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Editorial

Replay to Editorial Comment on article "Usefulness of PET scans in diagnosing recurrent prostate cancer. Prostate with PSA level <5ng/ml"

Respuesta al Comentario editorial al trabajo "Valor de la PET en la recurrencia de cáncer de próstata con PSA < 5 ng/ml"

The September issue of *Actas Urológicas* published an *Editorial Comment*[1] on the original article *"Usefulness of PET scans in diagnosing recurrent prostate cancer with PSA level > 5 ng/mL"*[2].

The editorial, after emphasizing two limitations already discussed in our manuscript and detailing some of the strengths of our study (such as the sensitivity and specificity results), pointed out other limitations which, in our view, require some clarifications.

1. The last edition of the Clinical Guidelines on Prostate Cancer of the European Association of Urology (EAU) states, in the section of diagnosis of recurrent prostate cancer, that positron emission tomography (PET) may be a useful tool, but cannot be used in clinical practice. Clinical studies are therefore required to establish its true role. This has been our aim since our center purchased the PET equipment in 1995 (the first to be used in Spain, at the same time as one in Madrid)[3] and since we had choline available for the first time in 2004[4].
2. As regards the lack of pathological confirmation and a control group (with no evidence of disease), this was discussed in the article and may easily be explained. Since this was the first Spanish center using ^{11}C-labeled methylated choline, such information was not available for many patients referred by other centers. In patients from our center in whom PET showed a lesion amenable to biopsy, this was performed with positive results, although they were not subsequently included in the analysis. Results will be published when a larger series is available.
   In a non-standardized review of the literature on PET and prostate cancer published in indexed journals of both specialties, clinical and metabolic criteria were accepted as valid in the absence of pathological confirmation[5-13]. All series reviewed had no control group, as occurred with similar studies conducted using other imaging procedures such as computed tomography (CT) or magnetic resonance imaging (MRI). In this study, the normal reference is provided by the clinical bases themselves of the diagnostic indication and the physiological bases of phospholipid metabolism of choline.
3. As to the procedure used, the editorial comment[1] states that hybrid studies enhance the sensitivity and specificity of the investigation because dual or hybrid procedures combine a metabolic (PET) and a morphological (CT) technique. While the combination of both procedures has obvious advantages[14-17], it is also true that when PET started to be used alone in oncology, a decade before the advent of multimodal equipments, it was already shown to have a great diagnostic value, often superior to conventional imaging procedures, in a wide variety of malignant tumors. The Spanish Ministry of Health itself, through the Agency for Evaluation of Healthcare Technology of the Carlos III Institute, published in November 2005 extraordinarily favorable results on the value of PET for tumor diagnosis, based on an assessment of use supervised by the agency itself. Results were obtained before the advent of the PET-CT equipments[18,19]. It should also be reminded that not only ^{11}C-choline, but other radiopharmaceuticals such as 18 fluoro-2-deoxyglucose (18FDG), ^{11}C-methionine, ^{18}F-DOPA,^{11}C-acetate, ^{18}F-, ^{13}NH3, ^{82}Rb, H_2 ^{15}O, etc. had been used in medicine for many years before the advent of the PET-CT multimodal equipments. Although the diagnostic yield of PET-CT in recurrent prostate cancer has special interest because of the better topographic location of the lesion, this does not mean that the results of PET in the first series of patients, before multimodal equipments were available, should be invalidated.

In addition, it was considered more important to start the study at the time the nuclear medicine team was able to label methylated choline with ^{11}C[4], rather than when a combined PET-CT equipment became available at the center. This is the reason why 24 patients were studied with PET and another 68 patients with PET-CT, because of the novelty of the series and the lack of information in the literature.

4. Another limitation discussed in the editorial was the high median prostate-specific antigen (PAS) levels in patients with biochemical recurrence (3.88 ng/mL in the overall series). This value is indeed high for a group of patients undergoing prior radical treatment, because it is influenced by atypical outliers. Although these patients should be considered as in clinical progression, they were enrolled because all other imaging diagnostic procedures had been negative in them. For PET evaluation in biochemical recurrence in order to guide a salvage therapy, a PSA cut-off point of 4.3 ng/mL was set because it provided better sensitivity and specificity values for a diagnostic test of these characteristics. Subsequently, and in order to increase the clinical value of the test, a PSA cut-off point of 1 ng/mL was established. This is accepted in the literature as the cut-off value for rescue after radical prostatectomy and is lower as compared to new definitions (Phoenix definition[14], PSA nadir + 2 ng/mL) of recurrence following external radiotherapy[15]. Reading of this cut-off point, while having its limitations, is highly significant because the false negative rate, i.e. the chance of "failing" with a PSA level of 1 ng/mL is 24%. These values are better than reported to date in the literature[9,10,16].
5. As regards the yield of PET radiopharmaceuticals in diagnosis of prostate cancer, limitations of ^{18}FDG have already been discussed in the literature[17]. Our group has shown a very clear position in this matter[3,20,21]. Just because of this limitation and the limitations of other imaging procedures in the study of early recurrence of prostate cancer, other radiopharmaceuticals such as acetate[11], methionine[13], testosterone[22], and anti ^{18}F-FACBC (anti1-amino3-12-F-fluorocyclobutane-carboxylic acid)[23] have been developed, in addition to choline itself[2]. Two types of PET radiotracers are available in nuclear medicine, those based in a metabolic pathway (FDG, choline, methionine, etc.) and those which bind to a specific receptor (cG250, ^{18}F-FDHT (testosterone). The latter, such as membrane PSA (mPSA)), are more specific for the prostate, but are not available for clinical use yet.
6. The superiority of ^{11}C-choline over ^{18}FDG for investigation of recurrent prostate cancer was initially shown by Picchio[12] and subsequently validated by a great number of authors[2,7]. In the future, labeling of choline with ^{18}F, already available at some foreign centers, will allow for wider use of this radiopharmaceutical, although we agree with the editorial in that it is foreseeable that other more specific agents under development may have a predominant role in the future[24,25].

As stated in the editorial, imaging diagnosis of early recurrence of prostate cancer is a problem as yet unresolved. It should be noted, however, that studies of these characteristics combining imaging techniques such as PET with molecular profiles[26] and PSA kinetics data (trigger PSA, PSAdt, and total PSA)[27] have improved the diagnostic yield of these tests. We agree with the comments that their widespread use cannot be cost-effective. However, the need for performing studies of this type using a scientific approach and with the mind open to research may allow for a progress which, according to very conclusive early considerations, cannot be expected in the near future.

Finally, it should be noted that editorial comments such as the one by Dr. Rubio Briones improve the scientific level of any article, which is enriched by its discussion and makes the final result much more illustrative. Unfortunately, such comment could not be answered by the authors of the article in the same issue of the journal due to changes in the publisher.

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