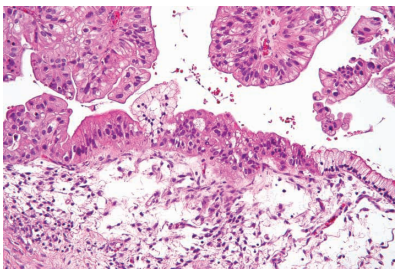
Nephron

Ovarian cancer

of 11.1 years, mortality rates from ovarian or fallopian tube cancer did not differ among the three groups (Lancet 2016;387:945–56). But the data suggested that after 7 years, death rates were leveling off in both screened groups, raising hopes that longer follow-up would uncover a benefit.

However, the latest UKCTOCS findings, reflecting a median follow-up of 16.3 years, were negative. Mortality rates remained identical across all three groups: 0.6%. Screening did catch more cancers at an early stage. For instance, in women who were offered CA125 testing, the incidence of stage I and stage IV cancers was 47.2% higher and 24.5% lower, respectively, than in the unscreened group. But this so-called stage shift was too small to yield a statistically significant decrease in mortality.

The trial showed for the first time that early detection of ovarian cancer is possible, says lead author Usha Menon, MD, of University College London in the UK. To save lives, however, "we require a screening test that detects ovarian cancer even earlier—and in more women—than the screening strategy we used," she says. "General population screening cannot be supported or recommended at this point," she adds, cautioning that the trial findings cannot be extrapolated to women at high risk due to family history or who carry *BRCA1/2* mutations, for whom screening is sometimes recommended.

"It's an extremely well-designed study," says Karen Carlson, MD, of Massachusetts General Hospital in Boston, who wasn't connected to the research. For instance, instead of setting a cutoff for CA125, the researchers used an algorithm that detects trends in serum levels over time, a better way to flag worrying results, she says. "This makes it very clear there is no benefit" from screening. Given the negative findings, "the data suggest earlier-stage cancers are still likely to metastasize and recur," notes Kevin Elias, MD, of Boston's Brigham and Women's Hospital. "Improving survival will require interrupting these tumors even earlier in their development than previously thought."

The rarity of ovarian cancer—which afflicts one of every 2,500 to 3,000 women—is an obstacle, says Barbara Goff, MD, of the University of Washington in Seattle. "When you have a cancer that is that uncommon, it becomes very hard to screen for," meaning that researchers need to identify more specific biomarkers. Although some promising possibilities are under investigation, including tumor DNA and microRNAs from liquid biopsies, they won't be ready for clinical use anytime soon, she says. *–Mitch Leslie* ■

Combo Approaches for HPV16+ Cancers

Immunotherapies targeting the PD-1 axis have become a mainstay in treating cancers associated with human papillomavirus (HPV). Both nivolumab (Opdivo; Bristol Myers Squibb) and pembrolizumab (Keytruda; Merck) are approved for head and neck squamous cell carcinoma (HNSCC); the latter is also indicated for PD-L1+ cervical cancer. However, additional strategies are needed.

"The response rate of HPV-related malignancies to anti–PD-1 therapy is between 13% to 24%, but for the overwhelming majority of patients with eventual disease progression, there is no effective standard of care," said Julius Strauss, MD, of the NCI. During the American Society of Clinical Oncology 2021 Annual Meeting, June 4–8, he reported results from an ongoing phase II trial evaluating a cocktail of three therapies, each stimulating a different facet of antitumor immunity.

Study participants received a triple combination of PDS0101 (PDS Biotech), M9241 (EMD Serono), and bintrafusp alfa (Merck KGaA/GlaxoSmithKline). PDS0101, a peptide-based vaccine, can induce strong CD4+ and CD8+ T-cell responses against E6 and E7, two viral oncoproteins specific to HPV16, the biggest culprit in HPV-associated cancers worldwide. M9241 is a tumor-targeting immunocytokine, Strauss explained. It delivers IL12 to the tumor microenvironment—thereby increasing T-cell infiltration—via a monoclonal antibody that detects and binds to free DNA fragments found in areas of tumor necrosis. As for bintrafusp alfa, this bifunctional fusion protein is designed to trap TGFβ and target PD-L1, keeping two immunosuppressive pathways in check.

Strauss and his colleagues chose this cocktail because "preclinically, we saw maximum HPV-specific T-cell responses, tumor infiltration, and tumor reduction when all three agents were given together, compared with any one or two alone," he said. So far, 25 patients with HNSCC, cervical, anal, and vaginal cancers have been treated; 18 were genotyped as HPV16+.

Among the HPV16+ patients, the objective response rate (ORR) was 55.6%, including two complete responses. Six of 18 had not received prior checkpoint immunotherapy; their ORR was 83.3% and, at a median follow-up of 8 months, "all remain alive," Strauss said. The other 12 patients had checkpoint inhibitor–refractory disease; their ORR was 41.7%, but "the majority had tumor shrinkage, and 10 of 12 are alive," he added—which is favorable compared with the historical median overall survival of 3 to 4 months.

Discussant John Hyngstrom, MD, of Huntsman Cancer Institute in Salt Lake City, UT, noted that "despite the triple combination having potential for morbidity, the safety profile was reasonable." Anemia, flu-like symptoms, and lymphopenia were the main, clinically manageable side effects.

Alan Ho, MD, PhD, of Memorial Sloan Kettering Cancer Center in New York, NY, presented emerging data from a phase I/II study of two arenavirus-based vaccines, HB-201 and HB-202 (Hookipa Pharma). Both are "engineered to express a nononcogenic E6/E7 fusion protein, inducing robust antigen-specific T-cell responses in HPV16+ tumors," he explained.

The trial is still in the dose-escalation phase, with investigators assessing different treatment schedules in two cohorts—one comprising patients with HPV16+ HNSCC; the second, other HPV16+

cancers. Both groups are receiving either intravenous HB-201 monotherapy or HB-201 alternating with HB-202.

Preliminary efficacy has been seen, notably in those treated every 3 weeks, Ho observed. Among 11 evaluable patients with HNSCC given the two lowest doses of HB-201 alone, two had partial responses; six more experienced stable disease. In the other cohort, all four evaluable patients given the lowest dose of HB-201/HB-202 had stable disease. Side effects, including fatigue and fever, were low grade.

"We're also seeing signs of immunogenicity, which is important proof-of-principle," Ho said. "Up to 40% of circulating CD8+ T cells analyzed were E6/E7-specific and polyfunctional, producing IFNγ and TNFα."

These data "speak to the [vaccines'] priming potential in future combinations with checkpoint blockade, for instance, to augment response," Hyngstrom remarked. Both Strauss and Ho highlighted "novel exploitations of viral antigens," he added, with "promising initial efficacy that, hopefully, can be capitalized with larger studies and longer follow-up." *–Alissa Poh* ■

AI Pinpoints Origin of Unidentified Cancers

The origin of 1% to 2% of metastases can't be determined, making it difficult to choose the optimal therapy. In a recent study, researchers showed that an artificial intelligence (AI) tool can classify these unidentified cancers with about 61% accuracy by analyzing the tissue slides routinely made during cancer diagnoses (Nature 2021;594:106–10).

Patients with these cancers of unknown primary origin have poor odds of survival because oncologists lack the information needed to prescribe an appropriate targeted therapy or immunotherapy, often leaving chemotherapy as the only treatment option.

Recent studies have shown that machine learning algorithms that use genome or transcriptome sequencing data can uncover the origins of some of these cancers. However, sequencing isn't an option at many medical centers, and when it is, it's usually performed late in the diagnostic process, after other tests have yielded inconclusive results. Senior author Faisal Mahmood, PhD, of Harvard Medical School in Boston, MA, and colleagues wanted to develop an approach that could be widely available and provide an earlier diagnosis.

The researchers created an AI tool that relies on deep learning, in which networks that function similarly to interacting neurons in the brain are trained to draw conclusions from data. The tool analyzes scans of the standard histology slides produced after most patients' biopsies and factors in the sex of the patient—to eliminate a diagnosis of ovarian cancer in a man, for example—to predict tumor identity. It ranks the possibilities based on their likelihood. Mahmood and colleagues trained their system to recognize 18 cancer types by providing it with more than 22,000 digitized gigapixel slides of tumor samples from metastases and primary tumors with known identities.

The researchers first explored whether the system could generate accurate predictions for a test set of nearly 6,500 histology slides from metastases and primary tumors with assigned diagnoses. The algorithm was 83.4% accurate in identifying the cancer type, and it included the correct choice among its top three answers 95.5% of the time. The system could also distinguish whether a tumor was metastatic or primary.

Next, the researchers asked whether the tool could categorize 1,408 metastases for which a diagnosis was available. The algorithm correctly identified the origin of 82.8% of these tumors. The researchers then applied the algorithm to slides from 317 patients initially diagnosed with cancers of unknown primary origin whose tumors were later classified. For these slides, the system's accuracy was 60.6%, and it placed the correct answer in its top three choices 82% of the time.

The results indicate that "you can predict cancer origins from conventional histology slides rather than genomics," Mahmood says. The researchers are still considering how to employ the algorithm, he says, but it could help doctors determine what other tests to order, identify the origin of metastases more quickly, and suggest identities for problematic tumors. Researchers

are working to determine whether AI approaches that use genome or transcriptome data increase survival for patients with unidentified metastases; Mahmood notes that future work must also confirm that the histology-based algorithm does the same.

"It's a beautiful paper," says Joshy George, PhD, of the Jackson Laboratory in Farmington, CT, who wasn't connected to the research. The algorithm uses histology slides from patient samples that are almost universally available, and it could allow doctors in less-developed countries to upload digitized slides for diagnosis, he says. But first, George cautions, the researchers need to fine-tune the algorithm—for example, by training it to recognize more cancer types. "This is version 1.0. I want to see version 2.0." *–Mitch Leslie* ■

Liquid Biopsy May Guide EGFR Inhibitor Treatment

A liquid biopsy may select patients with metastatic colorectal cancer who are good candidates for additional anti-EGFR therapy after developing resistance to it earlier in their treatment. In a phase II trial, patients without resistance mutations in circulating tumor DNA (ctDNA) who received panitumumab (Vectibix; Amgen) had a 30% response rate to the anti-EGFR agent. Results were presented by Andrea Sartore-Bianchi, MD, of Grande Ospedale Metropolitano Niguarda in Milan, Italy, at the American Society of Clinical Oncology 2021 Annual Meeting, June 4–8.

In recent years, targeted therapies have emerged for patients with metastatic colorectal cancer—the most prevalent of which is anti-EGFR therapy for patients who lack *RAS* or *BRAF* alterations. "However, even with this molecular selection, all anti-EGFR–treated patients eventually develop resistance" due to the expansion of mutant RAS