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

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Supplemental Material

Detailed Methods

This study was approved by Mayo Clinic Institutional Review Board. CLL patients who were receiving treatment with a BCRi and underwent a PET scan for evaluation of potential disease progression between November 2012 and March 2019 were identified from the Mayo Clinic CLL Database.[1] CLL patients with no clinical suspicion of disease progression who underwent a PET scan for restaging (i.e., evaluation of BCRi 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.

Baseline clinical characteristics, treatment, follow-up, and pathological characteristics at the time of BCRi initiation were obtained from the CLL database. PET images were centrally reviewed by a Mayo Clinic nuclear radiologist (MSB), and overall SUVmax, SUVmax of biopsied lesion, and SUV of hepatic background and blood pool were recorded. Information on lesion biopsy (timing, site, type) and pathology diagnosis of the tissue biopsy were abstracted from electronic medical records. Pathology slides in a subset of patients who underwent a biopsy were independently reviewed by a Mayo Clinic hematopathologist (MS) for verification. All patients who underwent a biopsy were classified into one of the following four categories of diagnosis: 1) RT (either DLBCL or classical Hodgkin lymphoma); 2) CLL; 3) non-CLL related malignancy; and 4) infection/inflammation related changes.

Differences between groups were examined using Kruskal-Wallis test for continuous variables and Chi-square or Fisher's exact tests for categorical variables. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of different SUVmax thresholds for detecting RT (vs other pathology) were calculated. Receiver operating characteristic (ROC) analysis was performed to determine the optimal SUVmax cutoff. Overall survival (OS) was defined as time from date of PET scan to date of death from any cause or last known alive date, and analyzed using the Kaplan-Meier method and the Cox proportional-hazards model. All statistical analyses were done in SAS 9.4 (SAS Institute, Cary, NC), and *P* values <0.05 were considered to be statistically significant.

Impact of ibrutinib hold

The BTK inhibitor ibrutinib is associated with platelet dysfunction and is often temporarily held for tissue biopsy to reduce the risk of bleeding.[2] It was reported that temporary interruption of ibrutinib can cause disease flare, especially in patients already showing signs of possible progression.[3-5] It is unknown if holding ibrutinib prior to a biopsy can affect the sensitivity and specificity of PET scan in predicting RT.

In our study, a subset of patients (n=35) temporarily interrupted BCRi therapy before the biopsy, and the median time of BCRi hold before biopsy was 4 days (range 1-14). Eleven patients proceeded to biopsy without holding BCRi, and it was unclear whether the other 8 patients held BCRi for the biopsy. For the 35 patients who held ibrutinib for the biopsy, the pathology diagnoses included 17 (49%) RT, 11 (31%) CLL, and 7 (20%) second malignancy (**Supplemental Table 1**). For the patients (n=11) who did not hold ibrutinib for the biopsy, the pathology diagnoses included 4 (36%) RT, 5 (45%) CLL, 1 (9%) second malignancy, and 1 (9%) inflammation. The sensitivity, specificity, positive and negative predictive values for different SUVmax cutoffs in detecting RT in the 35 patients who held ibrutinib (**Supplemental Table 2**) appeared similar to those in all 54 patients who underwent a biopsy. These results, albeit small numbers, suggest that holding ibrutinib, at least for a short time, for biopsy does not seem to impact the sensitivity and specificity of PET scan in predicting RT vs progressive CLL. However, this needs to be confirmed, preferably in a prospective study.

Overall survival after PET scan

The median OS after PET scan was 10.8 months for the 54 patients who underwent a biopsy (**Supplemental Figure 1A**). The median OS was 5.7 months for those with RT, 11.3 months for those with progressive CLL, 4.4 months for those with a second malignancy, and not reached for those with inflammation (**Supplemental Figure 1B**). Among the 43 patients diagnosed with RT or progressive CLL, the median OS was 6.3 and 13.6 months for patients with a SUVmax ≥5 or <5, respectively (*P*=0.38; **Supplemental Figure 2A**), 5.7 and 13.4 months for patients with a SUVmax ≥9 or <9, respectively (*P*=0.57; **Supplemental Figure 2B**), and 5.7 and 13.4 months for patients with a SUVmax ≥10 or <10, respectively (*P*=0.39; **Supplemental Figure 2C**). In univariate Cox regression, a higher SUVmax was not associated with worse OS (HR=1.04, 95% CI=0.98-1.1, *P*=0.22) in patients with biopsy-proven RT or CLL.

Supplemental Table 1. SUVmax in patients who had BCRi held with different pathology on biopsy (n=35)

Pathology	N	Median SUVmax (range)	SUVmax <5	SUVmax ≥5 but <10	SUVmax ≥10
Richter's transformation	17	11.3 (4.6-24.0)	1	6	10
Progressive CLL	11	6.2 (1.8-12.5)	4	5	2
Second malignancy	7	9.7 (7.7-17.4)	0	4	3
Total	35	9.6 (1.8-24.0)	5	15	15

BCRi, B-cell receptor inhibitor; SUV, standardized uptake value; CLL, chronic lymphocytic leukemia.

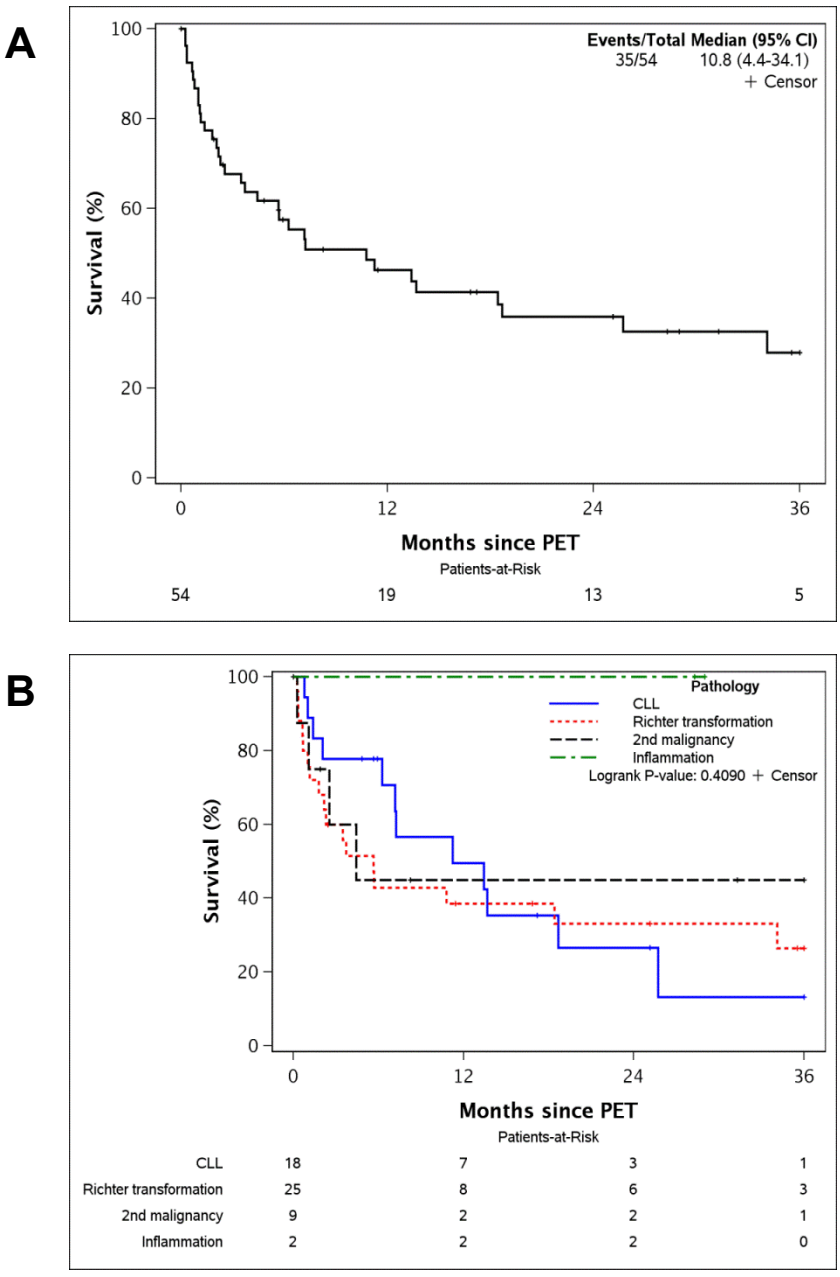
Supplemental Table 2. Sensitivity, specificity, and positive and negative predictive values of different SUVmax thresholds in detecting Richter's transformation in those who had BCRi held (n=35)

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
SUVmax ≥5	94%	22%	53%	80%
SUVmax ≥6	88%	22%	52%	67%
SUVmax ≥7	88%	44%	60%	80%
SUVmax ≥8	82%	61%	67%	79%
SUVmax ≥9	76%	67%	68%	75%
SUVmax ≥10	59%	72%	67%	65%
SUVmax ≥11	53%	83%	75%	65%
SUVmax ≥12	47%	89%	80%	64%
SUVmax ≥13	47%	94%	89%	65%
SUVmax ≥14	35%	94%	86%	61%
SUVmax ≥15	35%	94%	86%	61%

BCRi, B-cell receptor inhibitor; SUV, standardized uptake value.

Supplemental Figure 1. Overall survival after PET

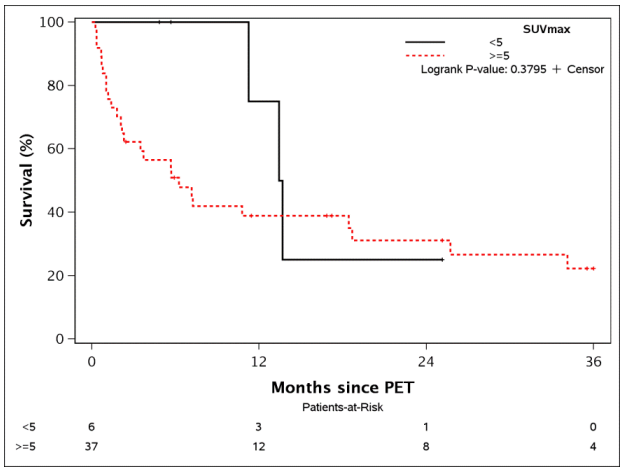
(A) Overall survival after PET in patients who underwent a tissue biopsy
(B) Overall survival after PET by pathology in patients who underwent a tissue biopsy



Supplemental Figure 2. Overall survival after PET by SUVmax

(A) Overall survival after PET in patients with biopsy proven CLL or Richter's transformation with a SUVmax < or ≥ 5
(B) Overall survival after PET in patients with biopsy proven CLL or Richter's transformation with a SUVmax < or ≥ 9
(C) Overall survival after PET in patients with biopsy proven CLL or Richter's transformation with a SUVmax < or ≥ 10

A



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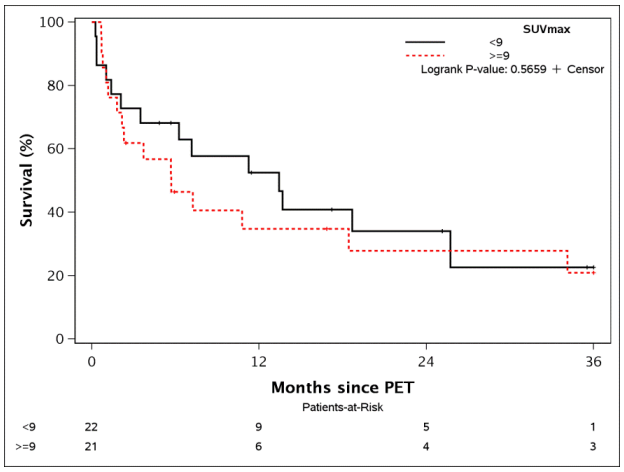

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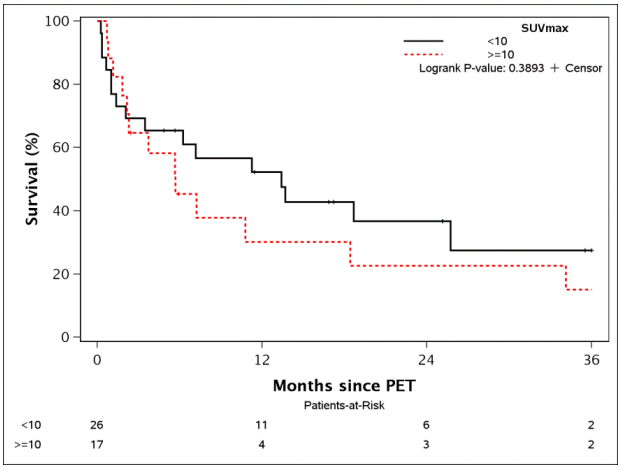

Supplemental References

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