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Polyomavirus Antibodies for Merkel Cell Carcinoma Recurrence Detection

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IMPORTANCE Merkel cell carcinoma (MCC) is typically caused by the Merkel cell polyomavirus (MCPyV) and recurs in 40% of patients. Half of patients with MCC produce antibodies to MCPyV oncoproteins, the titers of which rise with disease recurrence and fall after successful treatment.

OBJECTIVE To assess the utility of MCPyV oncoprotein antibodies for early detection of first recurrence of MCC in a real-world clinical setting.

DESIGN, SETTING, AND PARTICIPANTS This prospective cohort study used a data and specimen repository from 2008 to 2020 in Seattle, Washington. Patients with MCC with locoregional disease underwent serum antibody testing at diagnosis. Statistical analysis was conducted between 2020 and 2025.

MAIN OUTCOMES AND MEASURES The first posttreatment titer was necessary to establish a trend and was not used to assess risk (deferred). Subsequent titers were defined as (1) falling or negative, (2) rising, or (3) stable compared with the preceding titer.

RESULTS Among the 503 patients in the cohort (median [IQR] age at diagnosis, 70 [62-77] years; 40% female), 1402 tests were performed; 247 (49%) were seropositive. A total of 877 were falling or negative, 62 were rising, 317 were stable, and 146 were deferred. Median (IQR) follow-up was 4.2 (1.8-7.4) years. On average, antibody titers fell by half every 3 months among patients not experiencing a recurrence. After a falling or negative titer, the likelihood that a given patient would remain recurrence-free for 3 months was 99.3% (95% CI, 98.6%-99.8%). In contrast, after a single rising titer, the risk of recurrence over the next 3 months was 36% (95% CI, 22%-52%), increasing to 58% (95% CI, 40%-78%) by 12 months and 68% (95% CI, 48%-86%) by 24 months. A rising titer preceded clinical or radiographic evidence of recurrence in 57% of cases (20/35). The median (IQR) interval between a rising titer and clinical disease detection was 3.7 (1.1-7.5) months, with 90% of recurrences (18/20) occurring within 14 months of the rising titer. Recurrences and antibody titers were analyzed in 196 patients with multiple blood draws.

CONCLUSIONS AND RELEVANCE In this prospective cohort study, given a negative predictive value of 99.3%, a falling or negative titer may obviate the need for imaging, reducing radiation and contrast dye exposure. Conversely, a rising antibody titer should trigger closer follow-up, as it may lead to earlier detection of clinical recurrence and initiation of therapy.

Supplemental content

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Merkel cell carcinoma (MCC) is an aggressive skin cancer with rising incidence in the US, projected at 3284 cases in 2025.[1,2] Its 5-year mortality rate is 35%—significantly higher than melanoma at 6%.[3-5] Approximately 40% of patients with MCC develop recurrence, with 94% recurring within 3 years of initial treatment.[4] Individualized surveillance is essential to avoid unnecessary imaging and ensure timely intervention.

In the US, approximately 80% of MCC cases are thought to be driven by Merkel cell polyomavirus (MCPyV).[6,7] Serum antibodies to the MCPyV oncoprotein are detected in approximately 50% of patients[8] and typically rise with recurrence and fall after treatment.[8-10]

Although MCPyV oncoprotein antibody testing is included in National Comprehensive Cancer Network guidelines, long-term outcome data are limited.[11] Patients may show rising titers without detectable disease or titers may remain stable longer than expected. This prospective study includes long-term follow-up in a large cohort, offering practical guidance for interpreting serology results. These findings may help clinicians minimize unnecessary imaging and reduce patient anxiety while enhancing recurrence detection.

Key Points

Question In patients with Merkel cell carcinoma (MCC), how reliable are Merkel cell polyomavirus antibody titers in identifying recurrence?

Findings In this cohort study of 503 patients with Merkel cell carcinoma, after a falling or negative titer, the chance of remaining free of recurrence over 3 months was 99.3%. In contrast, the risk of recurrence after a single rising oncoprotein antibody titer was 58% by 12 months.

Meaning A rising oncoprotein antibody titer often precedes clinical or radiographic recurrence, prompting intensified surveillance, whereas a falling or negative titer has high negative predictive value, providing reassurance and potentially reducing the need for surveillance imaging.

Methods

Study Design and Patient Selection

We included 503 patients with MCC with stage I to III disease, who underwent baseline antibody testing within 90 days of diagnosis[12] and provided written informed consent for longitudinal studies between June 2008 and October 2020. The study was approved by the Fred Hutchinson Cancer Center Institutional Review Board (6585).

MCPyV Oncoprotein Antibody Detection

Blood draws occurred every 3 to 6 months.[11] MCPyV oncoprotein antibody serology assays (AMERK titers) were performed at the University of Washington Department of Laboratory Medicine & Pathology, as reported.[8] Patients with initial titers of 75 or greater standard titer units (STU) were considered antibody producers.

Oncoprotein Antibody Classification

Antibody titers were classified according to **Figure 1**. A 30% change threshold was used based on assay variability of 17% to 27%.[8] Titers were classified as negative if they were less than 75 STU, falling if they were still positive but decreased by 30% or more, and rising if they increased by 30% or more and were 150 STU or greater or they increased any amount after a previously rising titer. Titers were classified as stable if they did not meet the preceding criteria for the rising, negative, or falling categories. The first posttreatment titer was deferred, unless rising or negative, due to its high false-negative rate and was not interpreted in isolation, detailed in the Results section.

Statistical Analysis

Statistical analysis was conducted between 2020 and 2025. Detailed statistical methods are included in the eMethods in Supplement 1. Continuous variables were summarized using the median, IQR, and range. Categorical variables were summarized using numbers and percentage. Time to recurrence was defined as time from initial MCC diagnosis to first clinically detected recurrence and was censored at the time of last contact, with death treated as a competing risk. Associations between serology status and recurrence were estimated using Fine-Gray regression models and summarized using hazard ratios (HRs).

Individual antibody titer values up through a patient's first recurrence or end of follow-up were analyzed. Among patients with serial antibody titers (1 pretreatment titer and at least 1 posttreatment titer), the risk of recurrence was estimated separately for each titer category: rising, falling or negative, or stable. The unit of analysis was the titer (multiple per patient) so that time to recurrence could be defined as the time from a given blood draw to first clinically detected recurrence. Risk of recurrence was estimated using the cumulative incidence estimator, with death treated as a competing risk. The negative predictive value (NPV) and positive predictive value (PPV) for this test were derived from recurrence risk data. Specifically, NPV was defined as the chance of remaining free of recurrence after a falling or negative titer (1 – risk of recurrence) at different time points after the blood draw (eg, 3, 6, and 12 months). Similarly, PPV was defined as the risk of recurrence after a rising titer. Clustered bootstrapping was used to account for the nonindependence of multiple titers per patient for calculations of 95% CIs and P values.[13] P values were 2-sided, with a significance threshold of $P = .05$.

An additional patient-level analysis was performed to evaluate associations of titer categories with recurrence over time, using Cox models with time-varying covariates. Time was defined as days since diagnosis for each patient and the first antibody titer was used as the entry time. The titer category was a time-varying covariate in the model updated at each blood draw for each patient. Associations with recurrence were summarized as HRs between titer categories. Analyses were conducted using R version 4.0.3 (R Foundation).

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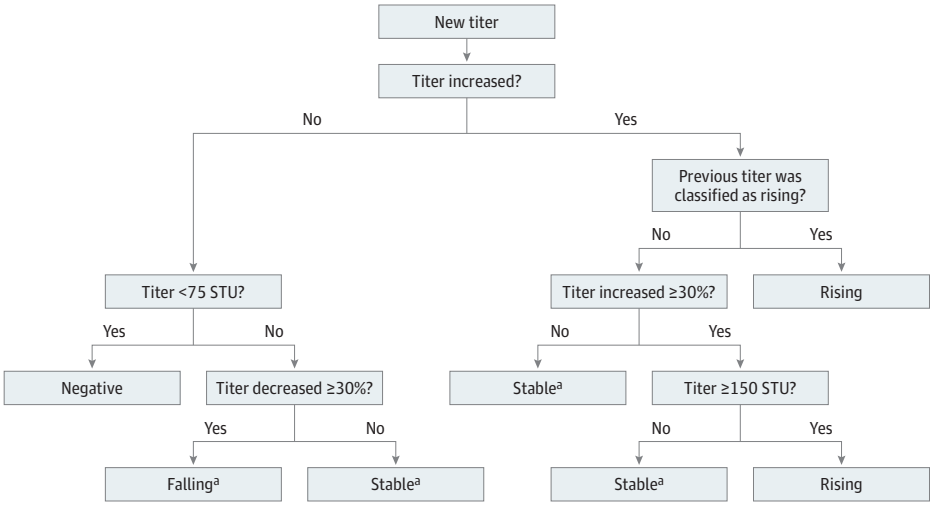
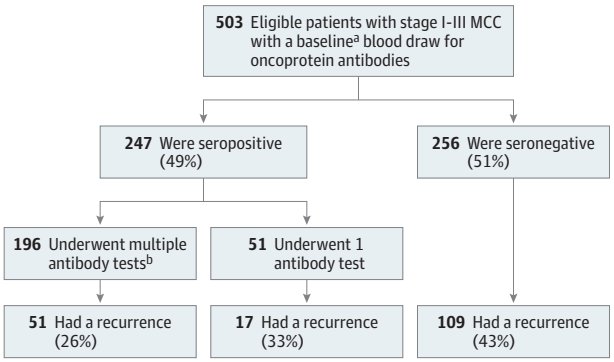
Figure 1. Flowchart for Interpreting Oncoprotein Antibody Titer Changes



Titers were classified as rising, falling, or stable relative to the previous titer. Titers were negative if less than 75 STU. Titers were rising if 150 STU or greater and increased at least 30% or increased any amount after a previously rising titer. Falling titers were at least 75 STU and decreased at least 30%. Stable titers were those that did not meet the preceding criteria for the rising, negative, or falling categories. STU indicates standard titer units.

[a]A titer was classified as deferred if it was the first posttreatment titer and was not rising or negative.

Figure 2. Flow of Patients in a Study of Polyomavirus Antibodies for Merkel Cell Carcinoma (MCC) Recurrence Detection



The MCC registry included 1542 patients for analysis. A total of 549 patients were initially excluded for the following reasons: 31 with unknown diagnosis date, 329 diagnosed prior to antibody test availability, 77 with unknown stage at diagnosis, 1 with in situ MCC, and 111 with stage IV MCC. Of the remaining 993 patients, an additional 490 patients were excluded for the following reasons: 476 without an antibody test within 90 days of diagnosis, 8 without any follow-up after the first antibody test, and 6 enrolled more than 180 days after diagnosis. The final analysis cohort consisted of 503 eligible patients with stage I to III MCC. Of the 503 eligible patients, 247 (49%) were seropositive. The 196 patients who were seropositive with multiple antibody tests were included in the longitudinal analysis of antibody titers and subsequent outcomes.

[a]Within 90 days of diagnosis.

[b]Total of 1598 antibody tests (mean, 8.2 tests/patient).

Results

MCPyV Seropositivity

The median (IQR) time to baseline blood draw was 29 (20-48) days after MCC diagnosis. Of the 503 patients, 247 (49%) had detectable oncoprotein antibodies (seropositive), consistent with the previously described prevalence of seropositivity in MCC[14,15] (**Figure 2**). A total of 256 patients (51%) did not produce detectable antibodies to the Merkel cell polyomavirus (seronegative). This group included both virus-negative tumors and, presumably, virus-positive tumors without a measurable antibody response. To assess this possibility, we analyzed 44 patients who were seronegative who underwent testing for intratumoral MCPyV large T antigen expression (CM2B4 antibody immunohistochemistry).[16] Indeed, 34% of these tumors were positive for MCPyV oncoprotein expression (Allred score ≥3), indicating a substantial subset of seronegative patients had virus-positive tumors.

Serostatus, Prognosis, and Patient Characteristics

Baseline patient characteristics by serostatus were collected via electronic health records and are summarized in the **Table** and align with prior studies.[15] Compared with patients who were seropositive, patients who were seronegative were older at diagnosis (median [IQR] age, 68 [61-75] years vs 72 [64-80] years; $P < .001$); more often immunosuppressed (5% vs 20%; $P < .001$); and presented more often with tumors in sun-exposed areas, such as the head and neck (21% vs 54%; $P < .001$). Patients who were seropositive more often had unknown primary tumors (18% vs 9%; $P = .002$) and larger tumors at diagnosis (37% vs 18% >2 cm; $P < .001$); nodal involvement was similar between groups (47% vs 40%; $P = .13$).

Median (IQR) follow-up was 4.2 (1.8-7.4) years (range, 33 days to 13 years). The 5-year recurrence risk was higher for patients who were seronegative: 45% (95% CI, 39%-51%) vs 30% (95% CI, 24%-36%) than for patients who were seropositive (HR, 1.77 [95% CI, 1.31-2.40]; $P < .001$) (**Figure 3**A). This difference persisted after adjusting for sex, age, immunosuppression, tumor site, and stage (adjusted hazard ratio [aHR], 1.63 [95% CI, 1.19-2.24]; $P = .002$), consistent with an independent cohort's findings (aHR, 2.1 [95% CI, 1.3-3.3]).[15]

Oncoprotein Antibody Titers and Recurrence Risk

Of 247 patients who were seropositive, 196 had serial blood draws. In total, 1402 posttreatment antibody titers were collected before disease recurrence or last follow-up, averaging

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Table. Baseline Patient Characteristics

Characteristic	No. (%)			*P* value
		Baseline antibody status		
	All patients (N = 503)	Seropositive (n = 247)	Seronegative (n = 256)	
Sex				
Female	199 (40)	107 (43)	92 (36)	.10
Male	304 (60)	140 (57)	164 (64)	
Age at diagnosis, median (IQR), y	70 (62-77)	68 (61-75)	72 (64-80)	<.001
Immunosuppressed				
Any type	63 (13)	12 (5)	51 (20)	<.001
SOT, CLL, or other hematologic malignant neoplasm	38 (8)	5 (2)	33 (13)	<.001
Autoimmune disease or HIV/AIDS	25 (5)	7 (3)	18 (7)	.04
Site of primary				
Head and neck	192 (38)	53 (21)	139 (54)	<.001
Trunk	45 (9)	24 (10)	21 (8)	.64
Extremity	200 (40)	126 (51)	74 (29)	<.001
Unknown primary	66 (13)	44 (18)	22 (9)	.002
Primary size >2 cm[a]	117 (27)	76 (37)	41 (18)	<.001
AJCC 8th Edition stage				
Local (pI-II, cI-II)	283 (56)	130 (53)	153 (60)	.13
Nodal (pIII, cIII)	220 (44)	117 (47)	103 (40)	

Abbreviations: *AJCC*, *American Joint Committee on Cancer Staging Manual*; CLL, chronic lymphocytic leukemia; SOT, solid organ transplant.

[a] Excludes 66 patients with unknown primary.

8.2 titers per patient (median [IQR], 6 [3-12]; range, 2-30). The median (IQR) interval between draws was 3.3 (3.0-4.6) months.

The median (IQR) baseline titer was 1347 (263-11 450) STU, with 9 patients (3.6%) reaching the assay's upper limit (115 000 STU). Higher baseline titers were significantly associated with larger tumor size (adjusted correlation, 0.37; $P < .001$) and more advanced stage (adjusted mean difference, 134%; $P < .001$) (eResults and eTable 1 in Supplement 1). Patients in the upper tertile of baseline titers had higher recurrence risk than those in the lower tertile (aHR, 2.24 [95% CI, 1.19-4.21]; $P = .01$) (eResults in Supplement 1).

Figure 3B shows antibody trajectories starting from baseline in the 247 patients who were seropositive. Among patients without recurrence, titers dropped by 50% a median (IQR) of every 3 (2-4) months on average, decreasing to less than 75 STU by a median of 13 months after diagnosis (25th percentile: 5 months; 75th percentile: 80 months).

Titers were grouped according to the classification scheme shown in Figure 1 as follows: 62 rising, 877 falling or negative, 317 stable, and 146 deferred. Titer values and categories over time for the 247 patients who were seropositive are shown up to the 5-year time point in Figure 3C. Patients who eventually recurred within 1 year of their last titer are highlighted. Recurrence risk by titer group is summarized in **Figure 4**A and eTable 2 in Supplement 1.

Falling or Negative vs Rising Titers

After a falling or negative titer, the chance of remaining free of recurrence (NPV) was 99.3% at 3 months (95% CI, 98.6%-99.8%) and 98.8% over 6 months (95% CI, 97.8%-99.6%). In contrast, a single rising titer carried a 36% recurrence risk (PPV) at 3 months (95% CI, 22%-52%), increasing to 58% at 12 months (95% CI, 40%-78%) and 68% by 24 months (95% CI, 48%-86%) (Figure 4A).

Among 35 recurrences preceded by a nondeferred titer, 20 patients (57%) had a rising titer before their disease was detected and 6 (17%) had a rising titer at the time of detection. The median (IQR) lead time from their first rising titer to recurrence was 3.7 (1.1-7.5) months (range, 12 days to 46 months). The remaining 9 patients (26%) did not have a rising titer prior to recurrence detection. Within 90 days after the clinical recurrence, 3 of these 9 patients had a rising titer and 3 had a stable titer. For the final 3 patients, 1 had a negative titer drawn on the day recurrence was detected, and 2 had negative titers (5 and 8 months prior), with no titer drawn within 3 months of recurrence.

A rising titer did not always indicate imminent recurrence. Of 39 patients who had at least 1 rising titer, 14 patients remained recurrence-free for 1 year or longer. Titers later became negative in 3 patients, fell in 9, and remained stable in 2. None of these 14 patients died of MCC (median [IQR] follow-up, 4.9 [2.8-5.6] years). One died of a non-MCC cause and 3 recurred more than 1 year after but were alive at last follow-up. In contrast, among the 23 patients who recurred within 1 year of their first rising titer, 8 died of MCC, with an estimated 32% (95% CI, 14%-51%) MCC-specific mortality rate within 2 years. Two patients had less than 1 year of follow-up after their rising titer.

Stable Titers

Figure 4B assists clinicians in assessing recurrence risk for patients with a stable titer relative to the prior draw. Importantly, for such patients, the recurrence risk depends on the preceding titer category. Without considering prior status, stable titers had a low or intermediate recurrence risk of 2.2% at 3 months (95% CI, 0.6%-4.6%; n = 317). In contrast, if a stable titer followed a rising titer, risk increased to 24% at 3 months (95% CI, 0%-50%; n = 13). Recurrence was rare when stable

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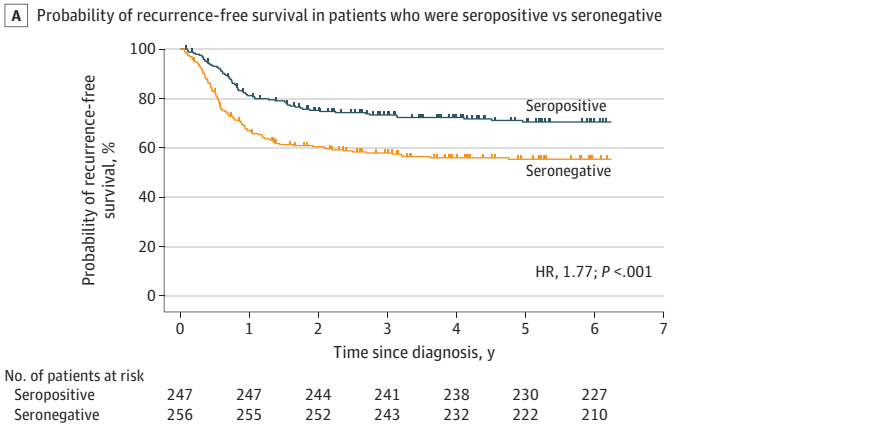
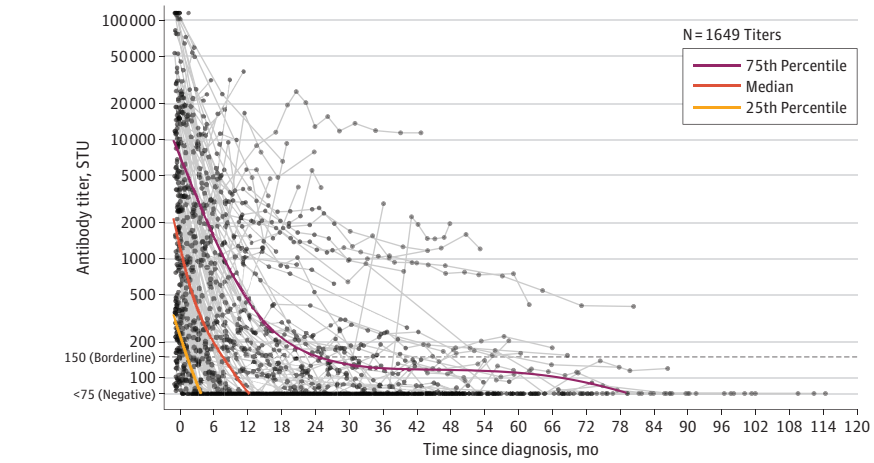
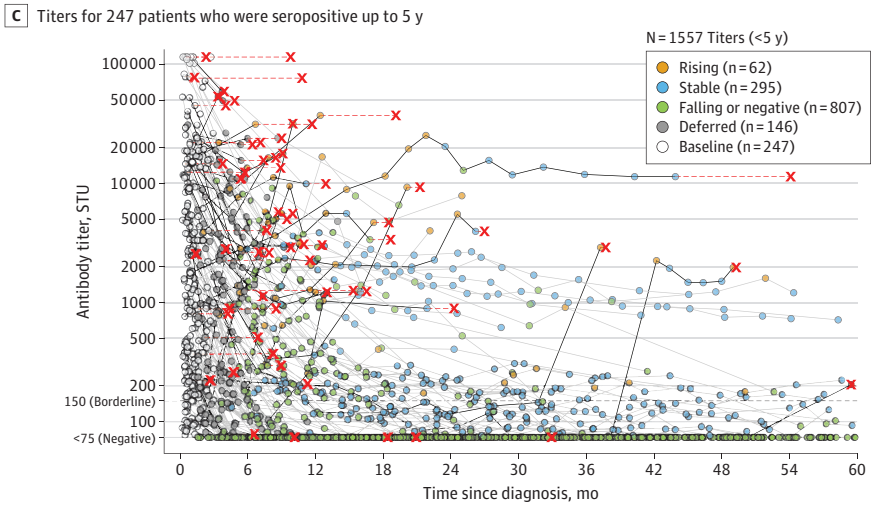
Figure 3. Antibody Status and Recurrence Risk Over Time Across 503 Patients







A, Patients with a negative antibody test (seronegative) at baseline had a significantly higher rate of recurrence compared with patients who were seropositive. This difference persisted after adjusting for sex, age, immunosuppression status, anatomic site of the primary tumor, and stage. B, Serial antibody titers of 247 patients who were seropositive up to 10 years (1649 titers total; 247 pretreatment and 1402 posttreatment) are shown as gray dots with lines connecting titers from the same patient. The horizontal dashed line indicates the borderline positive level of 150 STU. Smoothed quartiles (25th percentile, median, and 75th percentile) are shown as color-coded curves to illustrate titer decay rates after initial treatment. C, Titers for 247 patients who were seropositive up to the 5-year time point. Patients who eventually recurred within 1 year of their last titer are denoted with black lines that end at the time of first recurrence (red X). During follow-up, 61 patients recurred (red X) within 1 year of their last titer and 186 did not. Recurrences are depicted at the level of the last titer drawn before the recurrence, with a dashed red line connecting each recurrence to the corresponding patient's titers. Titer categories (baseline, rising, stable, falling or negative, and deferred) for each result point are color-coded. HR indicates hazard ratio; STU, standard titer units.

titers followed a stable titer (1.0% [95% CI, 0%-3.5%]; n = 212) or a falling titer (0% [95% CI, 0%-4.6%]; n = 79).

Another important factor was whether the stable titer exceeded the patient's original baseline titer prior to treatment. This often occurred after a rising titer, where a recurrence was not initially identified, and subsequent titers then stabilized at a higher level. Among 19 such cases, recurrence risk was 26% at 3 months (95% CI, 5.9%-67%) and 59% at 12 months (95% CI, 20%-100%), similar to rising titers (Figure 4C).

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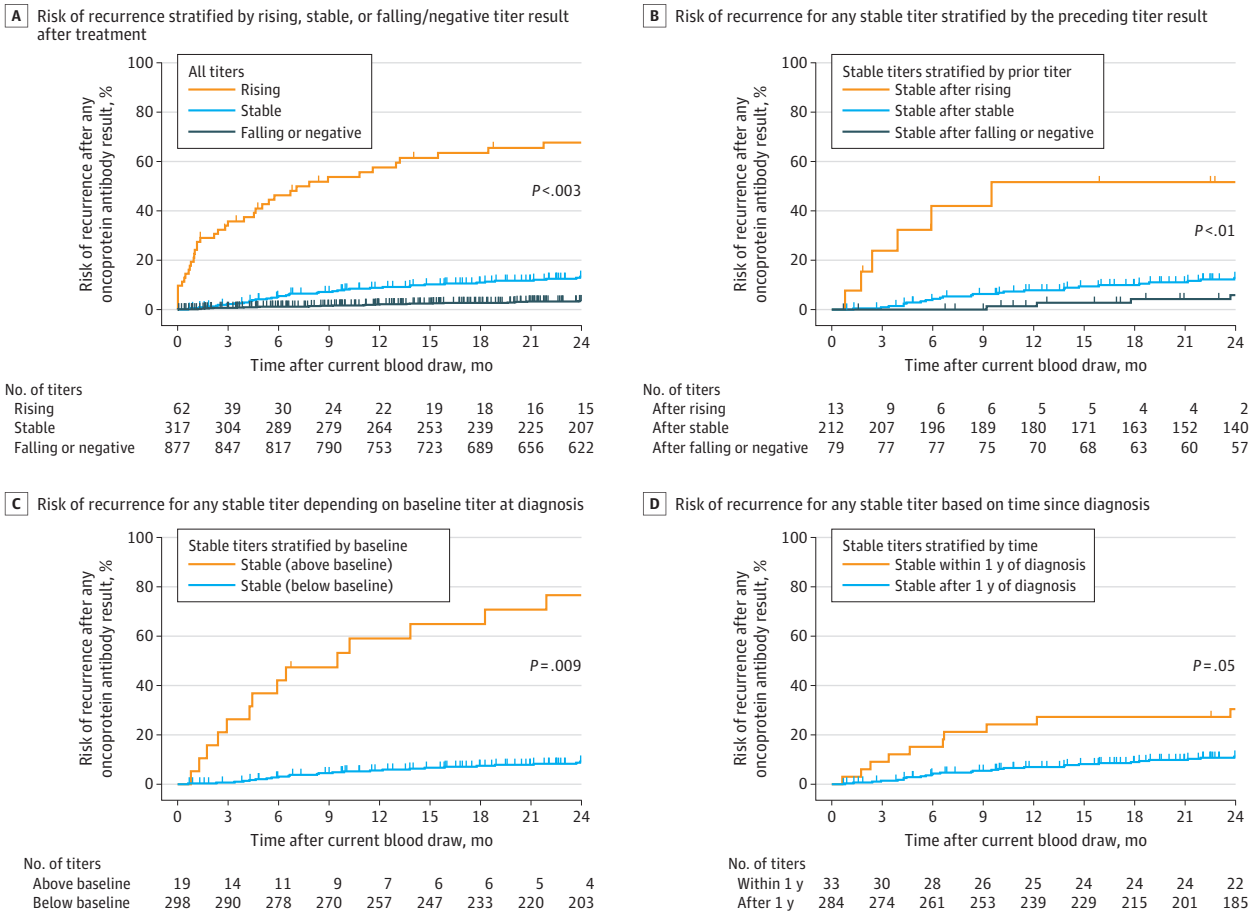
Figure 4. Risk of Recurrence After Any Oncoprotein Antibody Titer Result



A, Risk of recurrence stratified by a rising, stable, or falling or negative titer result at any time after treatment exclusive of the first posttreatment (deferred) titer. This showed that rising titers were associated with a significant risk of recurrence over the next 24 months compared with stable ($P < .001$) and falling or negative titers ($P < .001$). It also showed that stable titers predicted a significantly higher rate of recurrence compared with falling or negative titers ($P = .003$). B, Risk of recurrence for any stable titer stratified by the immediately preceding titer result (rising, stable, or falling or negative), demonstrating a significantly increased risk of recurrence for stable titers immediately following a rising titer compared with those that followed a stable ($P = .01$) or falling or negative titer ($P = .008$). C, Risk of recurrence for any stable titer depending on whether the titer value was above or below the patient's baseline titer at diagnosis. The risk of recurrence for a patient with a stable titer above their baseline was much higher than if a titer was stable below their baseline. D, Risk of recurrence for any stable titer based on time since diagnosis, showing that there was a trend toward a lower risk of recurrence for patients whose titers remained stable more than 1 year after diagnosis compared with stable titers drawn within the first year. The first posttreatment titer (deferred) was not used in determining recurrence risk and is not shown. Recurrence after deferred titers can be seen in the eFigure in Supplement 1.

Figure 4D shows that a stable titer obtained within the first year after diagnosis had a 12-month recurrence risk of 24% vs 7% ($P = .05$) for a stable titer obtained more than 1 year after diagnosis.

Deferred Titers

The first posttreatment blood draw (deferred) was not reliably predictive of recurrence. Despite appearing stable (n = 27) or falling (n = 119), 3- and 6-month recurrence rates were 6.9% (95% CI, 3.4%-11%) and 13% (95% CI, 8.1%-19%), respectively (eTable 2, eFigure in Supplement 1). These recurrence rates were much higher than after either stable (2.2%-5.5%) or falling or negative titers (0.7%-1.2%) drawn after the initial posttreatment titer (Figure 4A). This elevated false-negative rate was likely due to the slow clearance of antibodies from the initial tumor, with a half-life of approximately 3 months (Figure 3B). A small antibody increase from early recurrence may be masked by this slow decline. Although the deferred draw should not guide clinical decisions in isolation, it provides an important reference point for interpreting the subsequent titer.

Patient-Level Analysis

Because clinicians interpreted each titer as an individual test result, our analysis focused on the prognostic value of a given titer relative to the prior titer. However, a longitudinal patient-centric approach across multiple blood draws was also of interest to clinicians. Cox models with time-varying covariates were used to assess patient outcomes over their clinical course. As with analysis carried out on a per-test basis, patients had a

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substantially higher risk of recurrence after a rising titer compared with the risk after a falling or negative titer (aHR, 51 [95% CI, 21-122]; $P < .001$) or stable titer (aHR, 12 [95% CI, 4.0-38]; $P < .001$). Patients also showed an increased recurrence risk after a stable titer compared with a falling or negative titer (aHR, 4.2 [95% CI, 1.3-13]; $P = .02$).

Discussion

MCC recurs in 40% of patients, and accurate surveillance tools for MCC are important. Prior studies show that in patients who are seropositive, MCPyV oncoprotein antibody titers reliably increase with recurrence.[8] However, large-scale longitudinal data have been limited. This study demonstrated that a negative or falling titer is highly reassuring, with a 99.3% chance of remaining recurrence-free over 3 months. In contrast, a rising titer is associated with a 58% recurrence risk within 1 year. These findings can guide more targeted use of imaging for patients at higher risk.

Whereas imaging modalities like contrast-enhanced computed tomography (CT) or positron emission tomography (PET)/CT have a detection threshold of approximately 0.3 cm to 1.0 cm,[17,18] the immune system may detect recurrence earlier. In most patients who recurred, a rising titer preceded detection by imaging or physical examination. However, in 26% of patients (9 cases), serology did not rise before clinical or radiographic detection of recurrence. For 5 of these 9 cases, titers rose shortly after or were not drawn within 3 months of the recurrence, limiting assessment of true false negatives. Nevertheless, in settings with high pretest probability—such as shortly after treatment of high-risk MCC—serology should not be used as a substitute for imaging.

The ability to detect subclinical disease raises management questions. Although most recurrences occur within 12 months of a rising antibody titer (58%), several patients had longer delays prior to developing evident disease (up to 46 months). Reassuringly, patients who remained recurrence-free for 1 year or longer after a rising titer had better disease-specific survival, possibly reflecting immune control of minimal residual disease.

Despite the predictive value of a rising titer, immediate systemic therapy is not warranted in the absence of clinical disease. First, not all patients respond to immunotherapy, which carries risk of toxicity. Second, some patients will never develop clinical recurrence. Third, locoregional recurrences may be effectively treated with surgery or radiation.

Two blood-based biomarkers are now available for MCC recurrence detection: oncoprotein antibodies and circulating tumor DNA (ctDNA).[19] Both tests offer similar reported PPVs and NPVs.[8,19] Oncoprotein antibody testing is unique in that it provides insight into the etiology of the patient's tumor, as antibody-producing patients invariably have virus-positive tumors. Of note, a baseline oncoprotein antibody titer should be obtained within a few months of diagnosis to determine whether a patient produces antibodies, as this has prognostic implications as well. This test cannot be used for recurrence monitoring in patients who are seronegative, who often have more aggressive tumors.[16] In contrast, ctDNA detects bespoke tumor-specific mutations regardless of viral status and does not require a baseline test. However, it depends on sufficient tumor tissue for whole-exome sequencing, which may be unavailable in needle-only biopsies. The half-life of ctDNA is only a few hours, and this test will thus represent disease status promptly following treatment.

For patients with a rising titer and no clinical disease, a short-interval repeat oncoprotein antibody test can be performed to confirm the trend. ctDNA testing can also be used to corroborate findings. Based on clinical experience, imaging studies should not be performed more than every 3 months in response to a rising titer. When available, PET/CT is preferred for its higher sensitivity in MCC detection.[20]

Limitations

This study has limitations. First, as a real-world observational study, there was variability in the timing of titer collection, clinical examinations, and imaging. Patients with rising titers may have undergone more frequent imaging or physical examinations, thus creating surveillance bias and potentially shortening the interval between serologic and clinical detection of recurrence compared with standard 3-month surveillance intervals. This may impact PPV to some extent, although mostly at times less than 3 months after a rising titer. However, the NPV is less likely to be affected given that patients with falling or negative titers were typically followed up with standard surveillance intervals. Second, due to the observational nature of the study, we cannot establish a causal relationship between antibody levels and disease recurrence.

Conclusions

MCC treatment continues to evolve, with several ongoing clinical trials—some of which require knowledge of viral status for eligibility. Oncoprotein antibody testing offers a cost-effective method to determine MCPyV-driven disease. A formal comparison of ctDNA and oncoprotein antibodies is an important next research step, including their combined value in determining recurrence risk. A multi-institutional cohort study to address these issues is ongoing.

For patients who are seropositive, MCPyV oncoprotein antibody titers can offer meaningful reassurance or early detection of recurrence. Identifying disease at an earlier, lower-burden stage may improve outcomes through timely treatment initiation.[21] Conversely, patients who are seronegative—who cannot be monitored by this test—may benefit from ctDNA surveillance or more frequent imaging when ctDNA is unavailable.

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Author Contributions: Dr Nghiem had full access to all of the data in the study and takes

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responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Gunnell, Hippe, Park, Akaike, Lachance, Doolittle-Amieva, Nghiem.
Acquisition, analysis, or interpretation of data: Gunnell, Hippe, Fu, Akaike, Lachance, Cahill, Doolittle-Amieva, Nghiem.
Drafting of the manuscript: Gunnell, Hippe, Park, Lachance, Cahill, Nghiem.
Critical review of the manuscript for important intellectual content: Gunnell, Hippe, Park, Fu, Akaike, Doolittle-Amieva, Nghiem.
Statistical analysis: Hippe.
Obtained funding: Nghiem.
Administrative, technical, or material support: Gunnell, Lachance, Cahill, Nghiem.
Supervision: Gunnell, Park, Akaike, Nghiem.

Conflict of Interest Disclosures: Mr Hippe reported receiving grants from GE HealthCare outside the submitted work. Dr Nghiem reported receiving support to his institution from Incyte Corp Research, Bristol Myers Squibb, and EMD Serono; and consulting for EMD Serono, Merck, and Sanofi/Regeneron outside the submitted work. No other disclosures were reported.

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Data Sharing Statement: See Supplement 2.

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