Prof. Lukas Bubendorf: the pros and cons of using cytology specimens in molecular testing

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Editor's note

The 18th World Conference on Lung Cancer (WCLC) organized by the International Association for the Study of Lung Cancer (IASLC) was held in Yokohama, Japan from 14–18 October, 2017. As the world's largest multidisciplinary oncology conference on lung cancer, it gathered more than 7,000 key opinion leaders, professionals and researchers from over 100 countries, who came together to unfold a series of in-depth academic exchanges and collaborations. In the meantime, AME seized the opportunity to conduct interviews with a number of experts.

Expert introduction

Lukas Bubendorf (*Figure 1*) currently serves as a professor and pathologist at the Institute of Pathology, University Hospital Basel, Switzerland. He is actively involved in research areas including non-small cell lung cancer (NSCLC), epidermal growth factor receptor (EGFR), radiotherapy, targeted therapy in lung cancer as well as biomarkers of lung cancer for the early detection of this disease. At WCLC 2017, he made a speech and shared his findings on "*Molecular Testing Using Cytology Specimens*".

Interview

TLCR: You are an expert in the field of lung cancer, especially in NSCLC. What actually triggered you to engage in this field?

Prof. Bubendorf: I am a pathologist. I got into this field by chance. At some point of my career, I went into the cytology field in addition to histology. Cytology was automatically linked to pulmonary pathology because it is tightly connected to biopsy. If a patient gets a bronchoscopy, he/she gets the cytology and biopsy on the same day. That's how I got the chance to enter this field 16 years ago.

Figure 1 Prof. Lukas Bubendorf (middle) and our editors (left and right) at WCLC 2017.

TLCR: As a pathologist, what challenges have you met so far in treating patients/in research?

Prof. Bubendorf: From the pathology perspective, the challenges have been increasing in the past decade. In the past, we only had to deliver diagnoses, like a yes or no, or identify the type of non-small cell carcinoma, and later on the sub-classification of it. The next level of progress came at 10–12 years ago. We encountered another challenge that we had to deliver predictive EGFR gene mutation data from small biopsies and cytological specimens. We had to make the best use of the materials we had. We developed approaches like laser microdissection. We reviewed all samples we had from a patient and learned to best manage and use the specimens optimally.

TLCR: Over the past decade, what have been the biggest advance in the treatment of NSCLC?

Prof. Bubendorf: The biggest advance in the treatment of NSCLC has been the concept of personalized medicine. It actually started with the testing for targeted treatment, and then specific rearrangements, like *EGFR*, *ALK* and *ROS1*,

followed by, of course, immunotherapy and the related biomarkers.

TLCR: What are the pros and cons of using cytology specimens in molecular testing?

Prof. Bubendorf: This remained a very controversial topic a few years ago, but it is commonly accepted nowadays that we can, and should, use cytology for all molecular testing.

For the cons, we often have large variability of pre-analytical procedures in cytology: specific type of specimens, liquid based, non-liquid based, ethanol, formalin, fixed cell blocks These preparations are all under the umbrella of cytology. Histology is less complex. We have a piece of issue—fix it with formalin and process it in a very standardized manner. But for cytology, international standardization is more difficult. Another disadvantage is that the expertise in cytology is not uniformly spread worldwide. The quality of cytology varies in different countries, where standardization is necessary.

Besides, most assays have been established on histological specimens or based on clinical trials built on histological specimens. They are not tailored to cytology and require adaptation from what we know from the assays. Cytology application of these assays requires an intermediate step of laboratory development tests for cytological preparation.

For the pro, nowadays we have a lot to do with mutation testing from extracted DNA. Cytological preparation provides excellent DNA quality. It's been recently shown that it's not so much the quantity of DNA, but primarily the quality that counts. As there is no formalin in non-cell block cytology, there is no cross linking of DNA like in formalin fixed specimens. Another advantage is that we know exactly what cells we want to collect for mutation. We are using the diagnostic specimens. We identify the cells that we use for DNA extraction.

Apart from analysis of extracted DNA, we use fluorescence in-situ hybridization (FISH) as a standard to detect chromosomal aberrations including rearrangements and amplifications. By doing this on cytology specimens, you get superb images from intact cell nuclei showing the true number if chromosomal signals, since these cells are not truncated as in histological tissue sections.

TLCR: What factors have to be taken into account when you formulate an individualized approach for each particular patient?

Prof. Bubendorf: As a pathologist, I do not make decisions on how to treat a particular patient. When I get the specimens to my microscope, I do not know everything about the patient, say his actual conditions, his social background and so on. What I can see are his age, sex and whether he is a smoker or not. Yet, I would say age is the main observational factor—I might think of a 90-year-old patient differently from a 50-year-old patient. Still, there are no official restrictions relating to age or sex when it comes to biomarker testing.

Therefore, I primarily look at the type of specimen and get the most out of it in terms of precise diagnosis. In that way, each patient is different due to a unique composition of specimens. I do not know the patient, yet I will think in favor of the patient and see how I can bring him most benefits from what I can comprehend from the specimens. Only then will I bring the results back to the interdisciplinary conference, where a final decision is made based whole context of the patient.

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Footnote

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