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Clinical case discussion on non-melanoma skin cancers

Dr Rembielak: Hello everyone, I'm Agatha Rembielak and I am a radiation oncologist with special interest in skin cancer. On behalf of the European School of Oncology and our expert panel today, I would like to warmly welcome all of us to today's first case discussion session on non-melanoma skin cancer. I would like to thank all our contributors who submitted their cases. For today's session we decided to present three of them and please, post your questions during the discussion. Without further ado I would like to welcome Primus Ochieng who is linking from Nairobi and he will be presenting his first case. Primus, the stage is yours, thank you.

Dr Ochieng: Thanks so much, and thank you so much also for giving me this opportunity to present this challenging case. So, the case I'm going to present today is a case of squamous cell carcinoma inoperable resource limited setting. So, I'm presenting to you a case of a 37-year-old lady, we recorded as E.W and, she was provided by the mother because of being mentally retarded and she also has a background history of xeroderma pigmentosum. So, the mother gave a history that she was swell until she was 5-years of age, when she noted that there were skin rashes and changes dryness mainly on the face and on the hands. And with the mental retaliation, she didn't go to school until when she was about 35-years of age, that was 2020. She develops also ulcers on the face, on the right side. It wasn't not associated with any trauma. And then, she went into the local dispensaries, she got treatment with antibiotics, she was done undressing and there wasn't any improvement for about two years after which then she was sent to the tertiary hospital where she could be investigated. So, the times she came to our tertiary hospital said that ulcer on the face was foul smelling and also had intermitted bloody discharge. Other history is nulliparous and she hasn't had a period for the last three years. So, the family history is she is a second born in a family of two, a first sister died at the age of 35 and the mother said she had a short illness and the death was unknown, no family history of any skin cancer or any skin disorder. And because of her condition, the mother is not employed, she is single and she a sole caregiver. So, at examination when we saw her in the month of September that's last month, she looked healthy but was very hyperactive and had a very impulsive behaviour and the tendency to self-mutilate. And main findings were on the right front orbital scalp region where he had a huge ulcer of about 10 cm x 10 fungating crossing the midline. It was malodour with serosanguinous discharge. And the lesion actually had covered the whole eye so you couldn't see the eye on that side. Ocular examination on the left eye was difficult but we managed with the light and least was showing that she had reduced vision. And on the face and neck examinations she had one bucco-facial and large node and right submandibular adenopathy. We managed to examine her oral cavity just to confirm that she didn't have any mucosal lesion and there were no lesions at all. Further skin exams showed that she had a lot of freckling and scaling of the skin, hypopigmentation, hyperpigmentation involving the entire body. You couldn't do very good neuro-

examination because of a mental condition and impulsive behaviour. So, she had a skin biopsy which was done last year in December, and which confirmed that it was a well-differentiated squamous cell carcinoma. Now, you could wonder why it took so long, it's because of a social status and also the mother being single and our country, we don't have medical aid or we don't have any assistance to those who can't afford it and she struggled to look for money so that they couldn't come to tertiary hospital. So, at follow-up she had a CT scan of the head, they couldn't afford MRI, it was done in March, this year, and it showed that there was an extensive soft tissue mass on the right, frontal and peri-orbital region and it was encasing the right orbit globe, it was crossing the midland and infiltrating the skeletal tissues around it. Also, approached that there was frontal intracranial extension of the frontal bone and there was marked brain atrophy with a ventricular dilatation. In the other imaging of the chest and abdomen, there were no other lesions or visceral involvement, all the bones looked okay or any other pathology radiologically. So, we can say that this 37-year-old had a locally advanced, locoregional squamous, non-metastatic cutaneous squamous cell carcinoma of the head and neck. So, she was assessed by the surgical team who referred to the oncology because they were not able to offer any palliative surgery. And the reason why they sent it to us is because of the malodour serosanguinous and the fungation, so that if possibly we could offer some palliation with radiation. But as you know, the question I'm bringing forward for the discussion today is that in literature radiotherapy in serosanguinous pigmentosa it is a question which has been not well-resolved, all literature indicated that because the defect is in the DNA damage and radiation work through DNA damage, there's a risk of further damage to the normal tissues and that makes the reason why oncologists are reluctant to use this as a mode of palliation. And also, I would want to know whether there is any role of systemic therapy, like cytotoxic, if there's any visceral metastasis, also, in a resource limited setting, the only systemic therapy we have access to is chemotherapy. But then, the other is that if you look at this lady, she has a quite good performance status and just want to know that if you had all the resources available how would you manage such a case? Thanks so much.

Dr Rembielak: Thank you very much. I encourage our participants, to post your questions or comments and share your reflections with us. In the meantime, just to help with discussion, I have prepared a very short few slides regarding treatment, and if I can go into the next slide or I can ask our support team to move to the next slide. Thank you very much. So, just a quick background, xeroderma pigmentosum is a genetic disorder and it's autosomal recessive. And what we see in patients is unfortunately the decrease ability to repair DNA, therefore, any damage caused by ultraviolet can be significant. And these patients from a very, very early age, they do develop severe sunburn and hyper-pigmentation, and it's also known that they may develop neurological problems and I don't know whether that was the factor contributing to Primus case, but it seems likely, with poor coordination, loss of intellectual function, hearing loss, and in addition, in your case, it was a problem with vision problems as well because of the growth. Those patients unfortunately are at very high-risk of developing skin cancer, and the literature is basically saying that about half of them would have skin cancer by the age of 10, if there are no any preventive efforts, they may also develop cataracts and they have also high-risk of other cancers including brain cancer. So, we have to think about it in our diagnostic process. The average life expectancy with no-neurological symptoms is 37, and 29 if they have neurological symptoms. So, in your situation the patient is... her life expectancy is above average at this stage. And can I ask for the next slide? Thank you very much. And what can happen in those patients, we can see paraneoplastic syndrome, so definitely full profile with blood test is required and unfortunately, there is no cure for xeroderma pigmentosum. And there is general recommendation in literature, these cases are extremely rare so it's difficult to really have guidelines, but the general suggestion is to treat skin cancer as per-skin cancer guidelines. And I looked through the literature and you can see on the panel those supporting by literature reviews. It's usually surgery followed by radiotherapy and chemotherapy, what we see in literature, with cisplatin. But there are also some reports on the use of neoadjuvant chemotherapy especially, to reduce mass and then it is followed by oncological resection. If chemotherapy is considered, it's usually cisplatin or cisplatin and 5FU, what is mentioned in the literature. And in terms of how radiotherapy is working, and can

I ask for the next slide. I agree that there is a concern that radiotherapy can induce skin cancers but in terms of palliative treatment, I think it's worth to help those patients especially with pain, with large masses threatening vital structures. And actually, when I looked into supporting literature, we have quite a lot of information about the use of radiotherapy, everyone is saying it should be used with caution, but with relatively short life expectancy of those patients I think there is nothing for us to lose in offering this treatment. And in terms of side effects, you have another example by Kim where they say that actually radiotherapy could be given without any serious acute side effects and they have cases presented in this literature. In terms of cellular response, clinical response, another publication is saying that radiotherapy response is similar in patients with xeroderma pigmentosum comparing to patients without this condition. So, maybe, we shouldn't be really so worried about radiotherapy. And you have also another publication in front of you regarding radiotherapy techniques which is not really clearly defined. So, I think for your patient, radiotherapy is the right way to go. I think it's more with palliative intent, in terms of chemotherapy, we have evidence of cisplatin 5FU. I found also from our Italian colleagues a publication on the use of cemiplimab. So, this is a new probably avenue that we will be seeing for those patients, and I would be really interested how you treated this patient and whether she is still with us and how is she doing. Thank you. So, well do you have any update or she's actually waiting for your decision?

Dr Ochieng: We have already made a decision to offer palliative radiotherapy which she started on Monday this week. So, two days at 4-fraction, we are giving 30 Gy in 10-fraction. The challenge is that we are a high-volume centre, the fact is that she can't take instruction with a cognitive dysfunction, she has to be sedated every day. But so far is going on well and we'll be able to give you update once we complete the 30 Gy.

Dr Rembielak: And your comment about cognitive function is also important when you consider chemotherapy or immunotherapy because you need to have some cooperation from those patients. And the question is whether she would be able to be compliant with toxicity of this treatment, which can be sometimes life threatening. So, maybe, radiotherapy is the right way to go, I absolutely agree and support you in it, and we would be very interested on the update. I'm conscious about time, I would like to thank you very, very much. It's a really interesting case. We are moving now to the second presentation, and I'm giving the stage to our colleagues from Manila, welcome, and Dr Tagliaferri will be your expert on the case. Thank you very much, Ariz.

Dr Reillo: Okay, good day everyone. I'm Ariz Reillo, from Memorial Medical Centre from the Philippines, and I'll be sharing a case that I've been working on. I've worked on with my senior Dr Ciocon. So, this is a case of gluteal hidradenocarcinoma that was initially diagnosed basal cell carcinoma, treated with neoadjuvant RT followed by wide excision and inguinal lymph node dissection. So, we are presented with a case of a 44-year-old Filipino female, presenting with the chief complaint of a right gluteal mass. History started 12 years prior to consult where patient noted a small brownish and pedunculated nodule in the right gluteal region, which bled persistently after wearing tight clothing. Patient sought consult and underwent excision biopsy which showed adenocarcinoma of eccrine origin with positive margins, immunohistochemical staining was suggested and further ancillaries but was lost to follow-up. Interim was unremarkable with no evidence of gross lesion, until six months prior, patient noted erythema in the previous excision site which evolved into a plaque with a central ulceration associated with foul smelling discharge. Thus, whole abdominal CT scan was requested which showed lobulated minimally enhancing soft tissue mass measuring approximately 4x8x5 cm in the cutaneous-subcutaneous region of the right gluteal area. This appears to extend medially and superiorly into the perineal region with suspicious involvement of the anal verge. Enlarged and rounded lymph nodes were also identified in the right inguinal region and external iliac regions. Repeated excision biopsy done showed at adnexal tumour with considerations including trichoblastoma or basal cell carcinoma. Immunochemical stains were also requested which showed positive pancytokeratin p63 and ki67 with negative CK20 marker. These signs were consistent with basal cell carcinoma. Metastatic workup included chest CT scan which showed no-evidence of pulmonary nodules or mediastinal lymphadenopathy. Bone scan

was negative and repeat CT was also requested which showed slight interval increase in the size of the mass, now approximately measuring 5x9x7 cm with stable lymphadenopathies. Patient was then referred to our department for neoadjuvant RT prior to surgical intervention. For the review of systems, it was generally unremarkable. Past medical history was non-contributory. Patient was a non-smoker and there's no history of familiar cancer. Physical examination showed a large lobulated mass with areas of ulceration and purulent discharge in the right gluteal region which extends to the peri-anal region. Palpable right inguinal lymphadenopathy was also appreciated. So, at the time, the diagnosis was of basal cell carcinoma in the right gluteal region, stage IV clinically pT3 N2b and without evidence of metastasis, post-excision biopsy. Patient underwent radiotherapy using 3D conformal technique, 2 Gy per-fraction in 33 fractions with a total dose of 66 Gy to the cross tumour and pathological lymph nodes and 50 Gy to the regional lymph nodes. Post-RT MRI about two months after the last RT showed partial interval decrease in the size of the gluteal mass now measuring around 6x6x5 cm previously 5x9x7 cm. No significant change in the size of the pelvic lymphadenopathies were appreciated. Patient underwent wide excision and inguinal lymph node dissection, and the final histopathology showed hidradenocarcinoma 5 cm in widest dimension with negative surgical margins. Positive LVSI and lymph nodes showed tumour cells in the inguinal lymph nodes. So, for the final diagnosis of this patient is hidradenocarcinoma, right gluteal region, stage IV pT3N2b and M0 with the following surgical intervention. So, hidradenocarcinoma is an extremely rare primary eccrine carcinoma. It accounts for less than 0.001% of all tumours. And in the SEER database from 1973 to 2008, there has only been around 200 cases reported, and today there is no consensus for the treatment of this malignancy, and surgery remains the cornerstone of this treatment. However, the local recurrence rate ranges from 10 to 50% with post-surgical survival rate reported to be less than 30%. There are currently no prospective or randomised clinical trials due to the rarity and aggressive nature of this malignancy. And the technique and dose of radiotherapy is not consensual and doses ranging from 50 to 70 Gy are recommended. The role of adjuvant chemotherapy for this has been investigated with small results, and showing no clear survival advantage or effect on local control. And with the initial diagnosis of basal cell carcinoma, which carries an excellent five-year survival of almost 100%, it is reported that hidradenocarcinoma has worse prognosis despite the surgical intervention with less than 30% surviving after five years, and that warrants more aggressive management. So, for this case, our dilemma would be, or our inquiries would be, how would you have managed this patient and what would be the treatment sequencing, the RT-dose and technique? And there's a question for the final histopathologic diagnosis, what would you have requested for the immunohistochemical stains? What further adjuvant treatment can we offer or how would you follow-up this patient? Thank you.

Dr Tagliaferri: Thank you, thank you, Ariz, it's a very, very excellent presentation, very interesting case, very rare disease. Congrats and so, we have five minutes for the discussion, and your questions are very interesting and require a multidisciplinary approach in my opinion. So, for this reason, regarding the second question, and in addition, I would like to ask the rule of chemotherapy or systemic therapy in general in this kind of condition. I would like to involve in the discussion Iris. Iris, regarding the second question, we can improve the precision of diagnosis in this kind of case? And the second question is the role of systemic therapy, especially, with new drugs.

Prof Zalaudek: This is a good point because of course we are now facing a new era in immunotherapy especially in the adjuvant and neoadjuvant treatment, and at the last ASCO and ESMO they presented especially, in the realm also of melanoma, but of non-melanoma skin cancers, quite interesting data. So, definitely, here we have to look in the future. Of course, these are very rare skin tumours, but even single cases may give us some answers in the future. And regarding immunohistochemistry, of course, it has been supposed that this is helpful in the final histopathology diagnosis. But in a mass like this, I think, sometimes, we have to find the right way to do the right biopsy and it's well-known that this tumour is a differential diagnosis with basal cell carcinoma.

Dr Tagliaferri: Thank you. Thank you, it is a very clear answer. So, we have other three minutes, and I would like to invite Bruno, Dr Fionda, to show some slides regarding the role of radiotherapy in this kind of condition. And finally, I would like to give you a comment regarding the rule of interventional radiotherapy, the potential role of interventional radiotherapy. Please, Bruno.

Dr Fionda: Thank you, thank you so much, Luca. Well, of course, this is a very rare disease, and as you may see, this is the most recent and largest database, the SEER based observational study, which we may find in literature, and a couple of important concepts can be derived. The first one is that the overall prognosis is somehow quite good compared to what we thought in the past. And the second important point is that the site of the primary tumour is the only factor that actually correlates with the prognosis of these patients. Of course, as it has already been said, surgical approach is the first step, but of course, we may use radiotherapy as an adjuvant treatment. And we know this from the first studies, which were performed in the early nineties, with doses up to 70 Gy to the primary tumour and up to 50 Gy to the lymph nodes. Such doses may be given also in case of recurrence. And very interestingly, also, interventional radiotherapy may play a role. This is a case described of cervical hidradenocarcinoma, which has been treated with a combination of external-beam and interventional radiotherapy. Also, the combination, of course, of systemic treatment and radiotherapy can be used in cases when there is a lymph node involvement.

Dr Tagliaferri: Thank you, thank you, Bruno. No question from the audience regarding this case. So, a final comment, I think that radiotherapy could play a role in this kind of disease. It is very important the dose, the final dose, the dose that we deliver to the target. And I would like to invite you to consider, as already Bruno told, the interventional radiotherapy brachytherapy boost after radiotherapy, and also, intra-operative radiotherapy on the tumour bed just after surgery. In this case, we could improve the local control and of course, the outcomes of our treatment. So, just in time, sorry, with one minute late, please, Agata, if you wanted to introduce the next speaker.

Dr Rembielak: Thank you very much. We are moving now to the third speaker and I would kindly ask Iris to introduce the next speaker, please.

Prof Zalaudek: So, the next presenter is Dr Carolina Pereira from Portugal and she will present a very interesting case as well on a complete response, please.

Dr Pereira: Hi everyone, thank you. So, yes, I'm presenting this case of an 86-year-old male with a good performance status of 1, and he has a past medical history of ischemic heart disease, arterial hypertension and he's been controlled under medication for both these conditions. No history of smoking or alcohol and not very relevant family history in this regard. And he has shown a skin lesion in the chest that's been growing slowly over two years. And so, he finally went to the doctor to see about this in 2018. And the excision of this lesion showed a malignant melanoma with a superficial extension Breslow 2.9 mm, no ulceration and so, this was staged as a pT3a, and it was BRAF wild-type. And so, he underwent a CT of chest, abdomen and pelvis that showed no distant metastasis. And because of this he was proposed to do a wide local extension excision and a sentinel node biopsy performed in November that same year, and one of the nodes had a metastasis of melanoma. And during this procedure, a second skin lesion was seen and removed in the right lumbar area and this one proved to be a squamous cell carcinoma. So, with a 25 mm no tissue or vascular invasion, and with free margins. And so, this was staged as a pT2. And at this point, we have this elderly patient with two diagnoses of skin cancer, one melanoma stage 3b and the cutaneous squamous cell carcinoma. And due to the high-risk melanoma, he was proposed to do a right axillary lymphadenopathy, but he refused. So, we closely monitored this patient and less than one year after the excision of the lesions, right axillary lymphadenopathy was shown on PET/CT and ultrasound and the histology was metastasis of the squamous cell carcinoma. And we performed the right axillary lymph node dissection, only one of the other nodes were positive for metastasis of squamous cell carcinoma. And after this, he underwent adjuvant radiotherapy to the axilla. And at this point, we had the possibility to include this patient in a clinical trial for adjuvant

pembrolizumab for advanced squamous cell carcinoma of the skin. But the patient refused and so, we continued with only monitoring and one year later, the PET/CT showed a single lung nodule and at this point we thought it could be even another primary tumour. So, he underwent an EBUS with a biopsy to confirm the diagnosis, and biopsy could only tell that it was a carcinoma. So, we disregarded a melanoma at this stage, but it's true that it could be another primary tumour. But because of the history and high-risk squamous cell carcinoma of the skin, we went with this diagnosis and at this point this was a metastatic patient. And for this reason, he started first-line palliative immunotherapy with Cemiplimab every three weeks. And the CT chest after six cycles, you can see this was the first CT of the lung nodule, and after only six cycles it was only residual changes that remained on the upper right lobe and the rest of the CT was clean. The only toxicity this patient had were grade 1 fatigue and decreased creatinine. And currently, this patient actually continues with cemiplimab, he underwent 31 cycles at this point, and complete response, he sustained. So, the image you see below is the last CT scan he did. And you can only see only residual fibrotic changes where the nodule used to be and no new toxicities for this patient. And so, my questions at this point would be, if we can consider stopping immunotherapy after two years if complete response continues to be sustained, like we have some evidence to do in melanoma, but maybe not for squamous cell carcinoma. And if this patient ever progresses, what are other options can we have to treat this elderly patient that already has a history of ischemic heart disease? So, currently he's fit but we know he has some comorbidities that could impair some treatments in the future. And if the progression is confirmed to be melanoma and not a squamous cell carcinoma, whether is it reasonable to consider treatment with a different anti-PD-1, like nivolumab or pembrolizumab at this stage? Thank you.

Dr Rembielak: Carolina, thank you very much. This is really a quite interesting case from different aspects. First of all, the squamous cell carcinoma made metastasis disease and not the melanoma which we had considered because I mean the data of the squamous cell carcinoma is so far not so high-risk as we are used to. The second issue is indeed... I have seen now three or four cases of patients with squamous cell carcinoma but also with basal squamous cell carcinoma that responded already after very few cycles, three cycles of PD-1, and very often what happens in these patients is that they see a benefit and then, they want to stop the treatment. And we have now one case that had complete response clinically and has an ongoing response of locally advanced tumour. So, I think it's a very, very good and very important question, especially in this elderly population to stop maybe treatment and also here the data are suggestive that if they respond well to the treatment, that they maintain the plateau of response even after treatment discontinuation. For me also a question is how long, are even two years too long? If you achieve response after six cycles and there is no stuff we could even discuss earlier discontinuation. Regarding, let's jump to the third question, now what would we do if we have a confirmed melanoma progression? Good question. I mean you would change indication for the treatment, Also, you would need a switch to another drug to get it reimbursed in the indications. So, most probably you should go on with a drug that is an anti-PD-1. And other options, and I think again here in the realm of squamous cell carcinoma definitely Radiotherapy can make miracles and of course, this would be then more a local approach, but as we know it's used, it's considered still second line treatment in many guidelines, so, radiotherapy would be an option and of course, radiotherapy associated with immunotherapy would be the strongest arm most probably. So, but I see Agata and also Luca raise the hands. So, please, Agata.

Dr Rembielak: Thank you very much. This is when I hear radiotherapy, I always put hands-up. I just wanted to ask Carolina because it's extremely interesting and what Iris said, I wouldn't expect squamous cell cancer pT2 to get into the lungs. So, you mentioned that biopsy showed, EBUS, carcinoma, but have you considered surgical management at any point if it's like a single lesion? Because that would give us really information, it could potentially still be lung.

Dr Pereira: Yes, it's true, at the time we considered that because although the patient had no history of smoking, it was the other almost obvious diagnosis, but at the time our surgical team didn't consider the

hypothesis to operate due to his comorbidities, although, they've been stable over the years. So, that's why we decided to go with the immunotherapy even though we only had that biopsy that wasn't any more conclusive. So, it was impossible to take more information. So, we even reviewed with the pathologist and there was nothing more they can tell us,

Dr Rembielak: Yeah. so stereotactic treatment would be the other option for this patient, if it's like a single, which we would use also for solitary lung metastatic before getting on to cemiplimab, Luca, you are next.

Dr Tagliaferri: Thank you, thank you. So, Iris, you told regarding radio-immunotherapy, you know that it's not-topic, and so based on the experience published for other diseases, we have very encouraging results, and the preliminary experience on skin cancer showed with good results. So, I would like your opinion regarding advanced squamous cell carcinoma. If in your opinion in the future radio-immunotherapy could become the first- line therapy?

Prof Zalaudek: Well, I think yes. So, I'm quite sure yes, because we also have to say that we are moving really into an era of medical radiotherapy treatment also of the primary tumour, we very often have to deal with locally or even not so locally advanced lesions, but situations where we would know that surgery will not solve the problem of the patient. In our aim, primary aim should be always as doctors to solve the problem of the patient and not to create other ones by doing repeated surgeries. We know all these patients, and if I look at the cases that we had now, these were, if you have a good surgeon, they would say, okay, let's do it. But the patient refused it and the primary tumours did well and we have a shared case together with our radiotherapist and what radiotherapy did in this case was a miracle.

Dr Tagliaferri: Thank you, thank you.

Dr Rembielak: So, we have only one minute, so, we have to stop the discussion here. I thank everybody for the presence, these were really outstanding cases, excellent discussions also by the experts. And there will be a next-session and maybe, because we got a lot of cases, interesting cases, a next one in March, 2023, and especially to the presenters, thank you for sharing your cases and experience with us.