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Large nuclear size correlated with better overall survival, Merkel cell polyomavirus positivity, and terminal deoxynucleotidyl transferase expression in Merkel cell carcinoma

To the Editor: The histologic appearance of Merkel cell polyomavirus (MCPyV)-positive Merkel cell carcinoma (MCC) has been reported to be distinctive: more uniform, round nuclei and less cytoplasm than cells in MCPyV-negative tumors.[1,2] In most of these studies, however, the described morphologic differences were identified by light microscopy, and morphometric analysis was done on a limited number of cases.[1,3] Extraction of nuclear features by computational methods from high-resolution whole-slide digital scans of histologic slides has been shown to improve accuracy and consistency.

In this study, we analyzed the whole-slide digital images of tissue microarrays stained with hematoxylin from 134 MCCs of 134 patients with the QuPath program,[4] a free and open-source quantitative whole-slide imaging software (Fig 1, *A*). Nuclear features, including nuclear area (NA), maximum (maxD) and minimum (minD) nuclear distance (longest and shortest axes along a 2-dimensional cut of a cell, respectively), and nuclear circularity (1.0 for a perfect circle and close to 0 for an increasingly elongated polygon) were extracted for each nucleus and aggregated per patient by mean, median, and SD and divided into 90-centile/50-centile/10-centile of the values using the R statistical package.[5] The extracted nuclear features, conventional histologic and clinical features, stage, MCPyV status, and terminal deoxynucleotidyl transferase (TdT) expression were correlated with patient outcome. Statistical methods included Kaplan-Meier curves and Cox proportional hazard modeling for survival analyses. $P < .05$ was considered statistically significant.

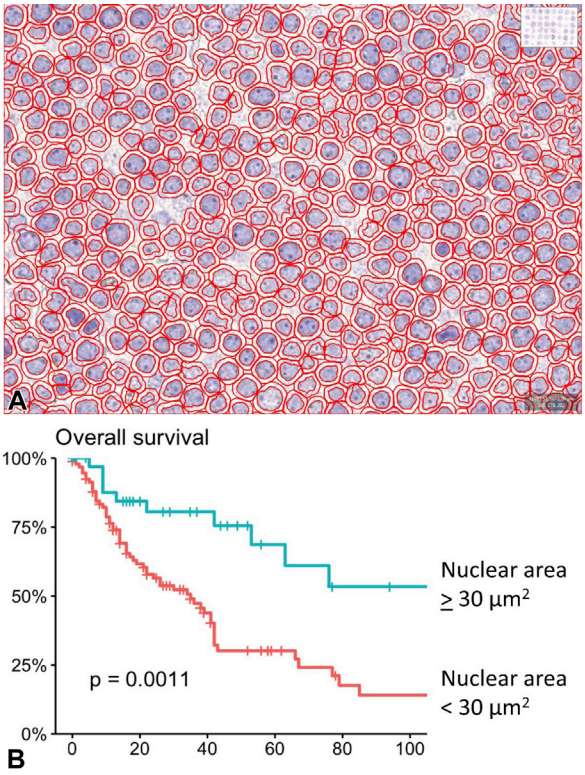

Fig 1. **A**, Representative image from tissue microarray in QuPath with cell detection and classification. **B**, Kaplan-Meier curves demonstrate significant correlation between better overall survival and larger nucleus area. The *y*-axis depicts percentage survival, and the *x*-axis depicts months.

The median number of evaluated nuclei for each tumor was 35,036 (range, 1817-94,401). The optimal cutoff or median for NA, minD, maxD, and nuclear circularity were 30 μm^2, 5.32 μm, 8.2 μm, and 0.7798, respectively. By box plots, large nuclear features significantly correlated with MCPyV positivity and TdT expression. By univariate Cox proportional hazard models and Kaplan-Meier curves, older age ($P < .0001$), higher stage (stages III and IV) at presentation ($P = .0066$), and ulceration ($P = .0051$) correlated with poorer overall survival (OS). There was no correlation between receipt of adjuvant therapy, including immunotherapy, and prognosis. Larger nuclear features (NA [$P = .0017$], minD [$P = .0057$], and maxD [$P = .048$]), MCPyV positivity ($P = .0061$), and high TdT expression ($P = .0019$) correlated with improved OS (Fig 1, *B*) (Table I).

Four multivariate models were evaluated—each for NA, minD, maxD, and nuclear circularity (Table I). Smaller NA ($P = .012$), older age ($P = .0017$), higher stage ($P = .032$), and low TdT expression ($P = .045$) remained independent

Table I. Univariate and multivariate Cox proportional hazards models

Variable	Overall survival	
	Hazard ratio	*P* value
Univariate model		
Age	2.38	<.0001*
Sex	1.31	.26
AJCC staging at presentation	1.9	.0066*
Site (head and neck vs nonhead and neck)	1.33	.23
Immunosuppression	1.33	.43
Size (>20 mm)	1.02	.95
Nuclear area	0.38	.0017*
Minimum nuclear distance	0.41	.0057*
Maximum nuclear distance	0.51	.048*
Nuclear circularity	0.55	.013*
Growth pattern (nodular vs infiltrative/mixed)	0.70	.14
Tumor thickness (>10 mm)	1.02	.93
Ulceration	1.98	.0051*
Mitoses (>40/mm^2)	0.99	.95
Necrosis	1.28	.34
Lymphovascular invasion	1.47	.11
Perineural invasion	1.82	.081†
Merkel cell polyomavirus	0.51	.0061*
TdT expression	0.47	.0019*
Multivariate model		
Nuclear area		
Age	2.25	.0017*
AJCC stage at presentation	1.72	.032*
Ulceration	1.43	.19
Nuclear area	0.43	.012*
Merkel cell polyomavirus status	0.96	.89
TdT expression	0.56	.045*
Minimum nuclear distance		
Age	2.43	.0011*
AJCC stage at presentation	1.80	.021*
Ulceration	1.43	.19
Minimum nuclear distance	0.41	.01*
Merkel cell polyomavirus status	1.03	.91
TdT expression	0.53	.027*
Maximum nuclear distance		
Age	0.93	.00054*
AJCC stage at presentation	1.51	.087†
Ulceration	1.4	.22
Maximum nuclear distance	0.65	.23
Merkel cell polyomavirus status	0.91	.73
TdT expression	0.49	.011*
Nuclear circularity		
Age	2.57	.00039*
AJCC stage at presentation	1.71	.027*
Ulceration	1.36	.27
Nuclear circularity	0.52	.0073*
Merkel cell polyomavirus status	0.90	.72
TdT expression	0.43	.0029*

AJCC, American Joint Committee on Cancer; *TdT*, terminal deoxynucleotidyl transferase.
*Statistically significant ($P < .05$).
†Approaching statistical significance ($P < .09$).

predictors of worse OS. Nuclear circularity and minD remained independent prognostic variables but not maxD. Owing to this discrepancy, NA appears to be a more objective and consistent measurement.

Similar to prior published findings, we found that MCC tumor cells with larger NA, greater nuclear diameter, and nuclear circularity were more likely to be MCPyV positive.[1-3] In addition, our study shows that large NA/size significantly correlated with better OS and TdT expression in MCC. Measurement of nuclear features by a computational method shows promise as an accurate and consistent tool for prognostication. However, additional studies would be needed to validate this method for clinical practice.

Jakob M. T. Moran, MD,[a] Przemyslaw Biecek, PhD,[b] Piotr Donizy, MD, PhD,[c] Cheng-Lin Wu, MD,[d] Janusz Kopczynski, MD, PhD,[e] Malgorzata Pieniazek, MD, PhD,[f] Janusz Ryś, MD, PhD,[g] and Mai P. Hoang, MD[a]

From the Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts[a]; the Department of Mathematics and Information Science, Warsaw University of Technology, Warsaw, Poland[b]; the Department of Pathomorphology and Oncological Cytology, Wrocław Medical University, Wrocław, Poland[c]; the Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan[d]; the Department of Surgical Pathology, Holy Cross Cancer Centre, Kielce, Poland[e]; the Department of Clinical Oncology, Tadeusz Koszarowski Regional Oncology Centre, Opole, Poland[f]; and Department of Pathology, Maria Sklodowska-Curie National Research Institute of Oncology, Cracow Branch, Cracow, Poland.[g]

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Correspondence to: Mai P. Hoang, MD, Department of Pathology, Massachusetts General Hospital, 55 Fruit St, Warren 828, Boston, MA 02114

E-mail: mhoang@mgh.harvard.edu

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Efficacy and safety of secukinumab in moderate to severe palmoplantar pustular psoriasis over 148 weeks: Extension of the 2PRECISE study

To the Editor: Palmoplantar pustular psoriasis is a debilitating inflammatory disease confined to the palms and/or soles and resistant to treatment.[1] Secukinumab, a fully human monoclonal antibody selectively targeting interleukin 17A, is efficacious in the treatment of moderate to severe psoriasis, with a sustained effect and favorable safety profile.[2]

2PRECISE was a phase 3b multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing secukinumab 300 mg (n = 79) and 150 mg (n = 80) to placebo (n = 78) in individuals with moderate to severe palmoplantar pustular psoriasis over 52 weeks. The primary objective was a response of at least a 75% reduction in Palmoplantar Pustular Psoriasis Area Severity Index (ppPASI75) with secukinumab at week 16 versus placebo.[3] Baseline patient characteristics, study design, and primary endpoint were previously reported.[3] Extension of treatment after week 52 was possible to up to 148 weeks, with patients who achieved meaningful clinical response in the investigator's judgment either maintained on secukinumab 300 mg (n = 36) or secukinumab 150 mg (n = 31) and placebo nonresponder patients who had switched to secukinumab 300 mg (n = 17) or 150 mg (n = 10) at week 16 of the core study.[3] Missing values were imputed using the last observation carried forward (LOCF).

The mean ppPASI at study baseline was 22.7 (standard deviation, 9.5) in patients who entered the extension period. The ppPASI75 response rates increased during the extension period in all groups (Fig 1). At week 148, the percentages of patients with ppPASI75 response had increased in all groups, with similar levels in the placebo/secukinumab 150 mg group (75.0%), placebo/secukinumab 300 mg group (77.8%), and initial secukinumab 300 mg group (78.3%), and 100% responders in the initial secukinumab 150 mg group. At the end of the extension treatment period at week 148, the mean ppPASI in the placebo/secukinumab 150 mg group remained at the same level, at 9.75, whereas it had decreased in all other groups (initial secukinumab 150 mg, 1.01; initial secukinumab 300 mg, 3.43; and placebo/secukinumab 300 mg, 4.19) (Fig 2). The overall incidence of adverse events in the extension treatment period was slightly lower under secukinumab 150 mg (61.0%) than under secukinumab 300 mg (69.8%), and no new or unexpected adverse events were observed. During the extension period, there were 5 discontinuations in the secukinumab 150 mg group (16.1%), 5 in the secukinumab 300 mg group (13.9%), 4 in the placebo/secukinumab 150 mg group (40.0%), and 4 in the placebo/secukinumab 300 mg group (23.5%).

The low numbers of patients in each group warrant caution in interpreting these results and render unfeasible any further analysis of efficacy by patient characteristics on entering the extension study. The apparently greater benefit observed for the 150-mg dose compared to the 300-mg dose may also be due to small group numbers and discontinuations. However, these data suggest a sustained clinical benefit and an acceptable safety and tolerability profile of extended treatment with secukinumab 300 mg or 150 mg in patients with