Subtitles and transcriptions

Subtitles and transcriptions are available for selected materials for purpose of helping users understand the contents of the educational sessions.

Uncertain words have been indicated with ?? before and after the part. Parts that could not be understood at all have been indicated as [Audio Not Clear].

Every effort has been made to faithfully reproduce the audio of the sessions as recorded. However, no responsibility is accepted for mistakes or omissions. ESO does not endorse any opinions expressed in the presentations.

e-Session n 577 - 17th June 2021

Updates in the diagnosis and treatment of anal cancer

Prof Franco: Welcome and good evening everyone. It's a pleasure to be here in this interesting and exciting e-ESO session. I am Pierfrancesco Franco, I'm a radiation oncologist. I work at the University of Eastern Piedmont, in Novara, Italy. And I have specific interest in lower GI malignancies and anal cancer. So, the topic of today is updates in the diagnosis and treatment of anal cancer. I'm happy to have as a discuss and Dr Berardino De Bari from Neuchatelois, Switzerland and, of course, feel free to ask questions and to contribute to the discussion. We will be more than happy to have your thoughts and opinion on this. So, I will start, trying to share my screen. Yeah, still in presentation mode. So, I think we can start this is the outline of the talk. We will be talking about epidemiology and risk factors in anal cancer. We will briefly touch upon diagnosis and we will mostly focus on the therapeutic option, including both radiotherapy, radiation in general and combination therapy. And we will end up talking and discussing about follow-up, survivorship and quality of life. So, whenever we talk about anal cancer, this is the anatomical region we are dealing with. So, we talking about tumors mostly squamous cell carcinoma, arising within the anal canal and within the anal margin. So, two potential different sub-sites that comprise a unique clinical pathological entity. Anal cancer is a rare disease. So, the incidence is about one to three new cases on 100,000 individuals in Western countries. So, it fits into the definition of rare cancer. However, the overall incidence is growing, both in the male and female gender, it comprises about 2% of the all GI-tract tumors. The female-male ratio favors or unfavors actually females and the median age of diagnosis is around 60 years. If you take a look at the overall numbers, we can see around 20,000 new cases of anal cancer are diagnosed in the male population and a little bit less than 30,000 cases in the female population. And this is like well-described in... if we take a look at the point prevalence and the per-year incidence of anal cancer which is steadily increasing starting from the late '90s, and this increase is ongoing in recent days and actually the steepness of the increase is even higher in these days. The annual percent change has been estimated in being around 7%. And this incidence increase is transversal to all stages, gender and racial groups. It is mainly due to mostly an increased exposure to HPV infection which is one of the most important determinants of the disease, but also, to the longer survival for the subset of patients who are also HIV-positive, due to effective antiretroviral therapy. So, we talk about HPV and HPV is the main cause of actually most of the anal squamous cell carcinoma. This has been seen in different studies. Mostly, the high-risk genotypes which are involved is HPV16 and HPV33. Around 80 to 90% of the patient are HPV-positive patients having squamous cell carcinoma. And actually, HPV positivity is also an independent prognostic factor for both disease-free survival and overall survival. And actually, it's a positive prognostic factor, meaning that HPV-positive disease has better outcome on average than HPV-negative disease. This is determined by a different mutational pattern from HPV-positive to HPV-negative disease. The p16 positive, so, HPV-positive disease is mostly underlying PI3KCA mutation and amplification in some part of the chromosome 11, while p16 negative anal cancer is driven by p53 mutation

and CDK mutational burden. What is interesting is that amongst HPV-positive patients, the presence of tissue infiltrate lymphocyte is also a prognostic factor. So, HPV-positive patients with high TIL level have better prognosis than those having low level of TILs and overall HPV-positive has a better prognosis than HPV-negative patients. A subset of anal cancer patients is also HIV-positive. And so, the question rises on how to treat HIV-positive patients? Offering them, let's say, treatment intensity as HIV-negative patients or de-escalate type of treatment because, of course, of the potential increased toxicity that they may undergo. And actually, there is a problem mostly in terms of hematologic toxicity. So, CD4, so lymphocyte, tend to be more prone to damage of radiosensitivity, but in general if the count is normal and the antiretroviral therapy is effective, on average, HIV-positive patients can undergo same treatment intensity as HIV-negative patients, knowing that we have already some data. This is like nice systematic review coming from Brazil, from South America, telling us that HIV-positive patients tend to have a higher toxicity profile in terms of skin toxicity, in terms of hematologic toxicity, particularly leukopenia and tend to have also, on average, a worse disease-free survival, compared to same stage of HIV-negative patients. What is interesting is also that following chemo-radiation, the time to complete response tend to be longer for HIV-positive patients, compared to HIV-negative patients. So, there is a global effort to join data. Of course, anal cancer is rare and the subset HIV-positive is even like a small subset in this setting. So, collecting data altogether is, of course, an option to be able to find evidence, provide evidence-based clinical information. And so, this is an effort to establish a global register collecting data on clinical outcomes for HIV-infected patients with anal cancer. And this is led by, Professor Rachel Riechelmann, in Brazil. So, of course, feel free to ask questions. We will be more than happy to take it. There are some interesting data and new information on the diagnostic profile for anal cancer. Magnetic resonance imaging is, of course, important is considered a mandatory exam to be taken in anal cancer patients. This is in the ESMO-ESTRO-ESSO guidelines. These are the sequence that are mostly to be taken when working with MRI in anal cancer. So, T2 images mostly on the axial, sagittal, and coronal plane but also, the chance to use diffusion-weighted images which are very helpful. It's also very helpful to have a standardized report, where all the information that the clinician needs to properly stage the disease are present, in terms of dimensional tumor, information, information on deviation parameter, information of lymph nodes. And actually, magnetic resonance imaging is, of course, crucial in staging the local disease. And here, we see some coronal images of T1, T2 and T3 disease. You can see that you can clearly see the anal sphincter. You can clearly see the disease, so, it's very helpful. It's even helpful for, even with a lower level of sensitivity and specificity for nodal staging. And here, we can see nodal involvement in the internal iliac, external iliac and inguinal nodes for anal cancer, but apart from staging, MR is also quite important in the evaluation of treatment response but with T2 images and diffusion-weighted imaging and we can see here on the bottom-right corner a sequence of a patient with an initial diagnosis and a complete response on MR imaging. Taking an MR during treatment, might have prognostic outcomes. So, for example, changes in MR taken in the first two weeks of treatment may be able to be prognosticator in this setting of patients, so, also MR being able to be a biomarker in this setting of patients. Another interesting diagnostic novelty is the use of narrow-band imaging. What is narrow-band imaging? This is if someone of you is exposed to head and neck cancer, this is the same technique that is used to explore the mucosal layer in head and neck cancer. So, basically, it's an optical technology which helps to visualize the vascular and the mucosal pattern of visceral organs and compared to white light endoscopy, the visions are more clear, less blur and the probability of missing a lesion is reduced. And there's good data on the use of narrow-band imaging in anal cancer, particularly, in pre-cancerous lesions, for example, high grade dysplasia or condyloma. So, in the monitoring of pre-cancerous lesions, this is a very useful technique and there's a prospective study going on in the US and Europe. So, shifting from diagnosis to treatment, this is a sort of outline of all the trials and studies, prospective studies that established the standard of care in cancer with the first-generation trial, establishing the superiority of concurrent chemo-radiation with 5-FU and mitomycin over radiation alone. And then the second-generation trial, trying to prove the benefit of the addition of induction chemotherapy or maintenance chemotherapy, which basically failed to demonstrate a benefit. And then, the RTOG, more recently the RTOG 05-29 trial, trying to explore the use of IMRT in anal cancer. And then, the trial exploring

the use of capecitabine over 5-FU, infusion of 5-FU in the setting of patients. So, the standard of care was set with the ACT UK trial and the EORTC trial, establishing the superiority of chemo-radiation over radiation alone, with an improvement in local control and colostomy-free survival, paying the price, of course, of an increased acute toxicity profile. The second generations trial, basically, failed to change the standard of care. So, the withdrawal of mitomycin-C was detrimental with respect to outcome, this is the RTOG 87-04 trial. Induction chemotherapy failed to prove an improvement in oncological outcomes in the RTOG 98-11 trial and the French trial. And again, maintenance therapy failed to prove superiority with respect to standard of care in the UK trial. So, still the standard of care, remains concurrent chemoradiation with 5-FU or capecitabine and mitomycin C. But of course, this standard of care can be declined in different ways. And for example, mitomycin C in the US is used with two cycles. In Europe and in the UK, in particular, is used with only one cycle. And actually, it appears that only one cycle of mitomycin C, the first cycle of mitomycin C is sufficient to provide good clinical outcomes. And adding a second cycle, probably, only increases the acute toxicity profile. Instead, of 5-FU infusion, there's also the chance to use oral fluoropyrimidines, basically, capecitabine. And this has been...the safety of this approach has been proved in several phase I-II prospective trials and also, in multicentric retrospective and prospective observational studies. And here, we have the data collection of the UK, where the combination of radiotherapy-capecitabine and mitomycin C was proven to be safe, to have similar level of overall major toxicity as compared to 5-FU and mitomycin C but probably, with a different pattern of toxicity, in particularly, with less hematological toxicity, compared to infusion of 5-FU. Another field of investigation was the addition to the standard of care in 5-FU and mitomycin C of EGFR inhibitors, basically, cetuximab as was done, for example, in head and neck cancer or also, panitumumab, that basically failed to prove efficacy in terms of oncological outcomes, conversely increasing the toxicity profile, particularly, skin toxicity. So, basically, EGFR inhibition and inhibitors weren't proven to be effective in this setting and were basically abandoned outside clinical trials. So, they are not definitely standard of care. If we go back to radiation, if we focus on radiation, there's a robust and important heterogeneity in terms of dose-prescription in anal cancer patients. And here, I summarize the different guidelines present, the ESMO-ESSO-ESTRO guidelines, NCCN, the French Intergroup guidelines in the UK, in terms of prescription for early-stage disease and for locally advanced disease. And you see there's quite a range of variety in terms of prescription-dose to the primary tumor, to the nodes and to the elective volumes. So, I think this is a field where the international community should put an effort to try to harmonize and provide the homogeneity in the prescription-dose. Again, please feel free to ask questions. We will be more than happy to take it. Whenever we talk about dose and we acknowledged the fact that the prescription-doses are heterogenous and really depends on the nations but also, on the hospitals. But we know that, probably, we are dealing with two different scenarios. So, early-stage disease is basically kind of different from locally advanced disease. And if you take a look at the curves here, which are basically dose-response curves, so, tumor-control probability curves, you see that the position of the curve is quite different between early-stage disease and locally advanced disease. So, to have the same chance of local control or tumor control probability, you need a higher dose for locally advanced disease, compared to early-stage disease. So, 5 Gy decrease in dose for early-stage disease leads to only a decrease of 3% in terms of local controls. But while the same decrease in dose for locally advanced disease, can reduce of around 30% the chance to control the disease. So, whenever we treat early disease, we can be on the safe side in terms of dose-prescriptions but definitely, we need more dose when we treat locally advanced disease. And this is the concept that led the UK investigators to run the PLATO trials, which is trial addressing the clinical question of personalizing the anal cancer prescription and radiotherapy dose. So, basically, this is an umbrella trial, made of three different open questions for three different specific subpopulations of anal cancer patients: the low-risk patients where particularly T1 and 0 disease of the anal margin, where the clinical question if adding low-dose radiotherapy to local excision can increase and improve the local control. The clinical question for intermediate-risk disease which is basically T1 and small T2 and 0 tumor, de-escalation of the dose to 41.4 Gy in 23 fraction combined with chemotherapy can be safe and achieve the same local control rate as standard dose of 50 Gy in 28 fraction. And the clinical question for high-risk disease, which is basically N+ disease or T3-4 disease, any. And if dose-escalations...

and here we're testing, the UK trials are testing two different dose-levels, 58.8 Gy and 61.8 Gy given in 28 fraction, compared to the standard of care, which is 53.2 Gy. So, this trial and the result of this trial will help us definitely to personalize dose-prescription in anal cancer patients, depending on the clinical stage at presentation. Another similar trial is UK trial which is called the DECREASE trial. And this is another trial addressing the topic of de-escalation for low-risk patients, T1, T2, N0 disease, small T2, less than 4-centimeter in size, comparing the standard of chemo-radiation, 50.4 Gy in 28 fraction to the microscopic disease and 42 Gy in 28 fraction to the electing volume. This is the standard of care for this type of disease in the RTOG 05-29 trial, compared to the experimental arm which is a de-intensified chemo-radiation regimen, 36.0 Gy in 20 fraction for T2 disease and 41.4 Gy for T2 disease. This is for the primary microscopic disease and elective dose to the CTV of 32 Gy in 20 fraction. Another trial addressing de-escalation and personalization of dose-prescriptions, depending on the clinical risk of the patient. So, we talk about heterogeneity in terms of dose-prescription but we also have heterogeneity in the selection and definition of clinical volumes. And here, I kind of collected the volume approach in the different trials. The old trial, the ACT-1 trial, the RTOG 87-04 trial, the 98-11 trial, and the more modern 05-29 trial, you see different types of volume selection. Of course, different techniques, and this is like trials run in very different times. So, 2D radiotherapy, 3D radiotherapy, IMRTs but different selection and definition of the treatment volume. And here, I think is also a field where the radiation oncology community should address the need for harmonization and trying to homogenize the selection and definition of treatment volumes in the setting of patient. Because, also, of course, given the heterogeneity it's also very hard to compare clinical results in different trials. What about IMRT? So, we might think that IMRT is the standard of care but actually, there's no prospective trial, apart from the RTOG 05-29 trial which is a phase II prospective trial, targeting, investigating acute toxicity, providing consistent proof of principle for IMRT. But still, if we take a look at real world data either retrospective and prospective, we can see that the clinical results of IMRT are very good, and are very good in terms of toxicity profile, the treatment is generally well-tolerated. And we compare the IMRT data with historical data and historical data can be the RTOG 98-11 trial. We see that in IMRT we have a consistent reduction in the acute toxicity profile for hematologic toxicity, skin toxicity, and gastrointestinal toxicity. So, I think the general feeling of the community is that, of course, the standard of care in terms of technique should be IMRT. And also, comparative data that are basically retrospective comparative data of match propensity score data, comparing 3D CRT and IMRT, of course, favors IMRT in terms of compliance of the patient and acute toxicity profile. And there, of course, clinical evidence also not only in terms of toxicity profile, but also in terms of oncological outcome, local control and disease-free survival, colostomy-free survival and overall survival that IMRT can provide very good treatment, particularly, if combined with image guidance. So, a reasonable margin expansion from CTV to BTB, allowed by the use also of image guidance. So, questions again, if you wish. What about the way to deliver IMRT? So, the normal sequence was for radiotherapy in anal cancer patient was sort of sequential sequence with a progressive shrinkage of the volumes but in more recent years, the use of simultaneous integrated boost has a reason in the clinical use, in the clinical practice. And here is the RTOG 05-29 approach. And here are the prescription-dose for the primary tumor, for the nodes and for the elective volumes. Another interesting approach is the UK approach to deliver a simultaneous integrated boost with IMRT in anal cancer with a prescription dose depending also here on the stage at presentation, 50 Gy or 53 Gy all the treatment is given in 28 fraction. And this is interesting because the elective dose to the nodes is very low, 40 Gy in 28 fraction which is biologically equivalent to 30 Gy in conventional fractionation, with a very low-rate of isolated nodal recurrences which kind of states the safety of this approach. So, what is better?

Go for a sequential boost and a progressive shrinkage of the volume or go for a simultaneous integrated boost? It seems that going for a simultaneous integrated boost which is proven to have dosimetric advantages and so, potentially a correlation to acute toxicity profile, is also safe in terms of oncological outcome. This is a study that we run with Dr De Bari, trying to compare sequential and simultaneous integrated boost approach. And simultaneous integrated boost approach seems to lead to the same

oncological outcome as sequential boost but with a dosimetric advantage and with a potential advantage on acute toxicity profile. And what is nice when you use IMRT and you use complicated techniques and then, for example, you can decide to target specific structures, organs at risk, which you think are important and relevant in terms of toxicity. And this is what we did targeting the bone marrow with a targeted bone marrow sparing approach to reduce acute hematologic toxicity profile in a cancer patient undergoing concurrent chemo-radiation. Always, of course, treat the overall treatment time as short as possible. We all know that squamous cell carcinoma of the anal canal is a highly repopulating tumor and we have the data of the pool analysis of the RTOG 87-04 and the RTOG 98-11 that keeping the overall treatment-time shorter, provides patients with advantage in terms of local control and oncological outcome in general. So, no more split-course radiation in anal cancer patients. The timing or response is another, of course, interesting topic. We know that some of our patients tend to respond very early, have a very early response but some others can have a delayed response. So, whenever the trajectory of the disease is a respondent-disease or the patient is a responder, then, we don't need to worry, we can wait and we can wait up to six months after the end of treatment. And the data of safety of this approach comes from the UK ACT II Trial. So, whenever the trajectory of the disease is positive and the patient is responding, don't be afraid to wait more to be able to achieve a complete clearance of the disease. There's an interesting growing in new combination, apart from the standard chemo-radiation with 5-FU capecitabine and mitomycin C. And the combination, of course, is with immunotherapy. And the anal canal is an interesting setting to try to investigate the use of immunotherapy. It's mostly an HPV-related disease. There's an importance of the tumor infiltrating lymphocytes. So, the microenvironment around the tumor is important and it can be important to trigger the response to radiation. So, the use of immunotherapy, starting in the metastatic setting with a KEYNOTE and CheckMate trials with nivolumab and pembrolizumab with some sort of objective response, particularly, in PD-L1 over-expressing tumors. So, then, from the metastatic setting, the immuno-drugs were kind of shifted towards earliest stage of the disease. And here, we have the outline of the Radiance trial, run in Germany where durvalumab is combined with 5-FU and mitomycin C in order to trigger and increase the response-rate. Durvalumab actually is given in the concurrent setting but also in the adjuvant setting, like a lung cancer-like for locally advanced lung cancer for one year and the primary endpoint here is three-year disease-free survival. And this trial is targeting basically higher-risk patients, larger T2 tumors or locally advanced disease. This is durvalumab, there's also an attempt to include nivolumab in the standard treatment of anal cancer patients. And here we have adjuvant nivolumab after combined chemo-radiation in high-risk anal cancer. This is an American trial. And the current trial is testing pembrolizumab, and is testing pembrolizumab with chemo-radiation in the concomitant setting, also, here, to try to establish a role for immunotherapy in the setting of patients. Another interesting news in the treatment of anal cancer is for the metastatic setting. The standard of care was 5-FU and cisplatin in the metastatic setting like also rough-type of chemoradiation but then, two different standards of care, a French standard of care and a more UK international standard of care came, the modified DCF. So, which is a triplet, so, docetaxel, cisplatin and infusional 5-FU. This is actually... this is used France, in general, in the metastatic setting. This is a very useful type of regimen that can achieve a very high-rate of complete response in this setting of patients. But it's also a quite toxic because it's a triplet chemotherapy regimen. So, it cannot be provided to all the patients. A little bit more tolerable type of approach is the standard that was set from the InterAct trial with carboplatin-paclitaxel, so, a doublet, a little bit more tolerable but still, with a good rate of complete response and a superiority in terms of disease-free survival and overall survival, compared to the standard cisplatin and 5-FU. This is the only trial, the carboplatin and paclitaxel with a comparison-arm while the DCF was a phase II mono-arm trial. Some news are also coming from CT DNA. So, in the attempt to include CT DNA in the treatment and follow-up algorithm of anal cancer patients, CT DNA can be a marker of response and a marker also of early-relapse of disease. So, including CT DNA in the follow-up of anal cancer patients can provide a tool to personalize treatment and to detect early recurrence. And for example, this is a very nice outline of a trial running in the Nordic country led by the Danish colleagues, where patients treated with chemo-rad and HPV-positive patients are randomized to standard of care follow-up or a follow-up which includes CT DNA evaluation and trigger further

clinical examination, basically, CT-pet for patients having a positivity in CT DNA, while provide standard of care follow-up for those who are negative in CT DNA. This is also a good way to implement the efficacy and effectiveness of CT DNA in the study of anal cancer patients. Last but not least is survivorship. And in general, quality of life, for the subset of patients. Fortunately, we are able to cure a lot of patients and a higher-rate of patients, particularly, for early-disease but also, in locally advanced disease. So, we have a high proportion of patients who are long-term survival. So, whenever we have surviving patients then we need to question ourselves and try to establish a good way to manage survivorship and to take care of quality of life of our patients. And so, the EORTC, so, the European organization for research and treatment of cancer, and particularly, the quality of life group is working a lot in quality of life in anal cancer patients, developing the ANL27 module which is a complimentary to do the quality of life, C30 general questionnaire of the EORTC, which has been developed by the EORTC Quality of Life Group, trying to monitor different patients' reported outcome and different functions in anal cancer patients, the bowel function, the sexual function, the stoma-related issue and the pain. The module has been evaluated and is now in the phase IV international validation in a subset of around a little bit less than 400 patients. The good thing is also that the EORTC is working on an extension of this module, not only for non-metastatic anal cancer, but also, for metastatic anal cancer which is a different subset of patients and localized disease with probably different issues in terms of quality of life or patient-reported outcomes, so, the EORTC is trying to adapt the questionnaire also to be able to take care of the quality of life of metastatic patients. I think that was the last slide of this excursus on anal cancer patients. And I want to close with this announcement. Here, you have quite nice and important conference which is the first, actually, it's the first live, because there was another one but it was online because of the COVID pandemic, 2020. It was a webinar, but the first live International Multidisciplinary Anal Cancer Conference, which is organized in Aarhus in Denmark, led by Karen-Lise Spindler and it will be a very good occasion to gather all the community of clinicians, biologists and general researchers working on anal cancer to collect idea, to collaborate, to increase the networking in this setting of patients. We said that anal cancer is a rare disease. So, coming together, collecting data and working together is really important to improve both for clinical practice, but mostly and for mostly for research. And here, you have the link to register, and the registrations are open. So, you're more than welcome to register to this very nice and important conference. I think with this one, I finished my presentation and I'm happy to open the discussion and to take your questions.

Dr De Bari: Thank you, Pierfrancesco, I'd like to congrats to you for your presentation. There is only a comment for instance and no questions, but we wait for them. And the comment is that, one of the participants said that headings in local concurrent radiotherapy dose about high-risk disease are wrong. Indicate opposite, that’s facts, true is reducing radiotherapy dose in high-risk causes reduced efficacy. So, just a comment on your slides board there's a typo or something like that.

Prof Franco: True.

Dr De Bari: Just to underline that reduce the dose in locally advanced, as you clearly said, the locally advanced tumor would relapse more than if we reduce the total dose of CTV is important. There are three comments. The first one is... and I would like to have your comment on my comment side. The first is about epidemiology. You clearly said that anal cancer is rare, that's for sure. The incidence is increasing, but as you know a lot of people are being vaccinated against HPV. You know about the great results that have been obtained for example in Australia, concerning cervical cancer that it is considered as defeated in Australia thanks to the vaccination. So, my question is, should we expect a reduction but not probably in the incidence of anal cancer patients but should we expect a reduction in HPV-positive tumors and an increasing incidence of the HPV-negative tumors? And so, of patients that can either a worse prognosis in the next 10 years or something like that, because, as you said, that for our history of anal cancer can be quite prolonged so, it is not something that will happen in the next two days. But again, is this something that we should expect? And so, should we prepare ourselves in this clinical scenario? That's my first comment.

Prof Franco: You want me to answer to this one or?

Dr De Bari: Yes, please.

Prof Franco: Yeah, I think it's better Yeah, thank, thank you Dino. It's a good point, for sure. So, HPV is not the only risk factor but of course, it's the main risk factor. And if we take a look at all the serious, the rate of HPV-positive in anal cancer is always around 80 to 90%. So, it's the highest, the high majority of anal cancer is HPV-related disease, which is much more higher, of course, than oropharynx cancer and the same level as cervical cancer. So, going there and doing primary prevention is, of course, a key-point. Now, the incidence is increasing because we are having this epidemic of HPV-related disease for the person who were not vaccinated, who were exposed to HPV. And then, after sometimes, develop HPV-positive tumor. This is probably as for HPV-related oropharynx cancer, as you mentioned for cervical cancer that this probably will happen also to anal cancer. And in the future, probably, we will see in like 10-20 years, a consistent reduction in terms of incidence of HPV-related forms, which are most of the forms of anal cancer, so, in general, in anal cancer. Of course, HPV is not the only factor, we have smoking, we have other factors. So, probably, the relative rate of HPV-negative, probably, will increase but just because the HPV-positive will decrease. And those are harder to treat, actually, tend to be more aggressive from a biological point of view, tend to be more locally advanced in the disease presentation. So, I think there, we will need to, we wouldn't have the vaccine because the vaccine wouldn't work for that, and there I think we should work on secondary prevention, so, early diagnosis. So, for example, the narrow-banding strategy and trying to monitor precancerous lesions for high-risk patients could be very important to try to prevent the patients from developing an infiltrating cancer by getting rid of the precancerous lesions. At the same time, for those getting a diagnosis of HPV-negative anal cancer, we will need to improve our treatment. And this is a biologically bad disease. So, we will need definitely to optimize our treatment, probably, to escalate our treatment and all the efforts that the international community is doing to try to personalize the dose, depending on the risk of the patient, are very, very important and will be also very, very important to target this subset of patients.

Dr De Bari: It's interesting to listen to the escalation of the treatment, where in a disease or where we are, we have some studies that are trying to de-escalate the treatment because, for instance, there are a lot of HPV-positive patients, that is clear. Probably, the future all the studies of de-escalation treatment could be re-discussed depending on the epidemiology or the relative epidemiology of HPV-positive and HPV-negative. And it's quite strange to listen to that also because anal cancer is a quite successful history for radiation oncology because we moved from abdominoperineal resection to exclusive radio-chemotherapy. So, we avoided a lot of abdominoperineal resections, probably we could come back to a multidisciplinary approach to need the surgeons if for the HPV-negative tumors would increase, and so, we will see, is it an history to be rewritten? For the second comment, the second comment is about IMRT. So, I have a conflict-of-interest disclosure, all my patients are treated with IMRT. So, I believe clearly in IMRT. But, when we look at the data of the trial that you showed about the RTOG trial 05-29, the trial, from a methodological and from a statistical point of view, it's negative. Trial is negative because they tried to reduce by 50% the incidence of severe toxicities. And finally, they didn't arrive to obtain these results. It's only a comment about that, it means, do you think that the real advantage of IMRT is because of the dose-distribution of IMRT? Or do you think that we should also consider the great impact that IGRT can give? Because if you can narrow the margin by, it's clear that you can improve the dose-distribution, meaning that you can spare better the organs at risk, and so, the results would be better. Do you think that is not only a problem of IMRT but also a problem of IGRT?

Prof Franco: Yeah, true, you are completely right. If you take a look at the RTOG 05-29 trial, which is a trial-design on acute toxicity as a primary endpoint, major acute toxicity, combining all the major events, this is... actually the results were negative. Because the doctors were unable to demonstrate an advantage in terms of the primary endpoint they chose. But then, if you look a little bit more into the details and you kind of stratify depending on... this is, of course, this is not the primary endpoint, you do subset analysis then, you

can always take that subset analysis or not. Take into account at the beginning, they are not in the trial design so, they can be a little bit less reliable. But if you take a look at the GI toxicity, I think G2 and more, the hematologic toxicity and the skin toxicity taken as a single endpoint, there's an advantage for IMRT. If we compare the prospective or retrospective data, the absolute rate of acute toxicity is lower than what we observed with 3D CRT and 2D CRT. So, this is not evidence-based, but there's a growing evidence, the feeling we all have is, of course, that is better. Technically, I think it's much more easier. Right? If you think how we were treating anal cancer, I've never treated anal cancer with 3D CRT but the memory I have is with the progressive shrinkage then you need to under-dose the inguinal nodes so, you need to go for electrons then, you need to fill junctions, it's much more complicated and expose the patient to a lot more uncertainties, in this respect. Then IMRT gives you the advantage of dose-painting. You cannot do dose-painting with 3D CRT. And with dose-painting you can use simultaneous integrated boost, which, generally speaking, provides you a general advantage compared to 3D CRT. So, overall, I would say IMRT is for sure one of the reasons because our treatments are better now for our patients. But then, we don't, you're completely right, we don't need to underestimate the value of IGRT. I think, in general, in radiotherapy in general, IGRT and Cone-Beam CT, let's say, which is the more common option for IGRT, was the one of the most important achievements that we had. Like seeing what we are treating and taking care of motion, taking care of setup errors. So, shrinking the margin is, of course, so important to have patients' compliant to treatment and reduce the toxicity profile. So, I agree with you, IGRT is crucial in pelvic tumors and probably, it will be even more important in the future when doing adaptive, we will be able to adapt the treatment, depending on the response of the tumor and the changes. And MR-LINAC and hybrid is a very good paradigm of that, where we would be able to have daily images, we will be able to daily monitor the changes in the tumor, the changes in the patient and we will be able to adapt the treatments. So, very exciting times for radiotherapy in general but for IGRT treatment choices.

Dr De Bari: Thank you, and then, my last comment was about the dose. As you clearly said, everybody does whatever wants. We have some ideas about the range of the dose. But clearly, we follow our institutional protocols and we go on.

Prof Franco: Yeah, and the other comment on this is that, of course, there's a high variability, but I don't know I always have the feeling that the range that we use is so narrow. You have a two-centimeter tumors, so you have a seven-centimeter tumors, and then, you go for 54 to 59. That is quite interesting, right, so?

Dr De Bari: I completely agree. My question was about two points. The first one is the point to the pelvis. As you know, I worked in a place in France and now, in Switzerland and the French protocol is the preferred one, meaning that we deliver 36 Gy in 26 fractions and sequential boost on the tumor. And looking at the results of the... generally speaking, the French series are globally speaking. I don't see that there is really any increased, an increased rate of local regional relapse. So, I don't want to find the consensus now between me and you, that's for sure. But what I want to say is that, probably, the 36 Gy considering that the good biology of HPV-positive tumor could be an option and are, for sure, less toxic than 45 or 50 Gy, that's my first comment. And the second one is about the total dose on the GDB because when we look at the French trial, the ACCORD trial showed that it's completely useless to go above 65 Gy in a population of T3-T4, N+ tumors, so, probably, the dose escalation is not the good way to do. Would you think that the alternate fractionation, would be of interest in anal cancer patients? It's an HPV-positive tumor, would you think that what we found in hyper-fractionation for head and neck could be something that we can explore?

Prof Franco: So, thank you, Dino. So, the first question is the dose to elective volumes, elective nodes. Actually, I agree with you. For example, I was used to use the RTOG 05-29 standard which is 45 Gy in 30 fractions for a high-risk patient, let's say and 42 Gy in 28 fraction for low-risk patients. This is doable, this is tolerable, probably, this is too high, I agree with you. If we take a look at what the French did, you say, 36 and then sequential. If we take a look at the UK, the UK treated with IMRT and IGRT, a prospective series, they use 40 Gy in 28 fraction, which is I think the dose per fraction is 1.5, if I'm not wrong, which is basically

30.6 Gy, EQD2 given in conventional fractionation. So, I think a dose probably between 30 and 36 UK in France, I think, it's something that could be enough, both the French experience and the UK experience didn't show an increased-rate of isolated nodal recurrence. So, I think that most of the problem is in the primary tumor and the affected infiltrated lymph nodes rather than treating a probability of microscopic disease. So, I agree with you. And then, the second one was the dose to the primary tumor. So, dose escalation, yeah, the ACCORD 0 trial is basically a negative trial. It was a two-per-two design, testing key induction and dose-escalation. I think the trial was negative. But the other thing there was a subsequent report, where there was some hints towards some sort of advantage in terms of a local control for dose-escalated arms. I think there, the problem is, also, the overall treatment time because whenever you combine induction chemo which increases the overall treatment time and then, you go for dose-escalation, probably, not getting an advantage with the dose-escalation, probably, partially, at least can be also due to the increasing in overall treatment time, due to the use of induction chemo for the arm that had induction. I think the PLATO trial, which is a very, very nice design trial and it's a trial addressing and targeting dose-level and stratifying dose-level, depending on the clinical stage basically, will answer our questions. And I think there we will know which dose to which disease a little bit better.

Dr De Bari: Thank you, there was a question or a question by the participants. I answered but I hope that you will agree with my answer, and they asked about the adoption of MRI, of co-registration of MRI in the treatment planning. I said that in our departments it is mandatory to have the co-registration of an MRI with simulation of CT scan, I think and I hope that you agree on that.

Prof Franco: Yeah, I think is mandatory. I agree with you but then, you need to talk to your colleagues at the radiology department to setup a proper protocol in terms of spacing, in terms of sequence, in terms of orientation. This is very, very important to make your life easier, to be able to co-register and easily and reliably, your images. But yeah, it's highly recommended.

Dr De Bari: Good point. Okay, so, thank you very much for your presentation, your comments. I don't see any other questions by the participants. So, I think that we can close the session. It has been very interesting and I hope that everybody enjoyed. And so, I will wish you a very good evening and do enjoy the next event of the European School of oncology that will be presented now. Thank you very much Pierfrancesco and keep in touch.

Prof Franco: Thank you, thank you, Dino. Thank you for joining, bye-bye.

Dr De Bari: Bye.