Circulating tumor DNA correlates with Merkel cell carcinoma tumor burden and helps early detection of recurrence

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Background

- Merkel cell carcinoma (MCC) recurs in ~40% of cases.[1]
- Early detection of recurrence results in better outcomes, and effective surveillance is critical in MCC management.
- Merkel cell polyomavirus (MCPyV) oncoprotein serology is useful in surveillance for MCPyV-positive MCC tumors.
- No blood-based biomarkers are available for MCPyV-negative MCC tumors; frequent imaging is required during surveillance.
- Plasma circulating tumor DNA (ctDNA) assay has been shown to be useful in monitoring disease progression in other cancers such as lung, breast and colon carcinomas.[2,3,4]

Objectives

- This prospective, multicenter study evaluated whether ctDNA can assess disease burden and detect recurrence regardless of virus status in MCC.

Methods

- This study reports an interim analysis of ctDNA in 125 patients (328 plasma samples) at various time points with a median follow-up of 6 months (range: 0-21 months) between April 2020 and January 2022.
- Whole-exome sequencing was performed on tumor tissue and matched normal blood to identify a set of clonal, somatic, single nucleotide variants, which were tracked in subsequent blood (plasma) samples using a personalized, multiplex PCR (mPCR)-NGS ctDNA assay (Signatera™).
- Clinically evident disease was defined as MCC noted either by physical exam or by imaging, and molecular evidence of disease was defined as a positive ctDNA test.
- The surveillance phase began once there was no clinically evident or molecular evidence of disease.

Figure 1. ctDNA assay design

References

1. Peter JA, et al. *J Clin Oncol*. 2005;23(28):7237-7238.
2. Reinert T, et al. *JAMA Oncol*. 2019;5(8):1124-1131.
3. Coombes C, et al. *Clin Cancer Res*. 2019;25(14):4255-4263.
4. Abbosh C, et al. *Nature*. 2017;545:446-451.

ctDNA testing can detect MCC recurrence early and is a promising clinical surveillance tool regardless of tumor MCPyV viral status.

Figure 2. Consort Diagram of ctDNA prospective observational trial

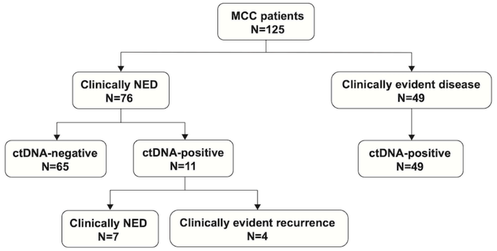
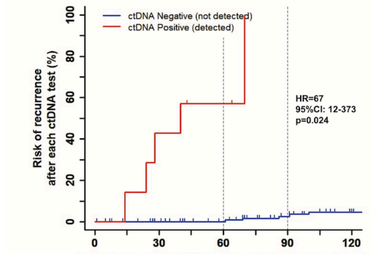


Figure 2. Patients are grouped based on their clinical status at enrollment and the result of their initial ctDNA test.

Figure 3. ctDNA positivity during surveillance is predictive of recurrence



Tests with F/U:									
ctDNA Negative:	145	139	133	125	122	113	101	92	84
ctDNA Positive:	7	6	4	2	2	0	0	0	0

Figure 3. Kaplan-Meier estimates demonstrating the risk of recurrence after a positive or negative ctDNA test.

- Of the 125 patients, 73 (58%) met the inclusion criteria of clinically NED and no molecular evidence of disease at some point after enrollment, indicating the start of their surveillance period. These 73 patients had 152 plasma samples during their surveillance period.
- Seven ctDNA tests were positive while 145 were negative.
- A recurrence was diagnosed in 5/7 patients with newly positive ctDNA tests.
- The estimated risk of recurrence was 57% within 60 days after a positive ctDNA test. After a negative ctDNA test, the risk of recurrence was 0% within 60 days, and 3% between 60-90 days.
- Compared to ctDNA negative test, ctDNA-positivity was associated with significantly higher risk of recurrence (HR=67,95%CI: 12-373, p=0.024).

Figure 4. Correlation between tumor size and ctDNA levels

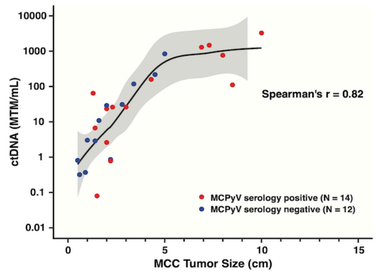


Figure 4. MCC tumor size is correlated with ctDNA levels.

- Primary MCC tumor size
  Median: 2.2 cm
  Range: 0.5-10 cm
- Three smallest tumors:
  Size: 0.5-0.9 cm
  ctDNA: 0.32-0.81 MTM/mL
- The nonlinear trendline was estimated using locally estimated scatterplot smoothing (LOESS) method.

MTM: mean tumor molecule

Figure 5. ctDNA analysis in a patient with unresectable MCC

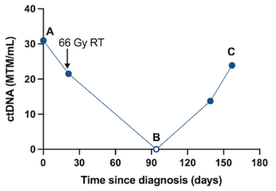
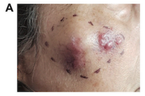
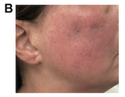


Figure 5. Utility of ctDNA in patients with MCC.

- A 61-year-old woman developed a rapidly enlarging, unresectable MCC on the right cheek.
- Negative baseline MCPyV antibody serology test; ctDNA levels: 31 MTM/mL prior to radiotherapy (RT).
- She was treated with 66Gy conventional radiotherapy.
- ctDNA clearance was achieved after RT.
- Two consecutive rising ctDNA observed during surveillance, which prompted FDG PET/CT revealing hypermetabolic uptake in the left thigh. This lesion was biopsied and compatible with distant metastatic MCC.


A. Before radiation therapy (RT)


B. Complete resolution after RT

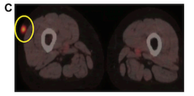
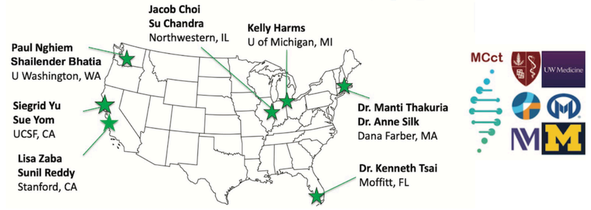

C. Two consecutive rising ctDNA prompted PET/CT; hypermetabolic uptake in the left thigh was observed

Table 1. Advantages of ctDNA testing over standard MCPyV serology test

MCPyV serology	ctDNA
Used in patients that have MCPyV+ tumors (50% of all MCC patients)	Used in all patients with MCC regardless of MCPyV status
Needs a baseline test within 3 months of initial treatment	Can be performed at any point in the patient's treatment or surveillance course
Provides information on MCPyV status	Provides information on TMB rates (from which MCPyV status can be extrapolated)
Less reliable after the first MCC recurrence or during treatment with immune checkpoint inhibitors	Can be used after recurrence and during treatment with immune checkpoint inhibitors
Half life: 25.8 days	Half life: <2 hours

Figure 6. Circulating tumor DNA (ctDNA) multicenter prospective study



This is an active multicenter study to assess the utility of ctDNA testing for MCC patients. Please reach out to Dr. Lisa Zaba (Lisa.zaba@stanford.edu) for any questions.

Conclusion

- To our knowledge, this is the largest study to explore ctDNA testing in patients with MCC.
- This study demonstrates that ctDNA testing can detect MCC recurrence ahead of imaging.
- ctDNA is a promising clinical surveillance tool regardless of tumor viral status.

Future directions for research

- Determine whether the level of ctDNA at initial diagnosis can identify the high-risk patients and correlate with prognosis.
- Assess if serial ctDNA after initial treatment can predict risk of relapse and identify recurrence ahead of radiological imaging in patients with MCC.

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