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[F^{18}]-fluoroethylcholine combined in-line PET-CT scan for detection of lymph-node metastasis in high risk prostate cancer patients prior to radical prostatectomy: Preliminary results from a prospective histology based study

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ABSTRACT

Purpose: To evaluate the diagnostic potential of PET/CT using ([F^{18}]fluorethylcholine (FEC) for lymph node (LN) staging in high risk prostate cancer (PCa) patients prior to radical prostatectomy (RP).

Patients and methods: Twenty patients with localized PCa and ⩾20% LN risk according to a published nomogram were prospectively enrolled. FEC PET/CT was done minimum 14 d after prostate biopsy. Afterwards, open RP and extended pelvic LN dissection (ePLND) was performed. Clinical stage, Prostate Specific Antigen (PSA) and biopsy Gleason Grading were assessed and histopathological evaluation of the RP-specimens and dissected LN has been performed. Results from PET/CT were compared with LN metastasis according to their anatomical site.

Results: Overall, 285 LN have been removed with a mean number of 15 nodes per patient (7–26). Of the 20 patients, 9 men were LN positive (45%), which corresponds to 31 positive LN with a mean size of 7 mm (0.8–12 mm). Dissection of the obturator fossa, external iliac artery/vein and internal iliac artery/vein revealed 36%, 48% and 16% of positive LN, respectively. FEC PET/CT did not detect one single positive LN, thus was false-negative in 31 metastasis and true negative in 254 LN.

Conclusion: Based on our results which confirmed experience from previous studies, FEC PET/CT scan did not prove to be useful for LN staging in localized PCa prior to treatment and should thus not be applied if clinically occult metastatic disease is suspected.

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1. Background

Lymph node (LN) metastasis in prostate cancer (PCa) patients is considered as systemic disease, since an only 10% biochemical progression-free survival rate following radical prostatectomy (RP) is obtained.[1] Nevertheless, reasonable long term survival is observed in LN positive patients if a multimodal approach is applied, comprising lymph node dissection (PLND) during RP to reduce disease burden followed by radiotherapy and/or systemic treatment.[2–4]

Since conventional imaging techniques such as magnetic resonance imaging (MRI) and computed tomography (CT) reveal disappointing ability for LN staging,[5] extended pelvic lymph node dissection (ePLND) templates[6] or the inclusion of radioisotope guided sentinel LN detection represent means to increase surgical nodal count.[7] Recently, novel MRI based techniques have been suggested with promising results including MR lymphography[8] or MR spectroscopy.[9]

The combination of CT with positron emission tomography (PET), which allows image fusion of anatomic and metabolic information, has been proposed as another means to advance LN staging prior to treatment.[10] Therefore, several radiopharmaceuticals have been investigated for clinical use. While ^{18}F-fluorodeoxyglucose (FDG) demonstrated disappointing outcome for PCa imaging,[11] more promising performance could be demonstrated by the application of ^{11}C or ^{18}F labeled choline derivatives.[10,12] Encouraging performance has been reported using ^{11}C–Choline PET/CT for LN staging prior to therapy (sensitivity ranging from 40% to 80% while consistently reporting high specificity),[10–13] whereas limited data is available addressing the potential of ^{18}F-fluoroethylcholine (FEC) (the commercially available and, thus widely distributed tracer) for detection of metastatic spread.[14,15]

Therefore, the aim of our study was to prospectively evaluate the diagnostic performance of FEC PET/CT for LN-staging in patients at high risk of nodal metastasis prior to RP. Our study design includes histopathological work-up of RP-specimens and lymphatic tissue for verification image findings, which may allow for analyzing on a per-patient and per-node basis.

2. Patients and methods

2.1. Patients and clinical assessment

Between February and October 2007, 477 patients with biopsy proven PCa suitable for RP were prospectively evaluated. Patient selection was based on a previously published nomogramm for risk assessment of nodal metastasis during RP and ePLND.[16] Accordingly, patients with a positive LN risk of $\geqslant$20% (e.g. PSA 15 ng/ml, cT2a, biopsy Gleason 3 + 4) were considered for study inclusion. Patients with a positive bone scan or neoadjuvant hormonal treatment were excluded from the study, leaving 20 patients eligible for prospective enrolment.

For all patients, clinical stage and PSA-measurement was reassessed at our institution, if initially performed outside. In addition, external biopsy specimens were re-reviewed by an institutional pathologist. Gleason Grading for prostate biopsy was done according to the 2005 Gleason Grading classification.[17] PET/CT was done at least 14 d following prostate biopsy. For all participants, informed written consent was obtained and the study protocol was approved by the institutional review board.

2.2. Radiopharmaceuticals, imaging protocol and image reconstruction

2.2.1. Production of FEC

^{18}F-fluorethylcholine (^{18}F-FEC) was synthesized at our institution by a 2-step 1-pot method as reported previously by Hara et al.[12] In brief, in the first step, the dried ^{18}F fluoride ions reacted with 1,2 bis(tosyloxy)ethane (Fluorochem Ltd.) in the presence of Kryptofix 2.2.2 phase transfer catalyst in acetonitrile at 80 °C for minutes yielding $^{2\text{-}18}$F-fluoroethyl tosylate. After completion of this reaction, the solvent was evaporated at 60 °C under helium flow, and 0.5 ml of di-methyl-aminoethanol was added to the dry residue. The second reaction took place at 100 °C, and resulted ^{18}F-FEC. The unreacted precursor was evaporated at 130 °C. The residue was dissolved in 2 ml of water and passed through a cation exchange cartridge (Sep-Pak Accel Plus CM; Waters Corp.). The cartridge was washed with 10 ml of ethanol and 10 ml of water subsequently, and ^{18}F-FEC was eluted with 5 ml of saline solution from the cartridge. The product was sterilized by filtration, and had a radiochemical purity of more than 99%.

2.2.2. PET/CT acquisition and image processing

Patients were instructed to fast for at least 6 h before the injection of 300–400 MBq FEC. Blood glucose level was measured before injection and 300–400 MBq FEC was administered at glucose levels <200 mg/dl. In order to delineate gastrointestinal tract on the CT images, 20 ml oral contrast media (Gestrolux, Sanochemia, Vienna, Austria) solved in 1 l water was given. All PET/CT images were acquired using a hybrid PET/CT (Gemini GXL10, Philips Medical Systems, The Netherlands). Sixty minutes after injection of FEC a whole body low dose CT scan for anatomic localization and attenuation correction was performed. The acquisition parameters were as follows: 120 kV, 50 mAs, slice thickness 5 mm, no gap, pitch 1.1, rotation time 0.5 s, matrix 512×512, shallow breathing. Immediately after CT acquisition whole body PET images were acquired from head to feet in craniocaudal direction. All PET scans were performed in 3-dimensional mode. Emission images were acquired for 1.5 min per bed position (effective axial field-of-view 180 cm per bed position). Transaxial images of the FEC distribution were reconstructed using the iterative 3D-LOR algorithm of the system software (matrix size 144×144, voxel $4 \times 4 \times 4$ mm). In plane spatial resolution was about 8 mm.

PET, CT and fused PET/CT images were available for review and were displayed in axial, coronal and sagittal planes. The PET data were displayed as non-corrected and attenuation-corrected images and also in a rotating maximum-intensity projection.

2.2.3. Interpretation and analysis of PET/CT images

An interdisciplinary team, including two nuclear medicine physicians and two radiologists, with knowledge of the pa-

tient's clinical history evaluated all studies. Primarily, PET and CT images were read independently: PET images were evaluated by two medical physicians (one with 12 years' experience and one with 2 years' experience) and CT images were evaluated by two radiologists (one with 15 years' experience and one with 2 years' experience). Finally studies were judged by consensus of physicians from both fields. The diagnosis of LN involvement of malignant disease on conventional imaging (CT) was performed by two expert radiologists who used morphologic criteria such as LN enlargement with a cut-off value for pathological lesions of $\geqslant$10 mm in maximal axial diameter.

Foci of increased FEC uptake are recorded. Studies showing at least one area of increased FEC uptake with intensity higher than that of surrounding tissues, localized by hybrid images to an area that do not correspond to the physiologic biodistribution of the radiotracer, are defined as positive.

2.3. Surgical approach and histopathological evaluation

As surgical procedure, an open RP was performed as described previously.[18] After removal of the prostate, ePLND was carried out including the region of the (1) obturator fossa (dorsal the external iliac vein, along the obturatorial nerve), (2) along the external and (3) internal iliac artery up to the common iliac artery. Lymph nodes were collected separately according to their anatomic site for selective histopathological work-up.

For histology, the prostate was processed in 3 mm mount sections according to the Stanford protocol.[19] The pT stage was assigned according to the 2002 AJCC staging system for PCa.[20] For standard histopathologic workup of lymphatic tissue [hematoxylin–eosin (H&E) staining], all LNs were totally paraffin-embedded and the resulting blocks were serially sectioned at 2–3 levels.

2.4. Statistical approach

Positive lymph nodes have been categorized in six anatomic fields according to their origin (left/right obturator fossa and/or left/right external artery and/or left/right internal iliac artery) and then compared with the corresponding anatomic site on preoperative PET-CT. Sensitivity/specificity analysis was selected to describe the diagnostic performance of FEC PET-CT LN staging. *Sensitivity* was defined as the proportion of reference test positive (LN metastasis) subjects who test positive with FEC PET-CT. Similarly, *specificity* is defined as the proportion of reference test negative (no LN metastasis) subjects who test negative with FEC PET-CT.

3. Results

Disease characteristics of all patients and those with positive LN are presented in Tables 1 and 2, respectively. Overall, 285 LN have been harvested with a mean number of 15 nodes per patient (7–26). With respect to the anatomic site, 154 (54%), 86 (30%) and 46 (16%) LN were found along the obturator fossa, external iliac artery/vein and internal iliac artery/vein, respectively (Table 3). Of the 20 patients, 9 men had LN metastasis (45%), which corresponds to 31 out of 285 (11%) LN with a mean size of 7 mm (0.8–12 mm). Dissection of the obturator fossa, external iliac artery/vein and internal iliac artery/vein revealed 36%, 48% and 16% of positive LN, respectively. FEC PET/CT did not detect one single LN metastasis, thus was false-negative in 31 metastasis and true negative in 254 LN. The largest LN metastasis not seen with FEC PET/CT scan was 12 mm. As we could not detect any positive lymph node with our method, we used the SUV for checking the quality of tracer. Indeed, we had elevated prostate accumulation with known PCa corresponding to the literature. In summary, these SUV values ranged from 2.1 to 4.1 and were merely determined for quality control, not for the identification of metastases.

Table 1 – Clinical and pathologic characteristics of the study cohort (n = 20).

Variable	No. patients (%)
Clinical stage (2002 TNM)	
T1c	9 (45)
T2a	5 (25)
T2b	5 (25)
T2c	1 (5)
Biopsy Gleason grade	
$\leqslant$3 + 3	1 (5)
3 + 4	2 (10)
4 + 3	10 (50)
$\geqslant$4 + 4	7 (35)
Pathologic stage (2002 TNM)	
pT2a-c	4 (20)
pT3a	8 (40)
pT3b	8 (40)
pNpos	9 (45)
Pathology Gleason sum	
3 + 4	8 (40)
4 + 3	9 (45)
$\geqslant$4 + 4	3 (15)
Age (years), median; 25–75th percentile)	64.5; 58–68.5
PSA (ng/ml), median; 25–75th percentile)	12.6; 8.1–27

As an example of imaging result, Fig. 1 demonstrates FEC PET/CT findings of patient No. 5 (see Table 4) with pathological FEC accumulation in the prostate (standardized uptake value [SUV] 2.5) but lack of tracer uptake in any pelvic LN. Histopathological evaluation revealed a bilateral prostatic tumor (6 cm in size) with bilateral extraprostatic extension and seminal vesical invasion, pT3b pN1, Gleason 4 + 3 with 4 LN metastases along the left external iliac artery (max size 12 mm).

4. Discussion

Radical prostatectomy combined with PLND and adjuvant treatment options has been demonstrated to provide reasonable long-time survival in men with *pN positive* disease.[3] Retrospective studies point to evidence that a survival benefit might be achieved if an ePLND is done to increase detection of micrometastasis[17,18]; however definitive confirmation is pending in absence of prospective randomized trials. Since conventional imaging modalities have severe limitations for

Table 2 – Disease characteristics of patients with positive lymph node during radical prostatectomy (9/20 [45%]).

Patient	TNM-stage	Rp Gleason	PSA (ng/ml)	No. of removed nodes	No . of positive nodes ($n = 31$)	Max. size of pos. node (mm)	Location of positive node
No. 1	pT3bpN1	4 + 3	56.0	7	1	6	Fossa obt.
No. 2	pT3apN1	4 + 3	49.0	6	1	5	Fossa obt.
No. 3	pT3apN1	4 + 3	12.6	10	1	0.8	A. illiac. Int.
No. 4	pT3apN1	3 + 5	8.5	15	2	1	A. iliac. Ext (2)
No. 5	pT3bpN1	4 + 3	45.0	19	4	12	A. iliac ext (4)
No. 6	pT3bpN1	4 + 3	10.80	14	4	7	Fossa obt (2) A. illiac ext. (2)
No. 7	pT3bpN1	3 + 4	7.80	22	4	10	Fossa 0bt (2) A. illiac ext (2)
No. 8	pT3bpN1	4 + 5	48.35	15	6	8	Fossa 0bt (3) A. illiac ext (2) A. iliac. Int (1)
No. 9	pT3bpN1	5 + 3	16.49	17	8	6	Fossa 0bt (4) A. illiac ext (2) A. iliac. Int (2)

Abbreviations: RP, radical prostatectomy; PSA, prostate specific antigen.

Table 3 – Distribution of removed and metastatic lymph nodes according to their anatomical site.

Nodal site	Number of removed nodes	Number of positive nodes
Overall	285 (100%)	31 (100%)
Obturator fossa	154 (54%)	11 (36%)
External iliac artery	86 (30%)	15 (48%)
Internal iliac artery	45 (16%)	5 (16%)

accurate LN staging, the use of nomograms represents a valid alternative to select patients for ePLND in order to reduce morbidity and/or overtreatment in men with non metastatic disease.[16–21]

Recently, the combination of conventional imaging-techniques such as PET/CT using radiolabeled Choline derivatives has merged as potential modality to improve LN staging prior to treatment.[10] Choline is a precursor of phosphatidylcholine, a major constituent of membrane lipids.[22] Membrane lipid synthesis is activated during cell proliferation leading to an increased Choline uptake. Encouraging, but partially conflicting clinical results for PCa has been reported for ^{11}C-Choline, ^{18}F-fluorocholine and ^{18}F-fluoroethylcholine.[10,13,14]

^{18}F-labelled Choline offers the advantage of a physical half-life of 110 min and is therefore more widely distributed as commercially available tracer. ^{18}F-Choline differs from FEC, by a single methylene group. Previous findings that ^{18}F-Choline and FEC have similar biodistributions in mice suggest that electronegativity effects of the α-fluorine atom are well

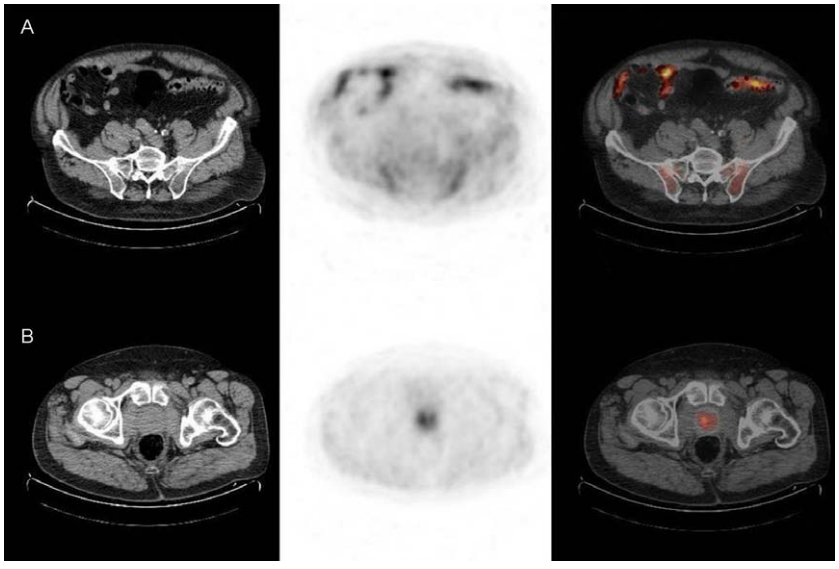

Fig. 1 – Conventional and PET transaxial images at pelvic level of patient No. 5 demonstrates lack of pathological tracer accumulation in 4 LN metastasis along the left iliac artery (A) but an increased Choline uptake (SUV = 2.5) in the prostatic tumor (B).

Table 4 – Histology based clinical studies for PET/CT based LN staging prior to radical prostatectomy.

Author	Tracer	N	No. of detected nodes (sensitivity)	Specificity
Hacker et al.[11]	F^{18}-Fluorocholine	20	n.a. (10.0%)	n.a.
Steuber et al.	0F^{18}-Fluoroethylcholine	20	0/31 (0%)	100%
Husarik et al.[12]	F^{18}-Fluorocholine	18	1/4 (25.0%)	n.a.
De Jong et al.[9]	C^{11}-Choline	67	n.a. (80.0%)	96.0%
Schiavina et al.[10]	C^{11}-Choline	57	17/41(41.0%)	99.8%
Budiharto et al.[19]	C^{11}-Choline	15	3/12 (25.0%)	n.a.

tolerated by the processes. The potential disadvantage observed for both, FEC and ^{18}F-Choline might consist of a notably higher secretion into the urinary system compared with ^{11}C-Choline, since the shorter residence time of FEC in the blood may limit the diffusion of tracer into areas that are poorly perfused. Hence, there is potential for poor sensitivity of this technique to detect malignant lymphatic tissue that is poorly perfused.[23]

Accordingly, histology based clinical studies using ^{18}F-Choline derivatives and PET/CT for LN-staging published so far reveal consistently disappointing outcome.[14,15] In our study, 20 patients with an intermediate to high risk of node positive disease according to the Briganti LN nomogramm[16] have been prospectively enrolled. After histopathologic evaluation of 285 LN, 31 metastases could be identified, ranging from 0.18 to 12 mm diameter in size. None of the metastases has been detected by F^{18} FEC PET/CT, which corresponds to 31 false negative but zero false positive cases.

Similar results have been reported by Hacker et al previously.[14] Among 20 patients with clinically localized PCa, ^{18}F-fluorocholine (FCH) PET/CT LN staging achieved 10% sensitivity compared with 80% sensitivity for radio guided sentinel LN dissection. Of note, the largest metastasis that was missed in their study by FCH PET/CT staging was 8 mm. More recently, Husarik et al. reported on 25 patients with 115 removed LN and only 4 nodal metastases at histology.[15] Only one of 4 LN metastasis with a size of >10 mm showed pathological FCH accumulation while 3 lesions with a metastatic burden of $\leqslant$5 mm in diameter size were PET negative. All authors concluded that FCH PET/CT was not suitable for LN staging prior to RP, which is in accordance to our own experience.

^{11}C-Choline offers the advantage of low secretion into urine, which is crucial for imaging urologic malignancies, however is restricted to on-site cyclotron centres due to a short physical half-life of only 20 min. A limited number of histology based studies using ^{11}C-Choline for LN staging prior to treatment are available. Remarkable diagnostic performance has at first been reported by de Jong et al. in 2003 who investigated 67 patients with clinically localized PCa.[10] Accordingly, 80% and 70% sensitivity could be achieved on a per-patient and per node basis, respectively. However, the mean pre-operative PSA was remarkably high (mean 123 ng/ml, range 12.8–500 ng/ml), which clearly does not reflect patient populations currently treated for localized PCa. Schiavina et al. achieved 60% and 41% sensitivity on a per-patient and per-node analysis, respectively while maintaining high specificity (97.6% and 99.8%, respectively).[13] Intriguingly, 70% of micrometastases (2.0–4.9 mm diameter) have not been detected while almost one third of macroscopic lesions (>10.0 mm) have been missed by ^{11}C-Choline PET/CT staging. Overall, ^{11}C-PET/CT LN staging demonstrated a higher specificity and accuracy than the Briganti nomogram[16]; however, the corresponding areas under the Receiver Operation Characteristics (ROC) curve were not statistically different. More recently, two further small series have been published with disappointing outcome. Budiharto et al. investigated 15 patients followed by ePLND.[24] Only 3/12 metastatic nodal regions haven been correctly identified by PET/CT (sensitivity 25%), but there were no false positive cases. Schumacher and colleagues reported on 30 patients without nodal metastasis but false positive PET-signal in 10/30 patients using C^{11}-Acetat PET/CT (33% false positive, 66% true negative).[25]

In conclusion, histology based studies on ^{11}C-Choline LN staging prior to treatment are limited and demonstrate conflicting outcome. The initially reported improvement over studies applying FDG-PET could not be convincingly confirmed in later studies. The subsequent virtual decline in the clinical performance of ^{11}C-Choline PET/CT could be the effect of enrolling less selected patient populations.

The concept of ^{11}C-Choline-PET/CT guided salvage PLND for occult local progression in patients with biochemical recurrence (BCR) following RP has been introduced by Scattoni et al.[26] After ^{11}C-Choline-PET/CT scan, salvage ePLND in 25 patients with a pathological PET-CT uptake has been performed. Sensitivity and Specificity on a per-lesion analysis was 64% and 90%, respectively. The true positive metastases had a mean maximum size of 15 mm versus 6.3 mm size for false negative lesions. Subsequently, several authors reported their experience using ^{11}C-Choline-PET/CT for patients with BCR following RP or radiotherapy to detect occult recurrent disease.[27,28] All investigators concluded that PET/CT imaging using ^{11}C-Choline might be a valuable tool for detecting progressing PCa and that imaging findings would have implications for local salvage treatment. However, results should be interpreted with caution. First, small sample size and retrospective design are commonplace. Second, patient populations considered for investigation are mainly selected towards men with a positive PET-result and, except of the work presented by Scattoni et al., histology has been gained from PET-positive lesions only. Thus, true prevalence of metastatic lesions, in particular number of false negative nodes remains unclear, which are inevitable for accuracy evaluation of a diagnostic test. Furthermore, median PSA-levels of patients with a true positive PET-scan in the outlined studies was high (median 3.1–15.2 ng/ml) which is far beyond the therapeutic window if local recurrence is suspected. Accordingly, radiation for BCR, the only established salvage treatment option gains best outcome in men with PSA levels

<1 ng/ml (5-year progression free survival rates of 50%),[29] a range clearly not covered by PET/CT. Corresponding survival rates in men with a PSA > 1.5 ng/ml are barely 20%.

Several limitations of our study deserve it to be mentioned. The number of 20 patients is rather small, however since 31 metastases out of 285 resected nodes have been harvested, we believe that increasing the number of patients would not have had any impact on our results. Lack of any pathological FEC uptake in histopathologically confirmed LN metastasis might also impact the generalizability of our results. However, pathological FEC accumulation in the prostate was seen throughout all patients and can thus be considered as positive control of our PET-CT imaging protocol. In addition, the same protocol is successfully applied for detection of PCa bone metastasis or macroscopic lesions of metastatic PCa at our institution.

5. Conclusion

Results from our histology based prospective study revealed disappointing outcome of LN-staging by ^{18}F FEC PET/CT scan prior to RP. According to our results, PET/CT using ^{18}F FEC often misses lesions <10.0 mm, resulting in a large number of false negative findings in clinically frequent small LN metastases in high risk pre-operative patients (poor sensitivity). Based on our results whilst taking into account cost-benefit aspects, ^{18}F FEC PET/CT cannot thus far be recommended for routinely clinical use to detect occult LN metastasis prior to initial treatment. Development of new tracers with considerably higher affinity to tumour cells and probably further developments of PET/CT imaging may represent challenges for future research activities in PET/CT based PCa staging.

Conflict of interest statement

None declared.

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