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Brachytherapy for pediatric tumors

Prof Chargari: Thank you for inviting me to discuss on the place of brachytherapy for paediatric tumour. I'm Professor Cyrus Chargari, a radiation oncologist in Paris, and I have expertise in brachytherapy. There will be a discussion with Professor Pierfrancesco Franco from the University of Eastern Piedmont, Novara, Italy, and with Doctor Luca Tagliaferri, from the Policlinico A Gemelli from Rome. Sorry. Okay. Paediatric cancer are rare tumours accounting for 2% of all the cancers, and among these very rare tumours, soft tissue sarcoma will be the tumour that can be treated with brachytherapy. This is the second cause of death between 5 and 14 years old, and rhabdomyosarcoma accounts for two-thirds of all paediatric sarcoma. It results only 7-8% of solid malignant tumours in the children. The objective in these young patients is dual. It's to achieve, of course, patient cure, with a five-year overall survival probability that is 85%, around 85%. And paediatric rhabdomyosarcoma are characterised by a good response to chemotherapy, high chemo-sensitivity. And in most of the cases, these patients, even in the case of complete response after chemotherapy, will need local treatment. And this local treatment can be surgery, can be radiotherapy or brachytherapy. There is only one exception, this is the exception of female genital tracts. And in specific cases, of vaginal cancer, we can avoid to do local treatment if there is complete clinical, radiological, and histological response at biopsy. But in other cases, in most of the cases, these patients will need a local treatment to achieve a high probability of cure. And I mentioned that this is a duality, because of course we need to cure these patients, but we also need to avoid, and to limit, the long-term functional sequelae, which is quite challenging in very young patients. And therefore, brachytherapy was developed to avoid the mutilation of radical surgery. For example, prostatectomy, in case of bladder prostate rhabdomyosarcoma, or cystectomy, hysterectomy. And we also tried to avoid with brachytherapy the long-term side effects of external beam radiotherapy, especially in the youngest patients. This brachytherapy is proposed as a multi-modal approach, and by combining brachytherapy, catheter placements, and surgery we have some advantages, such as good placements of the brachytherapy catheters. We also can avoid to place the catheter across the high-risk areas, such as the vessels or the nerves. We can also very well define the target volume, as for this perioperative approach, and to decide the dose and the volume to be treated according to the histopathological findings. And finally, we can use this multi-modal approach, this perioperative approach, to proceed with fertility-sparing strategies. There are some limitations of this perioperative strategy. First, this is a complicated organisation. There may be some oedema, some hematoma, that may modify the geometry of the applications. And we also need to manage post-operative complications. Here are four examples of what we can do with brachytherapy in children. The first one is bladder prostate rhabdomyosarcoma, involving the bladder neck and involving the urethra We have on the right a sarcoma, a prepectoral sarcoma and on the bottom of the slide we have two additional examples. On the left, rhabdomyosarcoma of the vagina and on the right, rhabdomyosarcoma involving the mouth floor and with left node extension. All these examples are a good example for brachytherapy. First, have a look on bladder and prostate rhabdomyosarcoma. Sarcoma involving the bladder neck, the trigone, and the prostate, account

for 12% of all rhabdomyosarcoma. The median age is 2.5 years, and these patients are quite very young. And it has been shown in the past that we can achieve, with a multi-modal approach, combining chemotherapy, conservative surgery and radiotherapy, a five-year overall survival of 82% in rhabdomyosarcoma intergroup IV. These patients need local treatment, because it's very complicated to ensure that there will be complete response. And we have seen, in the past, some local relapse in the patients who do not have an effective local treatment, even in the context of complete remission after chemotherapy. And the final decision of brachytherapy in this patient with bladder or prostate rhabdomyosarcoma is taken after chemotherapy, after four to six cycles. And it depends on the tumour size, the tumour locations, the accessibility of the tumour to brachytherapy, and of course, according to extemporaneous examination. You have there an example of bladder prostate rhabdomyosarcoma, the primary site is between the prostate and the bladder neck. This patient has a good response after chemotherapy, as you can see is very challenging to ensure that there will be a complete response. And that's why there is always an indication for local treatment in these patients. And this is an example of a very good indication for interstitial brachytherapy. If the patient has a disease that involves only the prostate, this is in most of the cases a good candidate for brachytherapy. If you have a big region of disease, more than 3 or 4 cm, you may need to have a higher number of catheters, but still, it's possible to do interstitial brachytherapy procedure in these patients. And you have there an example of a good, a very good, radiological response after chemotherapy, that in most of the cases consists of cyclophosphamide, vincristine, and dactinomycin combination. When there is an involvement of the bladder neck, of the bladder, you need to have a good topography of the tumour, meaning that if the disease is involving the bladder neck or the trigone, this is in most of the cases a good candidate for brachytherapy. If there is an extensive disease at the level of the anterior bladder wall, you may combine the partial cystectomy with brachytherapy of the bladder neck. But one challenging aspect of this brachytherapy procedure is that if your patient has an extensive disease in the posterior bladder wall, this anatomic area won't be a good candidate for brachytherapy, because we have some difficulties to implant the posterior bladder neck and the surgeon cannot do a partial cystectomy, a posterior partial cystectomy because you have the nerves of the bladder that are coming at this level, and if you do a dissection of the posterior bladder wall, you will generate neurogenic bladder, meaning that the bladder will not be functioning. This is an example of dose distribution for bladder prostate rhabdomyosarcoma. This patient was treated with four catheters, encompassing the prostate and the bladder neck. The catheters had been implanted according to the Paris system rules. As you can see, these procedures give the possibility to do a very good sparing of the rectum, of the bone structures, and this is a major difference with external beam radiotherapy. You can better spare the critical organs, compared to any other techniques, including proton therapy. Bladder prostate rhabdomyosarcoma are an example of multi-modal approach, with first chemotherapy, and you do the brachytherapy implant to treat the tumour residue at time of brachytherapy. You don't include the whole disease at time of diagnosis, but only the tumour residue after chemotherapy. And you combine conservative surgery, meaning that the surgery does not aim at being complete. We do accept microscopic and macroscopic tumour residue, because brachytherapy will be able to treat this residue with high probability of local control. Sorry. This is an example of a patient with bladder or prostate rhabdomyosarcoma, involving the anterior bladder wall, and involving also the prostate. This patient will be treated with a partial anterior cystectomy, that aims at being complete in its [Audio Not Clear] limit. At the level of the prostate, and at the level of bladder neck, the surgery does not aim at being complete because the strategy aims at treating with brachytherapy what the surgeon has not removed. And this is a conservative approach, because if you are doing conservative... if you're doing a radical surgery, you will remove the prostate and the bladder. By combining this conservative surgery and brachytherapy, you can achieve conservative organ-sparing strategy. You have there an example of the partial anterior cystectomy on the right, this is another example, with a patient having rhabdomyosarcoma involving the bladder neck and urethra. And you can see, this is the perioperative view, with this massive residual disease the surgeon will do a conservative surgery, removing all the macroscopic disease at the level of the bladder neck. This is not a complete surgery; we know that it'll be an incomplete surgery and with brachytherapy we will deliver the treatment at anatomic

level that has not been subject to radical surgery. Here is the perioperative view, after, and you can see the median scale of the cystotomy and the catheters that have been fixed to the external bladder wall. And in the middle of the picture, we can see the transperineal approach, and on the right, a reconstruction of the catheters and the prostate volume and the bladder neck volume and the rectum. We have looked at the long-term urological complications after this conservative local treatment, involving surgery, conservative surgery, and brachytherapy. And this is the experience of Gustave Roussy and the University Hospital Kremlin-Bicetre. And the data were published a few months ago, and we did not identify very strong predictive factors for long-term complications, but it seems that the younger age at the operation and the dissection of the posterior bladder wall were associated with higher probability of long-term complications. And this is on the right, the example of what is challenging in patients who have a very bulky disease or who have an involvement of the posterior bladder wall. If you want, sorry, if you want to remove this tumour, you will generate neurogenic bladder, because the innervation of the bladder is at this level, and these patients had non-functioning bladder after a conservative treatment, meaning that this was a failure of the conservative approach. Don't forget that it is important to perform conservation of the fertility, and these patients, young boys and young girls treated with brachytherapy, require in most of the cases a transposition of the gonads, testicular transposition or ovarian transposition to decrease the dose to the gonads and to allow, potentially, to keep fertility. We did the comparison between brachytherapy and proton therapy, and to do this comparison we did examine the dose distribution for treatment with VMAT and proton therapy, delivering 50 Gy to the PTV. For brachytherapy procedure in Gustave Roussy, the dose is 60 Gy, delivered through only pulses of 4.42 Gy, 10 Gy per day, up to 60 Gy to the CTV, without any additional margin from PTV. Of course, we consider brachytherapy, and as you can see, we compare 60 Gy of brachy and 50 Gy of EBRT with protons or VMAT. And what can be easily seen in this slide is that with brachytherapy, we have better sparing of the normal structures. We decrease the volume of the patients receiving low to intermittent dose. We increase the dose of the tumour, obviously, the dose delivered to the tumour, and we have a much better sparing of the bone tissues with brachytherapy, even if the dose was higher, the prescription dose was higher with brachytherapy. To look into the details in terms of numbers, what we can see in this table is that, the isodose volume was... the volume of the isodose, of the 20 Gy isodose was much lower with brachytherapy, 300 cc, compared to 900 cc with VMAT and 768 cc with protons. This is a very, very big difference, a huge difference for these very young patients. And if we look at the volume of the patients receiving 40 Gy, we also see a significant difference between brachytherapy and proton therapy, with a factor of 3-3.5 between brachy and proton therapy, meaning that with brachytherapy, we can clearly better spare the organs at risk and also decrease the integral dose to the patients, which may have an impact in terms of long-term side effects, but also the probability of second malignancies. If we look at the dose to the rectum for these patients, what we can see is that the mean dose to the rectum was clearly lower with brachytherapy, a ratio two, 23 Gy with 60 Gy of brachytherapy, versus 45 Gy with 50 Gy of proton therapy, and the median dose was also overall. Based on these data, we currently consider that we won't achieve as good sparing of the rectum with any EBRT techniques compared to brachytherapy. Let's see the example of gynaecological rhabdomyosarcoma, vulvar, which are a very rare disease, vaginal sarcoma are more frequent, but also tumour of the cervix that occurs usually in patients earlier than for the vaginal. These tumours count for 8-10% of the female rhabdomyosarcoma, and the median age is 2.5 years. And we have a very high probability of overall survival in these very young patients. Meaning that it's very important to be as conservative as possible. And this is the example of the importance of brachytherapy to treat only the tumour residual. And before the nineties, we were treating the initial disease, after 1990, it was thought that if we treat only the tumour residue, we have the same probability of local control and much less morbidity. The final decision to do brachytherapy is taken after four to six cycles and it takes into account size and the locations. If the disease is involving the cervix, we try to avoid to do brachytherapy, and we do conservative surgery, conization, or trachelectomy. If the disease is involving the vagina, especially the lower third of the vagina, brachytherapy would be the best opportunity to keep the organ and to keep the function and to minimise the risk of long-term complications. There are on the right two example of bulky tumours, and in

most of the cases, rhabdomyosarcoma of the vagina are very rare disease at the diagnosis, but with a very good response to chemotherapy. This is an example of this brachytherapy treatment, with a gynaecological examination that is of course performed under general anaesthesia to very well see the extent of the disease. We can also do vaginal impression, and as we can see, we can also identify some multifocal disease. Then we use a vaginal mode applicator which is tailored to each patient's anatomy and each tumour topography. And then, after chemotherapy, this mould is inserted into the vagina under general anaesthesia, and then, we deliver the dose to few millimetres, 2 to 3 mm depending on the case, to treat the vaginal wall. Sometimes we also need to insert a catheter inside the cervix, as on the example on the right, or to implant interstitial needles. But in most of the cases, these tumours are not very infiltrative, they are more bulky than infiltrative tumours. The results of brachytherapy in these patients have been published in this cohort of Gustave Roussy, and the median age at the diagnosis was 1.7 years. We had 42 patients with a median follow-up of 15 years, and 98% of the patients were alive at the last follow-up with a very high probability of local control. If we look at the long-term side effects, gynaecological toxicity was observed in 67% of the patients, many represented by vaginal stenosis, and in a few cases we had more severe complications. And if we look at the sexuality of the patients who were in age to have regular activity, to have an activity, sorry, 12 out of 14 declared that they had regular activity. And we also have some patients who gave birth to a child, which is a very, very, very good result in these patients treated at a very young age. If we look at the long-term side effects, the total number of late effects was higher for the period of treatment before 1990. And because these patients had a larger brachy volume, because, as I highlighted, we treated in the past all the vagina, and after 1990 only the residual disease. The cumulative dose is also a factor of complication, and as usual, the brachy volume was also a factor of complication. We looked at the probability of rectal complication according to the dose, and this is to my best knowledge the first dose-effect relationship that has been shown for pelvic paediatrics cancer. And we can identify a tracer that's 55-60 Gy, in terms of rectal complication, and with a PDR or HDR and using the stepping source technology, we can avoid the rectum and optimise dose distribution. The 10% probability of rectal complications of grade-2 or higher was reached for D-0.5cc of 52 Gy, meaning that probably these patients are more radiosensitive than adults, of course but also, we don't deal with the same volume. And D-2cc in very young patients is not really meaningful, not very relevant in terms of complications. That's why we need to look at very small volumes such as D-1cc or D-0.5cc. We can also treat a tumour of the limbs and trunk, and this is an example of the perioperative approach that removed the tumour and with implantation of the catheters, then, we can wait for a few days to have the histopathological results, and the decision in these patients who are referred at time of local relapse for possible brachytherapy, we decided to wait for these results and to do brachytherapy, and to adapt the dose to the histopathological findings. In these patients, we had some residual disease, in spite of good response to chemotherapy, and we decided to do 50 Gy to the operative bed, to focally increase dose to 60 in the area with higher risk for relapse, because of the margin. The largest experience of limbs and trunk rhabdomyosarcoma, brachytherapy for limbs and trunk rhabdomyosarcoma, has been published by colleagues from India, by Dr Laskar, and he published a series of more than 100 patients, with tumours involving the extremities, the trunk, head and neck but also, genitourinary, and in this experience, brachytherapy was performed as the only irradiation modality in most of the cases, with a low dose or high dose of brachytherapy. And as you can see, high probability of local control was achieved and high probability of survival. The prognosis is poorer than for rhabdomyosarcoma, because we have a high number of cases of rhabdomyosarcoma that are associated with a poor prognosis. And there is an example of the long-term side effects, there may be some dystrophic area, but compared to what will be achieved with EBRT or with mutilating surgery, this is for sure better. Let's see the place of brachytherapy for paediatric head and neck tumour. As you probably know, brachytherapy is better than EBRT, to spare the bone structures in head and neck tumours, for selected patients with selected tumours, of course. And the technique for brachytherapy is the same as in adults. The part that we need to be careful to specific aspects of paediatrics, such as very small volume, meaning that the catheters should be not too far from each other, with a spacing of 8-10 mm seems to be optimal. This is an example of a young patient with an alveolar rhabdomyosarcoma of the mouth

floor. She was treated with surgery and with FRET, and there was a positive margin, requiring an adjuvant treatment. And we decided to do an interstitial brachytherapy procedure and as we can see with this process, we can spare the mandibular from irradiation, probably better than what would be achieved with EBRT. Here is an example of the AMORE concept that was developed by colleagues from the Netherlands. And this is a concept that combined an ablative surgery, a mould technique brachytherapy and reconstruction, and all the process is done in one week. For these patients, treated with this conservative approach, the objective is to do a macroscopically complete resection of the tumour and then, to do a mould that will be inserted inside the operative cavity, and then there will be a PDR brachytherapy procedure, to irradiate the potential margin and the cavity, because this is not complete surgery, because of the conservative intent. And then, they do a reconstruction, with a flap to supply some fresh blood, some fresh tissue, and to increase, to improve the healing of these patients. For this AMORE concept, the patients undergo macroscopic radical surgery. As you can see there was a big tumour in the left top-lateral fossa, and then the brachytherapy treats the wound bed that possibly contains some microscopic residual disease. They deliver 40-50 Gy to the CTV, and the dose is prescribed to 5 mm from the mould surface, and it is delivered in four days. Here are the results in the preliminary publications in 2009 for non-orbital rhabdomyosarcoma. The authors published the outcome of 42 patients and the overall survival at five years was around 70%. And when they are looking for the complications by a comparison with another cohort of patients treated with external beam radiotherapy, this is not a direct comparison of two cohorts, but they observe lower probability of severe complications for patients treated according to the AMORE protocol with conservative surgery and brachytherapy, compared to external beam radiotherapy. The largest experience of brachytherapy was produced by colleagues from Gustave Roussy, with more than 300 patients. Median age was 2.2 years, and most of the patients had localised tumours, and they were treated with 2D brachy or 3D brachy with PDR, and most of these patients had bladder prostate rhabdomyosarcoma. This is the outcome of the whole populations with five years local control probability of 91%, which is very high, and the probability was higher among the patients referred at the diagnosis and not referred for brachytherapy at the time of relapse. The five years overall survival probability was 93% and DFS was 84%, and you have the results per tumour site with the best outcome for bladder prostate and gynaecological cancer. We had not a very high number of patients with limbs or trunk sarcoma, and therefore the statistics should be looked carefully, but for again bladder prostate there was a high number of patients. This is the probability of survival without complications grade-3 or more and it was 74% at 10 years, which is quite good. It's not perfect of course, we still need to improve our treatment and to decrease the probability of long-term side effects, but compared to EBRT or to mutilating surgery, it seems to be quite good. The compliance is quite good, because when we published our letter with PDR, we showed that patients have a good compliance, and sometimes we need to re-implant and to replace a catheter, because of a catheter displacement but in most of the cases, the brachytherapy can be done with a very good compliance. To conclude, we have with brachytherapy a high probability of local control, for a conservative intent to treatment, we can combine with fertility-sparing approach and probability of long-term complications is quite low compared to other data based on EBRT. There are some challenges in terms of patient selection, in terms of expertise. Of course, I think that it's mandatory to have a strong experience in adult brachytherapy if you want to do paediatric brachytherapy, this is a rare disease, we need to encourage referral network and to have a very good process in terms of workflow and coordination. And of course, there are some financial aspects because of a very poor reimbursement for brachytherapy in many countries in the world. Thank you for your attention.

Prof Franco: Thanks a lot, Cyrus. It's been an excellent talk and very, very, nice, and an interesting topic. So, we can open the discussion. Luca, do you have any specific aspect you want to start a discussion with?

Dr Tagliaferri: So, thank you. Very clear and very complete lecture, congrats. May I ask you some questions regarding the post-implant procedure? So, you have a very huge experience in PDR approach, and many, many patients are very young, so, I would like to know how we manage the postoperative sedation if the patients need to be under anaesthesia, and the compliance of the patients regarding this topic.

Prof Chargari: Thank you Luca for your question. In terms of catheter placements and control of the placement of the catheters, there are two options. If you do your procedure with a paediatric surgeon, this is an open surgery and you can see where are the catheters placed, surrounding the bladder. If it's not a perioperative strategy, in the example of the mobile tongue or mouth floor, we do the implantation as for adults and if you want, you can use radiograph to control the placement of the catheters. But in most of the cases, we don't need that. We can use, of course, ultrasound, I use the ultrasound to guide the placement of the catheters for perineal or for vaginal disease. And after the placement of the catheters, we wait for few days for bladder prostate rhabdomyosarcoma, because the postoperative time may be complicated, because of the pain, because it's an open surgery, because sometimes there have been a partial cystectomy and the surgeon keeps the patients in intensive care unit for few days, usually for four, five days. And the anaesthesiologist can deal with the pain, I take the patients in my brachy unit, at the time I was in Gustave Roussy, only when the pain is okay, but there is no general anaesthesia for the whole duration of the process. This is just for the placement of the catheter. Then the patient is not anymore sleeping, he's awake and there may be some partial sedation, if there is anxiety, if we don't... if we see that it's not possible because he's not quiet. But based on my experience, we have some patients who are young, but who are familiar with the hospital, because they have been since 3, 4, 5 months at hospital for chemotherapy. And they are not afraid of the nurse, afraid of the doctor. And when we moved from iridium wires to stepping source technology, we were afraid that there will be compliance issues, but there are not compliance issues, or at least very rarely. And with medication for the pain, for the anxiety, we can deliver the treatment, in most of the cases, without immediate difficulty. And these patients are treated in hospital with a paediatrician on board, and every day there is a paediatrician coming for the prescription and to ensure that the patient is fine, is okay.

Dr Tagliaferri: Thank you very much. Very exhaustive answer. I have another question. So, of course PDR are present in centres of excellence in the world, but many brachytherapy centres or interventional radiotherapy centres, as I like to call this technique, have only HDR. So, I would like to know your opinion regarding the use of HDR for young patients and if you have or you can report experience regarding the outcomes in terms of local control, but especially in terms of toxicity, if it's different between HDR and PDR.

Prof Chargari: For HDR, we don't have many, many cohorts of paediatric patients treated with HDR, but we know that, based on what we have seen in adults, we can hope to have the same toxicity profile if we decrease the dose, and by decreasing the dose, I mean not just looking at the acute D-2 and do the calculation. We have some series now from colleagues from UK, from Germany, with good research for bladder prostate sarcoma treated with HDR, and I think that this research still needs to have longer follow-up to ensure that we have the same outcome than for PDR or for HDR, but it seems to be encouraging and I think that this is something that is feasible. The question is not only, do we have access to PDR, I think that the two difficulties with this treatment is that we need to have a whole team involved in these treatments, the surgeon, the brachytherapist, the nurses, the anaesthetist the physicist. And if we have all that, I think that HDR or PDR can be do with the same, maybe, the same results. I prefer PDR in these patients because of the radiological models, we know that it may be better, but we need to still work, you see that our results at Gustave Roussy were quite good, but still, we had some long-term side effects. Maybe we can discuss on how to decrease the dose maybe 60 Gy is high, maybe 50 is enough. This is something that should be done progressively, step-by-step.

Dr Tagliaferri: Thank you. Thank you so much.

Prof Franco: And Cyrus, I would like to ask you, to add another point about the clinical selection of the patient. So, you nicely showed that, for prostate and bladder rhabdomyosarcoma, the choice to offer a patient brachytherapy depends on some clinical characteristics and it's mostly mandatory, while it's optional for gyne patients, and the triggers, the clinical factors that trigger your decision are the location, the size. So, I would like to ask you a bit more details on how you plan, on which patient to offer and to deliver brachytherapy. And the second, the follow-up of the question would be, are there any other, maybe, this is more a research

type of field, elements that can help you in deciding whether to treat or not a patient, coming from molecular biology, coming from radiomics? Are there other elements apart from clinical factors that might trigger your decision? Thank you.

Prof Chargari: Thank you very much for the question. For the bladder prostate, the question of the selection is important, because as you have seen, if we want to do a conservative treatment, if in certain situations, in some circumstances, if we do this conservative treatment and the bladder is not functioning, this is a failure of the conservative treatment. And that's why we have this selection criteria. For the vaginal rhabdomyosarcoma, we may have some big, some bulky disease after chemotherapy, but this bulky disease is usually exophytic and not infiltrative, meaning that we can do a removal of the bulky residual disease without surgery of the vaginal wall, just of the bulky disease inside the vaginal cavity. And then, we can place the catheter. It's very rare that we have extensive disease up to the pelvic wall that would prevent to do a brachytherapy procedure. That's why in these gynaecological tumours, in most of the cases, brachytherapy we prefer to ERBT. For bladder prostate, if we cannot do brachytherapy, we do protons or we do radical surgery, but we prefer to do protons, or photons, EBRT with photons. For gyne, in most of the cases, we can do brachytherapy. For the limbs, there will be some issues, if there is involvement of the wall, of course, this is a contraindication for brachytherapy for me, in any sites. If there is enough nodal involvement, it may be a contraindication to exclusive brachytherapy. We do EBRT and then, brachy boosts, we combine brachy with EBRT. This is the same for anal canal tumours, because of the sensitivity of the anal canal, I don't do exclusive brachytherapy in these settings. And for your second question, the place of molecular patterns in the selection process is unknown. This is something under investigation. We don't have any data in these patients to select the indications based on the molecular profile. The only factors that we take into account are clinical factors or no. But for sure there is some space for improvement to better identify the best patients.

Prof Franco: Yeah. Thank you very much. Thank you very much, Cyrus.

Dr Tagliaferri: So, if we have time, I would like to ask another question. So, when we discuss with surgeon the clinical practise, of course, the surgeon prefers to offer to the patient a surgery more conservative as possible. So, during your lecture you showed that the surgery could be not radical, but it's acceptable also R1 or R2 margin. So, it's acceptable that we have a residual tumour in the treating area. I would like to know, based on your experiences, if the prognosis of the patient is different, if the residual tumour is based on the volume of residual tumour and your personal opinion regarding the limit of the surgery. So, when is important to ask to the surgeon a radical surgery with R0 or R1, or when it's acceptable an R2?

Prof Chargari: This is a good question. I think that what you highlighted is clearly something very important because this is perioperative approach in most of the cases, meaning that you need to work with a surgeon who is familiar with this concept of conservative treatment. We don't have many comparisons between radical surgery and conservative surgeries. We just know from our study that we have a higher probability of survival if we are giving good chemotherapy and conservative surgery compared to radical surgery. But in our experience in Gustave Roussy, we didn't see any difference between those who had R2 and R1 disease. But also, because this is something which is difficult to be examined accurately, because when the surgeon is doing a partial cystectomy and we see the disease is of the bladder neck, we know that it'll be R2, but in many cases it's more difficult than that to make the difference between R1, R2. But we almost never have R0 surgery for bladder prostate, if you are looking at the conservative approach. For the limbs, we can have this discussion, because if the surgery is R0, I don't think it's necessary to do brachytherapy in very good prognosis tumours. But for alveolar histology we still do a treatment, local treatment, because of the high risk of relapse. For R1 and R2, the same. We don't have many comparisons, because in all cohorts of Gustave Roussy we adapt the dose according to this finding. And if we're looking at the outcome of the patient, we cannot, we don't have the data to make the difference in terms of survival between complete, incomplete surgery because all of the patients had an adjuvant treatment because of the uncertainty, is it complete, is it incomplete? It's very difficult for bladder prostate to ensure it's a complete surgery. Or it's mutilating.

Dr Tagliaferri: Thank you very much. Very clear. Thank you.

Prof Franco: Yes. So, thank you both. I think it's about time to close this very interesting session. So, I would like to thank Professor Chargari for the very nicely delivered lecture on this very cogent and interesting topic, and Dr Tagliaferri for the very nice and interesting discussion. Thank you, all the participants for listening to our session and ESO for hosting us.

Prof Chargari: Thank you very much.