcinomas of the esophagogastric junction who also underwent neoadjuvant chemotherapy. FDG-PET was performed at baseline and two weeks after the first cycle of chemotherapy and changes in FDG uptake were correlated with clinical and histopathologic tumor response after 3 months of chemotherapy. In clinical responders, FDG uptake decreased by 54% compared to 15% in non-responding tumors. Metabolic response defined by changes in FDG uptake did not only correlate with histopathologic response but also with patient survival. In 37 patients with adenocarcinoma of the esophagogastric junction two-year survival was 60% in metabolic responders compared to 37% in non-responders [133].

The close correlation between the decrease in FDG uptake after initiation of chemotherapy and histopathologic tumor response as well as overall survival seems to be a characteristic behavior of malignant tumors [99, 114, 133]. However, no study so far has evaluated the role of FDG-PET for prediction of response to neoadjuvant chemotherapy in ovarian cancer. This study was designed to evaluate sequential FDG-PET for prediction of response by imaging patients at baseline and within 16 days after the first cycle of neoadjuvant chemotherapy. As discussed above, previous studies have commonly used clinical or histopathologic tumor response as reference. Metabolic response was retrospectively defined by the threshold that best predicted clinical or histopathologic tumor response [99, 133, 137]. While histopathologic tumor regression is

a well-accepted endpoint for assessment of response to treatment in various tumors such as breast cancer, osteosarcoma, esophageal and gastric cancer, there are no histopathologic response criteria established for ovarian cancer. Therefore, the current study used overall survival as a reference. In the current study median overall survival was 38.3 months in metabolic responders compared to 23.1 months in metabolic non-responders (p=0.008). An important finding of the current study is that changes in FDG uptake predicted response to chemotherapy and patient survival better than clinical or histopathologic parameters. No correlation was found between clinical response criteria, including changes in tumor marker CA125 and overall survival (p=0.7 and p=0.5, respectively), and only a weak correlation was found between histopathologic response and overall survival (p=0.09).

4.2 Prediction of response after the third cycle

Few studies have evaluated the correlation between changes in FDG uptake after several cycles or after completion of chemotherapy and overall survival. Most studies in this setting have used a single FDG-PET scan after completion of chemotherapy to assess response to treatment. In 73 patients treated with neoadjuvant chemoradiotherapy for non-small cell lung cancer, a single post-treatment PET scan was the best predictor of survival. Patients with evidence of tumor on visual assessment had a four-fold higher death rate compared to those with no evidence of residual tumor [67]. However, quantitative assessment of changes in FDG uptake after chemotherapy may be more accurate than visual assessment of FDG-PET alone.

The current study was designed to assess response to chemotherapy by imaging patients with FDG-PET at baseline and within 23 days after the third cycle of neoadjuvant chemotherapy, prior to surgery. The decrease in FDG uptake was significantly correlated with overall survival. Median overall survival was 38.9 months in metabolic responders (≥55% decrease in FDG uptake) compared to 19.7 months in non-responders (p=0.005). A significant correlation between the decrease in FDG uptake after completion of chemotherapy and overall survival was also shown in esophageal cancer. In 17 patients studied with FDG-PET before and after neoadjuvant chemoradiotherapy, two-year survival was 63% in metabolic responders (≥60% decrease in FDG uptake) compared to 38% in non-responders [24]. Brücher et al. [12] studied 27 patients with esophageal cancer at baseline and three to four weeks after completion of neoadjuvant chemoradiotherapy. Median overall survival was 23 months in metabolic responders (≥52% decrease in FDG uptake) compared to 9 months in non-responders [12].

Post-hoc definitions of metabolic response are likely to overestimate the diagnostic accuracy of sequential FDG-PET. This is one of the first studies that applied a prospective criterion to define metabolic response after the first cycle of chemotherapy. A previously defined threshold of 20% decrease in FDG uptake was significantly correlated with overall survival (p=0.008). Median overall survival was 38.3 months and 23.1 months in metabolic responders and non-responders, respectively. Weber et al. [134] recently suggested this prospective criterion and defined metabolic response as a decrease in FDG uptake larger than two times the standard deviation of spontaneous changes, which is ≥20% for the standardized uptake value (SUV) approach [135]. In 55 patients with advanced non-small cell lung cancer, metabolic response 3 weeks after initiation of chemotherapy according to this definition was closely correlated with decrease in tumor size and overall survival. Metabolic responders had a median overall survival of 252 days compared to 151 days in non-responders (p=0.005) [134].

4.3 Potential clinical relevance of FDG-PET therapy monitoring

Although introduced more than 20 years ago, neoadjuvant chemotherapy for advanced ovarian cancer is still under active investigation [27, 83]. The additional use of sequential FDG-PET might help to individualize treatment and improve patient selection. This study showed that sequential FDG-PET provided important prognostic information and could potentially be used for treatment stratification in the future. Neoadjuvant chemotherapy could be continued in metabolic responders identified after the first cycle, whereas metabolic non-responders might benefit from immediate surgery followed by second-line chemotherapy. FDG-PET after the third cycle of chemotherapy provided a more accurate assessment of response and could aid in determining the extent and the aggressiveness of surgery. The poor prognosis of metabolic non-responders suggests that cytoreductive surgery could be performed less aggressively in these patients [1]. However, randomized prospective studies in a sufficient number of patients are needed before sequential FDG-PET imaging can be routinely used for treatment stratification in ovarian cancer.

4.4 Clinical response criteria

Clinical response criteria, including changes in tumor marker CA125, did not accurately reflect treatment response and did not correlate with overall survival after neoadjuvant chemotherapy in this study. No standard exists to date for clinical assessment of response to neoadjuvant

chemotherapy in ovarian cancer. Variable parameters are commonly applied, including patients' overall state of performance, regression of ascites, and regression of the ovarian bulk tumor as assessed by physical examination or intraoperatively, but none of these criteria have been prospectively validated. In the current study, clinical response was defined as response in at least 2 of the following 3 criteria: intraoperative residual tumor of less than 4 cm, regression of peritoneal carcinomatosis, and a decrease in CA125 of at least 75% from baseline or a complete normalization (<35U/ml). By applying these criteria, no correlation between clinical response and overall survival was found (p=0.7), despite a weak correlation between clinical response and metabolic response in FDG-PET.

The serum tumor marker CA125 is an early indicator of recurrence and has also been suggested for evaluation of response to postoperative and palliative chemotherapy [8]. The decline in CA125 levels during postoperative chemotherapy is known to be a prognostic factor associated with time to progression [30] and survival probability [108]. Recently, the Gynecological Cancer Intergroup has defined response to postoperative chemotherapy by a decrease in CA125 of at least 50% [93] and others have suggested a serial decrease over three samples of greater than 75% [8, 92, 95].

However, it remains unclear if CA125 response criteria can be translated from the palliative to the neoadjuvant setting. In the current study, all patients except one had a decrease in CA125 of at least 50% and 29 out of 33 had a decrease of ≥75% from baseline. No correlation was found between the decrease in CA125 and overall survival (p=0.5). Other groups have suggested normalization of CA125 or CA125 half-life to assess response to postoperative chemotherapy [32, 33, 50]. In the current study, patients with and without a normalization of CA125 levels after neoadjuvant chemotherapy showed no difference in overall survival (p=0.4).

Important differences between palliative and neoadjuvant chemotherapy have to be considered. In this study, the CA125 level prior to treatment was on average 2912±7404 U/ml and in many cases substantially higher than in the trials where the response criteria were established [95]. A decrease from 10,000 to 1,000 U/ml for example may be misinterpreted as a good response while the patient still has considerable residual viable tumor. Recent studies, including a meta-analysis of 19 phase II trials, indicated that CA125 response criteria tend to overestimate tumor response [37, 94]. Especially in the setting of neoadjuvant chemotherapy, the extremely high CA125 baseline levels (mean 2912±7404 U/ml in this study) are commonly associated with a major decrease during therapy (mean 87±20% in this study) and therefore may facilitate an

overestimation of response. Larger prospective trials are needed to evaluate the role of CA125 response criteria during neoadjuvant chemotherapy.

4.5 Histopathologic response criteria

Histopathologic tumor regression serves as gold standard for response evaluation after neoadjuvant chemotherapy in several types of tumors. Initially developed by Saltzer-Kuntschik et al. for osteosarcoma [97, 98], various grades of histopathologic response have been defined by the percentage of residual viable tumor after chemotherapy. An analogous regression classification was established for esophageal [70], gastric, and colorectal cancer [5] and is currently used for response evaluation at our university hospital (Klinikum rechts der Isar, Munich). Similar regression classifications exist for prostate [22], head and neck [7], pancreatic [28], breast [45, 111], and non-small cell lung cancer [56]. Patients histopathologically responding to neoadjuvant chemotherapy had a better overall survival compared to non-responders [5, 44].

However, there is no histopathologic response classification established for ovarian cancer. A recent study observed histomorphological changes after chemotherapy, including low nucleocytoplasmic ratio, nuclear enlargement and a decrease in mitotic activity [71], but did not propose a response classification and did not correlate the histopathologic findings with patient survival [71]. In contrast to other tumor types, the regression of ovarian cancer is characterized by a reduction in volume and size without significant residual scar or fibrotic tissue, making it difficult to determine the percentage of residual viable tumor. In the current study, histopathologic response was defined as no detectable residual tumor or residual tumor of ≤1cm with signs of regression such as marked necrosis, apoptosis or reactive inflammation. By applying these criteria, there was only a weak correlation between histopathologic response (6 out of 33 patients) and overall survival (p=0.09). It may be necessary to develop more specific criteria for histopathologic tumor response in ovarian cancer such as changes in the proliferative activity, markers of apoptosis as well as changes in the genomic and proteomic expression profile.

Overall, in the current study clinical criteria including changes in tumor marker CA125 seemed to overestimate response to neoadjuvant chemotherapy, whereas histopathologic assessment rather seemed to underestimate response to treatment.

4.6 Novel response criteria

Recently, various molecular markers, genetic profiling, the presence of tumor cells in the blood and *in vitro* testing for chemosensitivity have been suggested to be helpful in predicting response to treatment [19, 110]. Gene expression profiling with microarrays allows simultaneous assessment of several thousand genes potentially involved in the sensitivity or resistance of cancer cells to chemotherapy [101]. A number of studies including ovarian cancer, have identified gene expression profiles that are linked to the response of cell lines to chemotherapeutic agents [17, 107, 127, 128]. Most recently, Spentzos et al. studied tumor tissues of 68 patients with ovarian cancer and identified a gene expression signature of 115 genes with independent prognostic significance [116]. Nevertheless, principal limitations of this approach include the need for adequate tissue samples, tumor heterogeneity, as well as host factors such as drug delivery, tissue oxygenation, and metabolism, which may contribute to the chemosensitivity or chemoresistance of a tumor but may not be reflected by gene expression profiles of the tumor cells.

4.7 Technical aspects

4.7.1 Best threshold for definition of metabolic response

For clinical application, it is important to define an optimal threshold for decrease in FDG uptake to differentiate metabolic responders from non-responders. No generally accepted cut-off values have been established so far and most studies have used retrospective definitions of metabolic response [99, 114, 133].

The suggested threshold of 20% decrease in FDG uptake will not identify all metabolic non-responders. However, for clinical application it is preferable to use a relatively low conservative threshold to assure treatment continuation in responders even at the cost of not identifying all non-responders. In the current study, two patients with a decrease of more than 20% after the 1st cycle of chemotherapy were classified as metabolic non-responders after the 3rd cycle. More important, no metabolic responder after the 3rd cycle has been erroneously classified as non-responder by FDG-PET after the 1st cycle.

The definition of metabolic response later in the course of treatment, after several cycles or after completion of chemotherapy, may require a higher threshold, which is not just outside the range of spontaneous fluctuations. Several studies using FDG-PET for assessment of response

to chemotherapy have retrospectively found thresholds of a decrease between 35% and 55% in FDG uptake to optimally differentiate between metabolic responders and non-responders. In advanced ovarian cancer, the current study retrospectively determined a threshold of 55% decrease in SUV to optimally differentiate between metabolic responders and non-responders after the 3rd cycle of chemotherapy. Thresholds between 35% and 55% decrease in SUV showed a significant difference in the overall survival of metabolic responders and non-responders in this study, whereas a threshold of 20% was not found to be significant after the 3rd cycle of chemotherapy. In locally advanced breast cancer, Wahl et al. studied 11 patients undergoing neoadjuvant chemohormonotherapy and found a decrease in SUV of 47.6%±4.4% from baseline to day 63 in pathologically responding patients (8 of 11). Patients without a pathological response (3 of 11) showed no significant decrease in FDG uptake (19±18%; $p<0.0001$) [131]. Schelling et al. reported a series of 22 patients with locally advanced breast cancer, and found a threshold of 55% decrease in SUV to optimally predict histopathologic response to neoadjuvant chemotherapy [99]. Smith et al. evaluated FDG-PET for therapy monitoring in breast cancer, and found a mean decrease in SUV of 38.4% and 43.7%, respectively, in patients with a subsequent macroscopic or microscopic complete pathological response [114]. Weber et al. studied 37 patients with locally advanced adenocarcinoma of the esophagogastric junction, and found a threshold of 35% decrease in SUV from baseline to day 14 to optimally predict clinical response. A threshold of 45% was found optimal for prediction of histopathologic response. Metabolic responders (≥35% decrease in SUV) had a significantly longer median time to progression or recurrence than metabolic non-responders (16 versus 9 months; $p=0.01$) and a higher 2-year survival rate (60% versus 37%; $p=0.04$) [133].

In summary, these findings allow hypothesizing that a prospectively defined conservative threshold of 20% decrease in FDG uptake is optimal early after initiation of chemotherapy and may be applied to different types of solid tumors. In contrast, retrospective evaluation found higher thresholds to be optimal for differentiation of metabolic responders and non-responders after several cycles or after completion of chemotherapy. It may be necessary to develop and validate specific thresholds for decrease in FDG uptake, depending on the tumor type and the treatment regimen, for assessment of response later in the course of chemotherapy.

4.7.2 Influence of SUV normalization on prediction of response

Previous studies have demonstrated that standardized uptake values (SUV) provide highly reproducible parameters for tumor glucose utilization [73, 135]. Different methods for calculation of SUVs are commonly applied and the role of SUV normalization to blood glucose levels has not been conclusively evaluated. A recent report by Stahl et al. showed the operational reliability of the SUV approach for therapy monitoring [117]. The authors concluded that in gastric cancer, prediction of response to chemotherapy based on relative changes in SUV is not essentially influenced by the time delay after FDG administration, the normalization of SUV to body weight versus body surface area or lean body mass, or the normalization to blood glucose levels [117].

The current study confirms that response prediction based on relative changes in SUV is not essentially influenced by the specific method of calculation. SUV calculated for maximum and average activity values within a region of interest (ROI), with and without normalization to blood glucose (SUVav, SUVav-glc, SUVmax, and SUVmax-glc) were compared with regard to their ability to predict overall survival. At a threshold of 20% decrease in SUV after the 1st cycle of chemotherapy, the difference in overall survival of metabolic responders and non-responders was essentially equally significant for SUVav, SUVav-glc, SUVmax, and SUVmax-glc, respectively ($p=0.008$, 0.02, 0.03, and 0.004, respectively). When using a threshold of 55% decrease after the 3rd cycle of chemotherapy, the calculation of SUVav, SUVav-glc, SUVmax, and SUVmax-glc showed similar significance in differentiating metabolic responders and non-responders ($p=0.005$, 0.005, 0.02, and <0.001, respectively). Of note, the most significant difference in the overall survival of metabolic responders and non-responders was found when calculating SUV for maximum activity normalized to blood glucose (SUVmax-glc).

One may hypothesize a theoretical advantage of using SUV for maximum activity within the tumor ROI, normalized to blood glucose. The size of the ROI affects the radioactivity measurements, the larger the ROI, the lower the mean SUV. During treatment, marked decrease in the size of a lesion (close to the size of the ROI) or treatment induced necrosis at the borders of a lesion will lead to a lower mean activity value within a ROI. The maximum activity value might be more reliable under these conditions. Furthermore, the inverse relationship between FDG uptake (SUV) and blood glucose level can be taken into account for the interpretation of follow-up PET scans by correcting SUVs for blood glucose levels (assuming a linear relation between blood glucose and FDG uptake). The limited data in this

study suggest a potential benefit of normalizing SUVs to blood glucose levels in the situation of multiple sequential PET scans for therapy monitoring. Two recent studies reported an improved correlation between SUV corrected for blood glucose level and quantification by full compartment analysis [41, 61]. However, these reports did not correlate relative changes in SUV with patient outcome. Accordingly, the higher accuracy of SUVgluc in reflecting tumor FDG metabolism may not necessarily transfer into better response prediction. In the current study, the theoretical advantage of a correction of SUV to blood glucose levels did not translate into a detectable clinical benefit for therapy monitoring. Although SUVmax-gluc showed the highest significance in differentiating metabolic responders from non-responders, the best threshold for the differentiation of responders and non-responders was virtually identical (20% after first cycle; 55% after third cycle) for all investigated methods of SUV calculation (SUVav, SUVav-glc, SUVmax, and SUVmax-glc). These findings may facilitate the use of FDG-PET for therapy monitoring and the comparability of different studies.

In summary, when using FDG-PET for early assessment of therapy response the specific method for calculation of SUV seems to be less important than the fact that a highly standardized protocol has to be used for serial FDG-PET scans.

4.7.3 Reference lesion for sequential FDG-PET

FDG-PET imaging commonly shows multiple foci of increased FDG uptake in ovarian cancer, since the majority of patients present with advanced stages of disease and tumor spread in the abdominal cavity [15, 16]. This imposes the need to determine reference lesions for follow-up scans. In the current study, multiple metastatic tumor foci within one patient showed variable degrees of decrease in FDG uptake. This may be due to tumor heterogeneity and divergence in the chemosensitivity of distinct tumor clones. In the current study, the lesion with the smallest decrease in SUV served as the reference, based on the rationale that the lesion with the worst response to chemotherapy will ultimately determine survival. Changes in the FDG uptake of this reference lesion after the 1st and 3rd cycle of chemotherapy significantly correlated with overall survival ($p=0.008$ and 0.005). By using the mean of all metastatic lesions per patient, a decrease in SUVmean of 55% or more after the 3rd cycle showed a significant correlation ($p=0.007$) with overall survival. However, a decrease in SUVmean of 20% or more after the 1st cycle did not significantly correlate with overall survival ($p=0.06$). Larger prospective studies are needed to compare the mean of all metastatic lesions per patient with the lesion showing the

worst metabolic response, with regard to their capability to predict patient outcome. This question has not been addressed before. Previous studies evaluating FDG-PET for the purpose of therapy monitoring have commonly assessed primary tumors, e.g. in breast or gastrointestinal cancer that usually present with a solitary lesion/mass.

4.7.4 FDG uptake in tumor tissue

The mechanism of FDG uptake in tumors is not completely understood. The transport of the radiotracer through the cell membrane via glucose transport proteins (GLUT), especially GLUT-1, and subsequent intracellular phosphorylation by hexokinase have been identified as key steps for subsequent tissue accumulation [3, 11, 74]. In epithelial ovarian tumors FDG uptake was statistically related to the intensity of GLUT-1 expression (p=0.001), with a gradual increase in GLUT-1 from borderline to malignant tumors [64]. Numerous other factors including cellular density, blood flow and tissue perfusion, tissue oxygenation, blood glucose and insulin levels, cellular proliferation, cell-cycle status, adenosine triphosphate levels, receptor status, and others have an effect on the F-18 signal seen at PET [130]. Nevertheless, standardized uptake values (SUV) provide highly reproducible parameters for tumor glucose utilization [73, 135]. FDG-PET imaging measures the net effect of chemotherapy induced metabolic changes and may be seen as an integral over various factors contributing to the chemosensitivity or chemoresistance of a tumor.

An important advantage of imaging changes in tumoral metabolic activity by FDG-PET is the ability to monitor *in vivo* the overall effects of therapeutic chemotherapy, not only in the primary tumor but also in metastatic lesions throughout the body. The reported data showed a significant correlation between changes in the FDG uptake of metastatic lesions throughout the peritoneum and overall survival. This study thereby provides the first evidence that the use of FDG-PET therapy monitoring may be possible for distant metastases in addition to the primary tumor.

4.8 Future perspectives

PET/CT is a new imaging modality that allows for the acquisition of spatially registered PET and CT data in one imaging procedure [125]. Using a combined PET/CT scanner for monitoring therapeutic effects allows the assessment of changes in tumor size (RECIST) and FDG uptake

(metabolic response) at the same time. An alternate method of response evaluation combining CT measurements with FDG uptake is currently being discussed for ovarian cancer [78].

FDG-PET is already widely used to establish the diagnosis of recurrent ovarian cancer [9, 58, 88, 124, 141]. FDG-PET could also potentially serve as a surrogate endpoint in the treatment of recurrent ovarian cancer. Response prediction by FDG-PET after the first cycle of palliative chemotherapy would allow the early use of second- or third-line agents and help to reduce toxicity and side effects from an ineffective treatment. On the other hand, patients showing a good metabolic response in FDG-PET, which may precede response in tumor size or CA125 levels, may be spared the unnecessary prolongation of an effective yet non-curative chemotherapy. FDG-PET may potentially be used to define the optimal agent, dosing, and number of cycles during palliative chemotherapy in the future. Validation of the presented results in larger prospective trials is necessary prior to implementation of sequential FDG-PET for therapy monitoring in clinical routine use.

The evaluation of new therapeutic strategies may profit from an early prediction of response by metabolic therapy monitoring, using FDG-PET as a surrogate endpoint. FDG-PET could be considered in clinical Phase I-II trials to identify the biologically optimal dose and cytostatic activity of novel therapies, such as signal transduction inhibitors or receptor ligands. New chemotherapeutic agents might be safely continued in patients showing unequivocal metabolic response while patients without obvious metabolic response could be changed to a standard regimen. Eligibility for trials in which response rate is an endpoint could be broadened to include either RECIST or FDG-PET assessable patients, as many patients with peritoneal implants cannot be adequately assessed by conventional imaging techniques, but might well show initially elevated tumor glucose metabolism and therefore allow assessment of response by FDG-PET. Consideration could be given for early discontinuation of those study arms with significant inferior prognosis as defined by FDG-PET.

4.9 Limitations and strengths

The major limitation of this study is the relatively small number of patients (n=33), and the fact that not all patients underwent FDG-PET after the first cycle of chemotherapy. The current study focuses on a subset of ovarian cancer with advanced stages of disease, and the reported data may not necessarily be extrapolated to patients with less bulky disease. This study did not correlate FDG-PET metabolic response with progression free survival. Some patients received

further palliative chemotherapies that may have had an impact on overall survival that was not measured. The discussed criteria for metabolic response after the third cycle of chemotherapy were determined retrospectively and need to be further validated in a larger prospective study.
In contrast, the use of a previously defined threshold for decrease in SUV to define metabolic response after the first cycle of chemotherapy represents an important strength. Using a prospective criterion based on independent reproducibility studies may contribute to avoid the bias of overestimating diagnostic accuracy. The patient population investigated was homogenous with regard to pretreatment clinical, histopathologic and laboratory parameters and has been treated according to a highly standardized therapy protocol. A highly standardized acquisition protocol has been applied for the sequential FDG-PET examinations, which is known to be essential when assessing serial FDG-PET scans [88, 117]. An important strength of this study is the median follow-up of 49 months.

4.10 Conclusions

This thesis demonstrated a significant difference in an important endpoint, namely overall survival, between FDG-PET metabolic responders versus non-responders. Changes in FDG uptake in ovarian cancer assessed by sequential FDG-PET predicted patient survival as early as after the first cycle of neoadjuvant chemotherapy. Metabolic response criteria were more accurate than clinical or histopathologic response criteria including changes in tumor marker CA125 for prediction of overall survival. Therefore, FDG-PET appears to be a promising tool for early prediction of treatment response in individual patients. Sequential FDG-PET might be helpful in patient stratification for surgery versus continued chemotherapy and aid in the decision on the aggressiveness of cytoreductive surgery. Sequential FDG-PET is a promising tool to individualize treatment and reduce ineffective chemotherapy and could potentially also serve as surrogate endpoint in chemotherapy for recurrent ovarian cancer. Prospective trials are needed to validate the potential clinical use of sequential FDG-PET for treatment stratification in ovarian cancer.

5 Summary

This thesis prospectively evaluated the hypothesis that early changes in tumor glucose utilization assessed by sequential positron emission tomography (FDG-PET) predict the effectiveness of chemotherapy and subsequent patient outcome. The overall goal was to evaluate changes in tumor glucose utilization assessed by sequential FDG-PET as surrogate endpoint to determine response to neoadjuvant chemotherapy in patients with advanced stage (FIGO IIIC and IV) ovarian cancer. The study had three specific aims:

I. Evaluation of sequential FDG-PET for prediction of treatment response after the first and third cycle of chemotherapy.

II. A comparison of different methods for normalization of standardized uptake values (SUV) with regard to their ability to predict response to therapy.

III. Comparison of FDG-PET (metabolic response) with clinical criteria, changes in tumor marker CA125, and histopathologic criteria with regard to their ability to predict response to chemotherapy.

In an interdisciplinary collaboration between the department of nuclear medicine, the department of obstetrics and gynecology, and the institute of pathology at the Technische Universität München, 33 patients with advanced stage ovarian cancer were enrolled. Patients underwent three cycles carboplatin based neoadjuvant chemotherapy followed by tumor debulking surgery and postoperative chemotherapy. All 33 patients underwent quantitative FDG-PET of the abdomen and pelvis at baseline and after the third cycle of chemotherapy, prior to surgery. A subgroup of 26 patients also underwent FDG-PET after the first cycle of chemotherapy, at a mean interval of 16 days after initiation of chemotherapy. A total of 92 FDG-PET scans were performed.

FDG uptake in ovarian cancer was assessed semiquantitatively by calculating standardized uptake values (SUV) normalized to the injected dose of FDG and patient's body weight. Changes in SUV between baseline and follow-up PET scans were determined for each patient. Metabolic response after the first cycle of chemotherapy was evaluated by using a previously defined threshold of 20% decrease in SUV. In addition, the optimal threshold for differentiation between metabolic responders and non-responders after the third cycle of chemotherapy was determined retrospectively. The overall survival served as reference, with a median follow-up of 49 months.

In all patients, tumor deposits in the abdominal cavity showed increased FDG uptake at baseline with a mean SUV of 6.8. The FDG uptake decreased to a mean SUV of 4.9 after the first cycle (n=26) and to a mean SUV of 3.5 after the third cycle (n=33) of chemotherapy. Fifteen out of 26 patients were classified as metabolic responders (≥ 20% decrease in SUV) after the first cycle of chemotherapy and 18 out of 33 patients were classified as metabolic responders (≥ 55% decrease in SUV) after the third cycle of chemotherapy.

A significant correlation was observed between the decrease in FDG uptake after the first (p=0.008) and third (p=0.005) cycle of chemotherapy and subsequent overall survival. By using a previously defined threshold for decrease in SUV from baseline of 20% after the first cycle of chemotherapy, median overall survival was 38.8 months in metabolic responders compared to 23.1 months in metabolic non-responders (p=0.008). A threshold of 55% decrease in FDG uptake differentiated best between metabolic responders and non-responders after the third cycle of chemotherapy, with a median overall survival of 38.9 months in metabolic responders compared to 19.7 months in non-responders (p=0.005).

There was no correlation between clinical response criteria (p=0.7) or CA125 response criteria (p=0.5) and overall survival and there was only a weak correlation between histopathologic response criteria and overall survival (p=0.09).

In metabolic responders, the FDG uptake decreased by 50.1% after the first cycle and 76.2% after the third cycle of chemotherapy. In these patients, 65.7% of the overall metabolic changes occurred within the first two weeks after initiation of chemotherapy. In contrast, in metabolic non-responders, the FDG uptake decreased only by 7.0% after the first cycle and 27.3% after the third cycle. These findings emphasize the predictive information of changes in FDG uptake early after initiation of chemotherapy.

Prediction of response based on relative changes in FDG uptake (SUV) was independent from a specific method of SUV calculation. The use of SUVs based on the average versus maximum activity values within a region of interest (ROI), with or without normalization to blood glucose levels resulted in essentially the same difference in overall survival between metabolic responders and non-responders.

The limitations of this study include the relatively small number of patients, and the fact that not all patients underwent FDG-PET after the first cycle of chemotherapy. This study focuses on a subset of ovarian cancer with advanced stages of disease and the data may not be extrapolatable to patients with less bulky disease. No correlation between prediction of

response by FDG-PET and changes in tumor size according to RECIST (response evaluation criteria in solid tumors) was performed. The discussed criteria for assessment of response after the third cycle of chemotherapy need to be further validated in a larger prospective study. However, the use of a prospective criterion for prediction of response after the first cycle of chemotherapy (≥ 20% decrease in SUV) represents an important strength.

In conclusion, this thesis demonstrated a significant difference in an important endpoint, namely overall survival, between FDG-PET metabolic responders versus non-responders. Changes in FDG uptake in ovarian cancer assessed by sequential FDG-PET predicted patient survival as early as after the first cycle of neoadjuvant chemotherapy. Metabolic response criteria were more accurate than clinical or histopathologic response criteria including changes in tumor marker CA125 for prediction of overall survival. Therefore, FDG-PET appears to be a promising tool for early prediction of treatment response in individual patients. Sequential FDG-PET might be helpful in patient stratification for surgery versus continued chemotherapy and aid in the decision on the aggressiveness of cytoreductive surgery. Sequential FDG-PET is a promising tool to individualize treatment and reduce ineffective chemotherapy and could potentially also serve as surrogate endpoint in chemotherapy for recurrent ovarian cancer. Prospective trials are needed to validate the potential clinical use of sequential FDG-PET for treatment stratification in ovarian cancer.

6 Zusammenfassung

Die Positronenemissionstomographie (PET) ermöglicht unter Verwendung von F-18 Fluordesoxyglukose (FDG) eine semiquantitative Bestimmung des Glukosemetabolismus von Tumoren. Die vorgelegte Dissertation beschäftigt sich mit Veränderungen der FDG Aufnahme und damit des Glukosemetabolismus von fortgeschrittenen Ovarialkarzinomen (Stadium FIGO IIIC und IV) unter neoadjuvanter (präoperativer) Chemotherapie. Dazu wurde die FDG Aufnahme nach dem ersten und dritten (präoperativen) Chemotherapiezyklus mit der Ausgangsuntersuchung vor Beginn der Chemotherapie verglichen. Es wurde prospektiv die Hypothese getestet, dass Änderungen in der FDG Aufnahme von Ovarialkarzinomen unter Chemotherapie das Gesamtüberleben und damit die Wirksamkeit einer neodajuvanten Chemotherapie vorhersagen. Das Ziel dieser Arbeit war, die mit FDG-PET gemessene Änderung in der FDG Aufnahme als surrogaten Endpunkt zur Beurteilung des Therapieansprechens und Gesamtüberlebens zu evaluieren. Die Arbeit untersuchte drei spezifische Fragestellungen:

I. Die Vorhersage des Therapieansprechens und Gesamtüberlebens nach dem ersten und dritten Zyklus einer neodajuvanten Chemotherapie von fortgeschrittenen Ovarialkarzinomen mittels sequentieller FDG-PET Untersuchungen.

II. Den Vergleich verschiedener Methoden zur Berechnung und Normalisierung der FDG Aufnahme in Tumoren als „Standardized Uptake Values“ (SUV) im Hinblick auf ihre Vorhersage des Therapieansprechens.

III. Den Vergleich des metabolischen Ansprechens (Abfall der FDG Aufnahme) unter neoadjuvanter Chemotherapie mit histopathologischen und klinischen Parametern, einschließlich Änderungen des Tumormarkers CA125, im Hinblick auf die Vorhersage des Therapieansprechens (Gesamtüberlebens).

In Zusammenarbeit zwischen der Nuklearmedizinischen Klinik, der Frauenklinik und des Instituts für Pathologie des Klinikums rechts der Isar der Technischen Universität München wurden 33 Patientinnen mit fortgeschrittenen Ovarialkarzinomen (FIGO IIIC und IV) mittels FDG-PET vor und während neoadjuvanter Chemotherapie untersucht. Das Therapieprotokoll bestand aus 3 Zyklen einer platinhaltigen neoadjuvanten (präoperativen) Chemotherapie, gefolgt von einer Debulking Operation und anschließender postoperativer Chemotherapie. Bei allen 33 Patientinnen wurde vor Beginn der Chemotherapie und nach dem dritten Zyklus

(präoperativ) eine FDG-PET Untersuchung des Abdomen- und Beckenbereichs durchgeführt. Sechsundzwanzig Patientinnen wurden zusätzlich nach dem ersten Zyklus Chemotherapie mit FDG-PET untersucht. Es wurden insgesamt 92 FDG-PET Untersuchungen durchgeführt und ausgewertet.

Die FDG Aufnahme der Ovarialkarzinome und ihrer intraabdominalen Metastasen wurde semiquantitativ mittels „Standardized Uptake Values“ (SUV) bestimmt. Dazu wurde die in der PET gemessene Aktivitätskonzentration im Tumor auf die injizierte Aktivität (F18-FDG) und das Körpergewicht normiert. Bei jeder Patientin wurde die prätherapeutische FDG-PET Ausgangsuntersuchung mit den PET Untersuchungen unter Chemotherapie verglichen, und die prozentuale Änderung der FDG Aufnahme in den Tumoren bestimmt.

Die Tumorabsiedlungen im Abdomen und Becken zeigten bei allen Patientinnen in der prätherapeutischen PET Untersuchung eine erhöhte FDG Aufnahme mit einem SUV von 6,8±2,1. Nach dem ersten Zyklus Chemotherapie ging die FDG Aufnahme auf einen SUV von 4,9±2,8 (n=26) und nach dem dritten Zyklus auf 3,5±2,8 (n=33) zurück.

Basierend auf früheren Arbeiten an Lungenkarzinomen wurde ein Therapieansprechen (metabolisches Ansprechen) nach dem ersten Chemotherapiezyklus als ein Rückgang der FDG Aufnahme von mindestens 20% definiert. Zusätzlich wurde retrospektiv anhand der Überlebensdaten der optimale Schwellenwert für das metabolische Ansprechen nach dem ersten und dritten Zyklus Chemotherapie ermittelt. Das Gesamtüberleben der Patientinnen, mit einem medianen Nachbeobachtungszeitraum von 49 Monaten, diente als Referenz zur Beurteilung des Therapieerfolgs.

Die optimalen Schwellenwerte zur Erkennung des metabolischen Ansprechens (prozentualer Abfall der FDG Aufnahme) waren 20% nach dem ersten Zyklus und 55% nach dem dritten Zyklus Chemotherapie. Fünfzehn von 26 Patientinnen zeigten nach dem ersten Zyklus Chemotherapie ein metabolisches Ansprechen (≥20% SUV Abfall), und 18 von 33 Patientinnen zeigten nach dem dritten Zyklus Chemotherapie ein metabolisches Ansprechen (≥55% SUV Abfall).

Es bestand eine signifikante Korrelation zwischen dem Rückgang der FDG Aufnahme in Ovarialkarzinome nach dem ersten ($p=0,008$) und nach dem dritten ($p=0,005$) Zyklus Chemotherapie und dem Gesamtüberleben der Patientinnen. Patientinnen mit metabolischem Ansprechen nach dem ersten Chemotherapiezyklus hatten ein medianes Überleben von 38,8 Monaten, verglichen mit 23,1 Monaten bei Patientinnen die nach den oben genannten FDG-

PET Kriterien nicht ansprachen (p=0,008). Nach dem dritten Zyklus betrug das mediane Überleben 38,9 Monate bei Patientinnen mit metabolischem Ansprechen, verglichen mit 19,7 Monaten bei Patientinnen die in der FDG-PET nicht ansprachen (p=0,005).

Bei Patientinnen mit metabolischem Ansprechen ging die FDG Aufnahme in den Tumor um 50,1% nach dem ersten Zyklus und 76,2% nach dem dritten Zyklus Chemotherapie zurück. Damit fanden bei diesen Tumoren 65,7% der gesamten Änderungen der FDG Aufnahme (Glukosemetabolismus) unter Chemotherapie innerhalb der ersten zwei Wochen nach Therapiebeginn statt. Diese Beobachtungen unterstreichen die prädiktive Aussagekraft von frühzeitigen Änderungen der FDG Aufnahme in Ovarialkarzinomen und ihren abdominalen Metastasen unter Chemotherapie.

Die Vorhersage des Therapieansprechens basierend auf Änderungen der FDG Aufnahme wurde nicht wesentlich von der Methode zur Berechnung der „Standardized Uptake Values“ (SUV) beeinflusst. Die Berechnung des SUV aus der mittleren oder der maximalen Aktivitätskonzentration innerhalb einer Zielregion (ROI, region of interest), mit oder ohne Normalisierung auf die Blutglukosewerte, führte zu einem vergleichbaren Gesamtüberleben von Patientinnen mit und ohne metabolischem Ansprechen.

Neben den sequentiellen FDG-PET Untersuchungen wurden das klinische und histopathologische Ansprechen sowie Änderungen im Tumormarker CA125 ausgewertet. Das klinische Ansprechen war definiert als Ansprechen in mindestens zwei der drei folgenden Kriterien: Deutliche Regression der Peritonealkarzinose, Residualtumor nach drei Zyklen Chemotherapie (intraoperativ) kleiner 4 cm Durchmesser oder ein prozentualer Abfall des Tumormarkers CA125 um mindestens 75% bzw. eine vollständige Normalisierung (<35 U/ml). Das histopathologische Ansprechen war definiert als ein vitaler Residualtumor von höchstens 1 cm mit deutlichen Zeichen einer histomorphologischen Regression, wie verstärkte Apoptose, Nekrose und reaktive Entzündung, oder diffuse mikroskopische residuelle Tumorinfiltrate.

Sowohl das klinische Ansprechen als auch Änderungen des Tumormarkers CA125 waren nicht signifikant mit dem Gesamtüberleben der Patientinnen korreliert (p=0,7 bzw. p=0,5), und das histopathologische Ansprechen zeigte nur eine schwache Korrelation mit dem Gesamtüberleben (p=0,09).

Eine Limitation der vorgelegten Arbeit ist die relativ kleine Patientenzahl (n=33) sowie die Tatsache, dass nicht alle Patientinnen nach dem ersten Zyklus Chemotherapie untersucht wurden (n=26). Es wurden ausschließlich Ovarialkarzinome in fortgeschrittenen Stadien (FIGO

IIIC und IV) untersucht und die Übertragbarkeit der Ergebnisse auf Patientinnen mit niedrigeren Tumorstadien muss in weiteren Untersuchungen gezeigt werden. Die Beurteilung des metabolischen Ansprechens mittels FDG-PET wurde nicht mit Änderungen der Tumorgröße, beispielsweise mittels serieller CT Untersuchungen verglichen, da eine exakte Bestimmung der Tumorausdehnung nur eingeschränkt möglich ist. Der ermittelte Schwellenwert von 55% zur Erkennung des Therapieansprechens nach dem dritten Zyklus Chemotherapie bedarf der prospektiven Validierung. Demgegenüber ist die Bestätigung des prospektiv definierten Schwellenwertes von 20% Abfall der FDG Aufnahme zur Erkennung des Therapieansprechens nach dem ersten Zyklus Chemotherapie eine Stärke dieser Arbeit. Der potentielle Einfluss nachfolgender palliativer Chemotherapien auf das Gesamtüberleben wurde im Rahmen dieser Arbeit nicht untersucht.

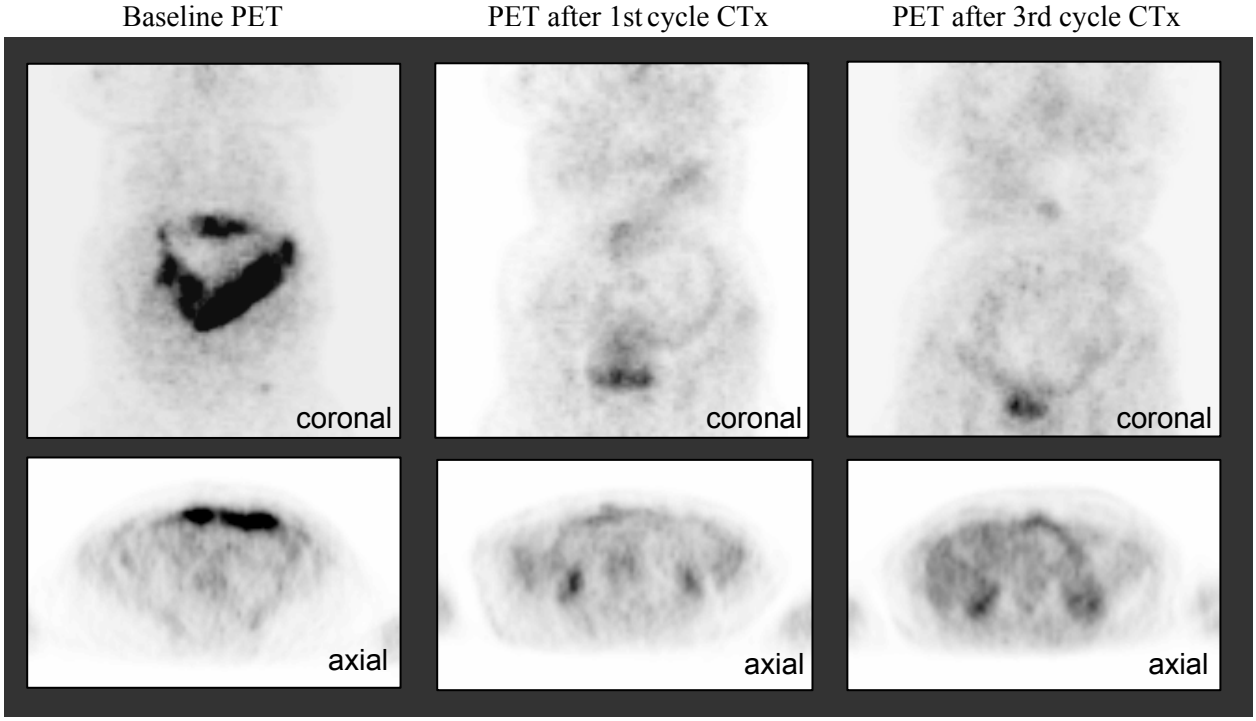
Zusammenfassend zeigte die vorgelegte Dissertation einen signifikanten Zusammenhang zwischen dem metabolischen Ansprechen (FDG-PET) von fortgeschrittenen Ovarialkarzinomen unter neoadjuvanter Chemotherapie und dem Gesamtüberleben der Patientinnen. Eine verlässliche Vorhersage des Gesamtüberlebens und Therapieansprechens mittels FDG-PET war bereits nach dem ersten Zyklus Chemotherapie möglich. Das metabolische Ansprechen war den bisherigen klinischen und histopathologischen Kriterien zur Vorhersage des Therapieansprechens überlegen.

Die FDG-PET scheint ein erfolgversprechendes Bildgebungsverfahren zur frühen Vorhersage des individuellen Therapieansprechens von fortgeschrittenen Ovarialkarzinomen unter neoadjuvanter Chemotherapie zu sein. Sequentielle FDG-PET Untersuchungen könnten zukünftig bei der Entscheidung zwischen einer Fortsetzung der Chemotherapie oder einer frühzeitigen Operation und bei der Entscheidung über das Ausmaß und die Radikalität der Operation helfen. Eine frühzeitige Beurteilung des Therapieansprechens mittels FDG-PET kann zu einer Individualisierung der Therapie beitragen und helfen, ineffektive Chemotherapien zu vermeiden. Die mögliche klinische Anwendung sequentieller FDG-PET Untersuchungen zur Therapiestratifizierung muss jedoch in weiteren prospektiven Studien validiert werden, wie auch das Therapiemonitoring palliativer Chemotherapien bei rezidivierten Ovarialkarzinomen.

7 Annex

Figure 1. FDG-PET metabolic responder (A) and non-responder (B).

A. Metabolic Responder



B. Metabolic Non-Responder

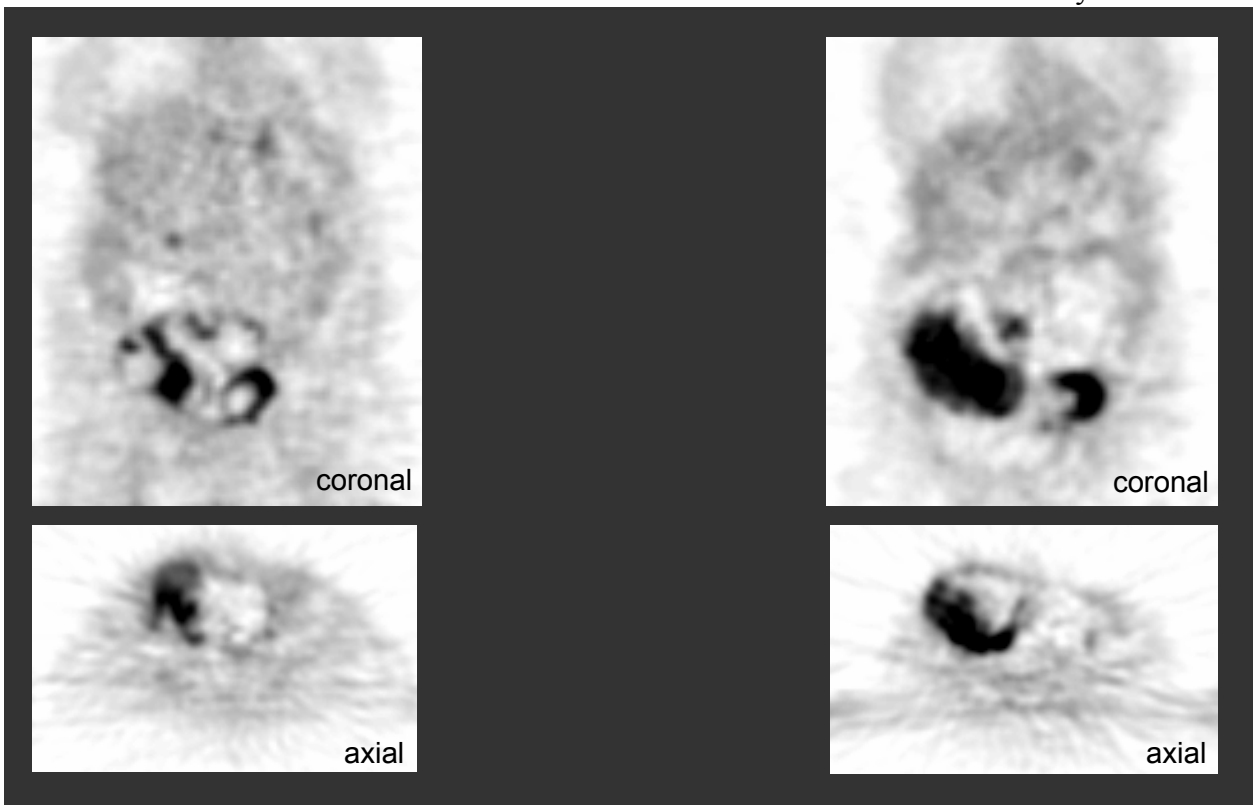


Table 1. FIGO (International Federation of Obstetrics and Gynecology) staging system for ovarian cancer, based on findings at surgical exploration.

FIGO	Findings
I	**Tumor limited to the ovaries**.
IA	Tumor limited to one ovary; capsule intact; no ovarian surface involvement.
IB	Tumor limited to both ovaries; capsule intact; no ovarian surface involvement.
IC	Tumor limited to one or both ovaries. Capsule ruptured, and/or ovarian surface involvement, and/or malignant cells in the ascites or peritoneal washings.
II	**Tumor extension within the pelvis, with one or both ovaries involved.**
IIA	Extension to the uterus or fallopian tubes.
IIB	Extension to other pelvic tissues or the pelvic wall.
IIC	Extension within the pelvis (IIA or B), and malignant cells in the ascites or peritoneal washings.
III	**Peritoneal implants outside the pelvis and/or involvement of regional lymph nodes, with one or both ovaries involved.**
IIIA	Microscopic peritoneal implants outside the pelvis.
IIIB	Macroscopic peritoneal implants outside the pelvis, <2 cm in diameter.
IIIC	Macroscopic peritoneal implants outside the pelvis, >2 cm in diameter, and/or metastases in regional lymph nodes (iliacal, obturator, inguinal, and paraortal).
IV	**Distant metastases** (except peritoneal implants)

Table 2A. Quantitative FDG-PET data for each patient at baseline and after the 1st and 3rd cycle of chemotherapy.

	PET baseline			PET after 1st cycle of CTx				PET after 3rd cycle of CTx			
Pt.	**Glc**	**SUVav**	**SUVmax**	**Glc**	**SUVav**	**SUVmax**	**%decrease (SUVav)**	**Glc**	**SUVav**	**SUVmax**	**%decrease (SUVav)**
1	141	6,7	8,5	139	6,4	7,6	4,2	188	5,3	7,0	21,3
2	93	7,0	8,6	97	6,4	7,2	7,6	98	5,2	6,0	25,6
3	104	7,4	8,6	114	4,4	5,5	40,7	118	2,6	3,0	64,6
4	86	7,2	8,5	87	5,8	6,8	19,6	89	4,6	5,3	36,4
5	112	5,0	5,9	107	3,0	3,0	39,9	102	2,7	3,2	46,0
6	87	4,4	5,2	87	4,2	5,0	4,3	115	2,8	3,4	36,0
7	111	4,2	6,0	104	2,3	2,8	45,8	104	1,2	1,5	71,0
8	113	6,2	6,8	97	4,9	5,7	20,9	100	1,5	1,9	80,5
9	86	6,4	7,5					102	1,9	2,3	69,7
10	97	3,7	4,4	99	1,8	2,1	50,0	120	1,2	1,5	67,5
11	59	11,5	12,9	86	14,0	15,7	-21,7	92	10,7	11,8	7,0
12	104	6,7	7,9	94	6,0	7,0	8,9	103	6,6	7,3	1,5
13	64	12,2	16,4					87	12,4	15,3	-2,1
14	120	7,8	8,7	100	3,9	4,7	50,1	100	2,6	3,2	66,5
15	100	8,4	8,9	121	7,1	8,4	15,7	106	4,2	5,2	50,1
16	97	5,7	7,4	114	4,4	5,8	23,0	126	1,6	2,4	71,9
17	122	7,5	8,6	99	7,9	9,4	-4,2	100	5,5	6,8	27,1
18	103	7,8	8,8	77	9,0	10,3	-16,3	111	4,6	5,4	40,9
19	90	7,2	7,9	116	3,8	4,3	47,0	123	1,8	2,3	74,7
20	108	3,7	4,4					107	0,9	1,2	76,0
21	108	4,7	5,1					84	2,1	2,6	55,0
22	102	8,0	10,5	99	7,4	9,6	7,7	94	6,8	8,5	15,1
23	99	5,8	7,8	92	1,5	1,8	74,7	106	1,2	1,5	79,7
24	116	5,7	6,8					157	1,6	2,3	72,0
25	87	10,7	13,3					91	6,6	9,2	38,8
26	107	5,1	5,5					96	5,4	5,7	-6,3
27	84	9,4	10,3	96	5,9	7,7	37,2	107	1,6	2,0	83,0
28	90	9,0	9,9	101	1,0	1,4	88,9	88	0,6	0,8	93,3
29	98	7,9	9,1	105	5,2	6,1	34,2	97	2,5	2,8	68,4
30	110	4,4	4,9	101	3,6	4,1	18,2	89	3,5	3,9	20,5
31	102	6,6	7,6	90	2,5	2,7	62,1	129	1,6	2,0	75,8
32	86	5,3	6,3	94	1,4	2,0	73,6	102	0,7	0,8	86,8
33	92	5,4	6,4	100	2,5	3,4	53,7	99	0,9	1,1	83,3
M	**99,3**	**6,8**	**8,0**	**100,6**	**4,9**	**5,8**	**30,2**	**107,0**	**3,5**	**4,2**	**51,4**
SD	**15,9**	**2,1**	**2,6**	**12,7**	**2,8**	**3,3**	**28,2**	**20,7**	**2,8**	**3,4**	**28,9**

Pt., patient identification number, Glc, blood glucose level; CTx, chemotherapy;

%decrease, relative decrease in SUVav from baseline to follow-up scan;

M, mean value; SD, standard deviation.

Table 2B. Cinical and histopathologic data for each patient.

Pt.	Response criteria		CA125 tumor marker levels [U/ml]					Residual tumor	
	Histopath.	Clinical	Baseline	Pre-op	%decrease	CA125 Response <35U/ml	CA125 Response ≥75%decrease	[mm]	</≥1cm
1	Non-Resp	Resp	42160,0	1120,0	97,3	Non-Resp	Resp	15	**≥1cm**
2	Non-Resp	Non-Resp	430,0	51,0	88,1	Non-Resp	Resp	8	<1cm
3	Non-Resp	Non-Resp	5437,0	153,0	97,2	Non-Resp	Resp	20	**≥1cm**
4	Non-Resp	Non-Resp	1910,0	311,0	83,7	Non-Resp	Resp	10	**≥1cm**
5	Non-Resp	Resp	3720,0	84,0	97,7	Non-Resp	Resp	10	**≥1cm**
6	Non-Resp	Resp	574,0	22,0	96,2	Resp	Resp	5	<1cm
7	Resp	Resp	529,0	16,0	97,0	Resp	Resp	0	<1cm
8	Non-Resp	Non-Resp	8590,0	47,0	99,5	Non-Resp	Resp	0	<1cm
9	Resp	Resp	1190,0	32,0	97,3	Resp	Resp	5	<1cm
10	Non-Resp	Resp	125,0	40,0	68,0	Non-Resp	Non-Resp	5	<1cm
11	Non-Resp	Non-Resp	2100,0	1010,0	51,9	Non-Resp	Non-Resp	22	**≥1cm**
12	Non-Resp	Non-Resp	194,0	50,0	74,2	Non-Resp	Non-Resp	18	**≥1cm**
13	Non-Resp	Non-Resp	646,0	123,0	81,0	Non-Resp	Resp	0	<1cm
14	Non-Resp	Resp	476,0	14,9	96,9	Resp	Resp	2	<1cm
15	Non-Resp	Resp	2080,0	15,0	99,3	Resp	Resp	8	<1cm
16	Non-Resp	Resp	1930,0	98,0	94,9	Non-Resp	Resp	5	<1cm
17	Non-Resp	Resp	112,0	19,4	82,7	Resp	Resp	0	<1cm
18	Non-Resp	Non-Resp	1200,0	38,9	96,8	Non-Resp	Resp	1	<1cm
19	Resp	Resp	534,0	22,0	95,9	Resp	Resp	12	**≥1cm**
20	Resp	Non-Resp	323,0	76,0	76,5	Non-Resp	Resp	5	<1cm
21	Resp	Resp	700,0	28,1	96,0	Resp	Resp	0	<1cm
22	Non-Resp	Non-Resp	94,0	32,0	66,0	Resp	Resp	10	**≥1cm**
23	Non-Resp	Resp	320,0	15,0	95,3	Resp	Resp	5	<1cm
24	Non-Resp	Resp	1940,0	419,0	78,4	Non-Resp	Resp	10	**≥1cm**
25	Non-Resp	Non-Resp	2600,0	58,0	97,8	Non-Resp	Resp	18	**≥1cm**
26	Non-Resp	Non-Resp	118,0	124,0	-5,1	Non-Resp	Non-Resp	35	**≥1cm**
27	Non-Resp	Resp	1290,0	37,7	97,1	Non-Resp	Resp	4	<1cm
28	Non-Resp	Resp	379,0	25,8	93,2	Resp	Resp	0	<1cm
29	Non-Resp	Resp	1810,0	92,2	94,9	Non-Resp	Resp	2	<1cm
30	Non-Resp	Resp	2450,0	74,5	97,0	Non-Resp	Resp	4	<1cm
31	Non-Resp	Resp	550,0	16,4	97,0	Resp	Resp	3	<1cm
32	Non-Resp	Resp	5600,0	25,4	99,5	Resp	Resp	0	<1cm
33	Resp	Resp	1200,0	151,0	87,4	Non-Resp	Resp	0	<1cm
M	**6** R	**21** R	**2827,6**	**134,6**	**86,9**	**13** R	**29** R	**7,3**	**22** <1
SD	**27** NR	**12** NR	**7303,7**	**255,2**	**20,2**	**20** NR	**4** NR	**8,1**	**11** ≥1

Pt., patient identification number;

Resp, Responder; Non-Resp, Non-Responder; M, mean value; SD, standard deviation;

R, total number of responders; NR, total number of non-responders;

Histopath., Histopathologic Response; Clinical, Clinical Response (see chapters *2.6.3.* and *2.6.2.*);

pre-op, preoperative CA125 level (after 3rd cycle CTx); %decrease, relative decrease from baseline;

Residual tumor, largest diameter of residual tumor after debulking surgery;

</≥1cm, optimal (residual tumor <1cm) versus suboptimal debulking.

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9 Curriculum vitae

Name	Stefanie Sassen
Geburtsdatum	4. April 1979 in München

Schulausbildung

1989-97	Gymnasium in Bad Aibling (Bayern)
Juni 1997	Abitur (Note 1,0)

Universitätsausbildung

1998-2000	Studium der Humanmedizin, Ludwig-Maximilians-Universität München
2000-2004	Studium der Humanmedizin, Technische Universität München
Februar-Juni 2001	Studium an der Université de Caen, Frankreich
1997-2004	Bayerisches Begabtenstipendium

Praktisches Jahr

Mai – August 2003	Harvard Medical School, Boston: Chirurgie
Sept. – Dezember 2003	Cornell Medical College, New York und Memorial Sloan Kettering Cancer Center, New York: Innere Medizin
Januar – April 2004	Universitätsspital Zürich: Gynäkologie
Studienjahr 2003/ 2004	Stipendium des Deutschen Akademischen Austauschdienstes (DAAD) zur Durchführung des Praktischen Jahres im Ausland

Ärztliche Prüfung

Mai 2004	3. Staatsexamen (Note 1,0), Gesamtnote 1,16
Okt. 2004	Approbation als Ärztin

Ärztliche Weiterbildung

seit Juli 2004	Assistenzärztin am Institut für Allgemeine Pathologie und Pathologische Anatomie der Technischen Universität München

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