Can SCLC be detected by low dose CT screening?

The current low dose CT technology is not able to detect SCLC. This is because SCLC cells grow very quickly due to the aggressive nature of the disease. We do not know how frequently LDCT scans need to be conducted to catch SCLC in the early stages. Researchers are looking at other technologies for the early detection of SCLC – such as blood-based circulating tumor cell assays. Eventually a combination approach, using both LDCT and such blood-based assays, will be used for the early detection of SCLC in individuals at high risk of developing the disease.

Can you tell us about biomarker testing in small cell lung cancer?

Biomarker testing, which is routinely conducted for advanced-stage NSCLC, is not commonly prescribed for SCLC. This is because scientists often did not have enough SCLC tissue to study. Studies in NSCLC have progressed because we have access to large tissue banks. But lack of tissue in SCLC is a very complex issue. Surgery (a source of tumor tissue) is not a common treatment modality for SCLC because the cancer often came back in patients who were treated only with surgery. Also, it is difficult to design clinical trials where you mandate a rebiopsy at the time when a patient progresses while on the trial. Unfortunately, that's the most critical part when you really need to understand the biology of the tumor. We want the tissue so we can study the resistance mechanism and why a particular treatment failed a patient. But it is very hard for a patient to undergo a biopsy at that time in their disease. The other problem is that many times a diagnosis of SCLC is made through a fine needle aspirate (FNA). You don't have a big sample of the tissue through an FNA, and that makes it more difficult to really robustly study these tumors. Therefore, the lack of tumor specimens has hindered the development of biomarkers. In NSCLC, we have certain subsets of disease that are driven by distinct mutations that respond to drugs (targeted therapies) that reverse those pathways and block the growth of the cancer cells. We haven't made those discoveries right now for SCLC.

But that is starting to change. We know that there are certain genetic hallmarks for SCLC like loss of the TP53 and the RB genes. We are starting to do more of next generation sequencing (NGS) on SCLC. And we are learning that there are subtypes of SCLC that respond differently to chemotherapy, and that these tumors have distinct genetic signatures. So, I think eventually we probably will have biomarkers in the future.

What options are there for patients who have progressed after the immunotherapy?

Being a radiation oncologist, I see a lot of patients that have been on some form of immunotherapy and who have undergone different types of progression. If the immunotherapy is controlling the metastatic disease but there is one area of progression (for example, a specific area in the adrenal glands), one option is top-down very focused stereotactic radiation to the area of cancer that's progressing especially if it's within a localized area. Radiation can be very effective at getting rid of those specific areas. There is a fair amount of preclinical and now clinical data that radiation and immunotherapy can be synergistic. If you give them together, you get a better result than giving one or the other alone. That's something that we are using relatively frequently at Emory for patients that start to progress in some areas when they have used or been on immunotherapy in the past. There are also clinical trials looking

at combinations of different immunotherapy drugs, or combination with PARP-blocking drugs. It is therefore important to ask your doctor about what clinical trial options would be available in that situation.

When is prophylactic cranial radiation (PCI) used?

PCI involves giving a low dose of radiation to the brain to reduce the likelihood of patients getting brain metastases in the future. There have been several clinical trials that have shown improved survival with this approach for both LS-SCLC and ES-SCLC.

The results from clinical trials with **ES-SCLC** have been somewhat conflicting. For example, in a trial run in Japan, when researchers compared people that got the PCI with people that did not get the PCI, but instead got very frequent brain MRIs (brain imaging every three months), they did not find that PCI improved survival. Therefore, doctors in the United States would rather do brain MRIs every three month, than have a patient go through the potential side effects from PCI. As a radiation oncologist, I generally support that approach for ES-SCLC as long as a patient is getting MRIs every three months. What that ensures is that a brain metastasis is caught early and can be treated. What we do not want is patients not being offered the PCI and then not getting any brain imaging.

For LS-SCLC, where the cancer has not spread, the standard is to do the PCI after the radiation and the chemotherapy. While this is currently the accepted standard of care, researchers are now asking whether an MRI brain imaging every three months can be conducted instead of PCI. There is a new clinical trial where patients with either LS-SCLC or ES-SCLC will get brain MRIs every three months instead of PCI. At this point, we do not know whether MRIs can replace PCI in LS-SCLC.

In summary, PCI is still standard for LS-SCLC but not ES-SCLC. There is one novel approach with radiation we are testing with PCI. It is referred to as **hippocampal-sparing PCI**. What that does is actually uses the radiation to carve out the area in your brain that creates new memories in the temporal lobes and sparing it during the PCI. Studies with NSCLC have shown that hippocampal sparing reduces memory problems in the long-term. Therefore, this method has a lot of promise for SCLC.