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e-Session n 562 - 04th March 2021

The endoscopic diagnosis of lung cancer: clinical studies in the real life

Dr Colella: Good afternoon to everyone and thank you for inviting me in this webinar. The topic of my presentation is The Endoscopic Diagnosis of Lung Cancer and Clinical Studies in the Real Life. We will start. What I'm going to talk? We will start with a small introduction about lung cancer and the endoscopic procedure, and then, we will see which outcomes should be considered in clinical trials and also, pre-clinical studies. All of this will be applied to peripheral lung nodules, endosonography, and especially, about mediastinal staging. So, about interventional pulmonology procedure in lung cancer, let's start with bronchoscopy. If we have an endobronchial lesion, we can take a biopsy directly with a bronchoscope, with either forceps or needle. And in case of lesion behind the tracheobronchial wall, that means that lung nodule not-visible in the tracheobronchial tree, we can take transbronchial biopsy, either with forceps or needle, and in case these lesions are out of the inner part of the thorax or in the front of the thorax, we can take samples also from the transthoracic wall. And we can consider, also, transthoracic biopsy in lesions that are attached to the pleura. In case of mediastinal abnormalities, that means lymph nodes, mediastinal lymph node abnormalities, or lesions of central lung lesion, we can take a biopsy with endosonography. In terms of EBUS, if we introduce the scope into the trachea or EUS, if we introduce the scope into the esophagus. With the EUS, we have the possibility also to sample subdiaphragmatic structure. We have, too, the possibility to sample liver metastases, abdominal lymph nodes and the left adrenal glands. In some particular cases, also biopsy from the right adrenal glands can be taken. In case of pleura abnormalities or pleural fluid, we have thoracentesis. And if the diagnosis of cancer is not reached with the thoracentesis, we can perform medical thoracoscopy. Let's see some outcomes in diagnostic study. One of the outcomes most commonly found is sensitivity. It is a ratio between the true-positive and the false-negative. So, to have sensitivity, it is required the rate of false-negative patients. That means that they have a negative biopsy, but the patient has cancer. It could happen that, for example, when we sample lymph node that we find inflammatory cells or granulomas. That does not mean that the patient does not have cancer. It is a false-negative result. Specificity is not commonly found in lung cancer because false-positive is not detected. It is nearly 100%. Sensitivity and specificity are also useful to evaluate the positive and the negative likelihood ratio, especially, the negative likelihood ratio for the reasons that I've told you before about the false-negative rate. And then, we have the post-test probability in terms of positive-predictive-value and negative-predictive-value. These two parameters are burdened by, respectively, the rate of false-positive and false-negative, but what is important is that negative-predictive-value could be also calculated taking into account, factoring in the prevalence of the disease. And this is very important to know the prevalence of the disease, and we will see about mediastinal staging, the importance of the prevalence. Receiver operating curves are not useful in lung cancer. It is not correct to me that it's a no-relevance to a bronchoscopy study, because it can be useful in ILDs. This is a curve that is drawn from a relationship between false-positive and true-positive. So, as you can

imagine, in lung cancer, it is not useful. And then, finally, we have diagnostic yield or diagnostic accuracy. Again, we need to have the true-negative rate. About true and false-negative patients, what we need? We need clinical follow-up, that is at least over six months to confirm that my negative result is really negative or a further invasive procedure. I can take a second endoscopic biopsy or, as in the case of mediastinoscopy, I can take also a surgical procedure. Common pitfalls and solutions. If I'm designing a trial for evaluating a new biopsy strategy, a single-arm study is not the best solution because I don't have comparators. So, a parallel trial with a control arm is advised. And especially, if I'm considering a randomized trial or a prospective comparative trial, I need those statistics because I need those statistics in the moment while I'm designing this trial, because my results will have more strength at the end. And about the strength, also, the lack of generalizability is a common pitfall because, for example, I can have a lack of generalizability if I select the patient. This happens, for example, in retrospective studies where, for example, I take in consideration only patients that underwent a certain procedure, but I'm not including in the calculation all the patients that underwent to my consultation. And also, to have performed procedure only in expert centers could be a problem because the technology that are found in expert or in high-volume centers is not commonly found. It could be not found in all centers or is not widely available. Demographic and clinical parameters should be reported, especially, if I'm considering two-arm studies, and there should not be any statistical difference between the two arms. And I reconnect with what I told you before about the false-negative result, I need of confirmation in case of a negative biopsy. So, at least a clinical that meets radiological follow-up is advised, even better if I have a pathological confirmation of my result. Moreover, we do not have to forget the mortality and the peri-procedural complications, for example, pneumothorax in tracheobronchial biopsy, the cost in comparison with other surgical and non-surgical techniques, and it is very important to consider, in some cases, the prevalence of the disease. Another point is sample adequacy. I have my histological or cytological sample. This sample could be either diagnostic or non-diagnostic. In case of a non-diagnostic material, I can have necrosis or no-cells or a sample is not diagnostic but could be still adequate. This is the case, for example, of EBUS in sampling mediastinal lymph node. I have lymph nodes, maybe, 30, 40% each field but no tumor cells. In case of a diagnostic result, I need not only the sample to be diagnostic, but especially in case of disseminated disease, I need that that material should be suitable for molecular analysis. Or the sample could be only diagnostic. This is the case, for example, it is very rare but a diagnosis of lung cancer with bronchial lavage, bronchial washing. I can have one single cell that allows me the diagnosis of cancer, but it doesn't matter because I cannot perform any molecular analysis on one cell. Why I need all these? I need all these because I need to write guidelines, and in writing guidelines, I have to consider the pyramid of evidence. In an even work, in writing guidelines, we have to consider all the randomized clinical trials, systematic reviews and meta-analyses of randomized trials, but sometimes, it's not possible to have this high level of evidence. And as far as I go, from the top to the bottom of this pyramid, my quality of evidence goes down, and my risk of bias goes up. So, that's why I need all these parameters to have high quality studies and to write some evidences in terms of guidelines. Also, preclinical studies are important. Think about a new biopsy strategy or new forceps or, like in this case, a new navigation system. Before to test it on a real patient, it is advisable to test it on human or animal cadaveric lung like it was done in this trial. 20 pulmonary nodules of around 2-centimeters in diameter were sampled in a human cadaveric lung under fluoroscopic guidance. All are performed fluoroscopy guide and radial EBUS, and the patients were randomized to receive either electromagnetic navigation and, afterwards, robotic bronchoscopy or robotic bronchoscopy and, afterwards, electromagnetic navigation. And as you can see from this table, robotic bronchoscopy performed significantly better than the other two. Let's say three, because we have also fluoroscopy, of other two guidance methods, in terms of localization and puncture. Moreover, we know that by using robotic bronchoscopy, the distance between the needle and the lesion was lower compared with the other methods. Just a quick stop to remember you that you can ask questions and comments at the end of this presentation. So, let's see all I've told you before until now in clinical studies. Taking a sample from a peripheral lung nodules or masses, as a general rule, as far as they go from the central to the periphery of the thorax, my diagnostic yield of bronchoscopy alone goes down, especially, in small lesions, smaller than

2-centimeter. This is why I need a guidance system. Guidance systems most commonly available are fluoroscopy and radial-EBUS. We may have also electromagnetic navigation, but it's quite expensive. And other guidance systems are under investigation, such as robotic bronchoscopy or the ultrathin bronchoscope. Planning a biopsy of peripheral lung nodules, what I have to consider? First of all, the presence of the bronchus sign. That is the third- or fourth-order bronchus leads to the lesion. We can see it at the CT scan. The dimension of the nodule, the guidance system I have in my unit, and if my lesion is in contact with the pleural surface. So, in this case, maybe, I can consider a transthoracic CT scan guided or ultrasound guided biopsy. Let's move to some trials. Peripheral lung nodules: radial EBUS versus conventional forceps. In this randomized trial, 206 patients were randomized to receive a biopsy with radial EBUS, 97 patients or conventional forceps alone, 124 patients. As you can see in the results in this table, the sensitivity and the accuracy was significantly higher in the radial EBUS group, and the sensitivity and the accuracy are also significantly higher in patients with lesions smaller than 3 and 2-centimeters. So, the conclusion was that radial EBUS in peripheral lung nodules performed better than forceps. No difference in lung masses, in lesions bigger than 3-centimeters. So, which are the strengths and limitations of this study? First of all, they have included consecutive patients. They have screened more than 3000 patients, so, all patients that underwent consultation for thoracic oncology, and then, they have selected almost 800 patients with peripheral lung lesion. And then, they evaluate patients that could be eligible for a biopsy, and patients that underwent to a clinical follow-up. So, they exclude patient-loss in follow-up. They did not find any differences in clinical and demographic parameters, and they made a subgroup analysis in lesion, according to the dimension. Other limitations. It is not clear if they use radial EBUS and bronchoscopic guidance. In this case, maybe, results should be treated separately. If the bronchus sign is present or not, and this is a single center study. Even if there it is a very high-volume center, but it's a single center study. Another trial. The design is quite different. They have 360 patients. The pulmonary nodules have a median diameter of 19-millimeters. Patients were randomized to receive biopsy with an ultrathin bronchoscope and a thin bronchoscope. This center has used three guidance systems, in this order: virtual bronchoscopy, radial EBUS, and fluoroscopy. The overall diagnostic yield was higher in the ultrathin group. Moreover, the ultrathin bronchoscope performed better in smaller lesions and lesions of malignant nature. There was no difference in patients with presence or not of the bronchus sign, but this difference was significant in the thin bronchoscope group. And no difference if the patient has solid or partially solid nodules. Strengths of the studies. Again, we have consecutive patients. We are one-year clinical follow-up after bronchoscopy. No differences in demographic and clinical characteristics. We have several subgroup analyses compared to the randomized studies that I showed you before. We have lesion-size, location of the nodule, if it was located in the inner third or out of the inner third of the thorax, the nature, the bronchus sign, the CT appearance, the bronchus level reached with the bronchoscope, with the two bronchoscopes tested, the location of the probe, the sampling procedure and the procedure time. Limitation. In this study, they have included all patients with pulmonary infiltrates. So, that means not only lung cancer patients, but this limitation was overcame because they make subgroups analysis. Three centers were included, but these three centers are very experienced centers. So, maybe, this reality is not reproducible in all units. At the time of writing this article, ultrathin bronchoscope was not widely available. They have used three guidance systems, and, as I told you before, this is commonly found in very expertise centers, but not in all centers. They have used a small and standard forceps, but they have not specified which ones in the thin bronchoscope group. And the final diagnosis was not pathologically confirmed in all patients. So, we have a clinical follow-up, but we don't have additional confirmation. Another new, brand new biopsy method is cryobiopsy. Cryobiopsy is well-known. The role of cryobiopsy is well-known in interstitial lung disease, and they start to be evaluated also in cancer. In that meta-analysis, they have included nine studies. All have used radial EBUS, and this meta-analysis is a non-inferiority trial that stated cryo is non-inferior to forceps biopsy. The complication was almost 2%, and the limitation could be that only one randomized clinical trial was included. And there was a huge procedural heterogeneity, as it is for interstitial lung disease, in cryobiopsy, in terms of probe diameter, freezing time, the use of bronchial blocker, and the use of fluoroscopy. So, what came out from these meta-analyses? Should I use cryobiopsy? Of course,

we can, because it has been written, it has been tested, and there are no particular problems. But maybe, it is advisable to use it in clinical studies, in a prospective, comparative, or multicenter studies. Evaluation, a careful evaluation of the standardization of the technique has to be done in terms of sedation, anesthesia, guidance system, cryoprobe diameter, freezing time, bronchial blocker, sample dimensions retrieved, and the adequacy of the sample and the efficacy, also, of the technique, according to the target lesion. I mean, if we have a bronchus sign, the level we reached with the scope, and the relation between the scope and the probe, and in terms, obviously, of safety. Again, I remind you that the comments and the questions will be at the end. About endosonography. Endosonography was quite a revolution in interventional pulmonology. With endosonography, we can take a biopsy, as I told you in the introduction, of lesion central in the thorax. That means mediastinal lesion or lung tumors. With EBUS, we can reach also inner structure. And with EUS, we can reach also a lymph node of this patient 8 and 9, liver metastases, abdominal paraaortic lymph node, and the left adrenal gland. This is the trial, that has the study that opened the way for the use of endosonography in lung cancer. They have included 241 patients, potentially operable for non-small cell lung cancer, and they were randomized to receive surgical staging alone or EUS followed by surgical staging. As primary outcome, there was the sensitivity for mediastinal nodal metastases. That means N2, N3 disease. In this case, the group endosonography plus surgery performed better. As a secondary outcome, there was the rate of unnecessary thoracotomy. Also, in this case, the group with the endosonography plus the surgery performed better than surgical staging alone. The diagnostic accuracy of EBUS and EUS was also evaluated in this meta-analysis. More than 2000 presences, and here, you can find an interesting data, N2/N3 disease prevalence. The median was 34 with a range of 23 to 71, and the overall sensitivity for EBUS plus EUS was 86. And the overall negative predictive value was 92. Adding EUS to EBUS resulted in an increase of 12% in sensitivity, whereas, adding EBUS to EUS resulted in an increase of 22% in sensitivity. And no differences if the EBUS scope or the EUS scope was introduced into the esophagus. What we have to considerate in evaluating mediastinal staging in evaluating N2/N3 disease? Two situations, mainly, abnormal and normal mediastinal by imaging. That means allotted or fit positive mediastinal lymph nodes. If I have an abnormal mediastinal and my endosonography is negative, I have still a 20% of probability to have a N2/N3 disease. This probability drops to 5 if I add the surgical staging. This situation is completely different with normal medistine because adding endosonography to imaging results in 10% of it still having N2/N3 disease, but this percentage is not affected, could be not affected if I add mediastinoscopy to endosonography. And this is why I need disease prevalence. In these systematic reviews, compared to the other meta-analyses that I have shown you before, the disease prevalence was 15% with a range from 6 to 24. They consider patients with the radiological normal mediastinum. The sensitivity of EBUS was 49, was quite low, lower, of course, lower than the one showed in the meta-analysis or in the ASTER trial. But the negative predictive value compared with the prevalence of the disease was 91%. That means that a negative patient, I'm quite sure, that has not the disease. This is an ongoing trial. Although, the design is similar to the ASTER study, the MEDIASTrial, we will have the results in the upcoming year, and this is going to evaluate endosonography compared to mediastinoscopy, in N2/N3 disease. But sometimes, a randomized study is not possible. A prospective comparative study is not possible to have. Like, for example, if I need to take a sample from the left adrenal gland, which could be my comparator, it's very difficult. This is the largest case series we have about EUS in left adrenal gland metastasis. 135 patients were included in two Danish centers over a two-year period. The prevalence of left adrenal gland malignancy was 30%. Samples were adequate in 87% of cases, where adrenal cells or malignant cells were found and no complications regarded. Of course, it is a retrospective study, but data were interpreted in an interesting way. They have adequate and not adequate samples. Among adequate samples, we have 40 malignancy. We have 51 patients lost in follow-up and 26 patients that were followed-up for six months and no malignancy was detected at the imaging. In case of not adequate sample, one patient underwent again to EBUS and was diagnostic. In 11 patients, disseminated disease was found. So, there was no need to take a biopsy, and 6 patients underwent a six-month follow-up. So, they performed two clinical situations, the best scenario and the worst scenario. In the best scenario, so, considering all patients lost in follow-up were negative, the diagnostic yield was 80, sorry, 97%, and the sensitivity was 98.

In the worst scenario, I have the 51 patients that were positive. The diagnostic yield was 63 and the sensitivity, 39. So, as a take-home message, in evaluating or design a clinical trial, we have to consider comparison with other biopsy methods, statistical analysis, the generalizability of the results in terms of prevalence of disease, infiltrate characteristics, consecutive enrollment, and multicenter trial, and also, tissue confirmation or follow-up. Preclinical studies can be useful to test a procedure before its introduction in clinical practice, and clinical trials are useful to have an overview about the best option to take a biopsy from uneven lesions but their applicability should be, could be limited on local availability and expertise.

Dr Bertolaccini: Thank you so much to Dr Colella for this beautiful presentation. We have some comments from the audience. The first question is how to evaluate the cost of a procedure in a clinical study?

Dr Colella: Thank you for this interesting, interesting question. I gave you the example of the ASTER study. After some months from the ASTER study, they have compared the cost of surgery and endosonography and the rate of thoracoscopy. And they found that the cost in the surgery arm was higher compared to the endosonography group. This because more patients, obviously, in

the surgery group underwent to a surgical procedure, that is usually more expensive than an endoscopic procedure. So, mainly, it's up to the biopsy strategy you are considering, because if you consider mediastinoscopy and endosonography, you have the cost of a surgical staging versus an endoscopic staging. If you are considering a potentially operable lung nodule, is the same, but if you are considering a disseminated disease, maybe, you have only the costs of a minimally invasive procedure. It's up to your procedure.

Dr Bertolaccini: And how to evaluate the quality of life?

Dr Colella: The quality of life is not commonly reported in the clinical trial. I show you the MEDIASTrial that is ongoing. I think that the patient will be followed for two years, if I'm not wrong, after enrollment and they are going to evaluate also the quality of life. There are some specific questionnaires about the quality of life that are validated to discriminate various groups. It's up to the operator choice, but the most valuable method to evaluate the quality of life is questionnaires.

Dr Bertolaccini: Okay. Thank you for your answer. Another question from the audience is: you have spoken about the preclinical studies in lung cancer, but which is the best model? A cadaveric model, the sheep, or which other?

Dr Colella: I think the human, because, maybe, for example, take the pig. The pig has an additional bronchus, for example. So, to test the maneuverability, for example, of an instrument, of course, the tracheobronchial tree is very similar, but there could be some differences among the human and the animal model. So, also, this parameter is up to the local availability, but I think that the human is more valuable to apply it in the clinical setting.

Dr Bertolaccini: Another question from the floor is, we have a thoracic surgeon who performs a mediastinoscopy, several mediastinoscopies, but which is the real role of mediastinoscopy in 2020?

Dr Colella: I answer to this question with guidelines, because the American College of Chest Physicians, as well as, the European Respiratory Society, I mean, many societies tell us that we have to consider first the endoscopic procedure. And then, in case of a negative result with endosonography, we have to perform mediastinoscopy if the pretest probability is high, but endosonography, in the first step, is highly recommended because the performance of a endosonography is very good. So, we don't need mediastinoscopy, but I can understand that it's up to the center because in some centers they prefer to perform mediastinoscopy. Maybe, but not for lung cancer, if I have a suspicion of a lymphoproliferative disorder, it could be reasonable to me because in some cases a needle biopsy but the EBUS could not give us the correct result. I mean, I can name a diagnosis, but for lymphoma it's completely different. I need a very

large amount of material, but these pitfalls could be overcome by using mini forceps or cryo. So, I think that it is really reasonable to perform endosonography first.

Dr Bertolaccini: I talked a little bit earlier with you. I am a thoracic surgeon, and in my center, the number of mediastinoscopies in one year is inferior to 5. And we have great interventions in the pneumology unit, with more than 800 procedures by year. So, only in few cases we perform a mediastinoscopy, and it's hard to explain the residents the mediastinoscopy procedure because the number are really a few.

Dr Colella: Ah!

Dr Bertolaccini: Another question from the floor is about the study in interventional pneumology or in thoracic surgery, because our panelist says, in oncology, we have a lot of prospective, randomized clinical trials but it's hard to design a randomized clinical trial for surgical patients or in interventional pneumology patients. So, which is the best study design if I want to perform a retrospective trial?

Dr Colella: The retrospective trial is a trial design. So, you mean that you take your case series, and you select patients for endosonography, for lung nodules. If you want to perform a prospective comparative trial, it's completely different. You can choose to randomize patients to receive, for example, a biopsy with cryobiopsy or with forceps biopsy, or we can do also prospective comparative not-randomized studies. Of course, if randomized patients, my study will have a certain grade of evidence. Also, in considering guidelines, I have a power. If I consider prospective studies or retrospective studies, the evaluation of the design could have some bias. So, the risk is that could be excluded among the literature to be considered, but it depends from what you are going to find because from lung nodules maybe is not so easy to design a trial. But as it is for mediastinal staging, I think it is the best solution. And of course, as Luca was saying before, if you don't have a high-volume of mediastinoscopies, as it is in 2021, maybe, randomize patients in endosonography and in mediastinoscopy group is not so easy. So, it is better to have a subsequent approach. That means that all patients receive endosonography, and only some of them receive mediastinoscopy.

Dr Bertolaccini: Thank you, and the last question from the floor is about the meta-analyses you could include in guidelines. Only meta-analyses of randomized clinical trial or all meta-analyses?

Dr Colella: No, no. You can include all meta-analyses in guidelines. By including studies in guidelines, it is a very careful procedure because, of course, if you include only meta-analyses of randomized clinical trials, it is the best option overall. We are at the top of the pyramid. But meta-analyses are useful because, in some cases, they sum up all the literature. So, they sum up prospective and retrospective trials, case series, and so on. So, if you include the meta-analyses, you can take that meta-analyses as a whole; that paper that include, for example, 20 other studies and then, you can decide to add other studies that are published after the meta-analysis, for example, with a large amount of patients. What is interesting in writing guidelines is that if I have to make a series of 1000 patients, is that the value is very low, because if it is a retrospective trial, of course, I have a huge experience. But for the intrinsic nature of the study, the risk of bias is very high. So, the risk is that it could be excluded from the study selection process.

Dr Bertolaccini: Thank you so much for the answer to the question of the floor, there are no other answers. So, thank you, Sara, for your beautiful presentation. Thank you to all the panelists for attending this session, and have a good afternoon, evening, or day.

Dr Colella: Bye.