

"Complementary Contribution of Positron Emission Tomography "PET" and MRI in the Management Of Prostate Cancer in Initial Extension Assessment and in Biological Relapse"

Alshemeili. Manea, Philippe. Got

Department of Nuclear Medicine, South Lyon Hospital, Faculty of Medicine, Claude Bernard Lyon 1 University, Lyon, France

Abstract

Introduction: Prostate cancer is currently the second leading cause of cancer death in men in Europe and developed countries, with about 300,000 new cases diagnosed each year. The respective roles of multiparametric MRI and nuclear medicine by PET with choline or other tracers for prostate cancer (CaP) exploration have expanded in recent years thanks to technical advances and the development of functional imaging.

Methods: From October 2017 to December 2018, 20 patients were included retrospectively to search local localization of prostate cancer with or without nodal and bone metastasis. The indication was 8/20 for initial assessment and 12/20 for biologic recurrence after prostatectomy or radiotherapy. All benefited a multi-parametric pelvic MRI (T2, diffusion, dynamic after injection) and a choline PET at the nuclear medicine department, XXX center using PET-CT (GE Discovery 710).

Results: Patients had 80% of identical results in PET scan and MRI, while 10% had a negative result in MRI and positive in PET-scan and 10% had a positive result in MRI and negative in PET-scan.

Conclusion: The innovative imaging modalities available today, using advanced MRI and PET technologies and the appearance of new tracers more sensitive and specific than choline can improve the diagnostic performance and strategies of treatment planning.

Keywords: Prostate. MRI. PET/TDM. Fluorocholine

Introduction

Global context

Prostate cancer is currently the second leading cause of death from cancer in humans in Europe and in developed countries, with around 300,000 new cases diagnosed per year. Despite an increasingly early diagnosis thanks to the assay of the prostate antigen specific (PSA) and the improvement of curative treatments, the recurrence rate remains high, of the order of 50% at ten years, whether after surgery and / or curative radiotherapy. D'Amico's classification allows tumors to be classified according to their aggressiveness potential at the time of diagnosis:

- Low risk: PSA <10 ng / ml and Gleason score ≤ 6 and clinical stage T1c or T2a.
- Intermediate risk: PSA between 10 and 20 ng / mL or Gleason score of 7 or T2b stage.
- High risk: PSA > 20 ng / mL or Gleason score ≥ 8 or clinical stage T2c.

The choice of treatment is guided by what are called prognostic factors. They determine the aggressiveness of the tumor and therefore the expected survival. Prognostic factors more important are the size and aggressiveness of the tumor. The spread of cancer is characterized by the international classification TNM.

**Address for Correspondence: Alshemeili. Manea, Department of Nuclear Medicine, South Lyon Hospital, Faculty of Medicine, Claude Bernard Lyon University, Lyon, Villeurbanne, France. Email- malhasouni@yahoo.com*

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Therapeutic strategy

- Localized prostate cancer: active surveillance or curative treatment (by surgery or radiotherapy);
- Locally advanced prostate cancer: curative treatment by surgery in the subject young or hormone-radiotherapy.
- Metastatic prostate cancer: hormone therapy.
- Prostate cancer in the castration resistance phase: hormonal manipulation if not very symptomatic (anti-androgen withdrawal syndrome, hormone therapy second line) or chemotherapy if symptomatic (bone pain, etc.);

The cure rate depends mainly on the stage of the disease at diagnosis (stage T, score Gleason, PSA level, lymph node and / or distant): the initial assessment of extension usually includes a CT or MRI for the loco regional extension assessment and a bone scan for remote metastasis. Prostate biopsies constitute the reference examination to establish the diagnosis and assess the prognosis of cancer of the prostate and bring histo-prognostic criteria [1]. A Gleason 6 score corresponds to a well differentiated tumor, Gleason 7 to a moderately differentiated tumor and Gleason 8 and 9 correspond to a poorly differentiated tumor. A Gleason 10 tumor (5 + 5) is said to be undifferentiated.

However, performing ultrasound-guided prostate biopsies is a relatively blind gesture where imaging is used more to locate the organ than to target the tumor. The progress of imagery made in recent years with the development of 3D localization systems allow to consider new practices.

Advantages and limits of MRI

Prostatic MRI allows the detection of cancer by combining morphological imaging and functional, also obtaining a tumor map. The information provided, such as estimation of tumor volume, location and aggressiveness of suspected foci (the cancers are aggressive if Gleason greater than 6 = 3 + 3), make it possible to adapt the strategy of biopsies, therapeutic management, monitoring of new targeted therapies and detection of recurrences after curative treatment, but MRI may not detect tumors of low grade [2]. These performances are however sub-optimal for the search

for secondary lymph node. Villers [3] found that perfusion imaging made it possible to detect tumor foci of more than 0.2 cc with a sensitivity of 77% and a specificity of 91%, homes of more than 0.3 cc with a sensitivity and specificity of 80% and those over 0.5 cc with a sensitivity of 90% and specificity of 88% [3, 4].

Advantages and limits of PET with choline

During the past 15 years, positron emission tomography (PET), coupled with computed tomography (PET / CT) has become a major imaging test widely practiced in oncology. It can detect the extension of cancer, second synchronous cancers or metachronous, during staging, restaging or in the event of a biological recurrence, and also to assess early the response or resistance of neoplastic localizations to therapy. Advances in prostate cancer-specific positron emission tomography have allowed to better understanding the patterns of recurrence of the disease. PcPET radiotracers emerging, including carbon choline 11 (C-11), the prostate specific antigen (PSMA) of gallium 68 (Ga-68), C-11 acetate and fluciclovier acid 18F-fluorocyclobutane 1-carboxylic (FACBC) offer localization possibilities. Recurrence of cancer prostate at an earlier stage in the course of the disease when the PSA level is low, for inform medical decision-making and to study local treatment led by PET. Positron emission tomography (PET) after F-choline injection improves the staging of CaP (lymph node status and occult metastases) and modifying its intake load, especially during relapse. Choline PET is not very effective for search for primary prostatic lesions because the intensity of fixation may be the same in the event of inflammatory lesion, benign hyperplasia or adenocarcinoma; choline PET is not absolutely not specific for prostate cancer. Other cancers also fix choline because they need to grow their tumors, so there is an increase in the capture of lipids. Sometimes, with distant lesions, it is not known whether it is a metastasis of cancer from prostate or other cancer; in particular, in the liver (hepatocellular carcinoma) and the assessment of hyperparathyroidism.

The objective of the study is the comparison between PET with choline and MRI during the initial assessment or biological recurrence of prostate cancer.

Material and method

Study population

Between October 2017 and December 2018, 20 patients were included retrospectively for performing a multi-parameter pelvic MRI (T2, diffusion, dynamics after injection) and a choline PET scan, 7/20 patients who had these examinations as part of an initial assessment of prostate cancer and 13/20 as part of a biological recurrence after prostatectomy or radiotherapy, after the elevation of the prostate specific antigen (PSA), the average PSA is 8.6 and Gleason from 7 to 9. PET choline exams were carried out in the nuclear medicine department using TEP-TDM (GE Discovery 710). The indication takes into account the TNM / Gleason / ISUP classification of Prostate Cancer, pathology being the gold standard.

CHOLINE PET protocol

3D PET acquisition of the eyebrows up to the root of the thighs, 1 hour after the injection Fluoromethylcholine intravenous - (18F) 3 Mbq / kg, with attenuation correction by @ CT (GE Discovery 710). Acquisition of the thoracic-abdomen and pelvis CT scan after IV of contrast product with parenchymal window reconstructions on the thorax and soft tissue on all four segments.

Interpretation of Images

The images were analyzed retrospectively using 2 TEW ADW consoles and a AW Server interpretation platform. The analysis was carried out starting with the acquisition pelvic region, the prostate gland, the pelvic and retro-peritoneal lymph nodes in mentioning the size of pathological lymph node formations > 8 mm and the fixations. The fixation of the axial and appendicular skeleton is analyzed and compared with the acquisition CT only in bone window (condensing or lytic bone lesion).

The main positivity criterion for hyper fixation was the presence of an intensity clearly detaching background noise. The quantification of the intensity of fixation, (measurement of SUVmax), is systematically performed and is used to reinforce the visual impression. No threshold of SUVmax is not used for lymph nodes and bone. In case of prostate still in place, a focal fixation considered suspicious in the framework of the study, does not formally rule out a non-tumor cause (infection or Benign hyperplasia). In the event of a history of prostatectomy and at a distance from surgery, an intense median pelvic fixation under bladder during activity. At the lymph node level, the positivity criteria are: a location compatible with a drainage territory, hyper fixation detaching from the background noise.

Note that a pathological size of the hyper fixing ganglion and a rounded appearance with loss of hilum fatty central support the suspect character, without being considered as secondary criteria to them alone. Non-hyper fixing ganglionic formations are considered to be negative regardless of their size. Moderate hyper fixations of suprarenal nodes are not exceptional and described as non-pathological, especially if their distribution appears harmonious at the mediastino-hilar level. At the bone level, focal hyper fixation clearly stands out from the background noise surrounding osteomedullary bone is considered positive, regardless of the CT aspect opposite, this being however mentioned (absence of CT anomaly, condensing lesion, lytic, or mixed). A systematic analysis of the bone structure was carried out in order not to ignore any very condensing lesions that may not have fixation significant (benign condensing ilot).

Other tracers in nuclear medicine

Gallium 68 PSMA: PSMA is a Tran's membrane antigen expressed by virtually all PCs; it has one enzymatic function of glutamate carboxypeptidase whose pathophysiological significance is not known. An antibody labeled with indium-111 for scintigraphy did not allow obtain the diagnostic performance expected in CP imagery and has never been registered in France. More recently, ligands or antagonists of this enzyme have been labeled with nuclides for PET imaging, one of which, labeled with 68Ga, 68Ga-HBED CC, or PSMA-11, meets a great interest. Studies relate to staff considerably more important than with GRPR antagonists; we perform in our PET / CT examination service at PSMA-11 since 2016. Compared to FCH, PET with a PSMA ligand better visualizes the CP in contrast to the background noise, which allows detection small lesions, especially lymph nodes or bone metastases intramedullary, because the physiological fixation by the bone marrow is less. However, the PSMA is not as specific to CP as its name suggests and may be overexpressed in other pathologies, neoplastic or not.

[18F] Fluciclovine

A leucine analog, 18F-FACBC, or 18F-fluciclovine, tested in humans since 2007, recently obtained a marketing authorization in the European Union for the detection of recurrence of CP. [18F] Fluciclovine is produced only once a month limiting its use to 48 patients per year. According to several studies, for the location of the primary tumor, 18F-fluciclovine, even in PET / MRI imaging, is not superior to multipara metric MRI. Marketing Authorization: Indicated for PET imaging to detect a recurrence of prostate cancer in adult men if there is a suspicion of recurrence on the basis of a re-ascend of the serum concentration of PSA prostate specific antigen after curative treatment first line. It has better efficacy than Fluorocholine because of less fixation physiological facilitating medical interpretation, alternative in 1st line PET if \nearrow (PSA) moderate and reduction of the decision making time for the therapeutic choice.

MRI protocol

We talk about multipara metric imaging: we study the anatomical sequences and the sequences functional. The anatomical (morphological) sequence will give us all the anatomical information on the prostate, its volume, the delimitation of the contours (capsule, transitional zone that called the adenoma, central area, peripheral part. The functional sequence (functioning of the tissues) will allow us to characterize an anomaly. For example, an anatomical abnormality may be due to prostatitis, inflammation, cancer ... So we need complementary sequences to help us differentiate what could be cancerous or benign. There are 2 types of functional sequence:

1) The diffusion sequence is very characteristic and important in pathologies because it allows us to observe the movement of water molecules. In cancer, these water molecules are retained (trapped), they can no longer move and will emit a particular signal. On an image, we will see black and white and schematically the white represents the retained water molecules.

2) The infusion sequence is obtained before and after the injection of a contrast medium (in the blood): gadolinium. The goal is to compare the images before and after injection

contrast medium. Prostate cancer has the distinction of being richly vascularized. The product will therefore very quickly reach the level of tumor lesions. This sequence will advance and characterize the lesions.

MRI has a very good sensitivity and specificity in the detection of cancer of the prostate both in the peripheral area and in the anterior. It's a very especially effective with a large tumor volume and when cancers are aggressive (Gleason greater than 6 = 3 + 3). However, the performance of the exam is lower for small tumors of low aggressiveness (Gleason 6). When the exam is normal, we have very little chance of missing a significant lesion (more than 5 mm, Gleason greater than 6) (day scientifique 2015 ANAMACAP).

Lymph node assessment is done at the same time as prostate MRI with a study of iliac and ilio-obturator chains, up to the bifurcation. The main semiological criteria are the size (8mm for obturator glands, 10mm in lumbo-aortic) and shape (rounded rather than oval). (French Association of Urology).

Interpretation of Images

The images have been analyzed bypassing the regions deemed suspicious. When a fabric of interest is visible on several consecutive sections (same image characteristics), it is contoured on each of the sections on which it is visible. In the following, the term ROI is therefore relates to all of these 2-D contours made to delimit a target tissue. The interpretation is conducted from the axial sections. The base and the apex are also studied on the frontal and / or sagittal cuts. The signs of extension to the posterior surface are searched for sagittal slices and signs of posterolateral or lateral extension on frontal cuts. Two plans are recommended for a full examination [5].

Results

20 patients are included in our study from October 2017 to December 2018, the average age is 68 years old. The indications of MRI and PET CT are the search for remote location during the initial assessment before a high Gleason score (7 patients out of 20, 35%) or the search for Location during a biological recurrence (13 patients out of 20, 65%). the average PSA is 8.6. The patients had 80% (16 of 20) identical results in the PET scan and MRI, while 10% (2 out of 20) had a negative MRI result and positive in the PET CT scan and 10% (2 out of 20) had a positive result in MRI and negative in PET. Among the 16 patients with identical results, we find 56% (9 out of 16) who had positive results on both exams and 44% (7 of 16) who had negative MRI results and PET CT at FCH. Within the 11 positive PET examinations (5/11 in recurrence assessment and 6/11 in initial assessment), the distribution of the detected targets was as follows (Table 1): at the initial assessment: 4/6 patients (66%) had only local involvement, 1/6 patients (17%) had local involvement with lymph node metastasis (lymph node lesions bilateral internal obturators and iliacs) (patient n.16), 1/6 patients (17%) had local involvement with lymph node and bone metastasis, 3 iliac lymph node lesions bilateral and multiple lytic or condensing bone lesions of the pelvis and spine dorsolumbar.

Recidivism assessment: 2/5 patients (40%) had only local recurrence, 2/5 patients (40%) had a local and lymph node recurrence (patient # 12 with involvement left iliac lymph node and patient # 17 with lymph node involvement bilateral obturators and right external iliac), 1/5 patients (20%) had a recurrence local and bone. (multiple bone lesions at the scapular level, costal girl, vertebra lumbar and right iliac wing). (patient n.7). Within the 11 positive MRI exams (5/11 in recurrence assessment and 6/11 in initial assessment) the distribution of the targets detected was as follows: 8/11 patients (73%) had only one local involvement (Figures 1 and 2), 2/11 patients (18%) had local and lymph node involvement (patient # 16 with two bilateral internal iliac ganglionic lesions, patient # 17 with two right external iliac ganglionic lesions), 1/11 patients (9%) had a recurrence local and bony, (a bony lesion of the right iliac wing). (patient n.7). Of the seven patients with negative results, 3 of them (42%) performed the 68GA-PSMA which was positive in the three cases with lymph node involvement (Table 1).

Table 1: The indications of MRI and PET CT are the search for remote location during the initial assessment before a high Gleason score

Cas	Age	PET	IRM	Biopsie		Initial	Recidive	
1	70	SUV max 7.7	Score 5/5	Gleason 8			Initial	
2	73	SUV max 7.4	Score 4/5	Gleason 7			Initial	
3	64	SUV max 2.4	Score +ve, lesion 10mm	Pas d argument pour infiltration cancreuse			Recidive	
4	78	SUV max 3.7	Score 2/5	Pas de lesion compliaue			Recidive	
5	67	SUV max 8.8	Score 4/5	Gleason 7			Initial	
6	54	SUV max 5.8	Aspect normale	Gleason 8			Recidive	
7	79	SUV max 6.3	Score 5/5	Gleason 9			Recidive	
8	72	Pas de fixation	Pas de lesion	Gleason 7 en 2014, apres radiotherqpie			Recidive	
9	66	SUV max 31	Pas de lesion	Aucun structure suspect			Initial	
10	56	SUV max 2.3	Score +ve, lesion 6mm	Gleason 7			Recidive	
11	68	SUV max 4.2	Score 5/5	Gleason 7 en 2012, apres radiotherqpie			Recidive	
12	67	SUV max 6.8	Aspect normale	Gleason 8 en 2012, apres radiotherqpie			Recidive	
13	67	Pas de fixation	Pas de lesion	Gleason 9 en 2013, apresprostactectomie	PSMA positive		Recidive	PSMA positive
14	71	Pas de fixation	Pas de lesion	Gleason 7 en 2014, apres radiotherqpie	PSMA positive		Recidive	PSMA positive
15	67	SUV max 8.5	Score 5/5	Gleason 8			Initial	
16	55	SUV max 9.7	Score 5/5	Gleason 8			Initial	
17	74	SUV max 4	Score 3/5	satsfaite sans complication			Recidive	
18	61	Pas de fixation	Pas de lesion	Gleason 7 en 2008, apres radiotherqpie			Recidive	
19	66	SUV max 8.1	Score 5/5	Gleason 8			Initial	
20	64	Pas de fixation	Pas de lesion	Gleason 7 en 2015, apres radiotherqpie	PSMA positive		Recidive	PSMA positive

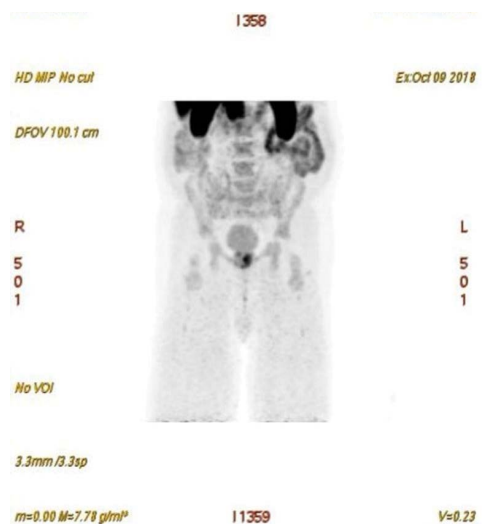


Figure 1. PET-18F acquisition in a 66-year-old patient. We find a zone of intense hypermetabolism focused in the left prostatic compartment.

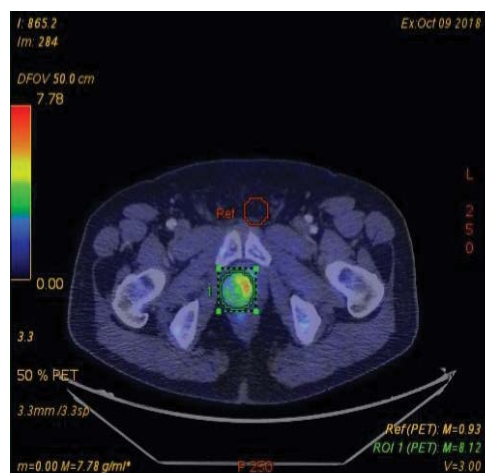


Figure 2. Intense hyper metabolism focused in the left side of prostate. Fusion 18F Choline PET CT, axial section of the pelvis.

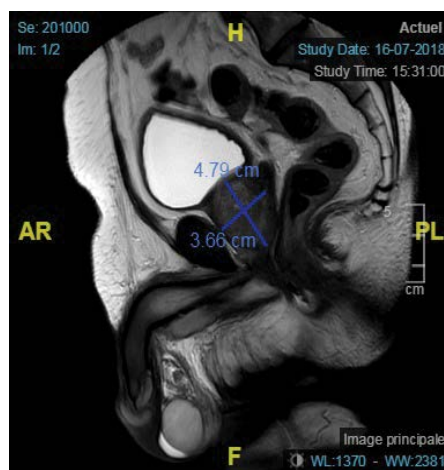


Figure 3. Pelvic MRI with lesion of the left side of prostate in the same patient.

Discussion

Contribution of PET / CT to 18FDG

The contribution of PET / CT to 18FDG may prove useful in aggressive cancers and dedifferentiated, but its contribution is limited in most prostate cancers which express only a few Glut-1 type carriers and do not concentrate little or no FDG [6-8]. The development of choline analog tracers labeled with 18F allows currently performing PET / CT exams in centers that do not have a cyclotron.

The diagnostic value of 18F-FCH PET / CT in the initial assessment is not yet validated, the results of the various published studies being contradictory [9-11]. Setting evidence of the primary tumor is variable and the specificity of choline is not sufficient to differentiate foci of prostatitis from a tumor focus. The value of PET / CT is also reported as lower than MRI for local extension assessment extraprostatic. Some authors have proposed the two-phase acquisition technique, early and late (by early pelvic acquisition in our study), based on the observation of a specific increase in intratumoral uptake compared with benign involvement [12,13]. If some authors believe that the

detection sensitivity of metastases lymph node is too weak, especially for small households, others have found more encouraging results, a size greater than 5 mm seems to be the detectability threshold, [14-16]. If 18F-FCH PET / CT is not recommended in the initial assessment, it may be useful in conducting targeted diagnostic biopsy in patients with PSA high and negative prior biopsies [17].

On the other hand, the use of PET / CT at 18F FCH is currently recommended for the detection and localization of recurrences in biochemical relapse patients [9,10,13,18,19]. The important things to take into account for the indication for an examination at the 18F-FCH are the PSA doubling time, the initial stage, Gleason score, and the time from response to initial treatment to relapse. The bone scan is still currently recommended for metastasis bone, the use of 18F-FCH being used most often only for the evaluation of response of metastases to a change in treatment, the activity of the tumor disease possibly be differentiated from a flare-response [20]. Its specificity even seems to be slightly higher 18F-NaF PET / CT scan, but the number of studies is limited and the characterization of lesions benign is not validated [21]. However, keep in mind that the 18F-FCH is not a specific tracer for prostate adenocarcinoma. This radiopharmaceutical has been studied in other types of tumors with equally promising results in carcinoma hepatocellular, breast cancer and brain tumors [22-24]. If this radiopharmaceutical makes it possible to differentiate a tumor recurrence from a sequel post-radiation therapy in the brain, caution is advised when interpreting uptake, even high, in the prostate gland and at a distance [25]. The specificity of the 18F-FCH lies in part on the selection of patients and their comorbidity. In comparison in our study, we found 85% (6 out of 7 patients) who had positive results in the initial assessment, either with localization only or with lymph node and bone metastasis with evidence of significant link between Gleason score and PET choline positivity. In our study, there was a 38% PET choline positivity (5 out of 13 of the patients) for the localization of local recurrences or with lymph node and bone recurrences. We found also seven patients with negative PET / CT 18F-FCH and MRI results, 3 of them (42%) performed the 68GA-PSMA test which was positive in the three cases with lymph node damage.

Comparison with MRI data

Prostatic MRI allows detection, localization, estimation of the volume of foci tumor and extension workup. This information coupled with the results of targeted biopsies allow to obtain a precise mapping of CaP and to better adapt the management therapy of each patient. MRI also has a role in monitoring treatments focused and detection of local recurrences after curative treatment. Monitoring the PSA level after radical prostatectomy, radiotherapy or focal therapies (brachytherapy and HIFU) allows the selection of patients at risk of recurrence. If the elevation of the PSA level after radical prostatectomy makes confirmation of local recurrence less useful on the other hand, by imagery [26], its localization can be carried out by MRI. Indeed, after radiotherapy or focused ultrasound, recurrences may benefit from remedial treatment [27,28]. This is to say the interest both of an early diagnosis, but also of a mapping early in this recurrence. After radiotherapy, the prostate appears in a diffuse T2 signal, with loss of zonal anatomy [29], which limits the value of this type of sequence. On the other hand, dynamic MRI with pelvic antenna only [30] and spectroscopy with endorectal antenna

[31] have given excellent results in the early diagnosis and localization of recurrences local after radiotherapy. Preliminary data also suggest that dynamic MRI would allow precise localization of local recurrences after HIFU treatment [32].

On the other hand, since the study by Epstein [33], extraprostatic invasion was classified in focal (or microscopic) and extensive (or extensive). The first is undetectable and its prognosis joins that of confined cancer [33]. The second is accompanied by biological progression after radical prostatectomy in approximately 70-75% of cases [34]. The distinction between these two types of invasion to assess the performance of MRI has been applied in two studies [35,36] One of them concludes that the focal invasion is not detectable by MRI [35] and the other reports a detection rate of 14% for a capsular crossing of less than a millimeter thick [36]. Both studies find a sensitivity of around 70 % to detect extended extracapsular extension. The Figure 3 of 95% in the series of Bartolozzi [37] without a drop in specificity can only be explained by

a selection bias patients probably with extensive lesions whose extraprostatic extension is detectable with high sensitivity. In comparison in our study, all patients underwent pelvic MRI multiparametric (T2, diffusion, dynamic after injection), we find 85% (6 out of 7 of patients) who have had positive results in the initial assessment which can be superimposed on that found in PET / CT at 18F-FCH. On the other hand, we find 38% (5 out of 13 of the patients) for the localization of local recurrences or with an extra prostatic extension.

New technology

PET-MRI in the loco regional extension report and in the relapse; The MRI presents an excellent resolution contrast at the soft tissue level, by delimiting markedly the prostate and seminal vesicles of fat and adjacent tissue. It stays insufficient in the detection of tumor and lymphadenopathy, this is why, the association with new techniques such as the enhancement study must complete it after injection of contrast (diffusion MRI or spectroscopy). PET-MRI is part of this development imaging, with parametric fusion of MRI images in T2 sequence with metabolic study brought by the PET.

Conclusion

18 (F) Choline PET / CT seems in our sensitive study like MRI in initial assessment or for detect local recurrence and diagnose lymph node recurrence or metastatic. The use of PET / MRI combination technologies and the emergence of new tracers even more sensitive and specific than choline can improve performance diagnostic.

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