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Non squamous carcinoma: vulvar and vaginal

Prof Grimm: Hello, my name is Christoph Grimm. I'm a gynecologic oncologist at the Medical University of Vienna. And within the next minutes, I'm going to present on the topic of non-squamous carcinoma with respect to vulvar and vaginal cancer. Thanks to the working group established by the ESGO and the GCIG, we have already a little bit of data and at least some guidelines we can attach to when talking about this very rare disease. The most important thing or the most important aspect is that we are really talking about rare variants of rare diseases. When we look at the lifetime risk for vulvar cancer, for a woman to become at any point, vulvar cancer as a diagnosis, it is 0.3%. So, very low. And only 20% out of the 0.3% account for non-squamous subtypes. So therefore, we are talking about very limited number of very heterogeneous diseases. Starting with vaginal cancer, we confer to the WHO classification from 2014 and there you see a quite a long list of different subtypes for these rare non-squamous vaginal cancers, ranging from adenocarcinomas to other epithelial tumors, high-grade neuroendocrine carcinomas, mesenchymal malignant tumors, sarcomas, LMS and rhabdomyosarcomas, undifferentiated sarcomas or even rarer others sarcomas, up to germ cell tumors, malignant melanomas or secondary tumors. The list is very similar when we look at the non-squamous vulva cancers. Also, adhering to WHO classification from 2014. We have subtypes ranging from glandular tumors, for example, Paget disease, which is quite a familiar and well-known disease to tumors arising from Bartholin and other specialized anogenital glands where the Bartholin gland carcinoma being the most prominent and most familiar one. Again, to high-grade neuroendocrine carcinomas, sarcomas, germ cell tumors, malignant melanomas and secondary tumors. In my talk, I would like to address the most common of these rare diseases. That will be, malignant melanoma, adenocarcinomas, Paget disease, and Bartholin gland carcinomas. Starting with melanoma, looking at the initial workup we have to do in these tumors. It is important that when we talk about melanomas of the vulva and the vagina, we will have to compare them to mucosal melanomas, not to cutaneous melanomas. That is particularly important when we talk about the therapeutic strategy and the adjuvant treatment. The best staging for these malignancies is unclear at the moment. We have the very comparable FIGO and AJCC classification and then, we have a kind of completely different classification, that's called the Ballantyne classification. As with all malignancies arising in the vulva and the vagina, initial biopsy is key, is crucial to confirm diagnosis. Whenever you have a suspicious lesion at the vulva or at the vagina, you have to biopsy. The key pathologic features, we need to confirm the diagnosis of melanoma and to be able to develop the most precise treatment strategy will be

tumor thickness, which is the most important one, presence of ulceration, number of mitosis, lymphovascular space invasion and the number of TILs or the rate of TILs in the tumor. With respect to imaging, we typically need a CT chest abdomen, which is kind of standard pre-op or pre-therapeutic work up. PET/CT is also feasible and is very commonly used for these rare malignancies and particularly important, we also need an MRI or at least a CT of the brain to rule out brain metastases. MRI of the pelvis is sometimes needed. We kind of recommend it for all vaginal melanomas and also, for larger vulvar melanomas which will require a larger, more aggressive resection or surgical procedure. And last but not the least, the genomic testing is becoming more and more important, particularly, in melanomas of the vulva and the vagina, because we can test for BRAF, c-Kit, NRAS, NTRK, ALK and ROS mutations. And these are already very clinically relevant mutations because they can trigger and alter adjuvant chemotherapy. Looking at the staging for melanoma of the vulva it is very comparable to the staging for squamous carcinoma with maybe the exception that the thickness is a little bit different and it's a little bit different between the FIGO classification and the AJCC classification, but overall, these two classifications are very comparable. A kind of completely different classification is the Ballantyne classification. It's a simplified staging system that originally has been intended for H and N melanomas, but also kind of apply to basically all the mucosal melanomas and there you have the stage I as a clinically localized disease. Stage II would be regional nodal disease. So typically, lymph node metastasis in the groins; and stage III would be a distant metastasis. So, very, very rough classification for the very pragmatic one. When it comes to primary treatment with respect to melanomas, typically, the most important aspect would be that if these patients are feasible or are eligible for a local wide excision. If that is possible, then surgical therapy is the first step of the treatment. And there, the tumor thickness is particularly important as you can see because if the tumor has tumor thickness of less than or equal to two millimeters, then we kind of only need clinical margins, tumor free margins of one centimeter. But as soon as the tumor thickness is more than two millimeters and the invasion is more than two millimeters, we will need clinical margins of two centimeters, which is very different to our squamous vulva cancers. If we have positive resection margins, of course, we have to consider re-resection. And if that is not possible, then, we have options like imiquimod 5% topical treatment or hypofractionated radiotherapy or close observation, depending very much on the localization and the general status of the patient. Something that is also very different is the management of lymph nodes because typically we would consider these patients eligible for sentinel lymph node resection or identification, and that is, again, very comparable to squamous vulva cancers, where we would do the unilateral side of sentinel lymph nodes when we have a lateral tumor, if we have a tumor close or crossing the midline, then we would do a bilateral sentinel lymph node. But if we have a positive sentinel lymph node, completion of this inguinofemoral lymph node resection is typically unnecessary and that's quite a significant difference to squamous vulva cancer. So, typically, in these patients, we would very literately apply adjuvant checkpoint inhibitors therapy, typically with a PD-1/PD-L1 inhibitor. It differs a little bit if the patient has a BRAF mutation. So, that's why this has been done in genomic profiling in this patient, it's particularly important. Another option is groin surveillance every three months for the first three years. So, if the patient has positive lymph nodes, but no grossly other lymph nodes, we can also monitor these patients with groin ultrasound alone or switching between groin ultrasound and CT scan. Completion of the inguinofemoral lymph nodes also is only necessary if we have enlarged lymph nodes or we have progressing disease in the groins. So, for grossly suspicious groin nodes it is unclear if complete lymph node resection is truly needed or just resecting enlarged lymph nodes. So still, even in enlarged lymph nodes, we would try to de-escalate the aggressiveness of the treatment and rather selectively resect the enlarged lymph nodes in the groins. If we have a locally advanced tumor, we try an extensive resection. So, if surgery is not the first-line, then exenterative procedures are reserved only for very highly selected cases. So, only for very few patients; typically, we would rather recommend immunotherapy alone if metastatic disease, of course, or if it's a localized, large localized tumor disease, then, would rather recommend immunotherapy and hypofractionated radiotherapy, including groin metastases, if necessary. So, with respect to the adjuvant treatment, of course, whenever we have a clinical trial open for this patient, a basket trial for example, we would try to put this patient into trials for sure. But if we consider like kind of the

standard adjuvant therapies, the standard as to be like stated with caution in this very rare disease, then, it is particularly important to have a genomic profile to assess for BRAF mutations in particular, because if there is no verified BRAF, V600E or V600K mutation, then these patients would rather receive a CPI single agent, typically pembrolizumab, nivolumab or ipilimumab. And if the patient has a verified mutation, then typically these patients are treated little bit in accordance to the melanomas with these types of mutations, with dabrafenib and trametinib. The hypofractionated radiation therapy for locally advanced, newly diagnosed melanoma cells, vulva and the vagina is particularly important. It is usually delivered every other day for six times, we have the target volume, which would be the gross disease with again, approximately one centimeter on top, kind for free margins. And again, in these patients, we can concurrently apply a single agent immunotherapy. If these patients respond exceptionally well and have only a small residual tumor, which we can resect without doing any exenterative steps, then, this can be considered in these patients. If these patients recur, then, again, we're in a highly individualized state of the disease. Whenever clinical trial is applicable, we'll try to put our patients into that, but if that's not the case, then, typically, we would differentiate between three different scenarios. Scenario one would be an isolated recurrence that is resectable, of course, then, we would consider resection in these patients. Again, exenterative procedures in highly selected situations because these patients have a high-risk for recurrence and then we want to avoid extensive surgeries and limitations for these patients following these surgeries. Again, we should consider adjuvant immunotherapy after surgical resection. Scenario number two would be isolated, but not resectable recurrence; in these patients, of course, we should consider the hyperfractionated radiotherapy if patients have not previously received that or we can even consider re-irradiation after hypofractionated radiotherapy, depending on the dose the patient received. And again, concurrent immunotherapy liberately recommended in these patients. And last but not least scenario number three, not isolated metastatic recurrent disease. And there typically we would use standard management options for cutaneous melanoma because this is the best data available and comparable for these patients. The second tumor, adenocarcinoma of the vulva and the vagina. In these patients, we directly apply to the FIGO staging system. Important factors to consider in these patients would be that with respect to vaginal tumors, we have various scenario of clear cell carcinomas that have been historically associated with the use of the estriol predominantly for 15 to 30 years. It's a very long time. We also can find mesonephric adenocarcinoma and in vulva cancers, the majority of adenocarcinomas derive from the Bartholin gland. The most important prognostic factors in these patients are as in most of tumors FIGO stage, size of the tumor and histology. And the risk of relapse is mainly related to tumor stage, interestingly. When it comes to primary treatment, typically surgical procedures for vulva tumors are the first-line treatment of choice. We have to assess in these patients whether we do a local wide-excision or we have to do a radical vulvectomy. In case of positive margins, we would aim for further resection if it's feasible, depending on the positive margins and the localization of these positive margins and in analogy to kind of the typical squamous cell vulva cancers, we would opt for radiotherapy if it is close to the urethra or the anal verge for example. Typically, in these patients, we'd perform an inguinofemoral lymph node dissection, but sentinel lymph node dissection is also feasible in these patients depending on the experience of the center. The surgical procedure for vaginal tumors depends a little bit on the localization of the tumor. It depends whether it is proximal to the uterus or it is distant and close to the vulva because that would be typically our two approaches. If it is close to the introitus so the vulva, we would do a radical vulvectomy with vagina resection. If it is close to the uterus, to the cervix of the uterus, then we would perform a radical hysterectomy with a vagina resection if it's feasible, if we are sure to achieve clear margins in these patients. Typically, in vaginal tumors we would not do any radical surgical lymph node staging. So, particularly, in these patients, the pre-op workup where the CT MRI, and even a PET CT in these patients to have the most precise evaluation of lymph nodes of the groin of the pelvis would be crucially important to rule out lymph node metastases in these patients. When it comes to systemic treatment and recurrences, we have adjuvant therapy in node positive patients, typically, radiotherapy kind of treatment for vaginal carcinomas, is primary radio-chemotherapy. And the therapy of recurrent disease is typically some sort of combination of radiotherapy, chemotherapy, radio/chemotherapy or in vulvar recurrences in selected patients, vulvar

resection. In selected patients after PD-L1 testing, we can even apply checkpoint inhibitors in these patients. Although, the rate of patients with positive CPS or TPS is rather low. The next topic would be the Bartholin gland carcinoma. Again, FIGO staging system is applied. And the important factors to consider in Bartholin gland carcinoma is that approximately 30 to 50% are squamous histology and the rest, so a little bit more than 50%, 50 to 70% typically includes adenocarcinoma. The lesions are typically deep within the vulva and very often they are misdiagnosed this Bartholin gland as abscess or a cyst. Again, the FIGO stage, size of tumor, histology and prognostic are the most important factors. And the risk of relapse is approximately 20 to 40%. So, rather high. Treatment again, surgical procedures, if you do local wide-excision or radical vulvectomy, in case of positive margins, we can consider further resection or radiotherapy depending on the localization on the other organs. Typically, inguinofemoral lymph node dissection is recommended, but again, sentinel lymph node dissection is feasible and for large tumors, we can sometimes consider neoadjuvant chemotherapy, to shrink the tumor down, and then, resect it in a second step. Adjuvant therapy, again in node positive patients, radiotherapy or combination of radio-chemotherapy. And alternative treatments if the tumor is not resectable would-be prior radio-chemotherapy. The therapy for recurrent disease, obviously, depending on the site and the previous treatment is surgery, radiotherapy, chemotherapy or a combination of two of these treatment-modalities. And then, a very common disease, Paget disease. The initial diagnosis is very comparable to the other tumors. We'll do a physical examination, then, particularly evaluate the extent of the tumor. Sometimes, in Paget disease we even need a cystoscopy and proctoscopy to rule out that there is any spread to other organs. We would do particularly a pelvic imaging, usually MRI of the pelvis, pelvic and the abdomen would be the imaging of choice and again, we would need a biopsy to evaluate the disease and confirm the diagnosis and in Paget disease, it is typically as it is usually locally more spread, would typically need multiple biopsies. And therefore, in these patients, very often, vulva mapping is considered or recommended. Important other factors is that we look at association with underlying malignancies so, for example, anorectal carcinoma or urothelial carcinoma and that's why cystoscopy and proctoscopy is very liberately recommended. Exclude breast or GI tumors. And then, it is a very crucial point is to differentiate between invasive Paget disease and intraepithelial Paget disease because these are like kind of completely different types of diseases and differ very much in treatment-modalities. If of negative margins in Paget disease and that's a very unique thing is that it doesn't preclude recurrences because it has this like very particularly pattern of spread. So, risk of relapse is very high with 30%. And the median time to relapse with three years is rather short. Disease-related mortality because it is not a very aggressive disease is well-below 10%. So, treatment again would be local wide-excision, vulvectomy or sometimes, even Mohs surgery, which is a layer-by-layer resection, because we have this very advanced, very local spread on the superficial epithelium. And most of the times, not a very aggressive invasion of the tissue. Then, again, in selected patients, if it's invasive, inguinofemoral or sentinel lymph node dissection and adjuvant therapy as in node positive patients, and would be radiotherapy, and the primary treatments are in Paget disease, imiquimod topically applied for intraepithelial disease, with very high success rates ranging up to 70 to 90%. So, an excellent treatment-modality in Paget disease for intraepithelial disease. In more aggressive types, radiotherapy, and in very advanced stages, for example, stage IV, then, we have to consider metastasis of undetected underlying malignancies. So, in these very selective patients, chemotherapy can even be a treatment-modality. Photodynamic therapy, laser therapy has been proposed, although, the data is rather limited on that. So, that would be our algorithm where we talk about Paget disease. Most important thing is to rule out other malignancies as differential diagnosis and then triage into intraepithelial Paget disease where we try to do rather limited surgery and if with positive margins or we cannot resect it, then think about imiquimod, which has an excellent response rate. Then in contrast, invasive Paget disease, where we would go for a surgical excision with wide margins due to the high-risk for local recurrence. In these patients even consider sentinel lymph node or systematic inguinofemoral lymph node dissection. Also, in these patients, but only in case of positive margins, we can consider imiquimod if re-resection is not feasible, or in selected patients, radiotherapy. So, the fallow-up for this rare disease would depend very much on the primary tumor. When we look at Paget disease, we really have to triage between intraepithelial and invasive Paget disease.

Typically, we need a local inspection, consider vulvoscopy and do a re-biopsy to confirm the recurrence and then assess whether we have a locally confined recurrence or we have distance spread with CT or MRI in case of advanced disease. For adenocarcinoma, typically, we have local inspection, ultrasound for nodal recurrences, again, select the patients, we can do CTs, MRI or PET CTs to rule out distant recurrences. And again, if these patients recur, do a biopsy very liberately, very low threshold to confirm the recurrence and maybe, in these patients do a genomic profile. With respect to melanoma, again, local inspection. In these patients, groins surveillance it's particularly important, every three months of first three years in node positive patients which is dramatically different to the management for squamous vulvar or vaginal cancer. So we can monitor and follow up these patients very closely, but that is kind of a safe treatment attentive do CT, chest, abdomen, pelvis and MRI of the brain to rule out brain metastases, that is particularly important in melanoma patients. And the frequency is very similar, three to six months and time distance for five years. So, to conclude my talk, all of these subtypes are extremely rare malignancies, so, we're talking about rare variants of rare diseases. That's particularly important to keep in mind. When we talk about melanoma of the vulva and the vagina, we usually compare it to mucosal melanoma was in fact treatment strategies. Bartholin gland cancers often misdiagnosed as an abscess or a cyst, that is particularly important. So, very often we have to deal with surgically treated partially resected tumors that we have to very aggressively re-resect. And with respect to Paget disease, we have to be very cautious to precisely differentiate between invasive and intraepithelial Paget disease, because these are kind of two different Pagets. And with respect to Paget disease, particularly, in intraepithelial Paget disease, topical imiquimod is an excellent treatment that we always have to keep in mind next to surgical treatment in these patients. So, thank you very much for your attention and I'm very much looking forward to your questions.