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Multidisciplinary session on rectal cancer

Prof de Mello: Hello, everyone. My name is Ramon de Mello and I'm very glad here to coordinate this multidisciplinary session on rectal cancer. Today, we have here experts throughout the world that will discuss multidisciplinary, how can we better approach rectal cancer in order to improve the outcomes? And we have two experts that will give their presentation, a Medical Oncologist, Dr Katia Perez, and Radiation Oncologist, Professor Maria Antonietta Gambacorta. So, we'll start with Dr Katia Perez, that will give a view of the Medical Oncologist in rectal cancer and after, we will end-up with Professor Gambacorta, that will give a view of the Radiation Oncologist in rectal cancer treatment. And in the end, we are open to questions and to discuss what you think is pertinent for this section. Katia, please, go ahead.

Dr Perez: Good afternoon, and it's a pleasure to be here today. And my name is Katia Roque Perez, and I'm going to present a review of multidisciplinary management on rectal cancer. Before 2020, there are two different standard treatments for locally advanced rectal cancer, a short-course of radiotherapy or long-course of chemo-radiotherapy, followed by TME surgery and adjuvant chemotherapy for patients with risk factors. While this multi-modal approach has improved the rates of local recurrence, it hasn't had significant effects on the rates of distant recurrence or overall survival. That is how important questions emerge about the benefits of each component of the multimodal approach. The first one, what is the optimal regimen for neoadjuvant radiotherapy, the short-course or the long-course? In Poland, Bujkio et al. compared pre-operatively short-course of radiotherapy, followed by surgery within seven days. With long-course of chemo-radiotherapy, followed by surgery in four to six weeks. The overall survival, disease-free survival, and local recurrence at four years were similar between the two groups. However, patients who received the long-course had higher pathologic complete response, with 16% versus 0.7%. Also, the Trans-Tasman Radiation Oncology Group compared preoperatively short-course of radiotherapy and long-course of chemo-radiotherapy in patients with T3 tumours. No significant difference in oncology outcomes were reported, but patients with short-course of radiotherapy had a higher rate of local recurrence with 7% versus 4%, and lower rate of pathologic complete response, with 1% versus 15%. At this point, we have one more question. What is the prognosis by lieu of pathologic complete response? A meta-analysis identified 27 articles based on 17 different data sets for long-term outcomes of patients with and without pathologic complete response. Primary outcome was five-year disease-free survival, and it was 83% for patients with pathologic complete response versus 65% for patients without pathologic complete response. Also, they have better long-term outcome, like locoregional recurrence, distant recurrence, and overall survival. It might be indicative of pathologic complete response a prognosis of favourable factor in local advanced rectal cancer. But what happens if we delay surgery? Optimal dosing and time to surgery were investigated in the Stockholm III non-inferiority trial. 840 patients with resectable rectal cancer were divided in three groups. Short-course of chemo-radiotherapy with immediate surgery, short-course of chemo-radiotherapy with surgery four to six weeks later, and long-course of chemo-radiotherapy. This outcome didn't interfere between the two groups,

but patients who underwent short-course of radiotherapy with delayed surgery, had a lower rate of post-operative complications, greater tumour regression, and a higher rate of pathologic complete percent, with 11% versus 1%, than patients with immediate surgery. Therefore, short-course of radiotherapy with delayed surgery is a viable alternative to long-course of chemo-radiotherapy. But what happened about chemotherapy? The Polish trial evaluated short-course of radiotherapy and consolidation of chemotherapy versus chemo-radiation with fluorouracil and oxaliplatin in rectal cancers with clinical T4 or 3. With a median follow-up of seven years, there was no difference in local and distant recurrence, disease-free-survival and overall survival. But, the group of short-course has less acute toxicity with similar pathologic complete response and proficient surgery. With a benefit of chemotherapy in adjuvant setting, do all patients need radiation? The phase II PROSPECT trial is currently investigating selective radiotherapy in patients with intermediate-risk who are eligible for a sphincter-preserving treatment. In the selective arm, patients received six cycles of neoadjuvant FOLFOX, followed with the responsible regimen with proctoscopy and magnetic resonance. Those with more than 20%, then surgery, patients with less than 20% received chemo-radiotherapy concurrent, and surgery. The data is awaiting validation, but is a promising study. Okay, at this point, the concept of total neoadjuvant therapy arrived. Neoadjuvant chemotherapy can be given either before chemo-radiotherapy as induction treatment, or after as consolidation, but both prior to surgical resection. These studies have outlined the effectiveness of chemotherapy in different time. The Spanish III, a phase II trial, which compared induction chemotherapy versus long-course of chemo-radiotherapy, the results showed no significant difference in disease outcomes, but a lower toxicity and improved compliance of treatment with induction are compared with the adjuvant chemotherapy were reported. On the other hand, the use of consolidation chemotherapy was explored in this multi-centre trial conducted by Garcia-Aguilar. There were four arms. The group one had total mesorectal excision six to eight weeks after chemo-radiation. Groups two to four received two, four or six cycles of FOLFOX respectively between chemo-radiation, and total mesorectal excision. They demonstrated good tolerance and significantly higher pathologic complete response in patients who received chemotherapy, with 38% for patients who received six cycles of FOLFOX. No difference in a sphincter saving surgery, R0 resection, technical difficulty, and grade 3-4 operative complications were reported. So, what is the optimal sequence of chemotherapy before or after concurrence? In the CAO/ARO phase II trial, patients with a stage 2 or 3 were assigned to group A for induction chemotherapy, or to group B for consolidation chemotherapy after concurrence with FOLFOX. Primary endpoint was pathologic complete response. In the intention-to-treat population, pathologic complete response was achieved in 17% in group A, and in 25% in group B, which is significantly higher for group B. Also, less grade 3-4 toxicities and better compliance during concurrence were reported for this group. However, we have to emphasise that the time delay for surgery in group B was the double than in group A. In ESCO 2020, Rapido phase III trial was presented. 920 patients with high-risk of rectal cancer where randomized to either short-course of radiotherapy followed with vast systemic consolidation with six cycles of CAPOX, or nine cycles of FOLFOX and TME surgery versus traditional long-concurrence, followed with the TME surgery. The primary endpoint was three-year disease-related treatment failure, defined as first occurrence of locoregional failure, distant metastases, new primary colorectal tumour, or treatment-related death. Disease-related death failure was 23% in the experimental group, versus 30% in the control-arm with a significant difference. Also, patients in the TNT arm achieve a higher pathologic complete response with 28% versus 14% and a lower three-year rate of distant recurrence with 20% versus 27%. The Prodige-23 phase III multi-centred trial, randomized 461 patients into arms, to either six cycles of FOLFIRINOX followed by chemo-radiation, surgery, and three months of adjuvant chemotherapy or adjuvant chemo-radiation followed by surgery and six months of adjuvant chemotherapy. Primary endpoint was three-year disease-free survival. Patients in the TNT arm had a higher rate of pathologic complete response with 28% versus 12%, higher rate of disease-free survival at three years with 76% versus 69%, unless distant recurrence, with 21% versus 28%. No difference in local recurrence or overall survival were reported. In conclusion, the ability to reduce the risk of systemic recurrence, the increased rates of pathologic and clinical complete response with TNT have opened opportunities in selected patients. Finally, based in patients with pathologic complete

response have excellent oncologic outcomes. Can surgery be avoided in patients with no clinical evidence of disease following adjuvant therapy? The Watch-and-Wait has been studied most extensively by Dr Habr-Gama's group in Sao Paulo. They reported that patients with resectable distal rectal cancer were offered a strict surveillance if they had complete clinical response based on magnetic resonance and endoscopy one-year after completion of chemo-radiotherapy. Complete clinical response was found in 27% of patients, and those patients were able to avoid TME. Locoregional recurrence was found in 25% of those patients, all of one underwent successful salvaged surgery. Other studies demonstrate high-rates of rectum preservation and successful salvage of local recurrence, but they were admitted by a small sample size, the heterogeneity of the study populations, and relatively short follow-up. Herein, we show a retrospective analysis of an international database of about 1000 rectal cancer patients managed with Watch-and-Wait approach. With similar report, 25% of patients had a local regrowth after a median follow-up of three-years, and only 8% of patients presented distant recurrence. What is more, 88% of recurrences were diagnosed within the first two years. And 97% was located in the bowel wall. Accordingly, surgical resection may be avoided in some patients. The final message, multidisciplinary management is essential. Pathologic complete response is now a prognostic factor. Neoadjuvant chemotherapy is now validated in local advanced rectal cancer. TNT approach offers an improvement in the rate of pathologic complete response, and treatment has been selected accordingly with risk factors of the patients. That's all. Thank you.

Prof de Mello: Thank you very much, Katia. It was a very nice overview of the Medical Oncologist's role in rectal cancer. Dr Zahel Lakkis, our surgeon that is also participating in this section here, will have the opportunity to comment in the end. I would like to ask now Professor Gambacorta from Rome, Italy, a city which I like very much, and I have been there 10 times, so, to talk about the Radiation Oncologist overview.

Prof Gambacorta: Okay. Thank you very much, Dr Bezerra, and thank you very much, Katia Roque Perez, for this very nice presentation. So, I'm just going to point out some aspects of the radiotherapy treatment. So, we know right now that the standard treatment to cure rectal cancer, they're presented by the TME surgery, okay. And radiotherapy and chemotherapy can be delivered before or after surgery, trying to improve oncological outcomes and to improve also quality of life. As Dr Perez showed us, we have two main ways to deliver radiotherapy, which is the short-course followed by immediate surgery, with surgery delivered in the week after the end of radiotherapy, which lasts five days And it is finished in one week, and long-course chemo-radiation, where you use smaller daily dose of radiotherapy delivered in five weeks to a dose between 45 and 50, together with concomitant chemotherapy, and then you have to wait between six to eight weeks before delivering surgery. So, this was the topic of the so-called the first-generation study. This first-generation study was started with short-course, it was compared with surgery alone, and where long-course pre-operative chemo-radiation was compared with post-operative chemo-radiation, or pre-operative radiotherapy. The aim was to see if there was an increase on long-term outcomes, and the trial that radiotherapy or chemo-radiation compared to radiotherapy alone, increased the rate of local control. However, they did not increase the disease-free survival or overall survival, except in two trials. The first one is the Swedish trial, which was a trial in which surgery was delivered without total mesorectal excision. So, it was before the introduction of total mesorectal excision, and the second is the Dutch trial, which is a trial which was conducted in patients with unresectable tumours. So, the first take home-message is that pre-operative radiotherapy or pre-operative chemo-radiation delivered together with surgery, which is the corrective treatment in rectal cancer, increase the local control. The other thing I wanted to say, going back to the previous slide is that with the short-course radiotherapy followed by immediate surgery, you can obtain an increased local control, whereas we deliver pre-operative chemo-radiation followed by delayed surgery for two reasons. The first one is because you intensify, and the second one is because you wait for the down-staging of the tumour, you also can achieve a down-staging. And down-staging, it is important for two reasons. First of all, is to improve the outcomes of the patients, in fact, you know, that a tumour in the mesorectal fascia or when you have positive resection margins after surgery, these may decrease long-term outcomes in terms of local recurrence, metastases, and overall survival. So, you know that when you deliver

pre-operative chemo-radiation, we delay surgery. You obtain down-staging [and downsizing of] the tumour which moves from the mesorectal fascia. So, in that case, we can obtain more resection with negative circumferential resection margin. And this may improve the local control, may decrease the distant metastases, and may improve the overall survival. And this was demonstrated in the Swedish trial. This is a focus on the Swedish trial, which was a trial in where there was an increase of local control, distant metastases, and cancer specific survival for those patients who received chemo-radiation therapy, [compared to those who received preoperative radiotherapy alone], who obtained a higher rate of R0 resection. So, pre-operative chemo-radiation by providing down-staging of the tumour, give the possibility to have a higher R0 resection and long-term outcomes. Not only local control, but also distant metastases. On the other hand, if we think to this first-generation trial, you know that a tumour can shrink also in the length. So, in the tumour length, and in the case the tumour moves away from the anorectal junction, the patients can receive a surgery with the preservation of their sphincter. However, in randomised trials, [no advantage was demonstrated] in sphincter preservation in those patients who received pre-operative chemo-radiation. But… if you have any question, please chat on the chat box. But what happened with these studies? that we faced the pathological complete response. So, we have seen that in a, which is around 20% in local advanced rectal cancer and may achieve 40% in earlier cancers. So, early T3 tumours or T2 tumours, patients who achieve a pathological complete response and as Katia already showed in her presentation, patients who had a pathologic complete response to pre-operative chemo-radiation have also better long-term outcomes in terms of local control, distant metastases, disease-free, and overall survival. So, the second-generation studies on pre-operative treatments, especially those studies with long-course chemo-radiation concentrated to intensified treatment. How? By the addition of oxaliplatin. So, in 2000, we faced studies in which oxaliplatin was added to 5FU in pre-operative chemo-radiation with the aim to improve pCR, and also to improve DFS, disease-free survival. As you can see, they failed to demonstrate the effect of oxaliplatin, except [two trials], the Chinese and especially the German trial, which has an increase of pCR, and also increase of DFS. And they explained these results, either by less acute toxicity and better compliance of the patients. So, they reduced the number of doses of oxaliplatin, and also, they reduced the dose of oxaliplatin delivered. And by this method, they had less acute toxicity and better compliance of patients, and this resulted in better short-term and long-term outcomes. This increase of pCR, since pCR means better long-term outcomes, led to put in place trials and nowadays, since 2015 up to now, we are facing a lot of trials which are trying to avoid surgery. So, trials and organ preservation that can be done with a Watch-and-wait approach, or with a local excision. And already, as Dr Perez showed, for example, for the Watch-and-Wait approach, we have very good results because, we know that of 20% of patients with complete response, 25% have a re-growth, but this re-growth is salvageable, and this salvage surgery leads to a very high-rate of overall survival and disease-free survival. It has also been seen that patients with complete response have a very low rate of distance metastases, even though you have to be careful because patients with local regrowth may have a higher-risk of distant metastases compared to those patients who maintain a clinical complete response over time. So, the idea is now how to increase the rate of patients with clinical complete response with complete response? Is the chemotherapy intensification. And as Dr Perez showed us, we are moving to the total neoadjuvant therapy, where we have seen that it seems to be better, the consolidation chemotherapy, so, chemotherapy after radiotherapy, than neoadjuvant chemotherapy. So, it is better to consolidate instead of using chemotherapy before radiotherapy or chemo-radiation. The second way to improve is the dose escalation, which was mentioned again by Dr Perez, was to increase the time between the end of radiotherapy and surgery and we're facing several trials also of chemo-radiation also moving from local advanced rectal cancer to early tumours. So, I will skip the chemotherapy intensification because Dr Perez already showed us a lot of results and we will move to the dose escalation in radiotherapy. As a radiation oncologist, we know that the higher is the dose, the higher is the tumour response on one hand, and the higher and bigger is the volume of tumour, the higher is the dose that you have to deliver. So, but which is the dose that we should deliver? It's been seen that to obtain a complete response in 50% of patients you have to deliver really high doses up to 90 Gy. You have to think that nowadays the dose that we deliver

in pre-operative radiotherapy of chemo-radiation, the standard is between 45 to 50 Gy. In even more cases, we can arrive up to 55 Gy and now there are some trials arriving up to 60 Gy. [Audio Not Clear] it's more than 60 Gy. You can have a higher rate of pathological complete response with the same rate of acute toxicity. And how we can improve the dose? In two ways. One way is called intensity modulated radiotherapy, I will show you later how it works, by which we can direct different doses to the targets according to the tumour burden, [So that] we can treat the volume where we think there are microscopic tumour cells with lower dose and at the same time we can deliver higher dose on what we call the GTV, the gross tumour volume, the macroscopic tumour, but we also achieve even higher doses by using local therapies, one of these is brachytherapy. So, it is a radiotherapy technique where you put the source, the radiation source, with an applicator directly in contact with the tumour. The contact therapy, which is a surface, a sort of surface radiotherapy, where you deliver very high doses of low energy x-rays, and you can remove the tumour layer by layer. And with this technique, you have very few acute toxicities because you just irradiate the tumour, avoiding completely the normal tissues. On the other hand, there is the time. This is a meta-analysis that we have done on, I think, seven randomised trials run in Europe to measure the rate of pathological complete response. According to time, we have seen that 95% of pCR appears after 10 weeks, and after the 16th week we have a plateau. So, if you want to wait for a higher number of pCR you have to wait more than 10 weeks, this is the message after pre-operative chemo-radiation. Then, I want to finish with the advances in radiotherapy. So, I don't know if you, in the audience, I don't think that you are all Radiation Oncologists, but you know that when nowadays, Radiation Oncologists, when we talk about radiotherapy delivery, we talk about the intensity modulated radiotherapy, or volumetric modulated radiotherapy, which is a way to modulate, to decrease the dose to the organ at risk and to modulate the dose inside the different volumes that we irradiate. The second advance that we had was the on-board imaging. You know, that we as Radiation Oncologists, we work with imaging because we have to point our rays on the target, so we have to work with images. And nowadays, we have the possibility to see the tumour, we don't use imaging only for the planning, but we use the imaging also during the treatment. And I will show you, which are the on-board imaging that nowadays we have available on our machines to see the tumour while we irradiate it. And the third one is, and this may help you, to adapt radiotherapy. That means that we do not decide the radiation dose at the beginning of the treatment, but that we can modulate the dose according to the tumour response during the treatment, and I will use three examples. The first one, this is what we call intensity modulated radiotherapy. In the 3D radiotherapy the target volume is included is all included in the field, however part of the organs at risk, they are included in the high-dose of radiotherapy. While in intensity modulation of radiotherapy dose, we can spare the organs at risk, especially those which are located inside the target volume. We can modulate the dose on the tumours, giving less dose where we want to eradicate microscopic tumour cells and higher dosing where the tumour is present. Okay? The second thing is this one. This is the image-guided radiotherapy. Nowadays, we have available in our department this machine which are more and more spread around the world, which is a hybrid machine in which we have a linear accelerator together with an MRI. It is called MRI-LINAC By this, we can see the tumour during each [fraction] how it moves. The blue line is if the tumour goes out of the blue one, the machine stops delivering the dose. This means that you can spare the organ at risk and you can decrease the margin around the tumour. Today, the patient can see where the tumour is. So, especially not in the case of rectal cancer, but especially for those tumours, which are located in the liver or in the lung, they can control their breath to let the tumour stay inside the blue line. And we also can see what happens through the treatment. So, you can see, this is the tumour at the first week of treatment, second, third, fourth, fifth, and at the end of the treatment. You can see that the tumour shrinks during the treatment. Moreover, you know that nowadays we have radiomics. Radiomics is a way to read quantitatively, I don't know how to say it, the MRI images. So, for example, in this case, looking at the shrinkage of the tumour and measuring radiomics at certain time, what we can do is that we can adapt the dose according to the prevision of the tumour response. And this is a trial, it is a mono-centric trial phase II that we are running in our institution with this MRI_LINAC, patients with rectal cancer, with intermediate-stage of rectal cancer. So, T2, T2 N1, or T3 N0 N1, or T4 N0. [These patients] are treated with pre-operative

chemo-radiation. Then, at the second week, we go to measure volume and we do radiomics on the image, and we do the Delta radiomics between the start and the treatment at two weeks. So, if we see that the tumour responds, we have a high chance of complete response. If this is the case, the patient can continue with the dose they started at the beginning. If we can, if our prevision is that the tumour will not achieve a complete response, we deliver a boost during the treatment, we arrive up to 60 Gy. That means that we modulate the dose, according to the tumour response. So, we adapt the treatment to the tumour's behaviour right during the treatment. So, that's just to say that my take-home message on the role of radiotherapy is that we know that radiotherapy nowadays increases local control, and as Katia showed, the complete response after chemo-radiation is related to better outcomes. And in those patients, we are trying to avoid surgery to improve quality of life. And the way to increase the complete response is done by intensification, so TNT, or radiotherapy dose, or we may also increase the lag, the time between the end of pre-operative treatment and that from the Radiation Oncologists point of view, and that from the Radiation Oncologists point of view, I wanted to show you new technologies that may help us to according to tumour response. So, thank you very much for your attention.

Prof de Mello: Thank you very much, Maria. It was a very, very nice presentation. I think we have a very good overview of how we can deal with rectal cancer's patients in a multi-disciplinary way. I would like to give the word to Professor Zahel Lakkis to understand a little bit his perception as a surgeon, how we can place chemo-radiation therapy before, after. I would like to hear a little bit about your opinion regarding TNT strategies to treat patients. So, please, give us your thoughts.

Dr Lakkis: Thank you, Ramon. First, I would like to congratulate both presentations because it was very, very good quality of slides. And I learned a lot about new technologies in radiotherapy, so, thank you very much. Before questions, maybe, I have just a comment. Here in France, we have adopted the Prodige-23 trial. In fact, very few centres use the Rapido protocol there are a lot of reasons, but as a surgeon, when now I have to explain to a patient that he will have to have three months of chemotherapy, then one month, five weeks of radiotherapy, then wait two months, then surgery, then he has to recover from surgery, then three months of chemotherapy, then, you have to close the stoma. So, for more and more young patients especially, who have to support a TNT, we are talking about a one-year protocol in fact, and it's not a question, it's just a remark that in some cases it could be very difficult for the patients to stop any work, any social life almost. So, it was just my comment, but the results are very, very good. In fact, we are improving the survival of the patient and now we have, and this is my really concern, my main concern, we have now almost 30% of complete response when we do a TME. So, my question would be maybe for both, how could we now maybe avoid 30% of unnecessary TME in patients with T3 N0 or T2 N1 patients, should we still perform a TME for all patients with a suspicion of clinical complete response after TNT protocols? What is your opinion about that? Because I think that as a surgeon, I'm doing 30% of almost unnecessary surgeries.

Prof de Mello: Maria and Katia, do you want to talk?

Prof Gambacorta: Go Katia, go Katia.

Dr Perez: Okay. In ESCO 2020, they presented the preliminary results of the trial, which is a phase III, evaluating a stage 2 or 3 rectal cancer, who received a total neoadjuvant and FOLFOX or CAPOX as induction or consolidation therapy, followed by watch-and-wait approach with one-year of follow-up. We have now results, preliminary results, at two-years of follow-up, which show 58% of patients in the consolidation arm have a sphincter preservation. And there are promising results, and we are waiting for more data. But I think that watch-and-wait is a good alternative for patients with distal rectal cancer and very young patients, which quality of life is a priority to develop.

Prof de Mello: Maria, what do you think?

Prof Gambacorta: I agree, because there is 30% of patients who achieve a complete response, but on the other hand, there are 70% of patients who do not. So, these patients receive very long, long treatment and then at the end, they finish to have a TME, so, we have to consider both. What is, in my opinion, is that we have to pursue we have to, in case the question of Dr Lakkis was, in these patients with complete response, do we have to avoid TME? I think, yes. However, I think that we should, nowadays, we don't have a real tool to preview which will be the patients who will respond. So, this is the way we have to go I think, in the future. So, prediction model, trying to predict who will respond and who will not, because in this case, we can select those patients who will respond and select those patients who will never respond. And in this case, they could directly go to a TME with better functional outcome compared to those patients who receive pre-operative treatment plus TME, together with a long time of treatment. You know? So, I think that the way to go is, to go for a prediction model to try to better select those patients who may be treated with radiotherapy alone, radiotherapy or chemo-radiation, on radiotherapy and chemotherapy to avoid surgery, and those patients in which avoiding all these treatments and go directly to TME because in some T3 N0 patients, TME is enough and they will have also good results, especially those in the mid rectum, or in the high rectum.

Prof de Mello: Yeah. Yeah. I totally agree with you. I think we can be less harmful for the patients and possibly try to predict what kind of response they will have; it will help to get these better decisions in the future.

Dr Lakkis: And maybe, if I can ask you one additional question, I don't know, in your experience, but in mine, we have more and more younger patients than 5, 10 or 15 years ago. And in my experience, I meet patients with tumours, with mucinous differentiation, and I have the feeling that those tumours don't have the same response with FOLFOX or FOLFIRINOX and even with chemo-radiotherapy, and these patients are the younger, we intensify the treatments, but those tumours are really in bad response. And do you think that we have to more and more intensify the treatments with increasing the dose of radiation? Because those tumours for me, in my practice, are really, really problematic. And I think that we are going to have more and more patients with these kinds of tumours. I don't know why, maybe this is some behaviour changes in our diet, or what, but I think it's really, because those patients were not involved and enrolled in previous trials. 15, 20 years ago, those tumours were very rare. And now, I have a feeling that we are confronting to more and more mucinous tumours.

Prof Gambacorta: To which kind of tumour are you referring?

Dr Lakkis: Tumours with the colorectal differentiation mucinous.

Prof Gambacorta: Ah, the mucinous. These mucinous tumours are very hard to treat.

Dr Lakkis: Yes.

Prof Gambacorta: And they usually develop metastases very early and also in unpredictable places, I saw metastases in the skin, in the kidney, and I really don't know because usually those tumours with a lot of mucins, they do not, sometimes, they do not respond. Other times, they, you find they apparently do not respond, and then on the pathological specimen, you just see mucin and you don't see any tumour cells, but I agree completely with you, which is very difficult. It might be that these patients, since they develop metastases earlier, or in unpredicted places, they could be, it could be given a priority to chemotherapy. I don't know. I don't know if Katia has an idea on how to treat these tumours.

Dr Perez: It's a very complicated to treat tumour. We don't have many cases, but the cases that we have usually with very bulky disease and advanced disease.

Prof de Mello: Actually, mucinous is very, it's not so chemo-sensitive, and it brings us challenges to this type of approach. And so.

Prof Gambacorta: No, usually these tumours are, correct me if I'm wrong, Katia, these tumours have usually the mutation of BRAF, are BRAF mutated, from what is my experience. So, I don't know if in the future we will develop a molecule that goes against this tumour. I think that there are some Medical Oncologists, there are some studies in this way trying to select these patients by the mutational point of view.

Prof de Mello: Yes, I think. All right. I think our time end-up, I would like to congrats everyone that participated here in this multi-disciplinary section for rectal cancer, I think it was exciting to discuss with you several aspects of this disease. That is very hard to treat as we saw here. I'd like to congrats all the speakers, all the panel, here, Dr Perez, Prof Gambacorta, and Prof Lakkis for their participation here. And I wish you a very nice rest of day or night, depending on the part of the globe you are. Thank you.

Dr Perez: Thank you.

Dr Lakkis: Thank you.

Prof Gambacorta: Bye-bye.

Dr Perez: Thank you. Bye.