[18]F choline PET/CT in Prostate Cancer

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1. Introduction

Many tumour lesions can be detected using standard anatomical imaging (CT and MRI), but this may be difficult in soft tissue areas or when there is distorted anatomy after previous treatment. In these situations functional imaging, for example with [18]F-FDG PET/CT, may provide good tumour detection, staging, response evaluation and re-staging. However, not all tumour types demonstrate a sufficiently elevated glucose metabolism to allow good discrimination from surrounding normal soft tissues. In addition, some normal tissues have a very high glucose metabolism that prevents detection of adequately FDG-avid tumours, for example the brain. Other pathways than glucose metabolism, e.g. choline metabolism, may provide an alternative detection strategy in these situations. The amino-alcohol choline is an essential part in the formation of the phospholipids in the cell membrane. Cellular proliferation requires synthesis of new membrane components, and thus choline is required for tumour proliferation. Choline can be labelled with [18]F to form [18]F-methylcholine (FCH). After intravenous injection, FCH is accumulated by cells with increased turnover of phospholipids. FCH cannot leave the cell after processing by choline kinase. The cumulative uptake of FCH thus reflects cell proliferation, although this relation is not linear with other measurements of proliferation such as Ki-67. Imaging with FCH PET can be applied for visualisation of tumour locations that may not (always) be detected with FDG PET.
Imaging with FCH has some disadvantages. Although the detection of several tumour types may benefit from FCH PET, evidence in literature is currently limited mainly to applications for prostate cancer. This evidence is derived from relatively small studies, some of which have used [11]C-choline, which is not entirely comparable to [18]F-choline. FCH is generally more expensive than FDG. Administration of FCH leads to radiation exposure for patients and personnel, although this is comparable to FDG PET. These disadvantages are generally accepted, because there are often no adequate alternative diagnostic procedures available for the indications listed in this document.

2. Methodology

This guideline is based on available scientific literature on the subject, the previous guideline (Aanbevelingen Nucleaire Geneeskunde 2007), international guidelines from EANM and/or SNMMI if available and applicable to the Dutch situation.

3. Indications

- Prostate cancer, restaging: at biochemical recurrence, when aggressive local salvage therapy is considered (e.g. if there is only local recurrence, solitary lymph node, or

a solitary distant metastasis), and when the chance of a positive scan is sufficiently high (PSA >5, or PSA >1 with PSA doubling time <3 months or with Gleason sum score >7).

- Prostate cancer, primary staging: when standard diagnostic procedures do not provide adequate staging of nodal or distant disease (e.g. doubtful CT or MR of lymph nodes and inability to achieve invasive confirmation). FCH PET may be considered as a replacement for bone scintigraphy for primary staging based on local availability and preference. FCH PET is not adequate for tumour visualization in an untreated prostate due to physiological uptake in functional glandular tissue.

4. Relation to other diagnostic procedures

There are multiple diagnostic strategies for restaging of prostate cancer when biochemical recurrence is detected. When salvage treatment is not an option due to patient factors, imaging may not be needed at all or may be limited to evaluation with bone scintigraphy. When salvage treatment of the prostate area, lymph nodes or distant disease is potentially an option, proper re-staging with imaging is required. Multi-parametric MRI (mpMRI) provides good sensitivity and specificity for local recurrence, reasonable sensitivity and specificity for regional lymph nodes, and good sensitivity and specificity for bone metastasis detection in the field of view (pelvic area). FCH PET provides limited sensitivity but good specificity for local recurrence, reasonable sensitivity and specificity for regional lymph nodes, and good sensitivity and specificity for bone metastases. Before local salvage therapy of a detected tumour recurrence is attempted, tumour activity elsewhere in the body must be excluded. Thus a patient will require MRI + bone scintigraphy + X-thorax, or FCH PET alone. A preference for one of these strategies is generally based on local availability and experience.

5. Medical information necessary for planning

- Patient weight
- Medical history
- Prior treatments for prostate cancer (surgical, radiotherapy, hormone)
- PSA level
- PSA doubling time
- Initial Gleason sum score
- Information on current hormone suppression treatment, and PSA response

6. Radiopharmaceutical

Tracer:	^{18}F-methylcholine
Nuclide:	Fluorine-18
Activity:	50-400 MBq
Administration:	Intravenous

The dose administered will be determined by balancing the scanner characteristics, radiation exposure, desired image quality, patient weight, imaging duration, costs, and indication. These considerations will be made based on local factors. The table below provides some doses that have been applied successfully in different centres using different scanners. These data can be used to find a locally applicable dose regimen.

	Emission time per bed position		
Scanner	**1 min**	**2 min**	**4 min**
Standard full-ring PET(/CT)-scanner (eg. Siemens ECAT Exact, Siemens Biograph, Philips Allegro, Philips Gemini, GE), 3D mode	---	4 MBq/kg Min. 200 MBq Max. 400 MBq	2 MBq/kg Min. 100 MBq Max. 200 MBq
next generation full-ring PET(/CT) scanner (eg. Philips Gemini TOF, Siemens Biograph True-V), 3D mode	4 MBq/kg Min. 200 MBq Max. 400 MBq	2 MBq/kg Min. 100 MBq Max. 200 MBq	1 MBq/kg Min. 50 MBq Max. 100 MBq

7. Radiation safety

The radiation exposure from FCH is estimated to be similar to FDG, i.e. about 0,02 mSv/MBq. This is well within the safe margins of clinical diagnostic imaging, and will not provide a significant risk for patients or caretakers.

8. Patient preparation/essentials for procedure

Patients need to be hydrated properly prior to the investigation, to limit radiation exposure to the bladder and kidneys. Further oral hydration is advised after the investigation, to reduce the radiation exposure to the gonads and bladder. Administration of furosemide or bladder catheterization are not required.

9. Acquisition and processing

- Patients are generally positioned on the scanner in supine position. Support materials are recommended to provide stable positioning with reduced chances of patient motion. The arms are preferably positioned upward to minimise attenuation and scatter in the areas of interest.
- The biodistribution of FCH is quick, and seems to occur largely within several minutes after intravenous administration.
- Imaging is generally performed from the groins upward, scanning the pelvic area early after administration to avoid images of the bladder containing a large amount of activity.
- It is currently unclear whether the bladder should be empty or partly filled at the time of injection. A full bladder should be avoided, because most patients will be at risk of incontinence after prior treatment of the prostate.
- There are multiple strategies for timing of imaging after intravenous administration. Due to the quick biodistribution, imaging may start within 2-3 min after injection, thereby aiming to image the pelvic area before unwanted (large) quantities of activity accumulate in the bladder. Dynamic imaging provides more flexibility with regard to

interpretation of the images relative to activity arriving in the bladder. Some centres report good results with late imaging, when some of the activity may already have been voided from the bladder, e.g. at 30-60 min after administration. Some centres prefer dual time point imaging, both early and late after injection, to maximize the chances of good image quality, and to allow for analysis of uptake trends over time (malignant lesions may show increasing uptake as a function of time after injection). This remains a matter of local preference.

- The acquisition duration per bed position and reconstruction parameters depend on the scanner model and the administered dose.
- Attenuation correction is not strictly required for visual interpretation. However (low dose) CT images will greatly improve the identification of small lesions in the pelvic area (e.g. lymph node versus ureter, or the anatomically corrupted prostate bed after prior treatment).

10. Interpretation

Increased uptake of FCH is generally correlated with proliferating tumour tissue. There is no validated quantitative threshold to discriminate tumour from surrounding normal tissue activity. This is especially true in primary staging, where physiological uptake in functional glandular tissue of the prostate may obscure or mimic tumour. The specificity of pathological uptake in the prostate bed after prior prostatectomy or radiotherapy is reported as high, but this will depend on the selected threshold. Most centres report good results using a visual threshold that identifies any uptake, in the prostate area, above normal muscle activity (gluteus maximus) as suspicious for local recurrence. Lymph nodes are generally interpreted visually, resulting in reasonable specificity for the presence of tumour (80-90%). Known false-positive lymph nodes are due to inflammation. The sensitivity and negative predictive value for small lymph node metastases are relatively low, especially on a per-lesion basis. Bone and pulmonary lesions can be identified visually, with good specificity for the presence of tumour. The sensitivity for liver metastases is low due to the high physiological uptake in normal liver parenchyma. Lymph nodes in the mediastinum and pulmonary hila often show relatively high uptake of FCH, which can generally be regarded as physiological or reactive.
The sensitivity of FCH PET for prostate cancer lesions can be reduced due to hormone suppression treatment, when the tumour responds with reduced proliferation. However, sensitivity will remain good if there is proven tumour progression despite hormone suppression treatment.

11. Report

The report should include the administered dose, time between imaging and administration, and a visual interpretation of image quality. A structured report should be provided and should mention uptake in the region of the prostate (or absence thereof), regional lymph nodes, and lesions suspected to be distant metastases, specifically including the bones and lungs. Imaging findings must be correlated with low dose CT in all cases, and with other available imaging where applicable (MRI, bone scan). The interpretation should be correlated with prior treatment and ongoing hormone suppression treatment where applicable.

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