Lobectomy Found Best for Older Patients with NSCLC, But Other Options Gaining Ground

BY KURT SAMSON

"The use of SABR has grown tremendously over the last seven years, disseminating from academic institutions to community hospitals. For those who are not candidates for surgery, it offers an alternative."

The largest population-based study to date to compare surgical treatments and outcomes in elderly patients with early-stage non-small-cell lung cancer (NSCLC) has found that removing the entire lobe of the affected lung appears to offer better overall and lung-specific survival times than those for partial resection, although sublobar resection was only slightly less so (***JAMA Surgery doi:10.1001/jamasurg.2014.556***).

The researchers also noted that treatment with newer stereotactic ablative radiotherapy (SABR) may in certain cases provide survival benefits comparable to those of total lobectomy, but that technique was introduced only about two years before the study closed and requires more research, especially in randomized clinical trials.

For the study—first author was Shervin M. Shirvani, MD, MPH—the team used the Surveillance, Epidemiology and End Results (SEER) Medicare database to compare data on 9,009 patients treated for NSCLC between 2003 and 2009, with survival rates compared through December 2012. The average age of patients was 75.

Unadjusted 90-day mortality was highest for those undergoing lobectomy, at four percent, followed by sublobar resection (3.7 percent), and 1.3 percent for those treated with SABR. After three years, the unadjusted mortality rates were 25 percent for lobectomy patients, 35.3 percent among sublobar resection patients, and 45.1 for those receiving SABR alone, however SABR was associated with worse three-year overall survival rates and lung cancer-specific survival rates compared with lobectomy.

Propensity score-matching analysis of well-matched SABR and lobectomy patients found similar overall survival rates in both groups, especially for SABR in patients with multiple comorbidities. SABR in combination with sublobar resection appeared to result in longer survival in certain cases and was associated with longer overall survival than lobectomy in the first six months after diagnosis, but shorter survival after that point.

Increasing Numbers of Cases of NSCLC Expected

The researchers noted that because of the rapidly aging population, the number of NSCLC cases is expected to surge in the years ahead. The disease is typically a cancer among the elderly, and because of its association with smoking, patients often carry other comorbidities, such as chronic obstructive pulmonary disease, coronary artery disease, and renal failure, which can complicate post-surgical survival.

Currently three treatment options are available for NSCLC: total lobectomy, sublobar resection—i.e., removal of the part of the lung—and SABR, a precise form of radiation therapy delivered to the affected area over three to five sessions.

The study included data on 7,215 patients, 79.3 percent of whom underwent total lobectomy, 1,494 who received sublobar resection (16.5%), and 382 patients treated with SABR.

Because SABR was introduced not long before the study's initial startpoint, the data reflect patients treated by the earliest surgeons to adopt the technique, the researchers said, adding that in some patients, SABR may offer the same survival benefit as total lobectomy.

Adjusted Findings

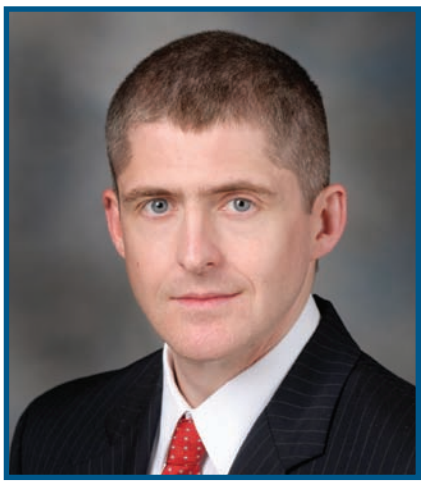
After adjusting for possible confounders, such as tumor characteristics, economic factors, and other co-variables, the results remained the same—a finding the researchers called surprising.

"The assumption was that for elderly patients with a number of co-morbidities, sublobar resection would be better than a whole lobectomy because there would be fewer surgical complications," the study's senior author, Benjamin D. Smith, MD, Associate Professor of Radiation Oncology at the University of Texas MD Anderson Cancer Center, said in an interview. "Yet, it appears that the ability to eradicate the cancer with the bigger surgery may be more important than minimizing surgical risk."

Among patients with similar baseline characteristics, lobectomy and SABR were associated with similar overall and lung-cancer specific survival rates, he added.

"This suggests that SABR is a very promising alternative to surgery for patients with very advanced age and multiple medical problems that were common in the matched populations."

However, because the findings were based on information from the SEER database, they are less conclusive than if they were from randomized clinical trials, although such trials in recent years have failed to recruit enough participants, he said.



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"Unfortunately we lack strong randomized clinical trials for how to best treat the disease—especially when it is discovered early, but in my experience, what we have reported seems to be pretty accurate. In specialized cancer treatment centers, however, full or sublobar resection may offer similar survival rates."

Treatment assignment of these patients is not random, he noted, adding that while the study was observational, he hopes the results will help inform physicians to be more cautious in recommending advising sublobar excision for their elderly patients out of concern for their overall health.

"We cannot control for differences in how these patients are treated at different locations, but we all want to know what is best for them. At the end of the day, our study was not randomized, but clinical trials conducted in the 1980s yielded similar results to what we found, which is reassuring.

"We tried to use both Medicare claims and cancer registries to record tumor size to minimize problems with the data," Smith continued. "Clearly, the incidence of early-stage lung cancer will increase dramatically in the next few years, and we need to be prepared to treat patients in the right way—

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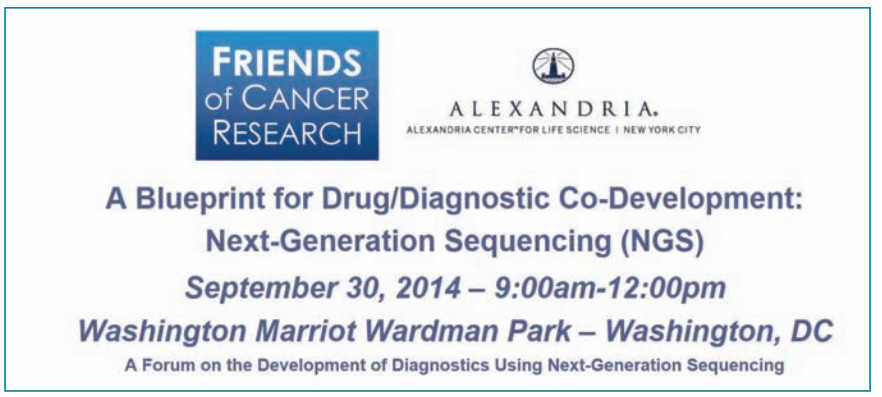
New Report Tackles Next-Generation Sequencing Challenges in Cancer Care

BY PEGGY EASTMAN

WASHINGTON — Advances in understanding the molecular basis of cancer have led to an escalation in comprehensive panels of multi-marker gene assays of cancer-driver mutations, as opposed to traditional single-marker assays. While such next-generation based cancer panels can be a boon in helping oncologists choose the right treatments for the right patients, the procedure is also fraught with problems and challenges—including reimbursement issues. So said speakers at a forum here sponsored by Friends of Cancer Research (FOCR) and the Alexandria Center for Life Science (ACLS).

The organizations released a new report suggesting strategies for dealing with those challenges, "A Blueprint for Drug/Diagnostic Co-Development: Next-Generation Sequencing (NGS) in Oncology." Speakers at the forum, known as the NGS Working Group, helped develop the report; they include representatives of academia, industry and government. FOCR, an advocacy organization for cancer patients, played a key role in helping to develop the Breakthrough Therapy designation for promising new drugs signed into law in July 2012. FOCR issued a previous related report, "A Risk-based Approach for In Vitro Companion Diagnostics Device FDA Approval Process Associated with Therapies that Have Breakthrough Designation" (***OT 10/25/13 issue***).

"This is a very complicated topic; I call this a geek conference," said FOCR's Chair, Ellen Sigal. PhD. "What we're trying to do is get this right for patients… that's our north star, and that's what this is about."



Another Working Group member, Karen Gutekunst, PhD, Vice President for Diagnostic Development at Illumina, Inc., said, "Anyone who's been in the field of oncology for the last five years knows how important sequencing is becoming. … It's already being used in many cancer centers. It's a critical tool."

Currently, for example, the Lung-MAP clinical trial is using a multi-drug, multi-arm, biomarker-driven approach for patients with advanced squamous cell lung cancer.

5 Proposals

The report sets forth five proposals to address the complexity and advance the science of next-generation sequencing in cancer care:

1. Define a regulatory pathway for multi-marker cancer panels intended to identify actionable oncogenic alterations that allows flexibility in the appropriate Food and Drug Administration medical device pathway;

2. Approaches for performing validation studies should be based on the types of alterations measured by the assay, rather than every alteration individually;

3. Determine the contents of a cancer panel by classifying potential markers based on current utility in clinical care and clinical trials;

4. Promote the standardization of multi-marker cancer panels through the use of a common set of samples to ensure reproducibility on each platform; and

5. Establish a framework for determining the appropriate reference method rather than relying on any single reference method for all studies.

Speakers described a next-generation sequencing landscape lacking standardization of tools, with little validation data and a broad diversity of specimen quality. There is also a lack of agreement on what is "actionable"—for example, some markers are very specific, such as BRAF, while others are broader, such as EGFR.

"What is actionable?" asked Elizabeth Mansfield, PhD, Director of

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balancing the effectiveness versus risk of treatment in elderly patients."

What are needed are randomized clinical trials of SABR, he emphasized, but such studies have been unable to recruit enough subjects in the past. "Even so, I think our results are very encouraging and are likely representative with what would be found in a large randomized clinical trial."

Looking Ahead

Asked for his opinion for this article, Roy Decker, MD, PhD, Associate Professor and Director of Clinical Research in the Department of Therapeutic Radiology at Yale University School of Medicine's Smilow Cancer Hospital, said that even as more oncologists across the country become experienced with providing alternatives to lobectomy, comparisons between the three treatments are likely to remain difficult in elderly patients.

ROY DECKER, MD, PHD, said that even as more oncologists across the country become experienced with providing alternatives to lobectomy, comparisons between the treatments are likely to remain difficult in elderly patients.

"The last randomized trial to examine this was conducted decades ago and also concluded that full lobectomy offered the best survival, but interest in sublobar resection remains high based on the assumption that techniques and outcomes have improved," he said.

Another clinical trial comparing the three methods is underway, but the results will not be available for at least six years. "SABR is still a relatively new technique. It became a standard treatment only in 2007, and it offers a very promising option for those patients who cannot undergo surgery," Decker said.

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the Personalized Medicine Staff of the FDA's Office of In Vitro Diagnostics and Radiological Health. She pointed out that even though there may not be a lot of data on a marker, it may still be useful in terms of referring a cancer patient to a clinical trial. She said FDA is "very receptive" to the concept of companion diagnostics based on next-generation sequencing, and "we want to move it forward."

Also a member of the Working Group, Janet Woodcock, MD, Director of FDA's Center for Drug Evaluation and Research, said, "In cancer what we're doing is unfolding complexities." Because setting up a clinical trial for every subset of cancer patients is not feasible, what is needed are standing clinical trials with standardized procedures and processes in order to "build a picture out of complexity, and not just chaos." Next-generation sequencing is a tool to help accomplish that goal.

The new report also notes that currently all of the marketed oncology panels have been developed by laboratories and do not require FDA approval. The FDA recently issued a guidance for companion diagnostics, which proposes a risk-based oversight framework for laboratory-developed tests (LDTs), especially genomic tests used to guide treatments for cancer patients. LDTs are currently regulated by the Clinical Laboratory Improvement Amendments (CLIA), but CLIA regulations do not assess the safety and effectiveness of LDTs offered by laboratories, nor do they evaluate the clinical utility of LDTs. Instead, CLIA regulations establish quality standards for laboratory testing in order to determine that the laboratory is in compliance with standards for good laboratory practices [*see OT's **10/10/14 issue** for reactions to the FDA actions from ASCO, NCCN, AACR, and ACS*].

'Wild West'

As cutting-edge technology, next-generation sequencing is "the wild west… the question is, how do different labs see this assay?" commented Mickey Williams, PhD, Director of the National Cancer Institute's Molecular Characterization Laboratory. "We need to think about the

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Many patients are at high risk for undergoing lobectomy and there are also personal and social considerations that make them hesitant to choose surgery, he noted, adding that previous clinical trials that have attempted to compare outcomes have failed primarily because they could not accrue enough older patients. "We might never know how older patients respond to these treatments compared with younger ones, so this kind of population-based study may be the only way to address this issue in the elderly."

However, some data do indicate that SABR might be as effective as lobectomy, with less morbidity, he said.

"The use of SABR has grown tremendously over the last seven years, disseminating from academic institutions to community hospitals. For those who are not candidates for surgery, it offers an alternative."

He also noted that the Medicare-linked SEER database lacks many confounding variables and significant health issues that need to be better understood and integrated into treatment analyses, such as pulmonary function data. "You cannot really match the surgical and SABR populations perfectly. You can determine a diagnosis of pulmonary dysfunction, but you cannot determine the severity.

"In addition, there are always other issues with patients that may or may not make them candidates for surgery, such as their level of physical activity. Medicare-linked SEER also reflects differences in community cancer treatment practices versus a clinical trial where these are considered, together with experienced oncologists with skilled staff when delivering treatment, he said.

"In our practice, for elderly patients who are ineligible for surgery, they can receive SABR while younger patients can undergo surgical procedures. If a patient is at high risk, though, we discuss both treatments."