Continuing Education

Update on the use of radiopharmaceuticals for positron emission tomography imaging of prostate cancer

Actualización del uso de radiofármacos en tomografía por emisión de positrones en el cáncer de próstata

J.R. García
CETIR Unitat PET, Esplugues de Llobregat, Barcelona, Spain

Introduction

Epidemiology

Adenocarcinoma of the prostate is the most frequent neoplasm in men, with 50% of males over the age of 70 years presenting this type of cancer. In addition, it is the second cause of oncological death.

The diagnosis of prostate cancer is well established, being based on the determination of the prostate-specific antigen (PSA), rectal tact, transrectal echography and prostate gland biopsy. The performance of a biopsy is guided by the echographically suspicious image but should be randomly performed by sextants to collect a sufficient number of samples from each lobe.

Histologic grading

The most commonly used histologic grading system is the Gleason scale: Gx, grade of differentiation cannot be evaluated; this scale includes Gleason 2–4 (G1), well differentiated (weak anaplasia); Gleason 5–6 (G2), moderately differentiated (moderate anaplasia); Gleason 7–10 (G3–4), poorly differentiated/undifferentiated (marked anaplasia).

TNM staging

With regard to TNM staging, shown in Table 1, several diagnostic techniques are used.

Most of the tumors are adenocarcinomas and magnetic resonance (MR) is the technique of choice for correct delimitation of extension: capsular infiltration, invasion of the neurovascular bundle and infiltration of the seminal vesicles.

Lymph node (N) staging

The prevalence of infiltration of the lymph nodes has been shown to be around 25% of the patients with prostate cancer, having a direct correlation with the T stage, PSA level and the Gleason scale. Moreover, lymph node infiltration is considered the greatest predictor of disease prognosis, with a reduction in 5-year survival of 85% in N0 patients and 50% in N1 patients.

Conventional imaging techniques show a low sensitivity in the localization of lymph node disease since the criteria accepted to define pathologic character is size and, on many occasions, the lymph nodes are subcentimetric. Thus, the sensitivity of computerized tomography (CT) varies greatly, being between 25 and 70% and from 75 to 78% for MR.

Harisinghani et al. reported a sensitivity and specificity of 35.4 and 90.4%, respectively for conventional MR sequences versus 90.5 and 97.8%, respectively with supermagnetic lymphotrophic nanoparticles. Nonetheless, these nanoparticles are currently not commercially available.

Pelvic lymphadenectomy is the gold standard technique for lymph node staging, despite being an invasive procedure associated with a morbidity of 5–7%.

Predictive normograms have therefore been developed, among which the most accepted is the Roach formula [% (2/3) PSA + (Gleason-6) × 10].

In this way patients who are candidates for lymphadenectomy may be selected, although there continues to be a controversy as to whether a standard or extended technique should be performed due to the lack of an imaging technique to aid in the localization of lymph node infiltration.

Metastatic (M) staging

The pattern of metastatic dissemination is hematogenous, with venous drainage from the prostate to the vena cava. Bone localization is the most frequent, predominantly in the lumbar vertebra and pelvis and with a mainly osteoblastic character. In this regard, bone scintigraphy has classically demonstrated a high sensitivity but a limited specificity. Whole body and diffusion techniques by
Risk groups

In addition, patients with prostate cancer are stratified into risk groups, with the most accepted classification being that proposed by D’Amico6 as: low risk (T1–T2a, PSA < 10, Gleason 2–7), intermediate risk (T2b, PSA 10–20, Gleason 5–7) and high risk (>T2b, PSA >20, Gleason 8–10).

Therapeutic options

The therapeutic options depend on the staging of the disease. There is, therefore, a wide spectrum of options, where, on occasions, these options are combined: wait and see, active surveillance, prostatectomy, brachytherapy, radiotherapy and hormone therapy.

The critical points in therapeutic decision making are, in addition to extraglandular involvement of prostate cancer, lymph node infiltration and dissemination with bone metastasis. These points make correct N and M staging of great importance to define and plan radical treatment or to make the decision to carry out systemic therapy.

Only patients with tumoral stages confined to the prostate and with a life expectancy of more than 10 years are candidates for radical retropubic prostatectomy, brachytherapy, radiotherapy and hormone therapy.

The rate of biochemical recurrence after prostatectomy is 20–50% at 10 years, and is from 30 to 40% following radiotherapy.12 Conventional imaging techniques including transrectal echography, MR, CT and bone scintigraphy show limitations in the localization of the disease, but the prognosis of recurrence is poor if the PSA is >2 ng/ml. This is why these patients have classically been treated blindly. Pelvic radiotherapy is the treatment after radical resection of the primary tumor; radiotherapy options are cryotherapy, brachytherapy or high intensity focused.12

PET radiotracers in prostate cancer

Mechanism of uptake

18F-fluorodeoxyglucose (18F-FDG)

The mechanism of 18F-FDG uptake is well known in relation to the increase in glycidic activity in the oncological processes, being an ideal tracer in undifferentiated tumors. The half-life of 18F is 120 min, being optimum to distribute the tracer from the cyclotron producer to the different positron emission tomography (PET) services. Nonetheless, its utility in differentiated tumors such as adenocarcinoma of the prostate is known to be limited. Thus, the sensitivity of the detection of a primary prostate tumor is reportedly 64%, with a trend to an increase in relation to the rise in the Gleason scale and poor tumoral differentiation. Furthermore, glycidic activity has been described in cases of benign prostate pathology. Finally, physiologic urinary elimination of the tracer hinders evaluation of the pelvic region due to ureteral and urinary bladder uptake, although the use of integrated PET/CT equipment diminishes this problem.13

Given the inconveniences of 18F-FDG in this disease, other PET tracers have been developed, which have shown promising results in prostate cancer. Among these tracers, 11C-labeled acetate and 11C- or 18F-labeled choline are of note. There is no study comparing these two tracers in the same population.14 In addition, at present the utility of 18F-fluoride as a PET bone tracer is increasingly more popular.

11C-acetate

Acetate is a natural precursor of the fatty acids, which converts into acetyl-CoA, a substrate for the tricarboxylic acid cycle. Thus, the mechanism of uptake of acetate, normally labeled with 11C, is based on its participation in cytoplasmatic lipidic synthesis which is raised in tumoral processes, especially in patients with low oxidative metabolism.15
11C-18F-choline

Hara et al. introduced the use of 11C-choline,16 posteriorly labeling the choline with 18F. 18F-choline requires previous fluorination of its molecule. At present, 18F-fluorothiocetylcholine and 18F-fluoromethyl-dimethyl-2-hydroxymethyl-ammonium are available. The behavior of these tracers is similar in their distribution, which no changes having been reported in their efficacy.14,17 Choline is one of the components of phosphatidylcholine, an essential element of membrane phospholipids. Tumoral proliferative activity requires consumption of choline to cover the demand of phospholipid synthesis for the membranes, which is a characteristic of well differentiated carcinomas.16 Although this is the principle mechanism of uptake of the tracer, it has also been described that dysregulation of choline-kinase triggers an enzymatic cascade which is overexpressed in neoplastic cell lines, among which those of prostate cancer may be found.18

18F-fluoride

In 1962, Blau et al. first described the synthesis of 18F-fluoride as an isotopic bone tracer, with its use being approved by the Food and Drug Administration in 1972.19 Nonetheless, with the availability of the generators of molybdenum/technetium and the introduction of kits based on bisphosphonates, the performance of bone scintigraphy became universalized. In the 1990s the introduction of integrated PET/CT equipment and the availability of cyclotrons reactivated the interest in this metabolic bone tracer.

The mechanisms of uptake of sodium 18F-fluoride is the same as that of the 99mTc-diphosphonates, being based on the interchange of the fluoride ion by a hydroxyl group of the hydroxypapatite present on the surface of the bone crystals, forming fluorapatite, mainly in sites with an elevated rate of bone remodeling. The fluoride ion posteriorly migrates toward the crystalline bone matrix. Lesional uptake therefore depends on the increase in regional vascularization and a rise in bone turnover. Thus, plastic metastases show greater uptake while the activity in the lithic metastases is around the lesion due to bone remodeling.19

Methodology

18F versus 11C-choline/11C-acetate

The methodology of the studies with 11C-choline/11C-acetate is conditioned by the short half-life of the tracer (20 min). Firstly, the cyclotron must be close to the PET camera, being in the same installation on most occasions. The PET camera should be prepared awaiting administration of the dose. The injection to the patient is performed in the camera room with immediate acquisition beginning with the performance of CT for correction of attenuation. Thus, whole body PET acquisition is initiated from the pelvis in a caudal-cranial direction approximately 5 min after the administration of the tracer. Only delayed images may be obtained, centered in the pelvis or the whole body, after the first acquisition, given the kinetics of the radiotracer, but with the advantage that a single CT may be used as correction of attenuation because the patient is not mobilized between the two acquisitions.17

The mean half-life of 18F-choline (120 min) allows its distribution between the producing center and the different PET services. This greater availability has increased the popularity of its utility. However, early images are required in the pelvic region to avoid uptake in excretory structures which may interfere in the interpretation of the images. This is why the first studies, some of which used dedicated PET cameras, performed dynamic studies of the pelvis immediately after tracer administration, even using diuretic stimulus (20 mg of furosemide) and a vesical catheter. Although this protocol seems to be in disuse in more recent studies, the performance of early static images of the pelvic region during the first 15 min after tracer administration without the need for a catheter continues to be advisable.20

In addition, the performance of delayed images may be necessary because of the different dynamics of the benign prostatic processes of the tumoral tissue as well as the presence of early uptake showing delayed clearance in reactive lymph nodes. Thus, for whole body acquisition including the pelvis, variable study times from 30 to 120 min postinjection have been described which allow an increase in the sensitivity and specificity of the detection of distant disease.20,21

In short, a recommendable protocol may be the following:

- Image of pelvic region: early, static, 3–5 min after tracer administration.
- Whole body study: delayed, including pelvic region, 1 h postinjection.

All the acquisitions should be post voiding leaving the indication for a bladder catheter up to the criteria of the nuclear physician based on the interpretative needs and the clinical situation of the patient.

In Spain, a retrospective multicenter study is currently in progress to analyze the utility of PET/CT with 18F-choline in prostate cancer in both patients with biochemical recurrence and in the staging phase, allowing determination of the diagnostic profitability of this technique in our country.

Physiological distribution

The first step in the interpretation of the studies should be to know the biodistribution of each of these tracers. Regardless of labelling the distribution of choline is similar with 11C or 18F, except in the difference in the visualization of the physiologic urinary elimination previously explained. More or less uniform activity is observed in the salivary glands, the liver and spleen, the duodenum-pancreas region, renal parenchymatous, as well as the bone marrow, with uptake in the intestinal loops being more variable in extension and intensity, mainly in the small bowel.18

11C-acetate presents low hepatic physiologic uptake, which allows the detection of metastatic lesions at this level, although these are infrequent.14

Furthermore, non oncologic uptake of the tracer, variation from normality, inflammatory processes and the possibility of other “diagnostic errors” should be taken into account. As described in some studies, the use of integrated PET/CT equipment allows false interpretations to be avoided.22,23

Sodium 18F-fluoride

Sodium 18F-fluoride shows lower binding to proteins compared to 99mTc-diphosphonates, with more rapid plasma clearance. These characteristics produce a bone/background clearance, approximately of two. In addition, it allows early acquisition of images, at 60 min after the administration of the tracer.19

The acquisition of the PET study does not vary with respect to that of 18F-FDG since they share the same radionuclide: 2–5 min/bed, iterative reconstruction. The skull and extremities should be included in the same or in posterior acquisitions. CT is necessary for correction of attenuation and should therefore be performed at a low amperage (30 mA s); it also allows the reduction of artifacts, the localization of active images and quantification of the studies.24
Dosimetry

18F versus 11C-choline/11C-acetate

For injected doses between 296 and 370 MBq, the effective dose of 18F-FDG (0.190 mSv/MBq) and 18F-choline (0.01 mSv/MBq) is greater than that of 11C-choline (0.0044 mSv/MBq) and 11C-acetate (0.0040 mSv/MBq), respectively, in relation to not only the half-life of the isotope (120 min vs. 20 min) but also in relation to differences in the clearance pattern of the organism.24

The target organs of 11C-choline are the liver and the spleen (0.062 mGy/MBq), the pancreas (0.01330 mGy/MBq) and the kidneys (0.0079 mGy/MBq), with the effective dose for 11C-acetate differing because of its different biodistribution: liver and spleen (0.0092 mGy/MBq), the pancreas (0.017 mGy/MBq) and the kidneys (0.0092 mGy/MBq).25,26

18F-fluoride

The energy of 18F is greater than that of 99mTc, but given the image qualities described in studies with 18F-fluoride, the dose administered is lower, thus the dosimetry of the two tracers in similar (18F-fluoride: 4.4–8.8 mSv; 99mTc-MDP: 4.2–6.3 mSv).

The dosimetry of the study should take into account that derived from the CT component. Thus, a CT for correction of attenuation (120 keV, 30 mA) produces an effective dose of 3.2 mSv.19,24

Clinical indications of positron emission tomography studies in prostate cancer

The value of PET/CT should be studied in all the clinical situations of prostate cancer and should therefore include the initial staging, biochemical recurrence and therapeutic response. There are no comparative studies to this end in the same population. We have therefore included studies performed with 11C-acetate, 11C-choline and 18F-choline, indicating which tracer was used in each on considering that no differences have been reported among them in the literature.14

Initial staging

T staging

Since the classical T staging techniques are transrectal echography and MR with an endorectal coil, analysis by sextants of glandular choline uptake is advisable. Thus, to localize the hypermetabolic foci we divide the prostate into the right and left and each half into apical, medium and basal regions (with the apical region being the inferior since the reference techniques are performed by the transrectal route).2

Prostate cancer is characterized by the presence of multiple, often small, foci. PET studies with 11C-choline have 2 limitations: firstly, the heterogeneity of the grade of uptake of the tumoral foci and, principally, the limited spatial resolution of the PET systems which do not allow the detection of lesions of less than 5 mm, especially those with mild activity. On the other hand, benign hypertrophy of the prostate lesions and prostatitis also show uptake of 11C-choline. In this sense, studies with correlation between the hypermetabolic foci and the histopathology show the coexistence of areas of uptake between inflammatory and tumoral processes without being able to differentiate between the processes. In fact, a pattern of heterogeneous uptake is suggestive of the presence of a benign process which will impede the identification of a possible tumoral foci.2

Thus, only the detection of a focal hypermetabolic activity on PET/CT with 11C-choline has a correlation with the presence of prostate cancer.23 Farsad et al.2 described sensitivity, specificity and diagnostic accuracy of 66, 81 and 71%, respectively. Other authors have established a SUV threshold valued at 2.65 with 11C-choline to obtain the best diagnostic safety in the differentiation between benign and malignant disease.27

The results of PET/CT findings are discordant. Some do not show any correlation between the uptake of 11C-choline and the PSA level, the Gleason scale or tumoral staging.2,28 Other studies describe a correlation with tumoral staging.27 These results have led several groups to attempt to perform technological innovations to improve these results. Studies with 18F-choline dual-phase imaging allows differentiation of different metabolic dynamics between the uptake of benign processes, with a reduction in activity (retention index –17%) in the malignant processes and an increase in uptake (retention index +14%).23 In reports with 11C-acetate dynamic studies have been performed to establish the tumoral peak which is detected at 3–5 min and plateau at 10 min. However, this pattern is also that of benign prostatic hyperplasia, with overlapping between the tumoral foci and benign prostatic hyperplasia.15

In summary, PET/CT with choline is not recommended for the localization of the primary tumor in patients with recently diagnosed prostate cancer.

Comparison with MR. One preliminary study showed that PET with 11C-choline allows lateralization of the maximum tumoral load in a greater number of cases than MR imaging and spectroscopy by MR26 (Fig. 1).

However, Testa et al. demonstrated that the sensitivity of 11C-choline is clearly lower (55%) in comparison with MR imaging combined with spectroscopy (81%), albeit with a similar specificity (67% vs. 76%). In addition, using different MR sequences such as diffusion, change of T staging is possible, with therapeutic implications.30

In this regard, integrated PET/CT equipment may allow better determination of the maximum tumoral load and correct T staging in the same study, with important therapeutic implications if combined with the new techniques of radiotherapy which allow image-guided radiotherapy (IGRT) and modulation of dosage (intensity-modulated radiotherapy [IMRT]).31

Localization of the biopsy. Around 20% of the patients present a persistent elevation in PSA with repeated negative biopsies. In these cases, PET/CT study with 18F or 11C-choline may localize the tumor which, on many occasions, is located in the anteroposterior peripheral transitional zone and therefore allows guidance for biopsy.3,32

N staging

The physiological activity of 18F or 11C-choline at intestinal and ureteral level hinders the individualization of possible lymph node infiltration. In doubtful cases, integrated PET/CT images allow correct localization of the metabolically active image.33

Early studies described a greater sensitivity with 11C-choline of 80% than conventional imaging techniques (CT and MR), with a sensitivity of 47% and a similar specificity (96% vs. 98%, respectively).3 This is due to the usual subcentimetric size of the lymph nodes. Nonetheless, in the studies with 11C-choline the rate of detection also diminishes with lymph node size, being 77% for lymph nodes > 1 cm, 43% for those >0.5 cm and 20% for those <0.5 cm in relation to the limitation of the resolution of the PET/CT systems.7 This difficulty in the detection of microscopic infiltration is translated into variable results with the different tracers, which range from 20% to 100% in studies performed with 18F-choline.34

A recent metaanalysis demonstrated this low sensitivity (49.2%) but with an elevated specificity (95%), indicating the heterogeneity of the studies, with differences in the study populations as well as in the methodology of the studies. More homogeneous studies which
evaluate the cost-effectiveness are therefore necessary. Nonetheless, it seems that the sensitivity in the last studies increases with no changes in the specificity, probably due to the integration of PET/CT and the learning curve.\textsuperscript{32}

Taking this limitation into account, some authors have carried out the sentinel lymph node technique, presenting an expected greater sensitivity of 97%. However, this technique involves great technical difficulty and is therefore not systematically performed.\textsuperscript{7}

The sensitivity of \textsuperscript{11}C-choline is similar to that of the predictive normograms (approximately 60%) with a greater specificity (97.6\% vs. 73.8\%).\textsuperscript{7} In addition, PET/CT allows the visualization of lymph node infiltration outside the field of standard lymphadenectomy, thereby suggesting that choline may be a good method for non-invasive lymph node staging with therapeutic implications: it could indicate the type of lymphadenectomy (standard or extensive) or even counter indicate this procedure in cases in which distant disease is detected.\textsuperscript{7}

One additional problem is the frequency of visualization of mediastinal hypermetabolic adenopathies due to the presence of inflammatory/reactive processes, rendering interpretation doubtful and requiring assessment in relation to tumoral aggressiveness and probably always needs a directed evaluation.\textsuperscript{35} The indication of lymph node staging in patients with medium-high risk according to the D’Amico classification is therefore accepted while study of the sentinel lymph node is required on suspicion of small lymph node volume.\textsuperscript{8,34}

**M staging**

The performance of delayed images with \textsuperscript{18}F-choline increases the sensitivity in the detection of bone metastases.\textsuperscript{23} Nonetheless, there is currently broad discussion as to the choice of technique for the detection of bone metastases, with many comparative studies including bone scintigraphy, new whole body sequences and MR diffusion as well as PET/CT with \textsuperscript{18}F-fluoride. These will be discussed in the section on suspicion of recurrence because of its greater frequency. The lung and the liver are 2 organs of metastatic localization, but the whole body technique of PET/CT with choline allows the detection of metastasis of infrequent localization or even the diagnosis of synchronous tumors.\textsuperscript{36}

**Therapeutic implications**

As a whole body diagnostic technique \textsuperscript{18}F-choline has shown a change in the therapeutic management of 15\% of the patients, with this percentage increasing up to 20\% in patients with high risk.\textsuperscript{5}

At present, the greatest implication is centered on the planning of radiotherapy. Taking into account the limitations described in the delineation of prostatic tumors, PET/CT with \textsuperscript{11}C-choline is not considered an adequate study for the new radiotherapy techniques.\textsuperscript{37} However, good preliminary results may be achieved in the control of the disease if localization of lymph node infiltration allows modulation of the dose (IGRT/IMRT boost > 60 Gy) in the lymph nodes with pathological uptake of \textsuperscript{18}F-choline without an increase in intestinal toxicity compared with standard radiotherapy\textsuperscript{38} (Fig. 2).

**Suspicion of recurrence**

**Localization of relapse**

**Local relapse.** With a threshold of SUVmax > 3.0 and a tumoral foci size > 1.7 cm, the sensitivity and specificity of \textsuperscript{11}C-choline in local relapse after prostatectomy are 73 and 88\%, respectively.\textsuperscript{39} Following radiotherapy there is, in many cases, reinforcement of glandular uptake which reflects inflammatory phenomena post treatment, although Albrech et al.\textsuperscript{12} established a threshold of SUVmax > 2.9 with \textsuperscript{11}C-acetate when there is a single focus.

In contrast to what occurs in the initial staging of prostate cancer, the utility of MR in local relapse after radical treatment is limited: signal changes are observed in T2 sequences following prostatectomy, with heterogeneity of activity; after radiotherapy the image is not useful requiring the performance of spectroscopy.

Only one very recent comparative study between MR with contrast and spectroscopy and PET/CT with \textsuperscript{18}F-choline has been reported, showing that the sensitivity of MR is greater than that of PET in local recurrences < 10 mm, with similar results in those > 10 mm in size in patients with an elevation in PSA after radical prostatectomy.\textsuperscript{40}

**Lymph node recurrence.** PET/CT with \textsuperscript{11}C-choline is a diagnostic tool with an elevated positive predictive value of 86\% (100\% with PSA > 2 ng/ml) in the detection and localization of radical post treatment lymph node recurrence in prostate cancer. However, on analysis by lesions, the negative predictive value is low, since it is not able to detect microscopic disease. In this respect, the mean diameter of the true positive results is of 15 mm while that of false negative results is 6.3 mm.\textsuperscript{41}
Nevertheless, evaluation of tracer uptake in mediastinal lymph nodes should be made with caution. This uptake is frequent, reportedly being of 50% with 18F-choline, and does not allow differentiation of cases of tumoral disease or those with inflammatory/reactive activity and therefore, on most occasions, requires directed evaluation.42

Bone metastasis. As expected, PET with 18F-choline presents a greater sensitivity than CT in detecting lesions without morphologic translation, particularly in vertebral bodies with medullar infiltration. The most common CT pattern of metabolically active bone lesions is blastic, although mixed and even lytic lesions have also been reported.44

Some studies have compared bone scintigraphy and choline. Fuccio et al. demonstrated that in patients showing a single lesion of bone M1 by bone scintigraphy, PET/CT with 11C-choline showed more lesions in 44% of the cases and, in addition, was able to detect extraosseous disease in the same study.45 It is classically known that bone scintigraphy often shows erroneous results requiring complementary studies. Picchio et al. reported a greater specificity and positive predictive value with 11C-choline over bone scintigraphy.46 However, all these studies compared two different technologies, a planar versus a tomographic whole body study of high resolution and with a CT component, and thus, some authors have suggested the need for studies comparing SPECT/CT vs. PET/CT.47

Comparative studies between isotopic bone tracers have also recently been published. Thus, the sensitivity of 18F-fluoride is greater than that of bone scintigraphy, being 100% vs. 57%, respectively, even with the performance of SPECT (sensitivity 78%). The specificity of SPECT and PET improves with assessment of the CT component of the integrated technique.48

Other authors are therefore inclined toward the use of 18F-fluoride, showing a superior, albeit not significant, global sensitivity to that of 18F-choline. To the contrary, 18F-choline allows early detection of medullary infiltration.

Finally, the increasing use of MR with diffusion sequences cannot be forgotten, reportedly presenting a sensitivity similar to that of PET/CT with 11C-choline49 being somewhat inferior to that of 18F-fluoride but with a greater specificity.50

All these comparative studies lead to the dilemma as to which studies should be performed in the screening of bone metastases and what algorithm or study order should be followed.

In view of the discordances between bone scintigraphy and PET/CT with 11C-choline, the use of 18F-fluoride has corroborated the presence of bone metastasis (Fig. 3), and may, thus, be an alternative to MR as a second tracer in bone imaging.51

Comparison between 18F-fluorodeoxyglucose and choline

Several studies have compared these tracers and have shown that the results of 18F-FDG are clearly inferior to those of 11C-choline in the detection of local recurrence (Fig. 4). These results are also inferior, but less significantly so, in the detection of tumoral lymph node infiltration, showing an improvement in 18F-FDG, with similar or even superior results (Fig. 5) in the detection of distant disease (Fig. 6), probably in relation to the greater tumoral aggressiveness in these cases.52 This hypothesis has been supported by other studies showing that the results of 18F-FDG are better in patients with a high Gleason score and comparable to those of 11C-choline.53

On analyzing the correlation with the elevation of PSA it has been observed that in the group with a PSA < 1 ng/ml, 11C-choline allows the detection of 40% of the recurrences, while 18F-FDG does not detect any relapse (0%). In the group with a PSA 1–4 ng/ml, 11C-choline allows the detection of 60% of the recurrences, with 18F-FDG detecting 27%. In patients with a PSA > 4 ng/ml, 11C-choline detects 83% of the relapses while 18F-FDG detects 50%. If we add the patients with a PSA < 4 ng/ml, 11C-choline shows a clearly superior capacity of detection of recurrence (47.5%) over 18F-FDG (15.5%).52

Patient selection

The rate of detection in the studies with choline rises in parallel with the level of PSA elevation. Thus, the rate of detection for PSA < 1 ng/ml is low, valued at 36% with 11C-choline54 and 20% with 18F-choline.55 A definitive threshold for the use of PET/CT with

Fig. 2. A 63-year-old patient diagnosed with prostate cancer T3a; Gleason 8; PSA 10 (Roach formula 26.7%). PET/CT with 11C-choline shows multifocal prostatic uptake and a single hypermetabolic lymph node in the left obturator fossa (A). Considered to be locoregional disease, implementing hormonal therapy (2.5 years), radiotherapy (45 Gy) of the prostate and pelvic lymph node with a boost (60 Gy) to the prostate and positive lymph node with 11C-choline (B). Disease-free at 2 years with no adverse effects from the radiotherapy.
Fig. 3. A 68-year-old patient with a history of prostatectomy 3 years previously. PSA 1.7 ng/ml. Bone scintigraphy did not show uptake images suggestive of bone metastasis (A). PET/CT with $^{11}$C-choline shows a single hypermetabolic focus in the right ischio-pubal branch suspicious of metastatic bone infiltration (B). A greater degree of uptake is also observed in the study with $^{18}$F-fluoride (C). A new revision of the bone scintigraphy allowed the detection of a slight uptake in this localization (A). Cytology by FNAP of the lesion corresponded to bone metastasis.

Fig. 4. A 71-year-old patient with a history of radical prostatectomy due to prostate cancer 24 months previously. PSA 2.7 ng/ml. PET/CT with $^{11}$C-choline shows a deposit of $^{11}$C-choline in the left surgical bed (A) not detectable with $^{18}$F-FDG (B). There was a significant fall in PSA following radiotherapy. Choline in the localization of biochemical recurrence has therefore not been described.

For these reasons, Castellucci et al. analyzed the kinetics of PSA elevation with the aim of improving the selection of patients in whom the performance of PET/CT with $^{11}$C-choline is indicated. These authors determined that the PSA value and the velocity of PSA elevation are independent predictive factors. In the group of patients with a PSA < 2 ng/ml, the time over which the PSA doubled in value (doubling time of PSA, PSAdt) was the predictive factor which allowed greater efficacy in the localization of early relapse. Other groups have determined the PSAdt threshold in patients with a PSA < 1.5 ng/ml, being described as 6.8 months by Giovacchini et al. and rising to 7.25 months according to Castellucci et al.

Therapeutic implications

On detection of an elevation in the PSA it is essential to differentiate between local or systemic recurrence since this information is fundamental for determining local or systemic treatment. Whole body PET/CT with $^{18}$F-choline allows changes in the therapeutic management of 48% of patients.

In contrast to initial staging, in biochemical relapse of prostate cancer the detection of local recurrence by PET/CT with $^{18}$F-choline allows the planning of radiotherapy without increasing the toxicity, with a 3-year survival of 92% and 90% of disease control. We have already described that this approach has shown its utility in IGRT which allows modulation of the dose (IMRT).

Therapeutic response

Antiandrogenic treatment reduces the volume of the prostate by causing glandular atrophy by a decrease in cellular turnover. Thus, a decrease has been observed by PET/CT in the uptake of $^{11}$C-choline (from 11.8 ± 5.3 to 6.4 ± 4.6) in patients diagnosed with prostate cancer in whom systemic treatment is performed as the initial therapy. Likewise, in hormone-sensitive patients with biochemical recurrence of prostate cancer, normalization of
the PET/CT with $^{11}$C-choline was reported in 9/13 patients, being correlated with the fall in PSA at 6 months ($17.0 \pm 44.1$ ng/ml vs. $2.4 \pm 3.1$ ng/ml). In the case of patients with bone metastasis controlled with hormone therapy, responder patients demonstrate a reduction in the uptake of $^{18}$F-choline prior to significant changes in the CT, indicating its utility in the early treatment of hormone therapy.

Nonetheless, when the PSA is elevated despite hormone treatment, the patient may be considered as hormone-refractory. If these patients already present rapid PSA kinetics, PET/CT with $^{11}$C-choline allows the localization of the disease and, on occasions, directed therapy.

At present, new therapies under development are currently being applied to hormone-resistant patients. These therapies have introduced new diagnostic dilemmas related to what studies are necessary and what sequences should be used to evaluate the efficacy of treatment. Preliminary results have demonstrated the importance of the metabolic changes by PET/CT with $^{11}$C-choline in the control of these patients, although evolutive algorithms remain to be developed.
Points of interest

- PET/CT with choline is not useful in the T staging of prostate cancer due to the limited spatial resolution of the PET systems and the uptake of the tracer in benign prostatic processes.
- In patients with medium-high grade prostate cancer according to the D’Amico classification, staging by PET/CT with choline has an impact on the therapeutic management, especially in the planning of radiotherapy based on the localization of the lymph node infiltration.
- PET/CT with choline demonstrates early detection of medullary infiltration in the diagnosis of bone metastasis in prostate cancer while the sensitivity seems to be greater using PET/CT with $^{18}$F-fluoride and/or MR with diffusion sequences. The algorithm is, therefore, remains under debate.
- PET/CT with $^{18}$F-FDG is not useful for the detection of biochemical recurrence of prostate cancer, since it only detects the disease when PSA values are elevated, when the disease has already progressed and when there are few therapeutic options.
- The detection of biochemical recurrence in patients with prostate cancer is the principal indication of PET/CT with choline since it achieves early localization of the disease and differentiation between local and systemic recurrence, thereby allowing modification of the therapeutic strategy.
- The rate of detection of biochemical recurrence of prostate cancer by PET/CT with choline has a direct relationship with the elevation of PSA. However, for patient selection it is more useful to establish a threshold level in the study of the kinetics of PSA, especially the PSA doubling time.

Conflict of interest

The author declares no conflict of interest.

Acknowledgment

We would like to thank the Grupo Multicéntrico Español de $^{18}$F-choline for the methodologic section of PET/CT with $^{18}$F-choline.

References

5. Prevedello DM, Bartlett DL,.player et al. In patients with medium-high grade prostate cancer according to the D’Amico classification, staging by PET/CT with choline has an impact on the therapeutic management, especially in the planning of radiotherapy based on the localization of the lymph node infiltration.


