Panel Recommends Mammograms Start at 50

The U.S. Preventative Services Task Force (USPSTF) has issued its final recommendations on screening for breast cancer, concluding that women at average risk can wait until age 50 to begin routine biennial screenings (Ann Intern Med 2016;164:279–96). The decision to start screening between ages 40 and 49 should be individual, the panel said, based on personal risks, values, and preferences.

“We believe the science supports a range of individual choices for women, including starting screening anytime during their 40s or waiting until age 50,” says Michael LeFevre, MD, MSPH, vice chair in the Department of Family and Community Medicine at the University of Missouri School of Medicine in Columbia and immediate past president of the USPSTF, who helped develop the recommendations. “These recommendations should empower women with the information they need to make decisions for themselves.”

Despite the opposition and concerns expressed by many oncologists after the draft recommendations were issued last spring, the USPSTF stands by the same age guidelines it issued in 2009, with screening for women in their 40s remaining as a C level recommendation, meaning the panel is moderately certain that the net benefit is small. Typically, private insurers are required to cover only procedures graded A (high certainty of substantial net benefit) or B (moderate to high certainty of moderate to substantial net benefit) by the USPSTF, but in 2009 Congress approved—and recently extended—an exception for mammography for women ages 40 to 49.

Nonetheless, many oncologists are concerned that the updated recommendations will be used to justify future coverage limitations.

“If the government acts on these recommendations and insurers start denying annual mammograms, a lot of women will die unnecessarily,” says Larry Norton, MD, a medical oncologist and deputy physician-in-chief for Breast Cancer Programs at Memorial Sloan Kettering Cancer Center in New York, NY. “I will continue to recommend that my patients get annual screenings starting at 40, but many women may decide against it if they won’t get reimbursed.”

The task force, an independent panel of nonfederal experts in evidence-based medicine, prevention, and primary care, reviewed randomized controlled trials and observational studies involving women ages 40 and older considered at average risk for breast cancer. It concluded that, while mammography screening reduces breast cancer mortality overall, that benefit is not as significant for women in their 40s compared with older women and must be weighed against the potential harms, including unnecessary testing and overtreatment.

“We looked hard for evidence that cancer treatment is less harmful when detected early versus later, and found very little to support that premise,” says LeFevre. “On the opposite side of the equation, it is precisely those very early cancers which are most likely to be over-diagnosed, particularly the ductal carcinoma in situ or noninvasive cancers.”

However, oncologists cannot predict at the time of diagnosis whether a tumor will lead to death if left untreated, says Norton. Most women would rather undergo treatment, even if it proves unnecessary, than risk a tumor going undetected at a potentially curable stage.

Norton notes that the task force based its recommendations on older studies that do not reflect advances in imaging technology. In addition, the group gives disproportionate weight to the potential harms caused by false-positive results, he says, including anxiety, repeat testing, and invasive follow-up procedures.

“The recommendations are based on a very subjective estimate of harm, which most often just means coming back to the office for another test,” says Norton. “But the real bottom line is that if a woman 40 or older wants to minimize her chances of dying from breast cancer, she should get an annual mammogram.” –Janet Colwell

Resensitizing Refractory ALK+ NSCLC: A Case Study

Drug resistance in ALK-positive non–small cell lung cancer (NSCLC), a known problem, can have unexpected twists. Researchers from Massachusetts General Hospital in Boston recently reported the case of a patient with advanced ALK-positive NSCLC, whose eventual relapse on the investigational ALK inhibitor lorlatinib (Pfizer) paradoxically restored her responsiveness to crizotinib (Xalkori; Pfizer) (N Engl J Med 2016;374:54–61).

The patient’s treatment regimen began with crizotinib, followed by ceritinib (Zykadia; Novartis) and then lorlatinib. “When she stopped responding to crizotinib, we profiled her tumor and found an ALK mutation, C1156Y, which causes resistance by increasing ALK’s kinase activity,” says Alice Shaw, MD, PhD, a thoracic oncologist and the study’s first author. “She didn’t respond to ceritinib, but upon switching to lorlatinib, her response was quickly apparent.”

Lorlatinib, which Shaw describes as “the newest next-generation ALK inhibitor, designed to overcome all known crizotinib-resistant mutations,” reduced the patient’s tumor burden by 41% in just 5 weeks. Unfortunately,
She relapsed again after 9 months, with worsening liver metastases and impending liver failure.

“...There didn’t seem to be any options left, but we decided to do another biopsy,” Shaw says. This time, the researchers found an additional ALK mutation, L1198F, on the same allele as C1156Y. Cell-line studies indicated that L1198F promoted resistance to lorlatinib and other next-generation ALK inhibitors, but unexpectedly restored sensitivity to crizotinib. Treatment with crizotinib was therefore restarted, “although we generally move toward more potent, selective ALK inhibitors, and almost never look back,” Shaw notes. The patient’s recovery was swift; she regained liver function within weeks, and her second response to crizotinib lasted nearly 6 months.

Through biochemical and crystallography analyses, the researchers determined that L1198F interferes with lorlatinib’s binding to ALK, but increases crizotinib’s affinity for its target. “We think the enhanced binding due to L1198F negates the increased kinase activity from C1156Y, thereby resensitizing tumor cells to crizotinib,” Shaw explains.

“It’s interesting that this subset of NSCLC retains ALK dependency; the tumor keeps mutating the oncogenic driver as we pressure it with different drugs,” says Christine Lovly, MD, PhD, an assistant professor at Vanderbilt Ingram Cancer Center in Nashville, TN. “This study highlights the importance of monitoring tumor heterogeneity and evolution throughout therapy.”

“Obtaining repeat biopsies from patients who relapse on targeted therapies, for molecular profiling, is key,” Shaw adds. “This isn’t standard practice, although I’m seeing more of it. Once blood tests assessing cell-free tumor DNA are validated and become mainstream, we’ll have a more efficient, less invasive way to pinpoint resistance mutations in ALK-positive NSCLC.”

Shaw and Lovly also advocate combining ALK inhibitors, which have so far been used as sequential monotherapy, to better keep resistance at bay. “Rational combinations would be particularly useful in the frontline setting, because that’s our first and best chance of achieving the most meaningful response,” Lovly says.

Lorlatinib is still in early-phase studies, but “as we continue to study resistance that emerges, we may see L1198F appear more often,” Shaw says. Meanwhile, she’s struck that this mutation alters the very leucine residue lorlatinib’s designers at Pfizer exploited to enhance the drug’s selectivity for ALK over other kinases.

“It’s intriguing, from a chemistry standpoint—how we may be able to anticipate mutations based on a drug’s design, and in doing so, perhaps find ways to overcome them,” she says.

—Alissa Pob

Expanding Therapy for Neuroendocrine Tumors

Results from two phase III studies indicate that the mTOR inhibitor everolimus (Afinitor; Novartis) and the radiopharmaceutical 177Lutetium-DOTATATE (Lutathera; Advanced Necroendocrine Tumors

Results from two phase III studies indicate that the mTOR inhibitor everolimus (Afinitor; Novartis) and the radiopharmaceutical 177Lutetium-DOTATATE (Lutathera; Advanced Accelerator Applications) both substantially delay disease progression in patients with advanced neuroendocrine tumors (NET) of the gastrointestinal (GI) tract. The data were presented by Simron Singh, MD, and Jonathan Strosberg, MD, respectively, during the American Society of Clinical Oncology’s Gastrointestinal Cancers Symposium, held in San Francisco, CA, January 21–23.

NETs occur most commonly in the GI tract, pancreas, and lungs. Each year, about 8,000 people in the United States are diagnosed with GI NETs, a subset broadly divided into midgut and non-midgut categories. The former includes tumors originating in the ileum, duodenum, and appendix; the latter encompasses tumors of the stomach, colon, and rectum. Surgery, chemotherapy, or somatostatin analogs (SSA), a standard hormone therapy, are the main treatments.

Singh, a medical oncologist at the University of Toronto’s Odette Cancer Center in Canada, reported results from a subgroup analysis of the RADIANT-4 study, in which 175 patients with advanced GI NETs were randomized to receive everolimus or placebo. Sixty of these patients had midgut NETs, and the rest had non-midgut tumors. In both categories, treatment with everolimus improved the median progression-free survival (PFS) by more than 6 months.

“This study enrolled both patients who had previously received SSAs, and those who hadn’t,” Singh noted. “Interestingly, everolimus was effective across the board, regardless of pretreatment.” The drug was well tolerated, he added, with the main side effects being mouth inflammation, diarrhea, and fatigue.

Strosberg, a medical oncologist at Moffitt Cancer Center in Tampa, FL, reported results from the NETTER-1 study, which evaluated 177Lutetium-DOTATATE, an SSA attached to a radiopharmaceutical. This is a type of peptide receptor radionuclide therapy (PRRT), Strosberg said, adding that it has been used to treat thousands of patients in Europe. “It enables the targeted delivery of radiation to tumors expressing somatostatin receptors, which many well-differentiated NETs do in high concentrations.”

The study’s 230 patients, all with advanced midgut NETs, had progressed on first-line SSA therapy. They were randomized to receive four 177Lutetium-DOTATATE treatments, or the SSA octreotide (Sandostatin; Novartis). The median PFS in the experimental arm has not been reached, Strosberg reported, “but it’s expected to be longer than 3 years, which is extremely impressive for this population.” By contrast, the median PFS in the control arm was just 8 months. He also noted that 177Lutetium-DOTATATE’s main side effect, nausea, was “mostly related to..."