Opinion and debate

Diagnostic imaging work-up for disease relapse after radical treatment for prostate cancer: How to differentiate local from systemic disease? The urologist point of view

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A B S T R A C T

About 40% of all patients undergoing radical treatment for localized prostate cancer (PCa) develop biochemical relapse (BCR) during lifetime but only 10–20% of them will show clinically detectable recurrences. Prostatic bed, pelvic or retroperitoneal lymph nodes (LN) and bones (especially the spine) are the sites where we must focus our attention in the early phase of PSA relapse. Time to PSA relapse, PSA kinetics, pathological Gleason score and pathological stage are the main factors related to the likelihood of local vs. distant relapse. Before an extensive diagnostic work-up in patients with BCR, is mandatory to understand if there is a therapeutic consequence or not for the patient. Current imaging techniques have some potential but many limits are yet encountered in the diagnosis of disease relapse. Transrectal ultrasound (TRUS) and Multiparametric Magnetic Resonance Imaging (MRI) have low accuracy in the detection of the recurrence. Today, Choline PET/CT may visualize the site of recurrence earlier, with better accuracy than conventional imaging, in a single step and even in the presence of low PSA level. In recent years, the new radiotracer 18F-FACBC has been proposed as a possible alternative radiopharmaceutical to detect PCa relapse. From a clinical point of view, first clinical studies showed very promising and reproducible results with an improvement in sensitivity is about 20–25% with respect to Choline PET/CT, rendering the FACBC the possible radiotracer of the future for PCa. In conclusion, many improvements have been recently achieved in imaging techniques for PCa restaging, essentially in Nuclear Medicine and MRI, but negative results remain in many cases. Low sensitivity, costs, availability of technologies and confirmation of the results remain the major limitations in most cases.

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Estudio de diagnóstico por imagen de recidiva tras el tratamiento radical de cáncer de próstata: ¿cómo distinguir entre la enfermedad local y la enfermedad a distancia? Punto de vista del urólogo

R E S U M E N

Alrededor del 40% de los pacientes que se someten a tratamiento radical de cáncer localizado de próstata (CaP) desarrollan una recidiva bioquímica (RB) a lo largo de su vida, aunque únicamente el 10–20% de ellos manifestará recidivas clínicamente detectables. El lecho prostático, los ganglios pélvicos o retroperitoneales y los huesos (principalmente la columna) son los emplazamientos en los que debemos centrar nuestra atención durante la fase inicial de la recidiva del cáncer de próstata. El tiempo transcurrido hasta la recidiva del PSA, la cinética del PSA, la puntuación patológica de Gleason y el estudio patológico son los principales factores relacionados con la probabilidad de una recidiva local frente a una recidiva a distancia. Antes de realizar un estudio diagnóstico amplio en pacientes con RB, es imperativo comprender si existe o no una consecuencia terapéutica para el paciente. Las técnicas actuales de imagen tienen algún potencial, aunque todavía siguen encontrando muchos límites en el diagnóstico de la recidiva de la enfermedad. La ecografía transrectal (TRUS) y la resonancia magnética multiparamétrica son poco precisas para la detección de la recidiva. Hoy en día, el PET/TAC de Colina puede visualizar el emplazamiento de la recurrencia de forma más temprana, con una mejor precisión que la imagen convencional, en un único paso e incluso en presencia de un bajo nivel de PSA. En los últimos años, se ha propuesto el nuevo radiotrazador 18F-FACBC como una posible alternativa radiofarmacéutica para la detección de la recidiva del CaP. Desde un punto de vista clínico, los primeros estudios clínicos mostraron unos resultados muy prometedores y reproducibles, con una mejora de la sensibilidad de alrededor de un 20–25% respecto al PET/TAC de Colina, lo que convierte al FACBC en el posible radiotrazador del futuro para el CaP. En conclusión, se han logrado recientemente muchas mejoras en cuanto a técnicas de imagen para la re-estadificación del CaP, principalmente en Medicina Nuclear y RM, aunque persisten los resultados negativos en muchos casos. La baja sensibilidad, los costes, la disponibilidad de las tecnologías y la confirmación de los resultados siguen siendo las principales limitaciones en muchos casos.

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About 40% of all patients undergoing radical treatment for localized prostate cancer (PCa) develop biochemical relapse (BCR) during lifetime but only 10–20% of them will show clinically detectable recurrences. Virtually, the disease progression is always preceded by a BCR. However, a precise and definite cut-off for PSA relapse does not exist. After surgery and radiation therapy there is a wide consensus regarding the definition of BCR, but for other primary treatments such as HIFU, brachitherapy and cryo therapy, the consensus has not been yet reached.1 Certainly, a consistent and clearly increasing PSA after radical prostatectomy (e.g. 0.03, 0.08, 0.10, 0.12, 0.19) may already be considered a BCR even with PSA lower than 0.2 ng/ml.

Although the natural history of recurrent prostate cancer is often one of slowly progressing disease, in some men it can be
rapid and may need a salvage treatment. Prostatic bed, pelvic or retroperitoneal lymph nodes (LN) and bones (especially the spine) are the sites where we must focus our attention in the early phase of PSA relapse. The risk of disease relapse in a particular location is related to the individual conditions.

Regarding local disease relapse after surgery, about 50% of pathologically high-risk patients (those with wide positive margins and/or pT3) and about 10% of those at low risk (negative margins and pT2) will develop a local relapse within 15 years from surgery. The absence of a complete prostatic capsule at the apex and the need to preserve the pelvic structures (essentially urethral sphincter and neurovascular bundles) are the principal reasons of this high incidence of local relapse. For LN relapse, about 30–50% of preoperative high-risk patients and 2–10% at low-intermediate risk present micro or macro-metastatic LN involvement at the time of radical treatment. The lymphatic spread of PCa cells generally follows a repetitive centripetal pattern that starts in the prostatic area, proceeds in the pelvis (by the obturator, internal iliac, external iliac, pararectal, and presacral nodes), continues to the external iliac nodes and finally expand to the retroperitoneum. In intermediate or high-risk patients, in whom pelvic lymph-node dissection (PLND) is considered mandatory, not doing a lymphadenectomy represents an important risk factor for a nodal relapse. Furthermore, presacral, pararectal, paraaortic and paracaval LNs (that are normally spared from the PLND) may be involved as a primary landing site in about 10–20% of cases, thus explaining many LN relapse in these atypical locations. Moreover, the “very high risk” patients may have a micro-metastatic involvement of the retroperitoneal or supra-diaphragmatic LN that account for many disease relapse after primary treatment. Last but not least, micrometastases in the bones are already present in about 30% of cases at the time of the primary treatment. There are two main reasons for this high incidence of bone metastases. Firstly, it has been demonstrated the existence of backward pathway through the veins from the prostate to the spine (the so called Batson hypothesis); in fact, well conducted autopic studies have demonstrated a gradual decrease in spine involvement from the lumbar to the cervical part, which in turn would fit well with a subsequent upward spread along spinal veins. Secondly, PCa cells have shown a characteristic, biologically determined organ tropism to the bone microenvironment (the “fertile soil” hypothesis) that probably represent the most important cause of bone metastases.

So, how to discriminate between local relapse and bone or nodal metastases and who are the patients that we should investigate? Time to PSA relapse, PSA kinetics (e.g. PSA velocity and PSA doubling time), pathological Gleason score and pathological stage are the main factors related to the likelihood of local vs. distant relapse. In general, PSA detectable after 1 year, PSA velocity >0.75 ng/ml/year, PSA doubling time >6 months, negative LNs, no seminal vesicle invasion, positive margins and Gleason score >7 are all factors related to higher risk of local relapse, while PSA detectable before 1 year, PSA velocity >0.75 ng/ml/year, PSA doubling time <6 months, positive LNs, seminal vesicle invasion and Gleason score >6, are related to systemic relapse. Based on these aspects, many risk tables and nomograms have been generated in order to address the clinicians in the diagnosis of the site of recurrence. However, in the clinical practice, it is not so easy to identify the origin of PSA. Currently, most of the patients receive androgen deprivation therapy (ADT) soon after PSA relapse and without any effort to localize the origin of the relapse. However, it is important to note that, before an extensive (and expensive!) diagnostic work-up in patients with BCR, is mandatory to understand if there is a therapeutic consequence or not for the patient. Moreover, great distinction should be made between salvage therapies with “palliative” intent (such as androgen deprivation therapy, bisphosphonates) and salvage therapies with “curative” intent (such as radiotherapy, bone irradiation, tomotherapy, HIFU, pelvic or retroperitoneal LN dissection, salvage prostatectomy); in fact, the complications and the side effects of these two approaches are totally different.

Current imaging techniques have some potential but many limits are yet encountered in the diagnosis of disease relapse. Regarding local relapse after surgery, transrectal ultrasound (TRUS) has low accuracy in the detection of the recurrence and indication for a TRUS-guided biopsy is still controversial. Generally, a negative biopsy does not exclude local relapse at all! In the absence of evident lesion, the probability of positive biopsy is extremely low and is fairly proportioned to PSA level and pathological stage. Nowadays multi-parametric Magnetic Resonance Imaging (MRI) may be better than TRUS-biopsy in detecting a local relapse: endorectal MRI with dynamic contrast enhancement (DCE) and Spectroscopy has been demonstrated slightly higher accuracy than TRUS-biopsy for very small lesions (about 5 mm) and very low PSA (0.2–2 ng/mL). So, multiparametric MRI may have a role in the early phase of PSA relapse (when there is a very low PSA and when TRUS and TRUS-biopsy are normally negative) but it is not cost-effective when there is a higher PSA (>2 ng/mL); in the latter case, larger lesions or palpable nodules are more frequently detected by less sophisticated techniques.

Regarding local relapse after “non surgical therapies”, TRUS-biopsy is indicated only when a local salvage treatment is planned. It is recommended to wait several months before having a biopsy (18–24 months after radiotherapy and 3 months after cryotherapy/HIFU) in order to find a viable cancer. Even in this scenario, multiparametric MRI improves the assessment of patients with a suspected relapse within the prostate. In general, identifying a recurrent disease using multiparametric MRI (especially with DCE) is easier, paradoxically, than the initial detection of cancer: this is due to the very different patterns between recurrence and fibrosis (post-surgical, post-radiation or post-coagulation necrosis). So, with the prostate left in situ, by using TRUS-guided biopsy or multiparametric MRI, we can assess the presence of a local relapse without difficulty and with good accuracy. Rather, the problem is concerning the histological interpretations and not the imaging technique used to detect the cancer.

It is essential to note that, even with a positive biopsy demonstrating a local relapse, we cannot rule out the concomitant presence of distant metastases. Before any salvage treatment for presumed or confirmed local relapse, an extensive imaging work up should be started to exclude a concomitant systemic relapse in order to choose a individualized treatment. Bone scan and abdominal CT or MRI are not useful in the detection of disease relapse unless the PSA is higher than 20 ng/mL or the PSA velocity is more than 20 ng/mL/year. In fact, few million of PCa cells are enough for 0.1 ng/mL of PSA in the serum but the power of resolution of these imaging techniques is not adequate for such amount of disease. When these conventional imaging detects a disease relapse, PSA and PSA kinetics are too high and patients are outside the window of curability in every case. So, conventional imaging is not suggested in the initial phase of BCR.

Today, PET/CT represent a very important tool in the follow-up of many tumors that allow to visualize the site of recurrence earlier, with better accuracy than conventional imaging and in a single step. Unfortunately, PCa cells have been demonstrated very limited glucose consumption, fluorodeoxyglucose has been abandoned for PCa detection. Direct comparison between the FDG and Choline in prostate cancer relapse has shown a clear superiority of the latter radiotracer, especially after surgery. Choline is the most studied and promising radiotracer in PCa. The only limitation of Carbonium-Choline is the limited half-life of Carbonium (about 20 min), limiting its use to centers with an on-site cyclotron.
The principal advantage of Choline PET/CT is its ability to visualize disease relapse even in the presence of low PSA level. In most of the studies, the detection rate of Choline PET/CT is about 30–40% for disease relapse after radical treatment, even in presence of low (<5 ng/ml) PSA.15

With respect to bone scan, it has been recently demonstrated that PET/CT can find bone metastases in about 15% of patients with a negative scintigraphy16 and that PET/CT is able to show additional lesions in at least 50% of patients with positive bone scan: thus Choline PET/CT allows to change the therapeutic approach in many cases. In the detection of pelvic or retroperitoneal LN, Choline PET/CT has shown better accuracy than cross sectional imaging; indeed both contrast enhanced CT or multi-parametric MRI can only assess a generic enlargement of the nodal chain and their accuracy is not sufficient to allow an aggressive approach to the LNs; on the contrary Choline PET/CT has also opened new therapeutic frontiers that were not imaginable in the past, such as salvage lymphadenectomy or LN irradiation with tomotherapy.17 Unlike other malignancy,18 the therapeutic role of lymph node dissection is still uncertain in PCa. Some recent series of salvage pelvic or retroperitoneal LN dissection have shown good initial results: in these series, the detection rate of Choline PET/CT may reach the 70–90% in the “per patient” analysis. However, to show the real accuracy of PET/CT, a complete nodal dissection in all of the patients with BCR (with or without positive PET/CT scan), would be necessary but this is impracticable for obvious reasons at this moment; so the real accuracy of PET/CT in the assessment of retroperitoneal or supra-diaphragmatic LN relapse is certainly lower.

The main limit of Choline PET/CT is the low resolution of scanners that is about 5 mm: when Choline PET/CT finds a suspected lesion, nearly twice as many metastases are present.17 How can the performance of Choline-PET/CT be improved in clinical practice? Important progress has emerged about the factors influencing its detection rate. Firstly, Choline PET/CT detection rate increases with increasing PSA level: so, a PSA level of about 1.5–2 ng/ml should be waited to be more cost-effective. Secondly, PSA kinetics is the second most powerful predictor of positive Choline PET/CT and it is important to evaluate the kinetics of PSA before performing a PET/CT in case of low PSA: so, in very selected cases, even with very low PSA (<1 ng/ml) and concomitant high PSA velocity (about 0.7–1 ng/ml/yr) or low PSA doubling time (<6–10 months), Choline PET/CT is adequately accurate.19 Finally, an unsolved issue is whether ADT should be temporarily interrupted before Choline-PET and which patients would benefit by discontinuing therapy. At this moment, no recommendations exist about this issue. In recent studies, it has clearly demonstrated that ADT is able to significantly modify the uptake of Choline, so ADT should be temporarily interrupted in androgen sensitive PCa.20 On the contrary, ADT can be continued in patients with castrate resistant PCa and rising PSA, because in these patients Choline PET/CT may easily identify the site of recurrence.21

Thus, Choline PET/CT represents today the most important imaging technique in the restaging of PCa patients. It has been reported that it allows changing the therapeutic strategy (from palliative to curative treatment and vice versa) in about 20% of cases. Confirmation of results, availability and costs remain the most important limitations. Furthermore, Choline PET/CT is now FDA (Food and Drug Administration) approved in the U.S. but only when other imaging techniques are negative.

New radiotracers for PET/CT are now under evaluation worldwide. In recent years the synthetic l-leucine analog (the anti-1-amino-3-18F-fluorocyclobutane-1-carboxylic acid, in brief anti-3-18F-FACBC) has been proposed as a possible alternative radiopharmaceutical to detect PCa relapse. Anti-3-18F-FACBC uptake is related to the functional activity of two different amino acid transporters and the distribution of the tracer in the body is more favorable than Choline (mild and diffuse uptake in the bone marrow and negligible uptake in the kidney with no activity in the urinary tract). This may reduce the risk of having small sites of disease relapse masked by a physiological presence of the tracer excreted in the urinary tract or in bones. Last but not least, the synthesis of anti-3-18F-FACBC is shorter and the half-life is long (109 min), and this render the radiotracer more available. From a clinical point of view, first clinical studies showed very promising and reproducible results: the improvement in sensitivity is about 20–25% with respect to Choline PET/CT, rendering the FACBC the possible radiotracer of the future for PCa.20

In brief, in patients with disease relapse of PCa after primary therapy, salvage treatment for a local recurrence should only be offered to patients with little risk of already having metastases; in these, patients a systemic imaging negative for metastases is mandatory, a positive biopsy is not always necessary before radiotherapy but is mandatory before salvage prostatectomy. In patients with a high risk of distant metastases and suitable for systemic salvage therapy (e.g. tomotherapy, lymphadenectomy, bone irradiation) a positive lesion must obviously be visualized with one of the currently available imaging techniques.

In conclusion, many improvements have been recently achieved in imaging techniques for PCa restaging, but negative results remain in many cases. Characteristics of PSA relapse and pathological stage are essential to guide the radiological work-up. Choline PET/CT and multiparametric MRI are the most important imaging techniques in the detection of PCa relapse at this moment, but new radiotracers for PET/CT are emerging. However, every time a radiological work-up for the restaging is started, it should have some therapeutic consequences for the patient. In these cases, more than one exam (for local and systemic relapse at the same time) is typically needed to complete the assessment of patients. Low sensitivity, costs, availability of technologies and confirmation of the results remain the major limitations in most cases.

Conflict of interest
None of the authors have any conflict of interest to declare.

References
5. Murphy AM, Berkmann DS, Desai M, Benson MC, McKiernan JM, Badani KK. The number of negative pelvis lymph nodes removed does not affect the risk of biochemical failure after radical prostatectomy. BJU Int. 2009;105:176.


