PET/CT IMAGING WITH [^{11}C]CHOLINE AS A RADIOPHARMACEUTICAL FOR THE DETECTION OF RECURRENT PROSTATE CANCER: A RELIABLE PRODUCTION METHOD AND QUALITY CONTROL

TCH-030

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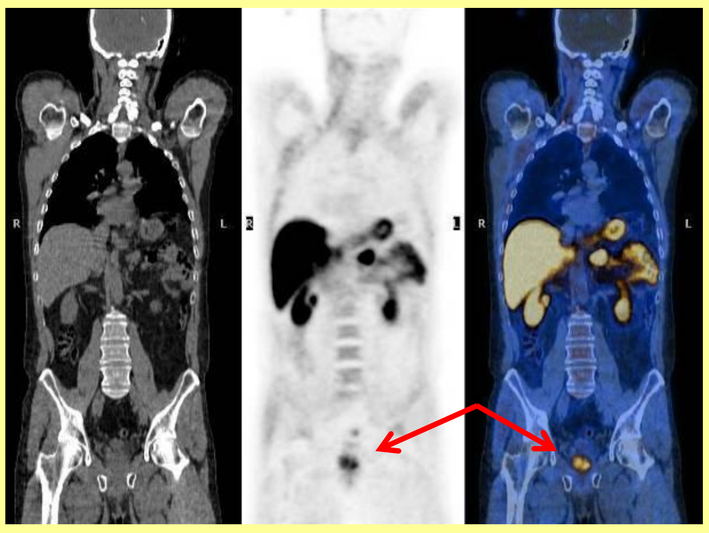
INTRODUCTION

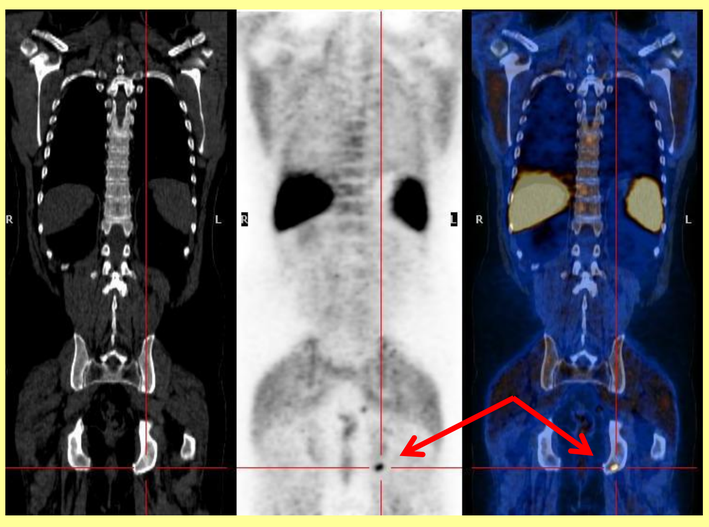
PET/CT Imaging with the radiopharmaceutical [11C]-choline has become a useful tool in the detecting of prostate cancer. Locally advanced prostate cancer is notoriously difficult to image. Current imaging modalities (including transrectal ultrasound, MRI, CT, and bone scan) demonstrate poor performances in the diagnosis and staging of disease. These techniques have not been shown to be sensitive or specific enough to detect metastatic or recurrent disease, defined as a PSA level increase in the blood after curative treatment with surgery or radiation therapy. PET imaging in prostate cancer is infrequent because of the limited success of clinical [18F]-FDG PET/CT.
[18F]-FDG is excreted by the kidneys in the urine, causing an early build-up of activity within the bladder and obscuring the prostate on imaging.
In comparison [11C]choline uptake is prostate specific, rapid, and stable and its urinary excretion is negligible. Tracer uptake on tumoral tissues is correlated to an increased synthesis of membrane substrates:[11C]choline is trapped by phosphorylation taking part on phosphatidylcholine turnover.

MAIN CLINICAL INDICATIONS:

- at staging prostate cancer patients (intermediate-high risk patients) because of the increased possibility of extra-prostatic involvement;
- in patients with biochemical relapse for small LNs and small bone metastasis detection.



PET findings above: intense uptake of [11C]-choline in the prostate gland on both lobes: no evidence of other lesions
PET findings below: evidence of a left ischiatic bone lesion
(left:CT scan, center:PET scan, right: PET/CT fusion)

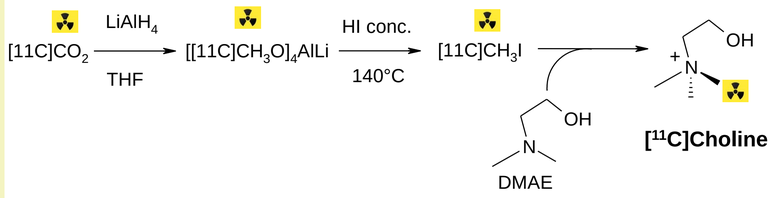


PET-choline was first investigated in the late 1990s although no specific monographs are included in main Pharmacopoeias. The use of this powerful tracer is now based on Clinical Trials but, on September 2012, the FDA approved the production and use of “Choline C11 Injection” to help the detection of recurrent prostate cancer.

OBJECTIVES

This work is aimed to define the key role the pharmacist plays in the preparation of [11C]-choline IMPD for Clinical Trials.
Here we propose this tracer production using an automated synthesizer combined with the use of a disposable cassette. Besides we present the related quality controls (QC) for releasing [11C]-choline as “solutio iniectabilis”.

CARBON-11 LABELING REACTION BASED ON WET-CHEMISTRY APPROACH



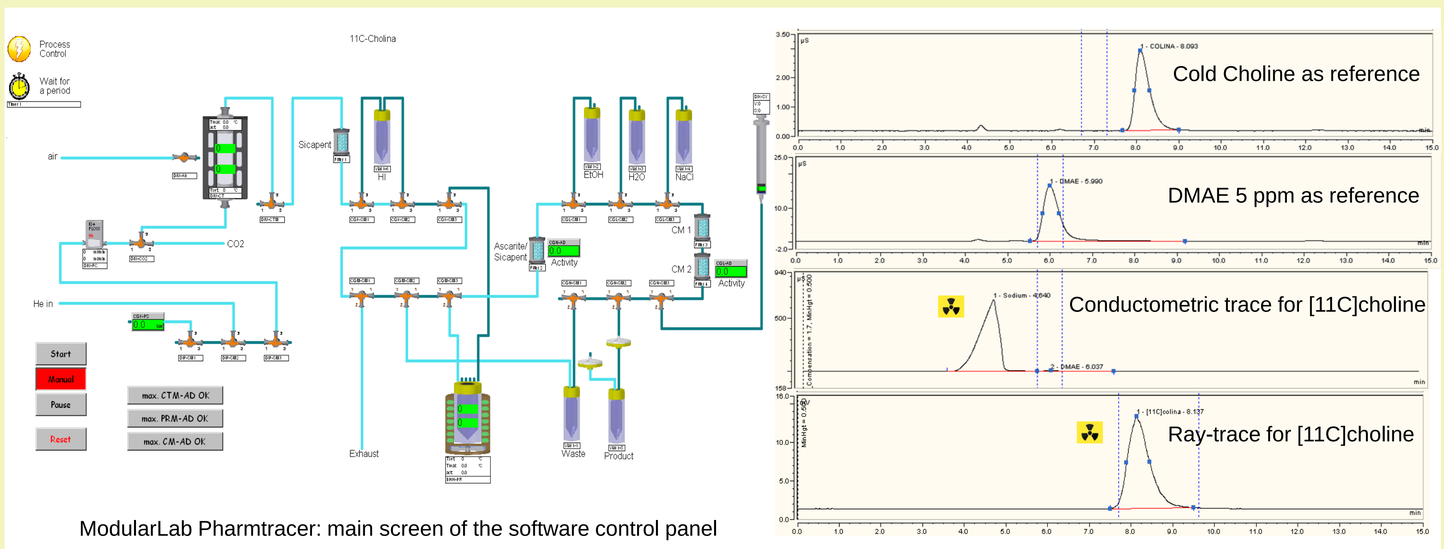
GMP certified reagents and disposables:

$LiAlH_4$ Lithium Aluminum Hydride in tetrahydrofuran (ABX, Germany)
HI conc Hydroiodic Acid 57% (ABX, Germany)
DMAE DimethylAminoEthano (ABX, Germany)
Water, Ethanol 99% and Saline (Bbraun)
C4-C11-MEI-COL disposable cassette (Eckert & Ziegler, Germany)

[11C]choline	Reference	Average	SD
Final volume (ml)	-	10,0	0
Activity (MBq) End Of Synthesis	-	9900	460
Synthesis time (min)	-	16	1,2
Yield (ndc) %	-	18.9	1,3
Yield (dc) %	-	22,7	3,7
Appearance	Clear	Clear	-
pH	5,5-8	6,5	0,7
DMAE conc. (mg/l)	< 5	1,6	1,1
Unspecified Impurities (%)	< 1	nd	-
Radiochemical Purity (%)	> 95	> 99	0,02
Radionuclidic Purity (%)	> 99	>99.9	-
Residual Solvents : Ethanol (mg/mL)	< 5	1,5	1,2
Residual Solvents : Methanol (mg/mL)	< 3	nd	-
Residual Solvents : THF (mg/mL)	< 5	nd	-
Sterility	sterile	sterile	-
Colony-forming units cfu/ml)	0	0	-
Bacterial Endotoxines(IU/ml)	< 17.5	< 1	-

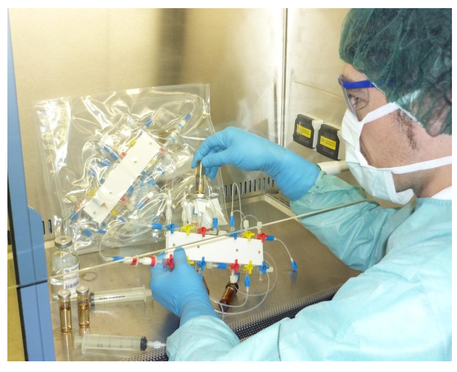
Table 1: Results during validation (mean of 3 syntheses); nd not detectable

REMOTE CONTROLLED PLATFORM FOR SYNTHESIS AND HPLC [^{11}C]CHOLINE TRACES

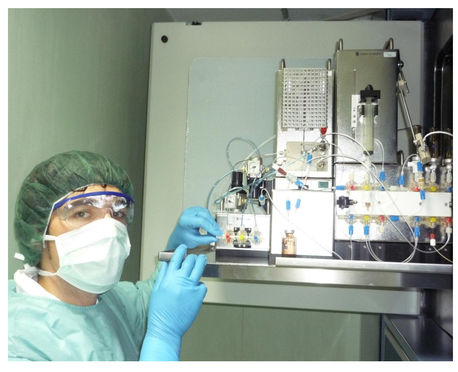


ModularLab Pharmtracer: main screen of the software control panel

[^{11}C]-CHOLINE SYNTHESIS AND PATIENT DOSE PREPARATION FOR ADMINISTRATION



Fast and easy preparation adhering to GMP production standards for the disposable cassette



Insertion of the disposable cassette with reagents on the automatized synthesizer

Preparation of the radioactivity dose for patient administration of [11C]choline

MATERIALS AND METHODS

General

The “Guidelines on Good Radiopharmacy Practice (GRPP)” issued by the Radiopharmacy Committee of the EANM (European Association of Nuclear Medicine) is a useful reference for quality guarantee for small-scale preparation of radiopharmaceuticals. Addressing to this document and literature we prepared and validated our “[11C]choline injection” production starting from GMP grade reagents and disposables [1].

[11C]choline production

Synthesis was performed on a ModularLab PharmTracer (Eckert & Ziegler) [2]. [^{11}C]CO_2 produced by a 11 MeV cyclotron (Eclipse, Siemens) was first trapped on a molecular sieves column and then released at 400°C into the reactor module under Helium flow (20ml/min), through a dehydrating agent P_2O_5 (Sicapent). [^{11}C]CO_2 was bubbled in a solution of $LiAlH_4$ (0.3ml, 0.2 mol/l in THF) and the solvent was evaporated at 80°C. Hydroiodic acid 57% (0.3 ml) was then added and the reactor was warmed at 140°C. The produced [11C]CH_3I was distilled, purified by a column of P_2O_5/Ascarite. and delivered to a cation-exchange resin Sep-Pak (Access CM) where DMAE (dimethyl amino ethanol, 50 microl, 493 mmol) was previously loaded. The cartridge was then washed with absolute ethanol (6 ml), to eliminate the excess of precursor DMAE and sterile water (9 ml). [11C]choline, which was retained on a cartridge, was eluted with saline (6 ml) and delivered in a vial containing saline (4 ml). During collection [11C]choline was sterilized by passing a 0.22 microm filter.

[11C]choline quality controls

QC were performed applying, if possible, prescriptions to [18F]FDG monograph (residual solvents, endotoxin test, sterility and pH). The chemical and radiochemical purity of [11C]choline were determined using HPLC as follow: column Ion Pac CS12A 4x250 mm (Dionex), eluent methan-sulphonic acid 20mM, Flow 1 ml/min, 15 min run, 25°C, radio/cathionic conductometric detectors [3].

RESULTS AND CONCLUSIONS

Due to the short half-life decay (20 min) [11C]choline production must be performed in PET facilities with on-site cyclotron and radiopharmacy [4]. Here we report a method for [11C]choline production based on the use of an automatized module and disposable cassettes. The setup is simple and the process quick. In 16 min, 10 GBq of [11C]choline (chloride) is obtainable from 52 GBq of [11C]CO_2. The final product is a sterile and pyrogen-free [11C]choline injection. Decay and not decay corrected values of radiochemical yield, synthesis time as well as quality control results are reported in Table 1. When final product was analyzed by HPLC, there was only a single peak at the retention time of 8 min (radiochemical purity almost 100%). On the other hand, the mass peaks were DMAE (6 min) and NaCl, (4 min). DMAE content was below than 5 ppm and residual solvents were in the Pharmacopoeia limits. The above observation showed that the radioactivity was totally associated with the tracer, and since cold choline was not detected, no specific activity was calculated. This approach demonstrated to be reliable and reproducible, providing high throughput, constant radiochemical yield (19% not decay corrected) and high radiochemical purity in a short synthesis time.
In conclusion we presented a safe and reliable method for preparing [11C]choline useful for 2-3 PET scans.

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