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# VALEUR PRONOSTIQUE DES PARAMETRES DERIVES DE LA TEP/TDM AU 18FDG CHEZ DES PATIENTES PRESENTANT UNE PREMIERE RECIDIVE METASTATIQUE D'UN CARCINOME MAMMAIRE

**THESE**

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# SERMENT D'HIPPOCRATE

*"Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.*

*Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.*

*Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.*

*J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.*

*Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.*

*J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.*

*Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.*

*Je donnerai mes soins à l'indigent et à quiconque me les demandera.*

*Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.*

*Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.*

*Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.*

*Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.*

*J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.*

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# TABLE DES MATIERES

# TABLE DES TABLEAUX ET FIGURES

# ABREVIATIONS

| | |
|---|---|
| ASCO | American Society of Clinical Oncology |
| BC | Breast Cancer |
| BW | Body Weight |
| CAP | College of American Pathologists |
| CT | Computed Tomography |
| ER | Oestrogen Receptor |
| FDG | Fluorodeoxyglucose |
| HER | Human Epidermal Growth Factor Receptor |
| MBC | Metastatic Breast Cancer |
| MTV | Metabolic tumour volume |
| OS | Overall Survival |
| PERCIST | PET Response Criteria in Solid Tumors |
| PET | Positron Emission Tomography |
| PR | Progesterone Receptor |
| ROI | Region Of Interest |
| SUL | lean body mass corrected SUV |
| SUV | Standardized Uptake Value |
| SUVmax | Maximum SUV |
| TLG | Total Lesion Glycosis |
| VOI | Volume Of Interest |

# Prognostic significance of FDG-PET/CT derived parameters in patients with first metastatic breast cancer relapse.

**ABSTRACT**

**Aim:** To investigate the prognostic value of metabolic tumour volume (MTV) determined by fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in patients experiencing a first recurrence of metastatic breast cancer (MBC).

**Methods:** From December 2006 to August 2013, 49 women with a first recurrence of MBC were retrospectively included. FDG-PET/CT was performed within one month before systemic treatment. Three sets of MTV were calculated with Beth Israel (BI) software: (a) based on an absolute threshold selecting voxel with standardized uptake value (SUV) >2.5 ($MTV_{2.5}$) ; (b) applying a per-lesion threshold of 41% of the maximum SUV ($SUV_{max}$) ($MTV_{41}$) ; (c) using a per-patient adapted threshold based on PERCIST definition of measurable target lesion defined by SUV> 1.5-fold greater than liver SULmean + 2 standard deviations (SD) ($MTV_P$). MTV analysis was dichotomised by median value and overall survival (OS) with each MTV methodology was determined by Kaplan-Meier survival curves and log rank test. Spearman rank order correlation was performed to establish the correlation between $MTV_P$ and CA15-3 value.

**Results:** Median follow-up period was 34 months (range: 8-72 months) during which 21 patients died. Median MTV value for $MTV_{2.5}$, $MTV_{41}$ and $MTV_P$ were respectively 24 ml (range: 0-1302), 34.5 ml (range: 1.4-876.8), 26.9ml (range: 0.38-1796.1). By log-rank analysis, a high (supramedian) MTV value was able to predict OS using all methodologies (p=0.031, 0.027 and 0.002 respectively). Time delay longer than 5-y between initial diagnosis and recurrence (26 of the 49 patients) was also predictor of OS ($p < 0.001$). When the patients were classified into four groups according to the

combined factors of $MTV_P$ and time delay, $MTV_P$ was predictive of OS in patients with a relapse time <5 years (mean survival time: 60 months versus 27 months; p = 0.026), but not in patients with time delay longer than 5-y. SUVmax and initial diagnosis stage were not predictors of OS. No statistically significant relationship was observed between $MTV_P$ and CA15-3 value. By multivariate analysis, only MTV remained independent predictor of survival.

**Conclusion:** In patients experiencing a first metastatic recurrence of breast cancer, a higher (supramedian) baseline Metabolic Tumor Volume defined by FDG PET/CT performed before treatment, predicts worse OS. This prognostic value of FDG PET/CT parameters appears complementary to clinical parameters such as time delay between initial diagnosis and recurrence.

# INTRODUCTION

Breast cancer (BC) is the most commonly diagnosed malignant disease among women and is one of the leading causes of cancer-related death among women (1) after experiencing a relapse and metastases. Despite major improvements in understanding breast cancer biology and in development of personalized therapeutic strategies, metastatic breast cancer (MBC) remains a therapeutic challenge, with a median survival of 29 months for *de novo* metastatic disease and 21 month for recurrent metastatic breast cancer (2–4). Thus, it appears worthwhile to develop new diagnostic strategies in order to stratify prognosis and to guide therapy.

$^{18}$F-fluorodeoxyglucose (FDG) Positron Emission Tomography/ Computed Tomography (PET/CT) is gaining usefulness in determining the prognosis of various types of cancer (5), and is now widely used for detection of disease recurrence in patients with breast cancer (6).

Moreover, FDG PET gives the opportunity to quantify tumor metabolism, using several parameters. SUVmax is mainly used in both clinical routine and research, as it is easily used and highly reproducible with modern computer software. However SUVmax limitations (mainly statistical noise) (7) prompted nuclear physician community to use derived formed of SUV. SUVmean is less susceptible to statistical noise but suffers from poor reproducibility. SUVpeak (SUVmean in a volume defined around SUVmax) was also introduced as a compromise between SUVmax and SUVmean. In order to approximate the whole volume of metabolically active disease, Metabolic tumor volume (MTV) and other measurement such as Total lesion glycosis (TLG) were introduced (8).

MTV and TLG usefulness in determining the prognosis in primary breast cancer, with positive axillary lymph nodes (9) and metastatic breast cancer (10–12) is starting to be proven. However none of these studies have specifically examined metastatic breast cancer relapse or original MTV thresholds.

The aim of our study was to investigate the prognostic value of FDG PET/CT derived parameters in patients experiencing a first metastatic recurrence of breast cancer, and specifically to confirm that quantitative measurements of FDG avidity (MTV and TLG) are predictors of overall survival and to test reliability of several MTV cutoff.

# MATERIALS AND METHODS

## Patients

A retrospective analysis was performed on consecutive patients with a history of BC and suspicion of recurrence who were referred for FDG PET/CT at our institution from December 2006 to August 2013.

This retrospective analysis was compliant with the ethical standards of the committees with responsibility for human experimentation (CPP Est I, France) and with the Helsinki Declaration of 1975, as revised in 2008. All patients granted permission to review medical records at the time of PET/CT imaging according to our institution's investigational review board guidelines for informed consent.

The inclusion criteria of the study were as follows: (a) a history of confirmed histologic diagnosis of primary BC treated initially with curative intent; (b) evidence of at least one distant metastasis on FDG PET/CT, confirmed by histological examination or evidence of progression on clinical and/or imaging follow-up; (c) availability of follow-up data for at least 6 months following PET/CT; (d) unequivocal determination of clinical status at the time of the clinical follow-up.

FDG-PET/CT was performed within one month before starting the first line of metastatic systemic treatment. Patients receiving systemic treatment for metastatic breast cancer prior to PET/CT were excluded.

For all patients, medical records were reviewed to gather clinical data, including information on age, stage at the initial diagnosis (I, II, III or IV) tumor phenotype (HER+;

Triple negative: HER-, Hormonal receptor-; Luminal: HER2-/HR+), histology, CA15-3 serum levels and final outcome.

Immunostaging was performed on an automated immunostainer (Ventana XT, Tucson). We examined: oestrogen receptors (ER) using prediluted rabbit monoclonal antibody SP1, progesterone receptors (PR) using prediluted rabbit monoclonal antibody 1E2 and HER2 expression using prediluted rabbit monoclonal antibody 4B5.

ER and PR status were considered positive if tumor showed more than 10% of positive cells. HER2 status was considered positive according to HerceptTest scoring system if score was 3+. The 2+ scores had fluorescent in situ hybridization (FISH) (ZytoLight, SPEC HER2/CEN17 Dual Color Prob Kit) according to ASCO/CAP criteria.

**FDG-PET/CT acquisition and Processing**

Whole-body FDG PET/CT, performed at baseline before any systemic treatment, was acquired sequentially using a dedicated PET/CT system (Gemini GXL from December 2006 to December 2010 and Gemini TF from December 2010 to August 2013; Philips Medical Systems, Eindhoven, The Netherlands). Before FDG injection, all patients had fasted except for glucose free oral hydration for a least 6h. Their blood glucose levels were measured before the injection of the tracer to ensure levels below 10 mmol/L. Patients were administered 5 MBq/kg (Gemini GXL) or 3 MBq/kg (Gemini TF) of FDG through the antecubital vein. Whole body imaging began 60 minutes after injection and the examination was performed from midthigh level to the base of the skull. Emission data were all corrected for dead time, random and scatter coincidences and attenuation

before reconstruction using the three-dimensional row action maximum likelihood algorithm (3D-RAMLA; Philips Medical Systems Inc).

Transmission data used for attenuation correction were obtained from a low-dose non-diagnostic CT acquisition (140 kV and 40-120 mA), without contrast enhancement.

**FDG-PET/CT image analysis**

FDG-PET/CT findings were interpreted by an experienced nuclear medicine physician, using Beth-Israel PET-CT viewer plug-in for Image J software from FIJI (http://www.fiji.sc). Orthogonal CT, PET and fused PET/CT images were displayed simultaneously. The PET data were also displayed in a rotating maximum-intensity projection. Beth-Israel PET-CT viewer enable to draw spherical or non-spherical outlines to define adapted regions of interest (ROI) in order to measure metabolic parameters for every single metastatic site. The Standardized Uptake Value (SUV) was calculated as follows:

$$SUV = \frac{C(t)}{\frac{A}{BW}}$$

Where BW = body weight (g), C(t) = radioactivity concentration in volume of interest at time t (MBq/mL), and D = injected dose (MBq). The attenuation-corrected PET emission scan was expressed in Bq/ml; the non–attenuation-corrected PET emission scan, in arbitrary activity units; and the low-dose CT, in CT density units (Hounsfield numbers);

SUVmax (the single voxel within the ROI with the greatest SUV), SUVpeak were also recorded (3D peak VOI determined - when possible - using a sphere with a diameter of approximately 1.2cm to produce a 1.0 ml spherical ROI positioned such that the average value across all positions within the lesion is maximised) and SUVmean for every ROI were also recorded. Metastatic site (bone, lung, liver, lymph nodes) were registered for every ROI.

For every defined ROI and SUVmax recorded, measurements of MTV ($cm^3$) and TLG (SUVmean x $cm^3$) were obtained. MTV was defined as the volume of voxels with SUV above a defined threshold and TLG as the product of MTV and the SUV mean of voxels within the MTV. We used three different thresholds in order to determine the MTV:

(a) A fixed threshold of SUV=2.5 ($MTV_{2.5}$): every voxel in the ROI drawn around the focus of 18 FDG considered as a metastatic site having a SUV over 2.5 was included in the calculation of the MTV.

(b) A relative per-lesion threshold of 41% of $SUV_{max}$ ($MTV_{41}$): every voxel in the ROI drawn around the focus of 18 FDG considered as a metastatic site having a SUV over 41% of the SUVmax measured in the ROI was included in the calculation of the MTV.

(c) A per-patient adapted threshold inspired by PERCIST definition of measurable target lesion ($MTV_P$): every voxel in the ROI drawn around the focus of 18 FDG considered as a metastatic site having a SUV over 1.5-fold than liver SULmean (calculated in 3-cm-diameter spherical ROI in the right lobe of the liver) + 2 Standard deviations (SD) (13) was included in the calculation of the MTV.

All measurements were recorded as maximums for each metastatic site.

**Statistical Analysis**

All quantitative data were expressed as mean +/- standard deviation (SD) or median as appropriate, and qualitative data were expressed as numbers and percentages.

The correlation between different MTV values calculations was computed using Pearson coefficient and the differences were assessed using Bland-Altman analysis and Student's t-test.

The primary outcome measurement was Overall Survival (OS). Estimates of OS were computed using the Kaplan Meier method, a log-rank test was performed to analyse the effects of the following PET/CT parameters on outcome: SUVmax (corresponding to the highest SUVmax of the whole malignant lesions), MTV ($MTV_{2,5}$, $MTV_{41}$, $MTV_P$) and TLG ($TLG_{2,5}$, $TLG_{41}$, $TLG_P$), all dichotomised by median value.

Spearman rank order correlation was performed to establish the correlation between $MTV_P$ and CA15-3 value.

Two separate cox regression multivariate analysis were performed to determine independent predictors of survival.

# RESULTS

## Patient characteristics

Forty-nine patients with a first metastatic breast cancer relapse were included in our study. Demographic of the patient, histologic type and grade, stage at the initial diagnosis, disease free interval and metastatic sites are summarized in **Table 1**.

The median age of the 49 patients was 51.2 years at the time of initial diagnosis (range, 32.5-73.2 years) and 58.9 years at the time of the first recurrence (range, 36.1-82.2 years). Median follow-up period was 34 months (range: 8-72 months) during which 21 patients died (43%). Median relapse time was 69 months (range: 14-250 months).

| Characteristics | Number of patients (%) |
|---|---|
| Histology | |
| Ductal | 35 (72%) |
| Lobular | 5(10%) |
| Other | 1 (2%) |
| Unknown | 8 (16%) |
| Histological grade of the primary tumour | |
| 1-2 | 22(45%) |
| 3 | 21(43%) |
| Unknown | 6(12%) |
| Stage at the initial diagnosis | |
| I | 10 (20%) |
| II | 28(57%) |
| III | 11(23%) |
| IV | 0(0%) |
| Phenotype | |
| HER2 | 9(18%) |

| | |
|---|---|
| Triple negative | 36(74%) |
| Luminal | 4(8%) |
| Disease free interval | |
| <2 years | 4(8%) |
| 2-5 years | 18(37%) |
| >5 years | 27(55%) |
| Median n° of metastatic disease sites (min-max) | 5 (1-90) |
| Disease site | |
| Lung | 9(18%) |
| Liver | 6(12%) |
| Bone | 37(76%) |
| Lymph nodes | 30(61%) |

HER-2= Human Epidermal Growth Factor Receptor-2

**Table 1:** Patient characteristics.

**PET Parameters and comparison of MTV methodologies**

For the study population, the mean SUVmax value was 8.1 +/- 4.2 (range: 2.26 – 18.8), mean MTV value for $MTV_{2.5}$, $MTV_{41}$ and $MTV_{P}$ were respectively 84.4 ml (range: 0-1302), 80.2 ml (range: 1.4-876.8), 104.9ml (range: 0.38-1796.1), mean TLG corresponding value for $TLG_{2.5}$, $TLG_{41}$ and $TLG_{P}$ were respectively 406.6g (range: 0.0-7002), 361.4g (range: 5.7-5591) and 448.1g (range: 0.95-8023).

The median value, the 25 to 75 percentile, the 10 and 90 percentile of $MTV_{2.5}$, $MTV_{41}$, $MTV_{P}$ methodologies are reported in **Figure 1**.

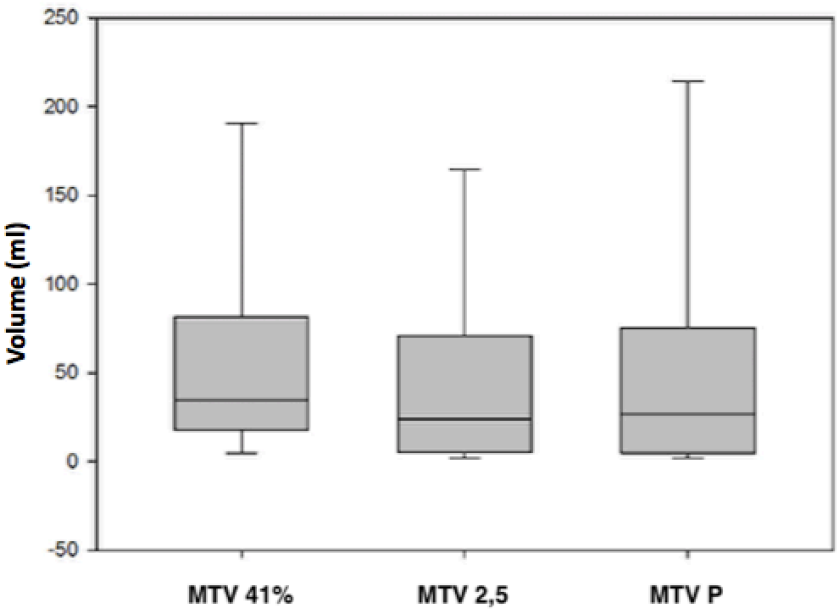


**Figure 1:** MTV distribution according to each methodology. MTV distribution with median (black line), 25 to 75 percentile (grey boxes), 10 and 90 percentile (edges) according to each MTV methodology

The Bland Altman analysis between the three different MTV methodologies are represented in **Figure 2**.

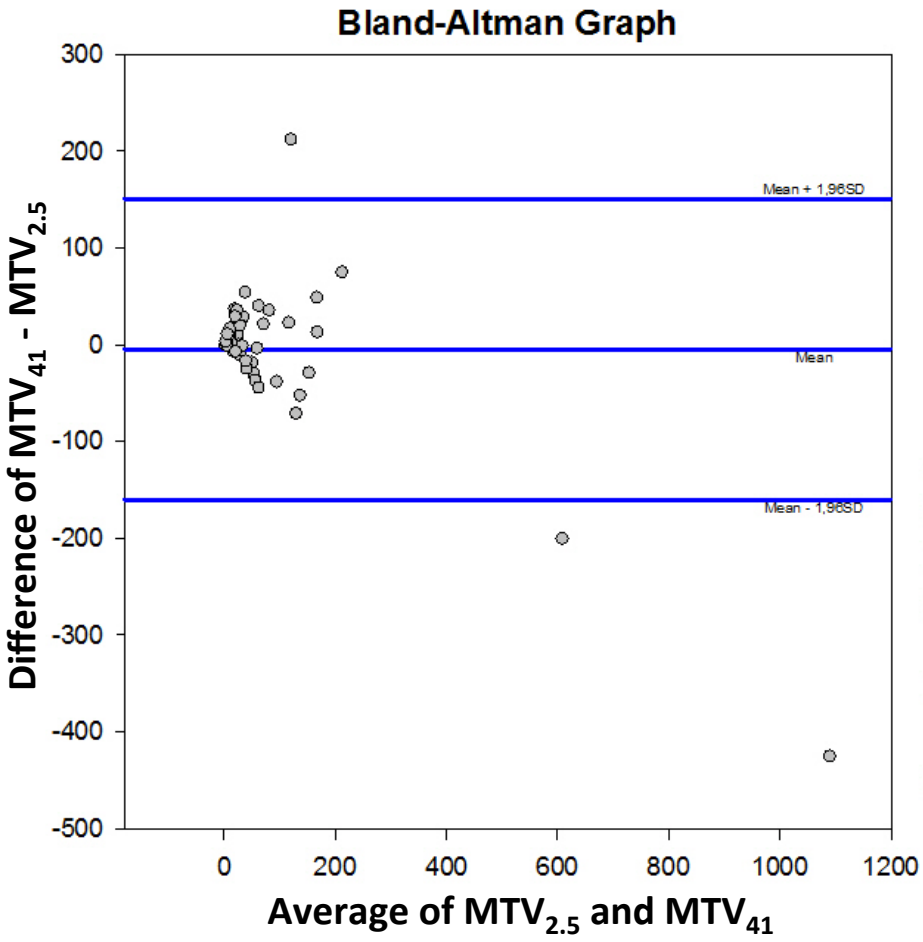


**Figure 2 (a):** Bland Altman analysis of different MTV methodologies. Bland-Altman analysis comparing MTV values of $MTV_{2.5}$ with $MTV_{41}$. Solid lines represent mean bias and limits of agreements.

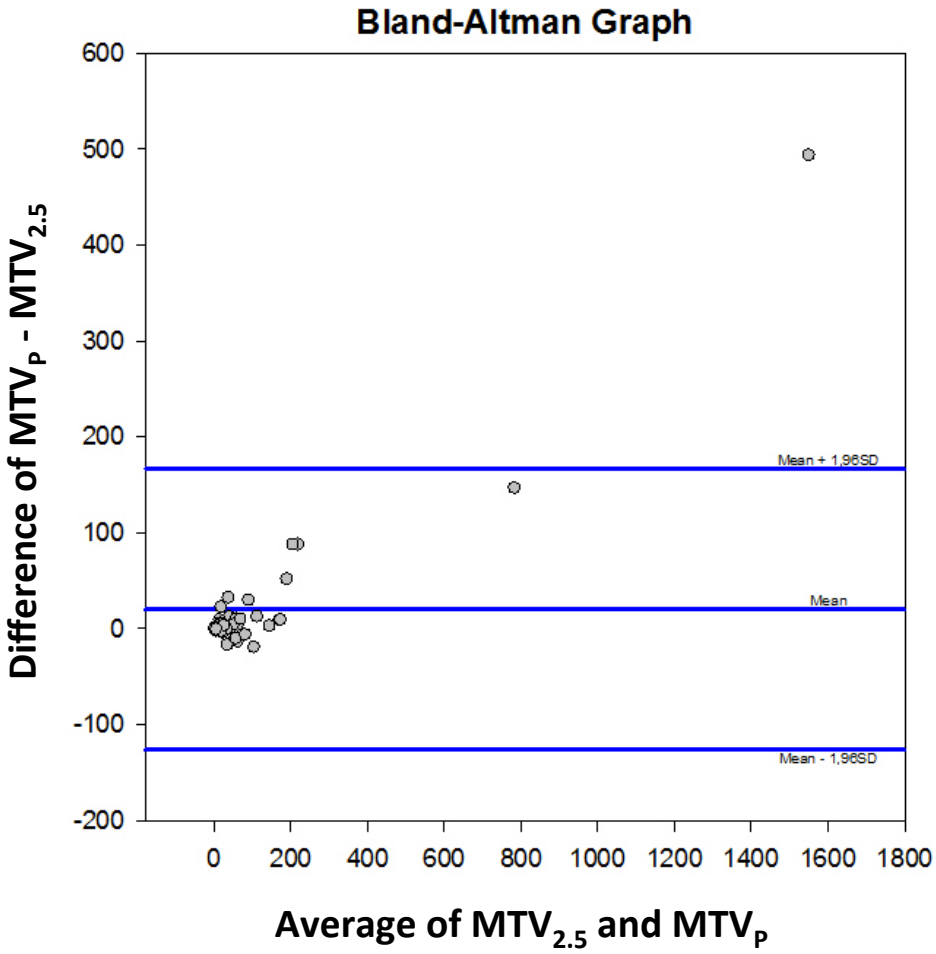


**Figure 2 (b):** Bland Altman analysis of different MTV methodologies. Bland-Altman analysis comparing MTV values of $MTV_{2.5}$ with $MTV_P$. Solid lines represent mean bias and limits of agreements.

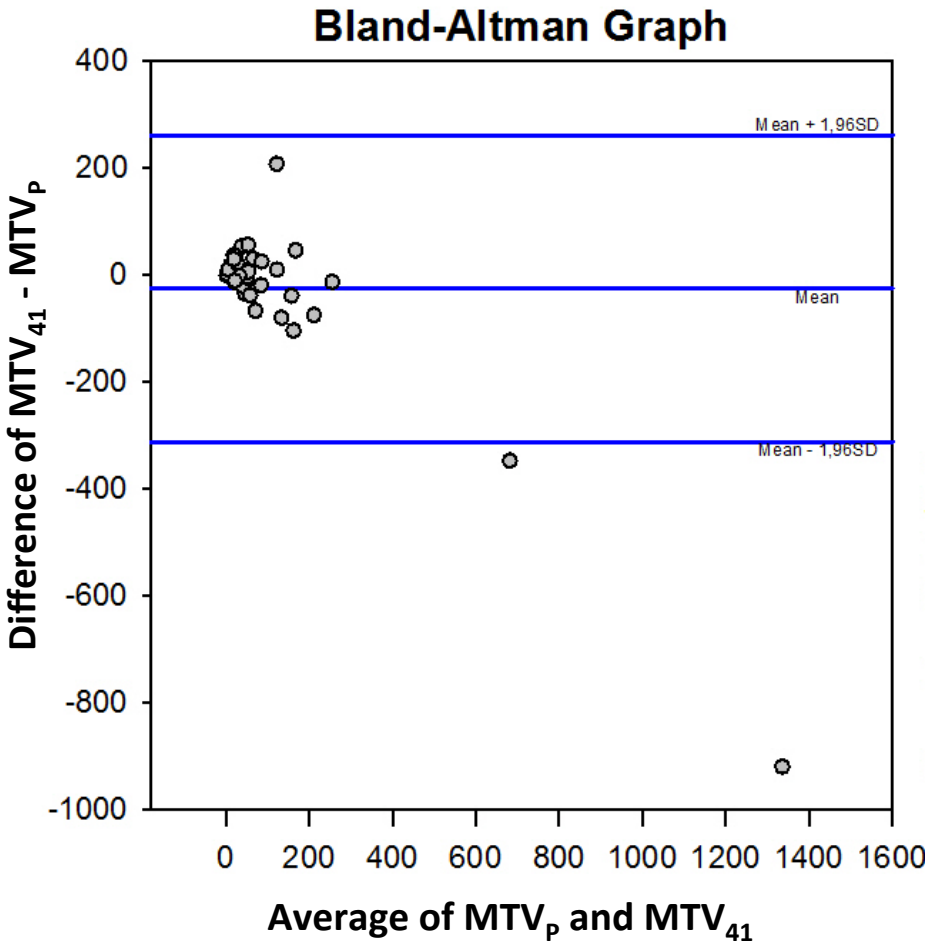


**Figure 2 (c):** Bland Altman analysis of different MTV methodologies. Bland-Altman analysis comparing MTV values of $MTV_P$ with $MTV_{41}$. Solid lines represent mean bias and limits of agreements.

$MTV_P$ and CA 15-3 did not show any significant correlation using spearman rank order correlation (correlation coefficient: 0.0974; p = 0.504)

**Kaplan Meier Survival analysis**

$MTV_{2.5}$, $MTV_{41}$ and $MTV_P$ methodologies were predictive of OS after dichotomisation by median value. Patients with high MTV value having an unfavourable prognostic (37 months versus 54 months mean survival time, p=0.031; 36 months versus 54 months mean survival time, p = 0.027 and 34 months versus 57 months mean survival time, p = 0.002 respectively) **(Figure 3 (a), (b), (c))**.

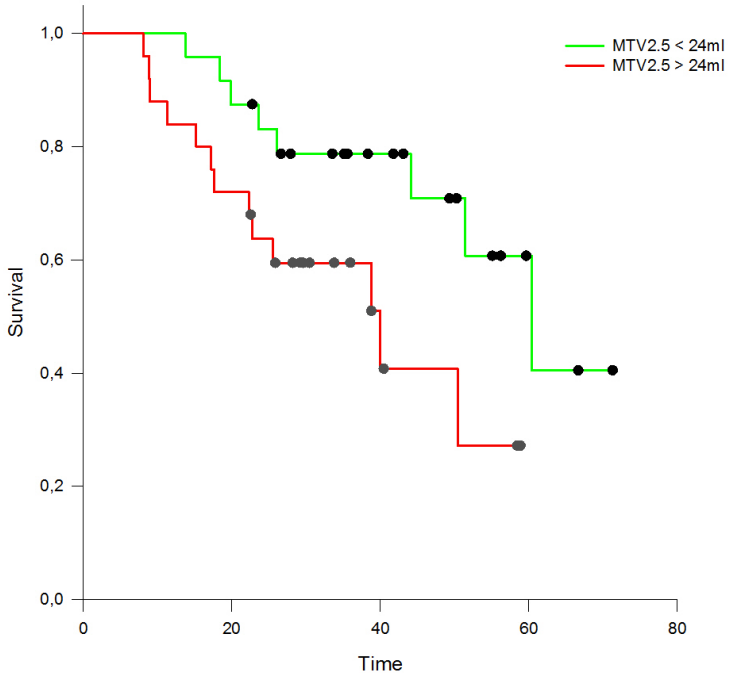


**Figure 3 (a)**: Overall survival dichotomised by $MTV_{2.5}$ median value.

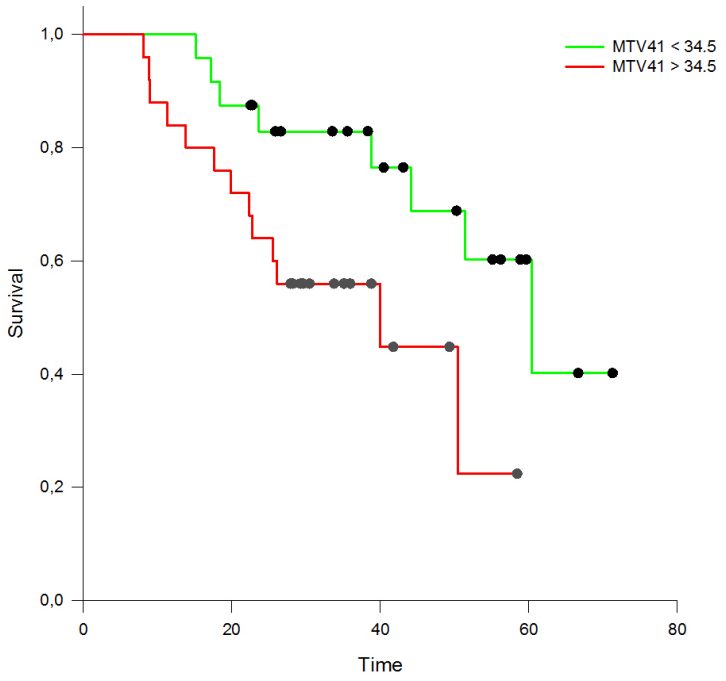


**Figure 3 (b)**: Overall survival dichotomised by $MTV_{41}$ median value.

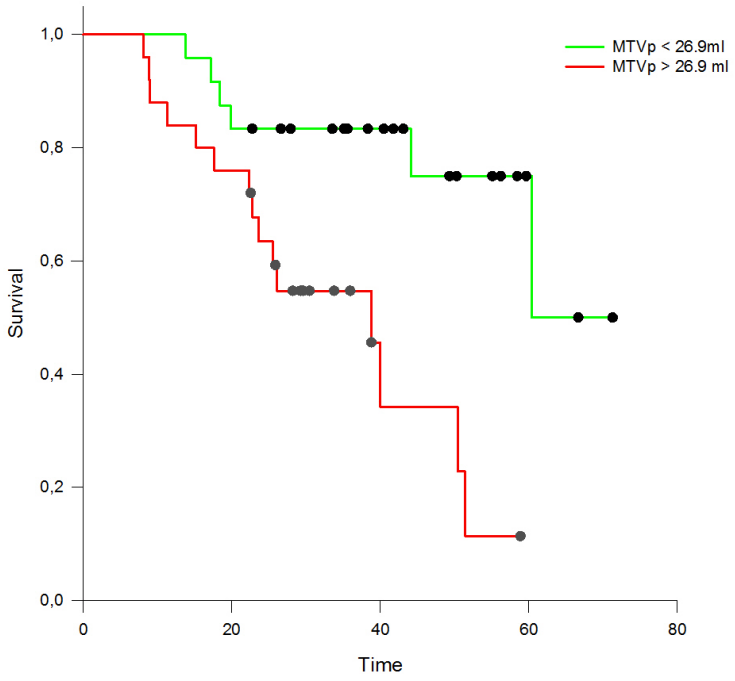


**Figure 3 (c)**: Overall survival dichotomised by $MTV_P$ median value.

In the continuity of MTV results, $TLG_P$ was also predictive of OS after dichotomisation by median value. Patients with a high TLG value also having an unfavourable prognostic (34 months versus 57 months, p=0,002) **(Figure 4).**

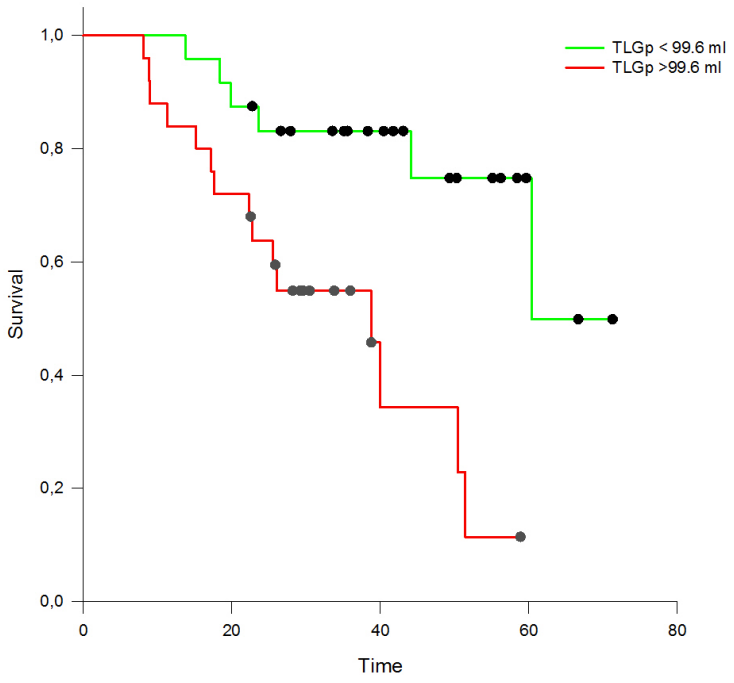


**Figure 4:** Overall survival dichotomised by $TLG_p$ median value.

Time delay between initial diagnosis and recurrence was also predictive of OS, patients with a time delay less than 5 years invasion having an unfavourable prognosis (39 months for short time delay recurrence versus 51 months for long time delay recurrence; p = 0.018 **(Figure 5)**).

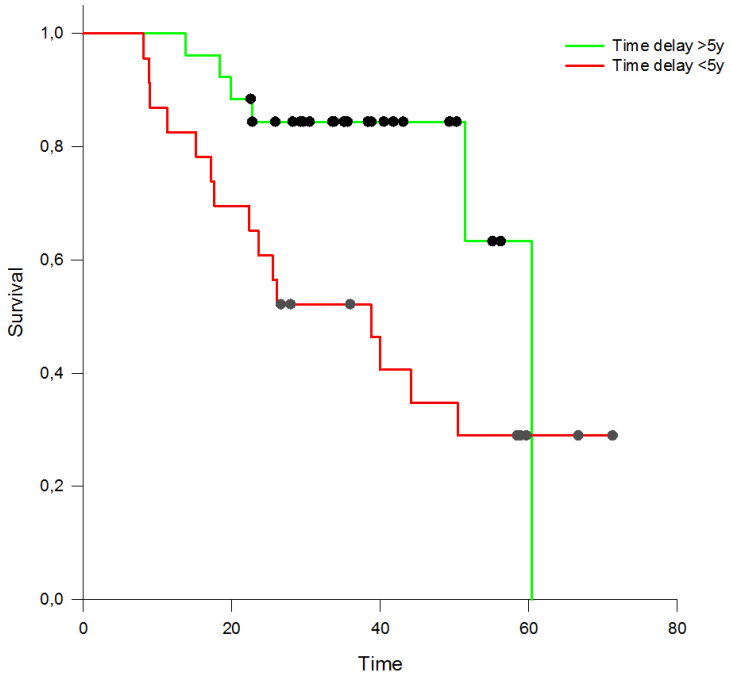


**Figure 5:** Overall survival stratified by time delay between initial diagnosis and recurrence (<5 years or > 5 years).

Then patients were divided into four groups according to $MTV_P$ and time delay: (a) $MTV_P$ < median value and time delay > 5 years; (b) $MTV_P$ < median value and time delay < 5 years; (c) $MTV_P$ > median value and time delay > 5 years; (d) $MTV_P$ > median value and time delay < 5 years. The OS of the four groups differed significantly (mean OS: 52 months, 60 months, 48 months and 26 months respectively; $p < 0.001$).

OS differed significantly between group (a) and (d) ($p = 0.004$) and between groups (b) and (d) ($p = 0.03$) **(Figure 6)**.

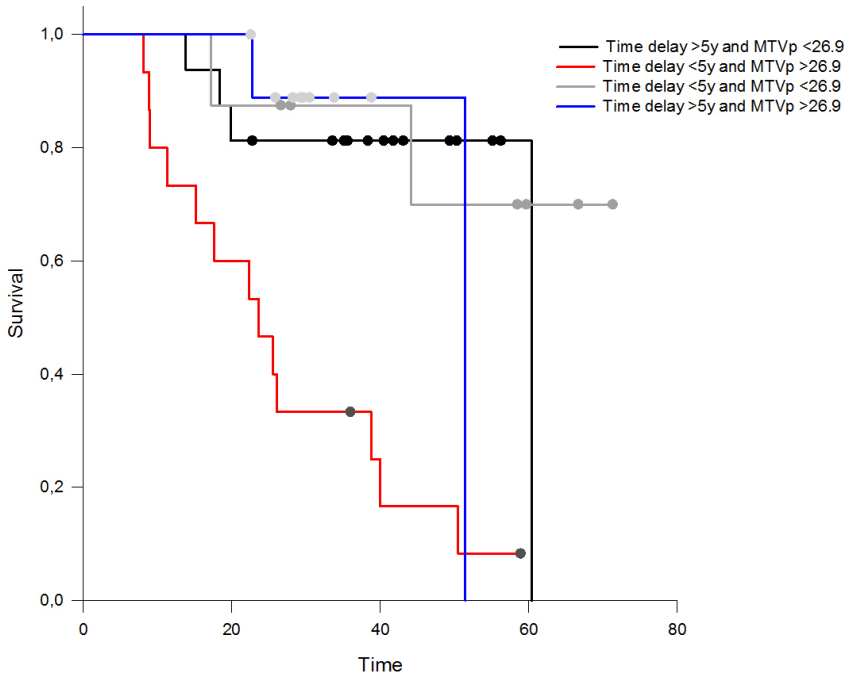


**Figure 6:** Overall survival stratified by Combined factor of $MTV_P$ (< median value or > median value) and time delay (<5 years or > 5 years).

**Cox regression analysis and overall survival**

Results of Cox regression analysis are shown in **Table 2**. Two multivariate analysis were performed in order to separate MTV and TLG prognostic value as they are closely tied to each other.

By univariate analysis, recurrence delay shorter than 5 years, MTV and TLG higher than median value were predictive of death. By multivariate analysis, only MTV and TLG remained predictive of death **(Table 2).**

| | Univariate analysis | | Multivariate analysis 1 | | Multivariate analysis 2 | |
|---|---|---|---|---|---|---|
| | HR [95% CI] | p | HR [95% CI] | p | HR [95% CI] | p |
| Initial T stage | 1.2 [0.7-227] | 0.48 | - | - | - | - |
| Initial N stage | 1.1 [0.7-1.7] | 0.64 | - | - | - | - |
| recurrence delay<5 years | 3.0 [1.2-7.783] | **0.024** | 2.46 [0.94-6.41] | 0.067 | 2.5 [0.96-6.41] | 0.061 |
| Triple negative phenotype | 2.5 [0.7-8.7] | 0.143 | - | - | - | - |
| SUVmax> median value | 1.5 [0.6-3.7] | 0.332 | - | - | - | - |
| MTVP> median value | 4.4 [1.6-12.5] | **0.005** | 3.86 [1.36-10.97] | **0.011** | - | - |
| TLGP> median value | 4.6 [1.6-12.8] | **0.004** | - | - | 4[1.42-11.39] | **0.009** |

**Table 2:** Results of Cox regression analysis and Overall Survival

# DISCUSSION

FDG PET/CT is known to play an important role in staging and restaging of breast cancer (6). Beyond lesion detection, FDG PET/CT gives the opportunity to quantify metabolic tumor burden, in patients with metastatic breast cancer. However, the interest of this quantification for prognostic stratification and development of therapeutic strategies remains to be clarified.

The results of our study demonstrate the ability of MTV to predict OS in patients experiencing a first metastatic recurrence of BC who underwent FDG-PET/CT before any systemic treatment. Moreover, evaluation of baseline MTV appears complementary to clinical parameters such as time delay between initial diagnosis and recurrence.

Several prior retrospective monocentric studies evaluated the prognostic value of FDG derived parameters and their correlation with clinical biomarkers (histologic subtype, phenotype or tumor grade) in the setting of breast cancer (14–17). Nevertheless none of theses studies evaluated MTV or TLG prognostic value. Later on, other studies then integrated MTV and TLG prognostic value evaluation. However these studies used methodological approaches and were used in clinical situations different from our study. First, Ulaner et al, in a population of 253 patients with MBC (including 26% of *de novo* metastatic disease) evaluated the prognostic value of FDG derived parameters (SUV, MTV and TLG) determined for each lesion site (bone, lung, liver and lymph nodes), but did not evaluated the prognostic value of global FDG derived parameters (12). Satoh et al and Son et al demonstrated the prognostic value of global FDG derived parameters only in de novo MBC patients (10,11). Finally, Taghipour et al showed that SUVmax, SUVpeak and TLG from baseline FDG PET/CT where significant prognostic factors in

case of recurrent BC but in a heterogenous population of 78 patients experiencing local (n=22), regional (n=12) or metastatic recurrence (n=44).

To our knowledge only Taghipour's study (18) have evaluated FDG derived parameters usefulness to predict OS in recurrent metastatic beast cancer and none have compared MTV's threshold efficiency (more specifically no study have evaluated a per-patient adapted threshold based on PERCIST definition of measurable target lesion).

OS study of recurrent metastatic breast cancer seemed more legitimate than mixed population of initial metastatic breast cancer and recurrences (10,12) as clinical presentation and prognosis for these different populations is known to be different (2,19–21). Excluding regional recurrence also seemed more legitimate as regional recurrence patients have significant better outcome than distant metastatic recurrence patients (22,23) ; regional recurrence allowing more specific and more effective treatments such as surgical removal or radiotherapy.

In our study, all MTV threshold methodologies were significantly related to OS, $MTV_P$ being the most significant. Metabolic tumor delineation is variable from one study to another as there are no recommendations for using a standardized method in solid tumors. Indeed, $MTV_P$ is the most significant; it is also adaptive threshold (as 41%) that are known to be more reproducible than fixed thresholds even if they induce a VOI drawing variability (24). Fixed thresholds (most used are SUV 2.5 and 3.0) are the simplest way to determine MTV, and may reduce inter-observer variability in calculating MTV value. However, fixed thresholds are strongly limited by the lack of reproducibility of SUV values between PET/CT examination and equipment's leading to a higher variability (7). Fixed thresholds are also limited for MTV calculation as zero set MTV

value is possible in patients having low FDG uptake tumors and has occurred for one patient in our study. A zero set MTV value is impossible for a relative per lesion adaptive threshold as its calculation is based on a percentage of a positive SUV (SUVmax of the tumor ROI). For the per patient adaptive threshold using PERCIST's definition of target lesion, a zero set MTV value is possible if there are no target lesions as defined by PERCIST which is quite unlikely. However, in this case if MTV value was measurable it would probably be very low whatever the threshold used.

Even if adaptive thresholds seem more efficient than fixed ones, they also have pitfalls. MTV may be underestimated in highly FDG avid tumors and heterogenous lesions for per-lesion adaptative thresholds. Such thresholds might also overestimate MTV in case of low tumor FDG uptake as 41% of the SUVmax may be lower than the surrounding background. The per-patient adaptive threshold has the advantage to avoiding heterogeneity issue described in per-lesion thresholds. Its limitation is intra and interobserver reproducibility to define the threshold based on liver FDG uptake measurements as no specific region in the liver is defined for placing the ROI. However liver FDG uptake being relatively uniform (25) , liver measurements should be similar and obtain comparable MTV calculations.

We defined the best MTV segmentation method as the one having the most significant statistical prognosis of OS, from which further statistical analysis were performed.

In our study, SUVmax was not significantly associated with survival, which is not coherent with previous works (11,12,18). However SUVmax relies on single voxel information, which do not represent the whole disease spread and aggressiveness. Thus,

other studies finding SUVmax significantly associated with survival admit MTV and TLG measurements are more valuable as they report the whole disease FDG avidity and have been confirmed for different solid tumors (26–28) and other studies even prove TLG superiority for OS prognosis (29,30) or clinical treatment response (8) over SUVmax.

Clinical and biologic parameters were also analysed. Time delay between initial diagnosis and recurrence is prognostic of OS, confirming recent studies (23,31,32). CA15-3 level did not show any significant prognostic value, neither did it show any correlation with $MTV_P$. CA 15-3 probably failed to be predictive of OS in our study probably due to our small population compared to studies showing CA15-3 statistical significance (33,34) .

We looked further at the value of FDG-PET/CT derived parameters combining them with clinical biomarkers. Population was stratified into four groups on the basis of $MTV_P$ median value and recurrence time delay (5 years). Results showed that patients with both high $MTV_P$ value and short recurrence time delay had significantly poorer survival compared to other patient groups. To our knowledge, there is no other study that has evaluated the prognostic value of combined clinical biomarkers and FDG-PET/CT derived parameters. Recurrence time delay is a significant prognostic parameter in our study, confirming results obtained on larger populations. This is probably due to the fact that a short recurrence time delay reflects more aggressive disease.

The strengths of this study include a long clinical follow up, a homogeneous population of patients experiencing first metastatic recurrence of BC, and uniform interpretation of PET/CT data using an adjustable software tool and an original MTV threshold definition.

Our median follow up of 34 months provides extensive data, knowing the median survival of metastatic breast cancer is less than 36 months. Our uniform population including only first recurrent metastatic breast cancer provides useful results in this particular population. Uniform interpretation of data and the use of an adjustable software maximized reliability of measurements, which allowed testing original and clinically relevant MTV threshold.

The major limitation of this study is its retrospective design that introduces multiples biases that are difficult to overcome. Small sample size was also a major limitation and probably explains absence of prognostic significance of well known biomarkers. Non-uniform treatments regimens as the medical oncologists were not blind to the FDG PET/CT imaging results was also a limitation and may have affected survival. Our software could not evaluate gradient method for MTV calculation which has shown promising results (35). A larger multicenter prospective study is needed to emphasize strengths and fulfil limitations in order for this preliminary data to come together.

# CONCLUSION

Our results suggest that in patients experiencing a first metastatic recurrence of breast cancer, a higher (supramedian) baseline Metabolic Tumor Volume defined by FDG PET/CT performed before treatment, predicts worse OS. This prognostic value of FDG PET/CT parameters appears complementary to clinical parameters such as time delay between initial diagnosis and recurrence.

Larger and prospective studies are needed to validate these preliminary results but in the near future, information on baseline metabolic tumor burden could be used to elaborate new therapeutic strategies.

## CONCLUSIONS

Les paramètres dérivés de la tomographie par émission de positons couplée à un scanner, utilisant le fluoro deoxyglucose ($^{18}F$) (TEP/TDM au 18FDG) tels que le volume tumoral métabolique (MTV), la glycolyse lésionnelle totale (TLG) ainsi que le délai de récidive métastatique, sont des facteurs pronostiques chez les patientes présentant une première récidive métastatique d'un carcinome mammaire. L'apparition de métastases dans un délai inférieur à 5 ans après le diagnostic initial est le seul paramètre pronostique indépendant en analyse univariée, mais la détermination du volume métabolique apparait complémentaire pour la stratification pronostique de ces patients.

Sur le plan méthodologique, parmi les différentes méthodes testées pour déterminer le MTV, celle utilisant un seuil adapté à chaque patiente, selon les critères PERCIST (PET Response Criteria In Solid Tumors) est le paramètre présentant la meilleure significativité pronostique et le moins de limites par rapport aux autres méthodes testées.

Ces résultats préliminaires permettent d'envisager l'élaboration d'études prospectives visant à tester de nouvelles stratégies thérapeutiques basées sur ces informations métaboliques.

Le Président du jury,

Pr. A. COCHET

Vu et permis d'imprimer

Dijon, le 31 MAI 2016

Le Doyen

Pr. F. HUET

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**TITRE DE LA THESE :**

VALEUR PRONOSTIQUE DES PARAMETRES DERIVES DE LA TEP/TDM AU 18FDG CHEZ DES PATIENTES PRESENTANT UNE PREMIERE RECIDIVE METASTATIQUE D'UN CARCINOME MAMMAIRE

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**RESUME :**

Objectifs : Evaluer la valeur pronostique de paramètres dérivés de la TEP/TDM au 18FDG tel que le volume tumoral métabolique (MTV) chez des patientes atteintes d'une première récidive métastatique d'un carcinome mammaire.

Matériels et Méthodes : 49 patientes atteintes d'une première récidive métastatique d'un carcinome mammaire ayant bénéficié d'une TEP/TDM au 18-FDG avant traitement, ont rétrospectivement été incluses entre décembre 2006 et aout 2013. Le MTV a été calculé selon 3 méthodes de sélection des voxels: un seuil fixe de Standard Uptake Value (SUV) supérieur à 2,5 ($MTV_{2,5}$), un seuil relatif de 41% du SUVmax ($MTV_{41\%}$) et un seuil adaptatif déterminé selon la définition d'une lésion mesurable défini par les critères PERCIST (PET Response Criteria In Solid Tumors) basé sur l'activité métabolique hépatique ($MTV_P$). Les courbes de survie ont été estimées grâce aux courbes de Kaplan Meier et le test du Logrank après dichotomisation par la médiane.

Résultats : La durée médiane de suivi était de 34 mois. La valeur médiane du MTV était respectivement 24ml, 34,5ml et 26,9ml pour les méthodes de calcul $MTV_{2,5}$, $MTV_{41\%}$ et $MTV_P$. Le $MTV_{2,5}$ (p=0,031), le $MTV_{41\%}$ (p=0 ,027) et le $MTV_P$ (p=0,002) ayant un impact significatif sur la survie globale. Un délai de récidive supérieur à 5 ans entre le diagnostic initial et la survenue de métastases était également un facteur pronostique de survie globale (p<0,001).

Conclusion : Pour les patientes présentant un cancer du sein métastatique avant traitement, le MTV et le délai de récidive sont des marqueurs pronostiques complémentaires. De plus la méthode du seuil adaptatif semble la plus appropriée pour la détermination du volume tumoral.

**MOTS-CLES :** CANCER DU SEIN METASTATIQUE, TEP/TDM 18 FDG, VOLUME TUMORAL METABOLIQUE, VALEUR PRONOSTIQUE