



## Original article

## Effect of scan duration on CT perfusion values in metastases from renal cell carcinoma



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## ABSTRACT

**Objective:** CT perfusion (CTp) values are affected by CT scan acquisition duration ( $t_{acq}$ ); their reproducibility is adversely affected by uncertainty in their measurement. The objectives were to assess the effects of  $t_{acq}$  on CTp parameter values in metastases from renal cell carcinoma (mRCC) in thoracic and abdominal locations.

**Materials and Methods:** 131 CTp evaluations in 53 patients with mRCC were retrospectively analyzed by distributed parameter modeling to yield tissue blood flow (BF), blood volume (BV), mean transit time (MTT), permeability (PS), and also hepatic arterial perfusion (HAP) and hepatic arterial fraction (HAF) for liver metastases and normal liver, with  $t_{acq}$  from 25 to 590 s. Penalized piecewise polynomial regression (SPLINE) characterized functional relationships between CTp parameters and acquisition duration,  $t_{acq}$ . Evidence for time-invariance was evaluated for each parameter at multiple time points by conducting inference on the fitted derivative to assess its proximity to zero as a function of acquisition time. Equivalence testing was implemented with three levels of confidence (low (20%), moderate (70%), high (95%)).

**Results:** Systematic and non-systematic variability was observed for CTp parameter values with limited  $t_{acq}$ . All parameters in all locations approached increasing stability with increasing  $t_{acq}$ . PS, HAP and HAF required longer acquisition times than BF, BV and MTT to attain comparable levels of stability. Stabilization tended to require longer acquisition in liver than other tissues.  $t_{acq}=380$  s was required to obtain at least moderate level of confidence for all parameters and organs.

**Conclusion:** Increasing  $t_{acq}$  yields increasingly more stable CT perfusion parameters, and thereby better reproducibility.

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## 1. Introduction

CT perfusion is an imaging technique that is able to interrogate the perfusion properties of tissues, including blood flow and tissue permeability. It has potential utility in oncology, where the perfusion properties of tumors can give insights into pathophysiology, mechanisms of action of therapies, and potentially also in prognostication [1–6]. CT perfusion imaging can yield a variety of tissue perfusion parameters depending to some extent on the specific physiological

model that is used to describe the behavior of administered CT contrast material. One such model is based on an adiabatic approximation of the distributed parameter model, which yields estimates of blood flow (BF), blood volume (BV), mean transit time (MTT) and permeability-surface area product (PS) [7].

The technique has been applied in a number of clinical studies, and in a range of therapeutic settings and in tumors in various locations in the body. The latter has included evaluations of lesions in the thorax, abdomen and pelvis. The imaging protocols, and importantly the durations of data acquisition, have varied widely, ranging from 30 s to 480 s [8–14].

The effectiveness of CT perfusion as a biomarker in clinical applications requires that the parameter values obtained are reproducible, with acquisition durations that are sufficient to yield stable and reproducible values; it would be highly problematic if their values varied simply due to the duration of data acquisition. Conversely,

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there are cogent reasons for limiting exposure to ionizing radiation as much as possible. There have only been a small number of studies which have investigated this aspect of parameter quantification. Some of the studies have suggested that acquisition times of 30–45 s might be satisfactory for quantification of some of the CT perfusion parameters, such as BF, but have not commented on PS [13,15]. One other study has suggested that 45 s would be satisfactory for PS [16]. A study in lung tumors has suggest that 125 s might not be sufficient to characterize perfusion parameters [17]. Yet another study, with liver metastases and normal liver, has suggested that 360 s might be necessary to attain a moderate degree of confidence in the stability in CT perfusion parameters [18].

The purpose of this study was to investigate the effects of the duration of data acquisition on resultant CT perfusion parameter values in metastases from renal cell carcinoma located within the thorax and abdomen.

## 2. Materials and methods

### 2.1. Patients

This retrospective study was approved by our institutional review board (IRB), with waiver of informed consent.

The study consisted of CT perfusion evaluations undertaken in a prospective randomized clinical study of patients with metastatic renal cell carcinoma (mRCC) treated with targeted agents. The targeted agents were everolimus (a mechanistic target of rapamycin (mTOR) inhibitor), bevacizumab (a vascular endothelial growth factor

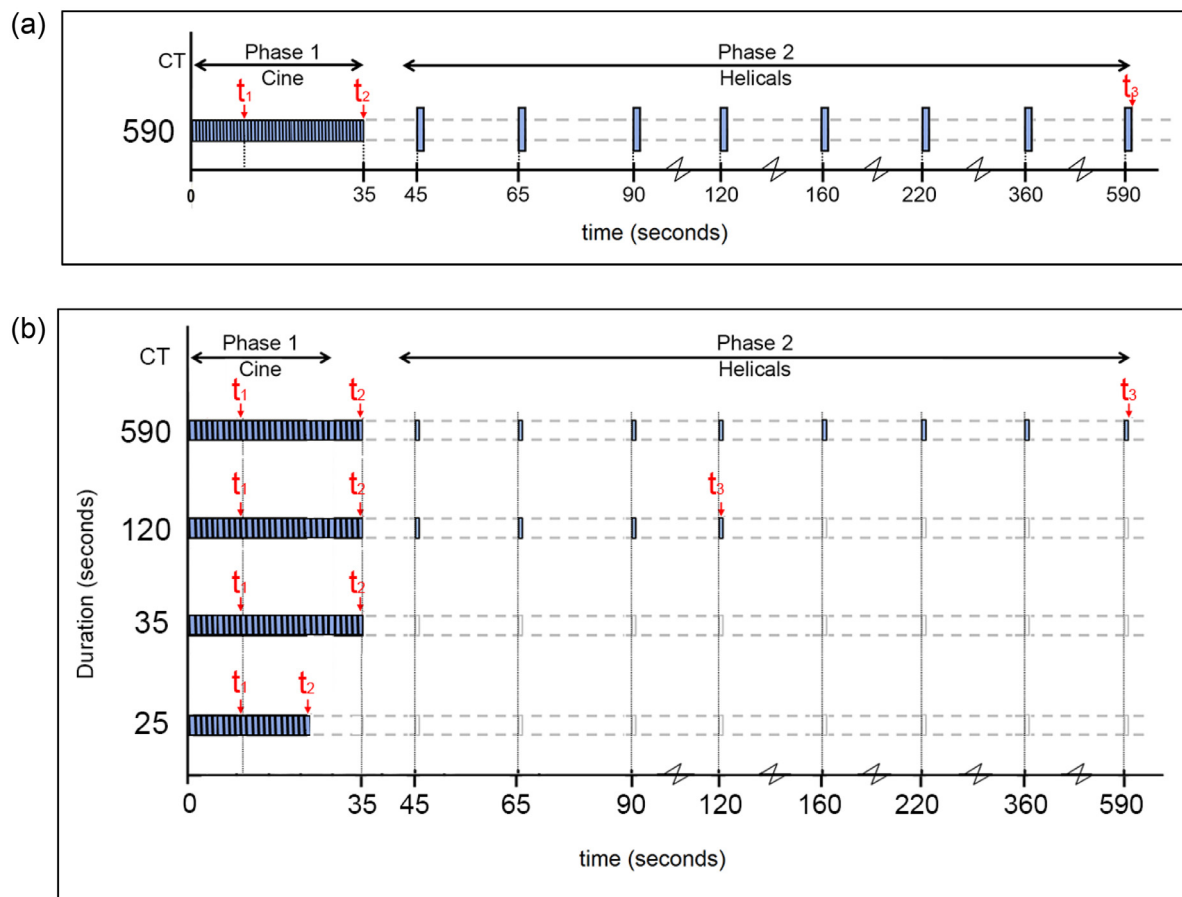
(VEGF) inhibitor), and pazopanib (a VEGFR inhibitor). CT perfusion evaluations had been obtained before and after 8 weeks of therapy, and in a subset of patients also at 2–7 days after the initiation of therapy. A single target metastatic lesion, required to be a well-demarcated, contrast-enhancing solid mass larger than 2 cm in diameter, had been identified on review of previous imaging studies prior to enrollment into the study. Sites of metastatic disease included intra-thoracic and intraabdominal locations.

### 2.2. CT perfusion scanning technique

CT perfusion images were obtained with a 64-row multidetector CT scanner (VCT, General Electric Healthcare, Waukesha, WI), and were acquired in two phases: Phase 1, cine acquisition during a 30–35 second breathhold, followed by Phase 2, consisting of eight intermittent short breathhold helical scans. The total acquisition duration was 590 s (further details in Appendix A).

### 2.3. CT perfusion analyses

The acquired CT perfusion images were anatomically registered using a semiautomatic rigid registration algorithm [19]. The resulting anatomically registered datasets consisted of images temporarily sampled at 0.5 s from the cine Phase 1 acquisition, together with eight images from the Phase 2 acquisition through to 590 s, with temporal sampling as shown in Fig. 1a and described in Appendix A. Each time point comprised 8 contiguous slices, each of 5 mm thickness;



**Fig. 1.** a. Schematic of CT perfusion acquisition b. Schematic of overall study evaluating effects of acquisition duration. First row: Reference dataset: anatomically registered eight contiguous 5-mm thick Phase 1 and Phase 2 images. Second row: Reduction in acquisition duration affecting Phase 2 ( $t_3$ ). Third row: Reduction in acquisition duration,  $t_2=35$  s. Fourth row: Reduction in acquisition duration affecting Phase 1 ( $t_2$ ).

thus the overall z-axis thickness was 40 mm. These data formed the reference dataset for the subsequent acquisition duration analyses.

CT perfusion analyses were undertaken using the CT Perfusion Body Protocol, or for patients with liver lesions, the CT Perfusion Liver Protocol (CT Perfusion 4D version 4.3.1, Advantage Windows 4.4; General Electric Healthcare, Waukesha, WI). This commercially available software uses the distributed parameter model [7]. CT perfusion parametric maps were generated after delineation of arterial input functions (AIF), and in the case of liver lesions, also of the portal venous input function (PIF) [20,21]. The algorithm requires three set-points to be determined: (i) *pre-enhancement* set-point ( $t_1$ ), which corresponded to the time when the arterial signal first began to rise; (ii) *post-enhancement* set-point ( $t_2$ ), which corresponded with the final time point of the Phase 1 data acquisition; and (iii) *last second phase* set-point ( $t_3$ ), which corresponds to the final Phase 2 image (Fig. 1a). The CT perfusion parameters generated were BF, BV, MTT, PS; and in the case of patients with liver lesions, this also included hepatic arterial perfusion (HAP) and hepatic arterial fraction (HAF).

Tumor regions of interest (ROI) were drawn freehand around the periphery of the target lesion on all CT slices on which tumor was visualized, using an electronic cursor and mouse. Reference was made to the perfusion parametric maps and the source cine CT images to ensure that the tumor remained strictly within the ROI at all time points.

For patients with liver metastases, parallel analyses were undertaken for normal liver parenchyma. Circular or oval ROIs, as large as possible and avoiding vessels and artifacts, were drawn in normal liver regions. Two normal liver ROIs on each of the 8 CT slices were delineated; and wherever possible, separate ROIs were placed in the left and right liver lobes (C.S.N. with more than 20 years' experience in interpreting CT studies).

Pixel locations which contained vendor-generated NaNs (not-a-number i.e. algorithmic failures) or  $PS > BF$  (which is not physiologically possible) were excluded across all corresponding parameters [22,23]. The pixel distributions were highly skewed for all parameters and were therefore normalized by log-transformations before obtaining their summary means. For PS, which contained a large number of zero values, the median was taken as the summary statistic.

All ROIs were saved within the software to enable identical placement in all the subsequent analyses.

#### 2.4. Acquisition duration

The effect of the duration of acquisition time on CT perfusion parameter values was explored by repeating the above analyses with systematic reductions in both the last second phase set-point and post-enhancement set-points between 590 s and 25s: (a) by sequential reductions of  $t_3$  at the discrete time points in Phase 2 (Fig. 1b, first and second rows); then by (b) reductions of  $t_2$  in Phase 1 at 5 second intervals (Fig. 1b, third and fourth rows).

All the above datasets were analyzed in the CT perfusion software using the identical vascular input (arterial and/or portal venous) and tissue ROIs as used in the corresponding reference analyses.

#### 2.5. Statistical analysis

Acquisition durations were evaluated for each CT perfusion parameter individually by tissue of origin. Penalized piecewise polynomial regression (SPLINE) modeling was applied to characterize functional trends in CT perfusion parameters as a function of acquisition duration, which captures both systematic and non-systematic variability. A parameter was considered stable if demonstrating time-invariance as a function of acquisition duration. Statistical evidence for stability was derived from a model's fitted derivatives and corresponding confidence intervals. Specifically, the equivalence testing framework was applied to fitted derivatives to assess their

proximity to zero as a function of acquisition time over a period of 25 s to 590 s [24]. Stability criteria were evaluated under three levels of confidence (low, moderate, and high) corresponding to inferences using 20%, 70%, and 95% confidence intervals, respectively. Larger confidence levels correspond to more stringent criteria for stabilization, requiring more evidence of time-invariance. Further details are provided in Appendix B. The specific statistical technique and software applied in this study was described in detail by Hobbs and Ng in a study of the stability of liver perfusion parameters [18,24]. Second-degree SPLINES were used for analyses in this study.

### 3. Results

The study cohort consisted of 53 patients with intrathoracic and intra-abdominal RCC metastases. Two patients were excluded from the original cohort of 55 patients because their target lesions were not within the thorax or abdomen (Fig. 2). The median age of the patients was 60.5 years (range, 34.9–83.0); with 37 male (median, 61.8 years (range, 41.9–73.2)), and 16 female (median, 57.5 years (range, 34.9–83.0)).

There were a total of 131 CT perfusion studies; 53 patients had both baseline and 8 week studies, and 25 had studies at 1 week. 24 patients had intrathoracic lesions: 13 with mediastinal or hilar adenopathy (33 CT perfusion studies), and 11 with lung metastases (28 studies). 15 patients had retroperitoneal implants/adenopathy or adrenal metastases (37 studies). 5 patients (12 studies) had pancreatic lesions. There were 9 patients (21 studies) with liver lesions and corresponding normal liver evaluations. The median size of lesions was 2.9 cm (range, 1.2 to 8.0 cm).

Summary CT perfusion parameter values using the reference acquisition duration (590 s), by tissue, are presented in Table 1.

The levels of confidence in stability of CT perfusion parameter values by acquisition duration are presented in Fig. 3 and Table 2. The results show that the stability of parameter values increase with increasing acquisition duration for all the CT perfusion parameters, as evidenced by higher levels of confidence in stability (pink to orange to green) with increasing acquisition times. The derivative plots are presented in Fig. 4.

The results also show differences in the acquisition durations for given levels of stability between different CT perfusion parameters and target/tissue locations.

Regarding tumor location, for example, for BF, high confidence in stability for metastases in the lung was attained by 120 s; while for liver metastases, 220 s was required to attain the same level of confidence in stability. Across the tumor locations, liver appeared to require the longest acquisition durations to attain comparable levels of stability as lesions in the other locations.

As regards the specific CT perfusion parameters, for example, high confidence in stability in BF was reached by 120 s for intrathoracic nodal metastases; while for PS, 380 s was required. Across the perfusion parameters, PS appeared to require the longest acquisition durations to attain stabilization, and indeed for some tumor locations was unable to attain high levels of confidence by 590 s (for example, lung, pancreas and liver) (Fig. 3, Table 2).

Both liver metastases and normal liver behaved in a substantially similar fashion across all the parameters (Fig. 3b). Namely, they required up to approximately 380 s to attain high levels of confidence in stability for BF, BV, and MTT, but achieved only moderate levels of confidence for PS, HAP and HAF within this time. High levels of confidence in stability were not attained within the available acquisition time for the latter 3 parameters.

### 4. Discussion

Our results indicate that CT perfusion parameter values are affected by acquisition duration, but importantly, that they attain

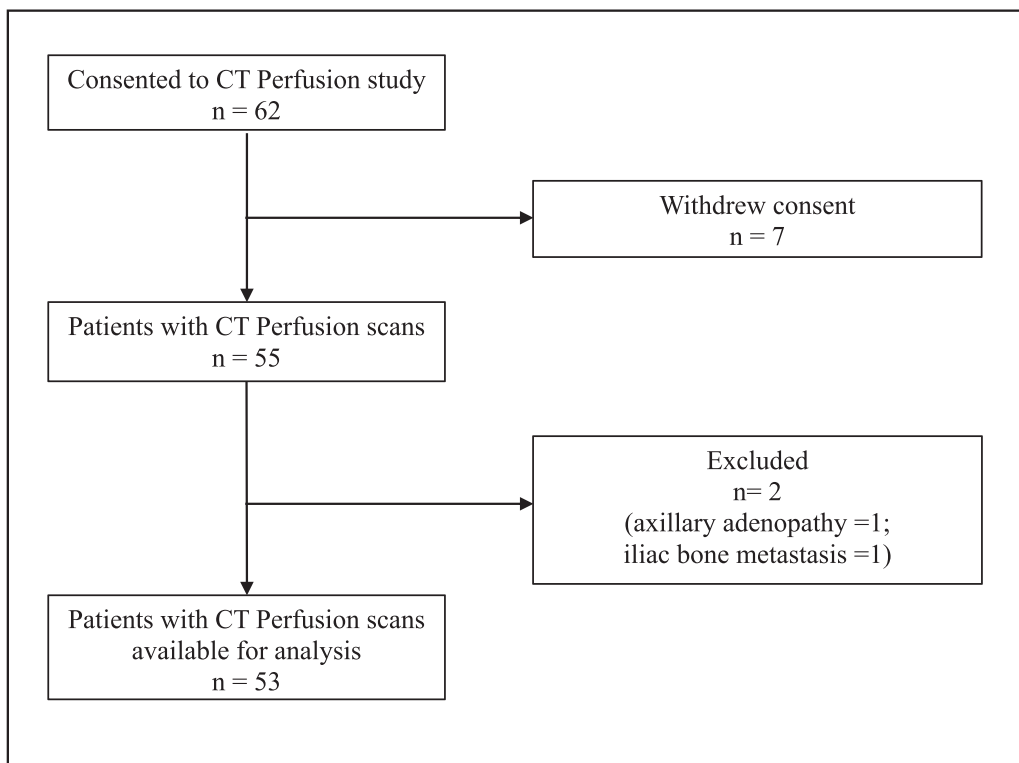


Fig. 2. Patient flow. n: number of patients.

some level of stability with time. The latter is an important observation, as a failure to stabilize would imply a substantial problem with the modeling and/or data acquisition, and be highly problematic for the reproducible implementation of the biomarker in clinical applications. The results indicate that all CT perfusion parameter values

approach increasing levels of stability with increasing acquisition durations.

The acquisition durations required to attain the various levels of stability vary by tumor location and CT perfusion parameter. As such, each acquisition duration is associated with different levels of

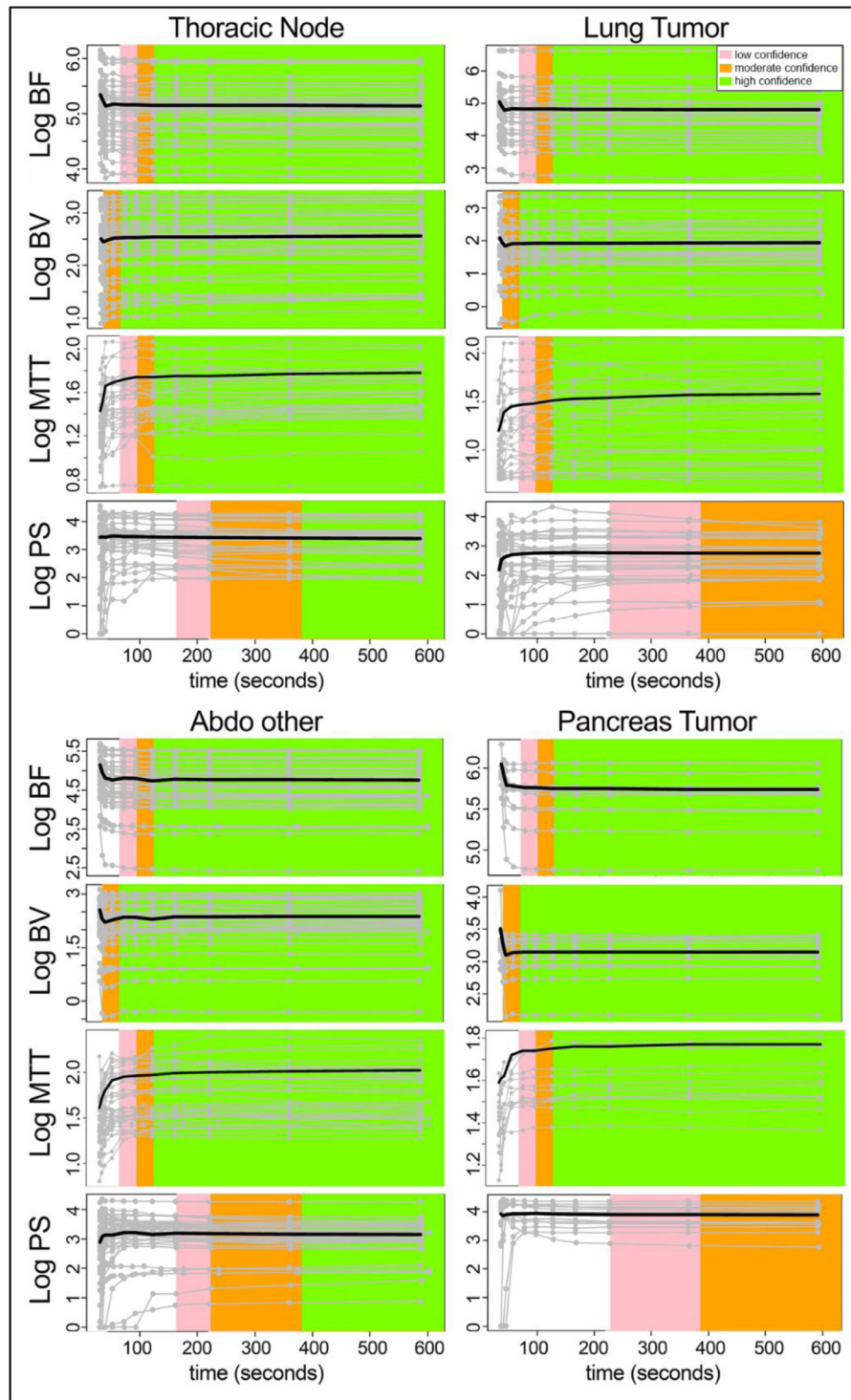
**Table 1**  
Summary of CT perfusion parameter values, using the reference acquisition duration (590 s). BF, mL/min/100 g; BV, mL/100 g; MTT, seconds; PS, mL/min/100 g; HAP, mL/min/100 g; HAF, no units.

Tumor/tissue location	CT perfusion parameter	Lower quartile	Median	Upper quartile
Lung parenchymal metastasis	BF	76.7	123.2	180.6
	BV	4.9	7.1	11.5
	MTT	3.0	5.1	7.0
	PS	9.8	17.7	27.1
Intrathoracic nodal metastasis	BF	118.4	175.3	224.1
	BV	9.2	14.5	18.5
	MTT	5.1	6.0	7.2
	PS	21.1	31.8	40.3
Abdominal nodal metastasis/implants	BF	88.1	126.9	166.0
	BV	9.7	12.4	16.4
	MTT	5.9	7.3	9.4
	PS	21.6	27.7	32.5
Pancreatic metastasis	BF	292.5	337.9	360.3
	BV	20.5	25.7	29.9
	MTT	5.3	6.1	6.5
	PS	37.7	50.3	65.1
Liver metastasis	BF	133.1	208.9	287.7
	BV	9.3	16.1	24.2
	MTT	6.9	8.6	10.1
	PS	11.8	16.8	31.2
	HAP	35.7	74.9	173.8
Liver normal	HAF	0.42	0.56	0.68
	BF	100.1	125.8	199.0
	BV	19.8	22.2	24.9
	MTT	13.8	17.7	20.1
	PS	12.4	17.1	20.7
	HAP	7.8	12.8	19.6
	HAF	0.11	0.13	0.16



certainty or confidence in its quantification depending on the tumor location and specific perfusion parameter. In order to facilitate interpretation, three confidence thresholds have been used (20%, 70%, 95%), but it should be noted that these definitions are in some respects arbitrary. Nevertheless, they demonstrate the ordinal nature of the evaluation.

For lesions within the thorax (namely, lung parenchymal or nodal metastases), and pancreatic and general abdominal lesions, high levels of stability were obtained for BF, BV and MTT by 120 s. However, longer acquisition times were required to attain corresponding levels of confidence for PS. For example, high confidence in PS required 380 s (for intrathoracic adenopathy and general abdominal lesions)



**Fig. 3. a:** Scatterplots of CT perfusion parameter values by thoracic and abdominal lesions. Gray lines connect the observed repeated measurements from the same ROI in a patient. Nonparametric regression fits are represented with black lines. Shaded regions show inferred levels of confidence for stabilization as functions of acquisition duration for three levels of confidence, low (20%, pink), moderate (70%, orange), and high (95%, green), as in Table 2. **b:** Scatterplots of CT perfusion parameter values by liver tumor and normal liver.

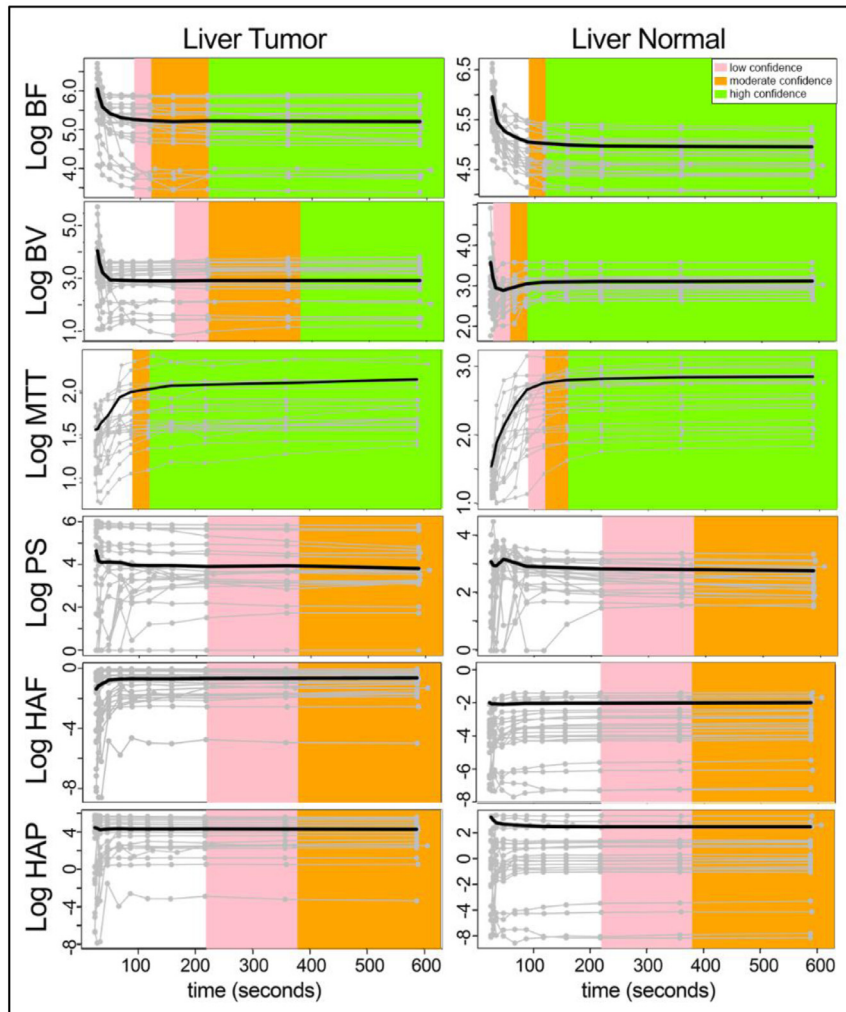


Fig. 3. Continued.

or were not achieved within 590 s of data acquisition (for other lesions).

Across the tissue locations, liver (both tumor and normal parenchyma) required the longest acquisition times to achieve stabilization for all parameters. High levels of confidence in BF, BV and MTT required 380 s; and such level of confidence in stability could not be attained within 590 s for PS, HAP and HAF.

The pattern across all tumor locations is that PS requires a longer acquisition time to attain comparable levels of stability as BF, BV and MTT. This is not surprising since PS is predominantly derived from the later parts of the time-attenuation curves than BF, BV and MTT [7]. Indeed, using a 90 second acquisition duration, Fournier and colleagues found that estimates of PS were “unreliable” and elected not to analyze this aspect of their data [25].

There have only been a small number of previous studies which have investigated the effects of acquisition duration on CT perfusion parameter values in body tumors or tissues. In a study of 10 patients with colorectal tumors, Goh and colleagues reported that an acquisition duration of 45 s was satisfactory for BF, BV, and MTT [15]. In a study of 30 patients with rectal tumors and retroperitoneal sarcomas, Kambadakone and colleagues suggested that an acquisition duration of 30 s would be satisfactory for BF and MTT (but not BV) [13]. Neither study commented on what they considered suitable acquisition times for PS. In a study of 11 patients with undefined lesions, Mazzei and colleagues reported that 40 s was an acceptable acquisition duration for PS [16].

The latter 3 studies arrive at their conclusions by making the general inference that the lack of statistical significance between parameter values at two (or more) time points indicates that the parameter values are equivalent. It is well known that the traditional formulation of the hypothesis-testing problem considers equality of effects under the null hypothesis, with the alternative hypothesis characterizing inequality. A statistical p-value provides a measure of evidence against the null hypothesis, not for it. Thus, the roles assumed by the null and alternative statements are logically asymmetric. Equivalence cannot be inferred from the absence of a significant difference, since, intuitively, any underpowered study would inevitably reach this conclusion.

In addition, Kambadakone and colleagues used analyses based on Pearson *correlation coefficients* among pairs of CT perfusion parameter values [13], which has been well established as inappropriate for evaluating equivalence or “agreement” [26]. Our statistical analyses used the entirety of the observed data (not just discrete pairs of points) to estimate the underlying functional relationship between CT perfusion quantification and acquisition time. Our conclusions follow from proper evaluation of the evidence for eventual time-invariance as a function of duration using an appropriate application of the equivalence testing framework.

The findings for liver tumor and normal liver in the current study are similar to those of our previous work with metastases to the liver from a different primary tumor (neuroendocrine carcinoma) [18]. Namely, that CT perfusion parameter values attain increasing levels

**Table 2**  
Confidence level of stability as a function of acquisition duration (Low (20%), Moderate (70%), High (95%) confidence).

Tumor/tissue location	CT parameter	Acquisition Duration (seconds)							
		30 s	60 s	90 s	120 s	160 s	220 s	380 s	590 s
Lung parenchymal metastasis	BF	–	Low	Mod	High	High	High	High	High
	BV	Mod	High	High	High	High	High	High	High
	MTT	–	Low	Mod	High	High	High	High	High
	PS	–	–	–	–	–	Low	Mod	Mod
Intrathoracic nodal metastasis	BF	–	Low	Mod	High	High	High	High	High
	BV	Mod	High	High	High	High	High	High	High
	MTT	–	Low	Mod	High	High	High	High	High
	PS	–	–	–	–	Low	Mod	High	High
Abdominal nodal metastasis/implants	BF	–	Low	Mod	High	High	High	High	High
	BV	Mod	High	High	High	High	High	High	High
	MTT	–	Low	Mod	High	High	High	High	High
	PS	–	–	–	–	Low	Mod	High	High
Pancreatic metastasis	BF	–	Low	Mod	High	High	High	High	High
	BV	Mod	High	High	High	High	High	High	High
	MTT	–	Low	Mod	High	High	High	High	High
	PS	–	–	–	–	–	Low	Mod	Mod
Liver metastasis	BF	–	–	Low	Mod	Mod	High	High	High
	BV	–	–	–	–	Low	Mod	High	High
	MTT	–	–	Mod	High	High	High	High	High
	PS	–	–	–	–	–	Low	Mod	Mod
Liver normal	HAP	–	–	–	–	–	Low	Mod	Mod
	HAF	–	–	–	–	–	Low	Mod	Mod
	BF	–	–	Mod	High	High	High	High	High
	BV	Low	Mod	High	High	High	High	High	High
	MTT	–	–	Low	Mod	High	High	High	High
	PS	–	–	–	–	–	Low	Mod	Mod
	HAP	–	–	–	–	–	Low	Mod	Mod
	HAF	–	–	–	–	–	Low	Mod	Mod

of stability with increasing acquisition times, and that longer acquisition times are required for PS. In both the prior and current studies, at 360 s, “high” levels of confidence in stability were attained for the majority of parameters, and only “moderate” confidence for PS.

The current work indicates that longer acquisition times are required for liver lesions/tissue to attain comparable levels of stability in CT perfusion parameters as compared to lesions in other locations. This may be due to the higher degree of complexity associated with the dual vascular inputs associated with the liver perfusion modeling. This would be expected to generate higher uncertainty in the curve fitting process in arriving at the parameter values, and hence the need for more data.

In terms of determining an acquisition time that should be used, this work indicates that a number of factors might be relevant, namely, tumor location, CT perfusion parameter(s) of interest and the desired degree of confidence in stability. Thus, if one were only interested in BF and intrathoracic lesions, and prepared to tolerate “low” confidence, then an acquisition time of 60 s might suffice; but if one preferred “high” confidence in the resultant BF values, then an acquisition time of 120 s would be required. If one sought *high* confidence results across all CT perfusion parameters (including PS) for these intrathoracic lesions, then one might require 380 s. However, if there were interest in at least *moderate* confidence across *all* parameters and the possibility of a *full range* of intrathoracic and intraabdominal lesions, including liver, then 380 s would be required.

Spectral CT may provide a surrogate measure of tissue perfusion (BF), with a single acquisition and lower radiation exposure, and is being investigated, but may not provide the full spectrum of perfusion parameters provided by CT perfusion imaging [27].

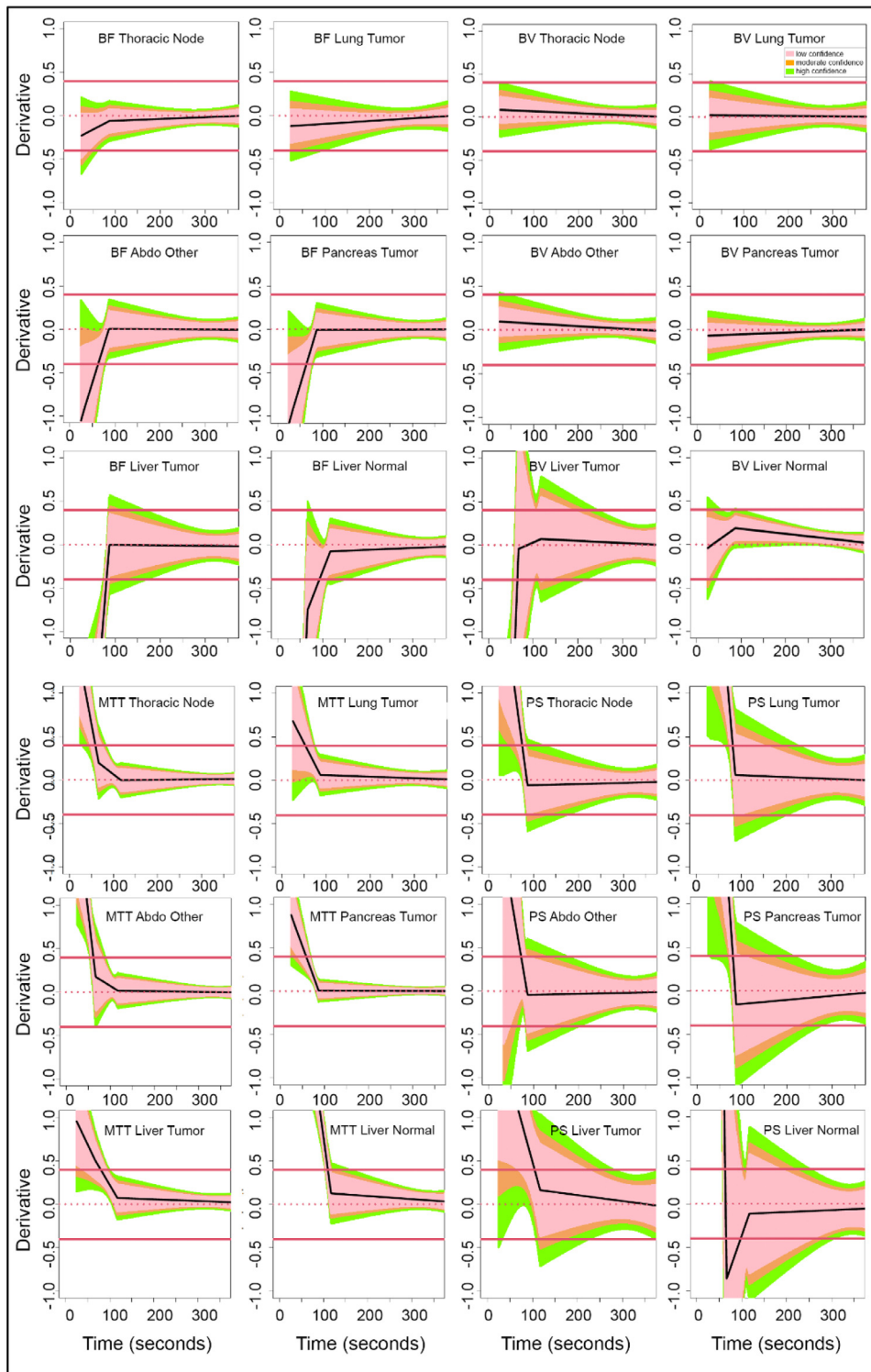
We recognize and acknowledge several limitations in our study. Unfortunately, our data did not allow for a determination of acquisition times for high confidence in stability of PS for several tumor

locations, and for HAP and HAF for liver. This was despite a relatively prolonged acquisition time of nearly 10 min. More extensive data acquisitions would be required to investigate this aspect.

Our study investigated only one specific CT perfusion model, the distributed parameter model, and one commercial implementation of it. However, it was the only platform we had access to, and an evaluation of other models was beyond the scope of this work.

We only investigated a single tumor type, and thus the extent to which the findings might be generalizable to other tumors and tissues would require further work. However, one would not expect the question at hand, namely, acquisition duration, to be particularly tumor-specific. Furthermore, with this single tumor we were able to investigate a range of metastatic sites/locations. Indeed, the locations of disease, namely, within the thorax and abdomen, and including the liver, are highly relevant as they are very common sites for primary and metastatic tumors. Regarding the latter analyses, we recognize that the numbers of patients/evaluations contributing to the individual subsets of tumor locations were relatively small. Nevertheless, each group contained a representative spectrum of pre- and post-treatment CT perfusion evaluations. Furthermore, the full cohort of 53 patients, with a total of 131 CT perfusion evaluation, is the largest investigating this issue, and it yielded a clear pattern as to the impact of acquisition time on the stabilization of CT perfusion parameters.

In summary, CT perfusion parameter values derived from the distributed parameter model and their reproducibility are affected by the duration of acquisition of data, and become increasingly stable and approach steady-state values with increasing acquisition times. The corollary is that shorter acquisition times would yield more variable and unreliable perfusion parameter values. The acquisition duration that one might want to select in practice would depend to some extent on the level of confidence in stability desired, and the perfusion parameter(s) and tissue(s) of interest, with in particular PS and



**Fig. 4. a:** Estimated derivatives for CT perfusion parameters as functions of acquisition duration, scaled by their respective estimated residual error standard deviations. Shaded regions are intervals of likely values for three levels of confidence: low (20%, pink), moderate (70%, orange), and high (95%, green). Stabilization requires that these confidence intervals be bounded. **b:** Estimated derivatives for HAP and HAF as functions of acquisition duration, scaled by their respective estimated residual error standard deviations.



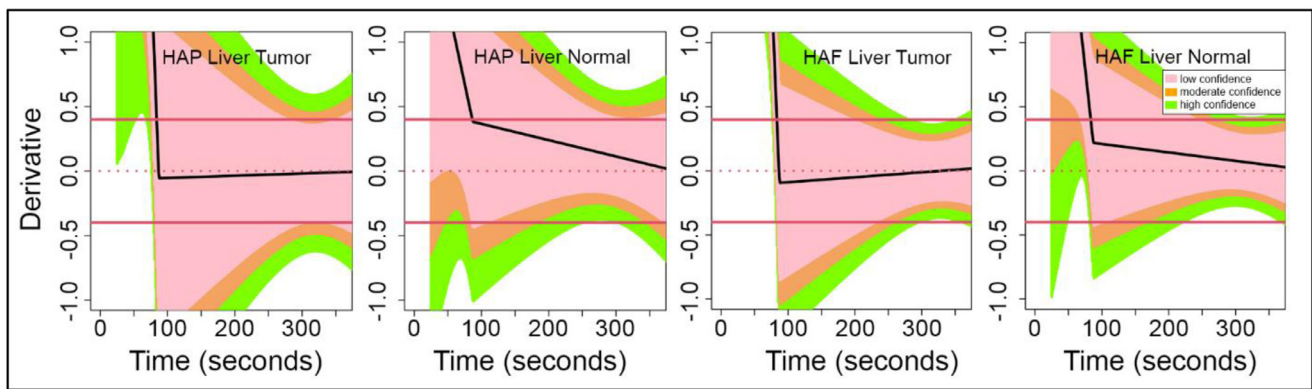


Fig. 4. Continued.

liver lesions requiring longer acquisition times to attain comparable levels of stability as other perfusion parameters and other tissues.

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### Declaration of competing interests

CSN is a consultant to GE Healthcare. AGC was previously employed by GE Healthcare. NMT is a Scientific Advisor to Nektar Therapeutics; Pfizer, Oncorena; Eli Lilly, Eisai Medical Research, And Consultant to Bristol-Myers-Squibb; Pfizer; Nektar Therapeutics; Exelisis, Inc, Eisai Medical Research; Eli Lilly; Oncorena; Calithera Bioscience; Surface Oncology; Novartis, Ipsen; Merck Sharp & Dohme. BPH is a Scientific Advisor to Amgen, STCube, Bayer HealthCare Pharmaceuticals Inc., Presagia. And Consultant to Pfizer. YC, WW have no disclosures.

### CRediT authorship contribution statement

**Chaan S. Ng:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Writing – review & editing, Writing – original draft. **Adam G. Chandler:** Software, Writing – review & editing. **Yanwen Chen:** Formal analysis, Software, Writing – review & editing, Writing – original draft. **Wei Wei:** Formal analysis, Software, Writing – review & editing. **Nizar M. Tannir:** Resources, Writing – review & editing. **Brian P. Hobbs:** Conceptualization, Formal analysis, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing, Writing – original draft.

### Author statement

We declare that the work has not been published previously, that it is not under consideration for publication elsewhere, that its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.redii.2023.100028](https://doi.org/10.1016/j.redii.2023.100028).

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