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Original Article

# Prognostic value of metabolic tumor volume and total lesion glycolysis in $^{18}$F-FDG PET/CT scans in locally advanced breast cancer staging☆

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ABSTRACT

*Objective:* To determine whether metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are able to predict recurrence risk in locally advanced breast cancer (LABC) patients.
*Material and methods:* Retrospective study of LABC patients who undertook neoadjuvant, local and adjuvant treatment and follow up. A $^{18}$F-FDG PET/CT study for initial staging was performed analysing in this study different metabolic parameters (MTV, TLG, $SUV_{max}$ and $SUV_{med}$) both in the primary tumor (T) as well as in axillary nodes (N) and whole-body (WB).
*Results:* Forty females were included between January 2010 and 2011; follow up until January 2015 was completed. The average follow-up was 46 months. Twenty percent presented recurrence: local disease ($n = 2$) and distant metastasis ($n = 6$); 3 patients died (38% of the patients which recurred and 7.5% from the total). $SUV_{max}$, MTV and TLG, in T, N and WB, were higher in those patients with recurrence. The MTV and TLG parameters in the tumor (T) were related to the recurrence rate ($p = .020$ and $p = .028$, respectively); whereas $SUV_{max}$ in the lymph nodes (N) was significantly related ($p = .008$) to the recurrence rate. The best cut-off points to predict recurrence where: MTV T $\geq$ 19.3 cm$^3$, TLG T $\geq$ 74.4 g and $SUV_{max}$ N $\geq$ 13.8, being 10–12 times more likely to recidivate when these thresholds where exceeded. Tumor grade was the only clinical-pathological variable which was related to recurrence probability ($p = .035$).
*Conclusions:* In this study of LABC patients the metabolic parameters which have a better relationship with recurrence rate are: MTV and TLG in the primary tumor, $SUV_{max}$ in the regional lymph node disease and whole-body PET data.



## Papel pronóstico del volumen metabólico tumoral y de la glucólisis tumoral total en los estudios $^{18}$F-FDG PET/TC de estadificación del cáncer localmente avanzado de mama

*Palabras clave:*
Volumen metabólico tumoral
Glucólisis tumoral total
PET/TC
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RESUMEN

*Objetivo:* Conocer si el volumen metabólico tumoral (VMT) y la glucólisis tumoral total (GTT) pueden predecir el riesgo de recurrencia en cáncer localmente avanzado de mama (CLAM).
*Material y métodos:* Estudio retrospectivo de pacientes con CLAM tratados con tratamiento neoadyuvante, local y adyuvante; en seguimiento. Se realizó una $^{18}$F-FDG PET/TC para estadificar la enfermedad, midiéndose diferentes parámetros metabólicos (VMT, GTT, $SUV_{máx}$ y $SUV_{med}$), tanto en el tumor primario (T) como en los ganglios metastásicos (N) y en el cuerpo entero (CE).
*Resultados:* Se incluyeron 40 mujeres entre enero de 2010-2011; seguimiento hasta enero de 2015. Con una mediana de seguimiento de 46 meses el 20% tuvieron recidiva, local (n = 2) o a distancia (n = 6); fallecieron 3 (38% de aquellas con recidiva y 7,5% del total). EL $SUV_{máx}$, VMT y GTT, tanto en T, como N y

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CE, fue mayor en aquellas que presentaron recidiva. En el T tanto el VMT como la GTT se relacionaron con la recidiva de la enfermedad (p = 0,020 y p = 0,028, respectivamente), mientras que en la N fue el $SUV_{máx}$ (p = 0,008). Los puntos de corte óptimos para predecir recurrencia fueron: VMT T ≥ 19,3 $cm^3$, GTT T ≥ 74,4 g y $SUV_{máx}$ N ≥ 13,8, existiendo 10-12 veces más probabilidad de experimentar progresión tumoral cuando superaban estos umbrales. El grado tumoral fue la única variable clínico-patológica asociada con la recidiva (p = 0,035).

*Conclusiones:* En este estudio de CLAM los parámetros metabólicos que más se asocian con la tasa de recidiva son el VMT y la GTT en el tumor primario, el $SUV_{máx}$ en la enfermedad ganglionar regional y los 3 índices PET en el cuerpo entero. Estos parámetros podrían utilizarse en la práctica asistencial para identificar a las pacientes con mayor riesgo.



## Introduction

Breast cancer is an important health care problem due to its high incidence and mortality. Prognostic factors are essential in order to predict the risk of disease recurrence and to provide increasingly more individualized treatment to patients. Up to now the most important prognostic factors have been lymph node status at diagnosis, tumor grade and the status of hormone receptors and human epidermal growth factor receptor 2 (HER2).[1,2]

Locally advanced breast cancer (LABC) has a poor prognosis and requires multidisciplinary treatment including chemotherapy based on predictive factors, local treatment (surgery and radiotherapy) and adjuvant chemotherapy.[3] Despite the advances in this scenario approximately 15% of patients present local and 30% distant recurrence.[4] At present, histological response following neoadjuvant treatment is the only factor clearly associated with the probability of recurrence.[5,6] Nonetheless, additional, more sensitive methods are needed to predict the prognosis after neoadjuvant treatments in these patients.

PET/CT with $^{18}$F-FDG has demonstrated to be a key tool in the staging of breast cancer at diagnosis and to evaluate response to treatment and suspicion of recurrence using the standardized uptake value (SUV) and its relationship with different predictive and prognostic factors.[7,8]

The SUV is the concentration of radioactivity present in normalized tissue based on the dose of radiotracer administered and the weight of the patient. The $SUV_{max}$ corresponds to the point with the highest SUV quantified within a region of interest (ROI) which only identifies the most active part of the tumor and may not represent the global tumor status. An elevated $SUV_{max}$ in the primary tumor represents the grade of radiotracer uptake of the tumor and provides information related to disease prognosis and is a good marker to predit the probability of recurrence.[9]

The role of other parameters that can be measured by PET/CT have been evaluated and these include metabolic tumor volume (MTV) and total lesion glycolysis (TLG) which combine tumor volume and the metabolic activity of the whole tumor. MTV is the volume of tumoral tissue with a determined activity of $^{18}$F-FDG uptake, representing the extension of FDG uptake by the tumor tissues beyond the intensity of uptake. TLG is obtained from the product between the MTV and the median SUV ($SUV_{med}$) and indicates the relationship between the grade of radiotracer uptake and tumor volume.[10,11] In several solid tumors the MTV and TLG seem to be metabolic parameters associated with the total tumor load and the grade of aggressiveness, and therefore, provide prognostic information of the disease.[12–15]

The aim of the present study was to determine whether the metabolic parameters, MTV and TLG, are able to predict the risk of tumor recurrence in the initial staging of disease in patients with LABC in not only the primary tumor but also in locoregional lymph node disease with the sum of the two being representative of the global disease of the whole body. We also compared these parameters with classical indexes of PET ($SUV_{max}$ and $SUV_{med}$) as well as other predictive and prognostic factors (age, cellular proliferation index, histological grade, hormone receptor expression, HER2 status and histological response following neoadjuvant treatment).

## Material and methods

### *Patients*

We retrospectively studied the cases histologically diagnosed over a one-year period with invasive breast cancer stage II and III (cT2-4 cN0-3 M0) according to the TNM classification of the 7th edition of the AJCC.[16] On inclusion these patients were also receiving neoadjuvant chemotherapy including 4–6 cycles of docetaxel every 3 weeks combined with trastuzumab in HER2 positive cases and carboplatin/adriamycin in HER2 negative patients following the criteria of a multidisciplinary team. Patients with diabetes mellitus, renal insufficiency, allergy to iodine contrast, males, metastatic disease known at the time of diagnosis and other concomitant oncological diseases were excluded from the study. Oncological surgery was performed on completion of the neoadjuvant treatment. Thus, patients received treatment with adjuvant therapy according to the standardized procedure of our center, consisting of standard endocrine therapy of hormone-sensitive tumors, anthracyclines in triple negative cases (if not previously received) and trastazumab in HER2 positive tumors. All the patients also received complementary radiotherapy, except for those with a T2N0 stage who underwent mastectomy.

### *Image acquisition*

All the studies were made in the same PET/CT equipment (*Biograph 6 TruePoint; Siemens*), after 6 h of fasting and with capillary glycemia less than 200 mg/dl prior to the administration of 5 MBq $^{18}$F-FDG per kg of body weight. After a 45–60-min rest period to achieve adequate distribution of $^{18}$F-FDG by the organism, image acquisition was begun. A thoracic inspiratory CT was first made after the administration of 130 ml of intravenous iodine contrast followed by a whole body CT from the axial orbits to the proximal third of the femurs. The parameters of the protocol were as follows: 120 kVp, 95 mAs, 0.5 s rotation of the tube, with slice thickness of 5 mm. A caudocranial PET was made with a time of 3 min per bed and overlapping of 20%. The corrected post-injection emission image was reconstructed using the *TrueX* algorithm with 3 iterations and 21 subsets using the *Gaussian* filter. The data obtained from the CT images were used for attenuation correction of the PET for fusion of the images.

### *Image analysis*

Two nuclear physicians and one radiologist interpreted the PET/CT images using the same work station for the analysis (Syngo™ software system; Siemens Medical Imaging). To