ANNA BUCHNER: Good morning everyone. So today I would like to talk about clinical application of chromoendoscopy in IBD patient. We hold that chromoendoscopy in IBD patient will lead to prevention of colon cancer. we can achieve this by dysplasia detection, by improving dysplasia detection through our screen incidence colonoscopy program. Forever dysplasia characterization with classification of a lesion and assessment of inflammatory activity.

Furthermore, we hope that we can also diagnose in vivo when we combine come chromoendoscopy with confocal endomicroscopy. And hopefully this will guide our endoscopic treatment, our endoscopic decision, regarding the treatment and future management colectomy versus endoscopic surveillance. And our ultimate outcome of interest is to decrease cancer, decrease mortality rates, and decrease colectomy rates in our IBD patients.

Dysplasia is defined as a neoplastic alteration of epithelium. So dysplasia is equivocal to neoplasia. Distribution can be unifocal and multifocal in IBD patients. Can be elevated or flat dysplasia. And furthermore, histologically we can define indefinite dysplasia, low grade, high grade dysplasia and adenocarcinoma. We all know that colorectal cancer independent of whether this is average risk patients or in our IBD patient, it starts from dysplasia. What are the risk of dysplasia? The modifiable risk factors would include to extent of a disease. So whether this is pancolitis, right sided or left colitis, duration of a disease.

And furthermore the coincidences with other [INAUDIBLE], such as primary sclerosing cholangitis. Family history of colorectal cancers also is important. The presence of inflammatory activity with inflammatory polyps is also identifies the risk for dysplasia. Furthermore, potentially modifiable risk factors include histological inflammation, adverse surveillance colonoscopy. Until recently, we had defined our dysplasia lesions according to microscopic classification from 2004, which included division into elevated lesions, such as dysplasia, associated lesions, and flat.

These elevated lesions with dysplasia associated lesions can be defined further into adenoma and non-adenoma-like. On the left, we see the figure illustrating that concepts. So we see dysplasia lesions within the colitis. And as it is opposed to

sporadic adenomas which are not within a colitis area. Furthermore, again this would be further illustration of constant that dysplasia associated lesions and mass can be divided into adenoma-like, so these are endoscopically resectable lesions, and non-adenoma-like, so endoscopically unresectable lesions. And the key thing in assessment of the lesions is evaluation of the borders of a lesion. So whether we can distinguish borders very well or not distinguish borders very well. And further, also look at the presence of any ulcerations, which would be a bad prognostic factor and would indicate potentially an unknown carcinoma.

Just this month, two important papers appeared in *Gastrointestinal Endoscopy and Gastroenterology.* And this is called semi consensus, international semi consensus was published this month. And the goal of this consensus is to simplify management and diagnosis of dysplasia. So the investigators of this consensus proposed using actually known Paris classification. Paris classification is well known to us, and allows us to classify lesions into polypoid lesions, type right here. And non-polypoid lesions. Sorry. And polypoid lesions will include pedunculated lesions and sessile lesions.

Non-polypoid would include superficial, elevated, flat, and depressed lesions. Furthermore, the specification tries to simplify and clarify the prior terminate the term of DALM, and actually abandon the DALM dysplasia associated lesion mass term. Furthermore, flat dysplasia would also be included as non-polypoid visible in addition to non-visible identified in random biopsies. When we use this classification, it's very important not only apply the strict classification, but to modify it and look at the features such as borders of the lesion. So the question is whether we can identify the borders, the next question is whether there are any signs of ulcerations within the lesion present.

And this is an example of a lesions identified in patients who underwent surveillance colonoscopy. The goal of this was-- the patient was referred to us to assess whether this lesion is deemed to be endoscopically resected. Initially our perception was that we can do it when we looked on with high definition white light. However, upon the application of methylene blue, we realized that the borders are much more difficult than we thought, and we cannot really distinctively define these borders. And the lesion was much more extensive than we thought.

Currently we think that we can see most dysplastic lesions in IBD patients based on the evidence available. 70% to 90% dysplasia was found to be visible in patients and cancer-- up to 100% of cancer was visible in our IBD patients. We think this is overachieved with using our current endoscopic imaging. We use broad view technologies to detect and characterize lesions, and this would include traditional chromoendoscopy with dye based application.

Furthermore, we also have virtual narrow band imaging started in IBD patients. However, all the studies determined that narrow band imaging is not useful in detecting dysplasia in a characterization of dysplasia. Furthermore, we also utilize small view techniques to characterize and diagnose the lesions further. And this is achieved using confocal endomicroscopy. This is, of course, not standard occurrence. Only used in a setting of 30 hour centers who have this confocal endomicroscopy available.

This is another example of a lesion. So we can see of a lesion in white light followed by narrow band imaging. And again, we don't appreciate the bodies are pretty much clear at this point. However when we apply methylene blue, our assessment of that lesion changed quite a lot. And we realized that the lesion was much more extensive as we initially thought. And this lesion was, again, deemed not to be endoscopically resected, and the patient was referred for colectomy.

So combine imaging technologies in IBD he has been utilized in academic center using chromoendoscopy and confocal endomicroscopy. The evidence of the utility of this comes from the study by German group Grafkischlick where chromoendoscopy showed at least four-fold increased diagnostic yield in detecting dysplasia. And furthermore, with application endomicroscopy, investigators were able to reduce the number of biopsies taken per patient. This is another example of utilization of confocal endomicroscopy in patient who had dysplastic lesion. And when we look at this, we can define some inflammatory activities over mucosa, as well as we looking for any lividity from structures which would represent adenoma.

In this case, patient was found to have low grade dysplasia in the settings of existing colitis. Again, studies done by Grafkischlick group confirm the utility of a combined approach, chromoendoscopy with confocal endomicroscopy, and achieved goal was the reduction of a number of biopsies taken per patient. So nowadays we do

screens of colonoscopy. So screening colonoscopies, we start to do in every IBD patients who have disease for this eight years duration. Our goal is to determine the extent of colitis, and furthermore, to evaluate for any presence of dysplasia or cancer. We took four quadrant random biopsies every 10 centimeters, and we always do targeted biopsies any lesions or suspicions mucosal abnormality.

And this follows by surveillance colonoscopy, which are done regularly to, again, identify dysplasia by using random biopsies and using targeted biopsy cell biopsies directed at any mucosal abnormality. So how we do surveillance nowadays? We do random biopsies ever 10 centimeters. And also targeted biopsies of any mucosal lesions, nodules, mass, and structure. This means a lot of biopsies. And this comes with notion of taking random biopsies comes from other papers which define that in order to have 90% confidence in finding dysplasia, we need to take 33 biopsies.

This means only visualizing a very small portion of colon, which basically represents 0.1% of colon, which is very minimal. The study shows that's actually this type of biopsy, so biopsies, have very low yield in finding dysplasia. There's a study published in *American Journal Gastroenterology* last December by a Dutch group. The investigators looked at various surveillance program of ulcerative colitis patients over 10 years, and they were able to identify that only 24 random biopsies out of over 11,000 had dysplasia, which means 0.2 per biopsy yield. It means that we can find dysplasia only 1 in 500 random biopsies.

So this type of surveillance, a screening program, leads to interval cancers. You increase interval cancers and increase missed cancers in IBD patients. This is the study done by Mayo croup analyzing medical data over 55,000 patients over a period of time 1919 to 2005. And as we see in the figure, there is remarkable increase in interval cancers in IBD patients compared to non-IBD patients. 15% percent of patients were diagnosed with colon cancer had screen or surveillance colonoscopy done within three years prior to the their diagnosis.

Question is, what do we actually do? What do gastroenterologists do, do we really perform random biopsies? Studies show that actually now-- it includes British studies done in 2000 which show only 2% gastroenterologists took more than 20 biopsies. The favored study also shows that only 54% percent of gastroenterologists reported obtaining at least 33 biopsies. And that study also confirmed that in

almost 73% percent patients, gastroenterologists took fewer than 30 biopsies. American gastroenterologists according to an abstract publishing in *Gastroenterology* a few years ago, only the 18% percent were taking biopsies. So basically random biopsies we don't routinely do as we are supposed to do.

So the question is, should we abandon random biopsies? Based on this new consensus, there's no unanimous agreement whether we should abandon the biopsies. 45% of experts agreed, and 35% disagreed with performing random biopsies when using high definition white light, whereas only 25% agreed, 60% disagreed with performing random biopsies when we use come chromoendoscopy. Studies show that targeted biopsies during chromoendoscopy detect dysplasia. Though a few meta-analysis studies done over the last few years. And most recent one confirming that when we do chromoendoscopy with targeted biopsies, there's 9% more likely to detect dysplasia. And also we are 5 times likely to detect non-polypoid dysplasia.

There is 93% lower likelihood to miss dysplasia compared to targeted biopsies. Number needed to treat patients, number of patients who require a procedure, was 14, in order to find one patient with dysplasia. And based on the status currently European guidelines and endorse doing chromoendoscopy with targeted biopsies. It's important to mention that all the studies done so far comparing chromoendoscopy with targeted biopsies versus white light traditional colonoscopy were down comparing chromoendoscopy with older systems of endoscopic system with standard imaging.

And over the next last decade, we actually have an introduction of high definition endoscopes which provides high image resolution. And furthermore, we don't have a real answer how this affects our surveillance when we use high definition white light imaging. What do our American guidelines say? So we have the guidelines from 2010 *AGAHGE*. And basically they do emphasize the importance of taking random biopsies. However *AGA* guidelines mention that if an endoscopist is an expert at chromoendoscopy, then the chromoendoscopy with targeted by biopsies is recommend. This is different from European guidelines, which all actually recommend doing chromoendoscopy with targeted biopsies.

So what is chromoendoscopy? Chromoendoscopy is basically an application of

topical dye to mucosa. We have two types of dye. Contrast dye, which is indigo carmine, and we have also absorptive dye with is methylene blue. Here we see an example of an application of indigo carmine. We can delineate the borders between normal tissue and abnormal tissue. The contrast in the mucosal grooves with better delineation of this colonic mucosa normal and abnormal. This can be washed easily. The cost is also not very high.

On the other hand, we also have methylene blue which is absorptive dye, which also allows the same effect, so increased contrast between normal and abnormal tissue. This unique consensus analyse these two types of dyes and basically propose using chromoendoscopy for two purposes. One is lesion detection, so using pan-chromoendoscopy, so applying a lower concentration of dye during colonoscopy. During withdrawal, we basically apply this dye from our water pump. And this allows us to detect more lesions. And further, once we detect something abnormal, we can do targeted pan-chromoendoscopy.

So apply higher concentration of methylene blue or indigo carmine to allow even better delineation and characterization of a lesion. It's important to stick to surface guidelines which were developed by a German group. And basically what it means, making sure that we select our patients correctly. So patients who have active flare-up should not undergo surveillance screening colonoscopies to detect dysplasia. We have to make sure that bowel prep is also good. Sub-optimal bowel prep will actually not allow us to see these lesions very well. Then we can also optionally use agents to reduce peristaltic waste, such as glucagon. And furthermore, we do staining of entire colonic mucosa with a lower concentration of dyes followed by augmented detection with a targeted chromoendoscopy.

This all leads to allowing us better characterization called a pit pattern. And furthermore, directing our endoscopic biopsies or our endoscopic treatment of a lesion. So again, this will allow us to look at the mucosa closely and define pit pattern. And we know that pit pattern one and two, so round and oval, would represent non-neoplastic, inflammatory, or hyper-plastic. And followed by neoplastic, IIIs, S25. And if we can identify these lesions, we should biopsy.

This is again an example of a standard white imaging, and then application of methylene blue led to better characterization to actually see the lesions. Initially, we

could have missed this lesion very easily if didn't apply this method of chromoendoscopy. This is based on the first study from [INAUDIBLE] group comparing dye chromoendoscopy with standard definition white light imaging. This month a publication of a SCENIC consensus might help to simplify or help us to perform surveillance colonoscopy. May or may not. We know definitely that there's all these definitions of high definition colonoscopes over standard definition colonoscopes.

And most of our endoscopy suite already have high definition scope. Furthermore, the guidelines look at the benefit of chromoendoscopy over high definition chromoendoscopy. So comparing typical dye based chromoendoscopy with high definition white lights. And the evidence here is not good, actually. Because there are no studies. There's one small observational study, Mayo Clinic, which reported an advantage of using chromoendoscopy compared to high definition white light in detecting more dysplastic lesions.

But otherwise, the studies are-- there are no more studies. So that's why the consensus is conditional. And when performance surveillance with high definition colonoscopy chromoendoscopy suggested rather than high definition white light imaging. Furthermore, the SCENIC consensus stated that after compete endoscopic removal are visible, polypoid dysplastic lesions, surveillance colonoscopy is recommended rather than colectomy. In the case of non-polypoid dysplastic lesions, surveillance colonoscopy with chromoendoscopy is recommended, rather than colectomy. And this conditional recommendation again based on the fact that we don't have many studies.

For patients with endoscopic invisible dysplasia, so dysplasia found on random biopsies, a referral is suggested to the centers which can actually perform chromoendoscopy. And furthermore, as I mentioned earlier, random biopsies with high definition of chromoendoscopy are not abandoned yet. So there was now unanimous consensus reached regarding continuing performing random biopsies. Slight majority of experts do favor doing that.

So what is the role of chromoendoscopy in surveillance? Chromoendoscopy with targeted biopsy is proposed surveillance technique by the SCENIC international consensus. And it's an alternative to random biopsies. As evidence technique

mentioned in other guidelines-- so AG guidelines and the Crohns and Colitis Foundation guidelines. However, as of today, it's not standard of care yet. This is a slide illustrating a graph of pancolonic chromoendoscopy in targeted biopsy. So again, the main thing is to visualize the lesions, asses the lesions, access Paris classification, assess borders of a lesion and the presence of an ulcer. And then determine whether we can endoscopically resect the lesions or not.

And further management follow that first initial assessment. And in addition, it's also important to analyze the area adjacent to the lesion and take biopsies. And this would help us to define whether the lesion is endoscopically resectable, a colectomy is advised in the future. What are the challenges of chromoendoscopy? Suggest two challenges. We can divide them into operational barriers, so availability of dye, equipments, billing, and reimbursement, time of the procedure, and confounding findings of inflammation. Furthermore, there are knowledge barriers.

So we still don't know natural history of dysplasia detected by chromoendoscopy. We were very select of risk stratification of patients. And not every patient requires chromoendoscopy. We have to certify these patient's accordingly to their disease severity. We have risk factors. There is also uncertainty of appropriate surveillance intervals. So there's still no data. We're basing this through our assessment of a lesion. And we know that a patient will face serious consequences if the lesion is not adequately removed. Thank you for your attention.

[APPLAUSE]