Comparison of different kinetic models for dynamic ^{68}Ga-FAPI-04 PET/CT imaging of hepatocellular carcinoma with various, also dual-blood input function

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Short communication

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Abstract

Aim: The aim of the study is to establish a ^{68}Ga-FAPI-04 dynamic model in hepatic lesions, to determine the potential role of kinetic parameters in the differentiation of hepatocellular carcinoma (HCC) from non-HCC lesions.

Methods: ^{68}Ga-FAPI-04 PET dynamic images of 7 HCC lesions and 5 non-HCC lesions from 8 patients were analyzed from their time-activity curve (TACs). Five kinetic models were applied to the TACs, using hepatic artery and/or portal vein as input functions. Results were analyzed according to Akaike and Schwartz information criteria.

Results: A two-compartment model using solely a venous input function was most preferred and showed significant differences between healthy regions and lesions in almost all model parameters. Using a two-compartment model with one arterial input function delivered significant differences between HCC and non-HCC regions in the case of K1 ($p = 0.03$).

Conclusion: The established FAPI PET dynamic model in liver lesions suggested that FAPI PET kinetic parameters have the potential to differentiate between HCC and non-HCC lesions.

Introduction

Hepatocellular carcinoma (HCC), the most common primary liver cancer, is a highly heterogeneous cancer[1]. there were shreds of evidence that limited sensitivity using FDG PET in detecting HCC [2].

Fibroblast activation protein (FAP) is over-expressed in cancer-associated fibroblasts (CAFs) in several tumor entities. Recently, its quinoline-based derivatives have been designed into radiopharmaceutical agents, showing superior tumor-imaging potential of FAPI in different tumor entities [3, 4]

Dynamic PET might have potential in differential diagnosis other than static imaging [5]. We previously introduced a simple two-tissue model using the portal vein solely to differentiate HCC from healthy liver tissues [6]. The objective of this study was to establish a ^{68}Ga-FAPI-04 dynamic model in hepatic lesions and to assess dynamic FAPI PET to recognize HCC lesions.

Materials And Methods

Patient Characteristics

Eight male patients with 12 liver lesions (age range, 47-70 y) were recruited. The pathology was evaluated by surgical resection or needle biopsy. Four patients had been histologically confirmed HCC, two intrahepatic cholangiocarcinomas, one liver metastasis of gastric cardia adenocarcinoma and one inflammatory granulomatous.

PET/CT Scan

PET/CT scans were conducted on a PoleStar m660 PET/CT scanner (SinoUnion Healthcare, Beijing, China). CT transmission scans (120 kV, 260 mA) were performed for attenuation correction. 60 min Dynamic PET was performed over liver region simultaneously after ^{68}Ga-FAPI-04 injection (96-260 MBq). PET images were reconstructed with 2 iterations and 10 subsets. The 120-frame reconstruction protocol consisted of 60 frames of 5s, 10 frames of 30s, and 50 frames of 60s.

Image Analysis

The volumes of interest (VOIs) were drawn manually overall visible lesions, healthy regions within a distant area in the liver, within the abdominal aorta (here denoted as A) as well as the portal vein (V) on the CT image on the Hermes Hybrid Viewer tool (Hermes Medical Solutions AB, Stockholm, Sweden). The corresponding concentration time-activity curves (TACs) in units of standardized uptake value (SUV), maximum SUV (SUV_{max}), and the volume sizes were exported. A representative PET/CT scan was shown in Figure 1.

Kinetic Models

Although the liver was supplied by a venous and arterial input [7], it was recently shown [6] that the portal vein was sufficient to classify kinetic processes of FDG. Five models were applied to all TACs (Figure 2) : two two-compartment with one input function from the aorta. In model A-4, four rate constants K_1, k_2, k_3 and k_4 were used; for model A-3 three rate constants K_1, k_2 and k_3. The third model used both input functions from aorta and portal vein according to the formulas [6]. The fourth and fifth model, denoted as V-4 and V-3, were identical to models A-4 and A-3, except the portal vein was used as input function instead of the aorta. The image derived venous or arterial input functions were fitted with a tri-exponential function starting from the peak maximum and with a linear increase before the maximum. With the rate constants and the fraction of the measured blood volume v_B as fit parameters, all model fits were performed according to the least-squares method and optimized with a Levenberg-Marquardt algorithm. The average and standard deviation of the rate constants, including $K_i = K_1k_3/(k_2+k_3)$, was calculated for all TACs, uncertainties of the fit parameters were obtained from the calculated covariance matrix and the residual sum of squares weighted by a factor for time frames (WRSS) was calculated. The initial parameters were chosen according to Geist et al [6]. The size of the delineated volume and SUV from the last 10 minutes was calculated.

Statistical Analysis

All models were compared using the Akaike Information Criterion (AIC), AIC unbiased (AICC) and Schwartz Criterion (SC) as suggested by Golla et al [8]. These tests were applied to every TAC and the percentage of TACs showing the minimum value was calculated. The paired student's t-test was used to assess significant differences in the rate constant between the lesion and healthy region, the unpaired student's t-test to detect differences between the HCC and non-HCC group.

Results

Lesion Characteristics

Eight patients with 12 available liver lesions were recruited. The 12 lesions were separated according to histology into a group HCC (n=7) and a group non-HCC (n=5), including 2 ICC lesions, 1 inflammation and 2 gastric metastases (group non-HCC). (Table 1).

Model selection

Model V-4 was preferred for all lesion TACs as well as for only HCC group lesion (Fig. 3). The averaged rate constant values for model V-4 were listed, and differences between all lesions and the corresponding healthy region were listed (Table 2).

Comparison between HCC and non-HCC

With model V-4, no significant differences were found between HCC and non-HCC lesions for all model parameters (Table 2). With model A-3, significant differences were found for K_1 with K_1 = (0.26 ± 0.06) ml/min^{-1} for all five non-HCC lesions and K_1 = (0.45 ± 0.18) ml/min^{-1} for all seven HCC lesions (P = 0.03, correlation coefficient r = 0.63) (Fig.4). Model A-3 showed less differences between healthy tissue and lesions, significant differences were only obtained in the case of k_4 (healthy region decreased by 0.07 min^{-1}, $p < 0.01$) and K_i (healthy region decreased by 0.09 min^{-1}, $p < 0.01$).

Discussion

As already found in the case of FDG [6], the best-preferred model is a simple two-compartment model with only a venous input function, suggesting that the lesions are mainly supplied by the hepatic artery. Since this is a methodological study, no corrections for partial volume or motion effects have been applied, therefore all rate constant values, especially for K1 and k_2, cannot be taken as absolute numbers. These effects might be almost negligible for the arterial input function derived from the aorta [9, 10], but they are certainly not in case of the portal vein, thus leading to error-prone and unnaturally high values for K_1 and k_2. However, it allows a proper differentiation between healthy and lesion tissue with significant differences in almost all model parameters.

Interestingly, model V-4 was not suitable to find differences between HCC and non-HCC lesions. Although not overwhelming, still significant small differences between HCC and non-HCC lesions could be found with one of the less preferred models using an aortic input function, A-3, in case of K_1. Given the fact that neither the aorta nor the portal vein input function was corrected, but motion and partial volume effects are small in case of the aorta, differences between HCC and non-HCC lesions could – if possible – only be detectable by the aortic input function. Since blood sample in case of the portal vein is difficult to establish, a similar study performed at a combined PET and magnetic resonance tomography (PET/MRI) scan allowing a proper motion and partial volume detection might solve this issue.

The presented data was very similar in comparison with the recently published data on FDG HCC lesions [6]. The obtained model parameters are much lower for k_3, k_4, K_i and v_B, i.e. showing less compartmental exchange after entering the tissue, but FDG in contrary delivers a better differentiation between HCC and healthy region. The higher model parameter values could indicate that FAPI is more suitable to investigate liver lesions; the better performance of FDG in case of differentiation might be related to the fact that for the reported FDG data, 14 HCC lesions were evaluated, for the presented results only 7 HCC lesions were investigated. A better statistic would probably also improve the differentiation between HCC and non-HCC with FAPI.

HCC tissue consists of heterogeneous tumor cells and stroma. Particularly fibroblasts in the stroma, cancer-associated fibroblasts (CAFs), are heterogeneously derived from a variety of cellular origins. FAP was overexpressed in heterogeneous CAFs. Thus, the discrepancy in K_1 within HCC group might be due to the heterogeneous CAFs phenotypes of different HCC lesions.

With regards to the differentiation of HCC from healthy regions, k_3, k_4 and K_i were zero in the healthy regions, suggesting that healthy regions have almost no interaction with FAPI.

Conclusion

In the present study, we established a FAPI PET dynamic model in liver lesions. Our initial data suggested that FAPI PET kinetic parameters have the potential to differentiate between HCC and non-HCC lesions.

Declarations

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Availability of data and materials

Please contact author for data requests.

Authors' contributions

BG and HX performed the data collection and analysis, drafted the manuscript. JW helped draft the manuscript. XS participated in the data collection. HZ, MH and XS participated in the design of the study. LH designed the study and revised the manuscript. XL helped revise the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institution and with the principles of the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all participants.

Consent for publication

Consent to publish was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

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Tables

TABLE 1 Standardized uptake value (SUV) and volume size of all investigated lesions

Group	Lesion	SUV	Size [cm³]
HCC	HCC-1	1.5	6.4
	HCC-2	3.0	1.7
	HCC-3	3.8	2.2
	HCC-4	4.9	83.0
	HCC-5	2.7	2.7
	HCC-6	1.6	1.6
	HCC-7	11.6	11.6
non-HCC	ICC-1	9.6	29.3
	ICC-2	5.9	60.7
	Inflammation	0.41	9.9
	Metas-1	7.2	16.9
	Metas-2	5.6	4.4

TABLE 2 Results for the obtained rate constants k of model V-4 for all lesions, all corresponding healthy regions as well as only hepatocellular carcinoma (HCC) regions

	K_1 [min^{-1}]	k_2 [min^{-1}]	k_3 [min^{-1}]	k_4 [min^{-1}]	v_B	K_i [min^{-1}]
All lesions	0.99 ± 0.65	1.0 ± 1.2	0.14 ± 0.12	0.05 ± 0.05	0.37 ± 0.2	0.16 ± 0.12
Group HCC	1.15 ± 0.73	1.11 ± 1.3	0.15 ± 0.13	0.05 ± 0.06	0.41 ± 0.23	0.17 ± 0.12
All healthy regions	1.6 ± 0.6	3.2 ± 1.9	0.00 ± 0.00	0.00 ± 0.00	0.22 ± 0.12	0.00 ± 0.00
Difference all lesions / healthy	-0.56 (P = 0.05)	-2.16 (P = 0.01)	+0.14 (P < 0.01)	+0.05 (P = 0.01)	+0.15 (P = 0.05)	+0.16 (P < 0.01)
Difference only HCC lesions / healthy	-0.17 (P = 0.60)	-0.90 (P = 0.18)	+0.15 (P < 0.02)	+0.05 (P = 0.06)	+0.25 (P = 0.02)	+0.17 (P < 0.01)
Difference only HCC / non-HCC	+0.39 (P = 0.33)	+0.22 (P = 0.78)	+0.04 (P = 0.56)	+0.01 (P = 0.82)	+0.10 (P = 0.40)	+0.02 (P = 0.82)

Values are shown as the mean value over all TACs in 1/min plus-minus one standard deviation. The difference between several groups and their p-values from student's t-Test are also shown, significant differences of $p < 0.05$ are underlined.