



Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Clinical Value of ¹⁸F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Response Evaluation after Primary Treatment of Advanced Epithelial Ovarian Cancer

J. Hynninen^{*}, M. Laasik^{*}, T. Vallius[†], J. Kemppainen[‡], S. Grönroos^{*}, J. Virtanen[§], J. Casado[¶], S. Hautaniemi[¶], S. Grenman^{*}, M. Seppänen[‡], A. Auranen^{||}

^{*} Department of Obstetrics and Gynecology, University of Turku, Turku University Hospital, Turku, Finland

[†] Department of Oncology and Radiotherapy, University of Turku, Turku University Hospital, Turku, Finland

[‡] Department of Clinical Physiology and Nuclear Medicine, Turku PET Centre, Turku University Hospital, University of Turku, Turku, Finland

[§] Department of Radiology, Medical Imaging Centre of Southwest Finland, Turku University Hospital and University of Turku, Turku, Finland

[¶] Research Programs Unit, Genome-Scale Biology Research Program, Faculty of Medicine, University of Helsinki, Helsinki, Finland

^{||} Department of Obstetrics and Gynecology, Tampere University Hospital, University of Tampere, Tampere, Finland

Received 30 March 2018; accepted 9 April 2018

Abstract

Aims: To prospectively evaluate the use of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG-PET/CT) in the definition of the treatment response after primary treatment of advanced epithelial ovarian cancer (EOC).

Materials and methods: Forty-nine patients with advanced EOC had an ¹⁸F-FDG PET/CT scan before and after primary treatment. The treatment response was defined with the currently used radiological and serological Response Criteria in Solid Tumors (RECIST1.1/GCIC) criteria and the modified PET Response Criteria in Solid Tumors (PERCIST). The concordance of the two methods was analysed. If the patient had a complete response to primary treatment by conventional criteria, the end of treatment ¹⁸F-FDG PET/CT scan (etPET/CT) was not opened until retrospectively at the time of disease progression. The ability of etPET/CT to predict the time to disease recurrence was analysed. The recurrence patterns were observed with an ¹⁸F-FDG PET/CT at the first relapse.

Results: The agreement of the RECIST1.1/GCIC and modified PERCIST criteria in defining the primary treatment response in the whole patient cohort was good (weighted kappa coefficient = 0.78). Of the complete responders ($n = 28$), 34% had metabolically active lesions present in the etPET/CT, most typically in the lymph nodes. The same anatomical sites tended to activate at disease relapse, but were seldom the only site of relapse. In patients with widespread intra-abdominal carcinosis at diagnosis, the definition of metabolic response was challenging due to problems in distinguishing the physiological FDG accumulation in the bowel loops from the residual tumour in the same area. The presence of metabolically active lesions in the etPET/CT did not predict earlier disease relapse in the complete responders.

Conclusions: In the present study, etPET/CT revealed metabolically active lesions in complete responders after EOC primary therapy, but they were insignificant for the patient's prognosis. The current study does not favour routine use of ¹⁸F-FDG PET/CT after EOC primary treatment for complete responders.

© 2018 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Key words: Epithelial ovarian cancer; FDG; PET/CT; RECIST; response evaluation

Introduction

Epithelial ovarian cancer (EOC) is usually diagnosed at an advanced stage. Primary debulking surgery (PDS) and

platinum/taxane-based chemotherapy are the cornerstones of treatment. In widely spread inoperable cases, the primary treatment may start with neoadjuvant chemotherapy (NACT) followed by interval debulking surgery [1,2]. In addition to the FIGO stage and surgical outcome, the response to platinum-based chemotherapy is a significant prognostic factor [3,4]. The response to first-line treatment is measured with radiological and serological parameters

Author for correspondence: J. Hynninen, Department of Obstetrics and Gynecology, Turku University Hospital, PL 52, FI-20520 Turku, Finland. Tel: +358-50-5383554; Fax: +358-2-313-2340.

E-mail address: johanna.hynninen@utu.fi (J. Hynninen).

<https://doi.org/10.1016/j.clon.2018.04.007>

0936-6555/© 2018 The Royal College of Radiologists. Published by Elsevier Ltd. All rights reserved.

Please cite this article in press as: Hynninen J, et al., Clinical Value of ¹⁸F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Response Evaluation after Primary Treatment of Advanced Epithelial Ovarian Cancer, Clinical Oncology (2018), <https://doi.org/10.1016/j.clon.2018.04.007>

[5]. A computed tomography (CT) scan is recommended at the end of first-line chemotherapy to define disease status. If the serum tumour marker CA125 is increased at the time of diagnosis, serial CA125 measurements can be useful in monitoring the treatment response [6]. A complete response to first-line therapy requires both normalisation of CA125 during treatment and no signs of residual disease in CT [5–7].

In clinical trials, an objective evaluation of drug response is essential. Tumour shrinkage during treatment and the time of progression are important end points. The Definitions of Objective Endpoints were refined when the World Health Organization criteria [8], first presented in 1981, were followed by the Response Criteria in Solid Tumors (RECIST) criteria in 2000 [9]. These criteria have subsequently been widely adopted by academic research groups and the medical industry for trials where the primary end points are an objectively measured response to treatment or disease progression. The updated RECIST 1.1 criteria [7] published in 2009 clarified some questions and impracticalities in the earlier version. In addition, RECIST 1.1 takes metabolic positron emission tomography (PET) imaging into account when evaluating disease progression.

Treatment response assessment with PET imaging is not included in the current generally accepted guidelines. The PET Response Criteria in Solid Tumors (PERCIST) criteria [10] were introduced in 2009 in order to unify the quality of scanning procedures and the evaluation of metabolic treatment response. The PERCIST categories for response to treatment (complete metabolic response [CMR], partial metabolic response [PMR], stable metabolic disease and progressive metabolic disease) resemble the anatomical RECIST categories. A recent practical guide [11] has helped with the implementation of the proposed criteria into clinical practice. Despite these efforts made to unify metabolic response assessment, a variety of treatment response methods are currently clinically applied.

The present prospective analysis focuses on treatment response evaluation at the end of EOC first-line therapy of advanced EOC. We compared the concordance of the currently used RECIST1.1/GCIC criteria and the modified PERCIST criteria. In addition, we evaluated whether an ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT scan at the end of first-line therapy could find prognostic subgroups in patients with complete response by conventional criteria. We hypothesised that complete response patients with increased metabolic activity in the end of treatment ^{18}F -FDG PET/CT (etPET/CT) scan would have earlier disease progression.

Materials and Methods

Patients

This study was conducted at the Department of Obstetrics and Gynecology, Turku University Hospital, Finland and was approved by the local ethics committee (ClinicalTrials.gov identifier: NCT01276574). All patients with suspected

advanced ovarian, fallopian tube or peritoneal cancer were eligible to participate in this prospective clinical trial. Patients with diabetes mellitus or a history of previous cancer were excluded. Between October 2009 and March 2014, 87 patients were recruited. The present analysis consists of 49 patients with FIGO stage III or IV disease who had an ^{18}F -FDG PET/CT scan at the time of diagnosis and at the end of first-line chemotherapy. All the patients received platinum/taxane-based chemotherapy. Bevacizumab became part of the EOC first-line treatment during the study period and six patients received bevacizumab maintenance therapy. The characteristics of the 49 patients included are presented in [Table 1](#).

PET/CT Scanning Procedure and Imaging Analysis

A pretreatment ^{18}F -FDG PET/CT scan from the base of the skull to mid-thigh was carried out within the 2 weeks before the PDS/diagnostic laparoscopy. The etPET/CT scan was scheduled 3–4 weeks after the six cycles of platinum/taxane chemotherapy in patients who underwent PDS ($n = 22$). For the 27 patients who received NACT, the etPET/CT was taken after a total of six to nine chemotherapy cycles.

The scanning procedure with whole-body contrast-enhanced ^{18}F -FDG PET/CT (with 64-row Discovery STE or VCT; General Electric Medical Systems, Milwaukee, WI, USA) has been described previously [12]. Briefly, all patients fasted for 6 h before the intravenous injection of 4 Mbq/kg ^{18}F -18F-FDG. The low-dose PET/CT (kV 120, Smart mA range 10–80) from skull base to mid-thigh was carried out 50–60 min after the tracer injection. It was followed by a whole-body diagnostic high-dose contrast-enhanced CT scan (kV

Table 1
Patient characteristics

Variables	Patients (n)	%
Total	49	100
Age, median (range)	63 (30–80)	
FIGO stage		
IIIB	2	4%
IIIC	24	49%
IVA	7	14%
IVB	16	33%
Origin		
Ovary	40	82%
Peritoneum	6	12%
Fallopian tube	3	6%
Histology		
High grade serous	43	88%
Low grade serous	5	10%
Clear cell	1	2%
Treatment strategy		
PDS	22	45%
NACT	27	55%
Macroscopic residual tumour in surgery		
No	13	27%
Yes	36	73%

PDS, primary debulking surgery; NACT, neoadjuvant chemotherapy.

120, Smart mA range 100–440) after an automated intravenous injection of the contrast agent. PET images were reconstructed with 128×128 matrix size in fully three-dimensional mode using an ML-OSEM reconstruction algorithm. Imaging analysis was carried out using an ADW4.5 workstation.

Two experienced nuclear medicine physicians analysed the PET/contrast-enhanced CT images taking into account physiological FDG accumulation. The baseline scans were evaluated with a detailed systematic assessment of all intra-abdominal and intrathoracic lesions. All the lesions with visually abnormal FDG uptake were further evaluated quantitatively with a determination of maximum standardised uptake value (SUV_{max}), and their anatomical counterparts were defined. Similarly, at the end of treatment, all the metabolically active lesions were also evaluated both visually and quantitatively.

Treatment Response Evaluation after First-line Therapy

At the end of primary treatment, the contrast-enhanced CT scans were analysed by radiologists who were blind to the PET/CT scans. The response to primary therapy was defined with RECIST 1.1/GCIC criteria. Each patient was categorised as a complete responder, a partial responder or as having stable disease or disease progression. If the patient had a partial response or stable/progressive disease, the etPET/CT scan was opened and used in treatment planning. In the complete responders, the results of the etPET/CT were not opened until disease recurrence. Consequently, the complete responder's treatment was not interfered with by any possible metabolic activity in the etPET/CT scan. The patients were monitored with regular follow-up visits according to the policy of the hospital.

Afterwards, the treatment response of all the 49 patients was defined retrospectively from etPET/CT scans with the modified PERCIST criteria. The etPET/CT findings were compared with the detailed analyses carried out on the baseline PET/CT scan. The PERCIST response categories were used, but instead of SUL_{peak} we calculated the change in the metabolic activity by using the pre- and post-treatment SUV_{max}. The main difference is that SUL (lean body mass-normalised SUV [SUV_{lbm}]) is less dependent on the

patient's weight compared with body weight normalised SUV [13]. A CMR was defined as the visual disappearance of all metabolically active tumours in the etPET/CT scan. For a PMR, a decrease of greater than or equal to 30% was warranted between the most intense evaluable lesion at baseline and the most intense lesion at follow-up (not necessarily the same lesion). For metabolic progression, either a 30% increase in SUV_{max} in the most intense lesion or a new metabolically active lesion/lesions were needed.

Data Analysis

The association of basic clinical parameters (FIGO stage, residual tumour in surgery, treatment modality PDS/NACT) and tumour response defined with modified PERCIST criteria was analysed with a Spearman correlation and a chi-squared test. *P*-values less than 0.05 were considered significant. The concordance of RECIST1.1 and PERCIST criteria in the treatment response evaluation was calculated by using a Spearman correlation and a quadratic weighted kappa (κ), which measures the level of agreement for categorical variables [14]. Here, we considered κ values above 0.6 as high agreement. The prognostic power of etPET/CT was evaluated in patients who had a complete response according to conventional RECIST1.1/GCIC response criteria. The patients with increased activity in etPET/CT were compared with patients with a negative PET/CT scan: the time from the etPET/CT to progression was calculated and Kaplan–Meier models were made. Data analyses were carried out in R version 3.3.3 [15].

Results

The treatment responses of the 49 patients measured with conventional RECIST1.1/GCIC criteria and with metabolic imaging are presented in Table 2. The agreement of the RECIST1.1/GCIC and modified PERCIST criteria was substantial ($\kappa = 0.78$). The dispersion was greatest with the RECIST1.1/GCIC partial responders ($n = 15$): 53% also had a PMR, whereas 33% had a CMR and 14% either stable or progressive metabolic disease. The reason for partial response by conventional criteria was residual disease in CT

Table 2

Epithelial ovarian cancer (EOC) primary treatment response in 49 advanced EOC patients defined with Response Criteria in Solid Tumors (RECIST1.1/GCIC) and modified PET Response Criteria in Solid Tumors (PERCIST) criteria. The grey boxes indicate the number of cases where the positron emission tomography/computed tomography (PET/CT) response was consistent with RECIST1.1/GCIC criteria

RECIST1.1	PET/CT response				Total
	Complete metabolic response	Partial metabolic response	Stable metabolic disease	Progressive metabolic disease	
Complete response	19	10			29
Partial response	5	8	1	1	15
Stable disease					0
Progressive disease				5	5
Total	24	18	1	6	49

Spearman correlation = 0.57.

Weighted kappa coefficient = 0.78.

in eight cases, CA125 above normal limit in three cases and both in four cases. In the six patients who received bevacizumab, the conventional and metabolic responses were quite concordant (six complete response/CMR and one complete response/PMR) and they were included in the analyses.

Increased metabolic activity detected in etPET/CT was not associated with the FIGO stage (III versus IV) ($P = 0.32$), residual tumour in surgery ($P = 0.62$) or the choice of primary treatment strategy (PDS versus NACT) ($P = 0.09$).

Forty-three of the 49 patients responded to the first-line therapy, 29 with a complete response and 14 with a partial response. The conventional RECIST1.1/GCIC criteria predicted the time to disease recurrence ($P < 0.05$) (Figure 1a). The median time from etPET/CT to progression was 5.8 (95% confidence interval 3.4–11.0) months in partial and 13.8 (95% confidence interval 10.8–26.1) months in complete responders. The partial responders relapsed earlier, even though half of them received extra chemotherapy cycles after the response evaluation scan.

The etPET/CT Findings of the Complete RECIST1.1/GCIC Responders

Twenty-nine of the 49 patients had a complete response to primary therapy according to RECIST1.1/GCIC criteria. Fifteen patients were treated with PDS and 14 with NACT; 12 had no residual tumour in surgery. Of the 29 patients, 34% (10/29) had residual metabolic activity in etPET/CT (Table 3). In seven patients, the metabolically active lymph nodes were the only abnormal finding in the etPET/CT. In six cases, the same lymph nodes were active at the time of diagnosis and remained active in the etPET/CT scan. In one case, when re-evaluated retrospectively, the mediastinal FDG activity in the etPET/CT was considered inflammatory. Three complete responders were considered to have

pathologically increased FDG uptake intra-abdominally. When the etPET/CT scans were compared with the progression PET/CTs, two patients were found to have probable false-positive findings on etPET/CT: one had physiological activation near the bowel loops (Figure 2a) and another had metabolic activity in the diaphragm due to an earlier pleurodesis.

A follow-up PET/CT scan at the first disease relapse was available in eight of 10 complete responders (Table 3). Six patients had disease activation detected in the same anatomical site that had showed activity in the etPET/CT. In addition, most patients had several new active lesions (Figure 2b). In one patient, who had disease progression 18 months after etPET/CT, the cardiophrenic lymph node metastasis, which was also active in etPET/CT, was the only site of recurrence.

The Prognostic Value of Metabolic Activity in etPET/CT in Complete Responders

The prognostic value of residual metabolic activity in the etPET/CT was only analysed for the RECIST1.1/GCIC complete responders, whose etPET/CT was not opened until recurrence occurred, and who received no extra chemotherapy after the etPET/CT scan. One non-blinded case was removed from survival analysis (remaining $n = 28$). The residual metabolic activity detected in the etPET/CT did not predict the time to progression in RECIST1.1/GCIC complete responders (Figure 1b).

Discussion

Imaging of ovarian cancer is challenging due to the typical spread pattern to the adjacent organs and around the peritoneal cavity. ^{18}F -FDG PET/CT is useful in EOC staging [12,16,17] and in detecting disease relapse [18], but

Table 3

The positron emission tomography/computed tomography (PET/CT) findings of the 10 patients who had a complete response to primary treatment according to conventional Response Criteria in Solid Tumors (RECIST1.1/GCIC) criteria, but abnormal metabolic activity in end of treatment PET/CT (etPET/CT)

Patients' number	Location of increased metabolic activity in etPET/CT	Lesion detectable in same anatomical site pretreatment PET/CT	Lesion detectable in same anatomical site first relapse PET/CT	Other new lesions in first relapse PET/CT
1	SdLN	No	No	Yes
2	SdLN	Yes	Yes	No
3	Intra-abdominal*	Yes	No	Yes
4	SdLN	Yes	–	–
5	Parailiacal lymph node	Yes	Yes	Yes
6	Intra-abdominal	Yes	Yes	Yes
7	SdLN	Yes	Yes	Yes
8	SdLN, para-aortal lymph node	Yes/Yes	Yes/Yes	Yes
9	Intra-abdominal	Yes	Yes	Yes
10	SdLN	Yes	–	–
Total	Intra-abdominal 3 Lymph nodes 7	9/10	6/8	7/8

SdLN, supradiaphragmatic lymph node.

* Multiple active lesions.

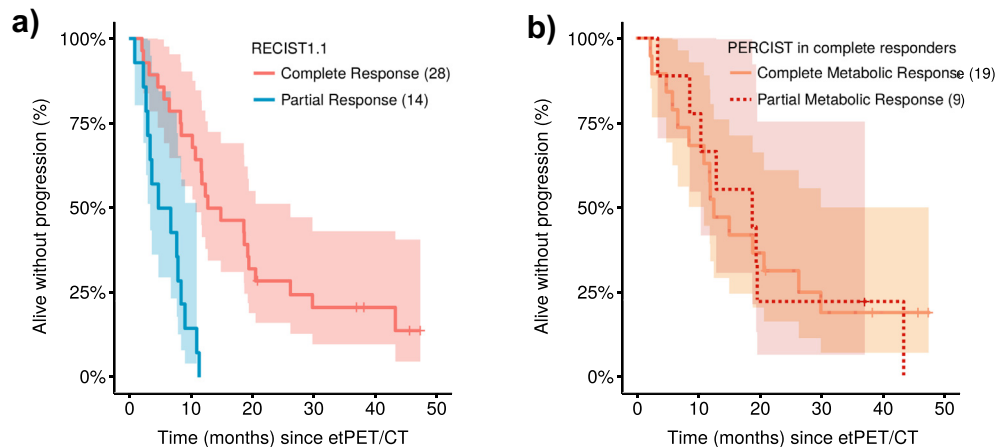


Fig 1. The Kaplan–Meier curves present the time from the end of treatment positron emission tomography/computed tomography (etPET/CT) to disease progression: (a) in the first-line therapy responders stratified by Response Criteria in Solid Tumors (RECIST1.1/GCIC) criteria ($P < 0.05$); (b) in patients with complete response according to RECIST1.1/GCIC criteria, stratified by metabolic response according to PET Response Criteria in Solid Tumors (PERCIST) criteria ($P = 0.93$).

the benefit of treatment response monitoring has not been shown [19]. ^{18}F -FDG PET/CT is a widely used metabolic imaging modality in cancer patients in response. In clinical practice, although patients wish to be monitored with the most effective imaging method [20], the referring physicians have expressed concerns regarding the possible over interpretation of the findings [21]. In the current study, 34% of patients with a complete response after EOC first-line therapy according to traditional RECIST1.1/GCIC criteria showed increased metabolic activity in an etPET/CT. Their disease, however, did not progress earlier than in patients with a negative etPET/CT. Therefore, we do not recommend routine response evaluation with ^{18}F -FDG PET/CT after EOC primary therapy.

The RECIST and PERCIST criteria have shown considerable difference in the treatment response assessment. In a pooled analysis of 268 patients with different cancers [22], the estimated overall response rates were significantly different between the two criteria (35.1% by RECIST versus 54.1% by PERCIST, $P < 0.05$). To our knowledge, there are no previous studies on the metabolic response according to the PERCIST criteria in ovarian cancer. In the present study, the overall agreement of the conventional RECIST1.1/GCIC criteria and modified PERCIST criteria was good (Table 2). The rate of CMR was lower when compared with the anatomical/CA125 response. This may lead to additional chemotherapy cycles being given to patients based on PET/CT.

In our study, the results of etPET/CT of the RECIST1.1/GCIC complete responders were not available when the patient's further treatment was planned and, therefore, the study protocol enabled an evaluation of the prognostic power of etPET/CT. When the etPET/CT scans were opened at the time of the disease recurrence, small active lesions not visible in the conventional CT were found in 34% of the complete responders. The pathological ^{18}F -FDG uptake in etPET/CT, however, failed to predict the time to disease recurrence (Figure 1b). There are two possible explanations. First, an over interpretation of the inflammatory or physiological ^{18}F -FDG accumulation as cancerous lesions is possible [23].

Accumulation of ^{18}F -FDG near the bowel loops in etPET/CT is especially challenging [23]. Physiological bowel uptake is a common finding, which can complicate the interpretation of the metabolic response of the preoperatively detected tumour in the same anatomic area (Figure 2a). An alternative explanation for the negative prognostic effect is that in the current study, the most common pathological findings in etPET/CT were metabolically active lymph nodes. Most complete response/PMR patients had metabolically active lymph nodes in the corresponding anatomical sites after primary treatment and at disease relapse. This indicates that the metabolically active lesions in etPET/CT were more likely true metastasis than over interpretation. The significance of ^{18}F -FDG accumulation in the lymph nodes during the course of EOC treatment needs further clarification and will be the subject of our next study.

Earlier, second look surgeries were carried out after the completion of first-line treatment to assess the treatment response and the intraperitoneal status. At that time, the ^{18}F -FDG PET/CT findings after the completion of primary therapy could be histologically verified [24]. In the study by Kim *et al.* [25], ^{18}F -FDG PET/CT, after the completion of primary therapy, had a similar prognostic value as the second look surgery. These findings are not in conflict with our current result. The practice of second look surgeries was discontinued, as the impact on survival could not be shown [26]. The predictive power of etPET/CT on progression-free survival based on a comparison with second look surgeries remains obscure.

The strength of our study is the careful evaluation of a prospectively collected cohort of advanced EOC patients. The scanning protocol was standardised: identical patient preparation and the same scanner was used in the pre-treatment and end of treatment scans. The unique prospective study design, where the etPET/CT scan was not opened in the RECIST1.1/CGIC complete responders, made it possible to observe these patients without the etPET/CT result affecting the further treatment.

There were some limitations in the current study setting, such as the size of the patient cohort being limited. In

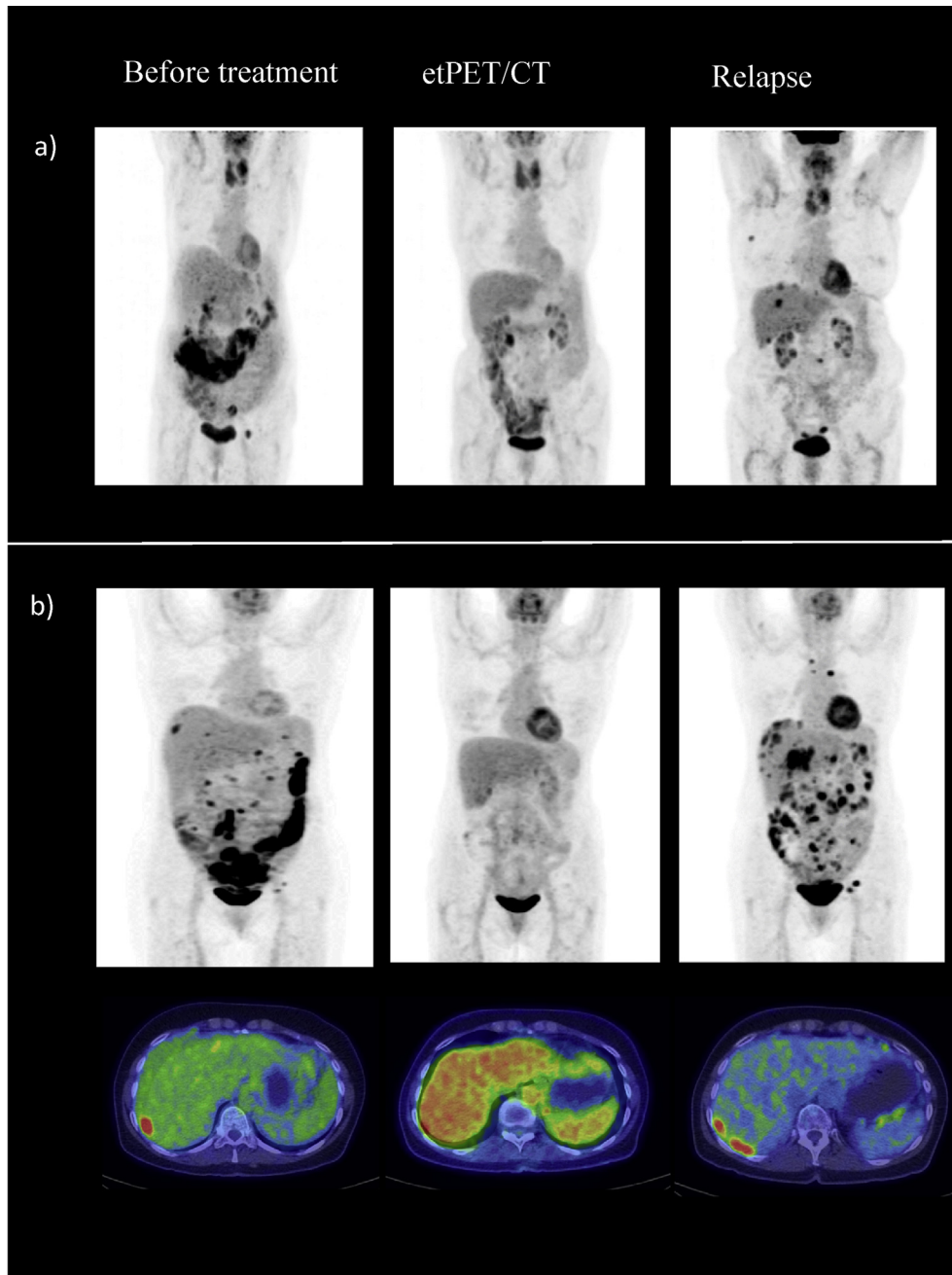


Fig 2. (a) An example of a patient with a probable false-positive finding in end of treatment positron emission tomography/computed tomography (etPET/CT). In the pretreatment scan, widespread epithelial ovarian cancer with typical 'omental cake' is present. After PDS there was residual tumour left with a carcinosis seeding on the subdiaphragmal peritoneal surface. The patient reached a complete response to primary therapy according to Response Criteria in Solid Tumors (RECIST/GCIC) criteria. In etPET/CT, the enhanced metabolic activity was measured in the mesenterium of the small intestine and near the caecum and was interpreted as a probable active disease. The disease relapsed later after 20 months of follow-up with multiple lesions on the peritoneal surfaces, lig falciforme and liver surface, but not in the caecum. (b) A 61-year-old patient with widespread disease was treated with neoadjuvant chemotherapy. In interval debulking surgery, a thin residual tumour seeding remained on the subdiaphragmal peritoneal surface and on small bowel mesentery. After primary therapy, a complete response was reached according to the RECIST/GCIC criteria. In etPET/CT, the only metabolically active lesion was seen on the peritoneal surface between the liver and diaphragm (fused transaxial PET/CT scan, bottom line). Relapse occurred after only 4 months with multiple intra-abdominal lesions.

addition, the ^{18}F -FDG PET/CT was compared with a combination of a CT scan and serological CA125 response, instead of comparing the two imaging methods, CT and PET/CT. However, this was the most reliable way to evaluate the additive value of ^{18}F -PET/CT with regards to the currently used methods.

If ^{18}F -FDG PET/CT is used in the monitoring of EOC first-line treatment outside clinical trials, several matters should be considered. The current guidelines on ^{18}F -FDG PET/CT imaging are focused on standardising the scanning protocols [27,28], whereas uniform principles on how to measure and interpret metabolic changes during

chemotherapy do not exist. In order to carry out a quantitative assessment of metabolic tumour response between the baseline and follow-up studies, identical patient preparation and the same scanner with comparable injected doses of FDG and uptake times should be used. In addition, the imaging results should be reported in a manner that the clinician can understand the meaning of the abnormal findings and the comparability of the consecutive scans [29].

In order to gain prognostic information from imaging, an ^{18}F -FDG PET/CT scan taken earlier during the cancer therapy may perform better. EOC first-line therapy consists of surgery and chemotherapy. Response evaluation with imaging or CA125 cannot distinguish between the effects of the two treatments. During neoadjuvant treatment, where the metabolic changes are dependent on chemotherapy alone, response evolution with ^{18}F -FDG PET/CT has shown some promising results. The PERCIST criteria were valuable in neoadjuvant therapy on rectal cancer, where an SUVpeak decrease predicted a pathological response [30]. Additionally, in oesophageal cancer, PERCIST, in contrary to RECIST, predicted disease outcome [31]. In ovarian cancer, an early metabolic response during NACT predicts patient outcome [32] and the histopathological response in the omentum [33].

In conclusion, based on the present study, residual metabolic activity at the end of treatment does not predict earlier disease relapse. This observation should be validated in larger trials. The PET-positive areas in etPET/CT tend to re-activate in disease recurrence, in many cases together with multiple new active lesions. The routine use of ^{18}F -FDG PET/CT offers no extra benefit to those patients who have a complete response after EOC primary treatment.

Acknowledgments

This study was financially supported by the Clinical Research (EVO) funding of Turku University Hospital and the European Union's Horizon 2020 research and innovation programme under grant agreement no. 667403. We are thankful to the staff of the Turku PET Center and the Department of Obstetrics and Gynecology at Turku University Hospital and Satakunta Central Hospital in Pori for their excellent help in imaging and treating patients.

References

- [1] Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *N Engl J Med* 2010; 363(10):943–953.
- [2] Wright AA, Bohlke K, Armstrong DK, Bookman MA, Cliby WA, Coleman RL, et al. Neoadjuvant chemotherapy for newly diagnosed, advanced ovarian cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline. *Gynecol Oncol* 2016;143(1):3–15. <https://doi.org/10.1016/j.ygyno.2016.05.022>.
- [3] Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20(5):1248–1259. Available at: <http://jco.ascopubs.org/content/20/5/1248.abstract>.
- [4] Aabo K, Adams M, Adnitt P, Alberts DS, Athanazziou A, Barley V, et al. Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. *Advanced Ovarian Cancer Trialists' Group. Br J Cancer* 1998;78(11):1479–1487. Available at: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2063202/>.
- [5] Ledermann JA, Raja FA, Fotopoulou C, Gonzalez-Martin A, Colombo N, Sessa C. Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl. 6):vi24–vi32. <https://doi.org/10.1093/annonc/mdt333>.
- [6] Rustin GJS, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, et al. Definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the Gynecological Cancer Intergroup (GCIg). *Int J Gynecol Cancer* 2011;21(2):419–423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21270624>.
- [7] Eisenhauer E, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45(2):228–247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19097774>.
- [8] Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment 1981 Jan 1;47(1):207–214.
- [9] Therasse P, Arbuck SG, Eisenhauer E, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92(3):205–216. [doi:10.1093/jnci/92.3.205](https://doi.org/10.1093/jnci/92.3.205).
- [10] Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. *J Nucl Med* 2009;50(Suppl. 1):122S–1250S. Available at: http://jnm.snmjournals.org/content/50/Suppl_1/122S.abstract.
- [11] OC, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET Response Criteria in Solid Tumors 1.0. *Radiology* 2016; 280(2):576–584. <https://doi.org/10.1148/radiol.2016142043>.
- [12] Hynninen J, Kemppainen J, Lavonius M, Virtanen J, Matomäki J, Oksa S, et al. A prospective comparison of integrated FDG-PET/contrast-enhanced CT and contrast-enhanced CT for pretreatment imaging of advanced epithelial ovarian cancer. *Gynecol Oncol* 2013;131(2):389–394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23994535>.
- [13] Tirkes T, Hollar M, Tann M, Kohli MD, Akisik F, Sandrasegaran K. Response criteria in oncologic imaging: review of traditional and new criteria. *RadioGraphics* 2013;33(5):1323–1341. Available at: <http://pubs.rsna.org/doi/10.1148/rg.335125214>.
- [14] Cohen J. Weighted kappa: nominal scale agreement provision for scaled disagreement or partial credit. *Psychol Bull* 1968;70: 213–220.
- [15] Statistical RCT. *RA language and environment for, computing*. Vienna: R Foundation for Statistical Computing; 2017. <https://www.R-project.org/>.
- [16] Risum S, Hogdall C, Loft A, Berthelsen AK, Hogdall E, Nedergaard L, et al. Does the use of diagnostic PET/CT cause stage migration in patients with primary advanced ovarian cancer? *Gynecol Oncol* 2010;116(3):395–398. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20042226>.
- [17] Nam EJ, Yun MJ, Oh YT, Kim JW, Kim JH, Kim S, et al. Diagnosis and staging of primary ovarian cancer: correlation between PET/CT, Doppler US, and CT or MRI. *Gynecol Oncol* 2010; 116(3):389–394.
- [18] Gu P, Pan L-L, Wu S-Q, Sun L, Huang G. CA 125, PET alone, PET–CT, CT and MRI in diagnosing recurrent ovarian

- carcinoma: a systematic review and meta-analysis. *Eur J Radiol* 2009;71(1):164–174.
- [19] Amit A, Person O, Keidar Z. FDG PET/CT in monitoring response to treatment in gynecological malignancies. *Curr Opin Obstet Gynecol* 2013;25(1):17–22. Available at: http://journals.lww.com/co-obgyn/Fulltext/2013/02000/FDG_PET_CT_in_monitoring_response_to_treatment_in.5.aspx.
- [20] Tan ASL, Gibson L, Zafar HM, Gray SW, Hornik RC, Armstrong K. Associations between cancer-related information seeking and receiving PET imaging for routine cancer surveillance—an analysis of longitudinal survey data. *Cancer Epidemiol Biomarkers Prev* 2014;23(3):481. Available at: <http://cebp.aacrjournals.org/content/23/3/481.abstract>.
- [21] Karantanis D, Kalkanis D, Allen-Auerbach M, Boggsrud TV, Subramaniam RM, Danielson A, et al. Oncologic 18F-FDG PET/CT: referring physicians' point of view. *J Nucl Med* 2012; 53(10):1499–1505. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22917886>.
- [22] Min SJ, Jang HJ, Kim JH. Comparison of the RECIST and PERCIST criteria in solid tumors: a pooled analysis and review. *Oncotarget* 2016;5(19):27848–27854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/27036043>.
- [23] Lakhani A, Khan SR, Bharwani N, Stewart V, Rockall AG, Khan S, et al. FDG PET/CT pitfalls in gynecologic and genitourinary oncologic imaging. *RadioGraphics* 2017;37(2): 577–594. Available at: <https://doi.org/10.1148/rg.2017160059>.
- [24] Sironi S, Messa C, Mangili G, Zangheri B, Aletti G, Garavaglia E, et al. Integrated FDG PET/CT in patients with persistent ovarian cancer: correlation with histologic findings. *Radiology* 2004;233(2):433–440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15516617>.
- [25] Kim S, Chung JK, Kang SB, Kim MH, Jeong JM, Lee DS, et al. [18F]FDG PET as a substitute for second-look laparotomy in patients with advanced ovarian carcinoma. *Eur J Nucl Med Mol Imaging* 2004;31:196–201. <https://doi.org/10.1007/s00259-003-1367-y> June-Key.
- [26] Greer BE, Bundy BN, Ozols RF, Fowler JM, Clarke-Pearson D, Burger RA, et al. Implications of second-look laparotomy in the context of optimally resected stage III ovarian cancer: a non-randomized comparison using an explanatory analysis: A Gynecologic Oncology Group study. *Gynecol Oncol* 2005; 99(1):71–79. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0090825805003744>.
- [27] Boellaard R, Delgado-Bolton R, Oyen WJG, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 2015;42(2):328–354. Available at: version 2.0. <http://link.springer.com/10.1007/s00259-014-2961-x>.
- [28] Shankar LK, Hoffman JM, Bacharach S, Graham MM, Karp J, Lammertsma AA, et al. Consensus recommendations for the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute trials. *J Nucl Med* 2006; 47:1059–1066.
- [29] Niederkohr RD, Greenspan BS, Prior JO, Schöder H, Seltzer M, Zukotynski K, et al. Reporting guidance for oncologic 18F-FDG PET/CT imaging. *J Nucl Med* 2013;54:756–761. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23575994>.
- [30] Kumar R, Dholakia AS, Smith JA, Leal JP, Chaudhry MA, Wild AT, et al. First report of the correlation of PET Response Criteria in Solid Tumors (PERCIST) criteria and pathologic change in patients with rectal cancer treated with neoadjuvant radiation. *J Clin Oncol* February 1 2013;31(Suppl. 4):261. Available at: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L71085053%5Cnhttp://meeting.asco.org/cgi/content/abstract/31/4_suppl/261?sid=8400706b-f935-437b-9c55-1abae9add70%5Cnhttp://gerion.green.es:443/sfxlcl3?sid=EMBASE&sid=EMBASE&issn=0732183X&id=doi:&title=First+report+of+the+correlation+of+PET+Response+Criteria+in+Solid+Tumors+%28PERCIST%29+criteria+and+pathologic+change+in+patients+with+rectal+cancer+treated+with+neoadjuvant+radiation&title=J.+Clin.+Oncol.&title=Journal.
- [31] Yanagawa M, Tatsumi M, Miyata H, Morii E, Tomiyama N, Watabe T, et al. Evaluation of response to neoadjuvant chemotherapy for esophageal cancer: PET Response Criteria in Solid Tumors Versus Response Evaluation Criteria in Solid Tumors. *J Nucl Med* 2012;53(6):872–880. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22582049%5Cnhttp://jnm.snmjournals.org/content/53/6/872.full.pdf>.
- [32] Avril N, Sassen S, Schmalfeldt B, Naehrig J, Rutke S, Weber WA, et al. Prediction of response to neoadjuvant chemotherapy by sequential F-18-fluorodeoxyglucose positron emission tomography in patients with advanced-stage ovarian cancer. *J Clin Oncol* October 20 2005;23(30): 7445–7453. <https://doi.org/10.1200/JCO.2005.06.965>.
- [33] Vallius T, Peter A, Auranen A, Carpén O, Kemppainen J, Matomäki J, et al. 18F-FDG-PET/CT can identify histopathological non-responders to platinum-based neoadjuvant chemotherapy in advanced epithelial ovarian cancer. *Gynecol Oncol* 2016;140(1):29–35. Available at: <http://linkinghub.elsevier.com/retrieve/pii/S0090825815301669>.