

## Medical News &amp; Perspectives

## Why Merkel Cell Cancer Is Garnering More Attention

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**M**ichael Hori, MD, wasn't prepared for the pathologist's sense of urgency. A few days earlier, Hori had excised a red lump from his patient's leg and sent the tissue for analysis. "I thought I was dealing with basal cell carcinoma," said Hori, an internist at the University of Washington Valley Medical Center in Renton.

However, the pathologist's diagnosis was Merkel cell carcinoma—a far more worrying type of skin cancer. "He made the comment, 'I just want to impress upon you how serious this diagnosis is and how important it is to get [the patient] someplace where they really know what they're doing,'" Hori recalled.

Fortunately, Valley Medical is part of University of Washington Medicine where Paul Nghiem, MD, PhD, has pioneered Merkel cell carcinoma research and clinical care. As head of the Division of Dermatology, he treats patients and oversees a laboratory that investigates immunotherapy for Merkel cell cancer.

"Ideally, a patient needs to be seen once at least at an expert center," Nghiem said. About a dozen such centers are located in the United States, he noted. But many cases will get a first look in a primary care setting, like Hori's patient.

"The single most important decision a primary care [physician] could make about this cancer is whether to do the biopsy," Nghiem said.

**Interest and Incidence on the Rise**

Merkel cell carcinoma has attracted growing interest in recent years for several overlapping reasons: It's rare but on the rise, the cause has been linked with a virus, and immunotherapy appears promising for many patients.

In fact, the incidence is outpacing that of other cancers. Nghiem and his colleagues recently reported that from 2000 to 2013, solid cancers increased by 15%, melanoma by 57%, and Merkel cell carcinoma by 95%. The number of newly diagnosed US Merkel cell carcinoma cases is expected to increase from 2488 in 2013 to 2835 in 2020 and to 3284 in 2025.

"Each year we get more and more new consults," said Manisha Thakuria, MD, director of the Merkel Cell Carcinoma Center of Excellence at the Dana Farber Cancer Institute in Boston. "We're at about 70 new patients per year."

Why the increase? In a word, age. Nghiem's data showed that the average age at diagnosis is in the upper 70s. In fact, the incidence increases by 100-fold from age 40 to 80 years, he noted. The leading edge of baby boomers is now in their early 70s, which dovetails with another risk factor: immunosuppression. With age comes diminished immune function. In addition, millions of US residents take immunosuppressive drugs because of HIV infection, organ transplants, and cancer.

"Most of our patients are older ... but a significant percentage of them are immunosuppressed," Thakuria noted. Immunosuppression increases the risk of developing Merkel cell carcinoma by 16-fold, Nghiem added.

What's more, it's an aggressive cancer. Hori said his patient's lesion grew to 1 cm in 2 ½ months and didn't appear to be slowing down. According to the [National Cancer Database Participant User File](#), the [5-year survival rate](#) was 51% among patients with localized disease, 35% for those with nodal disease, and 14% when the cancer metastasizes to a distant site.

"It's 3 times more likely to kill a patient than melanoma, which is usually thought to be the most dangerous type of skin cancer," Nghiem said.

Like melanoma, Merkel cell carcinoma is linked with exposure to UV light. However, what differentiates the 2 is that Merkel cell carcinoma was [linked](#) in 2008 to infection with a previously unknown polyomavirus. About [80% of Merkel cell cancers](#) are attributed to what's now called Merkel cell polyomavirus and the remainder to UV exposure.

The virus is widespread. "We are exposed to it when we're children," Nghiem said. "It's in daycare centers; it's on door-knobs." Usually it causes no symptoms. "Except for the 1 in 3000 people ... in whom this virus will lead to cancer," he added.

Examples of Merkel cell carcinoma of varying sizes in different locations



Paul Nghiem, MD, PhD/University of Washington

## A Tricky Cancer

When the pathologist called, Hori said he was “rather shocked” at the diagnosis and at “how little I knew about this disease.” His reaction is completely understandable, Thakuria said.

“This is a tricky cancer,” she noted. “It can fool even the best clinicians.” Although Hori suspected right away that his patient’s lesion was a malignancy, Merkel cell cases often appear harmless. “These really can look like innocuous tumors, mainly cysts and lipomas,” Thakuria explained. “You don’t necessarily [see] a big red nodule.” Although some of the lesions are red, others may be purple or skin colored. They’re usually painless and firm.

“These things are really boring-looking when you see it clinically. Even a talented dermatologist is often gonna say, ‘Forget about that,’” Nghiem added.

Many of Dana Farber’s patients with Merkel cell carcinoma have been referred by primary care physicians, Thakuria said. As the incidence increases with an aging population, she advised that primary care clinicians “try to increase your index of suspicion; try to think of it in the appropriate patients.”

Nghiem helped develop an acronym—**AEIOU**—for those very reasons. “A is for asymptomatic; E is for expanding rapidly,” he said. Immunosuppression is *I*. O is for older patients and U is for UV exposure. “Ninety percent of Merkel cell carcinomas have 3 or more of those features,” Nghiem said.

He also suggested the “ugly duckling” approach: Raising suspicion when lesions don’t resemble any other lumps or bumps the patient has or had. “Sometimes that should push [the physician] to say, ‘Well, maybe I should do a biopsy.’”

## Immunotherapy Shows Promise

Traditionally, the outlook for patients with metastatic Merkel cell carcinoma was grim.

Chemotherapy didn’t produce durable responses. “Only 5% of patients would have their cancer under control one year after starting treatment,” Nghiem said.

Last year, however, the treatment landscape improved considerably when the US Food and Drug Administration **approved** avelumab, the first drug cleared for treating Merkel cell carcinoma. In a class of immunotherapies known as checkpoint inhibitors, avelumab disables the PD-L1 (programmed cell death 1 ligand 1) protein on cancer cells, activating the immune system to attack the cells.

The approval was based on findings from part A of JAVELIN Merkel 200, an international phase 2 **trial** that involved 88 patients with stage IV Merkel cell carcinoma who had received previous treatment. All were treated with avelumab in the trial. After 10.4 months, 32% of patients responded to treatment; among them, 92% responded for at least 6 months.

In **part B** of JAVELIN Merkel 200, investigators evaluated avelumab as first-line treatment for patients with stage IV disease. Among 29 patients who were followed up for at least 3 months, 62% responded to treatment. Among 14 patients who were followed up for at least 6 months, 71% responded.

“The takeaway is that it’s clear that immunotherapy with avelumab, checkpoint inhibitors, is really the standard of care for all metastatic Merkel cell patients,” said Sandra P. D’Angelo, MD, an assistant attending physician in the Department of Medical Oncology at Memorial Sloan Kettering Cancer Center in New York City.

D’Angelo, lead author of the recent JAVELIN part B study, noted that guidelines from the **National Comprehensive Cancer Network** recommend avelumab or either of 2 other checkpoint inhibitors—nivolumab or pembrolizumab—for patients with disseminated Merkel cell carcinoma. “We

don’t distinguish that one is better or worse than the other,” she said.

For patients with early-stage Merkel cell carcinoma, who make up **65% of new diagnoses**, D’Angelo said systemic therapy isn’t recommended. “Many will be cured with just surgery and/or radiation alone,” she noted. “It’s all about weighing the risks and benefits of the therapy.” **Serious adverse events** associated with avelumab include acute kidney injury, anemia, abdominal pain, ileus, asthenia, and cellulitis.

Currently, published data only support using immunotherapy to treat patients with stage IV disease. But Thakuria and others are enthusiastic about the phase 3 **ADAM trial** designed to compare avelumab with placebo in patients with stage III disease who have undergone surgery with or without radiation. The primary outcome measure is relapse-free survival; other measures include overall survival and survival without distant metastasis.

The trial is recruiting patients and will have a site open at Dana Farber. But Thakuria said 1 of her patients with stage III disease will need avelumab before the trial begins there. “We’re considering [giving avelumab] because it seems like the appropriate thing,” she said. “In the appropriate patient that may be enough of a reason to go ahead.”

Five-year survival rates haven’t yet been calculated for patients with stage IV disease who’ve been treated with immunotherapy, but Thakuria said the outlook for those who respond is quite promising.

One of her patients enrolled in the JAVELIN Merkel 200 trial with a poor prognosis after treatment with chemotherapy. “We expected death in a few months,” she said. “But she’s still here. Four years later and she’s fantastic. That’s an anecdote, of course, but across the nation people are seeing this kind of story.” ■

**Note:** Source references are available online through hyperlinks embedded in the article text.