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Non-surgical management of advanced skin cancers

Dr Rembielak: Hello everyone. I'm Agata Rembielak and I'm a Clinical and Radiation Oncologist from The Christie. I would like to thank European School of Oncology, Promeditec team and also my discussant for allowing this presentation to happen. We will be talking today about "Non-Surgical Management of Advanced Skin Cancer." I have no conflict of interest to disclose, and in terms of learning objectives, after participating in this activity, we would be hoping that participants can describe the concept of high and very high-risk and advanced skin cancer, can understand the role of radiotherapy and also systemic treatment in advanced skin cancer, and also create management plan for patients with such disease. I would encourage participants to ask questions, post them in Q&A session. And at the end of today's session, we will be answering those questions. So, just a brief overview. I was trained in Poland and then I went on further education in Canada, Australia, and also in United Kingdom where I'm currently working at The Christie Hospital in Manchester. The gentleman you can see on the top of the slide is Mr Richard Christie, and I'm mentioning it because some people think that Christie Hospital was named after Agatha Christie, which is not the case. Non-melanoma skin cancer is regarded as the most common malignancy in adults. I would definitely encourage participants of this session to look into Globocan, which is online available for free statistics for cancers from more than 185 countries, and over 36 different cancers. As you can see on the screen, non-melanoma skin cancer is somehow in the middle lower end when we look into number of deaths, and that could contribute to the fact that it's usually underestimated disease and not many research is happening for non-melanoma skin cancer. But there is also an issue with under reporting, and some evidence, we can see that not many skin cancers non-melanoma are reported, registered, and even if there are registers in certain countries, usually, the first diagnosis is only recorded, while some people may develop several different separate non-melanoma skin cancers. It's also a very diverse group, but BCC, sometimes called rodent ulcer and cutaneous skin cancers are the most common. They are both called keratinocyte cancers. The others non-melanoma skin cancers are Merkel cell carcinoma, which tends to be really aggressive form of cancer, and some rare skin cancers, such as porocarcinoma. We usually have really limited literature to support our management. Given the fact how common these cancers are, they definitely pose substantial economic burden. The incidence is regarded around 18 to 20 times higher than of malignant melanoma. And the incidence is increasing, for BCC by 145%, and for skin SCC by 263% from 2000, 2010 in US. The reasons for it are multifactorial with increased UV exposure, ageing population, but also increased awareness, therefore people alert their general practitioners earlier. Local control in skin cancer is the key. We know that BCC rarely metastasizes, but unfortunately, skin SCC can pose a risk of nodal and distant metastases. Majority of keratinocyte cancers can be successfully cured by dermatology and surgical treatments. Any local treatment, especially local recurrence, is of significant risk to cosmetic and functional outcome, therefore advanced keratinocyte cancers remain therapeutic challenge. So, what about risk factors in BCC and skin SCC? Among high-risk factors for BCC, definitely recurrent disease, poorly-defined borders in patients who are immuno-suppressed, also size and

location, aggressive pathology and perineural invasion, also site of previous radiation treatment. But there are also high-risk factors for squamous cell cancer, including location, including size, depth of infiltration. For some prognostic factors, it's above 4-millimetre, for others above 6-millimetre. In some scales, people use deeper infiltration. For example, beyond subcutaneous fat, whether tumour was recurrent, poorly differentiation and perineural invasion. Also, we see higher rate or recurrence and metastatic disease in patients being immunocompromised, either because of their haematological malignancies or being organ-transplanted patients. So, what about those risk factors of progression? Just to look into summarising them. Definitely staging, so, the larger tumour or the more advanced there is the higher risk of progression. Clinical features such as anatomic location, size, recurrent tumours, but also neurological symptoms. There are also histological factors, including grade and subtype, tumour thickness, perineural invasion, growth pattern, perivascular invasion, comorbidities. So, host, whether people are immuno-compromised or immuno-suppressed. Some genetic conditions can be predisposing to skin cancer such as Ataxia-telangiectasia, or Gorlin syndrome. Also, skin cancer arising from previous burns or areas treated with radiotherapy. The other risk factor, especially in recent COVID situation, delays in care, but that could be also due to denial, neglect and access inequalities. And more and more, we are learning also about gene expressions and biomarkers leading to increased risk of progression. But that was about high-risk cancers, but there is also this term of advanced skin cancer. So, what does it mean in terms of skin cancer? And it is really sad that there is still no agreed definition among clinicians. People look into various risk factors, for some, even single factor can be a reason to call advanced skin cancer. For others, it's a combination of factors. When you look into various staging systems, there are multiple of them. I listed here the most commonly used. But for example, European Dermatology Guidelines from 2020 are not based on any staging system. In UK, we have British Association of Dermatology Guidelines, which are based on TNM and risk categories. But as you see on the right-hand side, introduction of low-risk, high-risk, and very high-risk, for some, is seen as very complex. When we talk about high or very high-risk, is it of local recurrence? Progression? Is it of nodal disease or maybe distant metastases? There are people also using this advanced term talking about locally advanced disease, but also about nodal and distant metastases. For some experts, advanced cancer means when management of this specific cancer requires involvement from at least two specialties, or it's very complex single multi-modality treatment. For example, skin cancer requiring very extensive reconstruction. What we will use specifically for this session talking about advanced is those patients who require radiotherapy or immunotherapy. And I appreciate that surgery is the mainstay treatment for many skin cancers, but this session is about non-surgical management. Again, as previously, I would encourage participants to post your questions on the Q&A, and we will be answering those questions at the end with my lovely discussant, Luca. So, what about skin radiotherapy? For many people, skin radiotherapy seems to be a very old technique. And when you see, look at the pictures on the left-hand side and compare with the one right-hand side, you can think that actually radiotherapy hasn't changed much over the years. And for many, especially our younger colleagues, is not very appealing for daily management. They are not very much interested in skin radiotherapy. But how radiotherapy is actually delivered in 21st century? We still use external-beam radiotherapy. Using x-rays, ranging from really very soft 10 to 20 kV through low-energy photons, superficial orthovoltage up to photon treatment in selected patients especially with nodal involvement or post-operative nodal radiotherapy. In terms of particle radiation, majority of patients would be treated with electrons. We don't really see many patients with skin cancer being treated with protons. But skin radiotherapy can be also delivered by brachytherapy, also called interventional radiotherapy. And this treatment mainly uses gamma emitters, such as, for example, Iridium-192. Brachytherapy can be delivered as surface or contact brachytherapy, and then we used flaps, moulds, and surface applicators. But in deeply seated lesions, we can apply interstitial brachytherapy in order to get a radiation dose deeply under the skin. But modern skin radiotherapy can use also IMRT, VMAT, stereotactic treatment, and IGRT. So, definitely, this trend from using one-single field and superficial radiotherapy is changing. So, what about evidence-based for primary disease? Unfortunately, skin radiotherapy, especially in terms of clinical trials, is very neglected. We don't have really many, if almost none, clinical trials, but there are some meta-analyses helping to guide our

management in clinic. So, 2017, Zaorsky published his meta-analysis of hypofractionation with almost 10.000 patients, with very good median/local recurrence of 2% at one-year and 14% in five years. And good physician's assessed cosmesis in 92% of patients. Gunaratne in 2018 published on hypofractionated radiotherapy. So, more than 2 Gy per fraction, with more than 12.000 patients affected by non-melanoma skin cancer, but only 24% of them were with SCC, over 40 publications. And local recurrence, 7.9 in majority of studies with follow-up between 2 to 77 months. His comment was that "Hypofractionation radiotherapy is an option that confers no obvious disadvantage in local control when compared to traditional more protracted radiotherapy schedules." And actually, this is really very helpful, especially in COVID and post-COVID area when we try to treat patients within reduced number of visits but still, without compromising on their care. In 2018, Zaorsky and co-authors published the SCRiBE meta-analysis, comparing external-beam radiotherapy and brachytherapy. Again, around 10.000 patients receiving external-beam radiation, and 553 receiving brachytherapy across 24 studies. And brachytherapy, actually, had favourable cosmesis over external-beam radiotherapy for BCC and SCC at commonly used fractionation schemes. And the other outcome of this meta-analysis was that prospective studies comparing external-beam and brachytherapy are warranted. When we think about clinical trials, as I mentioned, very little, mainly retrospective studies and case series. We have still insufficient evidence to identify high-risk features in which adjuvant radiotherapy in post-operative setting may be beneficial. Definitely margin status. So, in completely excised cases, it would benefit from adjuvant radiotherapy, but there is no clear consensus in literature what actually pathological margin is regarded as clear. In some publications, it's 1-millimetre. In others, it's below 2-millimetres. Another risk factor which is often seen as an indicator for adjuvant radiotherapy is perineural invasion. It is seen in 5 to 10% of skin SCC. It is seen as a risk factor for loco-regional recurrence and distant metastases. The fact that a perineural invasion is at high-risk of regional and distant recurrence, is prompting some authors to say that, adjuvant primary radiotherapy may not be beneficial, but we don't have still enough evidence. Therefore, patients with multi-focal perineural invasion with diameter of nerve over 0.1-millimetre or named nerve, they would be offered post-operative radiotherapy. What about post-operative radiotherapy versus chemo-radiotherapy? Again, only small cohort study, about 61 patients in head and neck region. Adjuvant radiotherapy versus chemo-radiotherapy, and better recurrence-free survival with adjuvant chemo-radiotherapy, although, no difference was noted in overall survival. And then TROG study came in 2018, which was randomised phase-III trial with concurrent post-operative radiotherapy, and chemo-radiotherapy versus radiotherapy in patients with high-risk SCC in head and neck region. And no observed benefit with the addition of weekly carboplatin, therefore those patients would receive radiotherapy only. For nodal disease, we generally see indications for nodal dissection and parotidectomy. There are no prospective randomised trials, basically, for patients with metastatic disease, especially involving radiotherapy. Three within patient-cohorts, following really the same group of patients, examined recurrence, surgical excision, adjuvant radiotherapy and compared to surgical excision alone. And these favoured the combined treatment for loco-regional and overall survival. Retrospective cohort study of parotidectomy with or without neck dissection for metastatic SCC supported surgery and adjuvant radiotherapy for metastatic SCC. And the use of sentinel lymph node biopsy has been investigated in several studies, but there are no conclusive data on the use of it in this specific condition. So, when we think about adjuvant radiotherapy of the draining nodal basin, it's usually recommended in patients with multiple nodal involvement, in large nodes, above 3-centimetres or extracapsular extension. Some evidence talks about elective nodal basin irradiation, and that should not be really routinely recommended. We have one single institutional study with 71 consecutive treated patients on face, ears or scalp. And actual regional control rate at five years was 96%, with no grade-3 or higher complication. And again, we have TROG 05.01 randomised phase-III study, which compared post-operative concurrent chemo-radiation in patients with high-risk head and neck SCC, with no observed benefit of the addition of weekly carboplatin when compared to radiotherapy only. For non-head and neck location, regional lymphadenectomy is advisable. The question about adjuvant radiotherapy remains a challenge. We have to think that radiotherapy in axilla or inguinal region can cause some toxicity, therefore it must be really discussed and benefits of radiotherapy must be weighed against possibility of toxicity. Again, please ask

questions in our Q&A session, we will be answering those questions at the end. I would like to give you a few examples from clinical practise. So, this is the patient who presented with advanced SCC, 12-month history of lesion on the nasal bridge. You can see clinical examination before radiotherapy. Surgery was not an option. Patient declined this treatment, and also, surgery would be very, very extensive. We decided to treat this patient with 55 Gy in 20 fractions that was with electrons. And you can see pictures, the patient about two months at follow-up, and then four months after radiotherapy. Another example of advanced skin cancer is of this poor gentleman who presented with ulcerated left parietal scalp lesion. And for about two years, his treatment was deferred due to significant comorbidities like multiple falls, heart failure, which were regarded as priority rather than his skin SCC, which became very large. And unfortunately, enhancing dural on MRI scan. We decided to treat this patient with palliative radiotherapy. He received 42 Gy in 6 fractions and treatment was delivered weekly. The reason why we decided to do it weekly is that the gentleman had very severe dementia and it was really difficult to get this patient for daily radiotherapy. But at the same time, we didn't want to leave him without any treatment, but you can see response to radiotherapy two months after with erythema around. But then, four months after, this gentleman didn't need any dressings. The area was not bleeding. There was no infection. So, his quality-of-life was definitely much better than at the beginning of his treatment. Another example of, this time, a 95-year-old lady who presented with BCC in her right medial canthus. Because of her comorbidities, she was not regarded the best candidate for surgery. The patient didn't even want surgery herself. We offered her single exposure of superficial radiotherapy with internal eye shielding. And you can see outcomes of radiotherapy in three months after treatment, with no evidence of disease, and she remains in follow-up with no evidence of recurrence. Another example from clinic, it is a gentleman who presented with very advanced Merkel cell carcinoma. Heavily bleeding, fungating, lots of discharge. And he received radiotherapy. It was treatment with photons, 50 Gy in 20 treatments. And you can see pictures taken during radiotherapy, where you can see significant melting, almost, of the disease, two months, and then six months after radiotherapy. So, even in those very advanced cases, we have to consider that radiotherapy is a very powerful treatment. As previously, I'm encouraging everyone, please, to post any questions and comments you may have on our Q&A post. Advanced skin cancer is not only radiotherapy. We have now new players, and that's systemic treatment. The main players are hedgehog pathway inhibitors, which work through SMO, which is smoothened protein. There are also receptor tyrosine kinases, which can be cetuximab, or erlotinib, and PD1 and PDL1 inhibitors in the form of cemiplimab, pembrolizumab, and other. So, what do we know about clinical trials? For BCC, there were three big trials, EVIRANCE, STEVIE and MIKIE, which led to FDA approval and also approval in Europe to use those drugs in clinic. For sonidegib, it was Bolt. You can see examples on the right-hand side from STEVIE about overall response in metastatic and locally advanced BCC, and median duration between 14 months for metastatic BCC, and 23 for locally advanced. Side effects sometimes can be limiting in terms of duration of this treatment, with mainly alopecia, dysgeusia, muscle spasm, and weight loss reported by patients. In terms of skin SCC, cemiplimab and pembrolizumab are definitely two big players. First cemiplimab trial was among 76 patients with locally advanced SCC. And the rate of response was seen in 43% of those patients with durable disease control rate of 63%. The phase-II trial EMPOWER-SCC-1 had up to three years of follow-up, and it showed continued responses and clinically meaningful survival and duration of response for cemiplimab. The overall response was 46%, complete response 16%, and median time to complete response 11 months in 89 responses. For pembrolizumab, it's KEYNOTE-629 study, monotherapy for recurrent or metastatic skin SCC. And it was Single-Arm Phase-II trial. Again, clinically meaningful, durable responses and acceptable safety profile, especially in elderly patients. Side effects, it's about new or worsening cough or shortness of breath, changes of heartbeat, severe headaches, confusion, and hallucinations, vision problems, muscle weakness, and neck stiffness. In February, 2021, cemiplimab received approval from FDA as a first immunotherapy drug indicated for advanced BCC, where patients were previously treated with hedgehog pathway inhibitors or for whom these drugs are not acceptable. So, what about current management pathways? So, for patients with BCC who are not amendable to regional therapy, depending on whether it's locally advanced disease, options include vismodegib or sonidegib. And for metastatic disease, vismodegib.

And then, upon disease-progression or intolerance, the question is, are they eligible for checkpoint inhibitors? And if yes, cemiplimab is an option. If no, consideration of chemotherapy, such as carboplatin, for example, with paclitaxel. For advanced cutaneous SCC not amendable to locoregional therapy, the question is, are they eligible to checkpoint inhibitors immunotherapy? If the answer is yes, the option includes cemiplimab and pembrolizumab. If no, then, the options remain systemic chemotherapy with, again, carboplatin plus paclitaxel or cetuximab. This is the example from our clinic at The Christie, 78-year-old gentleman with excellent performance status who in March 2018, her excision of ulcer and left parotidectomy that showed G2 SCC 28-millimetre in diameter disease SCC infiltrating underlying salivary tissue and extending... to deep margin. He received post-operative radiotherapy, 50 Gy in 15 treatments with electrons and custom-made lead cut out. In September, 2019, recurrent ulcer on the right cheek was found. Investigations confirmed recurrent SCC. And at that time, unfortunately, also lung metastases. In November, 2019, it was decided to treat him with cemiplimab. And following three cycles of this drug, the patient had an excellent response with resolution of the cheek recurrence. Radiological response was mixed with some areas of question, progression, or pseudo-progression. But patient was benefiting clinically and decision was made to continue with treatment. He has now received 33 cycles of cemiplimab and remains in complete remission. Cemiplimab has been very well-tolerated and patient did not have any toxicity. But the treatment with new drugs is bringing new challenges for our clinic. So, for example, there are now reports of the use of vismodegib in neo-adjuvant treatment of locally advanced BCC. And we have first results published from this VISMONEO study. Again, neo-adjuvant vismodegib followed by radiation in locally advanced BCC. So, another indication where radiotherapy can be used after neo-adjuvant hedgehog inhibitor. Similarly, in SCC, there are reports of neo-adjuvant immunotherapy in locoregionally advanced but resectable cutaneous SCC of the head and neck. And there is currently a trial registered on ClinicalTrials.gov. So, in terms of take-home messages, we all see rapidly rising incidents of non-melanoma skin cancer, especially in elderly patients. And advanced skin cancers remain unmet medical need. We can see excellent outcomes in skin radiotherapy in definitive adjuvant, but also in palliative settings in selected patients. It's all about appropriate selection of those patients that may benefit. And we can use advanced radiotherapy, and we can use interventional radiotherapy techniques, also called brachytherapy. We have new drugs for helping patients with advanced BCC, hedgehog pathway inhibitors such vismodegib and sonidegib. They are very highly active, but unfortunately, resistance is common. Toxicities can be predictable, but can be also treatment limiting. For cutaneous SCC, we have immunotherapy with cemiplimab or pembrolizumab. We have also other agents in phase II-III investigations. So, we all have to watch this space, and there are emerging opportunities about combination of therapies. Starting patients on systemic treatment with immunotherapy or with hedgehog pathway inhibitors, and then consideration of surgery or radiotherapy, or maybe both. And then, another question, if patients are already on systemic treatment and they tolerate this treatment well, when is the time to stop this treatment? Is it clinical remission? Is it how patient tolerate it? Or maybe we should put a cup, for example, two years or a number of cycles? So, all these questions, hopefully, we will be able to answer in nearest future. There are also some few learning opportunities and suggestions I would like to share with you. On the 1st of September, there is submission deadline for call for clinical cases, complex non-melanoma skin cancer, where we will be discussing on the 6th of October, 2020. So, I would definitely encourage to submit interesting cases for expert review. There is also ESTRO Skin Cancer course, which this year will be online in November 24th to 25th of November, and there is also ESTRO 22 Conference. And prior to this conference, there will be pre-meeting course on multi-disciplinary approach to high-risk cancer with special focus on skin brachytherapy. But contribution will be from oral specialties, including dermatology, medical oncology, surgical team, nursing team and also from geriatric team. And there is also special addition of clinical oncology journal dedicated to non-melanoma skin cancer, which I would suggest looking at. And there are subjects on surgical management, radiotherapy, systemic treatment and also about immuno-compromised patients. So, there is a lot of different opportunities, which I would highly recommend. I would like to thank you very, very much for staying online. Thank you.

Dr Tagliaferri: Thank you. Thank you. Thank you very much, Professor Rembielak, Agata. So, very, very excellent lecture. Very clear, very complete. Thank you. Thank you again. And we have some questions from the audience. Indeed, I would like to invite all attendance connected to use the chat in order to ask questions to Agata. The first question is... So, from Jose, Good job. Is there any chance for treating basal cell carcinoma using imiquimod? Agata?

Dr Rembielak: There is. It's regarded as topical treatment. So, that would be under our dermatology colleagues, at least in the UK. It depends on sickness. So, if we have really very thick BCC, imiquimod may not be the best approach. And generally, we don't see those patients in skin radiotherapy or in skin oncology clinic because they are all treated by our dermatology colleagues. But for thick basal cell carcinoma, I don't think I would be recommending this medication for this condition, but they would be treated with radiotherapy or surgery.

Dr Tagliaferri: Yeah, so I completely agree with you, Agata. And regarding radiotherapy, we have another question. What is your usual schedule for definitive radiotherapy for inoperable skin basal cell carcinoma or squamous cell carcinoma? And I would like to add the schedule for external-beam radiotherapy, but also for interventional of radiotherapy, brachytherapy, please, Agata.

Dr Rembielak: I think every single person would have their own schedules. The number of schedules that are using is enormous. We use schedules depending mainly on size of the lesion. So, we have schedules starting from single exposure of 20 Gy for superficial. Then, for slightly bigger, we use 35 Gy in 5 electrons. Then, we have a schedule for COVID, which is 14 in 8. Then, for larger, around 6, 7-centimetre tumours, we use 50 to 55 Gy in 16 treatments. Then, for larger 8, 10-centimetres is 50, 55 Gy in 20. And then, we have for very large tumours, we use 60 to 66 in 30 to 33 fractions. That's for standard daily radiotherapy. We do use also weekly radiotherapy for BCC, and that would be 42 Gy in 7 weekly fractions, 6 Gy per fraction. Sometimes, if we have no other choice, we would use it also for squamous SCC, but I'm very conscious about accelerated repopulation. So, it's mainly used in palliative setting. The brachytherapy schedule that we use, we currently use brachytherapy twice a day, over four days, and we use 30 to 32 Gy in 8 fractions. We don't use at the moment, in the centre where I work, interventional radiotherapy. So, Luca, if you could kindly, please share what is your interventional radiotherapy schedule for interstitial radiotherapy, please?

Dr Tagliaferri: Oh, thank you. Thank you, Agata. So, we use a different schedule for any sites. For example, for lip cancer, we usually use 4.5 or 5 Gy in 9, 10 fraction BID, in the morning and in the afternoon. For example, for nasal vestibule cancer, we prefer to use another schedule, 3 Gy for fraction in 12 fractions adding 1, 2 fractions first, and the last of 4 Gy with 7 days in total treatment-time. So, these are usually schedule for interstitial treatment. Another schedule is for orbital cancer, usually we use 10 Gy and 3.5 Gy for fraction. But in this case, we need to personalise also the treatment based on the organ at risk and the volume of the lesion. We have another question, but you have already... answered to this question, because Jose asked how to treat basal cell carcinoma, but of course, with radiotherapy or brachytherapy, interventional radiotherapy based on the thickness. But I would like to ask to you, Agata, because we have one minute. I would like to know your opinion regarding the margins, the margins of the treatment volume for squamous cell carcinoma and for basal cell carcinoma.

Dr Rembielak: I mean, we are in a very challenging situation in radiotherapy, because what we see is our target. So, it all relies on visual inspection. So, I'm not very keen to treat with radiotherapy those skin cancers which are very poorly-defined. Those patients, either I would recommend surgery, or if surgery is not a viable option, I go with mapping biopsies in order to know exact extent of the tumour. If I know, and can see tumour, for smaller BCCs, a margin would be around half a centimetre. And then, if we treat those patients with superficial radiotherapy, there is no really need for extending this margin. It could be 2, 3-millimetre for setup. But for electrons, on the top of this half a centimetre, we have to think about 1-centimetre margin for electrons and for bulging effect of isodoses. For larger BCCs and larger, I mean, more than 2, 3-centimetres,

the margin is bigger. So, I would normally recommend 1-centimetre margin. And then, on the top of it, either if it's treatment with superficial, just a half of centimetre margin for superficial radiotherapy or for electrons, again, to include bulging effect. So, the treatment for squamous cell cancer, it's about at least centimetre margin on the visible disease. For Merkel cell, I sometimes go even up to 3 to 5-centimetre margin, because this specific disease unfortunately has the tendency to spread through those micro-nodules, and then, we see spread of this disease. So, treatment for Merkel cell carcinoma means really large margins. For brachytherapy, we are in better situation, because we are very precise, we are not so worried about patient's movement, so, we can sometimes compromise on margins. But generally, for electrons, again, is this additional aspect of setup and adding for bulging of isodoses. I hope you use the same or similar.

Dr Tagliaferri: Yes, yes, yes. But thank you, Agata, because for this very clear answer.

Dr Rembielak: Okay.

Dr Tagliaferri: So, seven and three, so no additional questions from the audience. I would like to thank the organisers for a very good job. And I would like to thank, again, Agata, Professor Rembielak for this very excellent lecture. Thank you very much.

Dr Rembielak: Thank you. I wish I am Professor, but I'm not. But Professor Tagliaferri, I would like to thank you. And also, we have to thank Roxi and the Promeditec team for all support throughout the session and in preparation for it. Thank you very much.