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Usefulness of CA125 and their kinetic parameters and positron emission tomography/computed tomography (PET/CT) with fluorodeoxyglucose ([^{18}F] FDG) in the detection of recurrent ovarian cancer levels

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ABSTRACT

Background and objective: To assess the usefulness of cancer antigen 125 (CA125) serum levels and kinetic values, velocity (CA125vel) and doubling time (CA125dt), as well as fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography/computed tomography (PET/CT), in the detection of ovarian cancer recurrence. To assess the optimal cut-off for CA125, CA125vel and CA125dt to detect relapse with [^{18}F]FDG-PET/CT.

Material and methods: A retrospective analysis was performed of 59 [^{18}F]FDG-PET/CT (48 patients) for suspected recurrence of ovarian cancer. Receiver operating characteristic (ROC) curves were plotted and area-under-the curve (AUC) statistics were computed for CA125, CA125vel and CA125dt. The results obtained in the group with normal and high (>35 U/ml) CA125 levels were compared.

Results: Forty-four cases of recurrence were diagnosed (7 had CA125 ≤35 U/ml), whereas 15 showed no disease. All of them were correctly catalogued by PET/CT. In ROC analysis, the discriminatory power of CA125 was relatively high (AUC 0.835) and the optimal cut-off point to reflect active disease was 23.9 U/ml. The ROC analyses for the CA125vel and CA125dt showed an AUC of 0.849 and 0.728, respectively, with an optimal cut-off point of 1.96 U/ml/month and 0.76 months, respectively. In patients with normal CA125 and recurrence of ovarian cancer, the CA125vel was significantly higher than in patients without recurrence ($p = 0.029$).

Conclusion: [^{18}F]FDG-PET/CT is more accurate than CA125 parameters in the detection of ovarian cancer recurrence. CA125 serum levels are essential; nevertheless, CA125 kinetic values must be considered to detect relapse. Particularly in patients with CA125 within normal values, in which a higher CA125vel is indicative of recurrence.

Utilidad del CA125 y sus parámetros cinéticos y de la tomografía por emisión de positrones/tomografía computarizada (PET/TC) con fluorodesoxiglucosa ([^{18}F]FDG) en la detección de la recidiva del cáncer de ovario

Palabras clave:
[^{18}F]FDG-PET/TC
CA125
Velocidad

RESUMEN

Fundamento y objetivo: Valorar en la recidiva del cáncer de ovario la utilidad del CA125 y sus parámetros cinéticos, velocidad (CA125vel) y tiempo de duplicación (CA125td), y de la tomografía por emisión de positrones/tomografía computarizada (PET/TC) con fluorodesoxiglucosa ([^{18}F]FDG). Determinar el valour óptimo del CA125, CA125vel y CA125td para detectar recidiva con [^{18}F]FDG-PET/TC.

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Tiempo de duplicación
Cáncer de ovario
Recidiva

Material y métodos: Análisis retrospectivo de 59 estudios [^{18}F]FDG-PET/TC en 48 pacientes con sospecha de recidiva de cáncer de ovario platino-sensible. Realizamos un análisis ROC (Receiver operating characteristic) y el área bajo la curva (AUC) para el CA125, CA125vel, CA125td. Comparamos los resultados entre los grupos con CA125 dentro de la normalidad y CA125 patológico (>35 U/ml).
Resultados: Fueron diagnosticados de recidiva 44 casos (7 con CA125 ≤35 U/ml), mientras que 15 no mostraron recurrencia. Todos ellos fueron correctamente catalogados mediante la PET/TC. La curva ROC demostró una capacidad discriminatoria del CA125 relativamente alta (AUC 0.835), con un valour óptimo de referencia de 23.9 U/ml. El análisis ROC para la CA125vel y el CA125td mostró un AUC de 0.849 y 0.728, con un valour de referencia de 1.96 U/ml/mes y 0.76 meses, respectivamente. En las pacientes con CA125 en límites normales la CA125vel fue significativamente mayor en las pacientes con recidiva que en aquellas sin enfermedad (p = 0.029).
Conclusión: La [^{18}F]FDG-PET/TC es más exacta que los parámetros de CA125 en la detección de recurrencia de cáncer de ovario. Los niveles séricos de CA125 resultan esenciales, no obstante, los parámetros cinéticos deben ser tenidos en cuenta en la detección de la recidiva.

Introduction

Ovarian cancer is the main cause of death from gynaecologic malignancies. This poor survival rate is attributed to frequent persistence or recurrence of disease, with an overall recurrence rate of approximately 70% in the first 3 years.[1] However, recurrence varies from 10% for stage I to 85% for stage IV with suboptimal debulking.[2] After completion of adjuvant chemotherapy, a systematic follow up is needed. The epithelial marker cancer antigen 125 (CA125) has routinely been used for monitoring ovarian cancer patients who have reached a clinical complete remission on first-line debulking and chemotherapy. Regular measurements during follow up can detect recurrence of cancer months before symptoms or signs occur.[3,4] Nevertheless, there is no evidence of a survival benefit with early treatment of relapse based on a raised CA125 concentration alone.[5] Therefore, it is crucial to discriminate between relapse of ovarian cancer and benign increases in patients with ovarian cancer and elevated CA125 levels.

The rationale for our study is based on the association between a rise in the CA125 marker during follow up of patients in complete remission and recurrence, even with CA125 serum levels lower than the normal range.[6] Fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography/computed tomography (PET/CT) has been employed for years in cases of elevation of tumour markers with inconclusive imaging techniques, but it could detect ovarian recurrences, even with those titles of CA125.[7–9] Thus, the aim of our work was to assess CA125 and its kinetic values, expressed as CA125 velocity (CA125vel) and CA125 doubling time (CA125dt), as well as [^{18}F]FDG-PET/CT in the detection of ovarian cancer relapse and to evaluate the optimal values for CA125, CA125vel and CA125dt to select patients on whom to perform [^{18}F]FDG-PET/CT for ovarian cancer recurrence.

Material and methods

This study was performed with institutional review board approval, and informed written consent was obtained from each patient. We retrospectively enrolled consecutive patients with suspicion of epithelial ovarian cancer recurrence referred to our centre during the period of 2007–2015 for [^{18}F]FDG-PET/CT. All patients had been treated for ovarian cancer, with complete remission after treatment for at least 6 months, i.e. no evidence of disease from tests, physical exams or conventional imaging techniques. The suspicion of recurrence was based on elevated CA125 serum levels, alterations observed with conventional imaging techniques (computed tomography [CT] or magnetic resonance imaging [MRI]) and/or by the appearance of symptoms. Inclusion criteria were: (1) complete remission for more than 6 months after treatment, (2) high CA125 serum levels at diagnosis and (3) measurement of CA125 serum levels on two consecutive occasions, to calculate the kinetic values. Patients referred twice to our centre who met the inclusion criteria were included in the analysis in both cases. Patients referred to assess response to treatment or progression suspect were excluded.

For CA125 serum levels, the reference normal limit considered was 35 U/ml. The variation in CA125 levels was evaluated by using at least two measurements. CA125 velocity (CA125vel) was calculated according to the following formula: *(CA125a–CA125b)/time*. *CA125a* is the CA125 serum level closest to the PET/CT scan, with a maximum of 1 month between the scan and the measurement, *CA125b* is the measurement immediately preceding CA125a and *time* is the time in months between the two measurements. CA125 doubling time (CA125dt) was calculated by natural log of 2 (0.693) divided by the slope of the relationship between the log of CA125 and the time of CA125 measurement for each patient.

Imaging protocol and analysis

A hybrid PET-CT scanner was used to obtain images 60 min after administration of 370 MBq of [^{18}F]FDG. Images were obtained from the orbitomeatal line to the proximal third of the lower limbs. First, low-dose CT images were acquired (120 kV, 80 mA), followed by PET in three-dimensional (3D) mode with an acquisition time of 3 min per bed. PET/CT images were reviewed by two experienced nuclear medicine physicians who were unaware of the clinical data, and the diagnosis was reached by consensus. The diagnosis of recurrence was decided by the visual analysis of fusion images, independently of the FDG activity measured by the maximum standard uptake value (SUVmax). [^{18}F]FDG-PET/CT were classified as normal if there was no uptake outside of expected physiological locations. [^{18}F]FDG uptake concordant with an area of inflammation on the CT image was considered as negative. All the areas with an increased tracer uptake above the background in sites consistent with disease localizations were considered positive and therefore compatible with relapse. All ambiguous cases were defined by consensus.

The confirmation of the disease was made by surgery or by clinical–radiological follow up, longer than 6 months and with at least 2 imaging techniques.

Data analysis

Statistical analysis of data was carried out by using IBM SPSS statistical software v. 19.0®. The descriptive statistical parame-

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