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2023 literature update of lung cancer surgery

Prof Ng: Thank you very much for the kind invitation, to invite me to give this talk for e-ESO 2023 Literature Review. I've kind of chosen to give the theme, which "Is Less the New More for Lung cancer". And that will be discussed in separate sections within this talk, and I hope you'll find it interesting. So, with this theme, I've broken it down into three areas. One is about surgical access and whether we have some new data to support the access that we should be adopting for our surgery. The second area is about resection size, how much we take out as surgeons for a particular size of lung cancer. Clearly, there's a lot of new evidence in this area as well as for discussion. And thirdly, it's really to talk about localization. There's a lot of discussion and techniques that are used to localise small GGOs and small lesions, that these days are found on screening and what the future may hold for localization, and the answer may be more simple than most people think. So, for the first part with regards to surgical access, most people are familiar with open thoracotomy and in fact 3-port VATS is something which is, for most centres, bread, and butter for performing lobectomy. In our centre, we started in the 1990s and so, it's coming up I guess to almost 20 or 30 years, since our first VATS lobectomy. Over the years, particularly in the early days, there are a lot of retrospective studies. Some are quite small to look at the potential advantages of doing VATS such as lower morbidity, less blood loss, less pain, sort of a quicker recovery, shorter duration of chest drainage and also hospital stay. Patients also tend to have slightly better quality of life, better function of their shoulders and also more satisfied in terms of cosmesis. And there's been some biochemical markers that suggest the immune system may be better preserved as well. One or two studies have suggested that fats may be associated with quicker recovery, so patients can move on to earlier adjuvant chemotherapy as well. And controversially one or two studies also suggests that perhaps VATS has better survival than open surgery. Then things moved on, in 2012 in our hospital, we started doing uniportal or single port VATS lobectomy, after the movement was started by Diego Gonzalez-Rivas. This is a single point incision and specialised instruments and also staplers were eventually designed and adapted, so that things can be pushed through a single port. Things then moved on and Diego, basically, pushed the boundaries even more and got rid of the assistant who was holding the camera by using a robotic arm, that you can see here, for the more advanced uniportal surgeons, often they don't need to cNge the position of the thoracoscope very much during the surgery. So, this kind of approach is quite possible for, you know, standard cases and you don't get the assistant getting in the way. In fact, things kind of took a little bit of a, some would say, a step in a different direction by going back to a three or four port approach using a robotic surgery and that's different cams, the one cams that do uniportal, cams that do robotic and this is us using the Xi system in our hospital. This is myself doing Thymosis and more simple lung resections, using three to four port access as you can see here. And it's very comfortable to do that and it's another form of minimal access approach. Until in fact last year, Diego published this approach of using a uniportal, but using multiple arms from the robotic system that are put through a single incision, that you can see here. And again, changing the perhaps the paradigm of how we should be doing, you know, less

traumatic surgery. Now with so many approaches, we are all kind of a bit confused. So, you can see here that three years ago myself and also a number of distinguished doctors and surgeons, came together to try to piece together, using a systemic review and meta-analysis under the umbrella of ISMICS, which minimal invasive approach is the best. The first thing I need to talk about is that these are based on all retrospective studies, okay? And we got together 145 studies, were included in this analysis and we've actually thrown away a lot of studies that were did not meet the standard, looking at oncology outcomes, safety and function as well as the cost-effectiveness, of open, multi-port VATS which includes two-port and three-port VATS versus uniportal VATS, versus robotic VATS, which would be multi-port at that time. So, what we found as the main findings, was that out of 88.000 cases within those analysis, adverse events were less related to surgery, for multi-port VATS compared with open and there was less pain, associated with multi-ple VATS compared with open. Overall survival based on 16-000 patients, that were reported within those series, the survival was slightly better, marginally better in the VATS group. But bearing in mind this is all retrospective data and prone to bias as well. When we compare multiple VATS and uniportal VATS, the most significant finding, based on those retrospective studies, were that pain and analgesic requirements were slightly less for uniportal VATS. And the conclusion of that quite extensive meta-analysis was that it supports the role of VATS lobectomy for treatment of non-small cell lung cancer, in the early-stage and apart from potentially having slightly less pain and GS requirement, with uniportal VATS, different minimal invasive surgical approaches appear to have very similar outcomes. And this is reassuring and also a message, to say that really for those who are doing some form of minimal invasive approach, is already kind of good enough. Well, in thoracic surgery we don't often have randomised studies; big, randomised studies. And the VIOLET study is one such study, this really is a prospective study that was really started by Eric Lim from Imperial, looking at VATS, multiple VATS, most and also some uniportal VATS versus open lobectomy, in patients with early-stage lung cancer. And they reported that one-year result of this randomised control trial, almost three decades since the first VATS lobectomy. And they reported the abstract first of all in ASCO and followed by NEJM Evidence here. So, nine centres took part in this multi-centre RCT and over a four or five-year period and they randomised roughly equal numbers of 250 patients to VATS and also open group. And they found that VATS was associated with less post-operative pain on the VAS score, despite using less painkillers and also less incisional pain, up to one year after operation. There was a better-preserved physical function for those patients and the recovery was fast, was better up to five weeks, and overall improvement, in sort of the health status of the patient in their measurement. VATS was also associated with fewer in hospital, post-op complications but no difference in serious adverse events and they normally stayed one day shorter in the hospital compared with open. After discharge from the hospital, VATS had less serious adverse events that had lower re-admission rates, up to one year with minor difference, as you can see there. Those requiring post-op adjuvant chemotherapy, there was no difference in the time to uptake of the therapy, which is different from the retrospect, someone or two of the retrospective studies, that were reported in the past showing that adjuvant chemotherapy may be able to be started earlier with VATS. And there are some explanations with regards to this, including that the chemo that was offered may be in general at the later stage and not immediately after op, so close to after the operation anyway. The recurrence, progression-free survival and overall survival at one year was not different in the VATS and open groups and you know, more data is pending in this area. Moving on to the second section of "is less the new more for lung cancer." We want to explore how much we should be resecting, in this day and age for small, non-small cell lung carcinomas. Many of you would know this study back in the 1980s, by the LCSG trial group, by Ginsberg, that really coined lobectomy as the gold standard, for small early-stage resectable, non-small cell lung cancer, because it offered a better survival compared with sublobar limited resections. But there were many limitations of this study, including that not all patients had CT scans, not there was no PET scan in those days. A quarter of them had squamous cell carcinomas and disproportion may be different between centres these days and location and most of limited resections were limited to simple wedge resections and there were no margins that were reported for these resections, et cetera. So, there were a lot of things that were not ideal. And in addition, the numbers that entered this randomised trial were not huge either. People started to look

at registries and databases, in a retrospective manner, when in fact people started to think that we may not need to do such a big resection for 1 cm or up to even 2 cm adenocarcinomas. This is just one of many, many other retrospective analyses that looks at lobectomy versus sublobar resection, for less than 2 cm tumours. And this one is based on the SEER registry in the US, of about 8000 patients, using the eighth edition staging system. And in fact, when you adjust this for age, sex, lymph node quality, quantity, and also histological subtype, segmentectomy was not associated with worse overall survival or lung cancer specific survival in this particular context, compared with lobectomy, as you can see here. So, it triggered people to start thinking, you know, maybe we can do less and we don't need a lobectomy for everyone with small lung cancers. Then of course, we move on the next-level of evidence, beyond retrospective registry data. And these are the prospective studies that have come out very recently in fact. And we have a huge harvest of thoracic surgical prospective studies in the last two or three years to go through. And these two are very important. One is the JCOG 0802 from the Japanese oncology group, that compared lobectomy with segmentectomy, looking at the overall survival and recurrence free survival, as well as pulmonary function as endpoints. And the important thing is that they looked at resection of tumours up to 2 cm but with a relatively high solid component, because this is important as we all know, a high solid component tends to indicate a more aggressive nature and behaviour and if this was okay for a segmentectomy then maybe a segmentectomy is enough for this kind of small tumour. The CALGB group, the alliance study 140503 from the US is another study, of course, that looks at this kind of tumour size, of less than 2 cm but they allow wedge resections to be included within the sublobar resection group. And in fact, when you look at the evidence, large proportion of them were wedge resections. Again, looking at disease-free survival and overall survival, as well as pulmonary function, et cetera. So, the JCOG 0802 was published in the Lancet, in fact last year, early last year, during the recruitment they managed to recruit over 1000 patients and divided them roughly equally into lobectomy and also segmentectomy, according to the parameters that we just described in terms of size and also, the solid component and the medium follow-up was over seven years. Amazingly there was no 30-day or 90-day mortality, for all of these patients and complication rates between lobectomy and segmentectomy of grade two or worse were the same between the two groups. At one year, the lung function difference was only around 3% between the larger resection lobectomy and the smaller resection of segmentectomy. The five-year overall survival strikingly was in fact statistically significantly higher for segmentectomy versus lobectomy and by a couple of percentage and you'll notice that the percentage is actually very high, in the 90s. The reasons for the deaths in the lobectomy, there were more people who died due to other diseases; while for the segmentectomy group, there may have been more people who died due to perhaps like relapses or recurrences. Five-year relapse-free survival was 88% for segmentectomy, versus 87.9% for lobectomy. And the proportion of patients with local relapse was 10% for segmentectomy versus 8% for lobectomy. So, that was a difference there. This phase-III study really showed the benefit or the acceptance of segmentectomy versus lobectomy in this arena of size of lung tumour, in terms of overall survival, for non-small cell lung carcinomas. And the findings really suggest that this, perhaps, should be the standard using segmentectomy to treat this selected population of patients. The CLGB study was then actually presented in last year's JTO AISLC session, in August and in fact, just a few weeks ago, this study was published in New England Journal of Medicine, February the 9th. So, as I described earlier on, the criteria, again, less than 2 and up to 2 cm non-small cell peripheral lung carcinomas, lobectomy versus sublobar resection, with some of the patients having wedge resections instead of segmentectomies. It's a multi-centre study mostly across US centres. Randomised phase-III non-inferiority study, looking at peripherally located T1aN0 7th edition, less than 2 cm adenocarcinomas in 697 patients. And these patients were roughly split again in the two groups, randomised to lobectomy and sublobar resection and the sublobar resection included segmentectomy and also wedge resections; interestingly, roughly in about half and half proportion. So, there was a really large percentage of wedge resection within the sublobar group. The disease-free survival at five years, you can see was not particularly different, between the two groups. The lobar resection 64 and the sublobar resection 63.6% and the overall survival again very similar, between the graphs between lobar resection, also sublobar resection, even up to five years, as you can see there, this has a secondary

endpoint. Other secondary endpoints that they looked at including lung function. Again, importantly our belief that preserving a lot of lung function by segmentectomy versus lobectomy doesn't seem to hold in these studies. For the lobectomy that you can see here, there was 6% drop in lung function compared with baseline and for the sublobar resection group there was a 4% drop, from the baseline with a difference between the two of only around 2%, for FEV one and similarly around only 2% difference between the two groups, for FVC as well at six months. The conclusion really was that sublobar resection was not inferior as it was a non-inferiority study to lobectomy for disease-free survival. Noting again, I mentioned earlier on, that there was a big proportion of wedge resection, within the sublobar group and this really for me asked the question, of whether we can perhaps select, highly select patients that can undergo even a lesser resection than segmentectomy, for even smaller tumours or those that have less solid component. And of course, other trials are ongoing in this perspective. So, we kind of described the JCOG 0802, looking at patients up to 2 cm in size tumour, with a very large solid component and other studies that are phase-II that's been performed. For example, this one, the JCOG 0804, by the Japanese oncology group, looked at how wedge resection fared in up to 2 cm tumours, but with a low solid component. This particular study, a single arm phase-II study, in fact was published in JTCVS, about two and a half years ago and they targeted, I said, less than 2 cm tumour, peripheral with a less than a quarter solid component and they recruited 314 patients, over about a two-year period that, in the end, underwent mostly wedge resections, 260 and 56 segmentectomies there. One should note that the median tumour diameter, was 1.2 cm so, it was not quite up towards the 2 cm mark. So, you should take note of this with the results and in fact the median tumour consolidation component was around zero, so it was again towards the pure GGO side that they recruited in this study. The mean pathological surgical margin was around 15 mm in width. So, what they found really was that five-year relapse-free survival, with this single arm non-randomized study was using this approach, was 99.7% and the non-survivors were really, you know, there was no local relapse due to local relapse. In terms of complications, post-op complications of CTCAE, of grade III or higher was only 5.4%, using this sublobar approach, without any higher serious complications. So, quite amazing in terms of the survival rate for this group of selected patients. When you look at this chart, the sort of patients they recruited in this JCOG 0804, that I just described, is more kind of within this red dotted line area, with a slightly smaller lesion and with even less solid component, more almost complete GGO component. So, this should be taken into account when analysing or interpreting these data. Now, in other areas, not just in Japan, this one from China, in fact, also published in JTCVS last year, this is a retrospective study looking at treating a similar sort of cohort of patients. They looked at 1600 patients who had resections, over five years and most of the pathology came back as AIS and MIA and we'll have look at the size in the next slide. But essentially, when you are dealing, resecting with basically wedge resections of these very early-stage lung cancer, your recurrence-free survival can reach the late 90s or even a 100% in this particular study. And the implication really is that sublobar resection, even including wedge resection, without any kind of lymph node dissection, for this kind of non-invasive or very early invasive tumour, can be pretty much curative. In this study, you'll see that the size, that they resected was around 9 mm, so, a little bit smaller than the Japanese study, but they did have patients with solid GGOs, more solid GGOs, a slightly larger proportion, 22% with part solid GGOs and mostly 76% with pure GGOs, in this particular group that they treated. So, in this kind of subgroup, where we know about the cancer oncological sequence, for adenocarcinoma of the lung, of developing from AAH to adenocarcinoma in situ, to minimum invasive adenocarcinoma, so, on the size around this area of 2 or up to perhaps 2 cm, with a small solid component, even a very limited sublobar resection may give a very, very good five-year disease-free survival or overall survival. This brings us really to look at different types of local therapy, because if you can say that a wedge resection can provide a cure, then other local therapies can potentially too, including radiation and ablation. So, one of the study more hotter topics in the last two or three years has been the development of bronchoscopic ablation that our centre has been developing. And you can see here this is really what happens and you can imagine the tumour being within this area of ablation that's taking place over a 10-minute period that's been sped-up in this video and all of this area has been basically destroyed and giving if you are able to create a good margin around here then it is akin to being like removing a tumour

with a wedge resection with a good margin. So, this is something that is being looked at. We've been doing this ablation for around four years now and you can see that for a non-surgical candidate this one, in an 80-year-old, in the left upper lobe, that has poor lung function, we put a catheter through a tumour and after the ablation, the CT scan shows that this area has been destroyed, that encompasses the tumour and with a reasonable margin and this will give probably a good local control, if not a good local control up to five years. You know, why are we not ablating these AISs and MIAs and doing local therapy? You know, when you look at other specialties, they are doing exactly that. When you have a colonoscopy to screen for colon cancer, for example, for our GI surgical colleagues, when they see a polyp, they will do a polypectomy to remove it. If it's a little bit deeper, they may do a submucosal dissection, endoscopically, an ESD, and this is really to target this very early phase of the tumour development, where it has not gone to being locally spreading or metastatic in nature and the local treatment is already enough. So, when you look at this and you look at the complication rate, of therapeutic colonoscopy, of a perforation rate of 0.04 to 0.2%, with a significant mortality when it happens, a couple of percent of bleeding rate with therapeutic colonoscopy and also other kind of complications, but yet, they're doing this as a screening procedure for a population-wide screening. We should perhaps also be looking at the figures, for ablation and treating these very early pre-cancerous lesions that are small basically GGOs with no or very little solid component. Now, the complication rate in our centre for doing endobronchial ablation, akin to a therapeutic colonoscopy is a 3%, also pneumothorax rate and a perfusion rate about 2%, infection rate of 2%, 1% bleeding rate, that is dealt within the endoscopy or the operating room and currently, and including secondary tumours and also primary tumours that we are ablating, we have a recurrence rate of around 6 to 7%, up to about a year and a half, two years after treatment and we have no mortality so far. So, what it means is a very safe procedure and for small tumours we can be thinking about that, in that direction. So, just to put this into perspective, when you see an 8 mm GGO and you get a biopsy of an atypia, cannot exclude AIS MIA from your pathologist and you do a molecular test and it comes back as EGFR positive, what are you going to do? Are you going to do a segmentectomy, a wedge resection or do you think, you'll be happy with possibly an ablation, that could be good enough for cure, of this particular very early-stage, you know, disease within the lung? This ablation approach is also very interesting, as we are tackling cases that are more complex. For example, this young patient, 55-year-old who's already had a left pneumonectomy because of a lung cancer and now has a proven right upper lobe squamous cell carcinoma a few years after the pneumonectomy and he has very limited choice in terms of treatment. He can have radiation or some kind of local ablative treatment, he chose to have ablation which may allow him to go back to work much quicker, compared with repeated hospital admissions. So, this catheter has gone through the tumour, this is the predicted ablation zone, this circle and you can see that in fact after the ablation, you get a big area of ablated region that is destroyed and this is now a case of a 40-year-old lady and we are seeing younger and younger patients, particularly females who are non-smokers, with multiple multifocal lung cancer and she's already had a right lower lobe and also right upper lobe lung surgery and shown to have two double primaries already. Then, she develops left lower lobe and left upper lobe ground glass opacities, of less than 1 cm and with repeated CT scan they were persistent, they were not gone with antibiotics and these are probably early AISs as well on the left side, the patient choose to have ablation and who could blame her because she's had a lobe or a segment already in the other side of her lung and she doesn't want to lose any more lung and she may have other lesions coming up in the next few years as well and she wants to preserve lung function. So, this is what happened, we ablated her, this ablation zone for the two GGOS and we did it in one session and we are monitoring her for any new lesions. Now, of course, with the ablation, we are having new technology, that can take us to further into the lung, in a more accurate manner and these including robotic platforms, not just to do lung resection but robotic platforms, that go into the airway, to take you to these distal tumours, in order to perform ablation for example using microwave. And this is a case a couple of months ago, that we did for a patient. This is the robotic bronchoscope which is the Monarch system and this is the ablation system, which is the new wave system and we are able to destroy a tumour for a non-surgical patient. In the future, of course, there are other ways to in fact treat these small lesions and bronchoscopic steam basically, thermal vapour ablation is one such

possibility to treat these small lesions. In fact, there's already been a human study, an ablate and resect study by Australia group headed by Daniel Steinfort here, that you can see here with a tumour, in a non-surgical candidate and after the, sorry, a tumour in a treat and reset candidate, and after the treatment you can see here the whole sub-segment has been destroyed, including a tumour akin to a sort of, almost like an anatomical ablation if you like. And this is the future. With that I want to move on to the next part. The last part of this "is less the new more for lung cancer" and this is to look at localization techniques, that has evolved over time and where we are heading in the future. A lot of surgeons may wish to be able to see a pure GGO 1 cm or less GGO, such as this, during the operation, so that they can plan the resection and ensure adequate margins when they put the staples across the lung. Many people are using hook wire localization, I am very familiar with it, is a well-tested method and in the past, we have also been using this. But the problem with it is, when you have more than one lesions, multiple lesions, you start to have lots of wires sticking out of the patient and some of them can get dislodged, when you have one lung ventilation during the anaesthesia. Then, people started to develop the use of marking from inside from the airway side and tattooing the lung much like what other specialties do in for example colonoscopy, where they tattoo the colon where they suspect where the tumour is, so that the surgeon can do the appropriate laparoscopic colectomy, has been developed in the lung as well. So, we are now tattooing and dye marking nodules in order to localise it. In our centre, we do it using a electromagnetic navigational platform like this. It's easy to use but it's expensive technology and it's another level of technology that you know that adds complexity to the surgery. And we do it in a hybrid operating room. And once you inject it you may see the dye already, but if you use ICG with it as well, then when you turn on the near infrared camera, you will also be able to see the fluorescence of this dye. And this is with the fluorescence near infrared and this is with just normal light. We'd like to actually dye mark a very small distinct area. So, this is a standard ring grasper, this is about 1.5 cm in length, this hole and the length of this marking is about 1.5 cm and we don't want a hole, we don't want a large area to be marked and we want to be very precise. We've developed additional ways to mark deep nodules. So, this is a deeper nodule. We dye mark the surface of the lung, so we can see where it is on the surface and we put a metallic fiducial marker at the deep margin, where we want the resection line to be at. And during the operation, as you saw here, we're able to use a fluoroscopy, to make sure that the deep metallic marker is on the side of the resection specimen. So, we have gone deep to the marker to ensure that we have the 1 cm margin, that we desire. This is particularly useful when we have a very deep nodule. We've gone to even greater lengths and more expense if you like, to some of us and those in Europe and America, to use a robotic bronchoscope to get to these nodules, to dye mark them to put down fiducial markers, in order for us to very accurately see them in the operation to give the best surgery and to get the best margins. And you can see here in this left lower lobe ground glass opacity, which is near the intersegmental line, between the apical segment and the basal segment, of the left lower lobe, we are marking it out so that we can do a better segmentectomy. First with a cone beam CT followed by robotic bronchoscopy that guides us and takes us to the lesion. Using this bronchoscope is very easy, it's like playing a game console, you can see there with a control just now. And once we get there, we use imaging to confirm that we are actually at the lesion itself or where we want to be adjacent to lesion. We inject the dye that you can see here, that's blue. And then, we confirm again with fluoroscopy and CT, that we deposit another deep metallic marker. During the operation, we will see the lesion just now and we would, during the segmentectomy in fact, we would make sure that we include the deep metallic marker which marks the proximal margin of the lesion and at the end we have an apical segment, which is very close to the basal segmental plane, but includes the deep margin, as marked by the metallic marker, with this fluoroscopic image of the segment afterwards. Very complicated and very time-consuming and very expensive. And all these tools are very costly to run and very costly to maintain and it can drive you a little bit crazy as well, as you can see here. And interestingly enough, you know, as many of you have seen this guy on TikTok and YouTube, you know a lot of people are kind of making things more complicated in some ways and this guy is kind of taking the mickey and saying like, you know, why is everything so complicated? Can we make things less complicated and simple? Well, now, recently actually this year, earlier, there's been new development in the localization of nodules and you may

be able to do that with just one single injection just before the operation. So, this is on target laboratories and the product is called Cytalux and basically, you give an intravenous injection, just moments before you can do your surgery and because of the marker that is specific to lung cancer, that they have together with a fluorescent dye, that's attached to that marker, that marker will actually be taken up and attached to tumours within the lung. And in fact, what you saw there on the left-hand side, was really an near-infrared image, of the operation of identifying the lesion. So, no navigational bronchoscopy, no messy injections from the endo bronchial root, no hook wire localizations, just one intravenous injection, very shortly before operation, it will be able to... allow you to see a lesion as small as this, that you can see here on the right, that is this small on the CT scan, that pretty much had no activity on a PET scan and can be localised. And as you can see here on the video, in fact, this particular product supposedly cNged the surgical procedure for 29% of the cases, for the surgeon by either identifying additional lesions that they were not aware of in the operation that they may need to wedge out and so on. Vergent is another up and coming bioscience. This company is also developing a very similar product that has a fluorescent property, again, with an agent that will attach to the tumour surface lung cancer tumour surface and that will be able to light up these tumours. So, really in the last sort of 30 minutes or so talk, I have given my perspective on recent developments in the area of "is less the new more for lung cancer," for minimal invasive approach for how much we should resect and also, some new developments in localization. In terms of the access, I think we now have a good perspective randomised trial, to say that VATS has more favourable clinical outcomes than open lung surgery this is after almost 30 years, since our first VATS lobectomy using a single stable technique in the 1990s. And segmentectomy has more favourable outcomes than lobectomy up to 2 cm according to these recent randomised studies as well. When you look at the data more carefully and some of non-randomized large studies, wedge resection and other local therapies, may have a role in highly-selected patients with small tumours, possibly with small solid components. And this may be an option for patients to preserve more lung function and preserve more lung parenchyma, because they may develop other tumours in the future or they have already had multiple surgeries in the past. There are new compounds that can be used to localise lung cancers. These are very exciting developments and we may be able to let go of all the expensive and complex equipment that needs training and maintenance and is difficult to use. And interestingly, these chemicals have been shown to often identify more than what we intended them to do by identifying other unsuspecting lung cancers, in the same procedure. So, thank you all very much for kind attention for this talk.

Dr Bertolaccini: Thank you so much, Calvin, for your beautiful talk about the 2023 update on literature. I have some questions to discuss with you. Let's start with the results of the CALGB trial, published last week. In your opinion, wedge resection and anatomical segmentectomy are really comparable, is correct in your opinion to put them in the same group? Or do you prefer an analysis of wedge and an analysis of anatomical segmentectomy?

Prof Ng: Yeah, I think, thanks for the question, Luca. I think most people would prefer a more pure analysis, you know, of segregating the groups, in more well-defined categories. As you saw in the table, the Japanese are really trying to define the groups, not just by even just size, but in terms of the density, because they have produced a lot of data and most of us would tend to agree that there's a good relationship between the aggressiveness of the tumour and the density as well. So, you know, but the design of the study at that time was that they allowed both wedge resections and segmentectomy and in fact in the end, very interestingly it was almost half and half, half wedge resection and half segmentectomy, roughly in that proportion. And it seemed not to show that it was inferior to the lobectomy. But having said that I think a lot of people did point out that the five-year disease-free survival and the overall survival was a little bit lower than the JCOG 0802 trial, they were in the 80s and 90s and I think the CALBG trial was in the 60s or 70s. So, that's something to bear in mind I think, yeah.

Dr Bertolaccini: Thank you so much. The other question is about the RATS uniportal approach. You are one of the fathers of the uniportal technique and you write a lot of papers about this technique. In your opinion, the adding of the robotic approach could decrease the broader adoption of the uniportal VATS technique?

Prof Ng: Yeah, that's again a good question, but I think a lot of people are still using uniportal VATS technique, because the uniportal RATS, the robotic technique, obviously needs the robotic platform that is costly. So, I think until we really have some good data to show that the robotic approach, uniportal or multi-portal, has a significant advantage over uniportal VATS or multi-port VATS, it may be difficult, to have robotic approach uniportal or not, as a widespread adoption, given the costs and the maintenance and so on. There are of course a lot of other robotic systems, are coming out and those robotic systems, in fact, as you know, are not really designed for specifically for single port robotic approach. They are still going towards a multi-port approach. So, looking at those development and the industry, there's certainly not a big drive to go towards a uniportal RATS approach. For us in my hospital the cost of VATS, uniportal VATS, is very low and there's full reimbursement, whereas the patient will have to pay for robotic surgery, so, that is a big downside. I have yet to see it in real life, the uniportal RATS. And I would really love to see that very soon in person, to see its benefits.

Dr Bertolaccini: Thank you so much, Calvin. And the last question is, about the future of thoracic surgery. In your opinion, what will be the future of thoracic surgery? A future with more surgery or a future with less surgery?

Prof Ng: Yeah, I guess you are, kind of asking this question, Luca, because I've put in some elements of treatment, that may be more akin to being used by interventional pulmonologists like ablation and we are pushing towards less traumatic treatments based on the recent movement of lesser resection and so on. We actually in our centre who have adopted this kind of ablation approach and so on, have not seen a drop in lung resection cases. So, it hasn't really taken over in any way our lung resection surgical patients. But we have, actually, have to deal with a lot more referrals of small GGOs and also, patients who are not surgical candidates or very, very high-risk surgical candidates, for consideration of ablative type of therapy. So, it's actually an additional skill and an additional patient population that we are capturing. So, I still do see that lung resection, by the surgical resection means that we know of as of now, would still be the mainstream in the future and we will be doing it better, patients will be getting home earlier, with less complications and less adverse effects, based on the improved platforms. While there'll be an also another development of this kind of endobronchial approach, for highly-select patients who may not be suitable for surgery or who have a very specific pathology or who may have a very specific circumstance, where they have already had multiple lung resections and they can't or they don't want to have anymore. So, we can capture those within our arms as well. So, I do feel this is the future of thoracic surgery, as we know is very secure for sure.

Dr Bertolaccini: Thank you, Calvin. Thank you for your time, for your beautiful presentation. It was a pleasure to be your discussant.

Prof Ng: Thank you very much for the kind invitation to ask me to give this talk.