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Original Research Article

Comparison of time curves from dynamic ^{18}F-fluciclovine positron emission tomography and dynamic contrast-enhanced magnetic resonance imaging for primary prostate carcinomas

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ABSTRACT

Background and purpose: Multimodal imaging is increasingly included in the assessment of prostate cancer patients, and there is a need to study whether different techniques provide similar or complementary information. In the initial perfusion phase contrast agents and radioactive labelled tracers act as blood-pool agents and may show similar characteristics. The purpose of the current work was to compare time-activity- and time-concentration-curves (TCs) of dynamic ^{18}F-fluciclovine (^{18}F-anti-1-amino-2-[F]-fluorocyclobutane-1-carboxylic acid, FACBC) positron emission tomography (PET) and dynamic contrast-enhanced magnetic resonance imaging (DCE MRI).

Materials and methods: Dynamic FACBC PET and DCE MRI were performed on 22 patients with intermediate or high-risk prostate cancer within 23 days prior to robot-assisted laparoscopic prostatectomy. Index tumour was delineated in the images using whole mount tissue sections as reference standard. Tumour TCs from PET and MRI were compared visually and quantitatively by calculating correlation coefficients between the curves at different time points after injection.

Results: For the first minute post injection, the mean correlation coefficient between the TCs from PET and MRI was 0.92 (range; 0.75–0.99). After the first minute, MRI showed washout while PET showed plateau kinetics.

Conclusion: Dynamic FACBC and DCE MRI showed similar wash-in time curve characteristics. At later time points, FACBC plateaued whereas MR contrast medium washed out. In DCE MRI, the usefulness of wash-in information is well documented. Whether wash-in information from dynamic FACBC can provide added value remains to be documented.

1. Introduction

Prostate carcinoma is the most common type of cancer in men and the second leading cause of cancer death in the Western world [1]. Prostate carcinomas are characterized by biological heterogeneous behaviour. While some tumours remain indolent for many years, others progress rapidly to a life-threatening disease. Due to this heterogeneity, an increasing number of imaging modalities are included in the diagnostic work-up of these patients. There is a need to establish to what extent different imaging modalities provide similar or complementary information.

The discovery of angiogenesis as an essential step for tumour growth has led to increasing interest in non-invasive assessment of tumour vasculature. Blood perfusion, blood volume, and vascular

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permeability can be visualized through analyses of time-activity- and time-concentration-curves (TCs) obtained by continuous acquisition of 2D or 3D image series during the uptake and clearance of a tracer or a contrast agent. Dynamic contrast-enhanced magnetic resonance imaging (DCE MRI) may be applied for prostate imaging as part of multiparametric MRI (mpMRI) for detection and characterization of tumour foci [2–5]. The TC on DCE MRI after administration of a Gadolinium-chelated contrast agent reflects the underlying tumour vasculature. The three main characteristic TCs are persistently enhancing (type I curve), plateau (type II curve) or washout (type III), with type III being most suggestive of malignancy [4]. It has been reported that rate of uptake obtained from the initial phase of DCE MRI may improve tumour detection and differentiate low-grade from high-grade tumours [5,6].

^{18}F-labeled fluciclovine (also known as anti-1-amino-2-[F]-fluorocyclobutane-1-carboxylic acid (FACBC), brand name; Axumin) is a new PET tracer that was recently approved by The Food and Drug Administration (FDA) and The European Medicines Agency (EMA) for use in patients with suspected prostate cancer recurrence. The uptake mechanism of FACBC into cells is not fully understood, but it has been reported to primarily be mediated by the two amino acid transporter proteins ASCT2 and LAT1 [7,8]. The expression of ASCT2 and LAT1 is linked to prostate cancer aggressiveness [9], and FACBC PET could thus improve treatment stratification. Monitoring delivery and retention of FACBC from the time of injection provide dynamic image series that enable separation of perfusion [10,11] from more specific tracer distribution characteristics such as tracer-transport, binding and metabolism.

In the initial perfusion phase contrast agents and radioactive labelled tracers act as blood-pool agents, whereas tissue distribution and uptake depend on the chemical and biological properties of these agents. A prostate cancer study with dynamic ^{18}F-fluorodeoxyglucose (FDG) PET/MR revealed a possible additional value of dynamic PET [12]. There are some studies with dynamic FACBC PET/CT [13–18], but only two have explored the early dynamic phase [16,17]. None of these studies assessed if the dynamic information was similar to DCE MRI. One dynamic PET/MR study with ^{18}F-fluciclovine focused at finding the optimal time point to detect prostate cancer, but did not evaluate initial PET perfusion in detail and did not include DCE MRI [19]. Comparison of perfusion characteristics from DCE MRI and dynamic FACBC PET is lacking.

Hypoxia is associated with treatment resistance to radiotherapy. Accordingly, it could be beneficial to include perfusion information from PET in dose painting. MpMRI including DCE is currently used in clinical radiotherapy trials to guide focal boosting of prostate cancer [20,21]. Reliable mapping and characterization of the resistant lesion (s) within the prostate gland is a prerequisite for these strategies, and perfusion information may complement the metabolic information from PET.

The aim of the present study was to compare the TCs from DCE MRI and dynamic ^{18}F-FACBC PET for primary localized prostate carcinomas.

2. Material and methods

2.1. Study cohort

A total of 22 patients with intermediate or high-risk prostate carcinoma according to ÓAmico risk classification [22] referred to our institution for robot-assisted laparoscopic prostatectomy (RALP) between February 2013 and May 2016 were included in this prospective study. Patient and tumour characteristics are shown in Supplementary Table 1. The median age of the study cohort was 67 years (range; 46–74). Prostate specific antigen (PSA) ranged from 4.6 to 37 ng/mL (median; 8.9). Of the 22 patients, eight had Gleason score < 7b and 15 had tumour growth beyond the confines of the prostate (extracapsular extension). Both MRI and PET were performed less than 23 days prior to RALP. The mean time between MRI and PET was 5.4 days (range: 1–14 days). The Regional Committees for Medical and Health Research Ethics South East approved the study (REC 2010/1656). The study was carried out in accordance with the Helsinki Declaration and all patients provided written informed consent before study inclusion.

2.2. MRI

The MRI examinations were performed with a 1.5T MR scanner (GE Horizon, GE Healthcare, Waukesha, Wisconsin) and a phased array cardiac coil centred over the pelvis. The mpMRI examinations included morphological and functional sequences according to international recommendations [2] (Supplementary Table 2). The transversal DCE MR images were acquired with a 3D spoiled GE-Dixon sequence (Time to echo (TE) = 3.1 ms, time to repetition (TR) = 5.8 ms, field of view (FOV) = 240 × 240 mm^2, acquisition/reconstruction matrix = 160 × 160/256 × 256, number of slices = 10, voxel size = 1.5 × 1.5 × 2.6 mm^3, parallel imaging factor = 2). A total of 30 T1-weighted acquisitions were sequentially obtained with 11.4 s temporal resolution. Gadolinium contrast medium (gadoterate meglumine) was injected as an intravenous bolus at the start of the fourth dynamic scan through a peripherally placed cannula using an automatic injector (0.2 ml/kg body mass, 3 ml/s flow rate, Dotarem® (279.3 mg/ml, Guerbet, France)) and followed by 30 ml saline flush.

2.3. Dynamic ^{18}F-fluciclovine PET

FACBC PET and computed tomography (CT) images were acquired with a Biograph40 mCT (Siemens, Erlangen, Germany). The patients fasted for at least four hours and voided the bladder before the examination. A helical CT scan (CareDose 4D eff. 82 mAs, tube voltage = 120 kV, FOV = 78 cm, matrix size = 512 × 512, slice thickness = 1.5 mm) of the pelvis for attenuation correction was followed by intravenous bolus administration of 281–301 MBq FACBC and saline flush of 10–20 ml. A 15 min list-mode PET acquisition of one bed position (axial FOV of 21.6 cm centred above the symphysis, PET ring diameter FOV = 70 cm) was started before administration of FACBC. The list-mode data was rebinned into image time frames of 15 s for the first three minutes, 30 s for the next 1.5 min, 2 min for the next, and then 4 min for the remaining time. The images were reconstructed using 3D iterative ordered-subset expectation maximization (OSEM) with 2 iterations and 21 subsets, time of flight (TOF), point-spread function (PSF)-correction, slice thickness 1.5 mm, matrix size 128 × 128, in-plane reconstruction pixels size 5.5 mm × 5.5 mm, and a Gaussian post-reconstruction convolution kernel with full width at half maximum (FWHM) of 3 mm. All studies were transferred to a remote PC for further analyses.

2.4. Robot-assisted laparoscopic prostatectomy

All patients underwent RALP with a three-armed robotic DaVinci® system (Intuitive Surgical, Sunnyvale, CA, USA) with the surgical approach mainly based on the Vattikutti Institute technique [23]. The median number of days between MRI and RALP was 4.4 days (range 0–23) and between PET and RALP 9.8 days (range 1–18).

2.5. Histopathological assessment of tissue sections from resected prostate glands

The resected prostate was inked with three colours to identify left, right, and posterior aspects and fixed in 10% buffered formaldehyde for at least two days. Grossing was performed according to a standardized protocol where total prostate with seminal vesicles was embedded [24]. The apex and the base of the prostate were cut as sagittal sections using the cone method. The remaining body was cut into three to four mm transverse slices and prepared as whole-mount sections. The sections were stained with hematoxylin and eosin (HE) and examined by light