Table E1. Summary of Data Acquisition and Postprocessing Methods of Hepatic CT Perfusion Imaging Studies

Study and Reference No.	Journal/Year	Subject Type/No. of Subjects	Acquisition Parameters		Contrast Agent		Latest Scan Time (sec)	Analysis Model	Mean Radiation Dose (mSv)
			Scanner/Detector Rows	kVp/mAs	Amount (mL)/Concentration (mg iodine per mL)	Injection Rate (mL/sec)			
Blomley et al (33)	J Comput Assist Tomogr/1995	Human/51	SD CT	NA	25/300*	10	90	Maximum slope	NA
Leggett et al (35)	Radiology/1997	Human/27	SD CT	NA	50/300	≥ 7	37	Maximum slope	NA
Miles et al (36)	Br J Radiol/1998	Human/13	SD CT	NA	40–50/300	≥ 5–7	45	Maximum slope	NA
Cuenod et al (45)	Radiology/2001	Rat/11	SD CT	80/200	1 mL per body kg/350†	NA	30	Distributed parameter (dual-input)	NA
Tsushima et al (68)	Dig Dis Sci/2001	Human/35	SD CT	NA	40/320	5	85	Maximum slope	NA
Materne et al (46)	Clin Sci/2000	Rabbit/18, Human/10	SD CT	120/100	1 mL per body kg/350‡, 40/350§	1, 7	60, 120	Compartment (dual-input)	NA
Xiong et al (87)	Invest New Drugs/2004	Human/7	MD CT/NA	NA	40/320	7	35	Distributed parameter	NA
Kan et al (89)	Radiology/2005	Rat/20	MD CT/NA	120/80	0.15 mL per body kg/320	NA	50	Distributed parameter	NA
Shi et al (69)	Ai Zheng/2006	Rat/29	MD CT/4	80/150	2/NA	1	30	Maximum slope	NA
Sahani et al (62)	Radiology/2007	Human/30	MD CT/16	100/240	70/300	7	30–35	Distributed parameter	7.3–8.7
Zhu et al (63)	Oncology/2008	Human/33	MD CT/16	100–120/200–240	70/300	7	240	Distributed parameter	NA
Ippolito et al (58)	Acad Radiol/2008	Human/47	MD CT/NA	80/120	50/350	6	40	Maximum slope	10
Meijerink et al (27)	Eur Radiol/2008	Human/20	MD CT/64	120/80	100/300	6§	300	Maximum slope	24
Choi et al (90)	Invest Radiol/2010	Rabbit/14	MD CT/8	120/200	4/370	1	90	Distributed parameter	NA
Meijerink et al (115)	Ultrasound in Med & Biol/2010	Human/30	MD CT/64	120/80	100/300	6§	300	Maximum slope	24
Guyennon et al (55)	World J Radiol/2010	Human/16	MD CT/32	80/100	0.5 mg per body kg/350	4	125	Distributed parameter/compartment	NA

Ippolito et al (94)	World J Gastroenterol/2010	Human/32	MD CT/16	120/120	50/350	6	47	Maximum slope	8
Ippolito et al (60)	Eur Radiol/2011	Human/97	MD CT/16	80/120	50/350	6	47	Maximum slope	NA
Jiang et al (80)	Invest Radiol/2011	Human/23	MD CT/16	100–120/200–240	50–70/300	5–7	33–40	Distributed parameter	NA
Anzidei et al (79)	JCAT/2011	Human/18	MD CT/64	100/120	90/350	4[§‖]	60	Maximum slope/compartment	29.1
Ng et al (88)	AJR/2011	Human/24	MD CT/16	120/90	40/320	7	35	Distributed parameter	17
Petralia et al (83)	JCAT/2011	Human/18	MD CT/16	100/240	40/400	5[§]	120	Distributed parameter	28.8[#]
Kim et al (12)	Eur J Radiol/2012	Human/17	MD CT/64	80/130	50/370	5[§]	59.5	Maximum slope/compartment	NA
Reiner et al (54)	Acad Radiol/2012	Human/25	MD CT/128	100/150	60/370	5[§]	40	Maximum slope	18.4
Goetti et al (106)	Invest Radiol/2012	Human/30	MD CT/NA	100/150	60/300	5[§]	48.5	Maximum slope	30.6
Lefort et al (56)	Ultrasound in Med & Biol/2012	Human/16	MD CT/32	80/100	0.5 mL per body kg/350	4	120	Distributed parameter	13
Yang et al (91)	JCAT/2012	Human/24	MD CT/16	120/150	50/300	6	96	Maximum slope	NA

Note.—SD = single detector, MD = multidetector, NA = not available.

* Injection of 25 mL saline followed the contrast agent at the same rate of 10 mL/sec as a bolus chaser.

[†] Contrast agent injection was followed by 0.2 mL saline solution flush.

[‡] The contrast material was pushed by 10 mL of saline solution.

[§] Contrast agent injection was chased by 20–40 mL saline at the same flow rate to contrast agent injection.

[‖] Fractioned injection protocol (30 mL at 4 mL/sec, 10 mL at 2 mL/sec, 50 mL at 1 mL/sec) was used.

[#] Radiation dose was summed for the combined CT perfusion and conventional triple-phase CT of the liver.

Table E2. Summary of Clinical Study Results in Liver CT Perfusion Imaging

Clinical Application, Study and Reference No.	Journal/Year	Subject Type/No. of Subjects	Primary Site and No. of Subjects	Perfusion Parameters							Comments
				HAP	PVP	HPI	BF	BV	MTT	PS	
Alteration of CT Perfusion Parameters in Liver Tumors											

Metastasis											
Miles et al (36)	Br J Radiol/1998	Human/13	Colorectum, 9; stomach, 1; lung, 1; kidney, 1; unknown, 1	↑							Arterial perfusion was increased, both in metastases and in adjacent liver parenchyma
Blomley et al (33)	J Comput Assist Tomogr/1995	Human/4	Carcinoid, 2; stomach, 1; breast, 1	↑							Liver metastases showed an increased arterial perfusion; reproducibility of perfusion parameters was also assessed
Leggett et al (35)	Radiology/1997	Human/27	Colorectum, 27	↑	↓						Increased arterial perfusion appears to be an indicator of liver metastases, whereas reduced portal perfusion may indicate disease progression
Guyennon et al (55)	World J Radiol/2010	Human/16	Neuroendocrine, 16			↑	↑	↑	↓	↑	Metastatic neuroendocrine tumor showed significantly higher HPI, BF, BV, PS and significantly shorter MTT than adjacent parenchyma
Reiner et al (54)	Acad Radiol/2012	Human/20	Colorectum, 9; cholangiocarcinoma, 2; breast, 2; pancreas, 1; stomach, 1; melanoma, 1; sarcoma, 1; kidney, 1; lung, 1; anus, 1	↑	↓						Liver metastases showed a significantly increased arterial perfusion and decreased portal perfusion compared with adjacent normal parenchyma; arterial liver perfusion significantly correlated with ^{99m}Tc-MAA uptake ratio of the tumor
Lefort et al (56)	Ultrasound in Med & Biol/2012	Human/16	Neuroendocrine tumor, 16				↑		↓		Metastatic neuroendocrine tumor demonstrates higher BF and shorter MTT than adjacent normal liver; BF and MTT obtained at CT significantly correlated with normalized value at contrast-enhanced US
HCC											
Sahani et al (62)	Radiology/2007	Human/25					↑	↑	↓	↑	HCC shows higher BF, BV, PS and shorter MTT than normal liver; reproducibility of perfusion parameters was also shown
Zhu et al (63)	Oncology/2008	Human/33					↑	↑	↓	↑	HCC shows significantly higher BF, BV, PS and shorter MTT than background liver parenchyma
Ippolito et al (58)	Acad Radiol/2008	Human/47		↑	↓	↑	↑	↑			HCC shows higher BF, BV, HAP, HPI, and lower PVP than normal liver
Ippolito et al (60)	Eur Radiol/2011	Human/97		↑	↓	↑	↑	↑			BF, BV, HPI, and HAP values were significantly higher, whereas PVP and time to peak were significantly lower in HCC relative to the surrounding liver; no significant correlation was found between perfusion parameters and HCC grade
			Early Detection								
Metastasis											

Cuenod et al (45)	Radiology/2001	Rat/11	Colorectum, 11		↓		↓		↑		Occult liver micrometastases in rats generated changes in liver perfusion (PVP and MTT) that can be detected with CT; however, arterial perfusion was unchanged due to lack of hepatic arterial buffer response in rats
Tsushima et al (68)	Dig Dis Sci/2001	Human/35	Colorectum, 11; stomach, 3; gallbladder, 3; pancreas, 2; lung, 2; lymphoma, 2; prostate, 1; esophagus, 1; control, 10	↑	↓	↑					Patients with liver metastases showed increased arterial perfusion and HPI with a decrease of portal perfusion in apparently normal liver compared with controls
Shi et al (69)	Ai Zheng/2006	Rat/29	Walker-256 tumor cells, 19; control, 10	↑	↓		→				HAP was higher and PVP was lower in rats with micrometastases than in control animals
	Staging, Grading (Provision of Prognostic Information Based on Tumor Vascularity)										
Metastasis											
Miles et al (78)	Eur Radiol/2004	Human/80	Colorectum, 80			O					HPI ≥ 0.35 indicates poor survival of patients with colorectal cancer and no visible metastases on CT scans; stratification of survival risk by means of perfusion CT was superior to the Dukes classification
Leggett et al (35)	Radiology/1997	Human/27	Colorectum, 27		O						Reduced portal perfusion may indicate progressive disease
Miles et al (36)	Br J Radiol/1998	Human/13	Colorectum, 9; stomach, 1; lung, 1; kidney, 1; unknown, 1	O							There was a statistically significant association between longer survival of the patient and high arterial perfusion values in the metastasis
HCC											
Sahani et al (62)	Radiology/2007	Human/25					O	O	O	O	Well-differentiated HCC showed higher BF, BV, PS and shorter MTT values than moderately and poorly differentiated HCC
Zhu et al (63)	Oncology/2008	Human/33							O		Patients with progressive disease had shorter baseline MTT values than those with stable disease or partial responses
Jiang et al (80)	Invest Radiol/2011	Human/23							O		Patients with PFS > 6 months had significantly longer baseline MTT (8.27 sec ± 2.24) than those with PFS ≤ 6 months (5.64 sec ± 2.43) in 23 patients who received bevacizumab; however, baseline tumor size and attenuation did not correlate with clinical outcome

Note.—HAP = hepatic arterial perfusion (mL/min/100 mL of tissue), PVP = portal venous perfusion (mL/min/100 mL of tissue), HPI = hepatic perfusion index (%), BF = blood flow (mL/min/100 mL of tissue), BV = blood volume (mL/100 mL of tissue), MTT = mean transit time(s), PS = permeability surface product (mL/min/100 mL of tissue), ^{99m}Tc-MAA = technetium 99m-macroaggregated albumin. ↑ = increase in value, ↓ = decrease in value, → = no change in value, O = values that showed significant difference.

Table E3. Summary of Studies Reporting on Treatment Response Using CT Perfusion Imaging

Clinical Application, Study and Reference No.	Journal/Year	Subject Type/No. of Subjects	Therapy/Drug	Perfusion Parameters							Comments
				HAP	PVP	HPI	BF	BV	MTT	PS	
	Changes in CT Perfusion Parameters after Treatment										
Metastasis											
Ren et al (86)	Invest Radiol/2012	Mice/123	Chemotherapy/ antiangiogenic agent (bevacizumab) Radiation therapy				↓	↓		↓	BF, BV, flow extraction product of the tumors significantly dropped only 1 day after antiangiogenic agent (bevacizumab) treatment and radiation therapy and changes were faster than that of tumor volume
Xiong et al (87)	Invest New Drugs/2004	Human/6	Chemotherapy/ antiangiogenic agent (SU6668)				↓				There was a significant decrease of BF in six patients with liver metastases after one cycle administration of antiangiogenic drug (SU6668)
Kim et al (12)	Eur J Radiol/2012	Human/17	Chemotherapy/cytotoxic agent				↓			↓	There was a significant reduction of BF and flow extraction product in nine responders with liver metastases from colorectal cancer after one cycle administration of cytotoxic chemotherapeutic agents
Kan et al (89)	Radiology/2005	Rat/14	Transarterial chemoembolization				↓	↓	↑	↓	There was a significant decrease of BF, BV, and permeability and a significant increase of MTT after transarterial chemoembolization in 14 rats with liver metastasis; Changes in CT perfusion parameters tended to be greater in rats treated with a higher dose of embolic material
Choi et al (90)	Invest Radiol/2010	Rabbit/14	Transarterial chemoembolization				↓	↓	↑	↓	There was a significant decrease of BF, BV, PS and an increase of MTT in 14 rabbit VX2 liver tumors 1 week after transarterial chemoembolization
Meijerink et al (115)	Ultrasound in Med & Biol/2010	Human/30	Chemotherapy	↓	↑						HAP of the tumors was significantly smaller and PVP was significantly larger in patients (n = 14) treated with chemotherapy than in those (n = 16) without chemotherapy
Ng et al (88)	AJR/2011	Human/24	Chemotherapy/ antiangiogenic agent (bevacizumab) or interferon				↓	↓		→	There was a significant reduction of BF and BV in 12 patients with metastatic carcinoid tumor 2 days after initiation of bevacizumab treatment; however, no significant changes in BF or BV were detected in 12 patients treated with interferon
HCC											
Zhu et al (63)	Oncology/2008	Human/33	Chemotherapy/ antiangiogenic agent (bevacizumab) with gemcitabine and oxaliplatin				↓	↓	↑	↓	Substantial decrease in BF, BV, and permeability and an increase in MTT were observed in HCCs after bevacizumab administration

Jiang et al (80)	Invest Radiol/2011	Human/23	Chemotherapy/ antiangiogenic agent (bevacizumab) with gemcitabine and oxaliplatin			↓	↓	↑	↓	A significant decrease in BF, BV, and PS and increase in MTT were observed in advanced HCCs, 10–12 days after bevacizumab administration; changes in CT perfusion parameters were more substantial than decrease of tumor size and CT attenuation
Yang et al (91)	JCAT/2012	Human/24	Transarterial chemoembolization	↓	↓					A significant decrease in HAP and HPI was noted in HCCs at 4 weeks after transarterial chemoembolization
	Prediction of Clinical Outcome Such as Overall Survival or Time-to-Progression after Treatment									
Metastasis										
Anzidei et al (79)	JCAT/2011	Human/18	Chemotherapy/ antiangiogenic agent (bevacizumab) with oxaliplatin and capecitabine						O	Responding lesions to chemotherapy showed significantly higher PS at baseline CT perfusion than nonresponding lesions in 18 patients with colorectal liver metastases
Kim et al (12)	Eur J Radiol/2012	Human/17	Chemotherapy/cytotoxic agent			O			O	Mean reduction rates of BF and flow extraction product only 1 cycle after chemotherapy were significantly higher in the responder group than in the nonresponder group
HCC										
Zhu et al (63)	Oncology/2008	Human/33	Chemotherapy/ antiangiogenic agent (bevacizumab) with gemcitabine and oxaliplatin					O		Patients with progressive disease had a greater mean percent change in MTT after bevacizumab administration than those with stable disease or a partial response
Jiang et al (80)	Invest Radiol/2011	Human/23	Chemotherapy/ antiangiogenic agent (bevacizumab) with gemcitabine and oxaliplatin							Percent change of CT perfusion parameter 10–12 days after bevacizumab treatment for advanced HCCs was not significantly different between patients with PFS ≤ 6 months and with PFS > 6 months.
Petralia et al (81)	JCAT/2011	Human/18	Chemotherapy/ thalidomide			O	O			Baseline BF and BV were significantly higher in 12 HCC patients with progressive disease than in six patients with stable disease after thalidomide treatment; no differences were found in baseline MTT and PS
	Early Identification of Tumor Recurrence after Local Treatment									
Metastasis										
Mehnken et al (92)	AJR/2011	Human/53	Radiofrequency ablation		↑*					A locally increased arterial enhancement fraction after radiofrequency ablation for liver metastasis indicated an elevated risk for future tumor relapse in those areas at least 3 months later
Meijerink et al (93)	Acta Radiol/2009	Human/11	Radiofrequency ablation	↑	↓					Marginal lesions with high hepatic arterial perfusion and low hepatic portal perfusion represented recurred tumor tissue after radiofrequency ablation for liver metastases.

Choi et al (90)	Invest Radiol/2010	Rabbit/14	Transarterial chemoembolization			↑	↑	↓	↑	Marginal recurrence around TACE-treated areas showed increased BF, BV, and permeability and decreased MTT values on CT perfusion images; CT perfusion indexes of recurred tumors obtained 4 weeks after TACE were not significantly different from the indexes of primary tumors
HCC										
Ippolito et al (94)	World J Gastroenterol/ 2010	Human/32	Transarterial chemoembolization	↑	↑	↑				Residual tumors within TACE-treated areas showed significantly higher BF, HAP, and HPI than compactly lipiodolized area or adjacent cirrhotic parenchyma

Note.—HAP = hepatic arterial perfusion (mL/min/100 mL of tissue), PVP = portal venous perfusion (mL/min/100 mL of tissue), HPI = hepatic perfusion index (%), BF = blood flow (mL/min/100 mL of tissue), BV = blood volume (mL/100 mL of tissue), MTT = mean transit time(s), PS = permeability surface product (mL/min/100 mL of tissue). ↑ = increase in value, ↓ = decrease in value, → = no change in value, O = values that showed significant difference.

* Arterial enhancement fraction obtained from conventional triple-phase CT images.