Clinical Applications of the CT Angiography Spot Sign in Acute Intracerebral Hemorrhage: A Review

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Keywords

Intracerebral Hemorrhage; CT Angiography; CTA Spot Sign; Hematoma Expansion; Functional Outcome

INTRODUCTION

Spontaneous intracerebral hemorrhage (ICH) is the most fatal form of stroke, with one-month morality rates often exceeding 40% and rates of death or severe disability exceeding 75%.[1,2] Nearly twenty years ago, the first observational studies demonstrated that hematoma volume on presentation was among the most potent predictors of survival and functional outcome.[3] Subsequent studies identified the frequent occurrence of hematoma expansion after the initial CT scan.[4] Occurring in up to 40% of patients, this expansion further contributes to poor outcome.[5,6] These observations have made the arrest of expansion the most common target for acute clinical trials in ICH.[7-9]

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Thus far, the specific targeting of hematoma expansion in clinical trials has yet to yield improvement in clinical outcome. This may be due to difficulty in identifying those individuals most likely to benefit from the intervention, those who will suffer hematoma expansion. Risk factors for expansion include early presentation, baseline hematoma volume, and warfarin use.[4,10,11] Even among patients presenting within 3 hours, however, expansion severe enough to cause clinical deterioration occurs in no more than 40%.[4,6-8] The CT Angiography (CTA) 'spot sign' has emerged in recent years as a potent predictor of hematoma expansion, and a potential tool in guiding therapies in both research and clinical care.

CT ANGIOGRAPHY SPOT SIGN

Definition

First described in 1999[12], the CTA spot sign has evolved in its definition from the broader concept of contrast extravasation, comprising 'high-density material' or 'contrast leakage within the hematoma'[12-14], to encompass 'foci of enhancement within the hematoma' on CTA source images[15]. While definitions of the spot sign used in individual studies continue to vary, all are variations on this standard (Table 1). In 2009 a spot sign score was developed, incorporating the number, maximum attenuation (in Hounsfield units), and maximum dimension of spot sign(s) (Figure).[19] Currently, the term 'contrast extravasation' is reserved for the presence of contrast within the hematoma on post-contrast CT.[16,17] This terminology can be confusing because the spot sign is thought to *represent* contrast extravasation (contrast 'leakage' from the vessels into the hematoma), whereas the neuroimaging *definition* of contrast extravasation is used to describe the presence of contrast on a post-contrast CT. In this review we use the term 'spot sign' when referring to CTA source images and 'contrast extravasation' when discussing post-contrast CTs.

Imaging Acquisition

The identification of spot signs is dependent on technical imaging parameters of the CTA and may vary across institutions since CTAs are performed to visualize the cerebral vasculature. Delayed images collected after the initial study has been completed (normally obtained between approximately 40 seconds and 3 minutes after contrast injection), can yield spot signs not visualized on the initial CTA.[19,20] Studies have shown that contrast extravasation on post-contrast CT also increases the sensitivity of the spot sign in predicting hematoma expansion.[16,17] However, both delayed CTAs and post-contrast CTs are not routinely obtained at many institutions. Other parameters of the CTA technique also influence the detection and sensitivity of the spot sign; including the concentration of the contrast agent used and the speed of individual CT scanners. Technical refinement and standardization of CTA acquisition protocols may therefore be critical to further improve the accuracy of the spot sign.

Frequency

Variations in technique and the differences in definition probably account for the range of spot sign frequencies reported in the literature. The broader definition of contrast extravasation is associated with a higher frequency of 42% (139 out of 329 pooled patients; range from 18 to 59%), compared to 24% (426 out of 1802 pooled patients; range from 18 to 41%) for the stricter spot sign definition (Tables 2 - 4). Another factor with substantial impact on the frequency with which the spot sign is observed is the time elapsed between symptom onset and CTA. As the time from symptom onset to initial CTA increases, the frequency of spot sign appearance decreases.[12,18-20] Since only a few studies have examined the frequency of the spot sign in ICH patients whose initial CTA is performed beyond 6

hours of symptom onset, further research is warranted on the accuracy of the spot sign in this extended time window.

Pathophysiology

Although generally assumed to reflect continued bleeding from a ruptured vessel or vessels, very little is known of biological underpinnings of the spot sign. One study showed the spot sign to be associated with faster rates of contrast leakage measured as perfusion CT derived permeability, emphasizing the theory of continued bleeding.[25] In addition, warfarin exposure has been associated with both the presence of a spot sign[19,20,26], as well as the number of spot signs on CTA[15]. The association of the apolipoprotein E (APOE) ε2 allele with hematoma expansion and the spot sign in patients with ICH in the lobar brain regions[26,27] suggests a model of cascading small vessel injury following ICH as first described by Fisher.[28] In this model, expansion of the initial hematoma is caused by the rupture of small adjacent vessels surrounding the hematoma.[27]

Risk Factors

Several (clinical) risk factors for the spot sign have been identified. In addition to early presentation, anticoagulation, and APOE ε2 - large baseline hematoma volume, low GCS score upon presentation, mean arterial blood pressure of >120 mm Hg, and the presence of intraventricular hemorrhage have been associated with risk of spot sign.[12,14,19,20]

CLINICAL APPLICATIONS

Hematoma Expansion

Multiple retrospective single-center cohort studies have confirmed that contrast extravasation and the spot sign are potent, independent predictors of hematoma expansion (Tables 2 and 3). In addition, a single study has shown that a higher spot sign score is associated with risk of subsequent hematoma expansion.[19] Of note, definitions of hematoma expansion vary across studies, but different definitions have all been robustly associated with poor outcome.[6] Recently, the multi-center prospective PREDICT study confirmed these findings and showed a strong association (RR 2.3 [95% CI 1.6 – 3.1]) between spot sign and development of hematoma expansion of >6 mL or >33% from baseline ICH volume.[24] Most studies have been restricted to patients receiving their CTA within 6 hours of symptom onset. However, in studies that included patients whose initial CTAs were performed substantially later in the course of their ICH, the spot sign remained an independent predictor of hematoma expansion, even after adjusting for time from symptom onset to CTA.[14,19,20]

Functional Outcome and Mortality

Several studies have examined the value of the spot sign as a predictor of functional outcome and short- and long-term mortality (Table 4). All studies show a robust association of the CTA spot sign with both functional outcome and mortality. Similarly, the spot sign score has shown to be associated with both in-hospital mortality and poor clinical outcome at 3 months.[20] In the PREDICT study the 3-month morality Hazard ratio was 2.4 (95% CI 1.4 – 4.0) for spot sign positive patients compared to spot sign negative patients.[24]

Secondary ICH

Secondary causes of ICH (e.g. aneurysms, trauma, brain tumors) are generally excluded from spot sign studies, because of presumed differences in pathophysiology and the relatively frequent need for surgical treatment. Such secondary causes can mimic a spot sign, and vascular and non-vascular mimics are frequent and can impair its accuracy.[29]

However, one study showed the spot sign also to be predictive of functional outcome in secondary ICH.[30] An association with hematoma expansion in secondary ICH could not be assessed because nearly two-thirds of patients did not have a follow-up CT available due to early endovascular or surgical intervention.[30]

Clinical Implications and Ongoing Trials

The search for effective treatments that improve outcomes in patients with ICH continues to be challenging. The arrest of hematoma expansion continues to be a target for reducing final ICH volume and improving clinical outcome.[5,6] Selection of patients at highest risk for expansion has therefore been a strategy in recent clinical trials searching to improve outcomes.[7-9] Early presentation (within 4 to 6 hours) has been used in these trials as a surrogate for hematoma expansion, but even of the patients presenting ultra-early only 40% suffer from significant hematoma expansion.[4] Therefore, more than half of enrolled patients may be exposed to an intervention without an opportunity to benefit.

This challenge provides a potential role for the spot sign as a selection tool. With the spot sign as strong predictor of hematoma expansion, it may be possible to identify ICH patients who are most likely to have poor outcomes and treat them aggressively. Ongoing clinical trials including STOP-IT (ClinicalTrials.gov #NCT00810888) and SPOTLIGHT (ClinicalTrials.gov #NCT01359202) are using the spot sign to select patients for treatment with recombinant factor VIIa (rFVIIa). Aggressive blood pressure lowering, as currently tested in non-selected patients by INTERACT2[31] and ATACH-II[32], may also be guided by spot sign status. The ancillary study of ATACH-II, the SCORE-IT (Spot Sign Score in Restricting ICH Growth, National Institutes of Health – National Institute of Neurological Disorders and Stroke [NIH – NINDS] R01NS073344) study, is currently testing the hypothesis that patients with the highest spot sign scores benefit most from aggressive anti-hypertensive treatment.

Challenges and Future Directions

Although the CTA spot sign represents a substantial advance for the prediction of hematoma expansion in ICH, several important challenges remain. First, the relatively low sensitivity of the current definition of the spot sign. In PREDICT only 37 out of 73 patients (51%) with hematoma expansion demonstrated a spot sign, highlighting that a substantial number of patients will expand despite the absence of a spot sign.[24] Thus, because the spot sign negative group was nearly three times the size of the spot sign positive group, the absolute number of expanders either with or without a spot sign is roughly the same. Therefore, a study selecting its patient population based on the spot sign would leave the same number of expanders untreated (36 versus 37 in PREDICT). Technical refinement of the CTA spot sign may increase the sensitivity of the spot sign in order to capture more patients destined to expand and thus reduce the number of potentially treatable patients excluded from any trial.

Second, a potential benefit found in one of the ongoing trials using the spot sign as selection tool, will only be generalizable to those who can undergo CTA. Although CTA does not appear to increase risk of nephropathy following ICH[33], it has yet to be routinely applied in acute ICH other than for the purpose of identifying secondary causes of ICH.[34]

Third, all past and current studies only include patients in the first hours after symptom onset. So a considerable number of patients are left untreated, based solely on their presentation time. While early presenters are certainly at higher individual risk for hematoma expansion, the spot sign is an independent predictor of hematoma expansion when adjusting for presentation time.[14,19,20] This may allow the inclusion of patients within a broader time frame and should therefore be considered in future trials.

Future directions include phase II and III clinical trails to evaluate the spot sign as a selection tool for aggressive medical management and technical refinement of the spot sign to increase sensitivity. An unexplored field includes the possibility of patient selection for surgical treatment. No data is currently available on the re-bleeding rate in surgically treated spot sign positive patients. If the spot sign represents extensive small vessel damage, the risk of re-bleeding may be heightened and a spot sign should then preclude patients from undergoing surgical evacuation.

Despite the shortcomings of the spot sign, and biomarkers in general[35], its consistent association with hematoma expansion provides us with a robust radiographic marker of hematoma expansion. Therefore, phase III, randomized clinical trials are the only way to assess clinical effectiveness of patient selection by spot sign status. A potentially beneficial outcome from such a study can at least be seen as the first step in the long-awaited direction of treatment success in intracerebral hemorrhage.

Acknowledgments

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Spot sign characteristic	Points
Number of spot signs	
1 – 2	1
≥ 3	2
Maximum axial dimension	
1 – 4 mm	0
≥ 5 mm	1
Maximum attenuation	
120 – 179 HU	0
≥ 180 HU	1
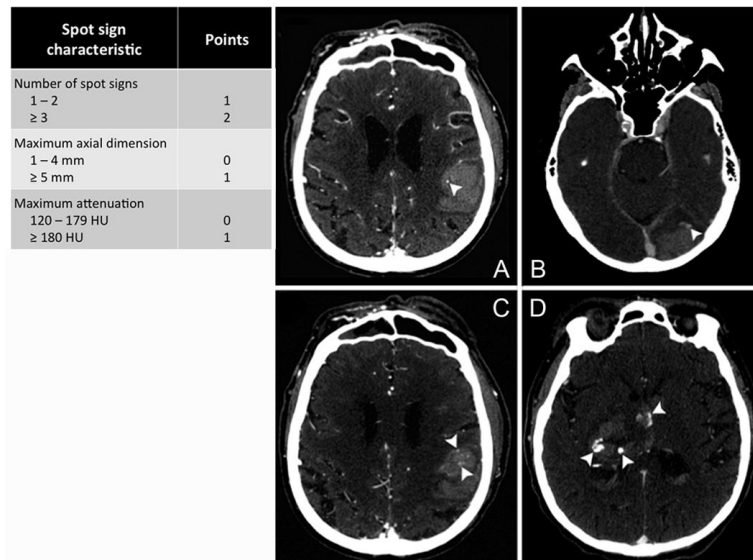
Figure. Examples of different spot sign scores

CT angiography of acute intracerebral hemorrhage representing different spot sign scores. (A) One spot sign with a maximal attenuation of 168 Hounsfield units (spot sign score 1). (B) Single spot sign with a maximal attenuation of 131 Hounsfield units and a diameter of 5 millimeter (spot sign score 2). (C) Multiple spot signs of which one with a maximal attenuation of 186 Hounsfield units (spot sign score 3). (D) Multiple spot signs with maximal attenuations of >200 Hounsfield units and two spots with a maximal diameter of >5 millimeter (spot sign score 4).

Table 1

Study definitions CT angiography contrast extravasation and spot sign

	Study	Year	Spot sign definition
Contrast extravasation	Becker et al.[12]	1999	Visualization of high-density contrast within the clot or ventricular system.
	Murai et al.[13]	1999	Leakage of contrast medium seen as a high-density area on helical CT images.
	Goldstein et al.[14]	2007	The presence of high-density material within the hematoma.
	Ederies et al.[16]	2009	The presence of contrast puddling within the hematoma on the post-contrast CT.
	Hallevi et al.[17]	2010	A hyperdensity (relative to the hematoma) within the hematoma on the post-contrast CT.
Spot sign	Wada et al.[15]	2007	Foci of enhancement within the hematoma on CTA source images.
	Kim et al.[18]	2008	High-attenuation contrast material within the hematoma.
	Delgado Almandoz et al.[19,20]	2009 and 2010	(1) 1 focus of contrast pooling within the ICH; (2) with an attenuation 120 Hounsfield units (HU); (3) discontinuous from normal or abnormal vasculature adjacent to the ICH; and (4) of any size and morphology.
	Thompson et al.[21]	2009	Spot-like and/or serpiginous foci of enhancement, within the margin of a parenchymal hematoma without connection to outside vessels, greater than 1.5 mm, and a Hounsfield unit density at least double that of background hematoma density.
	Ederies et al.[16]	2009	Based on Wada et al. (2007)
	Hallevi et al.[17]	2010	A hyperdense spot within the hematoma that was unrelated to a blood vessel.
	Wang et al.[22]	2011	Based on Wada et al. (2007)
	Li et al.[23]	2011	Based on Delgado Almandoz et al. (2009 and 2010)
	Demchuk et al.[24]	2012	One or more foci of contrast enhancement within an acute primary parenchymal haematoma visible on the source images of CTA (similar to Wada et al. [2007]).

Table 2

CT angiography contrast extravasation and hematoma expansion

Primary outcome	Hematoma expansion			
Authors (year)	*Murai et al. (1999)[13] **	*Goldstein et al. (2007)[14] **	*Ederies et al. (2009)[16] ***	*Hallevi et al. (2010)[17] ***
Study design	Prospective	Retrospective	Retrospective	Prospective
Number of patients	24	104	61	27
Number of patients with contrast extravasation (%)	5 (21)	58 (56)	11 (18)	13 (59)
Time window	<12 hours from symptom onset	All patients	<6 hours from symptom onset	<4 hours from symptom onset
Hematoma expansion definition	>15 mL increase from baseline ICH volume	>33% increase from baseline ICH volume	> 30% or >6 mL increase from baseline ICH volume	>20% increase from baseline ICH volume
Expansion (%)	3 (14)	14 (14)	18 (30)	16 (57)
Point estimate multivariate analysis (95% CI)	n/a	OR 18 (2.1 - 162)	n/a	OR 77 (4 – 1476)
Sensitivity	1.00	0.93	0.94	1.00
Specificity	0.90	0.50	0.79	1.00
PPV	0.60	0.22	0.65	1.00
NPV	1.00	0.98	0.97	1.00
Accuracy	0.92	0.56	0.84	1.00

ICH = intracerebral hemorrhage; 95% CI = 95% confidence interval; n/a = not available; OR = odds ratio; PPV = positive predictive value; NPV = negative predictive value

*
These two studies examined contrast extravasation, so accuracy measures refer solely to contrast extravasation.

**
For these two studies, accuracy refers to presence either of a spot sign on CTA source images or any contrast extravasation on post-contrast CT images.

Table 3

CT angiography spot sign and hematoma expansion

Primary outcome	Hematoma expansion							
Authors (year)	Wada et al. (2007)[15]	Delgado Almandoz et al. (2009)[19]	Ederies et al. (2009)[16]	Hallevi et al. (2010)[17]	Wang et al. (2011)[22]	Li et al. (2011)[23]	Demchuk (2012)[24]
Study design	Prospective	Retrospective	Retrospective	Prospective	Retrospective	Prospective	Prospective
Number of patients	39	367	61	27	312	139	228
Number of spot positive patients (%)	13 (33)	71 (19)	21 (34)	11 (41)	76 (24)	30 (22)	61 (27)
Time window	<3 hours from symptom onset	All patients	<6 hours from symptom onset	<4 hours from symptom onset	<3 hours from symptom onset	<6 hours from symptom onset	<6 hours from symptom onset
Hematoma expansion definition	>30% or > 6 mL increase from baseline ICH volume	>30% or >6 mL increase from baseline ICH volume	> 30% or >6 mL increase from baseline ICH volume	>20% increase from baseline ICH volume	>30% or > 6 mL increase from baseline ICH volume	>33% or >12.5 mL increase from baseline ICH volume	>33% or >6 mL increase from baseline ICH volume
Expansion (%)	11 (28)	56 (15)	18 (30)	16 (57)	77 (25)	32 (23)	73 (32)
Point estimate multivariate analysis (95% CI)	LR 8.5 (2.9 - 25)	OR 92 (37 - 227)	n/a	OR 77 (4 – 1476)	n/a	n/a	RR 2.3 (1.6 - 3.1)
Sensitivity	0.91	0.88	0.78	0.73	0.78	0.72	0.51
Specificity	0.89	0.93	0.84	1.00	0.93	0.94	0.85
PPV	0.77	0.69	0.67	1.00	0.79	0.79	0.61
NPV	0.96	0.98	0.90	0.75	0.93	0.92	0.78
Accuracy	0.90	0.92	0.82	0.85	0.89	0.89	0.74

ICH = intracerebral hemorrhage; 95% CI = 95% confidence interval; LR = likelihood ratio; OR = odds ratio; n/a = not available; RR = relative risk; PPV = positive predictive value; NPV = negative predictive value

Table 4

CT angiography spot sign and clinical outcome

Primary outcome	Clinical outcome and mortality						
Authors (year)	Becker et al. (1999)[12] *	Goldstein et al. (2007)[14] *	Wada et al. (2007)[15]	Kim et al. (2008)[18]	Delgado Almandoz et al. (2010)[20]	Li et al. (2011)[23]	Demchuk (2012)[24]
Study design	Retrospective	Retrospective	Prospective	Retrospective	Retrospective	Prospective	Prospective
Number of patients	113	104	39	56	573	139	211
Number of spot positive patients (%)	52 (46)	58 (56)	13 (33)	10 (18)	133 (23)	30 (22)	53 (25)
Time window	All patients	All patients	<3 hours from symptom onset	All patients	All patients	<6 hours from symptom onset	<6 hours from symptom onset
Functional outcome measure	In-hospital mortality	In-hospital mortality	In-hospital mortality and 3-month mRS	30-day mortality	In-hospital mortality and 3-month mRS	3-month poor outcome	3-month mortality and 3-month mRS
Overall mortality (%)	43 (38)	26 (25)	7 (28)	16 (29)	180 (31)	72 (52)	54 (26)
Point estimate multivariate analysis (95% CI)	OR 5.2 (1.60 - 17.1)	n/a	n/a	OR 4.7 (1.3 - 16.9)	OR 1.5 (1.2 - 1.9) OR 1.6 (1.1 - 2.1)	OR 10.5 (3.2 - 34.7)	HR 2.4 (1.4 - 4.0) mRS 5 vs. 3
Sensitivity	0.77	0.73	0.43	0.50	0.41	0.36	0.43
Specificity	0.73	0.50	0.69	0.83	0.85	0.94	0.81
PPV	0.63	0.33	0.23	0.53	0.56	0.87	0.43
NPV	0.84	0.85	0.85	0.80	0.76	0.58	0.80
Accuracy	0.74	0.56	0.64	0.73	0.71	0.64	0.71

mRS = modified Rankin Scale; 95% CI = 95% confidence interval; OR = odds ratio; n/a = not available; HR = hazard ratio; PPV = positive predictive value; NPV = negative predictive value

*
Studies used a definition of contrast extravasation instead of spot sign.