European Journal of Radiology 93 (2017) 107–113

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Research paper

F-18 FDG PET/CT metabolic tumor volume predicts overall survival in patients with disseminated epithelial ovarian cancer

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ARTICLE INFO

Keywords:
Epithelial ovarian cancer
Carcinomatosis
PET/CT
Survival

ABSTRACT

Objective: We evaluated the prognostic impact of quantitative assessment by maximum standardized uptake value (SUVmax), metabolic tumour volume (MTV) and tumour lesion glycolysis (TLG) on [F-18] FDG PET/CT for patients with peritoneal carcinomatosis from epithelial ovarian cancer (EOC).

Methods: Thirty-one patients with EOC underwent PET/CT for an early restaging after cytoreductive surgery, having been diagnosed with carcinomatosis (before chemotherapy). The SUVmax, MTV (cm^3; 42% threshold) and TLG (g) were registered on residual peritoneal lesions. The patients were followed up 20 ± 12 months thereafter. The PET/CT results were compared to overall survival (OS).

Results: The Kaplan-Meier survival analysis for the SUVmax did not reveal significant differences in OS ($p = 0.48$). The MTV survival analysis showed a significant higher OS in patients presenting with a higher tumour burden than those with less tumour burden ($p = 0.01$; 26 vs. 14 months), whereas TLG exhibited a similar trend though not significant ($p = 0.06$). Apart from chemo-resistance, the higher the MTV, the better will be the response to chemotherapy.

Conclusions: Quantitative assessment by MTV rather than by SUVmax and TLG on PET/CT may be helpful for stratifying patients who present with peritoneal carcinomatosis from EOC, in order to implement the appropriate therapeutic regimen.

1. Introduction

Epithelial ovarian cancer (EOC) is the most fatal gynaecological malignancy. Almost 22,000 cases are being diagnosed in the United States annually, and 14,240 estimated deaths are expected in 2016. [1]. The number of cases is similar in other developed countries, with an age-standardised rate per 100,000 women of 9.1 [2]. This disease is frequently diagnosed at advanced stages, because EOC spreads intraperitoneally through seeding, via direct invasion or via the lymphatic or vascular circulation [3]. This stage, called peritoneal carcinomatosis, represents a clinical challenge.

Although primary cytoreductive surgery (CRS) followed by taxane/platinum-based chemotherapy (CHTx) is considered the standard approach [4], unfortunately patients have a high death rate following this ineffective and somewhat life-threatening therapy. Several authors have suggested that maximal cytoreduction after surgery is one of the most powerful prognostic factors [5–7]. Nevertheless, the presence of residual large-volume disease after surgery does not preclude benefits from subsequent treatments.

The prognostic impact of the residual (loco-regional/peritoneal) tumour burden assessed by positron emission tomography/computed tomography (PET/CT) has not yet been completely investigated. In fact, the appraisal of the peritoneal involvement is usually performed by contrast-enhanced CT and magnetic resonance imaging, but sensitivity is reduced because the anatomical imaging considers only size criteria and does not distinguish the functional alterations that may occur

Abbreviations: EOC, epithelial ovarian cancer; CRS, cytoreductive surgery; PET/CT, positron emission tomography/computed tomography; MTV, metabolic tumour volume; TLG, total lesion glycolysis; SUVmax, standardized uptake value; [18F]FDG, fluorine18 fluorodeoxyglucose; FIGO, International Federation of Gynaecology and Obstetrics; GOG, Gynaecologic Oncology Group

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http://dx.doi.org/10.1016/j.ejrad.2017.05.036
Received 26 May 2016; Received in revised form 24 May 2017; Accepted 25 May 2017

within the tumour tissue.

Recently, the PET/CT has exhibited valuable diagnostic accuracy for identifying primary tumours, regional lymph nodes, distant metastases and significant peritoneal involvement resulting from EOC [8–10]. Moreover, some studies have shown that PET/CT is useful for monitoring response to treatment [11], both surgical and chemo-therapeutic, and for detecting residual disease during and/or after the completion of therapy [12,13].

Data that describe the role of PET/CT quantitative parameters for the prediction of outcome are limited. Metabolic tumour volume (MTV) and total lesion glycolysis (TLG) are measures of the metabolic activity of tumours derived from fluorine-18 fluorodeoxyglucose ([18F] FDG) uptake on PET/CT images. The purpose of this study was to investigate the relationship between the functional tumour parameters (SUVmax, MTV and TLG) and the clinical outcome in EOC patients who demonstrated residual peritoneal involvement after CRS and for whom adjuvant chemotherapy was planned.

2. Material and methods

We retrospectively reviewed the Institute tumour registry for patients who had an EOC histological diagnosis between January 2008 and August 2011. Among them, patients presenting with peritoneal carcinomatosis at CRS, as per II/III stage according to the International Federation of Gynaecology and Obstetrics (FIGO), were enrolled (Table 1). The patients were required to have undergone an [18F] FDG PET/CT study between the established diagnosis, at the time of surgery, and before any further scheduled chemotherapy (within 4 ± 1 months) with the intent of restaging, and to have received at least 8 months' follow-up. All subjects received CRS and no less than a complete pelvic excision (i.e. partial debulking). Additional inclusion criteria were age at entry of 18 years or older, a negative pregnancy test and Gynaecologic Oncology Group (GOG) Performance Status of 0, 1, 2 or 3.

Table 1
Patient characteristics.

Number	31
Age at diagnosis, years, median (range)	62 (35–79)
Histology	
Serous (%)	30 (97)
Endometrioid (%)	0
Clear Cell (%)	0
Mixed Type; neuroedocrine (%)	1 (3)
CA-125, UI/ml, median (range)	80 (12–420)
FIGO[a] stage	
I(%)	0
II(%)	3 (10)
III(%)	28 (90)
IV(%)	0
Tumor Grade	
1 (%)	1 (3)
2 (%)	3 (10)
3(%)	24 (77)
Unknown (%)	3 (10)
Apparent residual lesion after surgery	
Yes (%)	26 (84)
No (%)	5 (16)
Chemotherapy (6 cycles)	
Platinum-based combination fulfilled (%)	17 (55)
Platinum-based combination incomplete (%)	14 (45)
No (%)	0
Final patient status	
No evidence disease (%)	18 (58)
Alive with disease (%)	7 (22)
Death (%)	4 (13)
Unknown (%)	2 (7)

[a] FIGO; International Federation of Gynecology and Obstretics.

The patients who had received neo-adjuvant therapy or re-intervention, or were classified as stage IV, were excluded.

The histological specimen, grade, haematological parameters and Ca-125 serum levels, and the site of peritoneal involvement as well as the treatment adopted thereafter were retrieved from each patient's medical record. The surgical staging was assigned according to the FIGO stage. The timing of the scheduled chemotherapy was implemented in compliance with each patient's GOG state post-surgery and according to the referring physicians (Table 2).

The ethical committee of our Institute approved the protocol. All patients who underwent the study signed an informed consent form in accordance with the Declaration of Helsinki.

The patients underwent [18F] FDG PET/CT. Patients were well-hydrated before receiving [18F]FDG intravenously (370–555 MBq). Sixty minutes after the tracer injection, PET and CT were carried out with a commercial PET/CT scanner (GE Discovery VCT scanner; Waukesha, WI) that combined a PET scanner and a Light Speed VCT 64 row MDCT system. MDCT (pitchx 1.5; 120 mAs; 120 kVp) was performed without the use of intravenous and/or oral contrast mediums. The PET scanning was subsequently performed, acquiring 3 min per bed position and six to eight beds per patient, depending on patients' heights. The raw CT data were reconstructed into transverse images with a 3.75-mm section thickness. Sagittal and coronal CT images were generated by reconstruction of the transverse data. Raw PET data were reconstructed with and without attenuation correction into transverse, sagittal and coronal images. Attenuation correction was based on CT attenuation coefficients, which were determined by iterative reconstruction. Patients fasted 4–6 h prior to imaging. Blood glucose levels were determined in all patients before [18F]FDG administration, and a cut-off value of less than 8.04 mmol/L (145 mg/dL) was considered appropriate for performing the examination.

All images were reviewed by using a PET/CT fusion software (Volumetrix for PET-CT and Advantage Workstation, AW volume share 4.5; GE Healthcare, Waukesha, WI, USA). Each PET/CT study was interpreted by two experienced nuclear medicine physicians (G.S., and P.M., each with 15 years of expertise); one of them was also a radiologist. They were blinded to the patient histories. The examiners first evaluated the CT images alone.

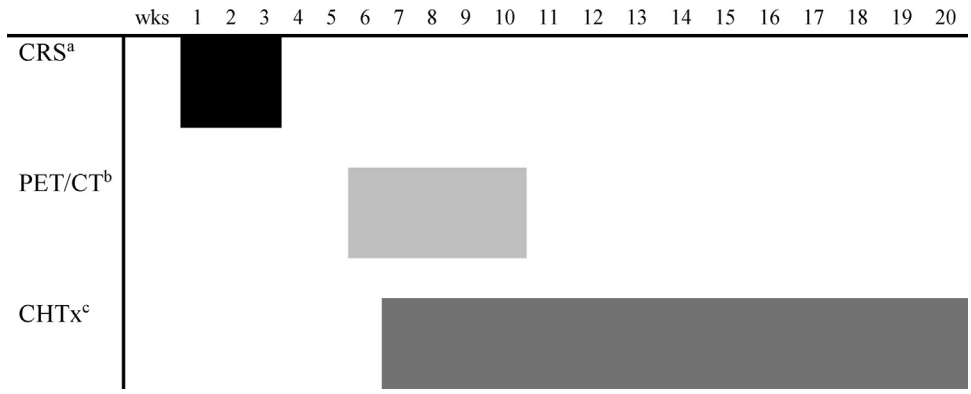
The mass size was visually estimated and measured for minimum and maximum diameters by using a vendor-provided software (Volumetrix for PET-CT; GE Healthcare, Waukesha, WI, USA). A lesion (site) was defined as an identifiable peritoneal mass (i.e. peritoneal coin or omental/mesenteric fat thickening) or a pathological lymph node with soft-tissue/abdominal window settings (i.e. n. 1 lymph nodes > 1 cm or n. 3 in cluster), within the pelvic/abdominal environment.

The PET studies were evaluated both visually and semi-quantitatively. A SUVmax cut-off value of 2.5 (established by a ROC curves analysis) is considered to provide excellent specificity and sensitivity for detecting lesions. Accordingly, an uptake higher than 2.5 was reported as significant. On the PET scan, the body-weight corrected maximum standardized uptake (SUVmax) values as well as the MTV (cm3; 42% threshold) and TLG (g) were determined using vendor-provided software (AW volume share 4.5 for PET-CT; GE Healthcare, Waukesha, WI, USA). Each residual peritoneal lesion that matched with the above-mentioned criteria was considered. The MTV was defined as the volume where SUV was more than 42% of SUVmax. TLG was derived from the multiplication of MTV and SUVmean of the MTV, definitively, as the product of SUVavg multiplied by the number of voxels. On a patient basis, we determined the sum of all MTVs and the cumulative TLG as per tumour burden.

For the volumetric analysis, 16 studies were examined twice by the same reader (intraobserver reproducibility) and were interpreted by two different readers (interobserver reproducibility).

The patients were categorized into two groups according to SUVmax, MTV and TLG cut-off points determined by ROC analysis. The

Table 2
Overall timeline of surgery, PET/CT and chemotherapy.



Wks; weeks, [a]CRS; cytoreductive surgery, [b]PET/CT; positron emission tomography/computed tomography, [c]CHTx; chemotherapy. Cross-talk between solid bars is related to the heterogeneous patients' timing.

performance status and the status of disease were followed up 20 ± 12 months thereafter.

The evaluation was carried out using clinical and haematological parameters during scheduled or unscheduled visits, on the basis of diagnostic imaging (i.e. CT) results (if any) as well as by phone interview.

Main events such as re-intervention, evidence of newly discovered distant metastases (not peritoneal; as per progression) or death constituted surrogate end-points. PET/CT results were then correlated to the disease outcome (overall survival; OS). OS was defined as the time from PET/CT until disease-related death or the time of the last censor.

Chemotherapy resistance was defined as a progression or event that occurred during the 6 months after completion of a platinum-based regimen.

Continuous data are expressed as mean ± 1 SD and median. Comparisons between the mean values were performed with an unpaired Student's *t*-test (two-tailed probability). Intraobserver and interobserver reproducibility for computing MTV and TLG was assessed by the repeatability coefficient, which is twice the SD of differences [14]. We may assume that 95% of differences are less than a repeatability coefficient.

The receiver-operator-curve (ROC) analysis was performed to estimate the optimal cut-off of SUVmax, MTV and TLG for differentiating patients at high risk of main events. The Cox proportional hazard model was used to assess prognostic variables estimating the hazard ratio (age, histology, grade, Ca-125 serum levels, metabolic parameters at PET/CT and the treatment adopted were tested).

The Kaplan-Meier method was used to plot OS. Predefined cut-off points for metabolic variables were implemented and curves compared by log-rank testing. A probability (p) value < 0.05 was considered statistically significant.

3. Results

Records from 110 patients with EOC were evaluated during the study period. Among them, 31 patients (mean age 61.3 ± 11 yrs) were eligible and 26 presented a III C FIGO stage. Individual patient data are reported in Table 1. The surgery confirmed the presence of a peritoneal carcinomatosis, and the pelvic primary tumour was removed in all patients. A nodal/peritoneal CRS was performed and 5 of the 31 patients had no "apparent" residual disease. The tumours were serous adenocarcinoma, except for one patient who presented an associated neuroendocrine component. The mean Ca-125 was 122 ± 143 UI/ml. Fourteen patients (45%) received subsequent chemotherapy up to 4 of 6 cycles, with chemotherapy being clinically unsustainable thereafter.

The PET/CT was reported as positive in all patients (i.e. significant uptake, visually detectable and higher than 2.5). Global median SUVmax was 7.6 (range 3–21), median summed MTV was 35.2 cm3 (range 11–368) and median cumulative TLG was 419.4 g (range 182–1097). Volumetric measurements have been recently introduced, and their practical implementation may result in a lack of reproducibility due to both operator experience and software weakness. Accordingly, for this analysis, the intraobserver and interobserver reproducibility was assessed, and the values of the repeatability coefficient are listed in Table 3. On the basis of the above-mentioned assumption, the reproducibility appears to be good for both MTV and TLG.

The ROC curve analysis recognising cut-off values of SUVmax, MTV and TLG for OS are showed in Fig. 1. The AUC for SUVmax was 0.620 and the cut-off value was 6.53. The AUC for MTV and TLG was 0.691 and 0.673, respectively, whereas MTV and TLG cut-off values were 44.7 and 317.2, respectively.

Five of 31 patients (16%) underwent second-look re-intervention, whereas two of 31 (6%) showed newly discovered distant metastases (one brain, another liver) and four of 31 (13%) died. The second-look re-intervention confirmed EOC histology (Fig. 2).

The median follow-up was 22 months (range 8–43 months). Among the parameters tested in a Cox proportional hazard analysis, only an association between MTV and OS was observed. A better outcome was associated with higher values of MTV, which significantly contributed to the prediction of time of survival ($p = 0.023$, HR 0.025, 95% CI 0.001–0.603). The Kaplan-Meier survival analysis for SUVmax did not show a significant difference in OS ($p = 0.48$; HR, 0.6, log-rank test). The survival analysis for MTV showed significantly higher OS in patients presenting a greater tumour burden as compared to those presenting lesser ($p = 0.01$; HR, 4.8, log-rank test; 26 vs. 14 months), whereas TLG exhibited a similar trend, though not significant, for discriminating among patients ($p = 0.06$; HR, 3.2, log-rank test) (Fig. 3).

Additionally, the group of patients (n 5) with no apparent residual disease at surgery presented MTV values below the cut-off (29 cm3) and poor outcome. Nine (64%) patients among those who did not finish chemotherapy showed MTV values below the cut-off.

Table 3
Intraobserver and interobserver reproducibility for MTV and TLG measurements by [F-18]PET/CT.

	MTV[a]	TLG[b]
Intraobserver RC[c]	0.167	0.194
Interobserver RC	0.316	0.414

[a] MTV; Metabolic tumour volume (cm^3).
[b] TLG; total lesion glycolysis (g).
[c] RC; repeatability coefficient for reproducibility.

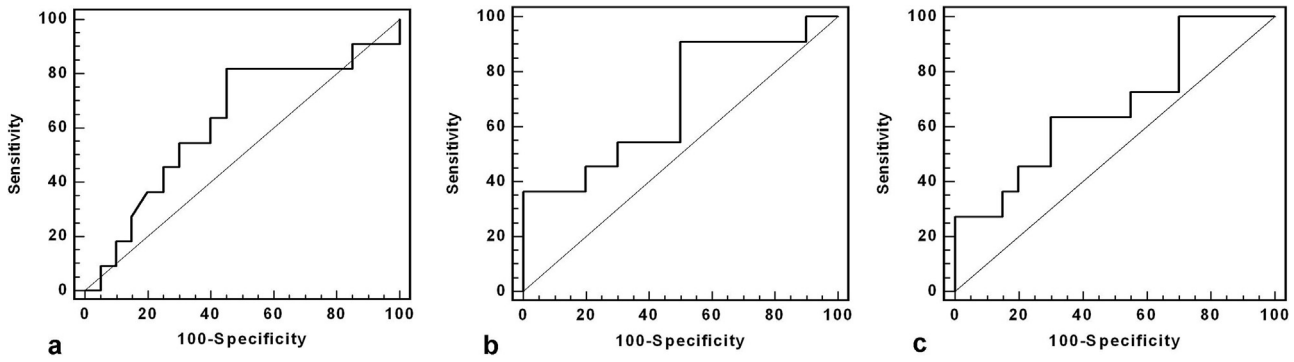


Fig. 1. ROC curve analysis establishing the cut off value of global SUVmax, summed MTV and cumulative TLG for predicting OS. The cut off value of SUVmax (**a**), MTV (**b**) and TLG (**c**) for stratifying patients was 6.53, 44.7 (cm3) and 317.2 (g), respectively.

We were able to exclude chemoresistance, because among the patients who reached the end-point, seven of 11 (64%) developed an event beyond the sixth month (settled point).

4. Discussion

Cytoreductive surgery followed by platinum-based systemic chemotherapy results in a complete response for up to 80% of patients with advanced ovarian epithelial carcinoma. However, only 30% of patients survive for at least 5 years because of relapse/residuals, post-surgery significant tumour burden or unsuccessful therapy. We investigated the relationship between functional tumour parameters by PET/CT and clinical outcome in patients with peritoneal carcinomatosis from EOC which was intercepted after the cytoreductive surgery, and for whom chemotherapy was planned. In this study, the sum of MTV computed from each identifiable abdominal lesion rather than indirectly thresholded parameters, such as the SUVmax and the cumulative TLG, was predictive of survival. Aside from chemo-resistance, the higher the summed MTV, the better the response to additional therapy will be in this type of setting.

Some authors [15–17] have already described various [18F] FDG PET/CT parameters in different solid tumours as emerging indicators of metabolic activity. In particular, SUVmax, MTV and TLG have been recently used as prognostic variables in EOC patients before surgery [18–21]. Alternatively, the potential prognostic role of the functional characterization by PET/CT in EOC has been reported in post-treatment

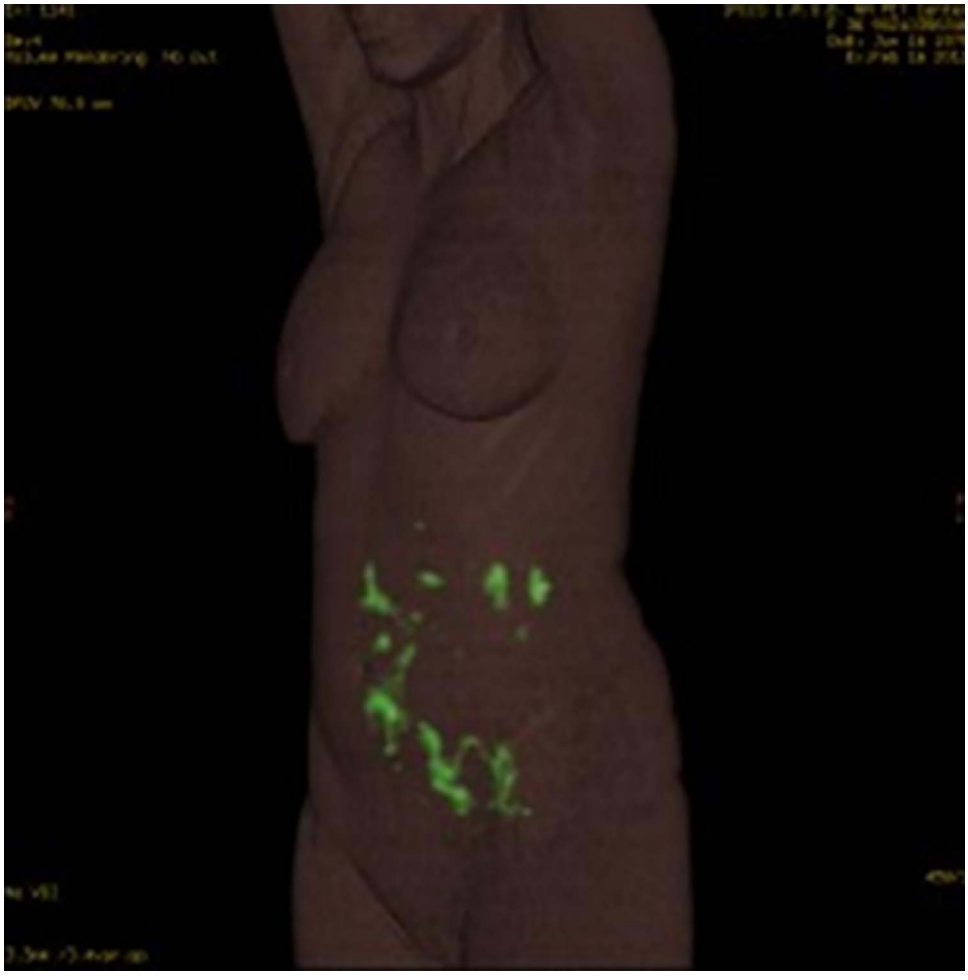


Fig. 2. Surface rendering image of patient with peritoneal carcinomatosis showing remarkable tumour burden (summed MTV: 45 cm3). The findings were confirmed at second-look histology.

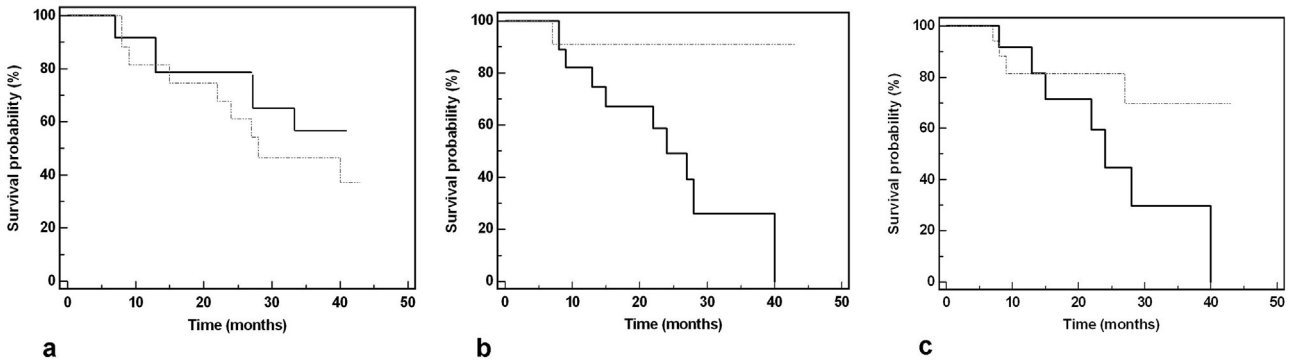


Fig. 3. Kaplan-Meier survival graphs indicate a significant difference in OS between the group of patients categorized by MTV. **a** Kaplan-Meier graph of global SUVmax and OS showing SUVmax above (dotted line) and below (solid line) the cut off of 6.53. **b** Kaplan-Meier graph of summed MTV and OS with MTV above (dotted line) and below (solid line) the cut off of 44.7 cm3. High MTV is coupled with prolonged survival ($p = 0.01$, log-rank test). **c** Kaplan-Meier graph of cumulative TLG and OS with TLG above (dotted line) and below (solid line) the cut off of 317.2 (g).

settings, following soon after the initial therapy [22–26] as well as for the definitive therapy assessment [9,27–32]. To our knowledge this is the first study that shows the prognostic value of functional parameters by PET/CT in patients with peritoneal carcinomatosis from EOC shortly after surgery and while awaiting chemotherapy.

Among these functional indicators, the SUV represents a validated measurement of the body-weight corrected metabolic activity which does not take into account the representative tumour volume, whereas the MTV and TLG evaluate tumour-energetic turnover throughout the volume of the lesion above a minimum threshold designed to exclude the background activity. Accordingly, volume-based parameters may reflect more accurately the metabolic burden of an active tumour than the hypermetabolic single-pixel-based SUV would.

In our setting, only the summed MTV, which was calculated considering the abdominal tumour residuals to surgery, was a statistically significant prognostic factor of survival. It is noteworthy that the patients presenting higher values of MTV showed a prolonged survival compared to those having lesser values, indicating that the higher the tumour burden the better the response to subsequent chemotherapy.

These data appear to be in contrast with previous and recent findings [18–21]. In fact, Chung et al. reported [20] that a poor outcome was associated with higher values for both the MTV and the TLG in 55 patients with EOC and Lee et al. [19] described that, in addition to the tumour stage, TLG is an independent prognostic factor for disease progression in a similar setting. However, in these studies, unlike ours, the PET/CT was performed before the cytoreductive surgery when the whole tumour load was still on-site, which could have influenced the results. In addition, other previous studies have indicated prolonged survival after the surgery once the all evidence of macroscopic disease seemed to be eliminated. These last data mainly focused on the primary tumour (and less so on the peritoneum) and did not consider the contribution of the PET/CT diagnostic [33,34]. More recently, some authors also compared the prognostic value of data from PET/CT with those obtained by contrast-enhanced CT (CECT) [24–26]. Rubini et al. showed that PET/CT had a diagnostic accuracy of 88%, higher than that of CECT, for detecting peritoneal carcinomatosis. However, these studies were carried out for testing the value of PET/CT to detect undiagnosed/unknown peritoneal carcinomatosis or for predicting outcome/post-relapse survival in patients complying with recurrent EOC distant from the initial treatment [24,25], while our patients had suspected peritoneal carcinomatosis and did not have a local recurrence. Moreover, there is evidence that volumetric assessment by PET/CT has a powerful prognostic value in EOC also after surgery [22,23,30]. Nevertheless, Chu et al. focused on the incremental value of PET/CT in improving prognostic accuracy, particularly in the subset of patients with negative CA-125 [22]. Recently, Vallius et al. evaluated whether PET/CT is useful for identifying unresponsive patients to neoadjuvant CHTx. Unlike us, they did not use volumetric parameters, but only SUVmax, and concluded that PET/CT can identify unresponsive patients who would benefit from second-line CHTx instead of debulking, thus endorsing the need for a substantial metabolic response [23]. Yamamoto et al. [30] reported that volumetric parameters MTV and TLG could serve as potential surrogate biomarkers for recurrence in patients who undergo both CRS and CHTx, identifying patients at high risk of recurrence. This group of patients differs from ours because the impact on findings of CHTx cannot be ruled out. Our patients constituted a particular setting compared to those of the latter studies. They had undergone cytoreductive surgery, since peritoneal carcinomatosis was suspected (then confirmed by surgery), they received at least a complete surgical pelvic intervention (on the primary tumour) and they had a PET/CT study for restaging before implementing a platinum-based therapy. The chemotherapy was timed or delayed according to their GOG score and the referring physicians.

Mayoral et al. and Caobelli et al. [31,32] also reported on the role of PET/CT parameters as useful prognostic predictors of outcome, but in patients with recurrent EOC [31] distant from the first remission, or for restaging, using only the SUV [32].

Although our findings appear unusual it is conceivable that patients presenting with metabolically active disease would respond better to chemotherapy along with the log-kill hypothesis. In fact, chemotherapeutic agents kill a constant fraction of cells, rather than a specific number of cells, increasing the likelihood that repeated cycles of chemotherapy will reduce the number of viable tumour cells toward zero, after the initial surgical reduction of tumour volume [35]. Therefore, the higher the MTV, the higher is the absolute number of cells killed every cycle (translating to tumour-shrinkage), and hence, the better is the response to additional therapy.

Moreover, most of the patients with lower MTV did not complete chemotherapy, which may partially substantiate their poor outcome. For them, at least, alternative approaches would have been envisaged.

Metabolic assessment after surgery and before chemotherapy might be helpful for stratifying patients with advanced EOC who are at high risk for not responding to treatment, and for those who may beneficiate from a complete aggressive therapeutic regimen albeit the considerable tumour burden. Accordingly, our findings support the idea that the volume-based evaluation in EOC peritoneal carcinomatosis, after the debulking, addresses the question of which patients warrant full-regimen/alternative chemotherapy (i.e. biologic drugs or intra-peritoneal) and which patients warrant a less aggressive approach sparing some treatment-related co-morbidities and costs. Our data also suggest that the PET/CT could be useful for an ad-interim restaging [36].

The lack of a gold standard against which to compare positive PET/CT findings could be disputed. Most of the patients had elevated Ca-125 levels. Those who experienced main events mostly underwent re-intervention with a histologically proven relapse.

We defined the chemoresistance as a progression/event that

occurred during the 6 months following the completion of a platinum-based regimen. Accordingly, because most of the patients who reached the end-point developed a main event significantly later (more than six months after completion of treatment), we definitively ruled out chemoresistance as a factor influencing the outcome.

From a technical point of view, it could be argued that summed MTV constituted a powerful indicator, whereas TLG, which is MTV-based, did not. However, similar to SUVmax, which considers a single hypermetabolic pixel, TLG contains the SUVavg as a straight non-thresholded parameter. It could be postulated that parameters without a threshold may result in a less accurate lesion/background discrimination in such a particular abdominal environment. Discrepancy on the value of TLG has been already reported in this setting [19,31]. Nevertheless, TLG results showed a trend similar to that of MTV, though not significant, and somewhat auto-referential to our Institution.

Assessment of disease by [18F] FDG PET/CT early after surgery may effect a number of false positive results, especially when an extensive abdominal surgery has been carried out. However, our patients underwent PET/CT 4 ± 1 months after surgery, when the confounding variables (i.e. inflammation) may be mainly ruled out. Although there is a lack of standardized criteria, the role of the volumetric analysis by [18F]FDG PET/CT in haematological [37] and solid tumours [38], such as in EOC, is promising.

5. Conclusion

The quantitative assessment by MTV rather than SUVmax and TLG on [18F]FDG PET/CT may be helpful for patients presenting peritoneal carcinomatosis from EOC after debulking and before chemotherapy, when a proper survival stratification is warranted. The role of the volumetric analysis by [18F] FDG PET/CT in solid tumours such as EOC is emerging, and justifies its use in larger settings.

Conflict-of-interest disclosure

The authors have indicated they have no financial conflicts of interest.

Disclosure

The study is not funded.

Acknowledgments

The Authors wish to thank Mr. Leggiadro F., Mr. Tempone A. and Mr. Volpicelli F. for their valuable contribute in performing the studies.

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