The role of ^{18}F-FDG-PET in detecting Richter transformation of chronic lymphocytic leukemia in patients receiving therapy with a B-cell receptor inhibitor

Chronic lymphocytic leukemia (CLL) is a low grade B-cell malignancy. Approximately 2-10% of CLL can undergo Richter transformation (RT) to an aggressive lymphoma, most commonly diffuse large B-cell lymphoma (DLBCL).[1-3] Management of RT is extremely challenging and the clinical outcome is dismal.[4] In CLL patients with suspected disease progression, distinguishing between progressive CLL and RT is critically important, as the management and prognosis are different.

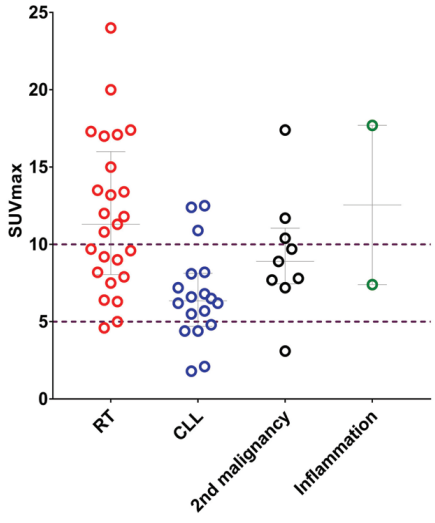
While tissue biopsy is the gold standard for diagnosing progressive CLL *versus* RT, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) may play an important role in the diagnostic workup. In the chemoimmunotherapy (CIT) era, several studies showed that a maximum standardized uptake value (SUV_{max}) ≥5 had high sensitivity (88-91%) and varied specificity (47-80%) in detecting RT,[5-7] and a French study[8] reported high sen-

Table 1. Baseline characteristics at the time of B-cell receptor pathway inhibitors initiation.

	Total (N=92)	Without biopsy (N=38)	With biopsy (N=54)	*P*
Age at BCRi initiation				0.36
Median	68	70	67	
Range	(43-89)	(47-89)	(43-81)	
Sex				0.22
Female	23 (25.0%)	12 (31.6%)	11 (20.4%)	
Male	69 (75.0%)	26 (68.4%)	43 (79.6%)	
BCRi				0.80
Ibrutinib	90 (97.8%)	37 (97.4%)	53 (98.1%)	
Idelalisib	2 (2.2%)	1 (2.6%)	1 (1.9%)	
BCRi as first-line treatment				0.32
Yes	13 (14.1%)	7 (18.4%)	6 (11.1%)	
No	79 (85.9%)	31 (81.6%)	48 (88.9%)	
Rai category				0.27
Rai 0: Low risk	14 (15.4%)	5 (13.2%)	9 (17.0%)	
Rai 1 or 2: Intermediate risk	26 (28.6%)	8 (21.1%)	18 (34.0%)	
Rai 3 or 4: High risk	51 (56.0%)	25 (65.8%)	26 (49.1%)	
Missing	1	0	1	
IGHV mutation				0.56
Unmutated	60 (80.0%)	25 (83.3%)	35 (77.8%)	
Mutated	15 (20.0%)	5 (16.7%)	10 (22.2%)	
Missing	17	8	9	
CLL FISH category				0.13
Del(17p)	19 (27.5%)	8 (25.8%)	11 (28.9%)	
Del(11q)	16 (23.2%)	8 (25.8%)	8 (21.1%)	
Trisomy 12	10 (14.5%)	4 (12.9%)	6 (15.8%)	
Normal	12 (17.4%)	2 (6.5%)	10 (26.3%)	
Del(13q)	8 (11.6%)	6 (19.4%)	2 (5.3%)	
Other	4 (5.8%)	3 (9.7%)	1 (2.6%)	
Missing	23	7	16	
TP53 disruption (*TP53* mutation or FISH del(17p)				0.75
No	49 (70.0%)	23 (71.9%)	26 (68.4%)	
Yes	21 (30.0%)	9 (28.1%)	12 (31.6%)	
Missing	22	6	16	
CLL-IPI risk group				0.90
Intermediate (2-3)	12 (20.0%)	6 (22.2%)	6 (18.2%)	
High (4-6)	31 (51.7%)	14 (51.9%)	17 (51.5%)	
Very High (7-10)	17 (28.3%)	7 (25.9%)	10 (30.3%)	
Missing	32	11	21	

BCRi: B-cell receptor pathway inhibitor; *IGHV*: immunoglobulin heavy-chain variable region gene; CLL: chronic lymphocytic leukemia; FISH: fluorescence *in situ* hybridization; IPI: international prognostic index.

A



B

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SUVmax ≥5	96%	21%	51%	86%
SUVmax ≥6	92%	28%	52%	80%
SUVmax ≥7	84%	45%	57%	76%
SUVmax ≥8	76%	62%	63%	75%
SUVmax ≥9	72%	72%	69%	75%
SUVmax ≥10	56%	76%	67%	67%
SUVmax ≥11	52%	83%	72%	67%
SUVmax ≥12	44%	86%	73%	64%
SUVmax ≥13	40%	93%	83%	64%
SUVmax ≥14	28%	93%	78%	63%
SUVmax ≥15	28%	93%	78%	60%

C

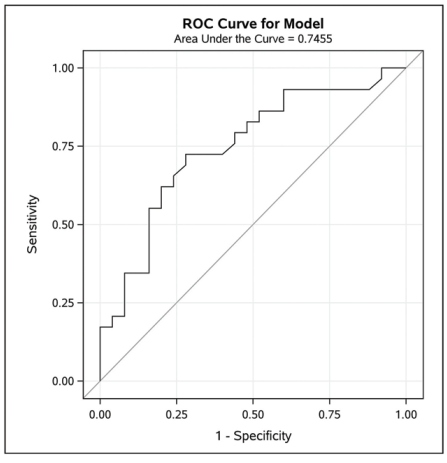


Figure 1. SUV_{max} on a PET scan. (A) Distribution of SUV_{max} by pathology. (B) Sensitivity, specificity, and positive and negative predictive values of different SUV_{max} thresholds in detecting Richter transformation (n=54): ©ROC analysis of SUV_{max} cut-off for identifying Richter transformation. SUV: standardized uptake value; PET: positron emission tomography.

sitivity (91%) and specificity (95%) using a cut-off of SUV_{max} ≥10.

B-cell receptor pathway inhibitors (BCRi) such as Bruton tyrosine kinase (BTK) inhibitor ibrutinib and phosphatidylinositol 3-kinase (PI3K) inhibitor idelalisib have significantly improved the outcome of CLL. However, CLL patients who progress through BCRi often develop clinically aggressive disease.[9-12] Recently Mato *et al.*[12] reported that in CLL patients who progressed on a BCRi therapy and were screened for participation in a clinical trial of venetoclax, SUV_{max} ≥10 on PET scan had a low sensitivity (71%) and specificity (50%) in detecting RT. However, this study included only eight patients with RT. Given the increasing use of BCRi in clinical practice and the importance of differentiating between RT and progressive CLL, we conducted a single-institution study to further evaluate the diagnostic role of PET scan in CLL patients receiving BCRi therapy with suspected disease progression.

CLL patients on a BCRi treatment who underwent a PET scan for evaluation of potential disease progression between November 2012 and March 2019 were identified from the Mayo Clinic CLL Database.[13] CLL patients with no clinical suspicion of disease progression who underwent a PET scan for restaging (i.e., evaluation of treatment response) were excluded. Patients with known RT or a second malignancy who underwent a PET scan for initial staging or restaging were also excluded. PET images were centrally reviewed by a nuclear radiologist (MSB). Pathology slides in a subset of patients were independently reviewed by a hematopathologist (MS) for verification.

Between November 2012 and March 2019, 92 CLL patients, who were on a BCRi (ibrutinib [n=90] or idelalisib [n=2]) and underwent a PET scan to evaluate for potential disease progression, were identified (Table 1). The median age at BCRi initiation was 68 years (range: 43-89), and 69 (75%) were male. Sixty (80%) patients had unmutated immunoglobulin heavy-chain variable region (IGHV). The CLL fluorescence *in situ* hybridization (FISH) panel showed del(17p) in 19 (28%) and del(11q) in 16 (23%) patients. The median time from BCRi initiation to PET scan was 14 months (range: 0.3-62 months). The median SUV_{max} was 7.0 (range: 1.1-27.3). The number of patients with a SUV_{max} of <5 was 33 (36%), ≥5 but <10 was 34 (37%), and ≥10 was 25 (27%). After the PET scan, 38 patients did not undergo tissue biopsy; among those, 34 were treated as persistent CLL (median SUV_{max} 3.6 [range: 1.1-10.3]), two were treated as presumed RT (SUV_{max} 19.5 and 27.3, respectively), and two died before a biopsy could be performed (SUV_{max} 7.8 and 13.5, respectively). There were no differences in baseline characteris-

Table 2. SUV_{max} in patients with different pathology on biopsy (n=54).

Pathology	N	Median SUV_{max} (range)	SUV_{max} <5	SUV_{max} ≥5 but <10	SUV_{max} ≥10
Richter transformation	25	11.3 (4.6-24.0)	1	10	14
Progressive CLL	18	6.4 (1.8-12.5)	5	10	3
Second malignancy*	9	8.9 (3.1-17.4)	1	5	3
Inflammation†	2	12.6 (7.4-17.7)	0	1	1
Total	54	8.6 (1.8-24.0)	7	26	21

*Six with recurrent malignancy (two metastatic squamous cell carcinoma of the skin, one each with low grade B-cell lymphoma with plasmacytic differentiation, metastatic melanoma, metastatic Merkel cell carcinoma, and metastatic lung cancer) and three with new malignancy (one each with renal cell carcinoma, soft tissue sarcoma, and metastatic carcinoma of unknown primary origin). †One with reactive gastropathy, the other with acute and chronic granulomatous changes due to herpes simplex virus. SUV: standardized uptake value; CLL: chronic lymphocytic leukemia.

tics between patients who underwent a biopsy *versus* those who did not.

Fifty-four patients (median SUV_{max} of 8.6 [range: 1.8-24.0]) underwent a tissue biopsy. The median time from PET scan to biopsy was 4 days (range: 0-40). The biopsy was targeted towards either the area of maximum SUV (n=29, median SUV_{max} 7.8) or an alternative area that was easier to access (n=25; median SUV_{max} 6.7, median SUV_{max} difference=2.7 compared to the maximum SUV area). The biopsy sites included lymph node (n=34; 10 excisional and 24 core needle), soft tissue mass (n=9; two excisional and seven core needle), bone marrow (n=3), cerebrospinal fluid (n=1) and other organ (n=7; spleen [n=2, splenectomy], kidney, lung, bone [n=1 each, core needle], and stomach [n=2, esophagogastroduodenoscopy]).

The final pathology was RT in 25 (46%) patients (21 with DLBCL and four with classical Hodgkin lymphoma), CLL in 18 (33%; 15 can be classified as histologically aggressive CLL according to the World Health Organization 2016 criteria, with the presence of expanded proliferation centers that are broader than a 20x field or becoming confluent, or a Ki-67 proliferation index >40%), second malignancy in nine (17%; six with recurrent malignancy, three with new malignancy), and inflammation in two (4%) patients (Table 2).

The median SUV_{max} was 11.3 (range: 4.6-24.0) for patients with RT, 6.4 (range: 1.8-12.5) for patients with progressive CLL (P<0.001 *vs.* RT; Figure 1A), and 8.9 (range: 3.1-17.4) for patients with a second malignancy (P=0.18 *vs.* RT; Figure 1A). Only 1 of 7 patients with a SUV_{max} <5 had RT. In patients with a SUV_{max} ≥5 but <10, 10 of 26 (38%) had RT; and in patients with a SUV_{max} ≥10, 14 of 21 (67%) had RT. The sensitivity and specificity for identifying RT (*vs.* other pathology) using a threshold of SUV_{max} ≥5 was 96% and 21%, respectively; and using a threshold of SUV_{max} ≥10 was 56% and 76%, respectively (Figure 1B). The negative predictive value (NPV) of SUV_{max} <5 in predicting RT was 86%, and the positive predictive value (PPV) of SUV_{max} ≥10 in predicting RT was 67%. Using the ROC analysis, a threshold of SUV_{max} ≥9 was determined to be the best discriminator for detecting RT *vs.* other pathology in all 54 patients who underwent a biopsy, with a sensitivity of 72% and specificity of 72% (Figure 1C). The PPV and NPV of this cut-off was 69% and 75%, respectively. Additional results regarding ibrutinib hold and survival after PET are available in the *Online Supplementary Materials and Methods.*

Our study confirms findings by Mato *et al.*[12] In CLL patients receiving a BCRi who underwent a PET scan for evaluation of potential disease progression, although a SUV_{max} of 9 was the best cut-off to discriminate RT *versus* other pathology, the sensitivity (72%) and specificity (72%) at this cut-off were both low. The sensitivity (96%) and NPV (86%) for identification of RT using a lower cut-off of SUV_{max} ≥5 was excellent, but the specificity (76%) and PPV (67%) remained low using a higher cut-off of SUV_{max} ≥10. The role of PET in detecting RT needs to be revisited in the novel agent era.

While tissue biopsy still remains the gold standard for diagnosing RT in CLL patients with suspected transformation of disease, a PET scan helps by i) determining if a biopsy should be considered if the SUV_{max} exceeds a certain cut-off; and ii) identifying the area with the highest FDG uptake for an excisional or core needle biopsy. Mato *et al.*[12] reported a sensitivity of 71% and a specificity of only 4% using a cut-off of SUV_{max} ≥5 and a sensitivity of 71% and a specificity of 50% using a cut-off of SUV_{max} ≥10 in CLL patients who progressed after BCRi. In our study, a cut-off of SUV_{max} ≥5 had a sensitivity of 96% and a specificity of 21%, while a cut-off of SUV_{max} ≥10 had a sensitivity of 56% and a specificity of 76%. We propose using SUV_{max} ≥5 as the cut-off to strongly consider biopsy given the high sensitivity (96%) and NPV (86%) in our study. In our cohort, only one patient with SUV_{max} <5 was diagnosed with RT on excisional biopsy of a cervical lymph node that was enlarging asynchronously. In contrast, approximately 40% of the patients with a SUV_{max} ≥5 but <10 and two-thirds of the patients with a SUV_{max} ≥10 were diagnosed with RT, emphasizing the need to perform a tissue biopsy in patients with a SUV_{max} ≥5.

CLL progression on BCRi can be associated with a relatively high SUV in a PET scan, as ibrutinib can change the metabolism of CLL cells by increasing glucose uptake,[14,15] and CLL progression developed on ibrutinib is often clinically aggressive.[9-12] It is important not to assume a diagnosis of RT even with a high SUV_{max} (e.g., ≥10), and tissue biopsy is still the gold standard to make a diagnosis.

The strengths of our study include a relatively homogenous study population from a single institution (CLL patients on BCRi therapy who underwent PET scan for the evaluation of disease progression), and a central review of PET images for SUV measurement/confirmation. The limitations include the retrospective design, lack of a tissue biopsy in a subset of patients (although the majority had a low SUV_{max}), incomplete central pathology review, potential referral bias, and the small cohort size.

In summary, the role of a PET scan in identifying RT in the era of novel agent CLL therapy has evolved owing to the changing biology of CLL with novel targeted therapy. A biopsy should be strongly considered in patients receiving BCRi therapy with suspected RT with a SUV_{max} ≥5 on PET. Prospective re-examination of the diagnostic value of PET in CLL patients with suspected transformation in the novel agent era with larger cohorts of patients and with central imaging and pathology review is warranted.

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Funding: SSK and SAP are recipients of the K12 CA090628 grant from the National Cancer Institute (Paul Calabresi Career Development Award for Clinical Oncology).

doi:10.3324/haematol.2019.240564

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